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REVIEW ARTICLE

Role of brain-derived neurotrophic factor in shaping the behavioural response to environmental stressors

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Brain-derived neurotrophic factor (BDNF) is an important neurotrophin involved in an integration of the brain activity in physiological and pathological conditions, with formation of a short- and long-term functional and structural neuroplasticity. This process proceeds, with a changeable dynamics, in the subsequent stages of ontogenesis. In addition to many other functions in the central nervous system, BDNF is also involved in shaping a response to stress stimuli in the form of precisely adjusted behavioural reactions involving the limbic system, and the endocrine system with stimulation of the hypothalamic-pituitary-adrenal axis (HPA). Although almost every stressor increases the activity of the HPA, the neuronal response to it can vary substantially. This may be due to involvement of different neurotransmitter pathways, neuromodulators and neurohormones, as well as changes in gene expression. It is widely accepted that BDNF synthesis and secretion are modulated by stress. Furthermore, age is an important factor influencing the BDNF expression in response to different stressors. In this work, we focused on the analysis of the role of mild stressful stimuli, which commonly occur in the natural environment, on changes in BDNF expression at various stages of ontogenetic development. Although, the presented data comes from animal studies, probably similar mechanisms of stress regulation are also present in humans.

This comprehensive review shows that the influence of stressors on the BDNF expression depends on many factors, including a type and duration of a stressor, time of neurotrophin detection, animal's resistance to stress, brain area, and genotypic characteristics of an individual. A more detailed understanding of the mechanisms shaping stress reactions, including the role of BDNF, may be of both theoretical and practical importance, allowing designing more effective strategies for preventing and treating stress itself and the stress-related disorders. (Folia Morphol 2021; 80, 3: 487–504)

Key words: aging, brain-derived neurotrophic factor (BDNF), glucocorticoids, ontogenesis, stress

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INTRODUCTION

Animal behaviour is a result of a coordinated action of functional systems within the central nervous system (CNS). The behaviour is a consequence of a reaction to external stimuli of different modalities, as well as the effect of a response to constantly changing parameters of internal environment in the organism. Finally, it is a consequence of elaborated reactions resulting from the conscious integration of stimuli in the brain cortical areas, reflexes, and instinctive or emotional reactions arising in subcortical structures of the brain. Stress stimuli of various natures, constantly affecting the body, play an important role in shaping the behaviour. Therefore, answering to these stimuli is an integral part of functioning in the natural environment. The reaction to stressful stimuli requires involvement and activation of many systems. In addition to the sensory and motor systems, they include the vegetative, endocrine and limbic systems, as well as various neurotransmitters, neuromodulators and signalling pathways, leading to changes in expression of transcription factors and gene activation. It is worth noting that the reaction to stressful stimuli is plastic and depends on interaction of numerous external and internal factors. It also changes its characteristics along ontogenetic development. One of the important factors shaping the response to stressful stimuli is brain-derived neurotrophic factor (BDNF). Despite systematic research, the role of this factor in shaping responses to different types of stressors at various stages of ontogenetic development is not fully elucidated. In research on the role of this factor many experimental models have been introduced to approximate the conditions of the stressors' action in the natural environment. This review summarises the current knowledge on the role of BDNF in stress at various stages of ontogenesis. A brief overview of the most commonly used tests to assess the expression of BDNF in response to stress stimuli is also presented.

STRESS REACTION MECHANISMS INTEGRATE FUNCTIONS OF THE ENDOCRINE, LIMBIC AND AUTONOMIC SYSTEMS

One of the most important functions of the nervous system is perception and transfer of information from both external and internal environment to the complex functional systems of the brain. This enables integration of stimuli and maintenance of physiological homeostasis, as well as elaboration of an adequate behavioural response. One of the most important systems involved in these processes is the hypothalamic-pituitary-adrenal axis (HPA) [67, 112, 157, 162]. Hypothalamus enables transfer and integration of neurogenic signals to the endocrine, limbic and autonomic systems. Within hypothalamus, the paraventricular nucleus (PVN) and, to a lesser extent, the supraoptic nucleus (SON) are the two areas involved in the stress response initiation [26, 169] and shaping this reaction, depending on the stressors' specificity [52, 105].

Taking into account the anatomical aspects related to the stimuli transfer between different functional systems in the brain, it can be suggested that influence of stressors on the HPA occurs in two ways: direct and indirect. The first one is used by physical stressors activating HPA directly [42, 67]. The second one is used by emotional stressors, influencing the HPA through activation of important structures of the limbic system, such as amygdala and hippocampus [23, 55, 130]. Activation of hypothalamus results in a rapid secretion of corticotrophin releasing hormone (CRH) — from the small cellular part of the PVN, and arginine-vasopressin (AVP) — from the large cellular part of this nucleus and from the supraoptic nucleus (SON). It is followed by a release of the adrenocorticotropic hormone (ACTH) from the pituitary gland [15, 108] and, ultimately, glucocorticoids or corticosterone from the adrenal cortex [69, 112]. Glucocorticoids, due to the negative feedback, influence hypothalamus and pituitary gland and inhibit the production of CRH and ACTH, respectively. This, in turn, results in reduction the HPA activity [68]. Despite the adaptive action of glucocorticoids in the short term, their long-term action lowers the body's ability to cope with stress and may affect the synaptic plasticity [100, 102].

INTERACTION OF GLUCOCORTICOIDS, NEUROTRANSMITTERS, AND BDNF IS NECESSARY TO ELABORATE THE STRESS REACTION

Stress may evoke changes in BDNF expression through signalling pathways triggered by glucocorticosteroids (glucocorticoids) [48, 86]. Barbany and Persson [16] reported that excessively high or low levels of glucocorticoids may alter the BDNF expression. It has been suggested that BDNF may reduce some of the negative effects of glucocorticoids [90] and its direct administration is able to restore the stress-reduced content of this neurotrophin, e.g. in the hippocampus [27, 82]. However, the results of these studies are inconclusive and not commonly ac-

cepted [63]. The interaction between glucocorticoids and BDNF can occur, among others, through their influence on expression of the TrkB receptor [72]. The studies conducted in animals with adrenalectomy (removal of adrenal glands) indicated that glucocorticoids negatively affected the BDNF expression in hippocampus and other cortical areas [71, 119, 150, 151]. However, adrenalectomy does not completely block the effects of stress on the BDNF concentration [151]. There is evidence that other factors, such as interleukin-1β, also contribute to the changes in the BDNF expression in hippocampus [17]. Also the animal activity is an important factor regulating the BDNF production in the rat hypothalamus [97]. The regulation involves classical neurotransmitters, such as glutamate, acetylcholine, serotonin and GABA [65, 76, 96]. It has been suggested that whereas glutamate, acetylcholine and serotonin increase the BDNF expression, GABA reduces its content in the CNS.

BDNF CONTRIBUTES TO MODIFICATION OF THE HPA ACTIVITY IN STRESS CONDITIONS

The role of stress as modulator of BDNF synthesis and release is well documented [108, 109]. The long-term stress affects the expression of genes responsible for signalling pathways related to glucocorticoids and neurotrophins, among them also BDNF [51, 54, 114, 159, 178]. Transcription of BDNF is under control of promoters which react differently to endogenous and exogenous stimuli (e.g. glucocorticoids and environmental factors, respectively) [80]. These stimuli are also responsible for triggering epigenetic modifications [155]. It is believed that epigenetic processes cause long-lasting or permanent changes in BDNF gene expression, which is reflected in the behavioural responses occurring during early development [130, 168]. Methylation of the BDNF gene is an important epigenetic process affecting its expression, thus inducing changes in the protein content initiated by stress. However, the consequences of this modification are differently interpreted by some authors [114]. The reason for this could be epigenetic changes at different loci within the same gene [91]. Additionally, there is evidence showing that changes in BDNF expression were also related with age [91]. It has been suggested that epigenetic modification of BDNF gene may be responsible for an occurrence of some pathologies induced by chronic stress, such as mental disorders or cognitive decline [167, 177].

Animal studies showed that chronic social stress in mice reduced BDNF expression in the hippocampus as a result of methylation within its gene [156].

Brain-derived neurotrophic factor plays an important role in integrating neuronal and endocrine responses to different stressors [140]. This is due to the direct influence of this neurotrophin on the HPA [73, 154]. Studies showed that both endogenous (already existing pool) and *de novo* synthesised BDNF regulated the HPA functioning and elaboration of an adaptive stress response [108]. It has been shown that a single injection of BDNF causes activation of the HPA [58]. Importantly, by modifying the HPA activity, BDNF facilitates adaptation to environmental conditions [140] and contributes to the maintenance of the physiological homeostasis [154]. By counteracting the adverse effects of glucocorticoids, BDNF is an important factor reducing the stress-induced psychosocial and psychological symptoms [90]. As mentioned before, the BDNF function in response to stressors relays on regulation of synthesis and release of hormones and neuropeptides, such as CRH and AVP in PVN and SON [4, 58, 97, 119]. The stress-induced increase in the BDNF concentration stimulates AVP and CRH synthesis [58, 97, 119]. It may also affect the intracellular content of neuropeptides [58].

REGULATORY ROLE OF BDNF IN SHAPING THE BEHAVIOURAL RESPONSE IS DETERMINED BY NEURONAL ACTIVITY AND FUNCTION, AS WELL AS STAGE OF ONTOGENETIC DEVELOPMENT

Brain-derived neurotrophic factor has important regulatory functions in neurons within the CNS, regardless of the stage of ontogenetic development [154]. The role of this neurotrophin is related to the activity of neural networks and synaptic plasticity, and it can differ depending on the stage of ontogenesis [58, 60, 90, 93, 146]. Neural activity affects the BDNF gene transcription, as well as synthesis of the BDNF protein. It also determines an expression of TrkB receptor, which is one of the most important signal transducers of this neurotrophin [61].

In the earliest stage of ontogenetic development, BDNF is involved in differentiation of neural stem cells into neurons, their growth and maturation [31, 175]. This is a consequence of BDNF regulatory function upon cell proliferation and migration, neuronal survival, as well as maturation of the axodendritic system and synaptogenesis [123, 175].

In the mature brain, BDNF regulates synaptic transmission [160] and has a protective function upon neurons [7, 89]. Consequently, BDNF has a role in promoting learning, cognitive and memory skills, as well as reduction of anxiety [37, 38]. During aging, BDNF is responsible for preventing neuronal degeneration, as well as for an enhancement of the regenerative and repair processes [98, 145, 154]. In many brain areas, including limbic structures such as hippocampus, amygdala and the hypothalamic nuclei, BDNF has been suggested to modulate the behavioural responses to stress [109, 116, 119]. However, its role in this process differs depending on the stage of development and brain area [93].

The variety of BDNF functions in the CNS suggests that alterations in the expression of this neurotrophic factor could be involved in the pathophysiology of the stress-related behaviours caused by long-term effects of stressful stimuli, such as orientation, memory and cognition disturbances and mental illnesses, such as depression, Parkinson's, Alzheimer's and Huntington's diseases [5, 104, 114]. Therefore, BDNF could be considered in future research on therapeutic agents aimed at treatment of several stress-related disorders.

CHANGES IN BDNF EXPRESSION DURING ONTOGENESIS AFFECT STRESS REACTIONS

Stimulation of the CNS with a mild stress evokes multidirectional effects. One of the ways in which this modification occurs is through activation of the HPA and its relationship with BDNF. This is indirectly related to involvement of BDNF in development of synaptic plasticity [58, 60, 79]. The intensity of this process varies during different stages of ontogenesis, which can be a consequence of changes in BDNF concentration [58, 108]. Following, we briefly discuss the CNS effects induced by the selected mild stressors (i.e. causing neither structural damage nor pain) often present in the animal's natural environment.

Early development

An early developmental stage, in rodents lasting approximately 2 weeks after birth, is called a stress hypo-responsive period (SHRP) [87, 132, 137]. During this time, activation of the HPA and a complete development of the stress response occur only after action of very strong psychological or physical stimuli [43, 139]. One can suspect that attenuation of the stress response during that time may protect the developing brain from negative effects of stress hormones (e.g. glucocorticoids) [132]. The high threshold of the HPA activation could be a consequence of the incomplete development of structures which control the stress response, one of which is PVN [125, 128]. It is also associated with a less efficient cooperation of the structures controlling the HPA [44].

Stress in the early period of life negatively affects development and functioning of the brain. It may be responsible for inducing anxiety, depression, and aggression also persisting later in life [2, 29, 70, 166]. However, in general, connection of stress occurring in the early life with psychopathological symptoms observed in adulthood is poorly understood and requires further research [167].

Maternal separation and social isolation. Maternal separation (MS) and social isolation (SI) are regarded as the most common causes of stress in the early life. Early periodic postpartum MS, as well as siblings SI are examples of stress that can cause disturbances in the HPA activity resulting in structural and functional impairments in later life [122, 126, 174, 177]. These two forms of stress in the early life also affect the BDNF mRNA and protein levels. The long-term MS-induced changes in the BDNF expression level in the hippocampus [21, 41] have been linked to learning and memory disorders [2, 30, 70, 174]. Ohta Ken-ichi et al. [111] showed that a long-term separation (6-h) from a mother, between postnatal day P2 and P20, reduced the expression of the BDNF genes in hippocampus of the Sprague-Dawley rats at P7. However, it had no effect on BDNF-ERK signalling after P14. MS between P2 and P14 induced a transient increase in the BDNF levels in hippocampus, prefrontal cortex [126], and amygdala of the Wistar rats [34]. Other studies showed that an early weaning (during the first week of life) had no effect on the BDNF levels in hippocampus [179]. BDNF increase was observed in the olfactory bulb, where this neurotrophic factor may play an important role in learning of the olfactory association [179]. The results confirm that stress sensitivity is lower and the HPA axis response is decreased in the early postnatal period [87, 132]. They also suggest that period of hyporesponsiveness to stress and duration of the postpartum MS may be important factors inducing changes in the BDNF expression in the various brain regions. It has been assumed that BDNF plays an important role in neuroprotection [92]. Hence, an increase of its expression could counteract the effects

of MS. However, there are data indicating that MS induced a decrease in the BDNF expression within 3 weeks after birth [33]. This stressor also induced a reduction in the BDNF mRNA in P16, followed by an increase in P30 and P60 in hippocampus [83] and in the medial prefrontal cortex (mPFC) of Wistar rats [174]. A long-term MS induces reduction in the number of dendritic spines and delay in maturation of the pyramidal neurons in hippocampus [111]. Thus, the MS may influence the BDNF-associated signalling during synaptogenesis [111]. These processes and an increased apoptosis coexist in the early postnatal period [29]. These observations indicate that the MS-induced abnormalities in hippocampus are associated with disturbances in the BDNF signalling pathway during the early brain development [111]. Studies showed that the burden of MS in rodents was responsible for changes in BDNF expression in adulthood and aging, often leading to emotional and cognitive disturbances [122]. Hence, MS causes a decrease in the BDNF concentration, which may lay at the basis of some characteristic functional disorders. A potential factor contributing to these processes are epigenetic changes in the BDNF gene, which may increase susceptibility to stress later in life [141].

In adult and older rodents, the long-term MS also resulted in reduction of BDNF expression in hippocampus [2, 45, 94, 152]. Furthermore, in adult rats, a decrease in BDNF was observed in amygdala [124] and prefrontal cortex [126]. However, in adult rats additionally subjected to prolonged swimming stress, no further reduction in BDNF expression in the prefrontal cortex was reported [126]. It is possible that a decrease in BDNF expression in the CNS early in life can result in an impairment of the plasticity mechanisms later on.

The results of studies investigating changes in BDNF expression after MS are not equivocal. Récamier-Carballo et al. [122] observed an increase in BDNF concentration in hippocampus and amygdala and a decrease in the frontal cortex in adult mice after the long-term MS. Study by Greisen et al. [62] showed an increase in BDNF concentration in hippocampus in adult rats subjected previously to MS in their early life, although they found no changes in the frontal cortex and PVN. On the contrary, van Zyl et al. [164] showed no effect of MS and a restraint stress on BDNF content in hippocampus of adult rats. These differences could be explained by the selection of various species and strains of experimental animals, differences in the experimental conditions and protocols concerning for example the time-point of the expression measurement of the neurotrophic factor.

Thus, various changes in BDNF expression were demonstrated in different brain areas, both in animals after MS and those subjected to additional stress in adulthood. This suggests the complexity of the regulatory mechanisms. The increase in BDNF expression in hippocampus of rats after MS could be a compensatory response to neonatal separation, keeping neurogenesis unchanged in adult animals. Reports on the SI effects on the CNS and especially their pathophysiological consequences are not equivocal. Biggio et al. [21] have shown that both 3 h MS between P3 and P14 and SI after weaning induce a significant reduction in BDNF expression in hippocampus of Sprague-Dawley rats. Despite the opinion that early SI exacerbates responses to stressors [167], its effects in adulthood are poorly understood.

Maturation

The maturation (from P14 to P90) is a phase of a rapid structural and functional changes relaying on an intense development and reorganization of brain structures, including final shaping of their connections. In this phase, the structures involved in the stress response undergo further development. During this period, they are more sensitive to aversive stimuli then in the adulthood [99, 106]. In adolescence, a response of the HPA to stressors is increased and prolonged [9, 93, 107]. This results in an increased concentration of glucocorticoids and a prolonged time of their secretion after a repeated exposure to a stressor [99, 165]. It may be a consequence of the incomplete development of the HPA feedback inhibition [59, 93]. According to some authors, this can explain the insufficient control of its activity [9, 93, 99]. Numerous studies have shown that exposure to potentially traumatic stressors in adolescence has a significant impact on the further development of brain structures and formation of their connections [9, 36, 158]. In development, stress triggers processes resulting in permanent changes in the neuronal plasticity and efficiency of the synaptic connections, which require the BDNF activity [18, 63]. Many authors emphasize that changes of environmental conditions influencing sexually immature animals, with not completely formed neuroendocrine regulatory mechanisms and neuronal connections, may lead to the long-term physiological and behavioural dysfunctions [24, 66].

Predator odour and social isolation. The predator smell is a strong, unconditional and psychogenic stressor for the rodents [18, 153, 180]. Animals exposed to this stressor demonstrate changes in activity, long-lasting and augmented anxiety behaviour [153, 180]. They are accompanied by an increased level of glucocorticoid release and an altered BDNF concentration [18]. The nature of the response to a predator's threat early in life is a species-specific feature. It is often associated with development of defensive behaviour and sensitivity to stress during later development [18, 153, 180].

Bazak et al. [18] assessed BDNF expression in the frontal associative cortex, CA1, CA3 sectors of hippocampus and the dentate gyrus (DG), after a single (10 min) and multiple exposures to a predator urine scent in the Sprague-Dawley rats at P24. The experiment was repeated at P60. It was found that both the early and late effects of the stressor induced a significant reduction in the BDNF mRNA and BDNF protein levels in the hippocampal CA1. The effect of re-exposure to stress was greater in rats exposed to the same stressor again, indicating a cumulative effect of this kind of stimulus.

Exposure to a chronic psychosocial stress may also alter the BDNF expression. A long-term SI caused changes in functioning of the HPA and an increase of anxiety and depressive behaviours [177]. They were accompanied by a reduction of the BDNF mRNA and BDNF protein concentration in hippocampus of the adolescent rodents. This suggests an important role of this type of stressor in the regulation of the BDNF content in the limbic system and, thus, in shaping the adequate behavioural responses during further stages of ontogenesis. However, consequences of these processes for the synaptic plasticity and the brain structure in the adulthood remain unknown.

Chronic mild stress. Several procedures can induce mild forms of stress. Among the most frequently used are: temporary deprivation of food or water, overcrowding in a cage, social isolation, using a soaked sawdust in a cage or tilting frames (45°), inversion of the light/dark cycle, and a short-term (5 min) forced swimming test [155]. These stressors applied in the Sprague-Dawley rats resulted in a reduction of BDNF mRNA in hippocampus and an induction of morphological and functional changes in the spino-dendritic system [155]. A decrease in the BDNF mRNA expression in hippocampus was also reported after application of a chronic, unpredictable, mild stress, in form of the open field test, for 8 to 28 days, in 2-month-old Sprague-Dawley rats [142]. These results confirm the possibility of using many types of mild stressors in modelling responses to harmless stimuli present in the natural environment of rodents. This gives the possibility of their use in studies on behavioural responses in animals at different ages and under influence of stimuli of various nature and duration.

Immobilisation. An immobilisation stress (IM) induces the BDNF expression [95]. It is responsible for the structural plasticity changes in hippocampus and amygdala, i.e. areas involved in development of cognitive and affective symptoms of stress [136]. The effects of an acute and chronic immobilisation stress on the level of BDNF expression were observed in the 8-week-old Wistar rats [84]. A day following 2 h immobilisation, the BDNF level increased in neurons of the basolateral amygdala (BLA), although it did not change in the CA3 sector of hippocampus. However, after a long-term (8 h) immobilisation, the BDNF level increased in the BLA and decreased in CA3. Additionally, the BLA neurons hypertrophy and the hippocampal CA3 neuronal atrophy were observed. In line with these results, Ueyama et al. [161] reported a reduction of the BDNF mRNA level after 8 h immobilisation stress in hippocampus of the 6-week-old male Wistar rats.

Forced swimming. A forced swimming (FS) stress is a type of stimulus experienced by rats in their natural environment [40]. Chronic FS combines psychological stimuli of novelty and an aquatic environment with a physical stimulus in the form of the forced motor activity [42]. In the 2-month-old juvenile Sprague-Dawley rats, a short-term (10 min) FS test in cold water caused a rapid increase in the BDNF mRNA and BDNF protein concentration in hippocampus, already 15 min after the end of stimulation. However, after chronic FS (10 min/21 days in 25°C water), the BDNF mRNA and protein expression in hippocampus decreased after 60 min from its termination [143]. Badowska-Szalewska et al. [13] assessed the effects of the long-term FS (15 min/21 days in 22°C water) on the density of BDNF-containing neurons in the pyramidal layer of the hippocampal CA1, CA3 sectors and the granular neurons of DG, as well as in SON and PVN nuclei of the hypothalamus, in juvenile (P28) and middle-aged (P360) Wistar rats [13, 53]. They reported a decrease in the density of the BDNF-ir neurons in CA1 and DG and in the nuclei of the hypothalamus.

It was concluded that the type of the stressor determined the changes in number of the BDNF-ir cells in juvenile rats. The different density of BDNF-ir in juvenile versus middle-aged rats can be explained by age-related changes in the demand for BDNF [13, 53]. Exposure to a mild long-term stress early in life is believed to attenuate the HPA inhibition, which may lead to an increase in the glucocorticoid levels [74, 99], as well as to a decrease in BDNF expression. Importantly, this may result in an impairment of the neuroplasticity and of the normal brain development at subsequent stages of ontogenesis. Consequently, this may also initiate formation of improper behavioural reactions during subsequent life periods.

High light-open field stress. The high light-open field (HL-OF) test reflects conditions in which the rats actively explore a new environment [46, 53]. The aversive stimulus in the form of a bright light can trigger emotional reactions and anxiety behaviours [64, 118]. However, a chronic exposure to HL-OF (15 min/21 day cycle), changed the density of the BDNF-ir neurons neither in the large-cell (PVm) and small-cell (PVp) part of the PVN, nor in the SON of the hypothalamus, in the Wistar rats in P28 [53]. This can be explained by an adaptation to the particular types of stressors [46]. According to some authors, it may be the result of the BDNF-dependent plasticity within particular brain structures, and it suggests a protective role of BDNF in the neurons of these areas [146].

Adulthood

Reaching a complete morphological and functional maturity the animal's activity and behaviour becomes characteristic for the adult representatives of particular species. This is related to the intensification of its interaction with the surrounding environment and, thus, an increased susceptibility to the stressful stimuli. As a result, in stress studies on adult animals a wide range of tests approximating the impact of stressors occurring in the natural environment is used [4, 6, 58, 108, 119]. Adulthood is characterised by the HPA functional efficiency [6, 58]. Most of studies investigating the role of BDNF in hypothalamus and/ /or other structures involved in the HPA regulation in response to stress are performed in the adult rats.

It is worth mentioning that neurogenesis in the adult brain occurs in two main areas, the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus [39]. Especially the latter area of proliferation is important for the proper shaping of processes related to spatial and contextual memory of stress-related events and reactions [49, 50, 101]. The effect of stressful stimuli is related to the reduction of neurogenesis and, consequently, it is also associated with a decrease in BDNF expression [47]. A further consequence of these processes is the disturbance of structural and functional plasticity in the hippocampus.

Restraint and immobilisation. Restraint and immobilisation stresses (RS and IM, respectively) combine the effects of psychological and physical stimuli [32, 147]. This combination of stressors occurs sporadically in the natural environment of rats. As expected, a complete immobilisation of an animal is more aversive than restricting its movements. Most studies on the effect of such stimulation on BDNF expression were focused on hippocampus. However, the results of studies investigating the BDNF mRNA and its protein level after stimulation by the acute or chronic RS or IM are unequivocal and inconclusive. Both acute (6 h) RS and chronic RS (lasting from 1 to 3 weeks) induced a marked reduction in the BDNF mRNA levels in hippocampus of the Sprague-Dawley rats [107] and C57BL/6J mice, and BALB/cJ mice [3]. Similarly, a decrease in BDNF level in the hippocampal pyramidal cell layer and in the granular layer of the DG was reported after 1 day in the 4 h/3days RS rat model [172]. In line with the previous results, Xu et al. [171] observed a decrease in BDNF expression and the neuronal proliferation in hippocampus after long-term (6 h/14 days) RS. Other authors showed that although the chronic RS leads to decrease in BDNF and the BDNF mRNA expression in the hippocampal CA3, it could initiate its increase in the BLA [19]. A significant decrease in the BDNF level after a single 3 h RS was also observed in the prefrontal cortex (PFC) of the Wistar rats [120]. However, Naert et al. [108] showed an increase in BDNF levels after chronic RS (3 h/21 days), not only in the hippocampus but also in the hypothalamus and pituitary gland in the Sprague-Dawley rats. Interestingly, there are also reports stating that an acute (3 h) and chronic (6 h/14 days) RS did not induce any changes in the BDNF mRNA levels or BDNF protein concentration in hippocampus and amygdala [121, 127].

Immobilisation for 2 h caused a decrease in the level of BDNF mRNA in hippocampus in the Sprague-Dawley rats, immediately after the end of the experiment [176]. Chronic IM reduced the BDNF levels and BDNF immunoreactivity in the hippocampal

pyramidal neurons, as well as in the DG granular neurons, in the Sprague-Dawley rats [173]. A comparison of the effect of 7-day vs. 21-day IM on the BDNF level in the C57BL/6J mice showed that after 21 days of this type of stress the BDNF level in hippocampus was lower than in the 7-day group [25].

The available data suggest an importance of the time of BDNF concentration measurement after performing the experiment, stressing the possibility of its fluctuations. Marmigère et al. [95] have shown that after a short-term (15 or 60 min) IM the BDNF mRNA level increased rapidly and then decreased approximately 2–3 h after the stressor termination. Similarly, after 180 min exposure to IM, BDNF expression initially increased, then decreased to the level observed in the control group [95]. Moreover, it was also revealed that IM as a stressor can transiently increase BDNF expression, despite high levels of stress hormones [95]. These observations suggest that the rapid changes in BDNF concentration in hippocampus may be a part of the strong compensatory response triggered to maintain homeostasis, or suggest induction of the neuronal plasticity mechanisms triggered in animals when confronted with new stimuli.

Interesting effects on BDNF expression were observed in experiments with combination of stress and learning stimuli. In response to both acute and repeated IM stress, BDNF expression decreased in hippocampus [133]. However, animals additionally subjected to learning showed an increased expression of BDNF in comparison to those which were only stressed. Thus, learning and stress have the opposite effect on BDNF level and the effect of learning, leading to an increase in BDNF, is outweighing the stress effect. This observation may be of important practical significance for modifying animals' behaviour.

An analysis of impact of the IM on the level of the BDNF mRNA in various brain areas showed significant differences between them. One-time 2 h or 8 h immobilisation, as well as chronic (2 h/day, for 7 days) immobilisation caused a decrease in the BDNF mRNA level not only in the hippocampal sectors, DG but also in hypothalamus and several cortical areas of the Sprague-Dawley and Fischer 344/N rats [149–151]. On the other hand, a short-term (15 min) IM caused a significant increase in the BDNF mRNA and protein expression in PVN and SON in hypothalamus [119]. Numerous studies showed that both short-term (2 h) and longer, repeated (7 days/2× daily) immobilisation increased the level of BDNF mRNA in the PVN,

lateral part of the hypothalamus and pituitary in the Sprague-Dawley and Fischer 344/N rats [149–151]. Fluctuations in the BDNF content, resulting from changes in the expression of genes regulated by the concentration of stress hormones, may contribute to alterations in a density of dendritic spines in structures of the limbic system [19]. A consequence of decreased BDNF expression may be structural changes and neuronal loss [148].

The diversity of the presented results, and a high dependence of BDNF level on duration of exposure to the stressor and its type, suggests the existence of complex regulatory mechanisms responsible for expression of BDNF mRNA and its protein in the CNS. One can expect significant differences in these mechanisms among various brain areas.

Social stress, social defeat stress. Pattern of BDNF expression in rodents, resulting from changing social hierarchy and living conditions modified in experiments, were the subject of previous studies [10, 134, 138]. Modified housing conditions and social hierarchy in the experimental animals (social stress) are natural stressors that can influence physiological parameters and behaviour [134]. A short-term (10 min) social stress in mice led to a decrease in BDNF mRNA content, 24 h after stimulation, in the CA1, CA3 sectors of hippocampus, DG, BLA, piriform cortex, thalamus and hypothalamus [116]. The BDNF mRNA levels normalised after approximately 5 days. According to the authors, the BDNF changes may be responsible for reactions relaying on inhibition of the territory defence behaviours and anxiety.

Changes in housing conditions and social stress are long-term acting stressful factors [10, 138]. Neither 7 nor 21 days of the social stress, based on exchanging animals in cages, influenced the BDNF level in hippocampus in C57BL/6J mice [25]. An exposure of the NMRI mice to 4 weeks of an intermittent stressor (by placing animals in a new cage or social hazard conditions) increased the BDNF expression in hippocampus among the socially endangered animals, but not in the mice placed in a new cage [113]. This can be explained by the role of BDNF in supporting mechanisms promoting behaviour related to defence of territory and offspring.

Other interesting observations come from studies conducted in a model which mimics conditions of the "isolation syndrome" and is based on depriving animals of social stimuli by placing them individually in cages [163]. The assessment of BDNF levels in

hippocampus, frontal cortex, hypothalamus, striatum and midbrain in C57BL/6J mice subjected to long-term social stress or social deprivation showed significant differences compared to the group with a stable social structure [20]. In the group of animals subjected to the social deprivation, an increased activity of the HPA and a lower level of BDNF were demonstrated in the examined brain areas, in comparison to animals from the group with the stable social structure. Thus, the chronic social deprivation, as opposed to the social instability, has been found to lead to emotional disturbance and neuroendocrine activation, combined with decreased BDNF levels [20]. In order to evaluate the effect of a long-term, 8 weeks partial social isolation on BDNF changes in hippocampus, the concentration of this neurotrophic factor was measured in the Sprague-Dawley rats placed in cages either single or in pairs [134]. Lower concentrations of the BDNF protein were present in the animals living in isolation. Reduction in the level of BDNF mRNA and protein after the chronic social isolation (social defeat stress) in rodents' hippocampus has also been reported by other authors [156, 177]. A recent study by Viana Borges et al. [167] presenting a comparison of the effects of a social isolation (breeding in isolation) and a social support (breeding in pairs) on the level of BDNF in hippocampus of the Wistar rats additionally subjected to chronic unpredictable stress (CUS) confirmed the above-mentioned results. Furthermore, in animals subjected to isolation the decrease in the BDNF level in hippocampus was accompanied by the long-term memory impairment [167]. Therefore, higher expression of BDNF in animals living in social groups indicates the important role of this factor in stimulation of the mechanisms developing social relationships and maintaining mental health [35]. It has also been suggested that a social support may contribute to protecting against some effects of the stress-induced epigenetic modulation of BDNF genes [167]. This may be manifested by the preservation of cognitive functions. However, the detailed explanation of these regulatory mechanisms requires further research.

Predator odour. To assess reactions caused by fear of predators (predator scent stress), a test involving exposure of rodents to a smell of predator urine has been developed [80, 81]. After a single, short-term (10 min) exposure to the stress factor, the level of BDNF mRNA in the CA1 sector of hippocampus was assessed 7 days after the exposure. Cat smell in-creased anxiety behaviour, which correlated with the long-term decline in BDNF mRNA [81]. It has been suggested that the action of the aforementioned stressor, via changes in BDNF expression, may lead to remodelling of the neuronal connections in hippocampus [81].

Chronic mild stress. In order to simulate unpredictable situations that may occur in the rodents environment, a model of chronic mild stress (CMS) was developed [170]. This model reflects many types of stimuli inducing anxiety behaviour. However, occasionally changes in physiological parameters and behavioural responses after its use are ambiguous. In hippocampus of the rats exposed to CMS an increase in the BDNF mRNA expression was reported, not a decrease, as it could be expected, despite a behavioural response resembling depression [85]. Other authors have reported reduced [78] or increased anxiety [77] after using this stress model. It has been suggested that this type of stressor affects emotional behaviour and, indirectly, also the activation of the HPA and the level of BDNF [110]. The substantial discrepancies in the results may be due to the interplay of different neurobiological variables. This means that various signalling pathways responsible for regulation of the BDNF expression may be activated, adapting the brain to different situational contexts and emotional states.

Osmotic stress. The sensitivity of the hypothalamic nuclei to the osmotic stimuli was the basis for elaboration of a test which is useful for detection of the BDNF protein and mRNA level changes [4, 6, 28]. Three and 4.5 h after intraperitoneal administration of 3 mL of hypertonic 1.35% NaCl solution, an increase in the BDNF mRNA and BDNF protein concentration in the PVN and SON was reported in the Sprague-Dawley and Wistar rats [4, 6, 28]. The obtained results suggest the existence of a mechanism regulating the BDNF content, associated with sensitive to the osmotic stimuli areas located in hypothalamus.

Forced swimming. There is a documented evidence that the FS is responsible for inducing compensatory homeostatic mechanisms to prevent or reduce cytokine activation during a stress response [115, 117]. Although mechanisms of such reactions are not completely understood, there are premises indicating that neurotransmitter systems (e.g. glutamatergic or monoaminergic) as well as the HPA axis are involved [115, 117]. Interestingly, studies showed that both a single (20 min) and a chronic (20 min/21 day) FS episodes did not cause changes in

the density of BDNF-ir neurons in the PVN and SON nuclei in hypothalamus of the adult Wistar rats [12]. One can assume that the relatively low harmfulness of the applied stimulus could have prevented changes in the density of BDNF-ir neurons.

High light-open field stress. HL-OF is a relatively strong stressor which may initiate structural and functional changes in several brain areas [64, 118]. The numerical density of BDNF-ir neurons in the PVN and SON was analysed in the Wistar rats undergoing HL-OF [12]. After a single 20 min exposure to HL-OF, an increase in BDNF-ir in the SON was observed, which most likely was related to an increase in the level of neurohormones (e.g. AVP), synthesized depending on the HPA axis activity. However, the long-term 21-day stimulation with HL-OF did not affect the density of BDNF-ir neurons. One can presume that the activity of the HPA was not maintained at a sufficiently high level for such a long period of time or that the experimental animals adapted to this type of stressor.

Aging

It is commonly accepted that animal's response to stress changes with age [93, 115]. Aging is a life period related with apparent changes of many functions of the limbic system and the neuroendocrine activity [112, 115]. One of the consequences of aging is an increased lability of the HPA, which can lead to changes in its activation [22, 103, 115]. This is due to an impairment of the controlling the stress response mechanisms regulating the HPA activity which involve several brain structures, among which the most important are hypothalamus, hippocampus, and amygdala [115, 144, 146]. All this limits the ability to response adequately to stress [112, 115]. The dysregulation of the system controlling stress response is manifested by a decreased inhibition of the HPA activity and termination of the stress response [57, 115].

An impairment of the negative feedback regulatory mechanisms of the HPA significantly modifies the action of glucocorticoids and their receptors [115]. It also influences the stress-dependent synthesis and secretion of the other neurohormones such as catecholamines [14, 93, 129], and increases the neuronal sensitivity to apoptosis [30, 131]. Importantly, during aging a stronger stimulus is required to induce a stress response, which in some cases may even increase the intensity of the reaction [112]. Finally, there are compensatory mechanisms activated during aging

that enable adaptation to changing environmental conditions [56]. Activation of systems involved in the stress response was observed even in the absence of the stressor, which could be regarded as a state of readiness [56].

Immobilisation and chronic mild stress. Data about changes in BDNF expression in aging animals under influence of a mild stressor is still incomplete. Immobilisation reduced BDNF expression in hippocampus in older rodents [149]. This effect was present both after short- and long-term immobilisation. In the 24 month-old Fischer 344/N rats, a decrease in the BDNF mRNA in the DG was observed immediately after 2 h immobilisation [149]. The chronic immobilisation (2 h/7 days) reduced the BDNF mRNA in hippocampus in old (24 month) male Fischer 344/N rats [148].

A CUS model has been used to evaluate changes in BDNF expression in hippocampus [88, 142]. After an exposure of different duration (up to 28 days) on chronic unpredictable mild stress, a decrease in the BDNF mRNA expression in hippocampus was reported in the 22-month-old Sprague-Dawley rats [142]. Similarly, a 3-week exposure to CUS induced a decreased expression of BDNF in the hippocampal CA3 and DG in the 15-month-old Wistars [88]. A mild stress-induced decrease in BDNF expression in the hippocampal neurons is of a particular importance due to enhancement of changes in cognitive functions, learning, and memory during aging [1]. They could be a result of the impaired long-term synaptic enhancement observed at this stage of ontogenesis [8, 75]. Less effective synaptic transmission prevents repeated neuronal stimulation which, in turn, may result in receptor desensitization and finally, prevents neuronal damage [154]. This process can be regarded as one of the positive compensatory mechanisms preventing structural and functional damage in the CNS during aging.

Forced swimming. The FS is useful for assessing changes in BDNF expression during aging. A short-term stressor of 10 min swimming in cold water at 4°C induced a rapid increase in BDNF and the BDNF mRNA in hippocampus in the 22-month-old Sprague-Dawley rats, already 15 min after its completion [143]. A long-term FS of 10 min for 21 days in 25°C water reduced expression of the BDNF mRNA and protein after 60 min [143]. FS stimulation was also used to assess changes in the density of BDNF-ir neurons of the hippocampal pyramidal cell layer of CA1, CA3, and granular neurons in DG, and in the PVN and

SON nuclei of hypothalamus in P360 and P720 Wistar rats [11–13, 53]. After 20 min FS, an increase in the density of BDNF-ir neurons in CA2 and CA3 sectors of hippocampus was reported in the aged animals (P720) [11]. However, no difference was observed in the density of BDNF-ir neurons after exposure to chronic FS of 20 min/21 days in P360 and P720 age groups compared to the control groups [11–13, 53]. The explanation of these results may provide a hypothesis assuming that the increase in expression of neurotrophins, including BDNF, after a short-term stress may be associated with the consolidation of information about a harmless event in order to prepare the future response to a new stressful stimulus [95]. The lack of increase in BDNF expression after prolonged stimulation with a harmless stimulus can be also explained by habituation.

High light-open field stress. An effect of stimulation with the HL-OF stressor on the density of BDNF-ir neurons was assessed in the pyramidal cell layer in the CA1, CA2, CA3 sectors of hippocampus, granule cells layer in the DG, and in the PVN and SON nuclei of hypothalamus in the Wistar rats [11, 12, 53]. While after exposure to an acute 20 min stress the density of BDNF-ir neurons increased in CA1–CA3 regions of hippocampus, it decreased in the PVN in P720 [11, 12]. However, a chronic 21-day HL-OF stimulation did not change the density of BDNF-ir neurons in the examined brain structures in both P360 and P720 [11, 12, 53].

The increase in the density of BDNF-ir neurons after a single HL-OF stressor stimulation can be explained by the change in the HPA activation leading to the raised release of neurohormones. Interestingly, the increase in the BDNF-ir density of pyramidal neurons after the short-term stressor exposure may stimulate memory in the aged animals [135]. The above-mentioned "state of readiness" or alert, may be responsible for prevention of the reduction in BDNF level after the chronic stress in the older animals [56]. The repeated exposure to the same stressor may also cause habituation [88].

CONCLUSIONS

Although almost each stressor is believed to increase the activity of the HPA, the response of neurons to individual stressors varies considerably. This may result from the number of involved neurotransmitters, neurohormones and neurotrophic factors, including BDNF. Based on the presented data, one can conclude that the effect of stressful stimuli on BDNF expression in the various brain areas at the specific stages of the ontogenetic development depends on several factors, such as species and genotypic characteristics of experimental animals, and their individual resistance to stress. In addition, the psychophysical condition seems to be of great importance, as it determines the way of coping with the stressful situations. Important factors to consider that may affect the results of research on stress mechanisms are: a type of stressor used, an experimental model of stress, an analysed brain area, the precision of the BDNF detection method, time of assessment of the neurotrophin level after stress stimulation, the tested form of neurotrophin (precursor or mature form of BDNF) and, finally, the BDNF mRNA level. The presented data, on the one hand, indicate participation of BDNF in response to a wide range of stressors. On the other hand, they point to a different dynamics of changes in this neurotrophin level, depending on the type of stressor and the stage of ontogenetic development. Results of the studies using various experimental stress models indicate the multidirectional effect of BDNF on shaping the response to stress. Further studies are warranted to better understand the role of this neutrophin in the CNS during a stress response, and to consider its potential use in designing new, effective strategies of stress prevention or treatment.

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