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Editorial

The Response of Glucocorticoids to Stress and Functional Alteration of Brain-Derived Neurotrophic Factor

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EDITORIAL

Glucocorticoids (GCs) are released from the adrenal cortex through activation of the hypothalamic-pituitary-adrenal (HPA) axis when stimulated by stressful conditions, and exert important functions, including an increase in plasma glucose levels and upregulation of anti-inflammatory mechanisms. It is suggested that chronic and excessive stress causes an increase in plasma GCs concentration which negatively affects brain function. Stress-induced elevations in GCs have been speculated to contribute to the pathophysiology of depression. GCs can act on two types of receptors: the mineralocorticoid receptor (MR; high affinity for GCs) and glucocorticoid receptor (GR; low affinity). Taking this into consideration, it is possible that high levels of GCs impact the central nervous system (CNS) through a GR-mediated mechanism. It is well known that the GR acts as a transcriptional factor and regulates expression of various genes [1]. However, recent evidence suggests that the GR influences neuronal functions through both genomic- and/or non-genomic mechanisms in which *de novo* gene expression is not involved [2].

Brain-derived neurotrophic factor (BDNF) is also implicated in depressive disorders. BDNF has multiple neural roles such as cell differentiation, cell survival, neurotransmitter release, and synaptic plasticity. BDNF binds to TrkB, a high affinity receptor for BDNF, and maintains neuronal viability and synaptic function by activating extracellular signal-regulated kinase (ERK), phospholipase C-gamma, and phosphoinositide-3kinase signaling. Interestingly, a close relationship between decreased expression of BDNF and the pathophysiology of mental disorders such as depression has been suggested [3]. Since neuronal production and secretion of BDNF is regulated by a neuronal activity-dependent mechanism [4], it remains to be seen whether BDNF downregulation is a cause, or a consequence of depressive disorder.

Moreover, there is a possible link between BDNF function and stress-induced release of GCs in neurons. BDNF plays an important role in CNS development by increasing synaptic protein expression. Interestingly, we found that GCs exposure negatively influences BDNF-mediated increases in synaptic maturation via suppressing ERK signaling [5]. In addition, BDNF is well known to be a positive neurotransmission regulator in the adult CNS. In our cultured cortical neurons, GCs exposure suppressed glutamate release, one of the excitatory neurotransmitters in CNS neurons that are stimulated by BDNF [6]. It is possible that such inhibition of BDNF-mediated synaptic function due to increased GCs causes a downregulation of BDNF expression, resulting in the onset of depression, though further study is required to clarify the molecular mechanism underlying GCs role in intracellular signaling.

It has been established that levels of plasma GCs show an oscillatory change due to the pulsatile activity of the HPA axis [7]. An alteration in dynamic GCs oscillation in response to stressful conditions remains an interesting topic requiring further investigation. Contrasting BDNF expression levels were found in the amygdala and hippocampus following immobilization stress, where elevated levels were found in the amygdala and decreased levels in the hippocampus [8]. As mentioned above, GCs action is complex (acute vs. chronic, dependency of receptors, genomic vs. non-genomic, and concentration dynamics), and BDNF function is likely affected by GCs stress in a region-specific manner. Ultimately, more useful *in vitro* and animal models are needed for further investigation of molecular mechanisms of depression. Therefore, detailed profiling (i. e. , region specificity and time course) is required to establish a useful model for depression.

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