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Dopaminergic system activity under stress condition – seeking individual differences, preclinical studies

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Summary

Dopaminergic system activity in limbic structures (reward system) is related to motivational processes and adaptation to changing environmental conditions. Stress conditions can cause dopaminergic dysfunction, reduce motivational processes and induce compensatory drug use. The susceptibility to stress is characterized by individual variability. Psychostimulants such as cocaine, amphetamine and its derivatives act as positive reinforcers, affecting mood changes. Prolonged use of psychoactive substances can cause persistent plastic changes in the limbic system (disruption of neurogenesis, neurons atrophy), resulting in addictions or other forms of psychopathology like mood disorders. One of the reason is dysregulation of the dopaminergic system and dysfunction of local dopamine release in the nucleus accumbens. Stress factors also inhibit neuronal plasticity. In turn, antidepressants may increase brain-derived neurotrophic factor (BDNF) and TrkB receptors expression and improve neuronal proliferation, restoring proper functioning of the limbic regions. An important manifestation of the distinct functioning of the dopaminergic mesolimbic system is the difference between the sexes and the aging process.

Epidemiological studies indicate that depression, anxiety disorders, and other emotional disorders often accompany drug abuse. The search for neurobiological basis of affective disorders and identification of factors, including epigenetic ones (interdependence of genetic and environmental factors), associated with different susceptibility to stress and predisposition to addiction to psychoactive substances is currently being carried out by many researches. Understanding the neurobiological factors of individual differences related to susceptibility

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to psychostimulants may aid in developing future therapies adapted to the patient's needs and more effective treatment of addiction.

Key words: dopaminergic system, individual differences, psychoactive drugs

Introduction

Perception, classification and encoding external stimuli, as rewarding or aversive, favor adaptation and allow the individual to adapt and function in stressful environment. The mesolimbic dopaminergic system in the structures of the so-called reward system: ventral tegmental area (VTA), amygdala, nuclei accumbens (NAc) and prefrontal cortex (PFC), plays an important role in the complex response to changing environmental conditions [1]. The reward system controls the emotional processes associated with motivation, in response to appetitive stimuli and anticipation of the reward [1, 2]. The nuclei accumbens participate in the processes of response conditioning; the prefrontal cortex is involved in the process of acquiring and retaining behavior or in suppressing it, while the amygdala plays a key role in creating association between the stimulus (rewarding perception) and the behavioral response [3].

The response to rewarding stimuli and stress situations is an individual feature. It may result from the interaction of genetic and environmental factors; from individual differences in the structure and activity of the dopaminergic system [4]. Stress situations activate the hormonal mechanisms of the hypothalamic-pituitary-adrenal axis (HPA), which in complex mechanisms dependent on, among others, corticoliberin (CRF) and glucocorticoid receptors, modulate the action of the dopaminergic system [2]. As a result, the dopaminergic system is impaired and motivational processes are weakened [5].

The individual differences in the functioning of the dopaminergic system may contribute to development of susceptibility to mental disorders (depressive disorders or addiction), and are also important for the individualization of therapy [5, 6].

The purpose of this paper is to briefly present and summarize the most important factors about the individual variable activity and reactivity of the central dopaminergic system to stress, anxiety and psychoactive substances. The articles were searched in the Pubmed databases, and the selection of publications concerned the functioning of the dopaminergic system in aspects of individual differences, motivation, effects of antidepressant drugs and psychostimulants.

Dopamine in the central nervous system

Dopamine stimulates dopaminergic receptors which, based on their molecular structure and pharmacological properties, are subdivided into D_1 and D_2 subfamilies. The D_1-like subfamily includes D_1 and D_5 receptors that induce an increase in the cyclic AMP synthesis (cAMP) and dopaminergic neuron activity. The D_2-like subfamily comprises D_2, D_3 and D_4 receptors that inhibit cAMP synthesis, which correlates with the decreased activity of dopaminergic neurons. The central effect of the receptor action depends on the interaction between both receptor groups [7, 8]. The location of

the individual DA receptors in the structures of the reward system is shown in Table 1. Each of the components of the dopaminergic system has different expression and may be the source of individual responses to stimuli.

Table 1. **Distribution of dopamine receptor in selected structures of the mammalian brain**

	D_1	D_2	D_3	D_4	D_5
Prefrontal cortex	+++	++		+++	+++
Nucleus accumbens	+++	+++	+++		++/+++
Amygdala	+/++	+/++	+	+	+/++
Ventral tegmental area	+/++	+++	++		

+++ – large; ++ – moderate; + – low density; modified according to [8]

Although the dopaminergic system is a key element in the reward system, its functioning remains in complex interaction with other neurotransmitter systems. Mutual interactions occur at the inter-structural, intra-structural and cellular level [9]. Research using modern techniques (optogenetic and epigenetic techniques) allows for the analysis of more complex relationships between dopaminergic and other neurotransmitter systems: noradrenergic, serotonergic, glutamatergic, GABAergic, endocannabinoid and endogenous opioid (β-endorphin) [9, 10]. Cocaine and amphetamine regulated transcript (CART) peptides play an important role in the regulation of many processes: stress response, hormone secretion, pain transmission and effects of psychostimulants. Previous studies have shown a complex relationship between CART and dopaminergic system. One hypothesis assumes that CART secretion leads to a decrease in the dopaminergic receptor activity, probably by competition with the mechanisms involved in intracellular signaling [11, 12].

Changes in the dopaminergic system with reference to individual differences – selected pre-clinical models

Under conditions of chronic stress, the functioning of the dopaminergic system may be disregulated. As a result, there is a reduction in the level of dopamine (dopaminergic system hypofunction) needed in the positive reinforcement process associated with learning and adaptation. Preclinical and clinical studies show individual differences in susceptibility to rewarding stimuli, stress-resistance and response to psychoactive substances that may be significantly related to the different activity of the dopaminergic system in the mesolimbic system [4].

Since the 1990's, there has been an increase in interest in the search for neurobiological background of individual differences in the response to stress and psychoactive substances. Preclinical models are used in studies of this issue.

Classification of animals by novelty seeking

Rodents (rats, mice) exposed to novel environment exhibit the increased exploratory activity (locomotion, sniffing). The reaction to new stimuli depends on the functioning of the dopaminergic system and is an important criterion for assessing individual animal differences in the response to psychoactive substances [13, 14]. It has been shown that animals more strongly responding to the new environment, classified as High Responders (HR) show higher locomotor activity after multiple doses of amphetamine and cocaine and stronger response to the context conditioned by the administration of psychoactive substances compared to those less strongly reacting called Low Responders (LR) [14]. HR animals are also characterized by a stronger response to cocaine self-administration and a weaker anxiety response in the dark-light test compared to LR animals [15]. The different behavioral response of these animals reflects activity of the nervous system [13, 14]. Experiments using microdialysis technique have shown that HR animals exhibit significantly higher basal levels of extra-cellular dopamine in nucleus accumbens than LR animals [16].

Classification of animals based on appetitive vocalization

In response to rewarding stimuli, rats vocalize (ultrasonic vocalization – USV) in the frequency band of 30–100 kHz, most often in the band of about 50 kHz [17]. The intensity of vocalization in response to stimuli shows individual variability and is characteristic for a given rat [17]. Studies indicate that the appetitive band (50kHz) vocalization correlates with an increase in the dopamine release in the mesolimbic pathway (NAc); therefore, variation analysis in the band 50 kHz USV may be a tool for investigating the dopaminergic system activity and individual differences in response to psychoactive substances [18]. Individual response to the effect of amphetamine on the basis of an increase in appetitive vocalization in a two-injection protocol of sensitization (TIPS) – difference in the number of vocalization episodes after the second administration of amphetamine compared to the first one – allows for the division of animals into High callers (HC) and Low callers (LC) [17]. It has been found that the amphetamine challenge dose after a two-week withdrawal period in HC individuals resulted in a higher increase in the expression of c-Fos protein (transcription factor, gene product of early cellular response, marker of the neuronal activity) in the cortical and dorsolateral regions of the striatum compared to LC animals [19]. However, in the amphetamine self-administration procedure, no differences in the expression of appetitive vocalization were found in HC and LC animals. It has been observed, however, that LC rats showed a stronger self-administration reaction compared to HC [17]. This data indicates that the individual appetitive vocalization in response to amphetamine and self-administration are likely to be controlled by different neuronal pathways.

Classification of animals based on the conditioned fear test

Increased anxiety is characteristic for many affective disorders, including depressive, cognitive and motivational ones [6]. The method of selecting animals according to response in the conditioned fear test reflects the individual differences in response to stress. The conditioning procedure consists in association of aversive unconditional stimulus (e.g., mild electrical shock) with an neutral conditioned stimulus (context–cage). Classification of animals as more and less anxious is based on the freezing response to aversively conditioned environment [20]. The learned fear response can persist for a long time. High-anxiety rats (HR) are more susceptible to stress compared to low-anxiety rats (LR).

Differences in the functioning of the dopaminergic system were observed in response to amphetamine in the model of animals with varying degrees of conditioned anxiety [20–22]. The studies using microdialysis *in vivo* showed that LR animals exhibited elevated levels of dopamine and its metabolite – homovanillic acid (HVA) in the amygdala and prefrontal cortex (PFC) in exposure to the aversive context and 7 days after the stress factor [23]. LR animals also reveal a stronger motivational response measured by 50 kHz USV appetitive vocalization in the model of two-injection sensitization method of the amphetamine effect (TIPS) and a stronger reaction to the amphetamine-conditioned context compared to HR animals (conditioned place preference – CPP) [23]. Differences in the amphetamine effects are reflected at the level of PFC, NAc and amygdala activity measured by changes in the concentration of DA and its metabolites and the c-Fos protein activity. LR animals exhibit higher activity in the cortical regions (PFC), which control motivational processes in the structures of the reward system (such as the amygdala) [24].

Table 2. **Differences in the activity of mesolimbic structures of the dopaminergic system in preclinical models**

Model	Behavioral parameters	Activity of dopaminergic system		Reference
Novelty seeking High reactivity (HR) in regard of Low reactivity (LR)	↑ locomotor activity	Nucleus Accumbens	↑ DA	Hooks et al. 1992, Verheij and Cools 2007
Appetitive vocalization in the TIPS procedure High callers (HC) in regard of Low callers (LC)	↑ 50 kHz USV	M1/M2	↑ c-Fos	Kaniuga et al. 2016
		CG1, Frontal cortex	↑ c-Fos	
		Striatum	↑ c-Fos	
Model of a conditioned fear response Low anxiety rats (LR) in regard of High anxiety rats (HR)	↓ conditioned fear ↑ 50 kHz USV	BLA	↓ c-Fos	Lehner et al. 2008
		Amygdala	↑ HVA ↑ DA	Lehner et al. 2014

↑ increase or ↓ decrease in regard of the reference group; TIPS – two-injection protocol of sensitization; 50 kHz USV – appetitive ultrasonic vocalization; M1/M2 – motor cortex, area 1 and 2; CG1 –

cingulate cortex; BLA – basolateral nuclei of the amygdala; DA – dopamine; HVA – homovanillic acid; c-Fos – transcription factor, marker of the neuronal activity.

Therefore, the susceptibility to psychoactive substances addiction may depend on the individual response to stimuli and the choice of behavioral strategies (stress avoidance), in response to changing environmental conditions. The change in the activity of the dopaminergic mesolimbic system, which is responsible for the motivational processes under stress conditions, shows individual variability. Preclinical models indicate that the predisposition to psychoactive substances addiction may manifest itself under the environmental stimuli (stress caused by novelty, aversive stress, previous exposure to psychoactive substances) depending on innate susceptibility and reactivity of the dopaminergic system.

The effect of antidepressants on the dopaminergic system

The key symptoms of depression are anhedonia and motivational deficits, which are associated with the weakened dopaminergic transmission in the reward system. This has been confirmed by functional magnetic resonance imaging studies that indicate the decreased activity of the ventral striatum in patients with unipolar depression awaiting a reward. Moreover, the weakened activity of this structure is apparent in patients in remission and also in the offspring of depressed patients who have not yet experienced a depressive episode [25].

Some antidepressant drugs stimulate the dopaminergic system (e.g., buproprion, nomifensine, amineptine) [26–28]. The monoaminergic hypothesis of depression assumes that this illness is probably due to a decrease in serotonergic, noradrenergic and dopaminergic neurotransmission [29]. Preclinical and clinical studies indicate that depression may also be related to neuronal atrophy in the hippocampus and the decreased expression of brain-derived neurotrophic factor (BDNF) in the cortical areas [30, 31]. BDNF is considered to be a marker of neuronal plasticity, i.e., acting via TrkB receptors and causing long-term neuroplastic changes in learning and memory processes [30]. Animal models of depression have shown that the prolonged use of antidepressants (fluoxetine, tranylcypromine, sertraline, desipramine, mianserin) results in the increased expression of BDNF and its receptor TrkB and enhanced neuronal proliferation in the hippocampus and frontal cortex. Consequently, antidepressants restore normal functioning in the limbic dopaminergic areas, reduce anhedonia and depressive behavior (e.g., shortening of latency time in the learned helplessness test in depressive response models) [32].

Numerous studies indicate that fluoxetine, a selective serotonin reuptake inhibitor, has a weak affinity for other monoaminergic receptors and has a significant effect on the dopaminergic system [27, 33]. In preclinical studies, the administration of fluoxetine reduced the incidence of amphetamine use in the self-administration model [33, 34]. Studies show that serotoninergic projection from the raphe nuclei to VTA activates the dopaminergic system, resulting in the increased dopamine release in the nucleus accumbens and prefrontal cortex [27, 35]. The results of the effects of concomitant administration of bupropion (selective DA and NE reuptake inhibitor without the sero-

toninergic activity) and fluoxetine are interesting. Preclinical studies have shown that the administration of fluoxetine followed by bupropion increased the concentration of DA in PFC, NAc and hypothalamus, compared to fluoxetine alone [27].

Plastic changes induced by the use of psychoactive substances

Psychostimulants (amphetamine, its derivatives and cocaine) induce an increase of the dopamine levels in the reward system, including NAc and VTA. These compounds produce behavioral effects similar to natural rewards, but their impact is stronger and longer-lasting [36]. These substances have a strong influence on the nervous system, which can lead to addiction [37–39]. It has been shown that after a single administration of psychostimulants, plastic changes occur in the CNS. The administration of amphetamine resulted in the inhibition of NgR expression (protein that inhibits the axonal growth) and an increase in the expression of the arc protein (activates the growth of dendritic spines) observed in many areas of the central nervous system, including the cortex, hippocampus and striatum [40]. Plastic changes resulting from the chronic administration of psychostimulants occur on multiple levels of the dopaminergic reward system and can be associated with synaptic reconstruction, neurogenesis and neuronal atrophy.

The chronic self-administration of cocaine leads to desensitization of D2 autoreceptors in the VTA. Similar changes were observed after five-day administration of amphetamine. The changes were accompanied by hypofunction of the dopaminergic system in the VTA. The DAT increase was demonstrated in the studies of changes in DAT transporter levels in self-administering animals and amphetamine addicts, which in turn may be related to the compensatory response to an elevated DA level [41]. Some studies suggest that the administration of amphetamine in a new environment intensified the reaction to this compound and induced a stronger activation of the structures of the reward system [42].

The repeated administration of psychostimulants has negative effects and can trigger persistent pathological plastic changes in the CNS leading to addiction or other forms of psychopathology, such as mood disorders, stimulant psychosis and memory disorders. Side effects of psychostimulants are more common with high doses. Some researchers suggest that low doses of amphetamine or its derivatives (e.g., lisdexamphetamine) may improve memory in healthy individuals and patients with ADHD who have weakened dopaminergic transmission in the prefrontal cortex [43].

Impact of sex and age on the functioning of the dopaminergic system

An important aspects of the functioning of the dopaminergic mesolimbic system are differences between the sexes and the aging process. It has been shown that men, compared to women, are characterized by a higher basal activity of the dopaminergic system, but lower reactivity to natural stimuli and psychoactive substances [44]. These differences are due to the impact of gonadal hormones on the reward system. Studies have shown that estrogen may increase the release of dopamine [45].

In the process of aging there is a gradual weakening of the functioning of dopaminergic transmission, which may affect the attenuation of cognitive function. However, progression of alteration show large individual differences. Studies using positron-emission tomography PET (using radiolabeled tyrosine) and functional magnetic resonance imaging fMRI found that the individual differences concern dopamine synthesis capacity and frontoparietal activity [46]. Furthermore, it was found that the level of expression of D1 receptor (striatum, frontal cortex), D2 receptor (frontal cortex, hippocampus, amygdala, thalamus) and DAT transporter activity (striatum) decreases with age [47]. Besides coexisting diseases and environmental factors, this process is particularly affected by genetic factors [48]. Many research centers are trying to identify polymorphisms in genes that encode components of the dopaminergic system, important in regulating cognitive functions and motivational processes. Meta-analyses suggest that BDNF gene polymorphism (valine to methionine substitution at position 66) may impair the function of the hippocampus, reduce its volume and decrease cognitive function. The polymorphism of the catechol-O-methyltransferase (COMT) gene (valine to methionine substitution at position 158) can reduce the activity of this enzyme, slow down the process of degradation of dopamine and other catecholamines. People with this variant of the COMT gene have been shown to achieve slightly higher scores on cognitive ability tests [49].

Epigenetic modifications in the dopaminergic system

Molecular studies indicate that the causes of interpersonal differences in response to stress, susceptibility to mental disorders or addiction may be related to the mechanisms of gene expression change that are activated by the environment [50, 51]. Epigenetic mechanisms may involve DNA methylation, posttranslational modification of histones and the action of non-coding RNA (miRNA). Changes caused by epigenetic factors can cause further permanent changes with consequences in later stages of life and manifest in the next generations. It has been shown that specific miRNA is involved in the mechanism of stress responses leading to depressive disorders in the model of isolation of baby rats from their mothers and in the procedure of chronic unpredictable stress. A stress factor in neonatal period resulted in an increase in the level of expression of D2 receptor mRNA and decrease in miRNA-9 in the striatum, while in adulthood, elevated the expression of mRNA and the D2 receptor protein level, and reduced the expression of miRNA-9 in the NAC. The changes correlated with the severity of depressive behaviors (decrease in the activity in the Porsolt test, reduced sucrose preference) [52].

It has been shown that the administration of cocaine increased the level of acetylated H3 and H4 histones in the NAC [50]. Studies indicate that the short-term increase in histone acetylation in the NAC correlates with the intensity of behavioral responses to psychoactive substances. However, prolonged histone acetylation inhibits the effect of cocaine and can lead to the fixation of epigenetic changes by activating methylation processes, such as histone H3 methylation [53]. Studies on epigenetic factors in the structures of the reward system are the current research direction aimed to assess the susceptibility to stress and predisposition to psychoactive substances addiction.

In conclusion, the neurobiological basis of individual differences in stress and psychoactive substances response are currently the focus of many researches and may soon lead to initial attempts to individualize therapy (e.g., the choice of drugs with a suitable pharmacological profile depending on the patient's reactivity to stressful situations). It is also possible to use drugs that inhibit, e.g., methylation of histones caused by environmental factors or psychoactive substances.

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