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Title

Insights into anticancer sonodynamic activity of IR-780 in an in vitro three-dimensional model of pancreatic cancer

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Background

Pancreatic cancer remains one of the most lethal forms of cancer with a 5-year survival less than 10%. Sonodynamic therapy (SDT) is an innovative approach for the selective treatment of solid tumors, where the interaction between ultrasound (US) and an US-responsive chemical compound (sonosensitizer), harmless per sè, provokes cancer cell death by reactive oxygen species (ROS) generation [1]. Thanks to nanotechnology, the sonosensitizer can be combined with other drugs in multifunctional nanoparticles to boost the antitumor efficacy of SDT [2, 3].

Methods

In this work human serum albumin nanoparticles (HSA), loading the sonosensitizer IR-780 (IR), the chemotherapeutic drug paclitaxel as dimer (PTX_d) and the immunomodulator drug indoximod as dimer (IND_d) (IR-PTX_d-IND_d@HSA), have been developed. The antitumor efficacy of SDT with IR-PTX_d-IND_d@HSA has been then investigated on in vitro two-dimensional (2D) and three-dimensional (3D) cultures of BxPC-3 pancreatic cancer cells by mainly flow cytometric and imaging assays.

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Results

First, the uptake and cytotoxicity of IR-PTX_d-IND_d@HSA were evaluated in 2D BxPC-3 cell cultures, to select the proper concentration and incubation time for SDT. IR-PTX_d-IND_d@HSA under US exposure determined a significant decrease of cell proliferation after 72 h ($p < 0.01$) along with a significant increase of apoptotic and necrotic cell death. In addition, a significant increase of specific damage-associated molecular patterns (DAMPs), like calreticulin (CRT) and high mobility group box 1 (HMGB1) proteins, was detected at 6 h ($p < 0.001$) and 24 h ($p < 0.001$) after SDT, respectively. According to the observed SDT-induced immunogenic cell death (ICD), the activation of dendritic cells (DCs) was investigated to confirm an effective immune response against tumor cells. Thereby, peripheral blood mononuclear cells (PBMCs) were co-cultured with BxPC-3 cells, previously exposed to SDT with IR-PTX_d-IND_d@HSA, showing a significant DCs activation after 1 h ($p < 0.001$). Finally, to confirm the data observed in 2D BxPC-3 cell cultures, BxPC-3 spheroids have been developed and studied extensively. 48 h after SDT, a significant volume reduction of the treated spheroids was observed along with a significant increase in necrotic cells ($p < 0.05$).

Conclusions

The anticancer effect achieved by US exposure of IR-PTX_d-IND_d@HSA was able to significantly promote the in vitro killing of BxPC-3 pancreatic cancer cells in 2D cultures, along with induction of ICD and DCs activation. Moreover, the SDT on BxPC-3 3D spheroids confirms the anticancer efficacy achieved in 2D BxPC-3 model but with substantial differences in the nanosystem concentration and US parameters, highlighting the importance of investigation on in vitro 3D cancer models for moving forward to in vivo studies.

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Title

Prescription appropriateness of antithrombotic drugs for prophylaxis of venous thromboembolism in hospitalized multimorbid older patients

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Background

To assess 1) the prescription prevalence from 2012 to 2019 of antithrombotic drugs for thromboprophylaxis (TP) in hospitalized older patients; 2) the appropriateness of their prescription or non-prescription, 3) in-hospital mortality rate in appropriately versus non-appropriately prescribed patients.

Methods

Patients aged 65 or older, admitted to the Italian internal medicine and geriatric wards participating to the REPOSI register from 2012 to 2019 were assessed for prescription of antithrombotic drugs for TP at admission or during hospital stay. The Padua Predictive Score (PPS) and the IMPROVE score were used to assess the thrombotic and bleeding risk. Patients were considered to be appropriately prescribed when had PPS≥ 4 and IMPROVE<7, and appropriately not prescribed when PPS≤4. Logistic regression model was used to assess whether or not appropriateness was associated with in-hospital mortality.

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Results

Of the 4836 patients included in this study, antithrombotic drugs were prescribed for TP in 1233 (25.5%). 70.3% of them were appropriately prescribed or non-prescribed but, among those prescribed, only 31.7% were appropriately prescribed, while among those non-prescribed, 83.5% were appropriately non-prescribed. The in-hospital mortality rate was lower in patients appropriately prescribed or non-prescribed than in those inappropriately prescribed (OR: 0.63; 95% CI: 0.46-0.83).

Conclusions

A high prevalence of multimorbid hospitalized patients were appropriately prescribed or non-prescribed for TP with antithrombotic drugs, appropriate non-prescription being mainly driven by a high bleeding risk. Since appropriateness of prescription or non-prescription was associated with a lower in-hospital mortality, the use of prognostic scores is advised to optimally manage antithrombotic drugs in this complex population.

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Title

Prescription Appropriateness of Drugs for Peptic Ulcer and Gastro-Esophageal Reflux Disease: Baseline Assessment in the LAPTOP-PPI Cluster Randomized Trial

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Background

Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD) are among the most widely prescribed, frequently without appropriate indications. This represents an important issue, as it leads to risk of adverse events for patients and unnecessary costs for National Health Service.

The aim of this study was to assess the prescription appropriateness of drugs for GERD, in the frame of the “Evaluation of the effectiveness of a Low-cost informative intervention to improve the Appropriate PrescripTiOn of Proton PumP Inhibitors in older people in primary care: a
cluster-randomized controlled study” (LAPTOP-PPI) (Clinicaltrial.gov: NCT04637750).

Methods

The appropriateness of drug prescription was assessed on data collected in administrative databases, by integrating information on concomitant medications, outpatient medical and laboratory procedures and hospital discharge diagnoses, according to the reimbursement criteria provided by the Italian Medicine Agency. We analyzed data of community-dwelling people aged 65 years and over, living in the areas of Bergamo (Northern Italy) and Caserta (Southern Italy), from July 1 to 31 December 2019.

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Results

Among 380,218 patients, 175,342 (46.1%) received at least one prescription of drugs for GERD. All in all, we found that only 41.2% of patients received appropriate prescriptions.

Conclusions

Given the potential risk of adverse drug reactions, especially in older people, educational interventions should be prompted for physicians, in order to improve the quality of prescription of drugs for GERD and, in turn, avoid unfavorable health outcomes and unnecessary costs.

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Title

Plasma and brain pharmacokinetic profile of cannabidiol in rats after subchronic treatment: a potential treatment for migraine?

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Background

Cannabidiol (CBD), a phytocannabinoid found in *Cannabis sativa*, has recently gained much attention due to its antioxidant, anti-inflammatory and analgesic properties [1]. In this study we evaluated cannabidiol pharmacokinetics in plasma and in peripheral/central areas involved in migraine pain in rats following intraperitoneal subchronic treatment.

Methods

Four sets of male Sprague-Dawley rats (n=5 for each experimental group) received CBD 15 mg or 30 mg/kg for 5 consecutive days and were sacrificed 1 h or 24 h after the last administration. After exposure the animals were sacrificed, plasma samples were collected and trigeminal ganglia, cervical spinal cord, meninges and medulla were quickly harvested. Rat plasma and brain samples were analyzed by online-SPE LC-MS/MS [2].

Results

Administration of cannabidiol to rats sacrificed 1 h and 24 h after the last administration leads to the following mean plasma CBD concentrations: 342±324 ng/mL and 18±4 ng/mL respectively in the group of animals treated with 15 mg/kg CBD, 1372±117 ng/mL and 47± 6 ng/mL in rats treated with 30 mg/kg of CBD. In trigeminal ganglia, cervical spinal cord, meninges and medulla of rats treated with 15 mg/kg CBD mean CBD levels after 1 h were 236±200 ng/gr, 361 ±340 ng/gr, 76±60 ng/gr, 501±469 ng/gr respectively and 19±7 ng/gr, 19±4 ng/gr, 7±2 ng/gr, 21±6 ng/gr respectively at 24 h post-treatment. In rats treated with 30 mg/kg CBD mean concentrations were 1085±111 ng/gr, 1852±300 ng/gr, 331±76 ng/gr, 2358±241 ng/gr after 1 h and 49±25 ng/gr, 44±7 ng/gr, 15±6 ng/gr, 55±9 ng/gr after 24 h (trigeminal ganglia, cervical spinal cord, meninges and medulla respectively). These findings confirmed that after repeated injections of CBD at doses of 15 and 30 mg/kg CBD levels increased in all areas under evaluation 1 h after the last injection with a substantial decrease at 24 h post-treatment suggesting that CBD does not accumulate in the brain.

Conclusions

Our data offer key information on the pharmacokinetic profile of CBD in plasma and in central/peripheral nervous system areas and suggest for the most effective administration route and time points for evaluation of analgesic effects in animal models of migraine.

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pharmadvances
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Title

Psycho-social events secondary to drug-induced impulse control disorders: network analysis in the FDA Adverse Event Reporting System.

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Background

Psychosocial sequelae bear a substantial burden on the life of patients and their caregivers and need to be included in drugs' safety profiles. The psychosocial burden of dopamine agonists, including both direct/primary (e.g., impulsivity) and indirect/secondary events (e.g., bankruptcy and divorce), is difficult to characterize. We aim to investigate the psychosocial impact of drug-induced impulse control disorders. A more comprehensive drug safety profile, acknowledging the ultimate psychosocial impact of drugs, will extend the medical focus beyond organic conditions and will empower the patients towards a more conscious therapeutical choice.

Methods

We cleaned the FDA Adverse Event Reporting System (January 2004 – March 2022). We investigated anti-Parkinson and antipsychotic dopamine agonist-induced impulse control disorders. Because we propose a new method, we chose as positive controls oxycodone and drug dependence, and as negative controls proton pump inhibitors and nausea. We calculated the reporting rates to quantify the psychosocial impact. To characterize primary and secondary reactions, we estimated a network for each drug class, with nodes representing psychosocial events recorded in more than 1% of the reports, and links representing partial correlations between the events.

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Results

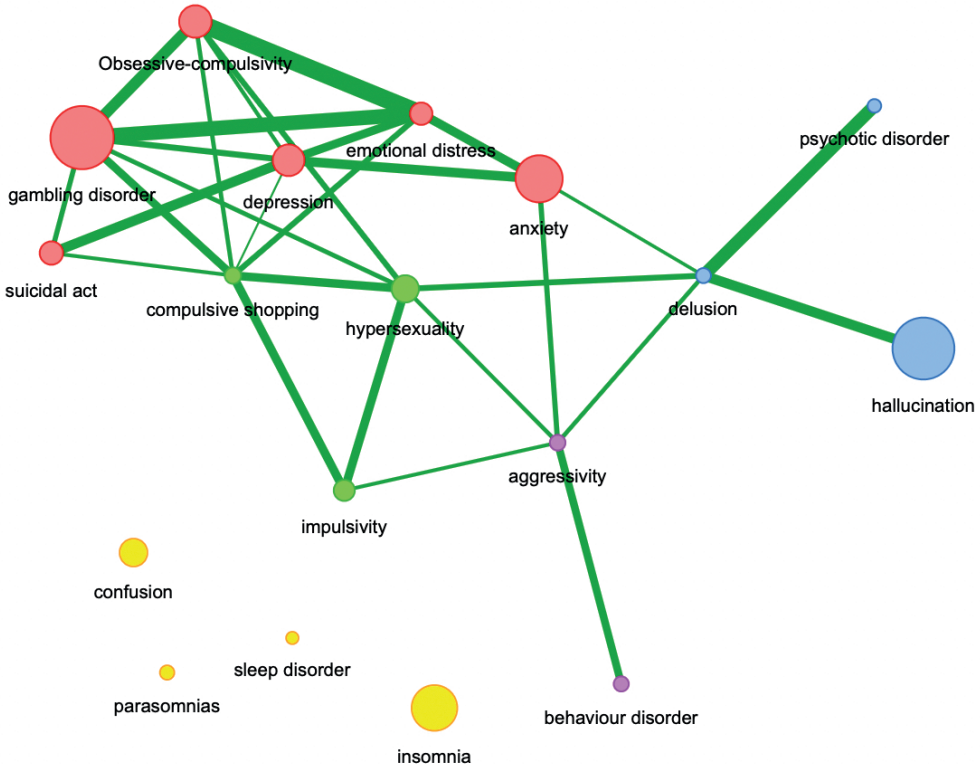
Dopamine agonists had high reporting rates of psychosocial events (37% for antipsychotics; 29% for anti-Parkinson agents). When restricting to impulse control disorders, we found a strong co-reporting of economic problems (47%; 6%), obsessive compulsivity (40%; 26%), emotional distress (29%; 19%), anxiety (26%; 14%), and suicidal acts or ideas (23%; 13%). The networks showed that the different impulse control disorder manifestations (e.g., pathological gambling and hypersexuality) were co-reported together and with economic problems and obsessive-compulsive symptoms. Further, drug-induced impulse control disorders were connected, via distress and anxiety, with aggressivity and psychosis, and with depression and suicide (Fig.1-2). Proton pump inhibitor reports seldom recorded psychosocial events (9%), primarily anxiety (2%). Most oxycodone reports recorded at least one psychosocial event (69%), primarily drug dependence (57%). Oxycodone drug dependence was linked to learning impairment and disability (via mental disorders), suicide (via depression), and crimes (via aggressivity)(Fig.3).

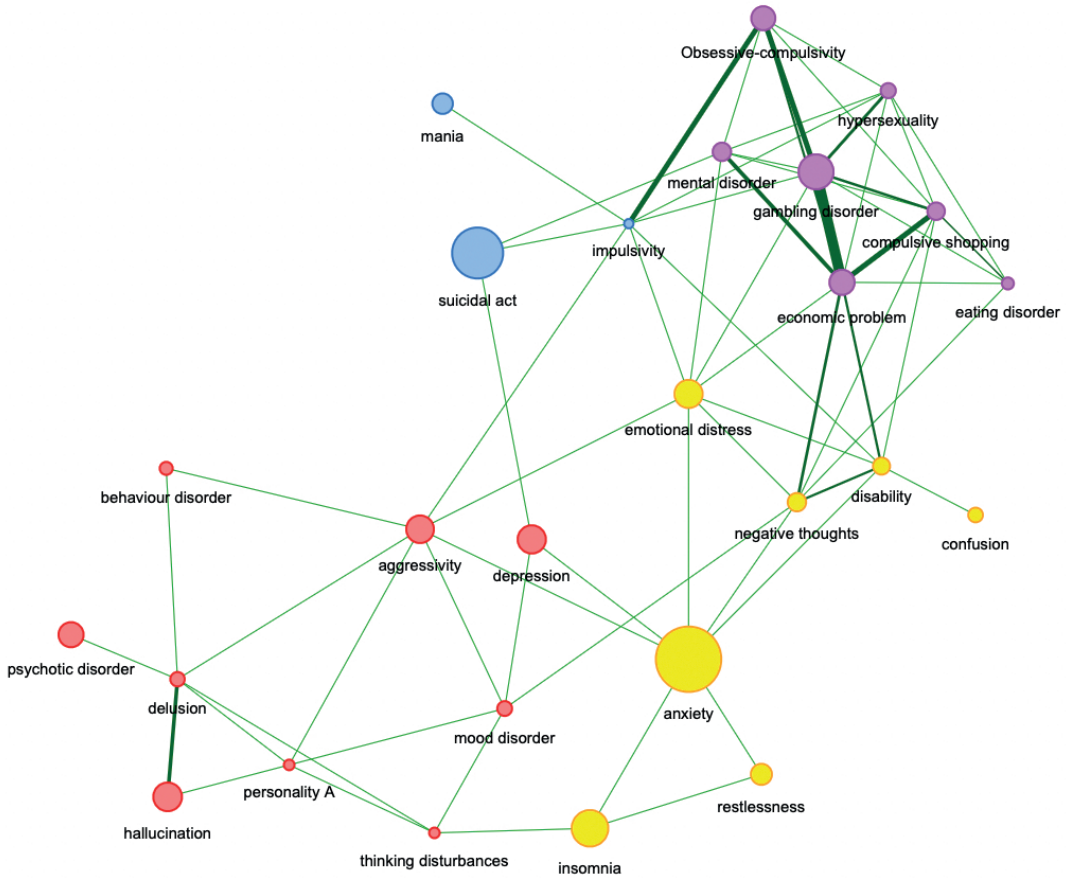
Conclusions

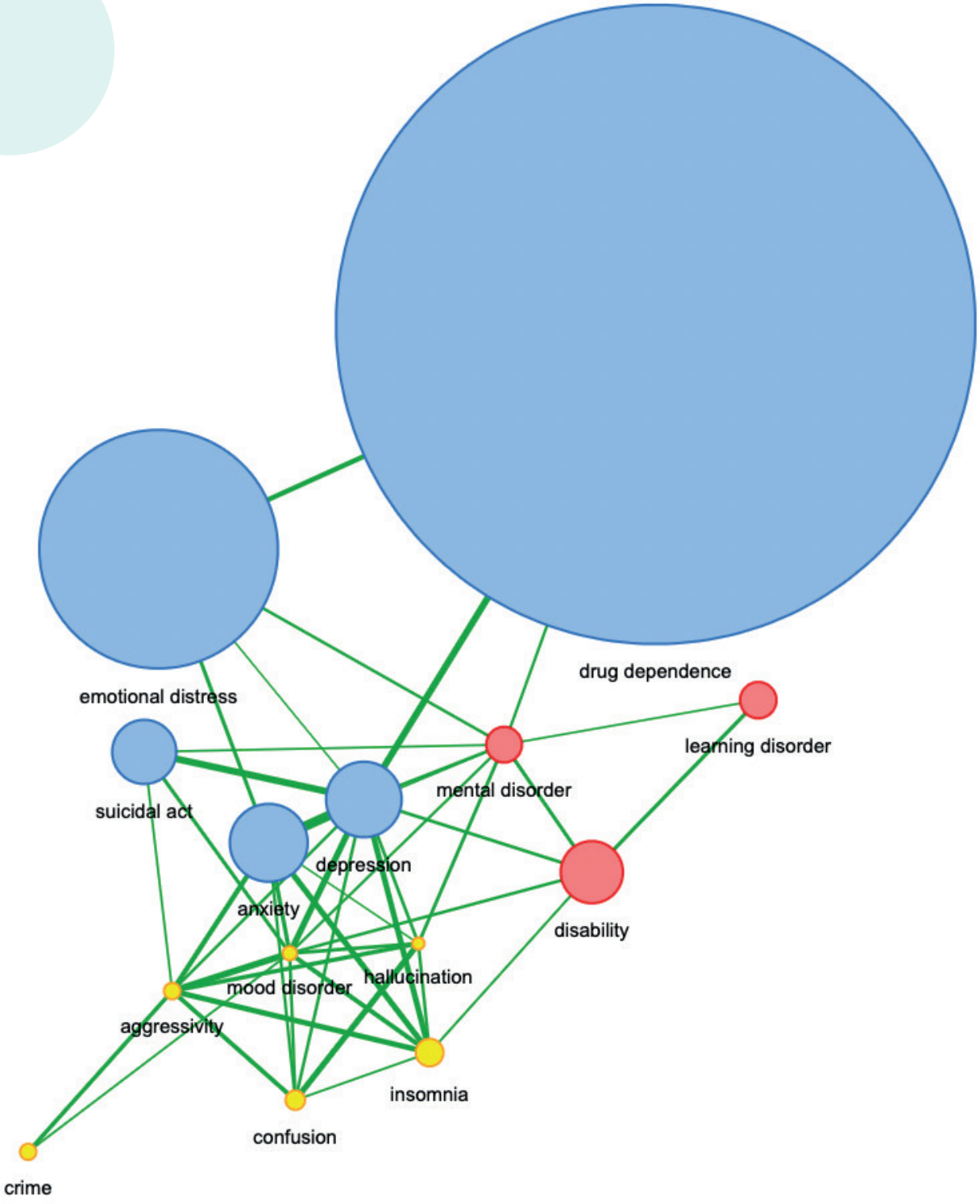
Using network analyses of spontaneous reporting data, we investigated drugs' psychosocial safety profiles. Drug-induced impulse control disorders had a high impact in terms of distress, anxiety, depression, and suicidal acts. We documented also strict comorbidity with obsessive compulsivity. Oxycodone had an even stronger psychosocial impact mediated by drug dependence. The psychosocial impact of proton pump inhibitors was negligible. Extending the monitoring of drug safety to primary and secondary psychosocial aspects will result in a better-informed benefit-risk assessment.

References

pharmadvances
Volume **5**, special issue **2023**







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pharmadvances

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Title

Mechanisms underlying drug-induced impulse control disorders: a pharmacovigilance-pharmacodynamic study

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Background

Impulse control disorders (e.g., pathological gambling, hypersexuality, compulsive shopping) may develop as adverse reactions to dopamine agonists. Mechanism hypotheses have focused on dopamine D3 receptor agonism, and management involves switching to therapeutic alternatives with different molecular targets. Nonetheless, the D3-hypothesis cannot explain all experimental data, and treatment failure is common. We aim to identify molecular targets potentially contributing to the development of drug-induced impulse control disorders. A better understanding of the pathogenesis of these conditions will benefit their management, pointing both to safer choices and new and repurposed pharmacological interventions.

Methods

We performed a pharmacovigilance-pharmacodynamic study on dopamine agonists and antipsychotics. We retrieved impulse control disorders using a previously developed query in the FDA Adverse Event Reporting System (January 2004-December 2021). We estimated disproportionate reporting as the Bayesian information component (significant when IC025>0). Using online public databases (IUPHAR, ChEMBL, PDSP, DrugBank), we calculated drug occupancies. For each molecular target, we interpolated information components and occupancies within dopamine agonists and antipsychotics. Fitting univariate linear regression models, we identified targets potentially contributing to the development of impulse control disorders.

Results

Among 19,887 reports of impulse control disorders, 5,898 recorded an antipsychotic, 3,100 a dopamine agonist. The strongest signals concerned aripiprazole (N=3,091; information component=4.51, 95%CI=4.45-4.55) and brexpiprazole (229; 4.00, 3.78-4.16) for antipsychotics, pergolide (105; 5.82, 5.50-6.06) and pramipexole (2009; 5.43, 5.36-5.48) for dopamine agonists. Significant positive associations between drug occupancy and impulse control disorder reporting were found for D3 receptor within dopamine agonists (beta=1.52; p-value=0.047) and the serotonergic receptor 5-HT1A within antipsychotics (1.92, 0.029). Significant negative associations were found for dopamine D1 (-2.511, 0.014), muscarinic M3 (-2.129, 0.025) and M4 (-1.951, 0.029) receptor antagonism within antipsychotics.

Conclusions

Our results corroborated the role of D3 agonism in inducing impulse control disorders by dopamine agonists. We also identified a potential role of 5-HT1A agonism for antipsychotics, pointing to the possibility of different drugs inducing impulse control disorders through different mechanisms. If this was verified, different drug-related impulse control disorders may in the future require different pharmacological interventions. The putative protective role of D1, M3, and M4 antagonism for antipsychotics should be further explored. Investigating these receptors may drive switching and drug repurposing towards more effective management of drug-related impulse control disorders.

References

pharmadvances
Volume **5**, special issue **2023**

Title

How to manage patients with elevated level of Lp(a) in clinical practice: evaluation of the magnitude of additional LDL cholesterol reduction needed to overcome the increased risk of atherosclerotic cardiovascular events caused by Lp(a)

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Background

Lipoprotein(a) (Lp(a)) concentration has been causally associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). As specific therapies targeting Lp(a) are not yet available, current guidelines suggest a more intensive control of other cardiovascular risk factors, such as low-density lipoprotein cholesterol (LDL-c) levels, in order to reduce the increased risk associated with elevated Lp(a). Therefore, to guide clinical management, we sought to estimate the magnitude of additional LDL-C reduction needed to overcome the increased cardiovascular risk caused by high Lp(a) concentrations.

Methods

A total of 445,744 participants enrolled in the UK Biobank with complete genetic and principal component data were included in the study (mean age: 57.3 years; female sex: 54.3%). For each participant, we calculated the LPA genetic score, by summing the number of alleles inherited at rs3798220 and rs10455872 variants, and the LDL polygenic risk score, by summing the number of LDL-increasing alleles inherited at each variant included in the score weighted by the LDL effect size of each allele. The primary outcome was major coronary events (MCE), a composite of fatal or non-fatal myocardial infarction, or coronary revascularization. We used Cox proportional hazards models adjusted for age, sex, and the first 10 principal components of ancestry, with age as the time scale, and the Kaplan-Meier curves to plot the trajectories of the lifetime risk of MCE associated with increased Lp(a) levels and the equivalent changes in LDL-c levels required to overcome the increased risk caused by different Lp(a) levels.

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Results

Considering an enter time of 40 years, we evaluated the trajectories of the lifetime risk of MCE for subjects with genetically determined high or low Lp(a) (median values 137.7 nmol/L and 15.1 nmol/L, respectively) and with the same level of LDL-c (147 mg/dL). Our analysis showed that the lifetime exposure to 19 mg/dL (?0.5 mmol/L) lower LDL-c, without a clinically significant change in Lp(a) concentration, was able to abolish the extra risk caused by elevated Lp(a) levels, reducing the risk to exactly the same extent observed in subjects characterized by low Lp(a) levels. It was therefore possible to produce a **table** reporting the LDL-c reduction needed to overcome the increased risk caused by Lp(a) based on Lp(a) levels and the age at which LDL-c lowering is started. Notably, since LDL-c has a cumulative effect over time, the magnitude of LDL-c reduction needed to overcome the increased risk caused by Lp(a) increases with the age at which LDL-c lowering is initiated.

Conclusions

While awaiting therapies specifically lowering Lp(a), the increased risk caused by increased level of Lp(a) can be overcome with additional LDL-c lowering that depends on a person's Lp(a) concentration and the age at which LDL-c lowering is started. Our results provide practical guidance for managing increased ASCVD risk caused by Lp(a) in the clinical setting.

References

Table Magnitude of LDL-C reduction needed to overcome the increased cardiovascular risk caused by Lp(a), compared with the median value in the population (*ref*), by age of starting treatment.

Lp(a) level [nmol/L]	Percentile	Δ Lp(a) [nmol/L]	HR for Major Coronary Events	Treatment starting age			
				30 years	40 years	50 years	60 years
20	50	***ref***	*ref*	*ref*	*ref*	*ref*	*ref*
70	75	**50**	1.17	0.20	0.24	0.29	0.38
120	82.5	**100**	1.37	0.40	0.47	0.58	0.76
170	90	**150**	1.60	0.59	0.71	0.87	1.14
220	93.5	**200**	1.87	0.79	0.94	1.16	1.52
270	97.5	**250**	2.19	0.99	1.18	1.45	1.90
320	99	**300**	2.56	1.19	1.41	1.74	2.28

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pharmadvances

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Title

Antiproliferative effect of cannabinoids and CBD-derived compounds in human cell lines

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Background

Cannabis sativa possessed biological and therapeutic properties that are principally linked to cannabinoids, the main constituent of the plant. Its clinical use is limited by the psychoactive effects of delta-9-tetrahydorcannabinol (THC) contained in cannabis, also if the therapeutic potential of cannabinoids has become increasingly evident, particularly in neurodegenerative diseases [1]. Cannabinoids interact with CB1 and CB2, two G-protein coupled receptors, mainly expressed in the central nervous system and in the peripheral nervous system, respectively [2].

We studied the antiproliferative effect of cannabidiol (CBD), THC and some CBD-derived compounds synthetized in the laboratory of Organic Chemistry of Prof. Barge: monomethyil-CBD, dimetyl-CBD and bis(oxiranylmethyl)-CBD. We performed antiproliferative assay on four cell lines, SH-SY5Y, a neuroblastoma cell line, THP-1, a human monocyte cell line, HT-29 and HCT-116 two colorectal cancer cell lines. The firsts two cell lines were chosen since in literature the neuroprotective effects of cannabinoids have been correlated not only to neuronal activity, but also to effects on immune system; the other two as screening on tumoral cell lines. Moreover, we evaluated the ability of these substances to reduce the cytotoxicity induced by 6-hydroxydopamine (6-OHDA) in SH-SY5Y, a Parkinson model in vitro.

Methods

The phytocannabinoids and the compounds have been tested for times ranging from 48 to 72 hours and concentrations between 0,4 and 30 µM. The anti-proliferative effect was assessed using the Cell-Titer Glo (Promega) assay. In addition, the ability of CBD, THC and all the compounds to reduce the cytotoxicity induced by 6-hydroxydopamine (6-OHDA) in SH-SY5Y, a Parkinson model in vitro, was evaluated [3].

Results

CBD and THC showed no toxicity in all the cell lines tested after 48-72 hours of treatment. Among the compounds, only the monomethyil-CBD wasable to inhibit cell viability in all cell lines, in a range of concentrations between 3,3-30 μM.

Conclusions

All the cell lines were insensitive to CBD, THC and other compounds. Only the monomethyil-CBD was able to reduce cell viability in all cell lines, in a concentration- but no time-dependent way. In the future, times of treatment will be modulated, and the compounds will be tested even in an in vitro Alzheimer model.

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pharmadvances
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Title

Influence of the alteration of the serotonergic system during perinatal periods on the development of psychiatric-like behaviors.

Authors

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Background

Serotonin (5-HT) plays various functions during different stages of life: in the perinatal life period, it acts as a neuromodulator influencing key developmental processes such as neurogenesis, synaptic plasticity, cell division, differentiation, and migration (Azmitia, 2001) whereas, during adulthood 5-HT is a neurotransmitter involved in important brain functions such as mood, cognitive functions, sleep and appetite (Canli & Lesch, 2007). Accordingly, dysregulation of the serotonergic system has been demonstrated to be implicated in the development of several psychiatric pathologies (Neumeister et al., 2002). Notably, it happens especially when this complex system is altered during perinatal development (Shah et al., 2018).

On these bases, here, by modulating the 5-HT system during different developmental stages of life through a pharmacological approach, we aim to identify a vulnerability time window during which the alteration of the 5-HT system may lead to a pathological phenotype.

Methods

Pregnant Wistar dams, and consequently the offspring because the drug can cross the placenta and accumulate in the breastmilk, were administered with the SSRI fluoxetine (FLX) (15mg/kg/die in drinking water) during pregnancy (prenatal period), breastfeeding (early post-natal period) or both the phases.

The male and female offspring were behaviorally tested during adolescence (PND35) and adulthood (PND70) in order to evaluate the anhedonic-like phenotype (sucrose consumption test), the anxious-like behavior (elevated plus maze test), and the cognitive functions (novel object recognition test).

The molecular analyses were focused on neuroplasticity markers and on the functionality of the hypothalamic–pituitary–adrenal axis.

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Results

The alteration of the 5-HT system during the prenatal period reduced the number of births.

Moreover, the survival of the pups, as well as the body weight, is mainly influenced if the drug is administered in the early post-natal life, while minor effects are attributable to the administration of FLX during gestation.

At behavioral level, we observed that the treatment modulates the anhedonic-like phenotype, the anxious-like behavior, and the cognitive functions with a specific temporal profile and with differences between the sexes.

Conclusions

In summary, our results support previous evidence demonstrating that this animal model is a good tool for investigating the etiological mechanisms underlying the onset of psychiatric diseases and for better identifying the time window of vulnerability in which alterations in the 5-HT system functionality can lead to a pathological phenotype.

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pharmadvances

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Title

Effect of lycopene in an experimental model of osteoblast impairment using hydrogen peroxide

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Background

Osteoporosis is a bone metabolic disease characterized by disruption of bone homeostasis due to excessive osteoclastogenesis or reduced osteogenesis. Bone fragility occurs mainly with an alteration of the dynamic balance of bone remodeling, in which bone resorption mediated by osteoclasts exceeds the osteoblastic activity of bone formation. The pathogenesis of osteoporosis is related to oxidative stress that increased with aging or in an inflammatory state, in fact, reactive oxygen species (ROS) suppress osteoblast differentiation while promote osteoclast activity. Thus anti-oxidant compounds might have a role in reducing bone loss, to this end we tested lycopene, a hydrocarbon carotenoid with a potent antioxidant and anti-inflammatory activity. As a matter of fact, lycopene promotes the dissociation of Keap1 from Nrf2, leading to the nuclear translocation of Nrf2 which regulates the transcription of detoxifying and antioxidant genes. The aim of this study was to evaluate the anti-inflammatory and antioxidant effects of lycopene in an experimental model of osteoblast impairment due to H_2O_2 stimulation.

Methods

Human fetal osteoblasts hFOB 1.19 (ATCC® CRL-11372™) were cultured under standard conditions and were stimulated with H_2O_2 at 300 µM for 6 hours, later on lycopene was added at different doses (0.5, 1 and 2 µM) for up to 24 hours. At the end of the experiment qRT-PCR and Western Blot were performed to evaluate the expression of Nrf2, pro-inflammatory cytokines, and proteins express during osteoblasts differentiation.

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Results

Results demonstrated that the expression of Nrf2 is increased using lycopene as a result of an antioxidant mechanism; H_2O_2 increased TNF-α, IL-1β and IL-6 levels, while lycopene inhibited the H_2O_2-induced production of these pro-inflammatory cytokines. This study showed that lycopene decreased apoptosis regulator and increased expression of osteoprotegerin, an osteoclastogenesis inhibitory factor, suggesting that lycopene has potential protective role. Furthermore lycopene increased the expression of proteins involved in osteoblast differentiation and bone remodeling.

Conclusions

These preliminary data suggest that lycopene, a component of Mediterranean diet, could be used to reduce inflammation and the oxidative stress related to osteoporosis.

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pharmadvances

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Title

Parenteral iron supplementation may shorten length of hospitalization of polymorbid patients with heart failure

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Background

Iron is crucial for several cellular and physiological processes, including enzymatic activity, neurotransmitter production and haemoglobin function[1]. Iron deficiency is a common finding in Internal Medicine (IM) patients. Recently, ferric carboxymaltose (FCM) has been widely used to supplement iron stores in outpatients. Moreover, it has shown a clear role in improving exercise capacity and reducing hospital admissions in patients with heart failure (HF)[2]. Nevertheless, few data concerning FCM role in complex inpatients are available. Therefore, we investigated real-world effectiveness of FCM in polymorbid patients admitted to IM wards.

Methods

We ran a query of ASST GOM Niguarda laboratory database to identify patients admitted to IM wards in 2018 who did ferritin test or seric iron plus transferrin tests.

Data regarding clinical parameters, comorbidities and therapies were extracted from medical records. Lab tests performed at admission and discharge were collected, too. Our primary endpoint was length of stay (LOS) of patients

who have been administered FCM vs those who have not.

Results

120 patients were continuously enrolled (Table 1). Patients had a mean age of 77.9 years (SD 11.3) and a mean Charlson Comorbidity Index of 6.9 (SD 2.8); in particular, 43 of them (36%) had HF. In this subgroup, age, sex and CCI were similar to those of general population (Table 2).

In overall population, mean LOS was the same regardless of FCM use, while in subgroup with HF, LOS was about 4 days shorter in patients receiving FCM compared to non-receiving ones (16,88 days– Standard error of mean 1,2 vs 20 days – Standard error of mean 1,4 respectively, p=0.083, Figure 1)

This work has some limitations, including a non-randomized design and a small sample size.

Conclusions

Polymorbid inpatients with HF who receive FCM have a shorter LOS compared to non-iron-supplemented ones. This effect could be explained by FCM long-term anti-anemic activity and prompt influence on cellular metabolism. Therefore, FCM extensive use may be justified because of its metabolic effect and its role in reducing LOS and consequently hospitalisation costs.

This difference is close to statistical significance; therefore a larger sample of patients is required to verify the observation.

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	HF	No HF	Tot
FCM	26	44	70 (58%)
No FCM	17	33	50 (42%)
Tot	43 (36%)	77 (64%)	120

Table 1: Population and patients charachteristics
(FCM: ferric carboxymaltose; HF: Heart Failure)

	Overall population	Patients with HF
Age (SD)	77.9 (11.3)	79.6 (9.2)
Sex F (%)	60 (50%)	20 (47%)
CCI (SD)	6.9 (2.8)	7.9 (3.0)

Table 2: Overall population and HF subgroup charachteristics

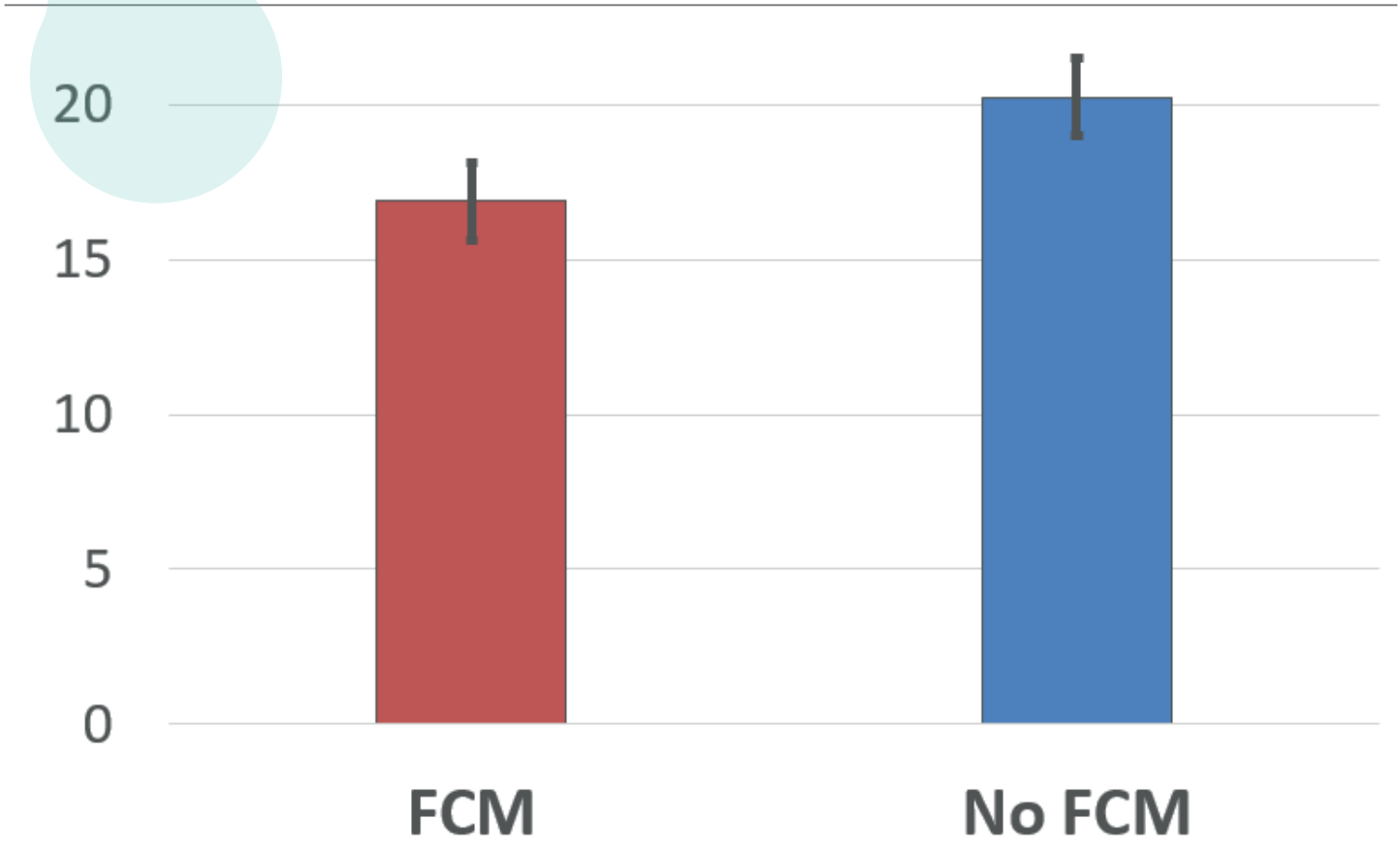

Figure 1: Length of stay in subgroup of patients with HF

SIF22290

pharmadvances

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Title

Previous positivity to SARS-CoV2 enhances mid- and long-term antibody response after BNT162b2 vaccination in healthcare workers

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Background

Clinical trials on COVID-19 vaccines have systematically excluded subjects with a previous SARS-CoV2 infection. Few published evidences showed a significantly higher response in pre-exposed with respect to unexposed subjects after the second dose[1]. However, evidence regarding the persistence over time of the antibody titer of naturally infected subjects is lacking.

Here we present the results of the sub-analysis of the RENAISSANCE Study: REsponse to BNT162b2 COVID-19 vacciNe-short- And long-term Immune reSponSe evAluatioN in health Care workEr on subjects with a story of SARS-CoV2 infection[2].

Methods

We enrolled all consenting subjects over 18 years old working at the Niguarda Hospital of Milan who completed the full course vaccination. We performed a withdrawal at 90 and 180 days from the second dose. We evaluated anti-S IgG and data were reported as Binding Antibody Unit (BAU). We identified subjects with a previous story of SARS-CoV2 infection according to a previous RT-PCR positivity or anti-N IgG positivity. Means and 95% CI have been estimated with Tobit mixed model.

Results

We enrolled 1080 subjects with previous natural SARS-CoV2 infection and 3840 without. Anti-S IgG titer geometric mean (GM) at 90 days differs significantly between the two groups (1453 BAU vs 696 BAU, $p<0.001$, Table 1). The mean percentage reduction between 90 and 180 days is 28% (CI95% 26%-30%) in the group with SARS-CoV2 infection and 50% (CI95% 49%-51%) in the group without ($p<0.001$, Figure 1). Differences were confirmed also correcting for age and sex. Moreover, female 90 days Anti-S IgG titers are significantly higher than male ones both in subjects with previous natural infections ($p=0.019$) and in those without ($p<0.001$) (Table 2).

Furthermore, Anti-S IgG titer remains significantly higher in subjects with a previous natural infection than in those without (GM 1045 BAU, CI95% 985 - 1109 BAU and GM 350 BAU, CI95% 338 – 362 BAU respectively) (Table 1)

Conclusions

Antibody titers are significantly higher in previously SARS-CoV2 infected subjects both at 90 days and 180 days from second vaccine dose. Moreover, females have a higher mid-term antibody response compared to males

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	History of Covid			No		
	GM	CI95%		GM	CI95%	
90 days	1453	1398	1511	696	676	716
180 days	1045	985	1109	350	338	362

Table 1. GM Geometric Mean of antibody titer, expressed in BAU (Binding Arbitrary Units); No: subjects without history of previous SARS-CoV2 infection

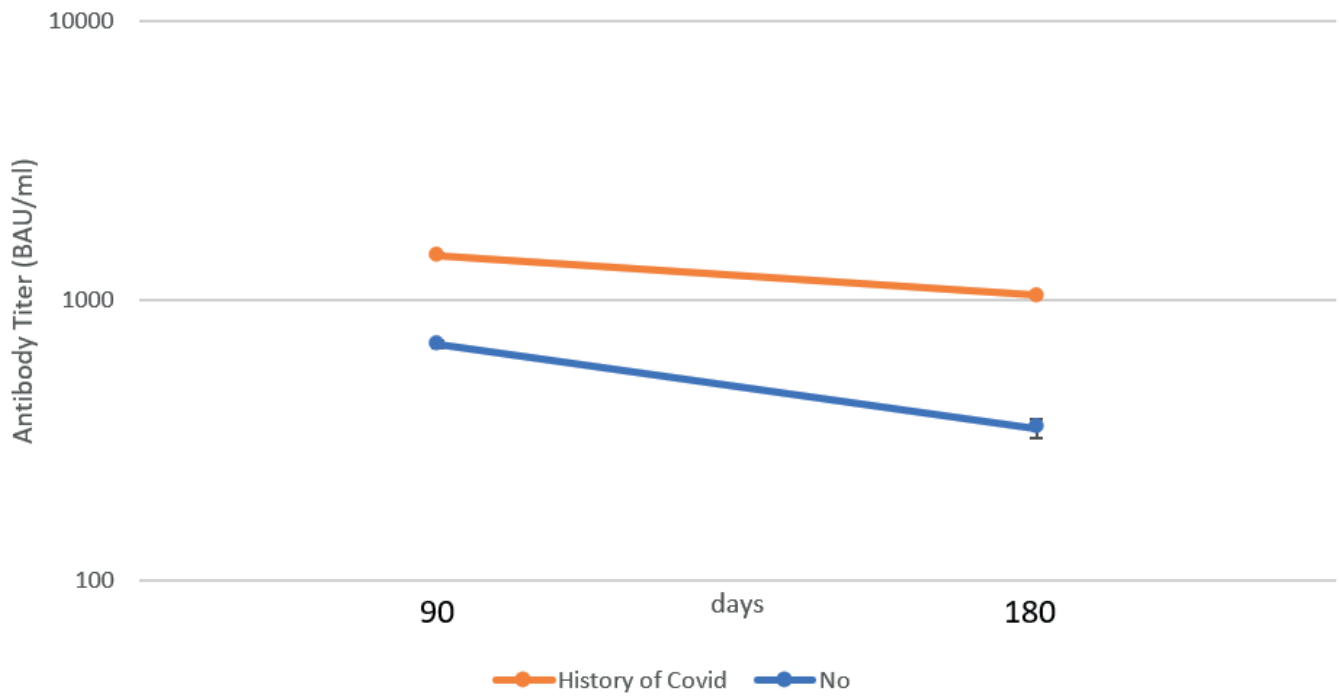

Figure 1. No: Subjects without history of previous SARS-CoV2 infection

	History of Covid F			History of Covid M			No F			No M		
	GM	CI95%		GM	CI95%		GM	CI95%		GM	CI95%	
90 days	1501	1436	1569	1350	1251	1458	732	708	758	617	586	651
180 days	1069	998	1146	992	886	1111	376	361	392	295	277	313

Table 2. GM Geometric Mean of antibody titer, expressed in BAU (Binding Arbitrary Units); No: subjects without history of previous SARS-CoV2 infection; M: Male; F: Female.

pharmadvances
Volume **5**, special issue **2023**

Title

Soluble urokinase plasminogen activator receptor levels as prognostic factor of COVID-19 severity in vaccinated and not vaccinated patients

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Background

One of the main challenges in the treatment of the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection is the early identification of patients at high-risk. Studies demonstrated that soluble urokinase plasminogen activator receptor (suPAR) serum levels in the early phase of the infection correlate with the development of the severe illness; however, data are limited and don’t concern the vaccination status of the study populations.

Methods

We analyzed medical records of 154 patients hospitalized with SARS-CoV-2 infection at Niguarda Hospital between December 2021 and April 2022, for whom suPAR serum level was available. We evaluated vaccination status, comorbidities and clinical outcomes.

Results

107 patients resulted fully vaccinated against SARS-CoV-2, as 42 were not. The vaccination status correlated with a higher suPAR level but the difference was not statistically significant ($p > 0.05$), neither comparing vaccinated patients with booster dose ($n = 61$) and those without it ($n = 43$) ($p > 0.05$). However, the difference in the mean and in the median of the World Health Organization Clinical Progression Scale (WHO-CPS) between patients with high suPAR plasma levels (≥ 6 ng/ml) and those with low levels (<6 ng/ml) resulted statistically significant at the baseline (mean,

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4.89 vs 4.53; median, 5 vs 5, p = 0,003), at day 7 (mean, 4.80 vs 3.64; median, 5 vs 4, p = 0,001), at day 14 (mean, 4.58 vs 1.69; median, 5 vs 0.5, p < 0,001) and at day 21 (mean, 4.18 vs 1.13; median, 4 vs 0, p < 0,001), showing an increasing difference between the two groups. However, there were no significant differences in Sequential Organ Failure Assessment (SOFA) Score (p = 0,094) and in the Murray Score for Acute Lung Injury (p = 0,981) at the baseline. Moreover, mortality at day 21 is significantly higher in the group with higher suPAR levels (p < 0,001).

Conclusions

Larger samples are needed to investigate the potential link between the vaccination status and suPAR levels as prognostic factors in COVID-19. However, this study confirms the correlation of higher suPAR levels with a more severe prognosis, as already showed in literature, suggesting the possible role of suPAR, that can be used to direct the therapeutic approaches for COVID-19.

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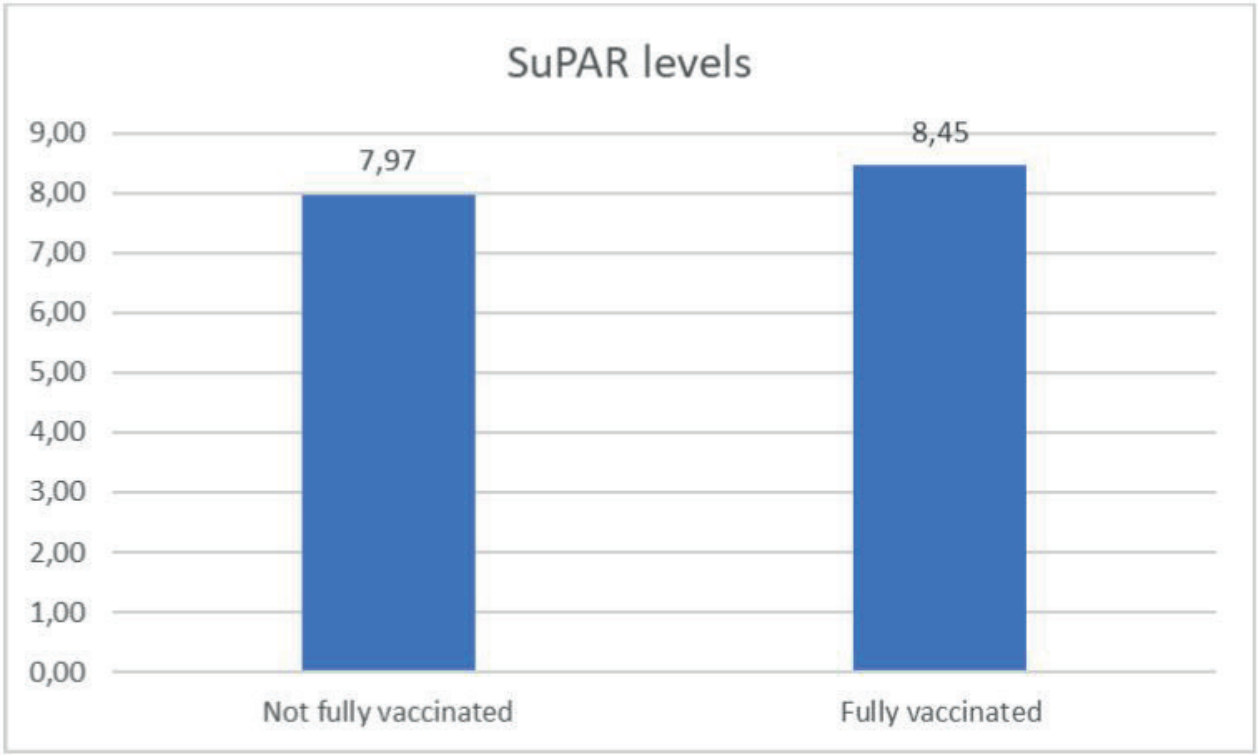

Figure 1. Mean suPAR plasma levels (ng/ml) in not fully vaccinated patients against SARS-CoV-2 and fully vaccinated patients.

pharmadvances
Volume **5**, special issue **2023**

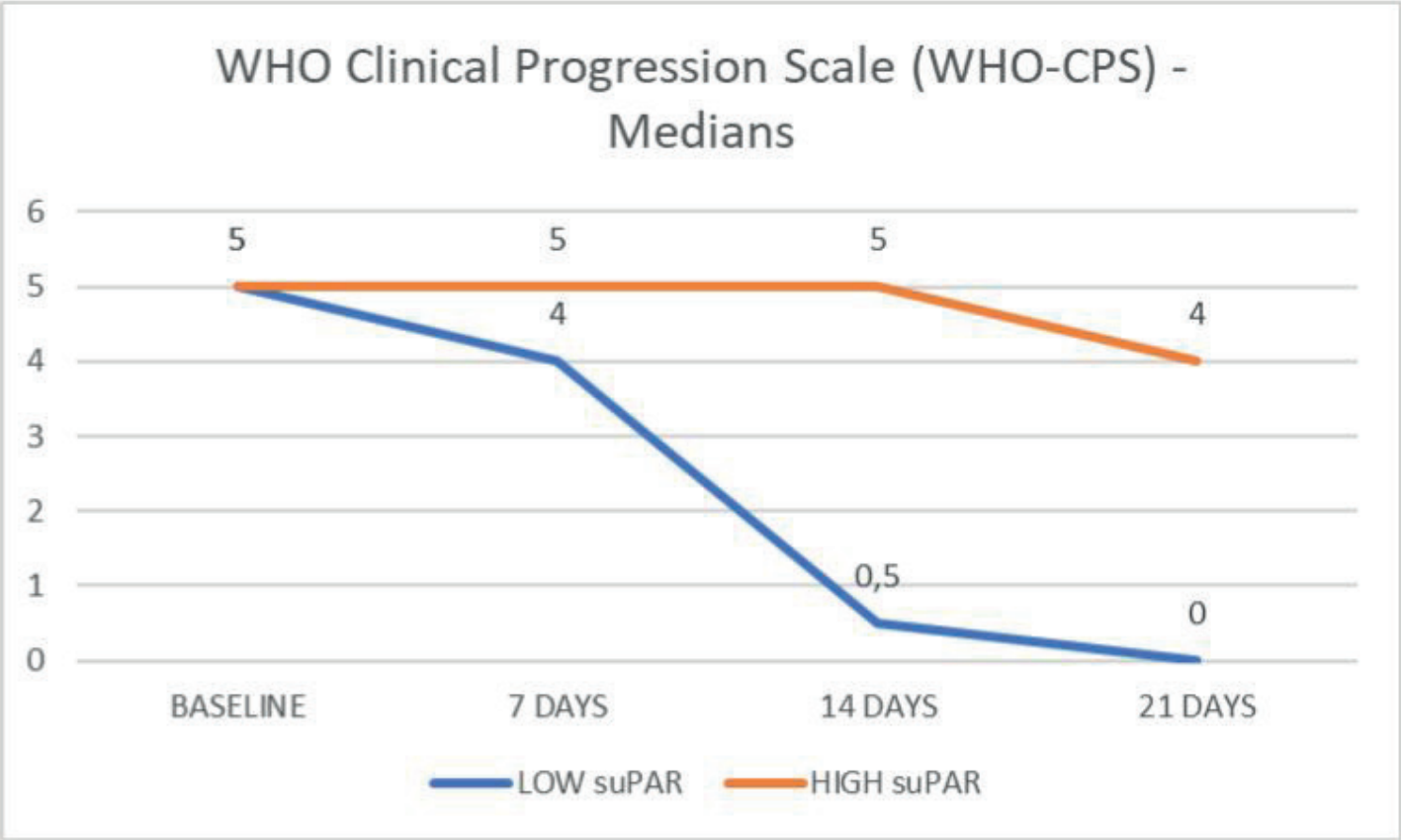

Figure 2. Median values of World Health Organization Clinical Progression Scale (WHO-CPS) at the baseline, at day 7, at day 14 and at day 21 between patients with high suPAR levels (≥ 6 ng/ml) and those with low levels (<6 ng/ml).

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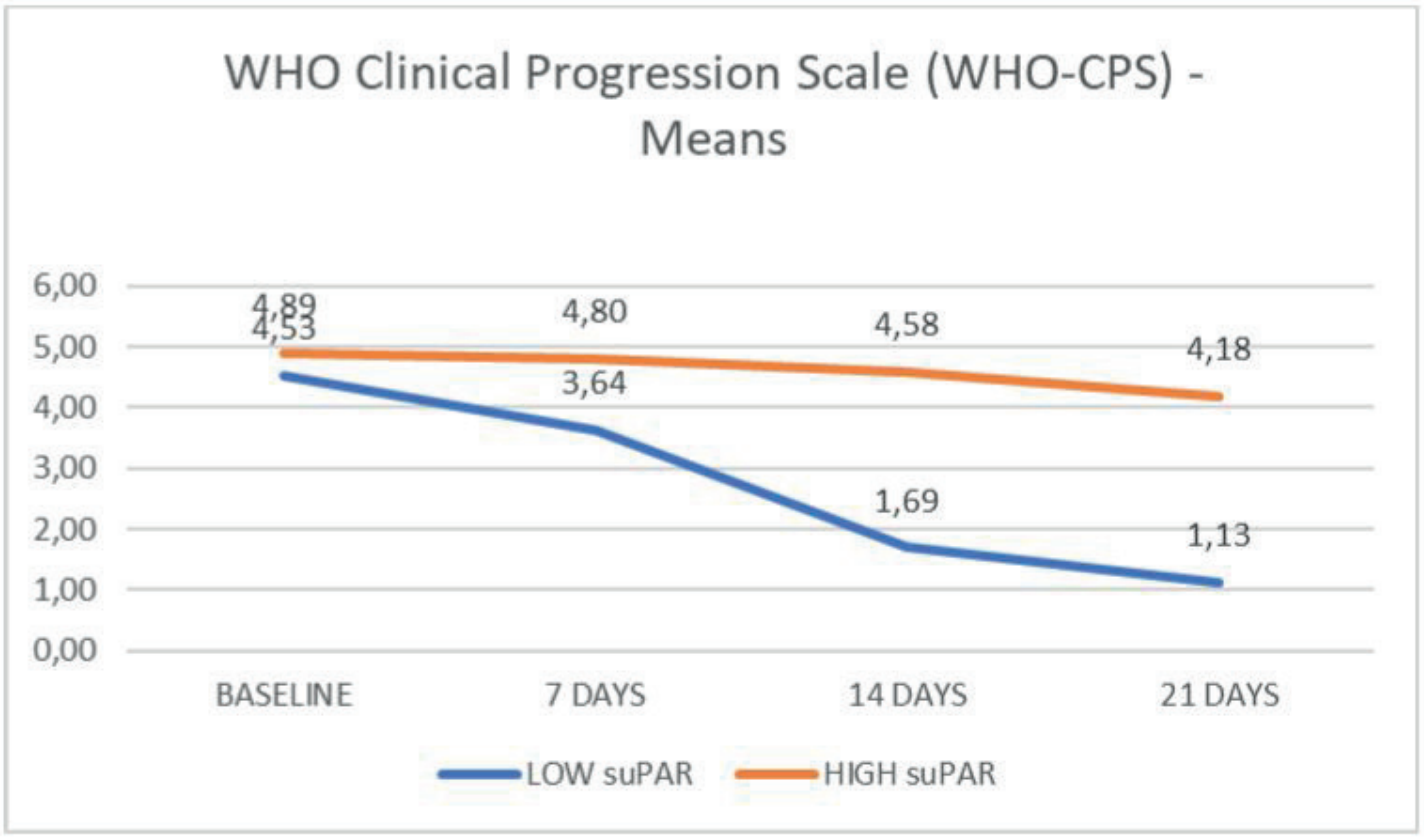

Figure 3. Mean values of World Health Organization Clinical Progression Scale (WHO-CPS) at the baseline, at day 7, at day 14 and at day 21 between patients with high suPAR levels (≥ 6 ng/ml) and those with low levels (<6 ng/ml).

SIF22654

pharmadvances

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Title

Use of Anti-Obesity Drugs in Older Hospitalized Patients: a Retrospective Observational Study from the RePoSi Register

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Background

Obesity is a multifactorial disease and represents one of the most important and challenging health issues across the world. The aim of the study was to evaluate the management of the elderly and obese patient admitted to internal medicine and geriatrics wards, analyzing their therapeutic management.

Methods

A retrospective study was carried out using the RE.PO.SI database. Patients with a diagnosis of obesity (ICD9=278) or with a Body Mass Index value (BMI) ≥ 30 kg/m² were defined obese. According to BMI values, obesity patients were classified in five groups: Normal weight, Overweight, Obese class I, Obese class II, and Obese class III. According to European Society of Cardiology (ESC), patients with high and very high cardiovascular risk (HCVr) were identified. Patients with a BMI values > 30,0 kg/m² or BMI > 27 kg/m² and affected by at least one of sleep apnea, hyperlipidemia, arterial hypertension, or diabetes mellitus (DM) were considered eligible patients for treatment with anti-obesity drugs. The Spearman's correlation rank test was applied to identify associations between BMI and all the variables of interest.

Results

Of the total of 8,417 recorded in the RE.PO.SI. register, 1,132 (13.4%) patients were defined obese, of them 195

(17.2%) had a diagnosis of obesity and 1,095 (96.7%) had a BMI value registered. In particular, 6 patients (0.5%) were normal weight, 32 (2.8%) overweight, 752 (66.4%) obese class I, 217 (19.2%) obese class II and 88 (7.8%) obese class III. Eligible patients to treatment were 1,083 (95.7%) of theme 1,057 had BMI values of ≥ 30.0 kg/m^2 and 26 had BMI values between 27.0 kg/m^2 and 29.9 kg/m^2 with at least one of the comorbidities. No use of orlistat or naltrexone/bupropion was observed. Only one patient used Liraglutide at admission and 3 patients at discharge, all affected by DM. The users of metformin were 150 patients at admission, (9 without DM), and 127 at discharge, (8 without DM). A significant higher frequency of HCVr subject was observed in obese patients compare to not obese, both at admissions (63.9% vs 42.1%; p<0.01, respectively) and at discharges (65.3% vs 44.7%; p<0.01, respectively). However, less than half of HCVr patients was treated with lipid-lowering drugs, both at admission (41.5%) and discharge (43.1%). BMI was directly related to dyslipidemia (rs 0.08; p<0.01), diabetes (rs 0.177; p<0.01), gout (rs 0.03; p=0.04), arterial hypertension (rs 0.13; p<0.01), ischemic heart disease (rs 0.04; p<0.01), heart failure (rs 0.07; p<0.01), atherosclerosis (rs 0.03; p=0.01), chronic respiratory diseases (rs 0.03; p=0.01), osteoarthritis (rs 0.05; p<0.01) and HCVr (rs 0.11; p<0.01). Conversely, BMI was inversely related to length of stay (rs -0.03; p=0.03), age (rs -0.17; p<0.01), bedsores (rs -0.047; p=0.002), psychosis (rs -0.05; p<0.01) and osteoporosis (rs -0.06; p<0.01).

Conclusions

The results emphasized a poor prescribing attitude of anti-obesity drugs as well as HCVr management to improve the health of the obese patients.

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Title

The environmental impact of antibiotics in Italy: integrating healthcare and eco-toxicologic data to assess antibiotics burden on surface water

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Background

Consumed drugs accumulate in surface water and can reach toxic levels for animals and plants. In 2018, EMA enforced the need for environmental risk assessment at marketing authorisation. This risk is estimated as the ratio between the Predicted Environmental Concentration (PEC) and the Predicted No Effect Concentration (PNEC, i.e., threshold for aquatic toxicity), without considering actual drug use. Antibiotics bear the risk of both eco-toxicity and antimicrobial resistance. The excessive use of antibiotics in Italy threatens to overload human and environmental disposal strategies. A better knowledge of their impact will raise awareness of the importance of good prescribing, dispensing, and use practices and drive the strengthening of environmental policies. This study aims to track the antibiotics' environmental impact on surface water in Italy.

Methods

We integrated healthcare and eco-toxicologic data to assess the burden of antibiotics on surface water in Italy. We extracted PNEC values from Pharmaceuticals and Environment, Swedish Medical Agency (FASS), and NORMAN ecotoxicological databases. For each antibiotic, we estimated the Italian PEC values as the ratio between the drug use (OsMed 2020), and the amount of wastewater produced. We considered the European Chemical Agency default values for volume of wastewater per capita (200 L/day × 60 million inhabitants), dilution factor by surface water flow (10), and removal rate (i.e., the portion of drug retained by purification plants, considered to be null). We calculated the PEC/PNEC ratio and reported it according to the FASS classification (high>10, moderate>1, low>0.1, insignificant≤0.1).

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Results

Starting from 56 antibiotics, we obtained the environmental risk measures for 30 of them because of missing data on consumption in the Italian territory. Among the antibiotics with full data, we found a high risk for one glycopeptide (vancomycin, PEC/PNEC=71.0), two penicillins (ampicillin, 43.4; amoxicillin, 41.4), one cephalosporin (cefazolin, 26.2), and one macrolide (azithromycin, 10.3). The risk was moderate for two fluoroquinolones (levofloxacin, 8.3; ciprofloxacin, 3.4), three cephalosporins (ceftriaxone, 5.8; cefepime, 2.2; cefixime, 1.9), two penicillins (piperacillin, 3.2; flucloxacillin, 1.4), and one macrolide (clarithromycin, 2.9).

Conclusions

Multiple antibiotics have a high/moderate environmental impact on surface water in Italy. Vancomycin had the highest PEC/PNEC. The appropriate prescription and adherence practices of these antibiotics reduce the negative impact on the environment. In hospital settings, better purification procedures may lower the amount of antibiotics reaching surface water. The environmental risk may also be considered already in drug development. In a world where drug use is widespread and where antimicrobial resistance is threatening to undermine the treatment of infections, it is not possible to neglect the impact of antibiotics on the environment anymore.

References

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References

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Title

Off-label use of medicines for pediatric patients affected by onco-hematologic diseases: a 7-years follow-up at the University Hospital of Catania

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Background

Off-label use "*relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information*". It is particularly widespread in pediatric population, often excluded from clinical trials, and in critical areas such as onco-hematology, and rare diseases.

In Italy, Law 94/1998 allows physician to perform off-label prescriptions if supported by published clinical evidence, but National Health System does not cover their cost. In the hospital setting, clinicians must request formal authorization, and costs are covered by the hospital budget. At the University Hospital of Catania the Clinical Pharmacology Program supports the assessment, approval, management and follow-up of off-label use.

Methods

We analyzed the off-label prescriptions made at the University Hospital of Catania from 2015 to 2021, in particular those related to treatment of pediatric patients with onco-hematologic diseases.

Results

From 2015 to 2021, among 1.338 off-label prescriptions 283 (21.2%) were performed by the Pediatric Onco-Hematology Unit for the treatment of 241 patients (1.2 prescriptions/patient; mean 40.4 prescriptions/year; Figure 1). Almost 11% of subjects received 2 or more off-label drugs, in combination or as subsequent line of treatment.

Table 1 shows the therapeutic indications for which the medicinal products have been prescribed.

Triptorelin was the most prescribed drug, for fertility preservation in female patients with cancer (n=49; 17.3%; Table 2), followed by aprepitant for prevention of nausea and vomiting in case of lack of therapeutic effect of alternative drugs (e.g., ondansentron; n=29; 10.2%).

Due to the high number of prescriptions and the supporting evidence, we submitted a specific dossier to the Italian Medicines Agency (AIFA) for the inclusion of GnRH analogues into the list of medicines reimbursed for unauthorized indication according to L. 648/1996; AIFA released a positive opinion in 2021 and the drug is now reimbursed according to this Law.

Conclusions

In the absence of a defined risk-benefit ratio, off-label prescription could increase the risk of inappropriate use, medical error, and adverse drug reactions. Therefore, appropriateness of off-label prescriptions must be carefully assessed in order to ensure this use occurs only in the presence of data supporting a favorable risk/benefit profile. Following the AIFA approval, in 2022 we started a pharmacovigilance project with the aim to improve the knowledge about the safety of oncologic treatments in pediatric population, especially in the case of unauthorized use.

The triptorelin example shows that a well-performed monitoring activity for off-label prescriptions in the hospital setting allows to detect unmet medical needs and to identify drugs with a favorable risk/benefit profile.

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Title

Postmarketing Reports of lack of efficacy: An Analysis of Spontaneous Reports at the University Hospital of Catania

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Background

Therapeutic failures include several situations potentially relevant for patients, such as e.g. drug–drug interactions, drug resistance, and pharmaceutical defects[1]. Therefore, the pharmacovigilance reporting about the unexpected absence, decrease or change of the therapeutic effect can help identify important therapeutic issues[2,3].

Data from the US FDA Adverse Event Reporting System (FAERS) database recently showed “drug ineffective” as the most commonly reported adverse event[4], mainly by consumers.

Thus, the aim of this study was to investigate the reporting of therapeutic failure in the Italian National Pharmacovigilance Network (RNF), in particular at the University Hospital of Catania, Sicily.

Methods

We analyzed the individual case safety reports (ICSRs) reporting therapeutic failure and collected in Sicily in the last 10 years (from January 1st 2013 to April 30th 2022). We captured all potential reports describing drug ineffectiveness analyzing individually each Preferred Terms (PTs) classified within the System Organ Class (SOC) ‘General Disorders and Administration Site Conditions’.

We performed a descriptive analysis of data collected into the Italian RNF by the University Hospital of Catania, compared in terms of patient characteristics, treatments, therapeutic indication, severity of reactions, and type of reporter.

Results

Overall, the number of ICSRs reporting therapeutic failure collected in the reference period in Sicily was 3,366 (Figure 1 a and b), including 789 (23.4%) reported by the University Hospital of Catania (Figure 2), with a progressive increase in the number of reports per year.

The most frequently reported drug classes were tumor necrosis factor-α inhibitors (n=379; 47.9%), mostly used in patients with psoriasis/psoriatic arthritis, and followed by vascular endothelial growth factor (VEGF) inhibitors by intravitreal route (n=91; 11.5%; Table 1 and 2).

Among biologics which have lost their patent, most reports of therapeutic failure concerned the use of biosimilars (Figure 3).

Almost all the ICSRs were spontaneously sent by physicians and other health care professionals for events observed in adults and elderly (98%) and female patients (52.6%). In the majority of cases, ADRs were classified as not serious (83.7%) with no available outcome.

Conclusions

This analysis showed an increase in the number of ADRs related to the lack of efficacy reported by healthcare professionals at the University Hospital of Catania in the reference period. These reports mainly relate to the use of drugs for autoimmune disorders with a high prevalence of biosimilars, probably variable according to the availability of the products on the market and the rate of prescription at the hospital services.

Further analysis will be useful to assess the possible effect of regulatory decisions on the reporting of therapeutic failure.

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Title

Smoking prevalence and intention to quit among medical school students attending e-learning courses on tobacco dependence in academic years 2019-2020 and 2021-2022

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Background

The importance of an adequate training in tobacco and nicotine dependence and treatment to Medical School students is largely underestimated, considering their future roles as both health models and key advisors for patients to quit smoking. The growing trend in the use of heat-not-burn products (IQOS), marketed as harm reduction devices, also raises new public health concerns. We introduced e-learning course and assessed their effectiveness of increasing knowledge on these topics. Students smoking habits and attitudes towards quitting tobacco use were also investigated.

Methods

We developed 16 didactic modules divided in 3 courses: tobacco dependence (TDI), treating tobacco dependence (TDII) and electronic products and tobacco control policies (TDIII). The courses were offered to 4th, 5th, and 6th year Medical School students of Sapienza University of Rome in academic years 2020-2021 and 2021-2022. To assess learning outcomes, we examined the pre- to post- changes in knowledge scores associated with each course. Demographic variables and characteristics of smokers were collected. Data from each academic year was analysed and compared using paired and independent samples t-tests and chi-square tests.

Results

A significant increase in knowledge was observed at the end of each course (p≤0.001). Comparing the two academic years, prevalence of current smokers increased from 19.8% to 20.9% and were mainly females (56.4% vs 60.0%). Among smokers, use of traditional tobacco cigarettes alone decreased from 72.7% to 59.1%, while IQOS use and dual use of IQOS and traditional cigarettes increased (15.3% vs 21.7% and 3.3% vs 7.8% respectively). Regarding intention to quit smoking, we found a significant increase in students reporting they “want to quit, but are not ready now” (44.4% vs 61.3%; p≤0.05) and a decrease in students “seriously considering to quit in the next 6 months” (28.3% vs 14.2%; p≤0.05). IQOS as a device to stop smoking was tried by 24.8% of students in 2021-2022 compared to the 13.4% of the previous years. After completion of course on tobacco dependence, we found an increase in students considering quitting in 6 month compared to the intention registered pre-course (20.2% vs 14.2%).

Conclusions

The e-learning courses were effective in increasing knowledge on tobacco dependence, treatment, and electronic nicotine products in advanced medical students. They also had a positive effect on intention to quit smoking. The data also confirmed a prominent increase in the use of heat-not-burn tobacco products. Additional studies will need to explore the perceived safety of IQOS use among students and clarify its possible effect on intention to quit. Today's medical students will play a prominent role in future efforts to prevent and control tobacco use. It is of great importance to consistently provide up-to-date training to future physicians during their university studies and promote and assist their motivation to quit smoking.

References

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Title

Antioxidant activity of fluoxetine and vortioxetine in a non-transgenic animal model of Alzheimer's Disease

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Background

Different neurobiological and clinical links exist between Alzheimer's Disease (AD) and depression, such as the impairment of transforming growth factor-β1 (TGF-β1), neuroinflammation and oxidative stress involved in both diseases. Second generation antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), are currently studied for their neuroprotective activity in AD. SSRIs could exert their therapeutic effect by suppressing the production of reactive oxygen and nitrogen species, and/or rescuing the antioxidant defense. By using a non-transgenic (non-Tg) animal model of AD, obtained by intracerebroventricular (i.c.v.) injection of Aβ oligomers in mice, we have recently demonstrated that the SSRI fluoxetine (FLX) or the multimodal antidepressant vortioxetine (VTX) reversed depressive-like phenotype and memory deficits Aβ-induced by a rescue of TGF-β1 hippocampal level. Aim of this study was to evaluate whether i.c.v. injection of Aβ oligomers could induce oxidative stress in the hippocampus of our non-Tg model of AD and if a long-term treatment with FLX or VTX could prevent Aβ-induced oxidative stress.

Methods

To obtain the non-Tg AD model, 2 µL of 10µM $A\beta_{1-42}$ oligomers solution were i.c.v. injected in 2-month-old C57BL/6 mice. FLX (10mg/kg) or VTX (5 and 10mg/kg) were administered intraperitoneal for 24 days, starting 7 days before Aβ injection. Gene expression analysis by qRT-PCR and protein expression by Western Blot (WB) analysis were carried out

on hippocampal samples. Mixed neuronal cultures were obtained from rats at embryonic day 15 and treated with Aβ oligomers (2μM) for 48h both in absence or presence of FLX (1μM) or increasing concentrations of VTX (100nM, 250nM, or 1μM) (pretreatment 1h) and Aβ-induced toxicity assessed by trypan blue exclusion assay.

Results

The long-term administration of FLX or VTX prevented the over-expression of inducible nitric oxide synthase and NADPH oxidase 2 in the hippocampus of Aβ-injected mice both at gene and protein expression. Antidepressant chronic treatment was able to rescue hippocampal mRNA expression of glutathione peroxidase 1 (Gpx1) antioxidant enzyme, but the results obtained by WB analysis showed that either the monomeric nor the dimeric form of Gpx1 protein in the hippocampus were not significantly affected by Aβ treatment. In mixed neuronal cultures Aβ-treated, we found that VTX pre-treatment started to exert neuroprotective effects at nM concentrations with a maximal effect at 1μM, similar to that observed for FLX.

Conclusions

Our data represent the first evidence that the long-term treatment with FLX or VTX, able to rescue TGF-β1 pathway, prevent amyloid-induced depression and cognitive decline by counteracting Aβ-induced oxidative stress phenomena in a non-Tg animal model of AD. In addition, by using a well-established in vitro model of Aβ-induced neurodegeneration, we were able to compare, for the first time, the well-known neuroprotective activity of FLX with the protective effects of VTX.

References

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Title

Sulforaphane Causes Cell Cycle Arrest and Apoptosis in Human Glioblastoma U87MG and U373MG Cell Lines under Hypoxic Conditions

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Background

Glioblastoma multiforme (GBM) is the most invasive and deadly primary brain tumor. GBM has an annual incidence of 3–5 cases per 100,000 people, while the disease can occur both in children and adults, median age at diagnosis is 65 years [1]. The vast majority of patients with glioblastoma do not have any identifiable risk factors for tumor development [2]. The overall survival period for GBM patients without postoperative treatment is 3–6 months. GBM exhibits microvascular hyperplasia and pronounced necrosis triggered by hypoxia. Hypoxia is a feature found in several solid tumors, and it indicates a poor prognosis. Hypoxia drives malignancy by promoting chemo- and radiotherapy resistance, alters the tumor cells' metabolism, generates strong genome instability, and increases angiogenesis [3]. Despite the enormous progress in diagnostics, the treatment protocol for GBM has remained essentially unchanged in past years [4]. For this reason, novel therapeutic strategies are urgently needed to treat this lethal disease. Sulforaphane (SFN), an isothiocyanate derived from cruciferous vegetables, has already demonstrated the ability to inhibit cell proliferation, by provoking cell cycle arrest, and leading to apoptosis in many cell lines.

Methods

Human GBM cell lines U87MG and U373MG were purchased from the Lombardy and Emilia Romagna experimental Zootechnic Institute (Italy). Cells were grown at 37 °C in a humidified incubator with 5% carbon dioxide (CO_2) in DMEM 10% FBS. For the hypoxic exposure, cells were placed in a sealed, self-contained Hypoxia Incubator Chamber connected to a Single Flow Meter for the precise control of gas flow to generate a hypoxic environment. After 10 minutes of insufflation a severe hypoxia environment was created, and the cells were kept in hypoxia as long as the SFN treatment (48 h). In each experiment cells were treated with different concentrations of SFN [20–40–80 μM] in DMEM 5% FBS under hypoxic (0.1% O_2, 5% CO_2, and 94.9% N_2) or normoxic (5% CO_2) conditions.

Results

In this study, we investigated the antineoplastic effects of SFN [20-80 µM for 48 h] in GBM cells under normoxic and hypoxic conditions. Cell viability assays, flow cytometry, and Western blot results revealed that SFN could induce apoptosis of GBM cells in a dose-dependent manner, under both conditions. In particular, SFN significantly induced caspase 3/7 activation and DNA fragmentation. Moreover, our results demonstrated that SFN suppressed GBM cells proliferation by arresting the cell cycle at the S-phase, also under hypoxic condition, and that these effects may be due in part to its ability to induce oxidative stress by reducing glutathione levels and to increase the phosphorylation of extracellular signal-regulated kinases (ERKs).

Conclusions

Our study may not only corroborate the chemopreventive activity of SFN, but also show new directions for the rational application of SFN in anticancer strategies against hypoxic tumors.

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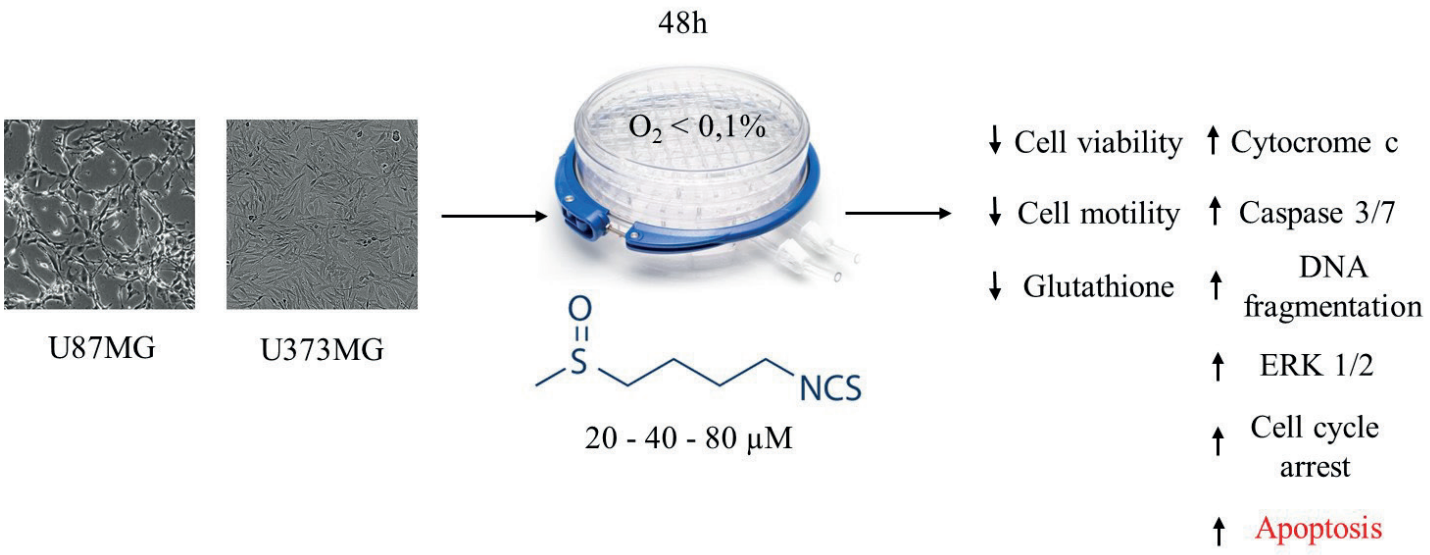

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Title

Ecotoxicological effects of three antibiotics on the bacterium *Aliivibrio fischeri* and crustacean *Daphnia magna*

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Background

Thousands of tons of antibiotics are currently in use and they have been found as environmental micro-contaminants as a single compound or in a mixture[1,2]. Antibiotics may cause environmental adverse effects on non-target organisms, including the antimicrobial resistance in environmental bacteria[3,4], which can be transferred to species associated with human infections.

Environmental concentrations are critical in establishing the link between their presence in the ecosystems and their biological effects[5]. Little is known about ecotoxicological effects of antibiotics on organisms, and more toxicity data are reported on aquatic ones, because they are mostly exposed.

Among aquatic organisms, *Aliivibrio fischeri* and *Daphnia magna* have been largely used for evaluating the acute toxicity of many pharmaceuticals, including antibiotics.

In this context, literature ecotoxicity data for *A. fischeri* and *D. magna* on sulfamethoxazole (SMX), ciprofloxacin (CIP) and tetracycline (TET), widely used in both human and veterinary medicine[6], are reviewed. Moreover, SMX experimental tests on both organisms are also discussed.

Methods

SMX, CIP and TET ecotoxicity (*A. fischeri* and *D. magna*) was reviewed from literature considering the most recent articles (2014-2022).

Experimental SMX data (*A. fischeri* and *D. magna* standard methods[7,8]) were expressed as effective concentration ($EC50^{15\text{-}30min}$ and $IC50^{24\text{-}48h}$). Various solvents (DMSO or methanol in distilled water) were also tested to obtain a good antibiotic solubility[9] and no solvent toxicity.

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Results

Only few recent studies report the acute ecotoxicity on the three antibiotics with both *A. fischeri* and *D. magna* (Tab. 1).

The review by Bombaywala[12] reports data from 2000 to 2016; more recent papers do not report a specific concentration. Finally, *D. magna* IC50 ^{24h} are reported only for SMX and EC50 for *A. fischeri* are reported only at 15 min.

Experimental tests with *A. fischeri* were performed dissolving 600 mg SMX/L in 3% (v/v) methanol; DMSO (0.6% v/v) was the solvent for *D. magna* tests (420 mg SMX/L) (Tab. 2).

The results were higher than those from literature. This could be due to different solvent used and to the solubilizing method adopted, that generally are not reported in the literature.

Conclusions

Although antibiotic effect concentrations of are higher than those found in environmental matrices[3], ecotoxicological data are crucial and have to be related to antibiotic sub-concentrations (minimum inhibitory concentrations, MICs); these concentrations are in the range of or more than the so-called minimum selective concentrations (MSCs), which exert a high selective pressure on environmental microbes[15], promoting the evolution and dissemination of antibiotic resistance.

Data on TET, CIP and on mixture of the antibiotics are currently in progress.

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pharmadvances
Volume **5**, special issue **2023**

Tab. 1 Literature data on ecotoxicity (effective concentration) of SMX, CIP and TET. The EC50 correspond to *A. fischeri* bioluminescence inhibition and IC50 to *D. magna* immobilization.

Antibiotic	Organism	Ecotoxicity Eff. Conc.$^{exp.\ time}$ (mg/L)		Ref.
SMX	*A. fischeri*	EC50 ^{15min}	50.5	10
	D. magna	IC50 ^{24h}	49.8	10
		IC50 ^{48h}	44	10
CIP	*A. fischeri*	EC50 ^{15min}	226.67	11,12
	*D. magna**	IC50 ^{48h}	36.5	13
TET	*A. fischeri*	EC50 ^{30min}	6.7	12,14
	*D. magna**	IC50 ^{48h}	8.16	12,14

* No data on IC50 ^{24h}

Tab. 2 Experimental data on SMX ecotoxicity. The EC50 (mean value ± s.e.) correspond to *A. fischeri* bioluminescence inhibition and IC50 to *D. magna* immobilization.

Organism	Ecotoxicity Eff. Conc.$^{exp.\ time}$ (mg/L)	
A. fischeri	EC50 ^{15min}	150 ± 51.6
	EC50 ^{30min}	200 ± 34.8
D. magna	IC50 ^{24h} =	105 ± 7.6
	IC50 ^{48h}	75 ± 9.6

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Title

Pesticides dispersion in aquatic environment: analysis of behavior and histological effects of Rotenone and Deltamethrin exposure on the animal model, Zebrafish

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Background

Chemicals dispersion in water is a serious threat to the environment, for wildlife organisms, and could be dangerous also for human beings. Studies confirmed the presence of pharmaceuticals, PFAS, and pesticides in many aquatic ecosystems [1], comprehending rivers, lakes, and seas. Given their ubiquitous presence, these chemicals can encounter several organisms that live in the aquatic ecosystem, leading to damage to both plants and animals [2]. In the latter, the hazard is high because of the capacity of certain pesticides to damage both the central and peripheral nervous systems [3]. This study aims to investigate the damage that common pesticides can induce. Pesticides are exploited in agriculture and in day-to-day usage and are present in many aquatic ecosystems in the range of µg/L [4].

Methods

Here we evaluated the chronic effects of two pesticides in the model organism Zebrafish (Danio Rerio), exposing the fish to 2.0µg/L rotenone for 28 days and 1.0 and 2.5µg/L deltamethrin for 15 days. We investigated the effects of chronic exposure to rotenone and deltamethrin with behavioral and histological investigations. The effect on anxiety and locomotion was assessed with the novel tank test while the integrity of the olfactory system, with the olfactory preference test. Histological analyses were focused on investigating the change in neurotransmitter expression through immunohistochemistry and immunofluorescence techniques. Instead, the metabolization and bioaccumulation of the toxins in zebrafish organism were monitored with Matrix-Assisted Laser Desorption/Ionization (MALDI) mass spectrometry analyses.

Results

Behavioral tests revealed that the treatments had an impact on locomotor parameters decreasing zebrafish total distance traveled and absolute turn angle. Stress and anxiety responses were also slightly increased. Immunohistochemistry confirmed these findings, indicating a swelling in brain tissue.

Conclusions

This project provides useful data for understanding the issue posed by the concentrations of pesticides found in environmental waters, clearly confirming that rotenone and deltamethrin in small concentrations are able to impair locomotion and cognitive functions in zebrafish. The research will continue with the assessment of the effects that pharmaceuticals induce in Danio Rerio, including non-steroidal anti-inflammatory drugs, hormones, and antibiotics.

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Title

Administration of Low-dose 7,8-Dihydroxyflavone after Status Epilepticus Prevents Epilepsy Development in the Pilocarpine Model

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Background

Temporal lobe epilepsy often manifests months or even years after an initial epileptogenic insult (e.g., stroke, trauma, status epilepticus) and, therefore, may be preventable (Simonato et al, 2021). However, no such preventive treatment is currently available. Aim of this study was to test a potentially anti-epileptogenic antioxidant agent, 7,8-dihydroxyflavone (7,8-DHF), that has been reported to be well tolerated and effective in preclinical models of many neurological disorders (Emili et al 2022). A possible issue with 7,8-DHF is that it has been found to act also as a TrkB receptor agonist, an effect that, based on the literature, may imply an anti- or a pro-epileptogenic effect.

Methods

The effects of 7, 8-DHF were examined by administering different doses (5 mg / kg and 10 mg / kg) to the animals for seven days, following the induction of status epilepticus (SE). The behavior of the animals was evaluated through behavioral tests (open field, elevated plus maze and object location task) at 3 time points: before inducing SE (baseline), at eight days (early phase) and at 20 days after induction of SE. Video/EEG monitoring was also performed, through which it was possible to determine the duration of the latency period and the number of spontaneous epileptic seizures for each animal.

Results

We found that low- (5 mg/kg), but not high-dose 7,8-DHF (10 mg/kg) can exert strong anti-epileptogenic effects in the pilocarpine model, and that these different effects correlate with differences in TrkB phosphorylation patterns and in activation of TrkB-dependent signaling pathways.

Conclusions

The present data suggest that it may be possible to develop drugs with desirable effects on the TrkB receptor, based on the selective activation of therapeutically relevant signaling pathways. Thus, also considering its antioxidant properties, 7,8-DHF represents a promising template for developing effective and well-tolerated anti-epileptogenic drugs.

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Title

Network Intervention Analysis: an innovative tool to investigate Symptom-Specific Treatment Effects in Major Depression and Bipolar Disorder

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Background

Major Depression Disorder (MDD) and Bipolar Disorder (BD) are very complex diseases, however, still today many aspects remain unclear. Precisely because of an extensive set of factors (genetic and environmental), that shape unique disease phenotypes, drug treatments are heterogeneous. Mood disorders can be defined as recurring disorders, and one of the most important aspects of treatment is the development of a long-term therapeutic strategy that will reduce the risk of recurrence and improve psychopathological conditions in disease-free stages. Network Intervention Analysis (NIA) is an extension of network analysis models whose aim is to follow the development of treatment-induced changes in symptoms and their associated structure over time while distinguishing direct and indirect effects[(1)].

Methods

A network analysis was performed on 129 patients (81 MDD and 48 BD) at T0 and on 52 patients that completed a 12-week treatment (28 MDD and 24 BB) (T1), using “R software”. We applied NIA to identify the interaction and changes in

network nodes and connections of 14 continuous variables with nodes identified as “Treatment” (three dichotomous factors according to the presence or absence of Antidepressants, Antiepileptics, and Generation II Antipsychotics in the therapy of each individual patient). The “qgraph” package and the Fruchterman-Reingold algorithm was used to represent the resulting adjacency matrix. In each network, the size of nodes was controlled to evidence those that displayed the greatest change between T0 and T1 (both positive and negative). The predictability of nodes was also studied using the package “mgm”[(2)].

Results

Both MDD and BD patient groups displayed a significant change between T0 and T1 on Depression Scales: the MDD group displayed significant change on the “Hamilton Depression Rating Scale” (HDRS) (ANOVA: F=10.807; sig = 0.001), while the BD group showed significantly change on the HDRS (ANOVA: F=5.631; sig = 0.02) as well as on the “Beck Depression Inventory” (ANOVA: F=4.561; sig = 0.036). Figure 1 shows the networks of MDD (top part) and BD (bottom part) patients before (T0 on the left) and after 12-weeks of treatment (T1 on the right). In both cases, “Treatment” nodes pass from having no connections to becoming central nodes (hubs) in the network. In addition, the type of drug influenced specific functions.

Conclusions

Network Intervention Analysis makes it possible to observe how the presence of a drug treatment reorganizes how neurocognitive functions interact. It also allows characterising on which nodes (functions) a certain drug has the greater effect and how this effect influences the surrounding variables. Finally, including predictability in the analysis, offers the possibility to estimate how much a node can be influenced by others with which it has connections. This approach fits well into precision medicine, being Predictive, Preventive, and, with the right conditions, Personalized.

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Title

Characterization of the acetylation of cyclooxygenase-isozymes and targeted lipidomics of eicosanoids in platelets and colon cancer cells by the new Aspirin formulation IP1867B versus Aspirin in vitro

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Background

Aspirin (acetylsalicylic acid, ASA) is used to prevent atherothrombosis and colorectal cancer (1). The current enteric-coated drug formulation, used to protect the stomach, may reduce bioavailability (2). Liquid formulations of Aspirin (L-ASA) could improve its pharmacokinetics. IP1867B is an L-ASA formulation that combines three ingredients, Aspirin, triacetin, and saccharin.

Methods

ASA and IP1867B were assessed in human whole blood and washed human platelets on cyclooxygenase (COX)-1 activity by measuring thromboxane (TX)B_2 [the major arachidonic acid(AA) metabolite in the platelet)] by immunoassay and the extent of acetylation of platelet COX-1 by LC-MS/MS(Fig.1) (3). In HCA7 (human colonic adenocarcinoma cell line), expressing COX-2, 5-lipoxygenase (LOX), and 15-LOX-1, but not COX-1 and 12-LOX, the two compounds were studied on targeted eicosanoid lipidome (4) and the extent of COX-2 acetylation by LC-MS/MS (5)(Fig.2).

Results

IP1867B was more potent to inhibit serum TXB_2 than ASA (IC_{50} mM: 0.70 and 4.8, respectively). Both compounds caused a comparable concentration-dependent COX-1 acetylation (max. effect 70-74%) and inhibition of TXB_2 biosynthesis in washed human platelets. ASA and IP1867B caused concentration-dependent acetylation of cancer cell COX-2 with comparable potency, and maximal acetylation was 50% (significantly lower than that of platelet COX-1). The biosynthesis of eicosanoids by HCA7 cells was assessed in the presence of physiological (0.5 and 10 mM) or high concentrations (100 mM) of exogenous AA (Fig.1). At 0.5 and 10 mM of AA, PGE_2 represented more than 96% of eicosanoids generated. The primary products were at 100 mM AA, 15S-hydroxyeicosatetraenoic acid (HETE), 15R-HETE, and PGE_2. 5S-HETE and 12S-HETE were also detectable, and some other HETEs were generated non-enzymatically. At AA 0.5 -100 mM, ASA and IP1867B caused a concentration-dependent inhibition of PGE_2 (Fig.2) with comparable IC_{50}, showing the irreversible nature of COX-2 inhibition. At AA 100 mM, a slight increase of 15R-HETE by the supratherapeutic concentration of ASA 1 mM was detected. The effects on the other HETEs were variable and marginal (Fig.2). 15R-Lipoxin (LX) A_4 (also known as aspirin-triggered LXA_4) was undetectable in all conditions, although the cells presented acetylated COX-2 (and generated 15R-HETE also at baseline) and active 5-LOX (Fig.1).

Conclusions

Although ASA and IP1867B caused TXB_2 biosynthesis inhibition and COX-1 acetylation in washed platelets with comparable potency, IP1867B was more potent in affecting serum TXB_2 generation than ASA. IP1867B formulation could be associated with higher levels of free drug concentration than ASA. The relevance of this finding remains to be evaluated in vivo in humans. In cancer cells, ASA and IP1867B acted by inhibiting PGE_2 generation associated with the acetylation of COX-2. ASA and IP1867B at clinically relevant concentrations did not substantially induce the biosynthesis of 15R-HETE and 15R-lipoxinA_4.

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pharmadvances

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Title

ELLAGIC AND PUNICIC ACIDS EXTRACTED FROM *PUNICA GRANATA* REDUCE EXCITOTOXICITY AND MODULATE AUTOPHAGY IN AN IN VITRO MODEL OF PARKINSON'S DISEASE

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Background

Excitotoxicity refers to neuronal cell death caused by activation of excitatory amino acid receptors and it is mainly linked to an impaired ability of glial cells to reuptake and respond to glutamate. Excitoxicity is considered one of the most common hallmark in many neurodegenerative diseases characterized by neuroinflammation, including Parkinson's disease (PD). Neuroinflammation can be reduced by the use of anti-inflammatory and anti-oxidative substances. Studies demonstrated that Ellagic and Punicic acids (EA, PA), found in several fruits including pomegranates, have these protective effects reducing neuroinflammation and its consequence on brain damage.

Methods

Neuroblastoma cells SHSY-5Y were stimulated with a neurotoxin that induces mitochondrial apoptosis and block dopamine receptors, MPP+ (1-methyl-4-phenylpyridinium; 50uM), for 24 h and then treated with Ellagic and Punicic acids alone or in combination at different concentrations (0,5-1 uM) for 24 h.

Results

Ellagic and Punicic acids increased cell viability, apoptotic pathway is down-regulated by the action of these two compounds, as represented by BAX and Caspases 3/9 expression and up-regulated Bcl-2 level. Pro-inflammatory cytokines, especially IL1-β, IL-6, TNFα and NLRP3 were reduced with the treatments. Furthermore, since autophagy is involved in regulation of neuroinflammation and excitotoxicity, AMBRA 1, BECLIN 1 and LC3B were the main targets to determine the efficacy of our treatments. The obtained results demonstrated that these two natural compounds reduce autophagy, ameliorating neuroinflammation caused by MPP+.

Conclusions

These preliminary data suggest that Ellagic and Punicic acids, in this pathological condition, reduce inflammation and modulate autophagic pathway.

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Title

Un modello predittivo di Intelligenza Artificiale come clinical decision support system: studio su pazienti affetti da COVID-19

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Background

The SARS-CoV-2 pandemic shows no sign of resolving itself, and health organizations to counter its spread urgently need advanced technological tools that are real-time adequate decision support.

This is where **Artificial Intelligence** comes in, enabling the design of software program systems capable of providing the electronic processor with performance that, to an ordinary observer, might seem to pertain exclusively to human intelligence.

To further investigate the potential in clinical settings of Artificial Intelligence, a predictive Machine Learning model was created to investigate the survival of hospitalized COVID-19 positive patients in relation to defined clinical variables obtained from patient records.

Methods

The **realization of an AI model** is performed in consequential steps. The first point is the definition of the question to be solved: the data base provided by the ASST Niguarda containing medical records data of 3662 COVID-19 positive patients hospitalized from 11.2019 to 6.2021 was used; the desired output is to calculate for each patient the mortality over time, time 0 is the day of admission. The second point is to find the algorithm and the software: was used Cox's Regression Model and R v4.1.2. The third step involves data preparation: subdivision of the final event into "Death" or "Alive" (1 or 0). The fourth point is identifying the variables that are statistically significant to predict the output and to be provided as input to the algorithm. The method used is the Cox model and the variables were evaluated one by one according to their p-value. The fifth point involves the implementation of the Machine Learning model. The sixth point is model validation and performance evaluation C-index parameter is used.

Results

The Concordance of the model is 0.85: **the model is rated robust, and the predictions are accurate**.

The following correlations associated with an increased likelihood of poor prognosis are highlighted: pre-hospitalization use of opioid therapy and increased mortality; the older age and the presence of cardiovascular comorbidities are risk factors for severity of COVID-19; the presence of cardiovascular disease finds a link with the pathogenesis of SARS-CoV-2 infection, independent of age; patients with dementia are at increased risk of severity and death from COVID-19.

In contrast, two factors that contribute positively to patient survival are taking antidepressants as home therapy and azithromycin as therapy during hospitalization.

Conclusions

The analysis was successful, for each individual patient it was possible to have a projection of the probability of survival as a function of time; therefore, **the model created is usable as a Clinical Decision Support System**.

Artificial Intelligence is changing the cultural paradigm of medicine: its applications may become increasingly indispensable for providing answers in contexts of high complexity and uncertainty and thus allow physicians more time to take charge of their patients' care needs.

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pharmadvances

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Title

Antitumor effect of *Glandora rosmarinifolia* (Boraginaceae) essential oil by inhibition of Topoisomerase II activity in an *in vitro* model of acute myeloid leukemia

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Background

The plant kingdom can represent one of the best sources of compounds with multiple pharmacological activities such as essential oils (EOs), characterized by low toxicity and often multi-target activity (1). The essential oil of *Glandora rosmarinifolia* has previously shown an *in vitro* antitumor action linked in part to a pro-oxidant mechanism on hepatocellular carcinoma and triple negative breast cancer cell lines (2). The analysis of its chemical composition showed a hydroxy-methyl-naphthoquinone among the most abundant compounds. Several pharmacological properties are attributed to naphthoquinones, including the ability to inhibit topoisomerases or by as catalytic inhibitors or topoisomerase II poisons (3).

Methods

The cytotoxic activity of the EO alone or in combination with etoposide or doxorubicin was evalued by MTS assays on an acute myeloid leukemia cell line HL-60 and on its MDR variant HL-60R. Pro-oxidant activity was examined by cell counting, adding N-acetyl-L-cysteine before EO. The kDNA decatenation assay and the plasmidic DNA cleavage assay were performed using nuclear extracts from untreated cells subsequently incubated with EO or with etoposide. Cell cycle was analyzed by flow cytometry.

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Results

Cell growth inhibition assays revealed that *G. rosmarinifolia* EO induced a decrease in tumor cell viability in an equivalent manner in the two cell lines. The resistance factor of EO on MDR cells was 1.0, much lower than that of the reference drug etoposide (RF 148.0). EO showed pro-oxidant activity in the two cell lines. The nuclear extracts from HL-60 and HL-60R cells incubated with EO reduced TopoII activity as inferred from the inability to convert kDNA to the decatenated form. EO did not induce linear DNA. Furthermore, EO induces a G-G_1 arrest, with a reduction of S-phase cells. In addition, the combination analysis of the EO with etoposide or doxorubicin showed a good potentiation effect in terms of cytotoxicity in both cell lines

Conclusions

The antitumor activity of EO on the HL-60 cell line and its MDR variant seems to depend by a pro-oxidant action. EO also appears to act as a modulator of TopoII but with a different mechanism than etoposide by not causing the stabilization of a TopoII-DNA covalent intermediate, acting as a catalytic inhibitor rather than a TopoII poison. Unlike etoposide, which induces arrest in the G_2-M phase of the cell cycle, EO induces a cell cycle arrest in the G-G_1 phase. The reduction of S-phase cells by EO supports the hypothesis that it acts by inhibiting TopoII at an early stage of its catalytic cycle. Furthermore, despite their different mechanism of action, the combination of EO with etoposide resulted in an enhancement of cytotoxic activity.

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pharmadvances

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Title

Pharmacological screening of fenamates as ClC-1 chloride channel modulators

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Background

Myotonia congenita (MC) is a rare genetic disease characterized by sarcolemma over-excitability inducing muscle stiffness. It is caused by loss-of-function mutations of the skeletal muscle chloride channel, hClC-1, which impair channel function or membrane expression [1]. Nowadays, no ClC-1 direct activator is known and the current first line therapy of MC is based on the use of mexiletine, a sodium channel blocker. Previously, we have demonstrated that the non-steroidal anti-inflammatory drug niflumic acid (NFA), a reversible ClC-1 inhibitor belonging to fenamates, may act as a pharmacological chaperone able to rescue trafficking-defective ClC-1 mutants causing MC [2,3]. We performed a pharmacological screening of clinically available fenamates on ClC-1 channel activity.

Methods

The HEK293 cells were transfected with pRc/CMV plasmid containing cDNA encoding for wild-type human ClC-1. Mefenamic (MFA), meclofenamic (MCFA), tolfenamic (TFA), and flufenamic (FFA) acids, as well as diclofenac (DCF) were prepared according to manufacturer instructions and tested at the concentration of 100 and 300 µM. Chloride currents were recorded using patch clamp technique in the whole-cell configuration, before and after drugs application. For each drug, percentage of block of steady-state chloride current were measured at -90 mV and +60 mV and compared with the relative control conditions.

Results

TFA was the most potent inhibitor of ClC-1 among all fenamates, including NFA. The acute application of 100 and 300 µM TFA caused a significant reduction of chloride currents at -90 mV, respectively of 77% and 84%. In addition, DCF, MFA and FFA significantly inhibited steady-state chloride currents, both at 100 and 300 µM, but to a lower extent compared to TFA. MCFA significantly blocked ClC-1 chloride currents only at 300 µM, whereas no significant effect was found at 100 µM. Thus, fenamates potencies in blocking ClC-1 followed the sequence TFA > MFA ≥ FFA > NFA > DCF > MCFA. These effects were fully reversible upon wash-out.

Conclusions

The pharmacological screening of fenamates on ClC-1 chloride channels revealed differences between compounds, which may represent the starting point for drug design of new hClC-1 modulators, with therapeutic potential for MC. The reversibility of drug effects would allow further investigation of the chaperone activity on trafficking-defective mutant of hClC-1.
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pharmadvances

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Title

Influence of melatonin and calcium supplementation upon irisin release and adipose tissue metabolic pathways

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Background

Irisin, a myokine whose expression is increased following activation of the PPARγ coactivator-1 α (PGC1α), has proven to influence the metabolic pathways in different tissues, including the adipose tissue, resulting in an increase in energy expenditure and thermogenesis. Melatonin is a neurohormone that has been associated to irisin release, but its effect has not been evaluated during physical exercise. Another important feature related to muscle function, and in turn, to metabolic activation is the presence of Calcium that can modulate energy expenditure. As a matter of fact, the effect of melatonin and calcium upon irisin release following physical activity and the related effects on the adipose tissue are still not clear.

Methods

Animals were trained for two consecutive weeks, and randomized to receive: i) melatonin; ii) calcium supplementation; or iii) saline solution. At the end of the experimental procedure, circulating levels of irisin were assessed and fat samples were collected to evaluate mRNA expression of irisin precursor and its transcriptional activator (FNDC5, PGC1α), targets of adipose tissue metabolic pathways (FASN, FABP4, SIRT1 and PPARγ) and inflammatory profile (Adiponectin, Visfatin, IL-6 and TNF-a).

Results

Results

Irisin concentration was increased at the end of the experimental procedure by either melatonin administration and calcium supplementation. Also physical performances in terms of strength were improved after the two weeks of training. Moreover, the adipose tissue metabolic profile was influenced by both types of treatments, suggesting that in physically active subjects irisin might promote adipose tissue remodeling.

Conclusions

The overall findings suggest that both melatonin and calcium supplementation are able to influence irisin activity, and differentially modulate the adipose metabolic profile, thus confirming a significant role of the myokine over this tissue.

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Title

A case report of an ischemic stroke during galcanezumab therapy for migraine and a review of the current literature.

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Background

Anti-calcitonin gene-related peptide (CGRP) have recently come into use for migraine. Randomized controlled trials (RCTs) have already demonstrated that galcanezumab (GLZ) is effective and safe (1). We describe a case report of ischemic stroke (IS) during GLZ. A 60-years-old man began this drug in November 2020. After 8 months, the 2nd of June, he presented paresthesias in his right upper limb a few minutes after drug administration, which resolved in 30 min. These symptoms recurred on June 21, without remission, so the patient was hospitalized and a MRI showed a left thalamic infarction (Fig. 1), requiring thrombolysis. He had a single risk factor (RF), i.e. hypertension in good compensation. Considering the temporal relationship, we decided to deepen this topic.

Methods

We performed a literature review using PubMed and clinicaltrials.gov database to highlight any correlation between GLZ and IS. Keywords were: “GLZ and IS/ictus/cerebral ischemia”, “ C G R P a n d I S / i c t u s /c e r e b ra l ischemia”.

Results

RCTs on GLZ did not evidence a specific cerebrovascular RF. Only one case of transient ischemic attack during GLZ was described with no statystical relevance (1). In our clinical research we found one case of an IS during another anti-CGRP antibody (2). However, from preclinical research on CGRP (3-4), this molecule was found to be capable of arteriolar dilation. CGRP in a preclinical model of cerebral ischemic damage could reduce infarct volume, cerebral edema, blood–brain barrier permeability (5). CGRP deficiency (in CGRP -/- mice) was associated with enhanced neuronal damage, inflammation, oxidative stress, slower recovery of cerebral blood flow and memory deficits VS controls (6). Pretreatment with CGRP inhibitors worsened prognosis of IS in mice (7).

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Conclusions

Our case report is unique in literature. Clinical evidence does not support a pathogenetic role of CGRP block in cerebral ischaemia events; however preclinical studies discussed above may. By applying different algorithms of causality assessment, our case of suspected drug adverse event is only “possible”. Nevertheless, we believe that a critical viewpoint should be taken in prescribing anti-CGRP antibodies especially in patients with vascular RFs, and that a robust post-marketing surveillance is necessary before establishing the actual safety of such drugs.

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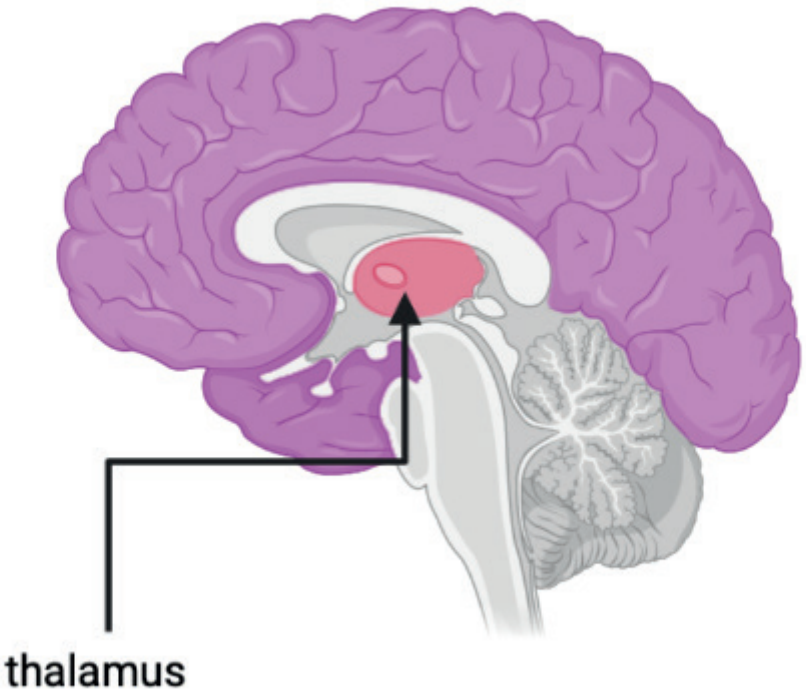

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pharmadvances

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Title

Developing a Limited Sampling Strategy to estimate of Mycophenolic Acid Area Under the Curve in Heart Transplant recipients co-treated with Tacrolimus

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Background

In Heart Transplant (HTx), Mycophenolate Mofetil (MMF) represents a cornerstone in the immunosuppressive maintenance treatment. Generally, it is administered at fixed dose, but inter- and intra-patients pharmacokinetic (PK) variability occurs and the relationship between Mycophenolic Acid (MPA) exposure ($AUC_{0\text{-}12h}$), the MMF active drug, and clinical outcomes is known[1]. Nevertheless, MPA $AUC_{0\text{-}12h}$ Therapeutic Drug Monitoring is not widely executed in clinical practice, since it is laborious, costly and time consuming. In this context, Limited Sampling Strategy (LSS), an algorithm-based strategy to estimate the entire $AUC_{0\text{-}12h}$ by few plasma samples, represents a practical and consolidated tool to overcome this issue.

In this study, we aim to determinate LSSs from a cohort of HTx recipients treated with MMF combined with Tacrolimus, according to clinical practice.

Methods

We analysed full MPA PK profiles deriving from 17 adult HTx recipients. Blood samples were collected at 0 (pre-dose), 0.5, 1, 1.25, 2, 4, 6, 8, and 12 hours after MMF morning dose. MPA was measured by HPLC/UV assay and MPA $AUC_{0\text{-}12h}$ values were calculated by Noncompartmental analysis using PK solver® software. We developed several LSSs by Multi Linear Regression Analysis. We compared and tested the agreement between the measured and the estimated $AUC_{0\text{-}12h}$ by linear regression and Bland-Altman analysis, according to Sheiner and Beal. The performance of the algorithms was tested evaluating the Mean Percentage Prediction Error (ME%)[2] .

Results

The two algorithms named LSS3 and LSS4 by the number of sampling schedule were the followings:

- LSS3:$AUC_{0\text{-}12h}$=-13.49+0.9409×$C0.5_h$+4.056×$C2_h$+8.875×$C6_h$
- LSS4: $AUC_{0\text{-}12h}$=-12.78+0.9259×$C0.5_h$+4.056x$C2_h$-0.1609×$C4_h$+8.942×$C6_h$

They were the most accurate algorithms which were able to estimate MPA $AUC_{0\text{-}12h}$ by few plasma samples, according to their coefficient of determination (R^2) (0.89; 0.89) and ME% (4.2%; 4.2%, respectively). The visual inspection of the Bland Altman plots does not reveal any particular pattern, excluding any dependence by the average of observed and estimated $AUC_{0\text{-}12h}$ and the difference between the estimated and observed $AUC_{0\text{-}12h}$. The percentages of estimated MPA $AUC_{0\text{-}12h}$ predicted within the 25% of the measured MPA $AUC_{0\text{-}12h}$ 88% and for both LSS3 and LSS4.

Conclusions

The two LSSs we identified are effective to estimate MPA $AUC_{0\text{-}12h}$, and LSS3 could represent a less invasive and more useful tool for TDM in the hospital setting, especially for fragile patients with high immunological risk. In order to be used in clinical practice these LSSs must be validated in an external cohort of HTXs recipients.

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Title

Novel disease-modifying drugs modulating alpha-synuclein/synapsin III interplay for the treatment of Parkinson's disease

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Background

Loss of nigrostriatal dopaminergic neurons and Lewy bodies (LB), fibrillary inclusions mainly composed of alpha-synuclein (aSyn), characterize Parkinson's disease (PD). Compelling evidence supports that aSyn micro-aggregation at synapses is a key event contributing to nigrostriatal neurons degeneration in PD.

We recently described that synapsin III (syn III), a phosphoprotein that by associating with physiological alpha-helical aSyn at dopaminergic synapses allows dopamine (DA) release, is a key component of aSyn fibrils in PD brains and controls aSyn aggregation. Indeed, syn III gene knock-out (ko) hampers aSyn fibrillation in an adeno-associated viral vector (AAV)-based mouse model of PD, and AAV-based *in vivo* syn III gene silencing in human aSyn transgenic (tg) mice at early PD-like stage enables aSyn aggregates clearing, halts degeneration and rescues DA release and motility deficits.

We also described that the monoamine reuptake inhibitor methylphenidate (MPH) recovers the motor activity of human aSyn tg mice through a DA trasporter (DAT)-independent mechanism, which relies on the re-establishment of the functional interaction between syn III and alpha-helical aSyn. This supports that the pathological aSyn/syn III interaction may constitute a therapeutic target for PD. We thus developed novel molecules that, by binding syn III, are able to stimulate its functional interaction with aSyn, enabling DA release, aggregates reduction and neuroprotection in experimental models of PD.

Methods

We synthesized compounds displaying elevated “in silico” syn III-binding ability and assessed if they could stimulate functional aSyn/syn III interaction and in parallel reduce the pathological aSyn/syn III interplay, thus resulting in the decrease of aSyn aggregates in different *in vitro* models of PD. The most efficient compound named PK1 was then tested in a human aSyn tg mouse model to assess whether its chronic daily i.p. administration could reduce aSyn aggregation and rescue the PD-like phenotype.

Results

We found that compound PK1 and PK7 exhibited a higher ability to stimulate the functional aSyn/Syn III interaction when compared to MPH. Notably, PK1 treatment efficiently reduced aSyn aggregation in SK-N-SH cells overexpressing aSyn, primary mouse dopaminergic neurons exposed to aSyn pro-aggregating stimuli and in the brain of human aSyn tg mice. In these animals, PK1 also prevented nigrostriatal neurons degeneration and recovered motility deficits.

Conclusions

These findings support that the compounds modulating aSyn/syn III interaction represent promising therapeutic approaches for counteracting aSyn aggregation, dopaminergic dysfunction and degeneration as well as motor deficits in PD.

References

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pharmadvances

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Title

Early life events induce sex- and age-dependent dysregulation of stress-related endogenous systems in the rat prefrontal cortex.

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Background

Social stimuli during early postnatal life can affect later the subject's behaviors including vulnerability to develop anxiety, alcohol abuse and addiction[1]. In this frame, environmental factors can affect the eCB system and its alterations could create an imbalance of the excitatory/inhibitory tone of certain brain areas, such as the prefrontal cortex (PFC). Similarly, alterations of the glucocorticoid system could impair the ability of an individual to adapt to the perturbations caused by external stimuli, thus creating the conditions for reduced or enhanced resilience to the development of psychiatric disorders later in life[2,3]. Based on this evidence, we investigated how early social life events may induce specific alterations of genes involved in neuronal plasticity and reward mechanisms.

Methods

Male and female Wistar rats were housed in standard (one female with her pups) or communal (three females with their pups) nesting conditions. From postnatal day (PND) 14 to PND 21, the early social isolation (ESI) protocol was applied, consisting in the isolation of each pup for 30 minutes/day. Control groups of male and female pups were left undisturbed. On PND35 or PND75, the PFC of animals was collected for gene expression analysis (Real-Time PCR) of cannabinoid receptor 1 (CB1R), the fatty acid amide hydrolase (FAAH), the glucocorticoid receptor (Nr3c1) and the peroxisome proliferator-activated receptors (PPARa, PPARg).

Results

Stress induced by ESI differently altered CB1R, FAAH, and Nr3c1 gene expression in male and female rat PFC. On

PND35, ESI did not cause any significant changes in males while it was able to increase CB1R and FAAH mRNA levels and decrease Nr3c1 expression in females, in both housing conditions. On PND75, ESI produced a down-regulation of CB1R, FAAH, and Nr3c1, in males raised in standard housing conditions. Differently, an up-regulation of these genes was observed in female rats subjected to ESI and raised in communal nesting conditions. These data suggest that females would appear to be more sensitive to ESI-induced effects. ESI protocol also affected PPARs gene expression, depending on sex, raising condition and time of assessment. In particular, isolation stress induced an increase in PPARs mRNA levels in male (PPARg) and female (PPARa) adolescent rats and altered in a sex-dependent opposite direction the expression of PPARg on PND75. Thus, given the existence of a cross-talk between PPARs and eCB signalling, the data on altered expression of PPARs may be related to the greater susceptibility of females to stressful events.

Conclusions

These data show that different housing conditions and stress stimuli induce age- and sex-related alterations of specific genes involved in the modulation of reward mechanisms and pathways linked to the onset of neuropsychiatric disorders.

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pharmadvances
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Title

What amount of cannabinoids is associated with an opioid-sparing effect? A systematic review of longitudinal studies

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Background

Evidence suggests that cannabinoids, by interacting with the opioid system, could reduce opioid doses while maintaining an effective analgesic effect in patients with pain (1,2). However, cannabinoid dosing that could be associated with a reduction in opioid use is not well known. We thus conducted a systematic review to assess the current state of evidence on the question.

Methods

We conducted a systematic review according to the PRISMA statement for reporting searching PubMed, Embase, Web of Science and PsycINFO databases until October 29, 2021. We included randomized controlled trials (RCT) and longitudinal observational studies reporting data on the doses of tetrahydrocannabinol (THC), cannabidiol (CBD), or other cannabinoids in relation to opioid dose change or opioid discontinuation. Studies not providing a measure of cannabinoid dosing were excluded. Two reviewers independently assessed the studies through title/abstract and full-text screening and extracted the data from eligible studies.

Results

From 4927 studies retrieved, eight satisfied inclusion criteria. Five RCTs (three for chronic pain) and two observational studies (one for chronic pain) satisfied the inclusion criteria. Among studies on chronic pain, one small RCT (with stage IV cancer patients) showed that a combined dose of 34mg of THC and 17mg CBD a day reduced baseline opioid use by >20% after three months. One observational study showed a significant reduction in opioid use with 30mg CBD/day within eight weeks. However, two RCTs showed that 18 mg of THC and 16 mg of CBD did not significantly reduce opioid doses after five weeks. Among studies on acute pain, one retrospective study found a significant reduction in morphine

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equivalent use with 10mg of THC/day. However, two RCTs found no significant decrease in opioid use after receiving 21-42mg of THC or 400mg of CBD.

Conclusions

The opioid-sparing effect of cannabinoids remains uncertain as very few studies assessed cannabinoid doses in relation to opioid reduction or discontinuation. Studies are thus needed to elucidate this important question in the context of the opioid crisis.

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pharmadvances

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Title

A systematic review on antidepressant drugs utilization in the community: preliminary results

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Background

Antidepressant drugs are first-line medications in the treatment of depressive and anxiety disorders. Their utilization has increased in the last decades, possibly because of better recognition of these conditions and favorable risk/benefit profiles of the newest medications (1–3). This study aimed to summarize the current evidence on antidepressant drug use in the community.

Methods

We have conducted a systematic review following the PRISMA guidelines (4) and MOOSE recommendations (5). We included all the observational studies that reported data on the prevalence of antidepressant utilization in the community published from January 2010 to April 2021. Studies focusing on hospitalized or nursing home patients and those on patients with specific diseases or conditions were excluded. The search strategy used a combination of keywords (e.g., “antidepressants”) and controlled vocabulary (e.g., “Antidepressive Agents”) and was adjusted for the Embase and MEDLINE databases. Pairs of reviewers conducted the study selection (by title/abstract and full-text screening) and data extraction of selected studies through standardized forms. The quality and the risk of bias were assessed using the Joanna Briggs Institute Critical Appraisal tool: Checklist for Studies Reporting Prevalence Data (6).

Results

Of the 22,425 studies retrieved after duplicate removal, 54 corresponded to the inclusion and exclusion criteria. The studies were generally of high quality with a low risk of bias (87.0% scored five or above). The majority (80.8%) were cross-sectional studies, and only a few had a retrospective (11.5%) or prospective (11.5%) design. The studies were conducted in various countries, mainly Europe (35) and North America (10). The source of data on antidepressant utilization was from the public (39) or private (2) drug insurances or academic data (21). The prevalence of antidepressant drug utilization was estimated mainly from claim (dispensation) and prescription data in 43 and 21 studies, respectively. Selective serotonin reuptake inhibitors (SSRIs) were the most studied drugs (22 studies), followed by tricyclic antidepressants (18 studies). Twenty-six studies on children and adolescents reported prevalence rates ranging from 0,1% to 9.6%. Among adults (22 studies) and the elderly (8 studies), prevalence rates were estimated from 1.5% to 29.8% and from 3.0% to 28.2%, respectively.

Conclusions

These preliminary results of a systematic review on antidepressant drug utilization in the community show that prevalence rates vary mainly depending on the country, data source, age sub-groups, sex and antidepressant class. A meta-analysis approach will generate estimates of antidepressant use prevalence across included studies and according to sex, age group, period, country, or other relevant variables.

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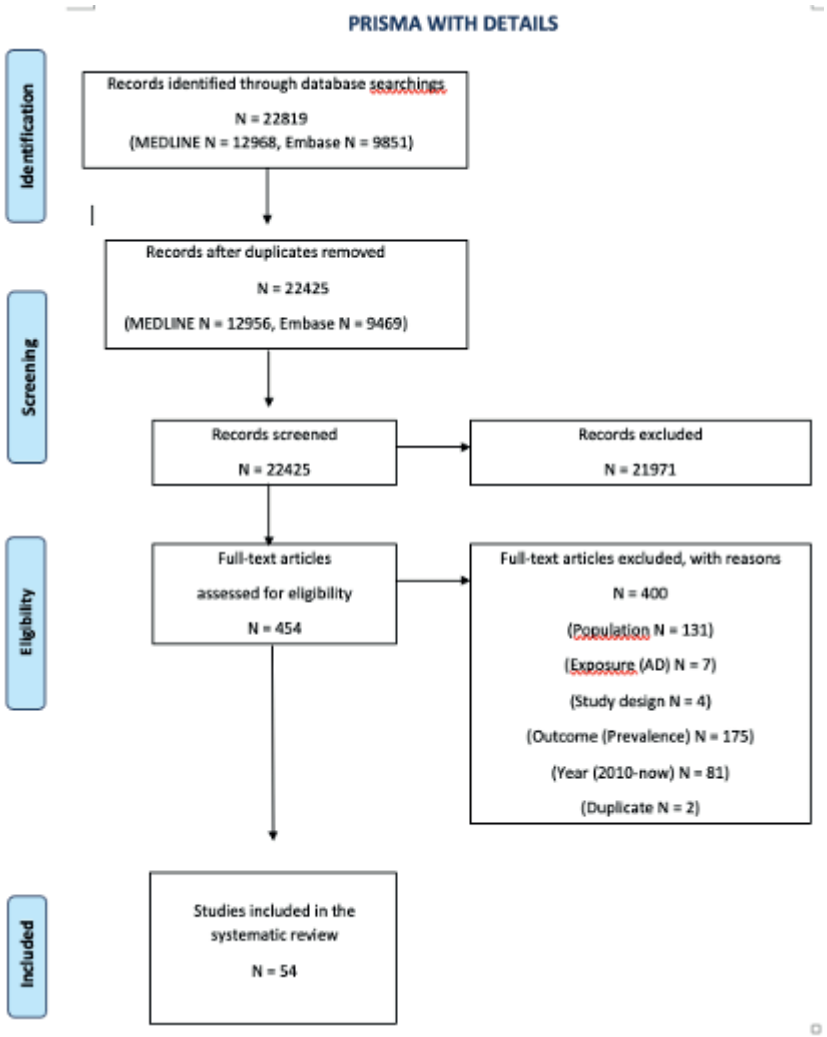

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Title

Real-word trends and patterns of psychiatric medication use in the year before and after a diagnosis of cluster B personality disorder in Quebec, Canada

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Background

Cluster B personality disorders (PDs) are heterogeneous and severe mental disorders associated with excess mortality, especially in the presence of psychiatric comorbidities (1,2). Psychotherapy is the first-line treatment(3), and the effectiveness of pharmacotherapy is not established beyond the symptomatic relief (4–6). Little evidence exists on the real-world utilization of psychiatric medications among PD patients. The aim of this study was then to provide evidence of the use of psychiatric medication classes in the one year before and after a formal diagnosis of cluster B PD and identify trends.

Methods

We conducted a population-based observational study using the Quebec Integrated Chronic Disease Surveillance System (QICDSS). Between 2002 and 2018, we identified Quebec residents (³14 years) insured with the provincial drug plan with a first diagnosis of cluster B PD recorded in the QICDSS (since 1996). We retrieved all the claims for main psychiatric drug classes (antidepressants, anxiolytics, antipsychotics, mood stabilizers, and attention deficit

edra

hyperactivity disorders [ADHD] medications) in the year before and after PD diagnosis. We calculated the proportion of individuals exposed to the different medication classes and, for each class, the mean number and mean days' supply of medications used. Results were presented according to the year of PD diagnosis to investigate prescription trends and by sex.

Results

Between 2002 and 2018, we identified 87,778 new cases of cluster B PD patients, with a mean age of 44.8 years (standard deviation: 19.5) and 57.5% women. The most prevalent psychiatric comorbidities were depression (50.9%), anxiety (49.7%), and psychotic disorders (37.5%). Most patients (71.0%) received at least one psychiatric medication in the year before PD diagnosis, and 78.5% received these drugs in the subsequent year. Similarly, the proportion of users increased for antidepressants (51.6-54.7%), antipsychotics (35.9%-45.2%), mood stabilizers (14.8%-17.0%), and ADHD medications (5.1%-5.9%), and remained relatively stable for anxiolytics (41.4%-41.7%). Trends showed increased use of antipsychotics and ADHD medications during the study period, while anxiolytics and mood stabilizers decreased, and antidepressants remained stable. Women used psychiatric medications more frequently, with differences according to drug classes.

Conclusions

Psychiatric medication use is highly prevalent among cluster B PD patients, even in the absence of evidence-based indications. There is an increase in antipsychotics, antidepressants, mood stabilizers and ADHD medications utilization in the year after a formal diagnosis is made, especially in more recent years. Further studies are needed to investigate whether medication use is associated with health-related outcomes.

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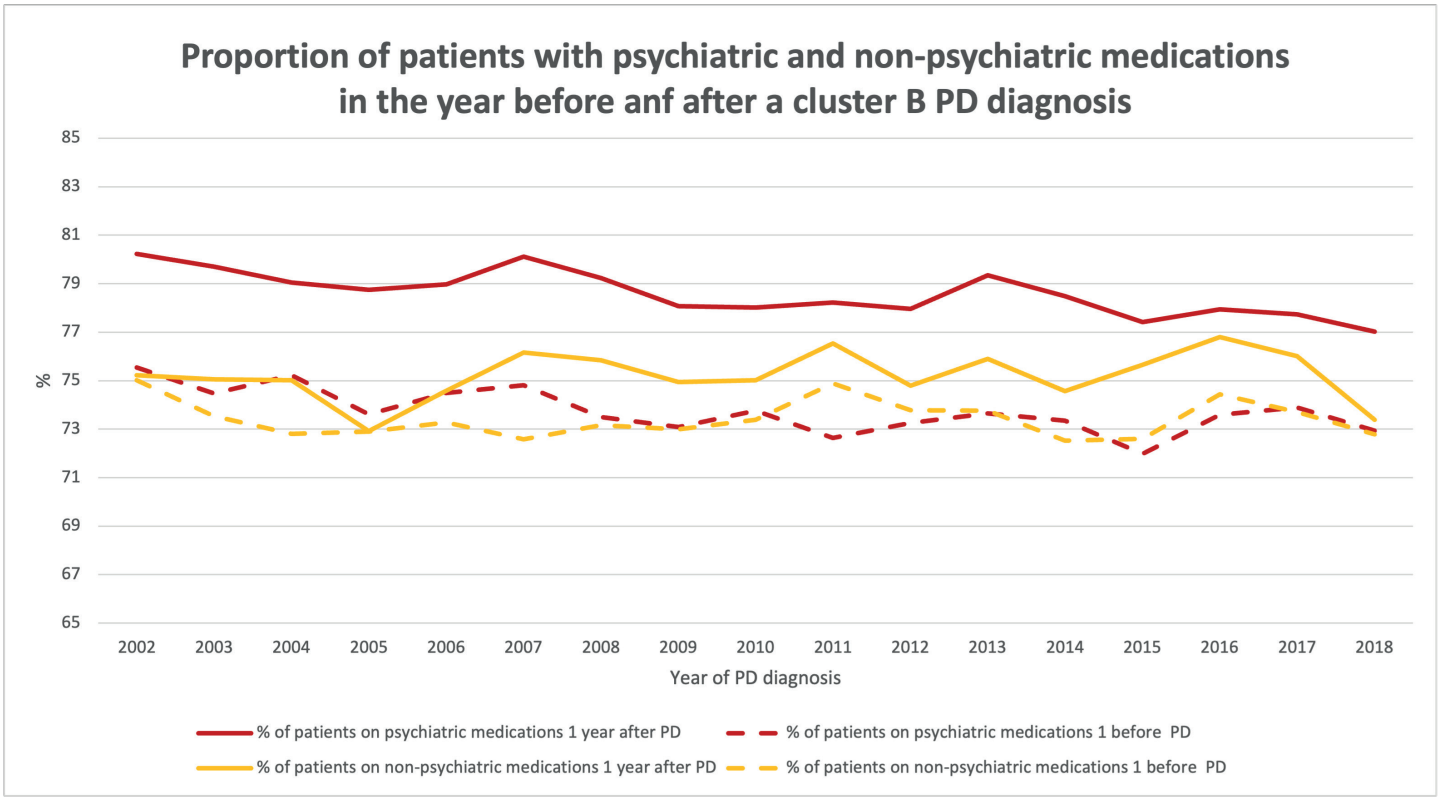
pharmadvances
Volume **5**, special issue **2023**



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Title

Prokineticin 2 is strongly increased in olfactory neurons of Parkinson's disease patients

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Background

Prokineticin 2 (PK2) is an insult-inducible chemokine abundantly expressed in the brain, where it mediates the neuroprotective response [1]. PK2 exerts its biological effects through two G-protein-coupled receptors, PKR1 and PKR2. In animal models of Parkinson's disease (PD), PK2 is strongly increased in dopaminergic neurons of the substantia nigra (SN) in the early stages of neurodegeneration and shows neuroprotective effects [2]. In PD patients, PK2 is increased in SN [2] and also in blood [3]. PK2 signaling is also critical for the development and survival of the olfactory system [4], which is one of the earliest sites of induction of neuropathology in PD [5].

The aim of this study was to investigate the expression of PK2/PKRs in the olfactory neurons of PD patients at different stages of disease and to correlate their expression with that of different α-synuclein species (total and oligomeric) and with the clinical parameters of the patients.

Methods

38 PD patients and 26 healthy control subjects (CTRLs) enrolled at Tor Vergata University Hospital (Rome) underwent nasal brushing to collect olfactory neuroepithelial cells (ONs). From all subjects, 2 samples of ONs were collected: one immersed in Cytofix fixing buffer (Diacyte, Diapath) for immunofluorescence analysis and the second immersed in TRIzol reagent (Invitrogen) for RNA extraction.

Results

We found that PK2 expression was significantly increased in ONs from PD patients compared with CTRLs. The PK2 increase was much higher in newly diagnosed (*de novo*) patients than in later-stage patients, suggesting that the PK2 pathway is activated in PD early in the disease course. Moreover, PK2 upregulation in *de novo* patients directly correlated with motor impairment (assessed by MDS-UPDRS-III in drug-naïve conditions) and with the accumulation of α-synuclein oligomers in ONs, which are pathological forms of α-synuclein thought to play a critical role in the pathogenic cascade of PD. In later stages of disease, in patients on dopaminergic therapy, PK2 expression instead decreased and did not correlate with key clinical features. The expression levels of PKR1 and PKR2 remained unchanged, although PK2 was overexpressed in ONs, suggesting that the increase in PK2 serves as a mediator and does not compensate for the loss of receptors due to neurodegeneration and cell depletion.

Conclusions

This study has shown that PK2 is highly expressed in the ONs of PD patients, especially in the early stages, and correlates with motor impairment and increasing synucleinopathy. All of this demonstrates the potential importance of PK2, either as a biomarker or as a disease-modifying treatment target for the early stages of PD.

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pharmadvances

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Title

PURPLE CORN ANTHOCYANINS AS A NUTRACEUTICAL APPROACH TO PROTECT AGAINST THE PROGRESSION OF MULTIPLE SCLEROSIS AND ITS ASSOCIATED SYMPTOMS

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Background

Functional foods enriched with specific bioactives are one of the most intriguing approaches to promote and restore health. Some dietary components, such as anthocyanins (ACNs), are endowed with specific anti-inflammatory and antioxidant properties and can modulate the composition and functions of the gut microbiota, the complex microorganism community that colonizes mammalian intestine [1]. In turn, gut microbiota contributes to the general well-being of the organism and controls brain functions through the so-called gut-brain axis. It has been recently hypothesized that the gut-brain axis can be modulated with a personalized approach, to be applied to the treatment of several diseases [2]. Thus, we aimed at verifying whether ACN-enriched purple corn can be exploited as adjuvant functional food to modify the onset and progression of multiple sclerosis (MS) and of one of its comorbidities, i.e. trigeminal (TG) pain.

Methods

Relapsing-remitting experimental autoimmune encephalomyelitis (EAE), the animal model of MS, was induced in male Dark Agouti rats by single intra-dermal injection at the base of the tail of MOG_{1-125} fragment in Incomplete Freund's Adjuvant (IFA) and sodium acetate [3]. Eleven days before EAE induction rats were divided in 3 groups drinking water, yellow corn (containing all classes of flavonoids except for ACNs and used as control) or purple corn extracts. From day post-immunization (DPI) 1 to 21: i) rats were weighed daily; ii) the development of EAE was evaluated by a scale from 0 to 7, based on the degree of ascending paralysis; iii) spontaneous TG pain was evaluated by von Frey test. Fecal samples were collected at significant time points for the analysis of microbiome composition and of ACN metabolites. After sacrifice, tissues were collected for subsequent analyses.

Results

Thanks to gut ACN metabolism, purple corn extract:

- facilitates the remission of EAE motor symptoms, protects against the development of relapses, and improves body weight recovery;
- delays and reduces the development of EAE-associated TG pain;
- limits glial cell activation;
- reduces the expression of pro-inflammatory and increases the expression of anti-inflammatory mediators;
- lowers the expression of purinergic P2X4, $P2Y_{12}$ and A_3 receptors, which modulate glial cell reactivity and are involved in pain transmission;
- changes the composition of the gut microbiota.

Conclusions

Our data demonstrate that ACNs from purple corn positively influence the progression of EAE and associated TG pain, suggesting a possible application of purple corn in combination with current drug therapies, either as a preventive or as an adjuvant approach, in order to reduce drug dosage and associated side effects.

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Title

COVID-19 vaccines during pregnancy: A report from the Florence Teratology Information Service

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Background

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is impactful in pregnancy experiencing an increased risk for coronavirus disease 19 (COVID-19) complications as well as higher rates of adverse pregnancy outcomes, such as preterm birth and stillbirth. A key mitigation strategy to the COVID-19 pandemic has been the development and roll-out of vaccines. However, the exclusion of pregnant individuals from the initial COVID-19 vaccine trials prevented the acquisition of pregnancy specific efficacy and safety data, thus limiting the ability of public health agencies to make evidence-based recommendations on COVID-19 vaccination in pregnancy. Post-marketing surveillance data, along with recent observational studies comparing perinatal outcomes between vaccinated and unvaccinated pregnant women, beyond confirming the effectiveness of vaccines at preventing severe SARS-CoV-2 infection, have not indicated any significantly increased risk of adverse outcome in pregnancy. Despite these data, vaccine hesitancy among pregnant women remains critical and it is essential for caregivers to provide a detailed counseling about the benefits of COVID-19 vaccination in pregnancy.

Methods

Methods: This prospective observational study, carried out on about 1200 women who called Florence Teratology Information Service between 1 January and 31 December 2021, aimed to investigate the uptake and safety of COVID-19 vaccination among pregnant and planning pregnancy women. Information on socio-demographic characteristics was extensively collected including current and past pharmacological treatments. Additional data were collected on COVID-19 vaccination uptake, vaccination type, gestational age at vaccination and any post-vaccination reaction. The mothers provided information regarding pregnancy and neonatal outcomes during the follow-up recall three months

after the estimated date of birth. Type of delivery, weeks of gestation, weight, length and cranial circumference at birth, and APGAR score were also recorded.

Results

Results: There were 2 distinct groups: 900 pregnant and 300 not pregnant women. Most women received the Pfizer-BioNTech BNT16b2 or Moderna mRNA-1237 vaccine, less than 1% received another product. Regarding gestational age at vaccination, 333 women received the first dose of vaccine during the second trimester of pregnancy and 567 women in the third trimester. Our preliminary data indicate favorable obstetric and neonatal outcomes following vaccination, with similar rates to general population. There were no additional adverse events of vaccination in pregnant compared with non-pregnant women. Furthermore, timing of vaccination during pregnancy did not affect the rate or profile of adverse effects.

Conclusions

Conclusions: Our findings further confirm that COVID-19 vaccination of pregnant women is safe and effective. Recommending vaccination during pregnancy should therefore be strongly considered in view of the maternal morbidity associated with COVID-19.

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pharmadvances

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Title

Cannabinoid concentrations in galenic cannabis oil: a descriptive analysis according to seasonality and inter-laboratory variability

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Background

Medical cannabis presents several pharmacological applications.

In the literature, several studies highlighed how cannabinoids showed satisfactory results in the treatment of different clinical conditions by actining on CB1 and CB2 receptors of the endocannabinoid system: such as in chronic pain; in nausea and vomiting caused by chemotherapy; as an appetite stimulant in cachexia, anorexia, in cancer patients or patients suffering from AIDS; in glaucoma and Gilles de la Tourette syndrome. (GU, 2015)

Cannabis phytocomplex is composed by 500 substances, which show pharmacological activity; the principal ones are Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabidiol (CBD)(Palermiti et al., 2021; Sirikantaramas et al., 2007).

Cannabis could be delivered as an extracted oil: different varieties are avaiable, such as Bedrocan® and Bediol®, with variable contents in Δ-9-THC and CBD.

Pharmacological active compounds of galenic cannabis oils show a high variability: for this reason, the extracted oil must been titrated before administration in order to ensure therapy optimization and in order to improving safety and

efficacy of the galenic formulation, choosing the best preparation for each patient.

The aim of this study was to investigate cannabinoid levels in cannabis oils, according to seasonality and interlaboratory variability.

Methods

Cannabinoid levels in cannabis oils has been described in a large cohort of galenic laboratories in Italy.

Quantification of CBD, cannabinol (CBN), THC, tetrahydrocannabinol acid (THCA) and cannabidiolic acid (CBDA) was performed by a validated method in UHPLC-MS/MS.

Results

4318 samples of Cannabis oil prepared by 83 galenic laboratories between January 2021 and February 2022 were analysed.

Seasonal variability in compound levels was observed.

All medical cannabis oil specialities showed statistically significant differences among galenic laboratories (p-value < 0.001).

Moreover, THCA and CBDA concentrations were measured as percentage of the extration yelds for total THC and CBD, showing different values in the same specialities among different galenic laboratories.

Conclusions

Compared to the literature, the present study described a wide range of oily samples from a large number of galenic laboratories.

In conclusion, understanding the exact oil composition is fundamental in the perspective of personalized therapy, improving safety and efficacy of the galenic formulation.

Further studies investigating the correlation between galenic composition and cannabinoids pharmacokinetics, clinical outcomes and toxic effects are needed.

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Title

POLYPHARMACY DETERMINANTS OF TORSADE DE POINTES RISK IN OLDER ADULTS WITH COGNITIVE IMPAIRMENT

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Background

Long QT syndrome (LQTS) is a condition in which the prolongation of myocardial repolarization may trigger torsade de pointes (TdP), a form of arrhythmia which sometimes degenerates into ventricular fibrillation [1]. LQTS may be inherited because of mutations in key ion channels controlling cardiac repolarization or acquired following the administration of drugs that interfere with their activity, such as antiarrhythmics, antipsychotics and antidepressants [2]. Different torsadogenic drugs may synergize in increasing TdP risk when combined in polypharmacy regimens. TdP risk may also be enhanced by concomitant factors, some of which may be drug-induced, such as hypokalemia, hypocalcemia, hypomagnesemia, vomiting and diarrhea [3]. The aim of the present work was to identify risky drug combinations in a group of polypharmacy patients represented by older adults with cognitive impairment, who frequently take TdP-inducing psychotropic drugs.

Methods

Study design was cross-sectional, observational. We revised drug prescriptions of patients at the Federico II Alzheimer Evaluation Unit from January to May 2022. Inclusion criteria were cognitive impairment, age older than 65, and treatment with at least 5 drugs. Torsadogenic risk was assessed using the credible meds database (https://www.crediblemeds.org/).

Results

36 patients (22 females) with cognitive impairment (9 MCI, 10 mixed type dementia, 6 Alzheimer's Disease, 2 frontotemporal dementia, 3 subjective cognitive decline, 6 other type dementia) entered the study. Their mean age was 76.9±5.7 years. Medication review showed that 52,8% (n=19, 11 females) of them were taking torsadogenic drugs. Drug therapy included two torsadogenic drugs in 25% (n=9, 6 females) and three or more in 27,8% (n=10, 5 females) of the patients. The most represented category of TdP-inducing drugs was psychotropics that were taken by 16 patients (13 antidepressants, 2 antipsychotics and 1 antidepressant plus antipsychotics) either for behavioral symptoms or for sleep disturbances. These drugs were combined with PPIs, which may increase the risk of TdP by inducing hypomagnesemia, in 10 patients, and, in 5 patients, with cholinesterase inhibitors, which may increase the risk of TdP by causing bradycardia. Other torsadogenic drugs used in combination with psychotropic drugs included flecainide (n=2), alfuzosin (n=3), sotalol (n=1), olodaterol (n=1) and diuretics (n=2). In three patients at risk for TdP no psychotropic torsadogenic drug was taken; they were, instead, treated with either cholinesterase inhibitors or with diuretics in combination with PPI.

Conclusions

Patients with cognitive impairment are a subgroup of older adults at high risk of drug-induced TdP since they very often are on polypharmacy including multiple torsadogenic drugs. Medication review may help reducing the risk by replacing one or more risky drugs with safer medicines.

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Title

ASIC1A-BLOCKING MONOCLONAL ANTIBODY RESTORES HIPPOCAMPAL SYNAPTIC PLASTICITY IMPAIRMENT INDUCED BY Aβ.

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Background

Acid Acid-sensing ion channels 1a (ASIC1a) are widely distributed in the mammalian nervous system and in particular brain areas including the hippocampus. ASIC1a is highly permeable to Ca^{2+} and its activation has a crucial importance in numerous physiological and pathological processes, including synaptic plasticity, learning and memory. To further understand the role of ASIC1a channels in the synaptic alterations induced by Aβ, we carried out electrophysiological experiments investigating the effects of a novel ASIC1a-blocking monoclonal antibody ASC06-IgG on hippocampal long-term potentiation (LTP) and long-term depression (LTD) using an *in vitro* model of Alzheimer's disease (AD).

Methods

We performed whole cell patch clamp recordings of CA1 pyramidal neurons in acute slices obtained from C57BL6J mice. NMDA- receptor dependent forms of Long Term Depression (LTD) and Long Term Potentiation (LTP) were elicited by electrical protocol. The *in vitro* model of AD was obtained applying Aβ (200 nM) on slices for 30 minutes before recording.

Results

We observed that blocking ASIC1a with the selective inhibitor Psalmotoxin-1 or with the novel ASIC1a-blocking monoclonal antibody ASC06-IgG restored the Aβ-mediated alteration of NMDA-receptor dependent LTP and LTD. Overall, these data demonstrate for the first time that ASIC1a is involved in the synaptic plasticity modifications triggered by Aβ.

Conclusions

These findings suggest a neuroprotective effect of ASC06-IgG and highlight ASIC1a as a potential pharmacological target to treat memory decline and cognitive impairments.

References

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Title

Involvement of *KCNJ8* (Kir6.1), *KCNJ11* (Kir6.2), *ABCC8* (Sur1), and *ABCC9* (Sur2-A/B) genes encoding for ATP sensitive K^+ channel subunits in cancer.

Authors

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Background

The role of the four genes ABBC8, ABCC9, KCNJ11, KCNJ8 encoding for the ATP-sensitive K^+-channels subunits (KATP) [1]-[4] in cancer progression requires accurate investigation. Several signals of their involvement in drug targets and diseases are reported in the literature[4]. In the present work, we investigated the possible association of the four genes and their variants in cancer[4].

Methods

Omics and Pharmacovigilance analyses were used to evaluate the correlation of ABBC8/Sur1, ABCC9/Sur2A/B, KCNJ11 /Kir6.2, and KCNJ8 /Kir6.1 genes of the KATP and adverse drug cancer reactions. Experimental immunohistochemical studies on samples from a minoxidil-induced (0.777-77.7 mg/kg/day) renal tumor in male rats and female not-metastatic breast canine cancer, a spontaneous animal model of disease, were also performed.

Results

The block of the Kir6.2-Sur1 channel with the sulfonylureas and glinides and the downregulation of the ABCC8/Sur1

gene, are associated with hypoglycemia and pancreatic cancer (Proportional-Reporting-Ratios P.R.R.>2) and drug-disease interaction. The high-affinity blocker of Kir6.1/2-Sur2A/B zoledronic acid shows the highest risk for cancers (P.R.R.>2) including renal and ovarian cancers, but not for pancreatic cancer, within these drugs. The ABCC9/Sur2 is a negative and positive prognostic gene respectively in breast and ovarian cancers, in line with the number of breast cancer cases (N=32) and ovarian cancer cases (N=1) in women under Kir6.1/2-Sur2 opener minoxidil treatments, and with the ZOL cases of ovarian cancer (N=23). Immunoreactivity to the Sur2B mab was detected in the cytosolic compartment of G3 cells in either animal tumor samples. The ABCC9, ABCC8, and KCNJ8 genes were associated with a low probability of survival in 7/10 tumors in the woman.

Conclusions

The ABCC9(Sur2) is therefore a novel cancer target responsible for drug-disease interactions with gender effects.

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Title

Software as Medical Device: the use of data science for shortening the diagnostic path in the field of rare diseases.

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Background

A disease is defined as rare when it affects no more than 100 individuals per million population [1]. Rare diseases pose particular challenges to affected patients, the doctors who care for them, and the researchers [2]. In particular, people with rare diseases and their caregivers face psychological distress throughout the diagnostic process, that due to the intrinsic rarity of the diseases often leads to early misdiagnosis and delay in access to the right treatment, when available. For clinicians, rare diseases represent a diagnostic challenge that is not easy to solve, which requires profound knowledge in various sectors of medicine and general pathology, not to mention therapeutic approaches and interventions that are not available for most rare diseases. A great effort is made to improve prenatal and newborn genetic screening. Although helpful, those tests cover less than 1% of the known rare diseases[3]. Our idea is addressed to the early diagnosis.

Methods

We developed an algorithm and a digital diagnostic tool, powered by databases such as Orphanet [4] and Human Phenotype Ontology [5]: an interactive tool that, in a limited number of questions, is able to indicate to the paediatrician or general practitioner a limited number of diseases, say from 1 to 10, for which molecular and genetic tests should be carried out to confirm the diagnosis. The tool itself can then orientate to centers of excellence and expertise for individual diseases.

Results

We created a Bayesian probabilistic chain optimized with data science techniques that returns a limited set of rare diseases. The result is based on the answers provided by the patient relating to the presence or absence of symptoms related to specific rare genetic diseases from datasets such as Orphanet and HPO. The questions are not proposed randomly but on the basis of a further probability function that takes into account the frequency of symptoms and diseases and the links between individual diseases (reconstructed using a network graph). Machine learning and natural language processing techniques are implemented to allow user-friendly interaction between the system and the user.

Conclusions

The output of the tool allows the expert in making an immediate acquaintance and connect the symptoms and phenotypes with the disease with more probability, thus saving time for diagnosis and speeding up access to therapy. The benefits for the healthcare system are the optimization of patient management costs, higher quality, and better performance of the treatment while improving the quality of life of the patients and their caregivers. The tool is under validation in the clinical setting for sensitivity and accuracy.

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pharmadvances
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Title

Aquaporin-4 aggregation and KATP channel functional expression drive the U87 cells to apoptosis

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Background

Glioblastoma multiforme is the most malignant and aggressive type of brain tumors with poor prognoses. This is due in part to the high resistance to apoptosis, and to the poor therapeutic response to conventional therapies. From our group it has already been shown that the aggregation dynamics of the astrocyte water channel protein Aquaporin-4 (AQP4) into supramolecular structures called orthogonal arrays of particles (OAPs) influences the biology of glioma cells [1] [2]. Aggregated AQP4 (AQP4-OAPs) triggered cell shape changes in glioma cells associated with alterations to the F-actin cytoskeleton and apoptosis [3]. Also, ATP sensitive K^+- channels (KATP) plays a role in cell shape changes seen during proliferation and apoptosis. In this study, we investigated the relationship between AQP4 and K channel in glioma cell fate.

Methods

The study was conducted on the U87 cell line derived from a malignant glioma, transfected with Human M1-AQP4 (tetramer forming isoform) or M23-AQP4 (AQP4-OAP forming isoform) and WT. Transfected cells were subjected to immunofluorescence for AQP4 and SUR2A expression and Patch clamp experiments. The currents were recorded under physiological concentration of K^+ ions in the bath and pipette. Transfected cells were also incubated with agonists or antagonists of KATP channel and then stained for AQP4 and Phalloidin to visualize F-actin. Quantitative analysis of round-shaped cells compared to AQP4 positive total cells per field was performed. Moreover, detection of condensed nuclei, quantification of the mean of the nuclear area, the length and the number of filopodia.

Results

AQP4 aggregation into OAPs increases the plasma membrane expression of the Kir6.2 / SUR2 in U87 cells leading to an increase in inward K^+current. Pharmacological inhibition of the Kir6.2 / SUR2 channel activity with the specific blocker

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zoledronic acid (10^{-5}M)[4] drives changes in OAP expressing U87 cells from irregular-shaped towards round-shaped and triggers apoptosis-associated nuclear condensation and fragmentation. Furthermore, zoledronic acid influences the dynamics of F-actin reducing ordinated structure and the number of membrane protrusions. No effects are observed with the application of the SUR1 and SUR2 blocker like glibenclamide ($5x10^{-8}$M) and repaglinide (10^{-7}M), or SUR1 and SUR2 agonists like diazoxide($2,5x10^{-4}$M) and minoxidil(10^{-4}M), respectively.

Conclusions

Zoledronic acid induced dual block of the Kir6.2 and SUR2 subunits triggers apoptosis in AQP4-OAP expressing glioma cells suggesting AQP4 and Kir6.2 as a potential drug target to modulate glioma cell fate.

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Title

TROXERUTIN: A NEW OPTION TO TARGET EARLY STAGES OF DIABETIC RETINOPATHY?

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Background

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus (DM) and it is characterized by degeneration of retinal neurons and neoangiogenesis[1]. Hyperglycemia, the DM hallmark, is a major risk factor for endothelial dysfunction and vascular complications. We previously demonstrated that, in rat retina, hyperglycemia activates protein kinase C βII (PKC βII), which in turn leads to a higher expression of vascular endothelial growth factor (VEGF) via the mRNA-binding Hu-antigen R (HuR) protein[2]. VEGF is a pivotal mediator of neovascularization and a known vasopermeability factor. Proper *in vitro* models are crucial for exploring DR pathophysiology to identify novel therapeutic targets[3]. Considering that endothelial cells are key elements in DR and that hyperglycemia triggers the PKCβII/HuR/VEGF pathway, we set up two distinct *in vitro* models applying two different stimuli. Given that preventive treatments for DR are limited and most of the available treatments are focused on end-stage disease, we also investigated the capability of Troxerutin, an antioxidant flavonoid[4], to counteract VEGF increase.

Methods

Human umbilical vein endothelial cells (HUVEC) were exposed to 100 nM PMA (phorbol 12-myristate 13-acetate) for 48 hours, while human retinal endothelial cells (HREC) were treated with a high glucose concentration (25 mM) for different times: 72 hours and 7 days. Western blot experiments were performed to explore the expression of PKCβII/HuR/VEGF proteins in both cellular models and the effect of Troxerutin (1 mM) was also assessed. ELISA was performed to evaluate the VEGF release in both *in vitro* models with and without Troxerutin.

Results

The results obtained on HUVEC indicate that PMA challenge induces a significant increase in the intracellular and extracellular content of VEGF following 48 hours of exposure. Troxerutin was able to counteract the increase of both PKCβII and VEGF, the latter both intracellularly and in the medium, induced by PMA treatment. The results obtained on HREC indicate a significant rise in VEGF protein levels detected after exposure to high glucose at both times of incubation. Troxerutin was able to counteract this increase in VEGF in both experimental conditions. Moreover, Troxerutin was capable to counteract the upregulation of the entire PKCβII/HuR/VEGF cascade following 7 days of glucose treatment.

Conclusions

Our findings confirm the key engagement of the PKCβII/HuR cascade as an early event triggered by hyperglycemia to promote the expression of VEGF. Further, we also show the capability of Troxerutin to hinder the hyperglycemia-induced increase in VEGF in both *in vitro* models, thus suggesting its potential use as a preventive treatment during the early phases of the disease.

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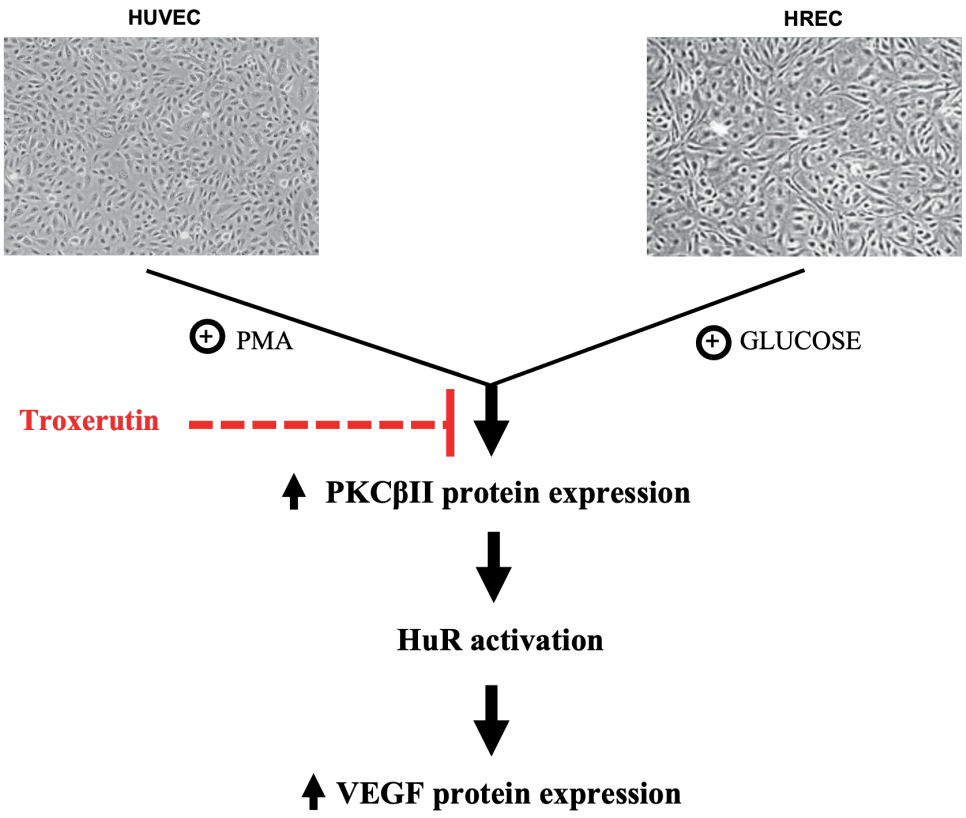

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Title

Morphological and functional alterations of colon organoids treated with faecal supernatants from viscerally hypersensitive mice affected by colitis

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Background

Visceral hypersensitivity is a hallmark of most intestinal pathologies, such as inflammatory bowel diseases (IBDs), and is responsible for both pain and altered motility. Several mechanisms have been proposed to contribute to visceral pain persistence; among them, are alterations in microbiota composition and metabolism[1]. Aiming to deepen the pathophysiology of visceral pain, we focused the attention on the intestinal epithelium which represents the first site of interaction between the microbiota and host and is also involved in the regulation of neuronal signaling. Colon organoids were used to model *in vitro* the complex physiology of intestinal epithelium[2] and to study its functional response to normal or altered microbiota-derived products. The relevance of epithelium modifications in the context of pain were investigated by employing cultures of dorsal root ganglion (DRG) neurons.

Methods

Murine colon organoids were established as described by Fan et al.[3], and epithelial cell diversity was assessed by

immunofluorescence. Gut dysbiosis was induced by exposing mice to 2.5% dextran sodium sulfate (DSS) in drinking water for 5 days. Faecal samples were collected 2 and 3 days after the end of DSS treatment, homogenized in the organoid medium, centrifugated and filtered to obtain faecal supernatants (FS). Hence, viability assays, morphological assessments and gene expression analysis (qPCR) were performed to study the effects of FS derived from healthy and DSS-treated mice on the development of colon organoids. Finally, the conditioned medium (CM) from FS-treated organoids was collected and added to isolated DRG neurons to evaluate their electrophysiological response.

Results

Colon organoids had positive staining for LGR5, chromogranin A, mucin 2 and E-cadherin, demonstrating the self-organizing ability of cell populations derived from a single intestinal stem cell. Healthy mice-derived FS enhanced organoid viability but the morphology was not improved compared to control. Conversely, DSS mice-derived FS negatively affected the organoid morphology without showing negative effects on their viability. The incubation of colon organoids with FS from healthy or DSS donors differently modulated the expression of genes involved in epithelial functions, assessed by qPCR analysis. Ultimately, exposure of DRG neurons to CM from organoids treated with FS led to changes in their intrinsic excitability. This result suggests that microbiota derivatives of mice with colitis stimulate the epithelium to release mediators capable of sensitizing sensory neurons.

Conclusions

Changes in the gut microbiota related to intestinal diseases have a negative impact on colonic epithelium functionality. Microbial-derived products may also sensitize nociceptive neurons through intestinal epithelium mediation, contributing to visceral pain.

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pharmadvances
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Title

Effects of a nitric oxide (NO)-donating prostaglandin analog in a model of ischemia/reperfusion induced by endothelin-1 in rabbits

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Background

Lowering intraocular pressure (IOP) is the only approved approach for glaucomatous patients, but it is important also the control of the optic neuropathy associated with visual loss. NCX 470, a nitric oxide (NO)-donating prostaglandin analog effective for the reduction of IOP[1] was studied for its ocular hemodynamics effects and neuroprotective activity in a model of retinal ischemia/reperfusion in rabbits.

Methods

Endothelin-1 (ET-1) was used to induce the retinal ischemia/reperfusion model. ET-1 was injected under the Tenon capsule twice/week for 6 weeks[2]. From week 3 to week 6, rabbits were treated with a nitric oxide (NO)-donating prostaglandin analog (twice a day) or vehicle. IOP, ophthalmic artery resistive index (OA-RI) and photoreceptor function (electroretinogram, ERG) were measured as functional parameters. Oxidative stress and inflammatory markers were studied in retina and ciliary bodies.

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Results

Injections of ET-1 progressively increased IOP and ophthalmic artery resistive index; moreover ET-1 decreased the functionality of retina, reducing rods and cones responses, as suggested by the diminished amplitude of ERG analysis. The treatment with the nitric oxide (NO)-donating prostaglandin analog restored baseline IOP, OA-RI and ERG amplitude at week 6. The treatment with the nitric oxide (NO)-donating prostaglandin analog reduced ET-1-induced alterations in oxidative stress markers and inflammatory cytokines in retina and ciliary bodies at week 6.

Conclusions

The nitric oxide (NO)-donating prostaglandin analog ameliorates functional parameters, specifically IOP, ocular perfusion and photoreceptor functions after ET-1-induced ischemia/reperfusion in rabbits. Moreover, oxidative stress and inflammation were reduced in retina and ciliary bodies. Taken together, these results support the retinal cell protective activity of the nitric oxide (NO)-donating prostaglandin analog NCX 470.

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pharmadvances

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Title

EFFECT OF CANNABIDIOL ON HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS AND CD4+ T CELLS: RELEVANCE FOR NEUROPATHIC PAIN

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Background

Cannabidiol (CBD) is the main non-psychoactive *Cannabis sativa* derivative and sees a wide clinical use in the treatment of different diseases (1,2), although its immunomodulatory potential, including possible analgesic and anti-inflammatory effects (2,3), received little attention so far (4,5). Inflammation and inflammation-related pain both cause disability, with pain being a frequent symptom, in particular in neurological diseases. We therefore decided to assess, in human peripheral blood mononuclear cells (PBMC), the effects of CBD on cell proliferation and on the production of proinflammatory cytokines (tumour necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-17A), which play a pivotal role in neuropathic and inflammation-related pain (6,7). Additionally, we investigated CBD effects on T lymphocyte differentiation, by assessing the mRNA expression of transcriptional factors (TF) and intracellular cytokine content in purified CD4+ T lymphocytes.

Methods

PBMC were isolated from buffy coats of healthy subjects by Ficoll-Paque Plus density-gradient centrifugation (8). Isolated PBMC were then stimulated (9) and cultured alone or in the presence of CBD 1 μM, which was shown to bear no toxicity in previous studies (4). The percentage of cytokine producing CD4+ T cells from PBMC was assessed by means of flow cytometry (10) while cell pellets and supernatants were collected after 48 h and stored at -80°C. mRNA

expression for cytokines and transcription factors was then assessed, by means of real time PCR technique. Supernatant was used for protein evaluation through ELISA assay and cell proliferation of PBMC was assessed after 120 h incubation by flow cytometry.

Results

CBD dramatically decreased intracellular cytokine content and expression of all measured TF. Additionally, stimuli-induced TNF-α, IFN-γ and IL-17A mRNA expression was decreased without affecting protein production and cell proliferation.

Conclusions

Results suggest CBD, which is already used in the treatment of various conditions with a particularly safe profile, might also exert positive effects on neuropathic pain, via inhibition of proinflammatory cytokines expression, without altering other physiological functions of treated immune cells. These promising findings point to an interesting immunomodulatory potential for CBD, which is worth of further and deeper investigation.

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pharmadvances

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Title

Immunomodulatory effects of *Pelargonium sidoides* DC and Resveratrol combination on macrophage cells

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Background

The immune system is thought as an integrated network of cellular elements and molecules developed to preserve the integrity of the organism against external insults. The immune system homeostasis is essential to avoid the occurrence of different disorders. Infact, always more evidence support an increase in immunological diseases and immunological-related disorders and a great attention has been focused on the development of molecules able to modulate the immune response. One of the more promising strategy is the use of natural products. The bioactive components of medical plants have always been an important source of clinical therapeutics and the study of their molecular pharmacology is an enormous challenge since they offer a great chemical diversity and, often, a multi-pharmacological activity.

Pelargonium sidoides DC (Synonym: Pelargonium sidaefolium (Thunb.) R. Knuth; Geraniaceae) is a perennial geophyte predominantly found in the Eastern Cape Province of South Africa and the Lesotho highlands. The plant is widely used by local communities as a traditional medicine for curing various ailments, including diarrhoea, colic, gastritis, tuberculosis, cough, hepatic disorders, menstrual complaints and gonorrhoea (1,2). In this study we evaluate the immunomodulatory efffect of *Pelargonium sidoides* alone and in combination with Resveratrol, a natural dietary plant compound that occurs mainly in grape skin and seeds but is also found in wines and various other types of plant foods with many properties including activity against glycation, oxidative stress, inflammation, neurodegeneration, several types of cancer, and aging (3).

Methods

The immunomodulatory activity was evaluated on murine macrophage cell line J774A.1 both in normal and in inflammatory conditions.

Results

Our results indicated that *Pelargonium sidoides* (10 – 1 µg/mL) significantly increase nitric oxide release as well as cycloxygenase expression in macrophages (P<0.001 vs control cells). The immunostimulatory activity also indicates the effect of *Pelagonium* in inducing tumor- necrosis factor-α and IL-6 release (P<0.001 vs control cells). These factors seems to be further enhanced combining *Pelargonium sidoides* with Resveratrol (1 – 0.001 µM). Moreover, preliminary data seems to indicate that *Pelagonium sidoides*, also in combination with resveratrol, influence macrophage activation also during inflammatory conditions, in Lypopolysaccharide from *E.coli*-stimulated J774A.1 macrophages, reducing NO release and COX-2 expression, (P<0.001 vs LPS- treated cells).

Conclusions

These results indicate that *Pelargonium sidoides*, alone and especially with Resveratrol, has potential immunostimulatory and anti-inflammatory effects.

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pharmadvances
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Title

Immunological implications of Endocrine Disrupting Chemicals (EDCs): RACK1 as a bridge between the endocrine and the immune systems

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Background

RACK1 (Receptor for Activated C Kinase 1) has a central role in the immune system due to a strong correlation between its expression and immune cells activation via PKC. This results in the modulation of pro-inflammatory cytokines TNF-α and IL-8 *in vitro*, *in vivo* and *ex vivo*. Thanks to a hormone-related regulatory element for androgens and glucocorticoids in RACK1 gene promoter, we hypothesized that hormone-active substances can affect the immune response via RACK1 modulation. EDCs (Endocrine Disrupting Chemicals) can induce immune alterations via inflammation-enhancing or immunosuppressive actions and a role for EDCs in the increased incidence of cancers, autoimmune diseases, and allergies has been hypothesized. Our study aims to assess how EDCs interfere with the immune response by modulating RACK1 expression and to elucidate the mechanisms behind their immunological implications.

Methods

Human promyelocytic THP-1 cells were treated with increasing concentrations of anti-androgen p,p'DDT, p,p'DDE, Vinclozolin (VCZ), Atrazine (ATZ) and Cypermethrin (CYP), estrogen-active compounds 17β-estradiol, 17β-estradiol-BSA, diethylstilbestrol (DES), zearalenone (ZEA) and ethynyl-estradiol (EE) and, finally, Perfluorooctanesulfonic acid (PFOS), Diethyl-phthalate (DEP), bisphenols A, AF and S (BPA, BPAF, BPS). Luciferase reporter assay, qPCR, Western blot analysis, specific sandwich ELISA and flow cytometric analysis were performed.

Results

p,p′DDT, p,p′DDE, VCZ, ATZ, CYP (all AR antagonists), PFOS and DEP (GR agonists) induced a significant decrease in

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RACK1 transcriptional activity, RACK1 expression, LPS-induced IL-8 and TNF-α production and CD86 expression. On the other hand, estrogen-active compounds (through GPER activation) increased RACK1 transcriptional activity and its expression, paralleled by an increase in LPS-induced IL-8, TNF-α production, and CD86 expression. Finally, while BPS displayed upregulating effects on RACK1 production and consequent cytokine release, BPA and BPAF initially downregulated RACK1 but mifepristone, flutamide and BAY 11-7082 unmasked upregulating effects and shed light on their mechanism of action.

Conclusions

The complex effect resulting from the activity as antagonist or agonist of hormone-active substances shows how RACK1 modulation and its PKC-mediated downstream effects in the immune context are of important interest. Therefore, RACK1 represents a bridge between the immune and the endocrine systems, indicating its relevance as target of steroid-active substances and EDCs. This offers the possibility to exploit RACK1 as a tool to screen EDCs for their immunotoxic potential.

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Title

Fenofibrate mitigates inflammation-induced functional alterations in the medial prefrontal cortex in a mouse model of Alzheimer's Disease

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Background

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder. In addition to amyloid beta (Aβ) peptides and neurofibrillary tangles formation, neuroinflammatory processes are attracting interest in the etiopathogenesis and progression of AD[1]. We hypothesized that an inflammatory insult might worsen disease progression in a validated mouse model of AD, the 3xtg-AD mice[2], assessed by electrophysiological recordings from medial prefrontal cortex (mPFC) neurons. Secondarily, we evaluated whether activation of nuclear ligand-regulated receptors (PPARs) would mitigate the effects of the inflammatory challenge. PPARs are promising targets to modulate inflammation in the CNS[3]. Hence, among the members of the PPAR family, PPAR-α are abundantly expressed in the brain[4] and act by modulating gene expression to attenuate neuroinflammation[5]. Thus we investigated whether inflammation altered the mPFC neuronal electrical activity in 3xtg-AD mice and evaluated the potential effects of PPAR-α agonist fenofibrate on the modulation of inflammation-induced effects.

Methods

In 4-months old female 3xtg-AD mice (APPswe, Tau_{P301L} and $PS1_{M146V}^{+/-}$), we induced inflammation by a single injection of polyriboinosinic-polyribocytidylic acid (Poly I:C), a synthetic double-stranded RNA, that triggers an innate immune

response. Starting 7 days before treatment, and for 19 total days, mice were administered a diet enriched with the PPAR-α fenofibrate (0.2% w/w). At 15 months, we performed *in vivo* single-unit recordings in anesthetized mice in the mPFC.

Results

Putative mPFC pyramidal neurons from Poly I:C-treated mice showed a reduced firing rate as compared with the vehicle-treated group. Interestingly, treatment with fenofibrate reverted this effect (two-way ANOVA, $F_{(1,54)}$=10.32; p=0.0022). No differences were detected in firing pattern, expressed as coefficient of variation. Moreover, Poly I:C-treated mice displayed a higher number of spontaneously active cells, an effect that was mitigated by fenofibrate (two-way ANOVA, $F_{(1,6)}$=6.45; p=0.0441).

No difference was detected in the firing activity or the number of putative GABAergic neurons following Poly I:C treatment.

Conclusions

Our results show that inflammation induced an alteration of the electrical activity in the mPFC of 3xtg-AD mice. Moreover, our preliminary data support modulation of PPAR-α as a possible pharmacological approach and suggest fenofibrate as potentially effective in preventing functional impairments.

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pharmadvances
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Title

Cannabinoids and epilepsy: the emerging role of microglia on the protective effect of cannabidiol

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Background

Cannabinoids (CBs) are implicated in multiple physiological and pathological mechanisms in the central nervous system. Over the past ten years the number of scientific studies demonstrating the efficacy of some of the most abundant non-psychoactive compounds present in Cannabis sativa has massively increased. In particular, cannabidiol (CBD) has been shown to be effective in the treatment of several types of neurological disorders and neurodegenerative diseases. Epilepsy is amongst the most common brain disorders, affecting more than 50 million people of any age worldwide. Despite the possible use of large therapeutic options, 30% of the patients still have uncontrolled seizures for their entire lifespan (Vergonjeanne et al., 2021).

Methods

Rat organotypic hippocampal slices, an *in vitro* model of epilepsy that we routinely used in our laboratory, were exposed to 5 µM kainic acid (KA) for 24 hours (Landucci et al., 2021), in presence or absence of cannabinoids. The cell death in the CA3 subregion of slices was quantified by propidium iodide fluorescence. Microglia activation and polarization was evaluated using Flow Cytometry and Morphology Analysis.

Results

When present in the incubation medium, CBD and natural compounds reduced CA3 injury, whereas incubation with Delta-9-tetrahydrocannabinol (Delta-9-THC) exacerbated hippocampal damage induced by KA. The neuroprotective effect of 10 µM cannabidiol was blocked by the receptors antagonist of TRPV1 (capsazepine 1 µM), TRPV2 (tranilast 50 µM), 5-HT1A (WAY-100365 0,1 µM) and PPARγ (G3335 0,1 µM). The neurotoxic effects of Delta-9-THC was attenuated

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only by the CB1 receptors antagonist AM251 at 10 nM. Incubation with KA leads to an increase in the M1 (pro-inflammatory) phenotype, whereas decrease the M2 (anti-inflammatory) phenotype. When present in the incubation medium, Delta-9-THC significantly increased the M1 phenotype compared to KA. CBD incubation significantly reversed microglia activation and transition from the M2 to M1 phenotype induced by KA.

Conclusions

Our study suggests that cannabidiol mitigates neuronal death by inhibiting microglial activation and promoting transformation from an M1 to an M2 phenotype.

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Title

Vulnerability or Resilience to Chronic Mild Stress: role of miRNAs and their targeted signalling

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Background

Exposure to chronic stress represents a risk factor for the development of different mental disorders (Gong et al., 2021). However, the response to chronic stress is highly heterogeneous: indeed, only some individuals express a vulnerable phenotype, whereas others develop coping strategies and maintain a resilient phenotype. Epigenetic mechanisms, including the modulation of miRNAs, represent a possible mechanism involved in the long-term effects of stress (Lopizzo et al., 2019). Therefore, the aim of the present work was to identify miRNAs and pathways respectively associated with vulnerable and resilient phenotypes in association to a chronic mild stress paradigm.

Methods

A group of adult male Wister rats was (CTRL) left undisturbed for all the duration of the experiment, while another group underwent a Chronic Mild Stress (CMS) paradigm, through the exposure to different mild stressors for three consecutive weeks. CMS animals were tested weekly for the sucrose consumption to identify Vulnerable (VULN) and Resilient (RES) animals. At the end of the experiment, animals were sacrificed and the brain regions of interested were dissected. Here we performed a miRNOmic analysis on the ventral hippocampus (VH) on the Affymetrix platform. The software Partek Genomic Suite was used to identify lists of miRNAs differentially modulated by applying a cut off of fold-change ?1.2?and a p-value <0.05 and the most significant miRNAs were also validated Real Time-PCR. Ingenuity Pathway Analysis (IPA) was used to perform pathway analysis.

Results

By using cut off of FC ?1.2?and p-value <0.05 different lists of miRNAs differentially modulated in VULN or RES animals were identified. We identified a panel of miRNAs specifically associated with a RES or a VULN phenotype that were also validated by Real Time-PCR. Among these miRNAs, miR-181d-3p and miR-411-5p were found specifically up-regulated in VULN rats (+28% and +41% respectively vs RES and CTRL; p-value <0.05 for both), whereas miR-30e-3p, miR-30e-5p, miR-6215 and miR-1249 were specifically modulated in RES animals (+45% and +27%, +36% and +22%; +45% and +36%; -23% and -25%; respectively vs CTRL and VULN, with p-value <0.05 for all).

A pathway analyses on the different sets of miRNAs identified pathways related to *Synaptogenesis Signalling (p-value=0,001)* and to the *Axonal Guidance Pathways (p-value=0,014)* in animals that developed a vulnerable phenotype, whereas an enrichment of pathways associated with inflammatory response, as the *B Cell Receptor Signaling (p-value= 4,074E-04), IL7 (p-value=0,003), IL6 (p-value=0,004) and IL22 (p-value=0,093) signalling pathways,* were specifically modulated in RES animals.

Conclusions

The development of a VULN or RES phenotype in response to CMS exposure is associated with the modulation of specific miRNAs which, in turn, may modulate mechanisms related to neuronal function or to inflammatory response.

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Title

Selected Growth Hormone Secretagogues (GHS) decrease mutant SOD1 toxicity in an in vitro model of amyotrophic lateral sclerosis

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Background

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease characterized by progressive degeneration of upper and lower motor neurons, resulting in muscle atrophy, limb paralysis, and finally respiratory failure. ALS pathogenetic mechanisms are still unclear even though (i) mutations of superoxide dismutase 1 (SOD1) and (ii) increased oxidative stress have been linked with several variants of ALS. SOD1 is an antioxidant enzyme, whose substitution of glycine 93 to alanine (SOD1-G93A) is a mutation present in about 20% of familial and 5% of sporadic ALS, and leads to gain/loss of function that enhances the accumulation of highly toxic hydroxyl radicals.

The current standard of care involves riluzole and edaravone, while all the other interventions are only symptomatic and palliative. Therefore, there is a strong need to characterise more effective drug.

GHS are a large family of synthetic compounds which have shown endocrine functions, through the stimulation of growth hormone (GH) release, and extra-endocrine properties, including stimulation of food intake and lean mass, at least in part by the binding to GHS-R1a, the receptor of ghrelin.

Among GHS, we have investigated the effects of (i) hexarelin, which has important neuroprotective and cytoprotective activities, both in vitro and in vivo; and (ii) JMV2894, which stimulates Ca2+ mobilization in vitro and GH release in vivo, and modulates mitochondria functioning and ROS production.

Methods

SH-SY5Y SOD1-G93A cells, a human neuroblastoma cell line that expresses SOD1-G93A enzyme, were treated with hydrogen peroxide (H2O2) and GHS to study the protective effect of GHS against increased oxidative stress. Photomicrographs of stained cells were quantified by skeleton and fractal analysis. The mRNA expression levels of caspase 3, caspase 7, Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic) were quantified by real-time PCR, while the protein levels of mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), and

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histone H2AX phosphorylated at Ser139 (γH2AX) were measured by western blot.

Results

The treatment of SH-SY5Y SOD1-G93A cells with H2O2 induces important changes in cell morphology which can be antagonize by hexarelin and JMV2894 incubation.

In addition, hexarelin exerts anti-apoptotic effects by modulating the mRNA levels of proteins belonging to the BCL-2 family as well as the activation of effector caspases.

The protective effects of hexarelin and JMV2894 are mediated by the activation of molecules that regulate apoptosis, promoting cell survival processes.

Conclusions

Hexarelin and JMV2894 are capable of protecting cells from H2O2-caused cytotoxicity, suggesting the possibility of developing new anti-oxidant and neuroprotective drugs with improved therapeutic potential. Further investigations are required to (i) clarify GHS molecular mechanisms of action, and (ii) whether their effects are mediated by GHS-R1a.

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pharmadvances
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Title

Use of immunosuppressive therapies: complex post-transplant clinical management and complications related to their use.

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Background

The aim of this project was to evaluate the reporting trend of adverse reactions (ADRs) associated with drugs used to prevent transplant rejection which were entered in the National Pharmacovigilance Network (RNF) by ARNAS “G. Brotzu” of Cagliari. The reports were analyzed using pharmacovigilance methods, compared to national data and related to patients receiving therapy through Direct Distribution of medicines (DD).

Methods

The analysis was conducted by extracting from the RNF all the ADRs related to drugs with ATC L04 inserted from January 2017 to December 2020 by the Region of Sardinia, and in particular by ARNAS “G. Brotzu”, with therapeutic indication of prevention of transplant rejection. National data were extracted from the RAM System (Adverse Reactions of Medicines report) of the Italian Medicines Agency (AIFA). The data of the DD dispensing were extrapolated from the AREAS (SISaR) management software, mostly from the list of movements of the EDF flow.

Results

In the 2017-2020 period, 1.794 reports of suspected ADRs to drugs and vaccines were entered by the Sardinia Region.

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Out of these, 20 (1.1%) were spontaneous reports of ADRs to immunosuppressive drugs (L04AA, L04AD and L04AX), with therapeutic indication of prevention of transplant rejection, 16 of which (80%) were entered by ARNAS “G. Brotzu” and concerned Mycophenolic Acid (MMF/MPA) (63%) and Tacrolimus (TAC) (37%). In 2019, 62.5% of total reports were entered. The average age of patients was 56 years and the most represented age group was between 18 and 64 years. 69% of the reports concerned female patients. All ADRs were reported by physicians and were rated as serious in 4 cases (25%) and as non-serious in 12 cases (75%). In 7 out of 16 cases (44%) the ADRs were completely resolved. The "not resolved" outcome was represented in 3 cases (19%) while in the rest of the cases it was not available. Almost 57% of reports referred to at least one gastrointestinal reaction and 50% of reports referred to general unwellness and reactions at the administration site. The most frequently reported Preferred Terms (PT) were diarrhea, nausea and vomiting. The percentage of cases of patients who, in the four-year period, received DD therapy and experienced ADRs to MMF/MPA and TAC did not exceed 2.3% and 1.9%, respectively. National data on MMF/MPA and TAC corresponded to a total of 640 reports. Reports inserted
by ARNAS “G. Brotzu” represented 2.5% of the total national ones.

Conclusions

The absence of delayed ADRs, known for this class of drugs at national level (such as neoplasms, infections and pathologies of the blood and lymphatic system) and the low incidence of patients who have presented ADRs are elements that could confirm the problem of under-reporting, which has always represented a relevant issue in the field of pharmacovigilance.

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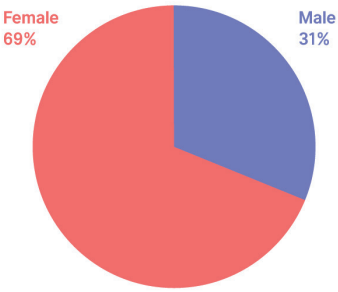
pharmadvances
Volume **5**, special issue **2023**

Distribution by onset time from administration

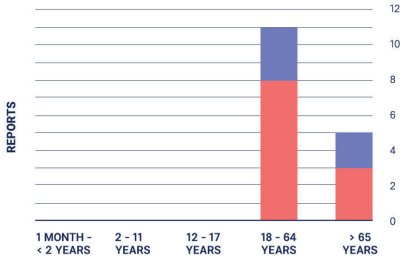
Onset time		N.	%
	0 days	6	38%
	1 days	1	6%
	2-7 days	5	31%
	>7 days	4	25%
	Total	**16**	**100%**

Distribution by onset date of event

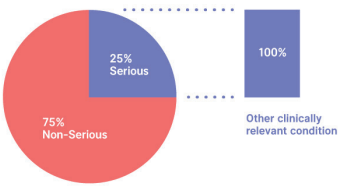
Distribution by gender



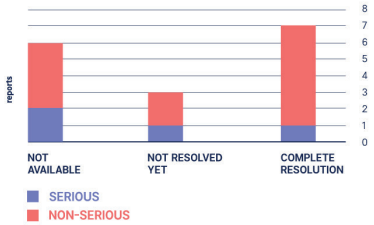
Distribution by age group



Distribution by seriousness



Distribution by outcome of reports



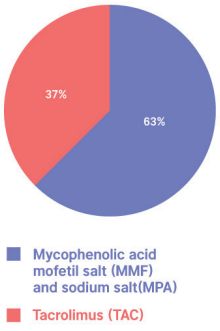
Distribution on the basis of the apparatus (SOC, MedDRA)

SOC	PT	N	%
Gastrointestinal disorders	Diarrhea, Nausea, Vomiting, Pain abdominal, Abdominal pain upper	9	56%
General disorders and administration site conditions	Asthenia, malaise	8	50%
Nervous system disorders	Altered attention, Dysarthria, Hypersomnia, Paralysis, Somnolence	5	31%
Skin and subcutaneous tissue disorders	Alopecia, Rash, Pruritus, Generalized itching, Hyperhidrosis	4	25%
Investigations	Increased blood pressure	1	6%
Respiratory, thoracic and mediastinal disorders	Dyspnea	1	6%
Ear and labyrinth disorders	Vertigo	1	6%

Distribution based on Preferred Term (PT)

SOC	PT	N	%
Gastrointestinal disorders	Diarrhea	8	44%
	Nausea	3	17%
	Vomiting	2	11%
	Pain abdominal	4	22%
	Abdominal Pain Upper	1	6%
	Total	**18**	100%

Distribution by type of drug



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pharmadvances
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Title

Investigating the role of telomere length in response to electroconvulsive therapy or psychotherapy in patients with treatment-resistant major depressive disorder

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Background

Telomere length (TL) is a hallmark of cellular aging, and while telomeres shorten physiologically after each cell division, this process can be significantly accelerated by several factors, such as acute or chronic stressors, inflammation, and chronic disorders, including mental illness. Findings so far have suggested that individuals with severe mental disorders show several biosignatures of accelerated aging, as well as increased incidence of age-related disorders. At the same time, contrasting findings on the role of TL in mental disorders have been reported.

Regarding pharmacological interventions, there is robust evidence that exposure to lithium treatment correlates with longer TL, but less is known about TL and response to non-pharmacological interventions. Here we present findings from two longitudinal studies aimed at investigating the correlation between leukocyte TL (LTL) and response to electroconvulsive therapy (ECT) or psychotherapy in patients with treatment-resistant major depressive disorder (MDD).

Methods

In the first study, LTL was measured in 30 treatment-resistant MDD patients before, at the end and four weeks after the ECT session, and correlated with treatment response and other clinical variables. In the second study, LTL was measured in 30 treatment-resistant MDD patients before, at the end and four weeks after the end of the psychotherapy session, and correlated with treatment response and other clinical variables. LTL was measured with real-time qPCR and statistical analyses were run using general linear models.

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Results

In the first study, LTL did not change significantly across the three time-points, and was not correlated with response to ECT, either considered as dichotomous trait or as changes in total MADRS scores (delta MADRS). In the second study, the difference in LTL between before and four weeks after psychotherapy (delta LTL: ((t2-t0)/t0)*100) was significantly larger in responders than in non-responders (model corrected for age, p=0.007; effect of treatment, p=0.054), an effect that appeared to be mediated by the presence of psychotic symptoms at baseline. Indeed, patients without psychotic symptoms in the responder group had significantly larger delta LTL compared to responders with psychotic symptoms and to non-responders (response*psychotic symptoms, p=0.002).

Conclusions

Our study on ECT confirms previous findings suggesting that LTL is not a predictor of response to ECT and is not influenced by the treatment. Our second study suggests that psychotherapy might be responsible for reduced telomere shortening, and suggests that larger difference in LTL between baseline and after the treatment could be a marker of response.

References

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Title

Management of Benign Prostatic Obstruction-Associated Lower Urinary Symptoms in the ASL TO4 Regione Piemonte (Italy): Prescription Behaviour and Twelve-Months Medication Persistence

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Background

Pharmacological treatment of benign prostatic obstruction (BPO)-associated lower urinary tract symptoms (LUTS) aims at improving patient's quality of life by managing urinary symptoms and preventing both complication and disease progression [1,2]. Current guidelines [3] recommend the use of: α_1-adrenoceptor antagonists (α_1-blockers, AB), steroid 5α-reductase inhibitors (5ARI), phosphodiesterase-5 inhibitors, muscarinic receptor antagonists (MRA), β_3-adrenoceptor antagonists and herbal drug preparations. However, poor persistence to medication has been reported in patients with BPO. The aim of this population-based, retrospective study was to describe prescription behavior and persistence to medications for BPO-associated LUTS in the ASL TO4 Regione Piemonte (Italy).

Methods

The sample population consisted of men aged ≥40 years who were first prescribed medications for BPO-associated LUTS during the index period April 1, 2018 - December 31, 2018. Only drugs reimbursed by the Italian National Health System were considered in the analysis: MRAs (ATC code: G04BD), ABs (G04CA) and 5ARIs (G04CB). The index date of the included patients was the first prescription of a study drug during the index period. Patients were followed for 12 months from the index date. The primary objective was to assess the existence of patterns in prescription data. The secondary objective was to quantify medication persistence, defined as the time from initiation of a pharmacological treatment until first discontinuation of the drugs.

Results

A total of 4,380 (median age 71.0, interquartile range 64–78 years) men were included. Of these, 3,273 received ABs, 1,407 5ARI and 82 MRAs, most often (91.3%) as monotherapies. The median time to discontinuation was significantly (P<0.001; Log-rank test) longer with 5ARI (188 days; 95% confidence interval, 180–210 days) than with either ABs (118 days, 101–120 days) or MRAs (20 days, 20–30 days).

Conclusions

This study suggests the need for new strategies to improve prescribing appropriateness by physicians and patient persistence to treatment for BPO-associated LUTS in the ASL TO4 Regione Piemonte (Italy).

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Title

Assessment of medication adherence and persistence among patients on antithyroid drug therapy in the ASL TO4 Regione Piemonte (Italy): a retrospective longitudinal cohort study

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Background

Hyperthyroidism (HT) is characterized by thyroid hormone excess and can be caused by different causes [1,2]. The clinical presentation of HT ranges from subclinical manifestations to thyrotoxicosis with overt adrenergic symptoms. In addition, the complications of either unrecognized or untreated HT include weight loss, cardio- and cerebrovascular disorders, embolic events, psychiatric disorders, cognitive impairment, bone loss and potential fatal events in case of a thyroid storm [3-5]. Methimazole (thiamazole), carbimazole and propylthiouracil are the antithyroid drugs (ADs) used to treat HT [6]. In a previous epidemiological study (period 2012-2018) it was found that in the Piedmont Region about 90% of the HT cases received at least one prescription for ADs, and methimazole accounted for 98% of all prescriptions [7]. However, persistence and adherence to these drugs has not been investigated. The aim of this retrospective longitudinal cohort study was to describe persistence and adherence to ADs in the ASL TO4 Regione Piemonte (Italy).

Methods

Drug dispensing data of the ASL TO4 were analyzed. The study population consisted of individuals aged 18 and over who were first prescribed ADs between April, 2018 and December, 2018. Patients with less than 2 dispensations were excluded. Only methimazole was considered for the analysis because carbimazole is not marketed in Italy, while propylthiouracil can only be prescribed to hospitalized patients. Patients were followed for 12 months starting from their index date. Persistence was defined as the time to discontinuation from the index date; adherence was quantified as the medication possession ratio (MPR) over a pre-specified period.

Results

A total of 1,140 patients (70.9% females) were included. The median age was 75.0 (interquartile range 62-82) years (72.0 [62-79] years and 76.0 [63-83] years for males and females, respectively). The median time to discontinuation was 100 days (50-180); patients under 70 years were significantly more persistent than those over 70 years (P<0.001; Log-rank test). The percentage of adherent patients (MPR ≥80%) at 6 months was 55.9% (95% confidence interval 53-58).

Conclusions

Suboptimal persistence and adherence to ADs were observed in this study. Initiatives should be implemented in the ASL TO4 to improve the use of ADs.

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Title

NICOTINE-INDUCED GENETIC AND EPIGENETIC MODIFICATIONS IN PRIMARY HUMAN AMNIOTIC FLUID STEM CELLS

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Background

Several epidemiological studies suggest that prenatal tobacco exposure may be associated with various detrimental health consequences for both mothers and offspring. According to a recent report by Lange et al. 2018 (1), in which estimates were calculated via meta-analysis for 43 countries and via statistical modelling for 131 countries the prevalence of smoking during pregnancy was 8·1% (95% CI 4·0–12·2) in the European Region. The amount of nicotine (NIC) in amniotic fluid (AF) depends upon different factors including the number of cigarettes smoked per day and NIC concentration found in the amniotic fluid of pregnant women smoking a minimum of 5 cigarettes/day may vary from 7 to 31 ng/ml, with a median of 11 ng/ml (0.07 µM). The detrimental effects of maternal smoking have been correlated with altered DNA methylation and dysregulated expression of microRNAs (miRNAs). Moreover, recent findings in animal models showed direct implication of perinatal NIC exposure on early adipogenesis and lipogenesis. In this study we used human amniotic fluid-derived stem cells (hAFSCs), an interesting alternative to iPSCs for identifying epigenetic marks in diseased gestation, to investigate the potential genetic and epigenetic modifications induced by NIC on the fetus.

Methods

Undifferentiated hAFSCs and differentiated hAFSCs into adipogenic lineage, obtained as previously reported (2,3), were treated with different NIC concentrations (0.01 to 10 µM) for up to 72 hrs. MTT assay, Real-time PCR and flow cytometry were performed to assess NIC effects on cell viability and differentiation potential. Methylation analysis was carried out

by pyrosequencing. Finally, next-generation sequencing was performed for MicroRNAs (miRNA) profiling.

Results

Nicotine treatment (0,1 µM a concentration close to that found in the AF of pregnant smokers) caused increased expression of pluripotency markers (Oct4, SOX2 and KLF-4) in undifferentiated cells, whereas, in differentiated hAFSCs a significant downregulation was observed. NIC also downregulated the expression of adipogenic markers (LPL, PPARG and FABP4). Furthermore, the promoters of Oct4, SOX2, C-Kit and H19 genes showed a significant change in CpG methylation in NIC-treated adipogenic differentiated cells compared to the undifferentiated ones. MicroRNAs profiling reported 1020 miRNAs, of which 441 were found to be expressed. Among them, 27 miRNAs were differentially expressed.

Conclusions

Based on our results, nicotine causes genetic and epigenetic modifications during hAFSCs adipogenic differentiation. Human AFSCs, derived from amniocenteses have a high proliferative potential, result gnomically stable and are not associated with ethical controversies, thus providing a useful in vitro model for studying the effects of tobacco smoking on the fetus. Further studies are needed to evaluate the effect of nicotine in combination with other smoking harmful derivatives such as benzopyrenes.

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Title

Involvement of miR-135a-5p downregulation in acute and chronic stress response in the prefrontal cortex of rats

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Background

Behavioral stress is recognized as a key risk factor in the onset of neuropsychiatric disorders. The response to stressful stimuli might follow different trajectories leading to adaptive or maladaptive changes depending on the ability to activate coping strategies. The study of the underlying mechanisms is particularly relevant in the identification of new targets for innovative treatments of stress-related disorders.

Clinical evidence on depressed patients highlighted volumetric reductions in corticolimbic areas (including the prefrontal cortex, PFC), and stress was reported to induce dendritic retraction/spine loss in the PFC of animal models, suggesting a role for synaptic plasticity remodeling in depression etiopathology. microRNAs (small non-coding RNAs) have been involved in mechanisms of neuroplasticity, stress vulnerability and pathophysiology of neuropsychiatric disorders. Among them, miR-135a-5p (miR-135) has been associated with stress response and dendritic spine remodeling in serotonergic neurons, as well as in antidepressant effect [1]. Here we used Chronic Mild Stress (CMS) [2] and Foot Shock Stress (FS) [3] on male rats to study whether miR-135 has a role in stress-induced changes in the PFC and to dissect possible underlying molecular mechanisms.

Methods

miR-135 expression was evaluated by RealTime PCR in the PFC of CMS and FS rats [2,3]. The direct effect of miR-135 modulation on neuronal morphology and dendritic spines was tested in primary neuronal cultures, by transfection with plasmids overexpressing/downregulating miR-135 [2]. A bioinformatic analysis was applied to find putative target genes of miR-135. The expression of the selected genes was evaluated by Western blot in primary neurons transfected with

miR-135 mimics and in the PFC of CMS and FS rats.

Results

miR-135 levels were decreased by both acute and chronic stress in the PFC of rats. In CMS rats, miR-135 was reduced only in stress vulnerable and not resilient rats. The downregulation of miR-135 in primary neurons reduced the density of dendritic spines, the overexpression exerted an opposite effect. Cplx, Rhot1, Rock2 and Kif5c were bioinformatically predicted as miR-135 target genes. However, in neurons transfected with miR-135 mimics, only Rock2 and Kif5c were decreased. The analysis in the PFC of CMS and FS rats showed selected changes in the expression of predicted targets.

Conclusions

miR-135 expression is decreased by stress in PFC glutamatergic neurons. Importantly, in CMS rats, the reduction is selective for vulnerable rats, suggesting an involvement in stress vulnerability mechanisms. Furthermore, miR-135 directly regulates dendritic spine density in pyramidal neurons and we identified some target genes putatively involved. Altogether, we found that miR-135 plays a role in stress response in corticolimbic areas and the underlying mechanisms might offer new targets for the treatment of stress-related disorders.

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pharmadvances

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Title

Metabolic Syndrome Management in the Hospital Setting: A Focus on use of Drugs in Older Patients

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Background

Metabolic syndrome (Mets) is a multifactorial pathology characterized by a complicated pharmacological management. The aim of the study was to investigate the pharmacological management of Mets in hospitalized elderly patients.

Methods

A retrospective observational study was conducted using the RE.PO.SI database considering all data collected from the period 2008 and 2020. Subjects with at least three of the following conditions, obesity, dyslipidemia, hypertension, and diabetes mellitus were defined MetS patients. Descriptive and comparative analyzes were carried out between patients with and without MetS on the use of antihypertensive, glucose-lowering agents, lipid-lowering and anti-obesity drugs in the subgroups of patients with the related pathologies, both at admission and discharge.

Results

Out of 8,417 subjects recorded in RE.PO.SI, 1,005 patients (11.9%) were defined Mets patients at admission. MetS patients were significantly younger (median, IQR:70, 72-82 vs 80, 74-85; p<0.01, respectively) and more female (55.6%

vs 51.1%; p<0.01, respectively) were observed than patients without Mets. Among the 6,292 hypertensive patients, only 85.6% of patients were on antihypertensive therapy at hospitalization. This percentage decreased by 5.6% at discharge. MetS patients were significantly more treated with antihypertensives drugs than patients without MetS, both at hospitalization (92.4% vs 84.3%; p <0.01, respectively) and at discharge (86.9% vs 78.7%; p <0.01, respectively). Among the 741 patients with dyslipidemia, 76.7% patients were on lipid-lowering therapy at hospitalization. This percentage decreased by 7.9% at discharge. In particular, MetS patients were significantly more treated compared to patients without MetS, both at hospitalization (76.7% vs 70.1%; p=0.04; respectively) and at discharge (70.0% vs 60.0%; p=0.01, respectively). Among the 3,907 diabetic patients, less than half (43.9%) were on glucose-lowering agents at admission and this rate reduced by 6.1% at discharge. In particular, MetS patients were more treated than those without MetS, both at hospitalization (52.1% vs 41.2%; p <0.01, respectively) and at discharge (48.1% vs 34.2%; p <0.01, respectively). No use of orlistat and naltrexone/buproprion was observed in the 724 obese patients. Only 1 patient was on liraglutide therapy at admission and 3 patients were on treatment at discharge, all with diabetes mellitus.

Conclusions

The results emphasized a difficult pharmacological management in patients affected by MetS. Furthermore, a greater prescription attitude by physician was observed in Mets patients compared to those without Mets.

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pharmadvances

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Title

Lifelong exposure to n-3 PUFA deficiency leads to anxiety-like effects in adolescent rats: impact of sex on immune modulation

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Background

Literature data report that women have higher prevalence rates of anxiety disorder and this condition is more disabling in women than in men (1). Although the reason of this gender difference is not fully understood yet, women show different response to sex hormones, that might ultimately influence behaviour and brain function. On the other hands, lower consumption of n-3 polyunsaturated fatty acids (PUFA) during developmental period has been associated with increased risk of mood disorders either in rodents or in humans (2, 3). Accordingly, we have previously found that lifelong exposure to n-3 PUFA deficient diet in female and male rats leads to depressive- and anxiety-like symptoms in early adulthood (3-5).

Methods

In order to evaluate possible sex-driven differences in the development of mood disorders induced by n-3 PUFA deficiency, we performed two behavioural paradigms of anxiety like behavior in male and female adolescent rats, such as the novelty suppressed feeding and the zero maze. In addition, considering the recent involvement of spleen-brain axis on mood disorders and considering that the spleen is crucial for neuroimmune communication as major immune organ innervated by the sympathetic nervous system, we correlated behavioral and neurochemical outcomes with peripheral immune activation by quantifying several biomarkers of glia spleen cells in treated rats.

Results

Our data indicate that in male and female animals fed for their entire life with a diet poor in n-3 PUFA an anxiety-like profile was evidenced compared to animals receiving a n-6/n-3 balanced diet. However, in male rats no differences were retrieved in cortical levels of GABA and glutamate, while in female n-3 PUFA deficient diet led to a reduced

glutamate and increased GABA levels. Peripheral levels of these neurotransmitters paralleled these outcomes. We found that n-3 PUFA deprivation induced a significant increase in spleen noradrenaline content only in female rats along with higher spleen expression of Glial fibrillary acidic protein (GFAP) and reduced expression of CD11b proteins, while no differences were identified for the pro-inflammatory biomarkers Tumor necrosis factor (TNF)α and Nuclear Factor kappa B (NFkB). Ultimately, plasma corticosterone levels were increased only in male rats receiving poor n-3 PUFA diet.

Conclusions

Taken together our data provide novel insights in the understanding of the underlying central and peripheral mechanisms leading to the development of sex-related anxiety-like effects and immune activation induced by n-3 PUFA deficiency.

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Title

Exploiting the role of NAMPT (nicotinamide phosphoribosyltransferase) in tumoral angiogenesis

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Background

The extracellular nicotinamide phosphoribosyltransferase (eNAMPT) is retained to have cytokine-like functions. eNAMPT is reported to induce endothelial angiogenesis by promoting endothelial cell proliferation and capillary-tube formation[1] and impact on EMT modulation in breast cancer cell line[2]. Moreover, eNAMPT has also been linked to cancer. In the context of breast cancer patients, its serum and plasma levels have been found increased and in most of the cases they correlate with the stage of cancer progression[3].

Methods

To study the effect of eNAMPT we provide a murine mammary carcinoma model (4T1 cells) in which NAMPT is fused to the signal peptide of immunoglobulin (SP-NAMPT) to enhance a massive and constitutive release of NAMPT in the extracellular milieu compared to control (SCR). Taking advantage of this construct we explored *in vivo* the eNAMPT role in tumoural progression and neo-vessels formation by injecting BALB/c female mice. Given our results, to better investigate the role of eNAMPT on pericytes we started an *in vitro* characterization of this cell line taking as tools both the recombinant NAMPT and the eNAMPT neutralizing antibody (C269)[4]. We investigate the modulation of the pericyte's proteome, their migration potential, and their ability to interact with 4T1 cells to resemble *in vivo* conditions.

Results

The massive release of NAMPT in tumour microenvironment (SP-NAMPT) leads to a decrease in tumour progression accompanied by an increase of $CD31^+$ (endothelial) and $NG2^+$ (pericyte) cells confirmed by histochemical, cytofluorimetry and western blot analysis. Given that the literature only correlates endothelial cells with NAMPT we decided to investigate the pericyte counterpart. After having monitored eNAMPT levels in an immortalized line of

pericytes, we moved on one of the main important pathways for pericyte recruitment over the endothelium. We explored the PDGFR expression which increases after eNAMPT treatment and decreases with C269 administration. Since pericytes are able to release a high amount of NAMPT we decided to analyse the pericyte proteome following the treatment with C269. Our data show that the neutralization of NAMPT leads to several pathways' deregulation on pericyte proteome indicating a strong involvement of this protein in pericytes physiology. Finally, given the massive recruitment of pericytes in our *in vivo* model, we monitor if NAMPT could be a chemotactic signal for pericytes using migration assays and co-culture of 3D spheroids.

Conclusions

Our data indicate a correlation between NAMPT and pericytes. We show that eNAMPT may act as a chemotactic signalling for pericytes paving the way to investigate the mechanisms. The characterization of eNAMPT effects will improve not only the knowledge about this cytokine on vasculature and angiogenesis in general, but also in tumour progression, to eventually set up a parallel therapeutic strategy.

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Title

Cannabidiol modulates dynorphinergic and BDNF system alterations in the anterior cingulate cortex and hippocampus of neuropathic pain suffering rats

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Background

Chronic neuropathic pain is a complex experience characterized by maladaptive plasticity within neural networks involved both in pain processing as well as in the modulation of affective state and cognition[1]. In the last years, much evidence suggested that cognitive and affective states could affect pain perception and, in this respect, recent clinical and preclinical studies highlighted the potential role of cannabidiol (CBD) in the chronic neuropathic pain treatment. Indeed, the ability of the repeated administration of this molecule to produce analgesic and anxiolytic effects, probably through the activation of the 5HT1 and TRPV1 receptors, has been reported[2]. In addition, the role of the dynorphinergic system in pain-induced negative affect has been underlined[1,3] and, in this frame, an interaction between this opioid system and the brain derived neurotrophic factor (BDNF) has been also suggested[3].

Based on this evidence, the aim of this study was to investigate the effects of the repeated CBD administration on the CNS neurochemical alterations associated with chronic pain conditions.

Methods

To this end, male Wistar rats were subjected to the spared nerve injury (SNI) model of neuropathic pain and treated with CBD (5 mg/kg, s.c.) or vehicle for 7 days, starting from day 7 after surgery.

Fourteen days after surgery, animals were sacrificed, brain areas were collected and mRNA levels for prodynorphin (pDYN) and its receptor KOP as well as for BDNF and TrkB receptor were assessed in the anterior cingulate cortex (ACC) and in the hippocampus (HIPPO), by quantitative RT-PCR.

Results

Results showed that the repeated administration of a low dose of CBD was able to counteract the pDYN gene expression increase caused by SNI in the rat ACC, while it did not alter the BDNF and TrkB mRNA up-regulation induced by surgery, in the same area. In the HIPPO, the CBD treatment did not modify the pDYN mRNA decrease caused by SNI, while it was able to induce a significant up-regulation of BDNF and TrkB gene expression, thus highlighting the ability of CBD to facilitate neuroplastic mechanism in this brain area.

Conclusions

This study, together with previous behavioural results[2], underlined the potential therapeutic value of CBD in neuropathic pain. Indeed, these molecular results indicated that the repeated CBD treatment can be useful to revert some chronic pain-induced molecular alterations in the ACC, generally associated with the development of negative affective states. Moreover, the CBD ability to activate the pro-neurogenic BDNF system in the HIPPO, could improve the cognitive-emotional deficits related to chronic pain condition.

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