

THE MULTIFACETED ASPECTS OF STRESS

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SUMMARY

The effects of stress depend on the nature and duration of the exposure, with the triggering of molecular mechanisms that allow individuals to react to the stressful context. In particular, while acute stress induces the activation of circuits to ensure normal homeostasis and mediates adaptive responses, chronic stress exposure has detrimental and long-lasting effects on brain functions. Indeed, chronic stressful life events act as precipitating factors for many psychiatric conditions, including major depressive disorders. In this context, it is worthy of mention that there are differences in individual susceptibility, with some people displaying vulnerability to stressful events and others being resilient to the same adversities. Moreover, exposure to chronic adverse situations may leave permanent 'scars' in the individual, which confer enhanced vulnerability for relapse since it is possible that not all the systems impaired by chronic stress are restored during the remission.

On these bases, it is fundamental to better understand the behavioral outcomes of stressful events as well as the molecular changes that may sustain them for the discovery of novel therapeutic targets and approaches to treat stress-related disorders and to promote resilience.

Key words

Acute stress; chronic stress; resilience; HPA axis; Bdnf.

INTRODUCTION

Every day we are exposed to different types of stress that lead to specific biological effects based on the type and duration of the exposure. Dhabhar and McEwen in 1997 gave an integrated definition of stress, which may recapitulate the large amount of information available in the literature: "stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates physiological fight or flight systems in the body (stress response)" (1). The responses to behavioral and physio-

logical stressors can be either adaptive or maladaptive (2): while exposure to acute stressors induces adaptive reactions that help the organism to adapt efficiently to experiences in daily life, extreme stress conditions may lead to maladaptive outcomes, including psychopathologies.

Stress is the major environmental factor for the etiology of depression (3), which causes stable changes in gene expression, neural circuit function, and behavior, which may be maintained by epigenetic modification. Actually, the interaction with the genetic background

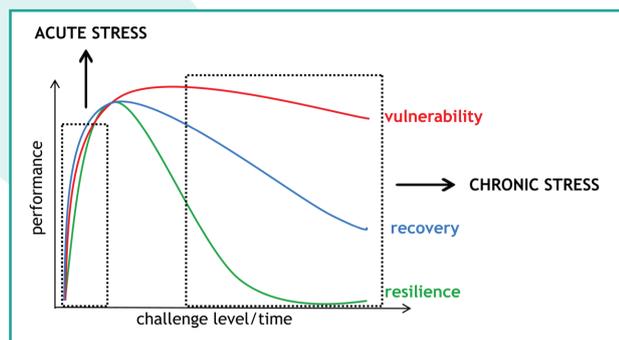


Figure 1. The different effects of stress exposure. Acute stress can have positive effects on the performance. Chronic stress can result in vulnerability (red line) or resilience (green line); moreover, the negative effects exerted by stress exposure may be recovered (blue line).

seems to be fundamental for the development of the disease, probably explaining the different responses to adverse events observed in humans, with some people displaying susceptibility and others resistance to maladaptive effects of stress. Indeed, by activating adaptive mechanisms, the brain has the ability to react to stressful changes, allowing continuous remodeling throughout the entire life (4) a concept known as resilience.

Moreover, the consequences of chronic stress exposure during adult life may have long-lasting effects or may be recovered, by the activation of dynamic processes to achieve a successful rescue (5). Nevertheless, a high percentage of depressed patients experience relapse after a period of recovery, suggesting that not all the systems impaired by stressful environmental factors are restored, thus representing scars of vulnerability, which in turn can promote the relapse to the pathology. On the opposite side, acute stress may have beneficial effects and increase the adaptive ability of the subjects to cope with stressors during life (figure 1).

To date, several attempts have been made to unravel the mechanisms underlying the different susceptibility to stress; however, we are still very far from fully clarifying the factors that draw the trajectory of the stress response. Accordingly, it is fundamental to

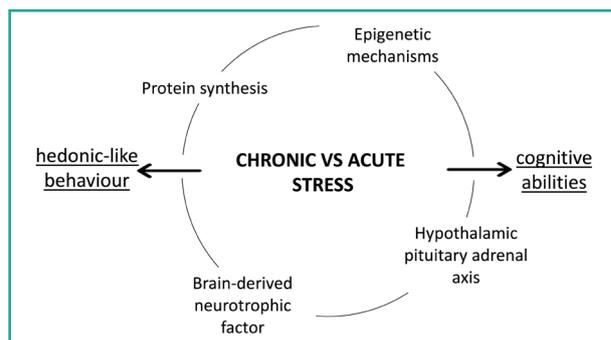


Figure 2. Molecular mechanisms investigated following chronic and acute stress exposure.

characterize the molecular alterations associated with the development of a pathological phenotype through preclinical studies. In particular, great interest is turned to animal models based on chronic exposure to stress protocols that are widely used to study the behavioral and neurobiological modifications that develop under these conditions, in the assumption that these may be a correlate of the human disorder.

In this review, I will summarize the main outcome of my Ph.D. thesis centered on the role of stress as a risk factor for psychiatric disorders as well as of beneficial challenge (short stressor) in improving a general performance (6-10) with the focus on different potential molecular mechanisms that may be responsible for stress consequences (figure 2).

MOLECULAR MECHANISMS UNDERLYING THE BEHAVIOURAL ALTERATIONS EXERTED BY STRESS EXPOSURE

Stress and local protein synthesis (6)

Alteration of synaptic plasticity has been related to depression and psychiatric disorders and an impairment of the regulation of the *de-novo* protein synthesis at synaptic levels has been associated with memory deficits (11).

One of the main mechanisms in protein synthesis-dependent memory is the signaling cascade associated with *de novo* protein synthesis linked with the mammalian target of rapamycin (mTOR) complex 1 and the eukaryotic initiation factor 2 (eIF2) (12, 13). Moreover, mTOR activation through NMDA receptors is also involved in peptide elongation, with the involvement of the eukaryotic elongation factor 2 (eEF2) and the translation of specific mRNAs.

By exposing animals to the chronic mild stress (CMS) paradigm, one of the main animal models, in the field, used to recreate the depressive-like behaviour in rodents (14), we demonstrated that exposure to 7 weeks of CMS induced the development of the anhedonic-like behaviour in around the 80% of stressed animals, while the remaining were resilient to the negative effects of stress. By contrast, when we looked at cognitive functions by testing the animals in the novel object recognition (NOR) test, we observed that independently from vulnerability and resilience, all the stressed animals show cognitive deficits in the NOR task, indicating that the mechanisms responsible for anhedonia are different from those related to cognitive impairment. Given the association between local protein synthesis and synaptic plasticity and memory, we observed that NMDA and mTOR activation following the NOR test in control animals led to newly synthesized protein at synaptic levels through the enhancement of the elongation factor 2 (eEF2), the factor that mediated the translation of specific mRNAs in the dorsal hippocampus (dHip), the subregion of the hippocampus mainly involved in cognition and spatial learning (15, 16). By contrast, the triggering of this intracellular signaling pathway was completely blunted in animals vulnerable to CMS, suggesting that deficits in these 'synaptic' mechanisms may indeed contribute to the cognitive impairment observed in stressed animals and highlighted a fundamental role of the elongation step of

the protein synthesis in the correct cognitive performance (6).

Stress and the hypothalamic-pituitary-adrenal (HPA) axis (7)

Psychiatric diseases are characterized by an altered function of the HPA axis (17, 18) that is deregulated in stress-related disorders, with a disruption of the feedback that leads to excessive activation of the axis.

Moreover, since a correct hormonal response is essential for learning and memory processes (19) alterations of this system may contribute to the development of cognitive deficits, debilitating symptoms of depression. Indeed, cognitive impairment may persist even when patients are successfully treated with antidepressants and remission is achieved, representing residual symptom that reduces everyday performance.

Glucocorticoids (GCs) act via genomic mechanisms, involving nuclear receptors, as well as via non-genomic pathways that require membrane-associated receptors.

In particular, the genomic action of glucocorticoid receptors (GRs) regulates the transcription of target genes that contain in the promoter the glucocorticoid responsive element (GRE), including genes playing a key role in synaptic plasticity and memory (20-22). Furthermore, in the non-genomic pathways, GCs can directly stimulate the release of excitatory amino acids, via the synaptic membrane-associated receptors, and can regulate mitochondrial oxidation and free radical formation through the binding with GRs on the mitochondrial membranes (4).

Thus, it is fundamental to investigate the changes occurring in the HPA axis following chronic stress and their potential involvement in the anhedonic phenotype as well as in the cognitive impairment that develops in animals vulnerable to stress exposure. Moreover, in the field of discovering potential mechanisms that may be critical for the ability to modulate different pathologic domains associated with psychiatric disorders, it should be critical

to study the effects of pharmacological treatments in counteracting the behavioral impairment due to chronic stress exposure and the possible role of the GRs in its effect.

The chronic administration with the antipsychotic drug lurasidone (LUR), high affinity antagonist of dopamine D_2 receptor, serotonin $5-HT_{2A}$ and $5-HT_7$ receptors, moderate affinity antagonist of adrenergic α_{2A} and α_{2C} and partial agonist of the HT_{1A} receptors, approved by the Food and Drug Administration for the treatment of different psychiatric conditions, normalized the anhedonic phenotype and reverted the cognitive deficits in the NOR test due to 7 weeks of CMS.

At molecular level, while the correct cognitive performance of non-stressed animals was associated with the GRs nuclear translocation and the subsequent transcription of glucocorticoid responsive genes in the dHip, we found that this mechanism was impaired in animals exposed to CMS, which showed cognitive deficits in the NOR test. Interestingly, the chronic treatment with the multimodal receptor antagonist LUR was able to normalize the alteration of the GR genomic signalling during the ongoing cognitive activity.

Regarding the non-genomic pathway, the membrane-bound receptors were increased by chronic stress, effect that may suggest alterations in synaptic mechanisms and in mitochondria functionality. In line, this effect was paralleled by increased levels of the active form of SYNAPSIN I, marker of the activity of GR at synaptic level, and by the enhancement of the expression of *Cox3*, one of the catalytic subunits of cytochrome c oxidase, the last enzyme. Interestingly, chronic lurasidone treatment was able to normalize the stress-induced alterations of the non-genomic mechanisms of GR.

These findings suggest that the activation of the genomic pathway mediated by GR may contribute to the correct cognitive performance, while chronic stress exposure inhibits this mechanism. Moreover, CMS, increasing the availability of membrane GR, seems to

direct preferentially the action of hormones more towards the non-genomic pathways, interfering with synaptic and mitochondrial signaling. At behavioral level, the anhedonic-like behavior and cognitive deficits may be related to both the altered genomic and non-genomic mechanism of GR and the dysregulations of these signaling in stressed rats might be indicative of the so-called "glucocorticoid resistant", a key feature of depressed patients.

Chronic lurasidone administration normalized the behavioral outcomes, induced by CMS exposure, by restoring the modification observed in the GR mediated effects, suggesting the potential ability of the drug in modulating dysfunction related to the HPA axis. These data provide new insights into the mechanism of action of lurasidone in modulating different pathologic domains associated with psychiatric disorders, as highlighted by the pro-cognitive effect we observed in the NOR task, which may be mediated by its intrinsic activity as antagonist of the serotonergic receptor $5HT_7$, important for learning and memory.

Stress and epigenetic mechanisms (9)

Epigenetics are mechanisms that in response to environmental stressors, both social and physical, can result in lasting changes that affect brain functions and neurobiological processes, including the neuroendocrine system (23), that in turn may contribute to develop psychiatric disorders.

They constitute important mechanisms by which transient stimuli can induce persistent changes in gene expression and in behavior (24, 25).

Moreover, many antidepressant drugs have been found to influence epigenetic processes, by acting as regulators of key mechanisms, thus exerting beneficial effects (26).

As mentioned, major depressive disorder (MDD) is associated with functional alterations of the HPA axis and fundamental players of the axis undergo changes in the methylation in the context of environmental adversities. Hence, we studied whether chronic stress

may cause alterations in the transcription of genes associated with GR, that are sustained by epigenetic modification, DNA methylation and miRNA expression in the prefrontal cortex (PFC), a brain region tightly connected with stress. In particular, we focused on the methylation status of the CGs located in the proximity of the glucocorticoid responsive element (GRE) sequences of selected genes named *Gadd45 β* , *Sgk1*, and *Gilz* to investigate the activity of GR as a transcription factor and the accessibility to its responsive element on the DNA. We explored the influence of the treatment with LUR in modulating the transcription of *Gadd45 β* , *Sgk1*, and *Gilz* possibly by acting at the epigenetic level and we studied the methylation status of these genes and the potential involvement of miRNA in chronic stress effects following a period of rest to explore whether the effects exerted by CMS were long-lasting.

We found that chronic stress altered *Gadd45 β* mRNA levels, and this transcriptional change was sustained by DNA methylation, effect still present after a period of rest from chronic stress, suggesting an enduring effect of the adverse manipulation. Interestingly, LUR administration reverted the stress-induced reduction of *Gadd45 β* expression and the changes in the DNA methylation status due to chronic stress exposure. Moreover, stress also had enduring effect on *Sgk1* methylation in the CGs of the GRE, independently from lurasidone administration and had negative effects on *Gilz* expression, both at the end of the stress procedure and following the rest period. Regarding miRNA, we observed that only the miR-143-3p of *Gilz* was still reduced after a period of wash-out from chronic stress.

All in all, these data highlight that chronic stress exposure results in persistent changes in DNA methylation in specific genes related to glucocorticoids signalling and that lurasidone act as a modifier of such mechanisms, suggesting its potential as modulator of the HPA axis that is compromised in different psychiatric disorders.

Stress and Brain derived neurotrophic factor (Bdnf): chronic (10) vs acute (8) exposure

As mentioned in the introduction, chronic stress exposure during adult life may have an adverse impact on the long-term course of MDD and it may increase the response to subsequent stressors, such as acute challenges. Indeed, it is possible that the impairment caused by stress exposure cannot be completely restored during the remission, thus leaving 'scars' of vulnerability that may facilitate the relapse to the pathology. Indeed, being depression considered a recurrent disorder, approximately 50% of patients affected by MDD experience relapse despite pharmacological treatments (27), indicating the importance of studying how long-term pharmacological treatments properly manage the chronic course of the pathology.

From the opposite side, acute stress may induce beneficial advantages, in a short-term, by activating protective functions or by preparing the organism to react with external demands. Furthermore, when the stress is short, it can have positive effects on memory and even be fundamental for good learning (28).

In the context of both negative and positive effects of exposure to chronic and acute stress exposure respectively, Bdnf plays a crucial role. Indeed, one of the main hypotheses regarding the pathogenesis of depression proposes a role for neurotrophic factors in the etiology of depression and its treatment, with Bdnf playing a pivotal role (29) and the detrimental effect of chronic stress on Bdnf in animal models of depression is well consolidated (30, 31).

Moreover, considering the positive effects of brief stressors in the activation of protective brain functions, the relationship between acute stress response and neuroplasticity is well-established (31).

In this context, starting from the negative effect of stress, despite the widely described outcomes of chronic stress exposure as main environmental factor able to induce depressive phenotype in rodents, limited information

is available on the long-lasting impact of stress as well as on the mechanisms that may promote or prevent relapse.

Hence, we investigated whether stress-induced changes may persist after a recovery period and if alterations in BDNF signalling may underlie the precipitation of a recurrent episode. To this purpose, after a period of rest from chronic stress, the animals were presented to an acute immobilization stress. We found that chronic stress induces prolonged molecular changes that impair the activation of BDNF signaling following a subsequent acute stressor and inhibit the ability of PFC to cope with an acute challenge. We observed an inhibition of the proper response of the HPA axis to the acute stressor in animals previously chronically stressed, whereas the activation of the immediate early genes *Arc* and *C-fos*, and of the early response gene *Gadd45 β* was preserved following the acute stress, despite a reduction of their expression following chronic stress exposure, suggesting that PFC preserves functional plasticity after the post-stress period.

With respect to neuroplastic mechanisms, we demonstrated that the acute challenge upregulated mBDNF and its receptor TRKB protein levels in non-stressed animals, whereas these modulations were completely blunted in rats previously exposed to chronic stress. The effects observed in stressed animals were reflected by the blunted induction of BDNF-TRKB intracellular-related pathways. The inability to activate BDNF cascades in response to acute stress in previously stressed rats suggested that the BDNF stress-induced changes were not completely recovered despite the period of washout and that some molecular scars, which inhibit the recruitment of the adaptive mechanisms activated in "healthy" subjects, are still present (10).

Concerning the adaptive effect of stress, we found that one hour of acute restraint stress led to an enhancement of total *Bdnf* mRNA levels and of its major transcript in the PFC at different time points following the challenge. Accordingly, we observed a positive

effect of the acute stress also on markers of neuronal activity, *Arc*, *Gadd45b* and *Nr4a1*, genes rapidly activated following acute environmental stimulations (32) and involved in brain functions including learning and memory (33). These results indicated that short stressors may trigger the modulation of neuroplastic mechanisms mainly within the PFC, thus contributing to store information that could serve to set up a response to a new stimulus including a cognitive task.

Moreover, at behavioural level, we demonstrated that exposure to the acute restraint stress improved cognitive function in the NOR task with a specific temporal profile, in particular in the time frame of one hour following the acute challenge, indicating the positive and beneficial effect of short stressor on cognitive abilities. In line, several studies showed that stress, in close association with learning task, facilitated memory consolidation (34).

At molecular level, this enhancement in the cognitive performance was associated with an increased expression of *Bdnf* in the prefrontal cortex, suggesting that the acute stress may transiently affect neuroplastic mechanisms, in line with the notion that neurotrophic factors are implicated in long-term potentiation and that stress may modify cognitive function through the control of *Bdnf* (35).

CONCLUSIONS

Studying the multifaceted effects of stress at adulthood provide evidence about the consequences of both negative and positive outcome on the adult brain. The analysis of several molecular mechanisms that may contribute to different aspects of stress exposure, from vulnerability to resilience (6, 7, 36, 37), from the recovery to relapse (9, 10) following chronic stressors and about acute stressor (8), is crucial to increase the knowledge to the field of pharmacological research for searching novel targets and approaches for the treatment of depression and stress-related disorders as well as for the promotion of resilience.

ETHICS

Fundings

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Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contributions

PB prepared and edited the manuscript, which was an overview of the literature of the experimental data obtained during the PhD training (2015-2018).

Availability of data and materials

No new data were generated or analysed in this research.

Ethical approval

N/A

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