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To cite this version:

Freddy Jeanneteau, Amélie Borie, Moses Chao, Michael J Garabedian. Bridging the Gap between Brain-Derived Neurotrophic Factor and Glucocorticoid Effects on Brain Networks. Neuroendocrinology, 2018, 10.1159/000496392 . hal-02368008

HAL Id: hal-02368008

https://hal.science/hal-02368008v1

Submitted on 21 Nov 2019

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Bridging the gap between BDNF and glucocorticoid effects on brain networks

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Keywords: stress; connectivity, salience network, action control, depression

Short title: Complementary roles of glucocorticoids and BDNF in the mesocorticolimbic system

ABSTRACT

Behavioral choices made by the brain during stress depend on glucocorticoid and BDNF signaling pathways acting in synchrony in the mesolimbic (reward) and corticolimbic (emotion) neural networks. Deregulated expression of BDNF and glucocorticoid receptors in brain valuation areas may compromise integration of signals. Glucocorticoid receptor phosphorylation upon BDNF signaling in neurons represents one mechanism underlying the integration of BDNF and glucocorticoid signals that when off balance may lay the foundation of maladaptations to stress. Here, we propose that BDNF signaling conditions glucocorticoid responses impacting neural plasticity in the mesocorticolimbic system. This provides a novel molecular framework for understanding how brain networks use BDNF and glucocorticoid signaling contingencies to forge receptive neuronal fields in temporal domains defined by behavioral experience, and in mood disorders.

Introduction

Cooperation between the mesolimbic and corticolimbic systems determines behavioral choices

Brain region-specific effects of BDNF and glucocorticoids on the mesocorticolimbic system

Bridging the gaps between BDNF and glucocorticoid effects in the mesocorticolimbic system

GR phosphorylation is influenced by BDNF signaling

Effect of BDNF and glucocorticoid signaling in health and disease

Summary

References

INTRODUCTION

Stress coping is paramount for survival in most species including humans (1). The neuro-endocrine stress response interacts with neuronal circuitry to select suitable behavioral strategies based on outcomes (2, 3). Processing of information in face of ongoing and future behavioral demands is crucial for maintaining health (4, 5). Therefore, it is essential that during stress the appropriate molecular mechanisms be engaged to promote vigilance, learning and adaptation (6, 7). What happens when this selection of actions goes awry? Cognitive distortions may result when integration of positive and negative events are devalued (8). Therefore, it is important to understand how the brain neural circuitry confronts the values of upcoming and previous actions (9). Growing evidence indicates that abnormal feedback sensitivity between various corticostriatal loops and the reward system could be associated with the occurrence of depressive episodes (8).

In this mini-review, we briefly describe the contributions of the mesolimbic dopaminergic and corticolimbic glutamatergic systems to the stress response. We describe the molecular mediators, signaling pathways and neuroanatomic feature that foster the adaptive and maladaptive response to stress. We also apply these concepts to how individuals respond and discuss clinical implications.

Cooperation between the mesolimbic and corticolimbic systems determines behavioral choices

The mesocorticolimbic system plays important roles in emotional and cognitive functions of the human and rodent brains. Disturbances in this system are associated with drug abuses, depression and autism (10, 11). While the mesolimbic system is involved in reward processes, the corticolimbic system mediates attention and cognitive processes. Both systems are interconnected at the ventral tegmental area (VTA), neocortical areas (e.g. PFC, hippocampus) and subcortical limbic areas including the nucleus accumbens (Nac) and the basolateral amygdala (BLA) (Figure-1). The

Nac serves as the interface between the limbic and motor regions to bring about motivation and selection of behavioral actions based on incentive stimuli (3). Beyond this core of motivationally salient neuronal network, additional regions like the insula, the orbitofrontal cortex, the septum, the extended amygdala and the hypothalamus code for the differential valence of stimuli (*e.g.* appetitive or aversive) via circuit-specific neuromodulators (*e.g.* CRF, catecholamines, vasopressin, oxytocin) and uses this information to select actions based on outcome (12).

The synchrony of mesolimbic and corticolimbic networks permits value-based learning (3). The mesocorticolimbic network uses a reward-prediction error system to calculate the costs versus benefits of future actions based on their consequences (13). The uncertainty associated with the novelty and unpredictability of a situation produces correlated activities of the anterior cingulate cortex (ACC) and the amygdala, which projects to (i) the locus coeruleus (LC) to control vigilance via the noradrenaline pathway, and to (ii) the hypothalamus to control the cost of actions through the hypothalamo-pituitary-adrenal (HPA) and glucocorticoid axis (2). The stress response has an adaptive function through glucocorticoids that is complementary to the reward-prediction error response of the mesocorticolimbic system as it facilitates vigilance, learning and adaptation (14). Noradrenaline increases neurotransmission of a "vigilant state" at cortical and amygdala synapses, which glucocorticoids can tune by modifying synaptic plasticity (e.g. LTP, LTD) to trigger adaptation. Glucocorticoids can also promote learning by facilitating new synapse formation and maintenance in face of behavioral demands (15-18). It is noteworthy that stress employs predictive coding through the interplay of mesolimbic and corticolimbic systems to reduce the uncertainty about selection of actions based on consequences.

Brain region-specific effects of BDNF and glucocorticoids on the mesocorticolimbic system

Functional alteration within the circuits of the mesocorticolimbic system or their connectivity could account for changes in behavior. This is influenced by environmental factors, and interactions among areas of the brain during developmental domains as well as in the course of ageing. Glucocorticoids and neurotrophins are well-established factors that contribute to the establishment, maintenance and remodeling of neuronal connections, which can be altered by environmental factors with lasting consequences (19, 20). According to the stress hypothesis of depression, the stress-induced glucocorticoid response conditions neuroplasticity mediated by the brain-derived neurotrophic factor (BDNF) (21). Excessive level of glucocorticoids or stress suppresses BDNF-mediated neuroplasticity in the corticolimbic pathway, which processes emotional experiences, while it bolsters BDNF-mediated neuroplasticity in the mesolimbic system, which manages reward pathways (22, 23). The rationale for this hypothesis relies on epigenetic, transcriptomic and proteomic regulation of BDNF expression in rodent models and human tissues (24-26). The consensus view is that expression of BDNF and/or its receptor TrkB is diminished in the corticolimbic system (mostly prefrontal cortex and hippocampus) whereas BDNF is upregulated in the mesolimbic system (mostly nucleus accumbens, amygdala, VTA) long after cessation to stressor exposure in animal models and in postmortem human brains (27-31). A reduction of BDNF/TrkB signaling in the corticolimbic areas of the brain is associated with synaptic loss, decreased neuronal plasticity and regressing network connectivity, while an elevation of BDNF/TrkB signaling in the mesolimbic areas of the brain is associated with synaptic growth, increased neuronal plasticity and expanding network connectivity (32-37). TrkB agonists in corticolimbic areas and TrkB antagonists in the mesolimbic areas reversed the consequences of chronic stress and depressive-like behaviors (Figure-2) (28, 38).

Typically, BDNF exerts positive effects on neural plasticity in cortical synapses and in striatal synapses (39, 40). In Nac synapses for instance, TrkB activated by VTA-derived BDNF, can sensitize

reward-seeking behavior and can facilitate social defeat stress (23, 41, 42). In other words, the BDNF/TrkB signaling can escalate behavioral sensitization to social stress and drug abuse by increasing the plasticity of VTA-Nac synapses. In fact, sensitization of Nac synapses is triggered by stress neuromodulators (e.g. CRF, glucocorticoids) that control secretion and signaling of VTA-derived BDNF (43, 44).

Bridging the gap between BDNF and glucocorticoid effects in the mesocorticolimbic system

The difference between mesolimbic and corticolimbic systems seems difficult to explain if considering only the modulation of BDNF by glucocorticoids. Perhaps, cellular reactions to glucocorticoids are also altered by BDNF signaling such that differential responses to TrkB agonists and antagonists in the mesolimbic and corticolimbic systems could be mediated via a glucocorticoid-dependent signaling route. As for the modulations of BDNF/TrkB, manipulating glucocorticoid receptors (GR) revealed contrasting results between the mesolimbic and corticolimbic pathways. On one hand, GR antagonists impeded stress-induced sensitization of the mesolimbic pathway but on the other hand, GR agonists prevented behavioral vulnerability to stress in corticolimbic areas (45-47). This reflects decreased GR expression in prefrontal cortex and hippocampus, and increased GR expression in the amygdala upon stress (48-51). Epigenetic reprogramming sets the stage for changes in GR expression associated with significant risk of depression and suicide (52, 53). This is evident in early life trauma where GR expression changes appear to be stable and persist even after stress is alleviated. By contrast, alterations in GR expression in the adult brain upon stress are not stable after cessation of stress, making it unlikely to be responsible for chronic depression in the adult (54).

What might be responsible for persistent changes in GR responses in the adult brain under chronic stress? It is speculated that alterations of GR activity, rather than its expression, can persist long after chronic stress in the adult brain. Consistently, GR activity is sensitized in the mesolimbic

areas of the adult brain while it is desensitized in the corticolimbic areas after stress (55, 56). A long-lasting loss of GR responsiveness consistent with glucocorticoid resistance in the corticolimbic pathway was monitored in peripheral blood cells of patients with major depressive disorders (57). When stable overtime, the normalization of GR functions correlates with relief of depressive symptoms after antidepressant therapies (58). However, relapse is common, associated with a lack of restoration of stable glucocorticoid sensitivity and efficacy (55, 59).

GR phosphorylation is influenced by BDNF signaling

Given that activation of TrkB responds to antidepressant drugs and that it is required for antidepressant-induced behavioral effects (60), it is possible that BDNF/TrkB signaling could condition GR responses (20). Pairing of BDNF and glucocorticoid signaling result in GR phosphorylation in the N-terminal transactivation domain at residues Ser155 and Ser287 (Ser134 and S267 in humans) that serve as docking sites for co-factors of signaling (61). Changes of GR phosphorylation impact GR-mediated transcription and neuronal plasticity. If GR is not phosphorylated on these sites, this results in a distinct GR genomic response and alteration in neuronal plasticity (62). Thus, it appears that the GR phosphorylation "code" is modified by BDNF signaling (Figure-3). Such glucocorticoid-independent protein modification provides cell- and signal-specific responses to GR signaling (63). These findings provide insight into the molecular basis of stress-induced neuroadaptations in the mesocorticolimbic circuitry and perhaps in other tissues. For instance, effects of BDNF signaling on GR are possible not only in brain but also in peripheral tissues given that BDNF is present in blood at high levels(64).

Effect of BDNF and glucocorticoid signaling in health and disease

Complementary actions of glucocorticoids and BDNF have important influence on behavior.

Both signaling pathways are required to produce actions based on consequences, to form new memories of contextual fear, and to cope with stress (31, 65-67). Given that glucocorticoids can readily access neurons in brain and BDNF is secreted in an activity-dependent fashion by neuronal networks responding to behavioral experience, it is likely that neuronal networks with ongoing BDNF signaling give rise to a unique GR response via changes in the GR phosphorylation "code" and alterations of the GR genomic response in a cell-type specific manner (63). This could explain differential modulation of GR activity in mesolimbic and corticolimbic networks. Deletion of GR phosphorylation sites in neurons belonging to corticolimbic brain areas interferes with the expression of GR-regulated target genes involved in cytoskeleton dynamics, mitochondrial functions, synapse formation and maintenance (62, 68, 69). What's more, BDNF-dependent GR phosphorylation sites reside near a caspase-1 site, whose cleavage causes partial loss of GR transcriptional activity in animal models and a disease of glucocorticoid resistance in humans (70, 71). Therefore, BDNF represents a conditioning factor that directs glucocorticoid responses through GR phosphorylation in the body including the mesolimbic and corticolimbic pathways that may lay the foundation for vulnerability or resiliency to stress maladaptations (60, 72). This notion is consistent with the theory of general adaptation syndrome whereby a normally well-tolerated degree of stress can become pathogenic if the glucocorticoid response to stressors is inappropriate in face of conditioning signals (*e.g.* BDNF, genetic and environmental factors…) (73). Therefore, deregulation of BDNF expression could compromise GR-directed glucocorticoid responses with consequences on neuronal networks and behaviors. This could explain why some individuals are more vulnerable than others to diseases of adaptation (e.g. mood disorders including depression) despite similar stressful experiences (74, 75). With this in mind, it is interesting that humans and rodents harboring the BDNF-Met66 genetic variant that suppresses activity-dependent secretion of BDNF, present with impaired reactivity to stressors and predisposition to depression (76-78).

Individuals differ in their responses to stress and drug sensitization (79-81). Whereas resiliency promotes value-based decision-making, stress devalues salient emotional stimuli (13, 14). Stress coping styles may differ depending on neuroadaptations in brain regions that mediate actions that control emotional valence (corticolimbic system) and salience (mesolimbic system) (82). For example, activation of CRF neurons controls BDNF secretion at VTA-Nac synapses in the animals that are vulnerable to social defeat stress (43). In this paradigm, vulnerability to stress required TrkB at Nac synapses whereas VTA-derived dopamine was dispensable (23). Stress-induced HPA axis activation is often elevated in those that respond highly to stress, whereas strategies to blunt such HPA hyperactivation could promote resilience (59, 83). Stress response required glucocorticoid receptors to increase the AMPA/NMDA ratio at VTA synapses, resulting in enhanced activation of glutamatergic synapses measured 24 hours later (44). The correct combination of glucocorticoid and BDNF signaling could delineate resiliency from vulnerability, and be mediated through BDNF-dependent GR phosphorylation. If true, then controlling stress exposure could provide vulnerable individuals with the coping skills to ameliorate a variety of phobia and post-traumatic memories (84).

SUMMARY

Proper maintenance of the balance between the corticolimbic and mesolimbic neural networks ensures behavioral choices that are commensurate with the costs and benefits of contextual demands (85). Integration of positive and negative events over time can induce mood fluctuations. For example, lack of motivation and inflexible maladaptive responses result when prefrontal BDNF-TrkB signaling is compromised and GR-mediated responses are desensitized. On the contrary, sensitization to rewarding or aversive conditioning result when mesolimbic BDNF-TrkB signaling is upregulated and GR-mediated responses are bolstered. Desynchronization of BDNF-TrkB and glucocorticoid-GR signaling pathways, in multiple neural networks, through alteration in the GR

phosphorylation "code", could explain how decisions are influenced and maladapted in stress-induced mood disorders. More studies are needed to characterize the relative contribution of the distinct neural circuits controlling risk/reward-seeking actions, their connectivity, their neuromodulators (e.g. oxytocin, vasopressin, catecholamine), and their interaction with genetic and environmental factors.

ACKNOWLEDGEMENTS

We thank the Fondation pour la Recherche Médicale (F.J, A.B.) and the National Institute of Health (M.J.G, M.V.C, F.J.). The authors declare no conflicts of interest.

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FIGURES AND LEGENDS

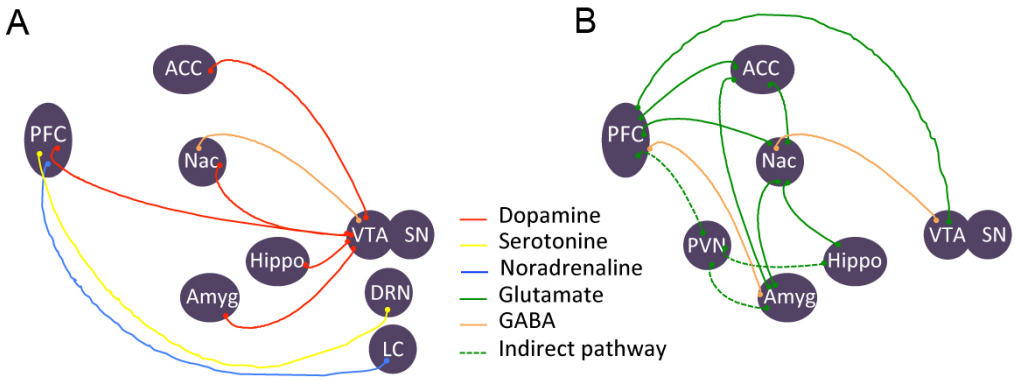


Figure-1 Schematic representation of the (A) mesolimbic and (B) corticolimbic networks. The core VTA-Nac-PFC dopaminergic pathway processes rewarding functions. The dopaminoceptive neocortical regions reciprocally project glutamatergic neurons to the Nac and VTA to control emotions and to the hypothalamus and amygdala to prepare for novelty via stress-controlled hypothalamic neurons. VTA: ventral tegmental area, SN: Substantia nigra, DRN: Dorsal raphe nucleus, LC: locus coeruleus, Hippo: hippocampus, Amyg: Amygdala, PVN: hypothalamic paraventricular nucleus, Nac: Nucleus accumbens, Acc: Anterior cingulate cortex, PFC: prefrontal cortex

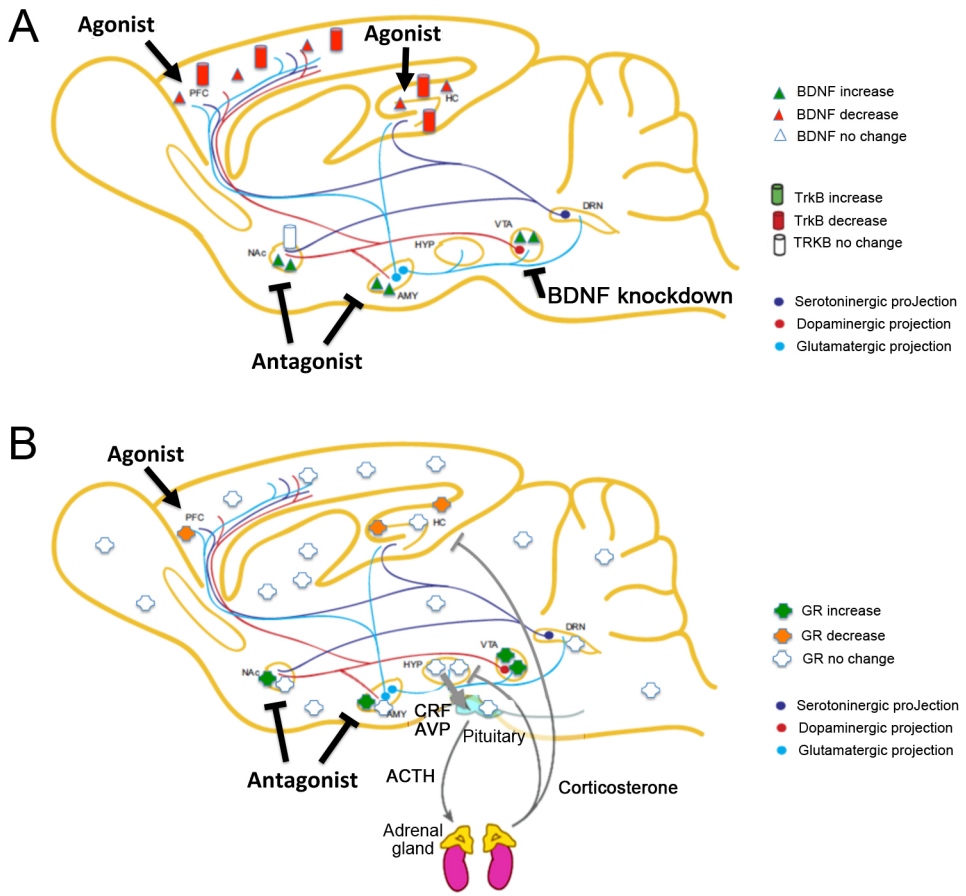
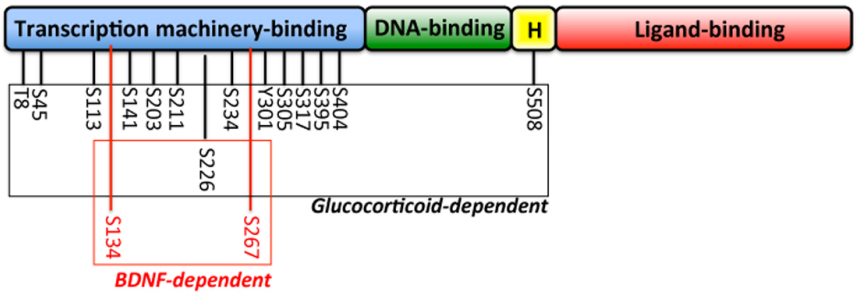


Figure-2 Expression of BDNF, TrkB and GR in mesocorticolimbic areas of the stressed brain adapted from (30). (A) Levels of BDNF-TrkB may decrease in brain areas of the corticolimbic pathway but increase in areas of the mesolimbic pathway. TrkB agonists (7,8 DHF) injected in prefrontal cortex (PFC) and TrkB antagonists (ANA-12) injected in the nucleus accumbens (NAc) can ameliorate stress-induced depressive phenotype. (B) Levels of GR may decrease in brain areas of the corticolimbic pathway but increase in areas of the mesolimbic pathway. GR agonist (corticosterone) injected in PFC and GR antagonists (RU486) injected in NAc or amygdala (AMY) can ameliorate stress-induced depressive phenotype. GR expression is relatively stable in the adult stressed brain, notably in regions controlling the secretion of ACTH and glucocorticoids in bloodstream. The hypothalamic-pituitary-adrenal (HPA) axis consists of stress-controlled CRF and AVP hypothalamic neurons that integrate excitatory stimuli from brainstem and inhibitory signals from cortical/subcortical areas into appropriate ACTH and glucocorticoid responses by the pituitary and adrenal glands, respectively. HC: hippocampus, DRN: dorsal raphe nucleus, HYP: hypothalamus, VTA: Ventral tegmental area, ACTH: Adrenocorticotropic hormone, CRF: corticotropin-releasing factor, AVP: Arginine-vasopressin.



Human	Rat	Mouse	Consensus	Kinase	Effector
S134	**S155**	**S152**	**R-S-T-S(p)-V/R-P-E**	Erk/JNK P38/AKT1 CDK5	14-3-3 PELP1 CREB1
S203	S224	S212	S(p)-X-R/K	CDK	GRIP1
S211	S232	S220	S(p)-X-R/K	CDK/p38	GRIP1
S226	**S246**	**S234**	**non-polar-X-S(p)-P**	JNK	GRIP1
S267	**S287**	**S284**	**L-S-S(p)-P-S-N/S**	Erk/JNK	CREB1

Figure -3 The GR phosphorylation code.

Phosphorylation of the transactivation domain and hinge region (H) at multiple sites conserved interspecies specifies co-factor recruitment for target gene expression. Most sites are dependent on glucocorticoid-binding but others respond to BDNF-TrkB signaling. Figure adapted from (63, 86-88).