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The Glucocorticoid Hypothesis of Depression: History and Prospects

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Abstract—An abnormality in adaptation to negative life events is considered as one of the main causes of the development of depressive symptoms. According to the corticosteroid receptor hypothesis of depression, stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the induction of psycho-emotional disturbances. The end products of this axis, glucocorticoids, are involved in the formation of many physiological and behavioral responses to stress. Although the increase in hormone levels following a short-term intervention is directed towards rapid mobilization of the body's efforts for overcoming a potentially dangerous situation, long-term exposure to stress or glucocorticoids may have negative consequences for the mood and behavior. With respect to the mechanisms of the changing effects of glucocorticoids from protective to damaging, glucocorticoid receptors (GRs) have received the most attention. These receptors are widely expressed in the brain. They are important regulators of the transcriptional activities of numerous genes, including the gene for a plasticity-related protein such as the brain-derived neurotrophic factor (BDNF), which has been implicated in psychiatric disorders. In addition to the direct effects on gene transcription, changes in the expression of the GRs themselves resulting from stress and/or glucocorticoid effects can in turn modify the functional responses to the subsequent stimuli. The purpose of this review was to analyze the available published data on the effects of stress and glucocorticoids on the expression of GRs in the hippocampus, which is traditionally considered as the most sensitive to stress brain structure. The review also addresses the implication of the interplay of GRs and BDNF in the pathogenesis of stress-related disorders.

Keywords: stress, glucocorticoid receptors, BDNF

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Despite the distribution of depression and its negative consequences in social life, the mechanisms of its development to a significant extent remain unclear, thus restraining the directed search for targets to develop effective pharmaceuticals. The solution of this problem is complicated by the numerous pathways involved in the induction of psycho-emotional impairments, as well as in the resistance to this induction, which finally masks the real impact of a distinct system or factor in disease pathophysiology. The negative conditions of life (including the death of relatives, divorce, abjection or defeat, unemployment, and deterioration of the financial state) are considered to be a serious risk factor for developing depression (Post, 1992; Kendler et al., 1999; van Praag, 2004; Larkin et al., 2012). Despite the extensive adaptive possibilities of the organism, which make it possible to overcome exposure to even severe stressors without any psycho-emotional consequences in the majority of individuals, stress-sensitive adults with specific sensitivity to depression caused by unfavorable environmental conditions at the early stages in ontogenesis might respond by depressive episodes on the negative life conditions. The meta-analysis of the data obtained from a sample consisting of 14 250 individuals confirmed a significant interrelation between depression and stressful life events (Risch et al., 2009).

The increased level of glucocorticoids caused by stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis is considered to be one of the most important factors providing depressive symptoms among different stress-induced changes in the organism. This widely accepted point of view was confirmed by the observation of depressive episodes as side effects of an increased level of glucocorticoids in patients with Cushing's disease (Kelly et al., 1983; Sonino et al., 1998) or accompanying hormonal therapy (Brown et al., 2007). According to such observations in human, rodents' treatment with corticosterone resulted in similar depressive-like behavioral modifications (Sterner and Kalynchuk, 2010). The most significant argument toward the hypothesis of an

interrelation between an increased cortisol level and affective disorders includes the well-known association of depressive-spectrum disorders and HPA axis hyperactivation (Gibbons, 1964; Holsboer and Barden, 1996; Pariante, 2003; de Kloet et al., 2007; Mondelli et al., 2010; Saveanu and Nemeroff, 2012; Herbert, 2013). Moreover, inhibitors of glucocorticoid synthesis have been actively propagated for several years as effective antidepressants (Jahn et al., 2004; Kling et al., 2009).

At the same time, together with the data reporting the association of glucocorticoids and an increased liability to psychopathology, an enhanced hormonal level appears to be highly important to provide an adaptive response to stressors, including behavioral ones (Oitzl et al., 2010; Putman and Roelofs, 2011). The data demonstrating the opposite effect of glucocorticoids on depressive-like behavior in animals depending on duration have been increasingly accumulated. For instance, the daily corticosterone exposure of male mice for 6 days resulted in antidepressant effects, whereas its exposure for 18 or 36 days had an insignificant prodepressant effect (Zhao et al., 2009). Moreover, glucocorticoids, which suppress neurogenesis in the hippocampus (Gould and Tanapat, 1999; Kim et al., 2004; Mayer et al., 2006), are directly involved in the etiology of depression (Snyder et al., 2011; Lehmann et al., 2013) and might also demonstrate neurotrophic activity in this brain region (Gray et al., 2013). An increasing amount of evidence of the association between a high glucocorticoid level and the antidepressant phenotype has been accumulated (Barbier and Wang, 2009; Xu et al., 2009).

The Role of Glucocorticoid Receptors in the Pathophysiology of Stress-Induced Depression

The simple association of an increased glucocorticoid level and the development of depression appears to be complicated by the involvement of different types of corticosteroid receptors, including mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the action of hormones (Reul and de Kloet, 1985). Some behavioral effects of MRs and GRs appeared to be specifically dependent on the brain region and even the opposite (Harris et al., 2013). MRs with high affinity to glucocorticoids are considered to be completely occupied by them even at the basal hormonal level, whereas the occupation of GRs requires an increased hormonal level in blood comparable to the stressor-induced one (de Kloet et al., 1993). These peculiarities have historically resulted in more attention being paid to GRs that predominantly regulate the stressor effects of glucocorticoids.

A diminished function and/or GR expression is considered to be responsible for the hyperactivation of the HPA axis observed in patients with depression (Holsboer, 2000; Pariante and Miller, 2001). Disturbance in the negative feedback mechanism in the HPA axis in the dexamethasone test is observed in about 50% of depressed patients. The hippocampus, prefrontal cortex, and hypothalamus are considered to be the brain structures mostly involved in the development of depression among those with a decreased GR expression.

Multiple studies demonstrated the role of stress and glucocorticoids in the modification of the GR expression in the brain (Sapolsky and McEwen, 1985; Reul et al., 1989; Fujikawa et al., 2000; Paskitti et al., 2000; Karandrea et al., 2002; Zhou et al., 2008; Wang et al., 2012; Shishkina et al., 2015). However, the reported changes appeared to be contradictory and could even depend on sex (Karandrea et al., 2002). The factors determining the character of the GRs' response to stress and glucocorticoids might include the time of detecting their expression after the beginning of exposure, which was shown by the Japanese group (Fujikawa et al., 2000). The GR mRNA level explored in this study in the rat dentate gyrus of the hippocampus at different time periods from the beginning of acute stressor exposure was significantly decreased at the beginning of the stressor's exposure (by 41% after 30 min), but was significantly increased 2 h after the exposure. The response of GRs might also depend on the organism's vulnerability to stress-induced depressive-like behavior. For instance, it was suggested that stress represented the highest effect on the development of psychopathology at early stages of ontogenesis due to its effect on the subsequent susceptibility to the disease in adulthood, especially in the case of additional negative conditions. The model experiments reported the changes in the character of the GR response to stress in adults. Namely, mature rat males, which were subjected to the stressful procedure of being deprived of their mother within three weeks after birth, demonstrated a chronic stress-induced significant decrease in GR-immune reactivity in the CA1 region of the hippocampus. In contrast to these results, the chronic stress caused increased GR-immune reactivity in the CA1 region in adult control animals, which had no history of maternal deprivation (Trujillo et al., 2016). The duration of stress action might also significantly affect the GR response to chronic stress. The receptors' immune reactivity was decreased in the dorsal hippocampus in rats after stress caused by the exposure to an elevated open platform within 5 days, but increased after 20 days of exposure (Robertson et al., 2005). The nature of stressors also appears to be important for the response. For instance, whether 4-week stress representing limited activity due to water dipping caused an increased GR expression in the rat hippocampus (Mizoguchi et al., 2003); in contrast, a daily strong sound for 30 days resulted in a decreased expression of these receptors (Eraslan et al., 2015). The stress- or glucocorticoid-induced decreased expression of GRs in the hippocampus was accompanied by the enhancement of depressive-like symptoms in several studies (Skupio et al., 2015; Chen et al., 2016), which

corresponded to the glucocorticoid hypothesis of depression.

In order to unravel whether the GR deficit resulted in the development of depression and whether it would provide the enhanced expression of receptors, transgenic animals were used. In 2-month-old FBGRKO mice, 60% of the hippocampal neurons were lack of GRs, at 4–5-month the number of such neurons increased to 90–100%, and after 6 month, GRs were absent in the whole hippocampus as well as in most cortical neurons (Boyle et al., 2005). The animals tested in the present study for behavioral helplessness and anhedonia did not differ from the control ones by these parameters at 2-month of age and demonstrated significant depression-like symptoms at 4 and 6 months. Ridder et al. (2005) observed an increased depression-like behavior even after a 50% GRs decrease in the hippocampus, while the overexpression of the receptors resulted in decreased behavioral helplessness after stress and enhanced the negative feedback in the regulation of the HPA axis. However, several studies reported that the diminished expression of receptors in the forebrain might not result in enhanced depressive-like behavior in not all the tests (Boulle et al., 2016) and might have no effect at all (Vincent et al., 2013), while its increase, as well as decreased GR expression, might increase the occurence of such behavior (Wei et al., 2004).

Interaction Between Glucocorticoid Receptors and the Neurotrophic Factor as a Response to Stress

The behavioral consequences of changes in the expression of receptors in vast regions of the brain might be comprised of the specific peculiarities of the effects from distinct regions, for instance, caused by the interactions of the receptors in these regions with other functional systems, primarily the serotonergic system, which is actively involved in the control of psycho-emotional behavior. Recently, the evidence of stressors' ability to change both the GR expression in the hippocampus and the functional responses in this region, including transcriptional ones (Datson et al., 2013), on the responses of this brain structure to the subsequent glucocorticoid exposure, which is considered to be a part of the molecular mechanism of sensitivity to stress-induced psychopathologies, were reported.

Glucocorticoid receptors appear to be important transcriptional factors, and a significant increase in the translocation of the hormone-receptor complex from the cytoplasm to the nucleus was observed in the brain cells of stressed animals (Noguchi et al., 2010; Caudal et al., 2014). In addition to the direct influence on the transcriptional activity of the target genes, stress-induced modifications in these receptors' expression might modify the following gene responses and related functions to stress as was reported for the expression of the brain-derived neurotrophic factor (BDNF) (Alboni et al., 2011). During the past few years, significant interest was directed toward the possible interaction between the stressor responses of GRs and BDNF for the efficacy of the psycho-emotional adaptation to stress (Arango-Lievano et al., 2015; Daskalakis et al., 2015).

With respect to BDNF, numerous previous observations of the changes in its expression as a response to stress and an increase in the glucocorticoid level initiated the suggestion of the neurotrophic hypothesis of depression. It was suggested that a low BDNF level resulting in a decreased number of neurons in the brain caused the development of depression, especially in stress-induced cases; while an increased BDNF level activating neurogenesis was the basis for the therapeutic effects of antidepressants (Duman and Monteggia, 2006). Glucocorticoids might regulate BDNF expression via GR activation as transcription factors (Hansson et al., 2006). Moreover, glucocorticoids might affect the functioning of the BDNF via activation of its Trk receptors (Jeanneteau et al., 2008). However, the BDNF expression in the brain, including the hippocampus, appeared to be both decreased and constant or even increased as a response to stress and glucocorticoids, while neurotrophin itself was insignificant in correcting many stress-induced negative modifications in the hippocampus (Gray et al., 2013). Additionally, it was detected that mice with a genetically enhanced GR expression in the regions of the brain, including the hippocampus, and characterized by resistance to stress-induced depressive-like behavior demonstrated a significant increase in the BDNF level in the hippocampus, prefrontal cortex, and amygdala compared to the wild-type mice (Schulte-Herbrüggen et al., 2006). Moreover, it was reported that BDNF might affect the GR-specific transcriptome, while the simultaneous addition of dexamethasone and BDNF in the neuronal cell culture induced the expression of GR-responsive genes involved in controlling neuronal growth and differentiation (Lambert et al., 2013). Such an effect as shown in the mentioned study might be caused by BDNF-induced GR phosphorylation.

To date the BDNF interaction with the GR is considered to be an important event in the pathogenesis of stress-induced psychopathologies. A combination of low expression levels of GR and BDNF simultaneously results in sensitivity to developing psychopathologies in both juvenile and adult periods, especially under the conditions of additional stress (Daskalakis et al., 2015). However, high levels of these parameters might also represent a risk of at least aggravating psycho-emotional behavior or even the development of depression. Hence, an individual's survival under threat conditions depends on both their momentary response to the stressor and the ability to memorize and integrate the information of the acting stressor for future use of this experience (Finsterwald and Alberini, 2014). Stress-induced GR activation is assumed to provide memory consolidation through the initiation

of the BDNF/CREB(cAMP response element-binding protein)-dependent pathway (Finsterwald and Alberini, 2014). However, it remains unclear whether it is congruent with the data of the suppressing role of stress and glucocorticoids on GRs and BDNF, as well as their involvement in the impairment of cognitive functions, including memory. In contrast to the adaptive form of memory, the long-term contextual memory of fear formed under stress conditions aggravates the negative stress-induced psychological consequences and complicates the rehabilitation. Recently, Revest et al. (2014) demonstrated that the interaction between GRs and BDNF was also responsible for the reinforcement of this memory. The authors revealed that stress-induced GR activation caused by intensive glucocorticoid secretion enhanced the expression of pro-BDNF proteins and tPA (tissue plasminogen activator). In turn, the induction of tPA increases the process of BDNF maturation from pro-BDNF, which also results in a higher BDNF level during the stress and the reinforcement of the contextual memory through the TrkB-Erk1/2*MAPK* signal pathway. The solution of the contradictions between causative stressors and glucocorticoids via cognitive impairment and the formation of adaptive and pathological memory and behavior, as well as the role and mechanisms of the GR action in these effects, require future research.

The data described in the present review illustrate the important role of GRs in the adaptable control of the organism's response to stress and increased glucocorticoid level, as well as the complex molecular pathways involved in the psycho-behavioral effects caused by these factors. An increasing level of evidence regarding the interaction between GRs and BDNF uncovering questions on the interaction mechanisms, especially at the early stages of ontogenesis, exists. Future research of these mechanisms and molecular pathways would lead to the development of novel therapeutic agents for psychiatric disorders caused by unfavorable stress conditions.

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CONFLICT OF INTEREST

The authors have declared that they do not have a conflict of interest.

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