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Review article

Spaceflight and brain plasticity: Spaceflight effects on regional expression of neurotransmitter systems and neurotrophic factors encoding genes

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ABSTRACT

The critical problem of space exploration is the effect of long-term space travel on brain functioning. Current information concerning the effects of actual spaceflight on the brain was obtained on rats and mice flown on five missions of Soviet/Russian biosatellites, NASA Neurolab Mission STS90, and International Space Station (ISS). The review provides converging lines of evidence that: 1) long-term spaceflight affects both principle regulators of brain neuroplasticity – neurotransmitters (5-HT and DA) and neurotrophic factors (CDNF, GDNF but not BDNF); 2) 5-HT- (5-HT_{2A} receptor and MAO A) and especially DA-related genes (TH, MAO A, COMT, D1 receptor, CDNF and GDNF) belong to the risk neurogenes; 3) brain response to spaceflight is region-specific. Substantia nigra, striatum and hypothalamus are highly sensitive to the long-term spaceflight: in these brain areas spaceflight decreased the expression of both DA-related and neurotrophic factors genes. Since DA system is involved in the regulation of movement and cognition the data discussed in the review could explain dysfunction of locomotion and behavior of astronauts and direct further investigations to the DA system.

1. Introduction

The microgravity is a major problem of deep space and orbital missions. Since the terrestrial life evolved in a relatively constant gravitational environment, exposure to microgravity and space travel is evolutionary unknown and unusual experience that produced neurological and physiological disorders (Blaber et al., 2010; Clement and Ngo-Anh, 2013; Clement and Reschke, 2008; De la Torre, 2014). Astronauts suffer from sleep deficiency (Barger et al., 2014; Flynn-Evans et al., 2016; Wu et al., 2018), alterations in vestibular (Clement et al., 2005; Lackner and Dizio, 2006), cognitive, perception (Strangman et al., 2014) and motor (Kozlovskaya et al., 1981) functions. MRI studies indicate narrowing of the central sulcus and CSF spaces at the vertex of the astronauts after long-duration flights (Roberts et al., 2017). The effects of long-term microgravity exposure on the brain plasticity are the milestone problem of space neuroscience (Van Ombergen et al., 2017a, b). The investigations of the brain mechanisms underlying the development of behavioral disorders in spaceflight are at the very beginning, and the identification of risk genes for long-term spaceflight is one of the first steps towards understanding long-term spaceflight consequences for human behavior and brain functioning.

The principal regulators of behavior and brain plasticity are neurotransmitters and brain neurotrophic factors. However, the investigation of the brain of the astronauts is technically limited. The validity of ground-based animal models of microgravity is questionable (Kulikova et al., 2017). Unique and important events in the study of effects of microgravity and the actual spaceflight on the brain were the flights of biosatellites launching experimental animals.

Current information concerning the influence of actual spaceflight and microgravity on the brain neurotransmitters and brain neurotrophic factors was obtained on animals (rats, mice) flown on the mission of five Soviet/Russian biosatellites (Cosmos 782, Cosmos 936, Cosmos 1129, Cosmos 2044 and Bion-M1), NASA Neurolab Mission STS 90 and International Space Station (ISS) (Table 1) (Culman et al., 1985; Hyde et al., 1992; Kvetnansky et al., 1983; Naumenko et al., 2015; Pompeiano et al., 2004, 2002; Popova et al., 2015; Santucci et al., 2012; Tsybko et al., 2015). The effect of spaceflight on the level and metabolism of noradrenaline (NA), dopamine (DA) and serotonin (5-HT) in rat brain was studied in the experiments carried out on Cosmos 782, Cosmos 936 and Cosmos 1129 biosatellites (Ballard and Connolly, 1990; Culman et al., 1985; Kvetnansky et al., 1983). Although the sample volumes in these experiments were representative (n = 5–7), the brain area was

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Table 1
List of the experiments on the effects of real spaceflight on the brain neurotransmitter systems and neurotrophic factors.

Mission	Year, Duration (days)	Species	Characteristics	References
Cosmos 782	1975, 19.5	Wistar rats	NA level, TH, DBH and MAO activities in the total hypothalamus	Kvetňansky et al., 1983
Cosmos 936	1977, 18.5		5-HT level in 8 discrete hypothalamic nuclei	Čulman et al., 1985
Cosmos 1129	1979, 18.5	Wistar rats	DA level in 6 discrete hypothalamic nuclei	Kvetňansky et al., 1983
Cosmos 2044	1989, 14	Wistar rats	Muscarinic and GABAA receptors densities in cingulate, motor, sensory, olfactory cortex and striatum	Hyde et al., 1992
NASA Neurolab Mission STS 90	1998, 15	Fisher 344 rats	Fos and Fra protein levels in brainstem vestibular and reticular structures	Pompeiano et al., 2002; 2004
International Space Station	2009, 91	C57BL/ 10 mice	BDNF and NGF proteins levels in the cortex, hippocampus, cerebellum and adrenal gland	Santucci et al., 2012
Bion-M1	2013, 30	C57BL/ 6 mice	The expression of genes encoding TPH2, TH, COMT, MAO A, MAO B, 5-HTT, DAT, 5-HT1A, 5-HT2A, 5-HT3, D1, D2 receptors in the frontal, visual cortex, hippocampus, striatum, hypothalamus, midbrain raphe, substantia nigra	Popova et al., 2015
			The expression of genes encoding BDNF, TrkB, p75 receptors, BCL-XL, BAX in the frontal, visual cortex, hippocampus, striatum, hypothalamus, midbrain raphe, substantia nigra	Naumenko et al., 2015
			The expression of genes encoding GDNF, CDNF in the frontal, visual cortex, hippocampus, striatum, hypothalamus, midbrain raphe, substantia nigra	Tsybko et al., 2015

Abbreviations: NA-noradrenaline, DA-dopamine, 5-HT-serotonin, TPH2-tryptophan hydroxylase 2, TH – tyrosine hydroxylase, DBH- dopamine-β-hydroxylase, MAO A, MAO B -monoamine oxidases A, B, COMT-catechol-O-methyltransferase, 5-HTT-5-HT transporter, DAT- dopamine transporter, NGF-nerve growth factor, BDNF- brain derived neurotrophic factor, GDNF- glial cell-line derived neurotrophic factor, CDNF- cerebral dopamine neurotrophic factor, TrkB- tropomyosin receptor kinase B.

restricted to hypothalamus, whereas the effects of spaceflight on other brain structures were not studied (Culman et al., 1985; Kvetnansky et al., 1983). The levels of the Brain-Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) in the brain and adrenals of C57BL/10 and transgenic mice with over-expression of pleiotrophin were investigated in the experiments carried out at the International Space Station (ISS). Regretfully, only one wild type and two transgenic mice returned after 91-day-long space mission (Santucci et al., 2012).

Representative study of the effects of actual spaceflight on the brain neurotransmitter and brain neurotrophic factor (BDNF, GDNF, CDNF) systems encoding genes was carried out on mice exposed to one month spaceflight on the Russian biosatellite Bion-M1, part of the Bion series of Russian space mission (Naumenko et al., 2015; Popova et al., 2015; Tsybko et al., 2015). The animal-carrying space capsule was launched into orbit of April 19, 2013, and returned to Earth on May 19, 2013. In order to differentiate the effect of microgravity from the effect of stress caused by cabin conditions and special diet, in addition to vivarium control, a special experiment on mice that spent the same amount of time in the same cabin that was used for spaceflight but under normal gravitation (cabin group) was carried out (Andreev-Andrievskiy et al., 2014).

The present review will discuss the effect of actual spaceflight on the expression of genes encoding metabolic enzymes and receptors of classic brain neurotransmitters (DA and 5-HT) and neurotrophic factors (BDNF, GDNF, CDNF). Brain neurotransmitters, 5-HT and DA, and brain neurotrophic factors BDNF, GDNF, CDNF are known as principal players in different kinds of plasticity – from neurons to behavior. 5-HT is involved in the regulation of behavior, sleep and stress response. Dysfunction of the brain 5-HT system is implicated in the mechanisms underlying neuropsychiatric disorders including depression, aggression, drug abuse and suicide (Hamon and Blier, 2013; Miller and Hen, 2015; Willner et al., 2013).

Brain DA represents another neurotransmitter that attracts attention given its well-defined role in the regulation of locomotion and muscle tone (Korchounov et al., 2010) and its involvement in exercise-induced central fatigue (Foley and Fleshner, 2008), tardive dyskinesia (Rana et al., 2013) and Parkinson's disease (Antonelli and Strafella, 2014; Poletti and Bonuccelli, 2013). DA is also a modulator of learning, motivation and reward-related behavior (Guzman-Ramos et al., 2012). Importantly, DA system is involved in the regulation of muscle and cognitive functions that altered in astronauts after long-term spaceflight. Until recently the effects of spaceflight on the DA system was completely unknown.

Brain neurotrophic factors, NGF, BDNF, GDNF, and CDNF, play critical role in neuronal development, function, survival and plasticity of mature neurons. Cross-talk between 5-HT and BDNF systems was shown in some kinds of behavior, stress response and antidepressant drug action (Popova and Naumenko, 2019). GDNF and CDNF are an important component of DA-related activity.

The effect of spaceflight on the brain neurotransmitters and neurotrophic factors is an important and intriguing problem. Largely, the review will focus on the data obtained from the Russian biosatellite Bion-M1.

2. Long-term spaceflight and the brain neurotransmitters

2.1. Dopamine

Brain DA is synthesized in a two-step reaction from amino acid tyrosine. The rate-limiting enzyme in DA biosynthesis is tyrosine hydroxylase (TH) converting tyrosine to DA precursor 3,4-dihydroxyphenylalanine (DOPA). Three enzymes catalase DA degradation - catechol-O-methyltransferase (COMT) and monoamine oxidase A and B (MAO A, MAO B). MAO A is also a principle enzyme in 5-HT degradation (Fig. 1).

Dopamine cell bodies are located in neighboring midbrain nuclei - the substantia nigra (s. nigra, A9 region), an area involved in the initiation of movement (Freed and Yamamoto, 1985; Meeusen et al., 2001), and ventral tegmental area (VTA; A10), and then projected to different brain regions. A rather small group of DA neurons is located in hypothalamus (Smith and Villalba, 2008). There are four generally

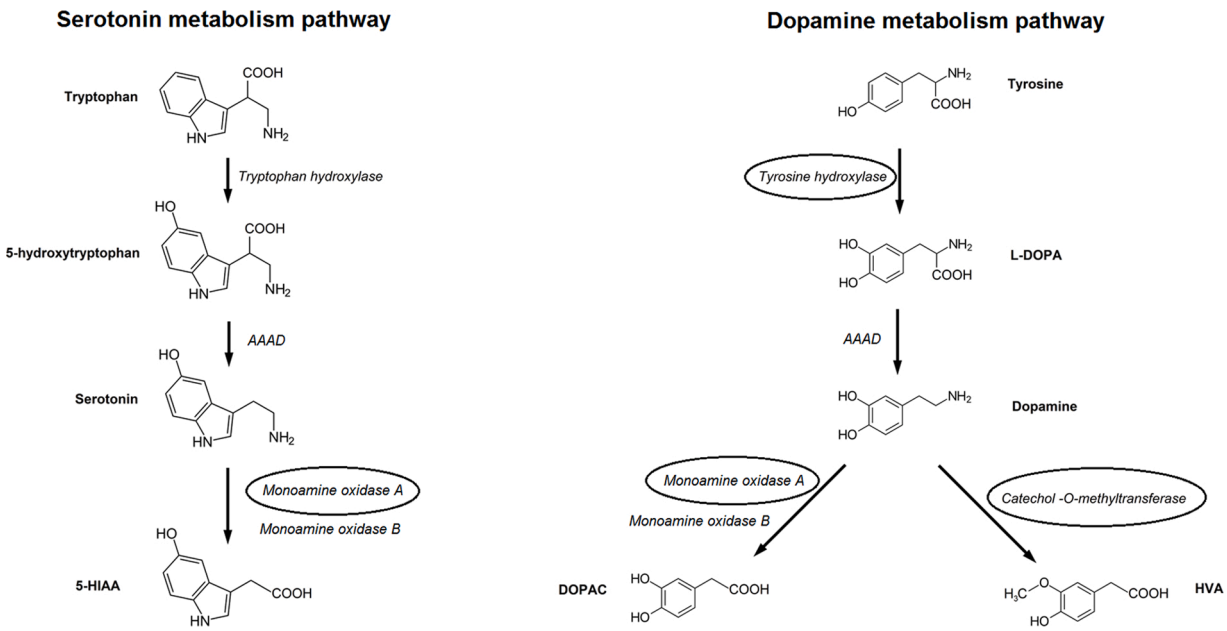

Fig. 1. Serotonin and dopamine metabolism pathways. Enzymes affected by actual long-term spaceflight on Bion-M1 biosatellite are highlighted by ovals. AAAD – Aromatic L-Amino Acid Decarboxylase; 5-HIAA - 5-Hydroxyindoleacetic acid; DOPAC - 3,4-Dihydroxyphenylacetic acid; HVA - Homovanillic acid.

acknowledged DA-ergic pathways: nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular pathways (Fig. 2).

Nigrostriatal DA plays an important role in movement regulation by acting on D1 and D2 receptors expressed by striatal medium sized spiny neurons (Cole et al., 2018). It has been generally accepted that DA-ergic input exerts a facilitatory effect on the D1 receptor and an inhibitory effect on the D2 receptor (Lanciego et al., 2012). Numerous experimental data demonstrated that DA metabolism, content and release increased during physical activity (Foley and Fleshner, 2008). Synaptic DA concentration increases immediately before the start of the movement and rises in the synapse during the movement from resting nanomolar to micromolar level (Korchounov et al., 2010). The loss of DA produced strong akinesia in experimental models (Duty and Jenner, 2011) and in Parkinson's disease. Parkinson's disease is neurodegenerative disorder characterized by progressive loss of brain DA neurons and motor and nonmotor (cognitive impairment with deficit of executive functions and episodic memory impairment) symptoms (Mahato et al., 2020; Poletti and Bonuccelli, 2013; Smith and Villalba, 2008).

For many years, the regulation of movement and muscle tone was considered as the main functional role of the brain DA. Yet recent studies have revealed another principle function of DA – the critical role of mesocortical and mesolimbic DA in reward-related motivation and learning, addiction, appetitive and aversive processes (Berke, 2018; Cole et al., 2018; Hamid et al., 2016; Salamone and Correa, 2012). DA

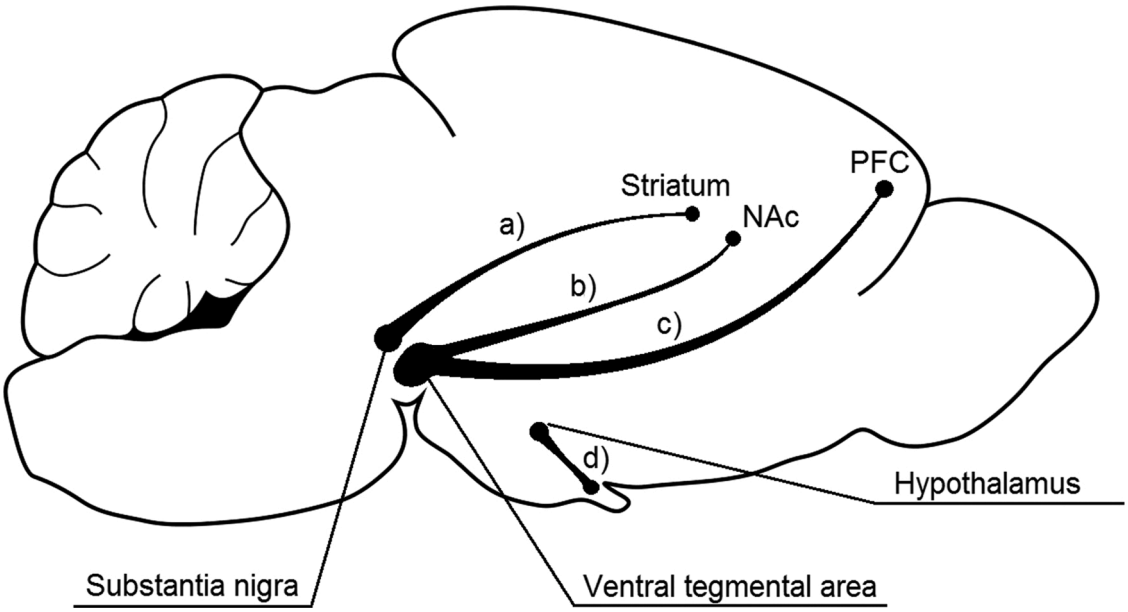

Fig. 2. Main brain dopamine projections: a) nigrostriatal pathway. Released in the s. nigra DA induces the activation of the primary forebrain target of DA, striatum (caudate putamen, globus pallidus and the subthalamic nucleus basal ganglia); b) mesolimbic pathway. DA is synthesized in the ventral tegmental area and transmitted to the limbic system (nucleus accumbens, amygdala, hippocampus); c) mesocortical pathway. Synthesized in the ventral tegmental area DA is transmitted into prefrontal cortex; d) tuberoinfundibular pathway. Synthesized in hypothalamus and stored in the pituitary DA regulates the secretion of hormone prolactin.

neurons have been shown to fire in two firing modes, tonic and bursts at higher frequency, "phasic", firing. Burst firing produces a transient increase in extracellular DA, while tonic firing causes a new steady-state level (Heien and Wightman, 2006). The recording of DA neurons in primates revealed brief bursts of activity, "phasic" DA firing that triggered immediate movement. It is important that DA cells responded to unexpected stimuli rather than to expected stimuli. "Phasic" firings of DA neurons are necessary to establish long-term memories associating predictive stimuli with rewards and punishments. Animals unable to synthesize DA lack the conditioned reflexes, they have only unconditioned consummatory reflexes (Wise and Robble, 2020). These findings were interpreted as the indication that DA cell firing in the ventral tegmental area signal the discrepancy between expected and actual rewards (reward prediction errors, RPEs), providing a learning signal to guide future behavior (Berke, 2018; Cohen et al., 2012; Montague et al., 1996). Decision-making RPEs are used to estimate values of future reward and to decide whether it is worth exerting the effort and expend resources (Hamlet's problem "to be or not to be"). The estimated desirability must be continuously revised through experience according to the discrepancy between the predicted and obtained rewards (Lee and Seo, 2007).

High mesolimbic DA supports the decision that engaging in temporally-extending work is worthwhile, but as DA is lowered animals do not bother, and may instead just go to sleep (Berke, 2018). Animals treated with blocking DA receptors neuroleptics had a deficit in the motivation to initiate voluntary movements (Wise, 2008). Fundamental component of depression is disordered reward processing as seen in the symptoms of reduced motivation and anhedonia. Many studies have established that dysregulation of the mesolimbic dopamine reward pathway is involved in pathophysiology of depression (Nestler and Carlezon, 2006).

Long-lasting spaceflight (one month on the Russian Bion-M1 spacecraft) considerably affected the genetic control of the brain DA (Popova et al., 2015) (Fig. 3). Spaceflight decreased the expression of genes encoding enzymes for both DA synthesis and degradation. The expression of gene encoding key enzyme for DA biosynthesis, TH, and genes of two enzymes for different pathways of DA metabolism - oxidative deamination (MAO A) and O-methylation (COMT), was significantly decreased after spaceflight. Importantly, the expression of the gene encoding TH was reduced in the main area of DA synthesis in the brain, the substantia nigra (Popova et al., 2015). The reduction of DA neurotransmission in substantia nigra could impair activation of the basal ganglia and reduce stimulation of motor cortex leading to central fatigue and a wide spectrum of RPEs including deficit of motivation to initiate physical activity (Foley and Fleshner, 2008). Microgravity and the spaceflight reduced the expression of the gene encoding pivotal enzyme of oxidative deamination of both DA and 5-HT, MAO A, in the frontal cortex. In the striatum it decreased the expression of the gene encoding enzyme for DA O-methylation, COMT.

Taken together with the decreased expression of dopamine D1 receptor gene in striatum and hypothalamus these data indicate substantial attenuating effect of long-term spaceflight on the genetic control of the brain DA system. At the same time, the expression of genes encoding the D2 receptor and the dopamine transporter (DAT) in all investigated brain areas (frontal cortex, visual cortex, midbrain, hippocampus hypothalamus, striatum and substantia nigra) was unaltered (Popova et al., 2015).

The data presented point to significant region specificity of the spaceflight effect. Substantia nigra, striatum and hypothalamus occurred to be risk brain structures highly sensitive to the effect of spaceflight (Fig. 3). In substantia nigra, the main area of DA synthesis in the brain, the expression of the key enzyme in DA synthesis, TH, and the expression of CDNF decreased. Region-variability of the effect of spaceflight may depend on high difference in the DA level and metabolism across brain region. Earlier, we have shown that the DA level in striatum of wild type mice was 100-times higher than in frontal cortex. The ratio of DA metabolite DOPAC to DA was more than 20 times lower than in frontal cortex and hippocampus (Popova et al., 2005).

In striatum of spaceflight mice, the decreased expression of genes encoding COMT, D1 receptor, GDNF and BCL-XL was shown (Naumenko et al., 2015; Popova et al., 2015; Tsybko et al., 2015). The decreased acetylcholine M1 receptor in striatum of rats after fourteen-days spaceflight on Cosmos 2044 mission was described (Hyde et al., 1992). Striatum has been shown to be involved in complex behaviors such as motor control, learning, decision-making, reward and aversion (Soares-Cunha et al., 2016). In hypothalamus, the expression of the D1 receptor, 5-HT_{2A} receptor, GDNF and BCL-XL gene has decreased. Hypothalamus is involved in the mechanisms of stress-response,

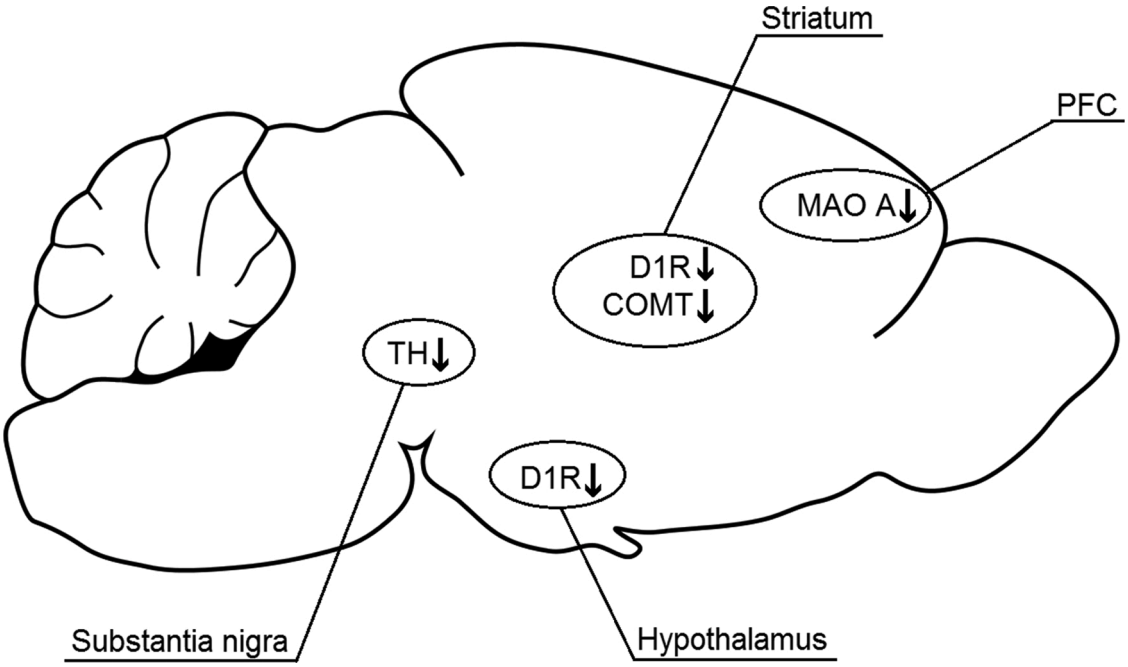

Fig. 3. Long-term spaceflight-induced changes in the expression of key genes of the brain DA system. PFC – prefrontal cortex; TH – tyrosine hydroxylase; D1R – Dopamine D1 receptor; COMT – Catechol-O-methyltransferase; MAO A – monoamine oxidase A. Down arrow - spaceflight-induced decrease of the gene expression.

stress-induced depression (Ge et al., 2013; Tennison et al., 2010), psychotic depression (Goekoop et al., 2012) and major depressive disorder (Carvalho Fernando et al., 2012).

These data give ground to suggest that a long-term spaceflight-induced decrease in DA-related gene expression in substantia nigra, striatum and hypothalamus could be among the causes of behavioral disturbances produced by prolonged spaceflight.

2.2. Serotonin

The brain 5-HT system is one of the fundamental neurotransmitter systems. The cell bodies of 5-HT neurons localizing in the raphe nuclei of midbrain send the terminals to all brain regions. Every cortical neuron receives about 200 serotonergic contacts (Gaspar and Lillesaar, 2012; Jacobs and Azmitia, 1992). In the brain, 5-HT is synthesized from the essential amino acid L-tryptophan by two brain enzymes, tryptophan hydroxylase 2 (TPH2) and aromatic L-amino acid decarboxylase (AAAD) (Fig. 1). TPH2 is the rate-limiting and the only specific enzyme of the 5-HT synthesis and metabolism in the brain (with TPH1 playing a similar role in the periphery) (Walther and Bader, 2003; Walther et al., 2003), while AAAD is the widespread and nonspecific enzyme (Albert et al., 1987). Synthesized 5-HT is stored in synaptic vesicles, transported to presynaptic terminals and released in the synaptic cleft by Ca^{2+}-dependent exocytosis which in its turn is regulated by the feedback mechanism involving the presynaptic 5-HT_{1A} and 5-HT_{1B} autoreceptors on the cell body of 5-HT neuron (Artigas, 2013; Barnes and Sharp, 1999). Released 5-HT interacts with 14 types of currently known 5-HT receptors coupled to four different mechanisms of signal transduction. Thirteen of 14 types of 5-HT receptors are coupled to Gs (5-HT_4, 5-HT_6 and 5-HT_7), Gi (5-$HT_{1A\text{-}1F}$, 5-HT_5) or Gq (5-$HT_{2A\text{-}2C}$) proteins and only one, 5-HT_3, forms the Na^+ ion channel (Pytliak et al., 2011). The presynaptic 5-HT_{1A} receptor regulates 5-HT secretion and some of 5-HT_{1A} agonists are anxiolytics (Popova and Naumenko, 2013). The postsynaptic 5-HT_{2A} receptor is considered to be involved in the mechanisms of psychopathologies (Carhart-Harris and Nutt, 2017). Released 5-HT is removed from the synaptic cleft into the presynaptic 5-HT neurons by the plasma membrane 5-HT transporter (5-HTT) (Grouleff et al., 2015; Spies et al., 2015). The up-taken neurotransmitter can either be stored in the vesicles or be oxidized to 5-hydroxyindoleacetic acid (5-HIAA) predominantly by the MAO A (Shih and Thompson, 1999; Shih et al., 2011) (Fig. 1).

The effect of actual spaceflight on the brain 5-HT system was studied on rats exposed to 18.5 days on the board of biosatellites Cosmos 1129 (Culman et al., 1985) and on mice after one month spaceflight on Bion-M1 (Popova et al., 2015). The level of 5-HT was unchanged in the majority of hypothalamic nuclei of rats subjected to spaceflight. The increased 5-HT level in the supraoptic nucleus and reduced 5-HT concentration in periventricular nucleus was recorded compared to the intact, but not shuttle cabin synchronous control. Therefore, the observed increase in 5-HT in the supraoptic and paraventricular nuclei may be resulted from cabin housing stress rather than microgravity. The authors suggested that either that spaceflight stress cannot be an intensive stressor or that during the flight rats already adapted to its long-term effect (Culman et al., 1985).

In the experiment carried out on Bion-M1 biosatellite, the expression of genes encoding TPH2, MAO A, MAO B, 5-HT_{1A}, 5-HT_{2A}, 5-HT_3 receptors was assayed in frontal cortex, visual cortex, hippocampus, hypothalamus, striatum, midbrain and substantia nigra. Expression of genes encoding the TPH2 and 5-HTT was assessed in the midbrain raphe nuclei (these genes are expressed only in 5-HT neurons located in midbrain) (Popova et al., 2015). Spaceflight did not affect the expression of 5-HT_{1A}, 5-HT_3 and MAO B genes in all structures, as well as 5-HTT and TPH2 genes in midbrain. At the same time, spaceflight decreased MAO A mRNA level in the frontal cortex and striatum, MAO B in the midbrain raphe nuclei and 5-HT_{2A} receptor gene in the hypothalamus (Popova et al., 2015). Double control (vivarium vs. one month shuttle cabin housing under normal gravity) allowed a) to conclude that the reduction of the expression of common with DA MAO A gene in the frontal cortex and 5-HT_{2A} gene in the hypothalamus of spaceflight mice was caused by microgravity, and b) to exclude from this list MAO A gene in the striatum and MAO B in the midbrain raphe nuclei.

Thus, actual spaceflight produces rather moderate effect on the brain 5-HT system: it did not affect the expression of key regulators of 5-HT system functional activity - the most specific for the 5-HT enzyme TPH2, 5-HTT and 5-HT_{1A} genes in midbrain raphe nuclei where the 5-HT cell bodies are located. However, spaceflight affects the 5-HT system in mouse frontal cortex, striatum and hypothalamus. Some of these alterations such as decrease in MAO A gene expression in striatum and MAO B in frontal cortex seem to result from cabin housing stress. At the same time, decreased expression of MAO A gene (common with DA) in the frontal cortex and 5-HT_{2A} receptor gene in the hypothalamus can be caused by spaceflight.

Although the frontal cortex participates in the mechanisms of numerous physiological and psychical functions, the observed relationship between the reduction of mRNA expression in this structure and the disorders of physiological and psychical functions caused by spaceflight remain obscure.

At the same time, the relationship between the decrease in 5-HT_{2A} receptor gene expression in hypothalamus and prolonged exposure to microgravity is more suggestive. Recently it was shown that decelerating gravity change from 2 g hypergravity to 1 g normal gravity increased 5-HT_{2A} receptor gene expression in rat hypothalamus (Ishikawa et al., 2017). The 5-HT_{2A} receptor is involved in the regulation of corticotrophin-releasing hormone in the paraventricular nucleus of hypothalamus (Hanley and Van de Kar, 2003; Heisler et al., 2007; Jorgensen et al., 2003, 2002; Jorgensen, 2007). Corticotrophin-releasing hormone activates ACTH secretion in pituitary gland and therefore corticosteroid secretion by adrenals. Short (5–7 days) or long (>14 days) spaceflights increased the plasma corticosterone level in rats (Macho et al., 1996). It suggests that spaceflight can affect the corticosterone level via hypothalamic 5-HT_{2A} receptors.

Also prolonged spaceflight frequently produced sleep disturbances in astronauts (Flynn-Evans et al., 2016; Wu et al., 2018). Brain 5-HT is involved in the regulation of the sleep-waking cycle. The firing activity of 5-HT neurons in the dorsal raphe nuclei was the highest during waking, decreased during slow-wave sleep and ceased during REM sleep (Atkin et al., 2018; Jones, 2005; Ursin, 2002). Ablation of the raphe nuclei increases wakefulness, while their tonic optogenetic stimulation induces sleep (Oikonomou et al., 2019). Studies with selective 5-HT_{2A} antagonists and reversed agonists as well as experiments on knockout mice indicate that the 5-HT_{2A} receptors promote slow wave sleep (Atkin et al., 2018; Popa et al., 2005).

3. Long-term spaceflight and the brain neurotrophic factors

Neurotrophic factors, BDNF, NGF, GDNF and CDNF are other possible players in spaceflight-induced nervous and behavioral disorders. Neurotrophic factors were identified as a major regulator of synaptic plasticity, survival and differentiation of neurons not only in early development but also in adult brain (Barde, 1990). At the same time, NGF, BDNF and GDNF have clearly emerged as targets in pathogenesis of many diseases of the nervous system including depression and neurodegenerative diseases (Gibon and Barker, 2017; Hu and Russek, 2008; Mondal and Fatima, 2019; Pittenger and Duman, 2008; Rocco et al., 2018; Schmidt et al., 2008). Numerous investigations demonstrated the interrelation of neurotrophic factors with classical neurotransmitters, 5-HT and DA. BDNF is closely linked with the 5-HT system of the brain (Popova et al., 2017), whereas GDNF and CDNF are known as DA-protecting neurotrophines (this characteristic is even reflected in the name of CDNF – Cerebral Dopamine Neurotrophic Factor) (Lindholm and Saarma, 2010) (Fig. 4).

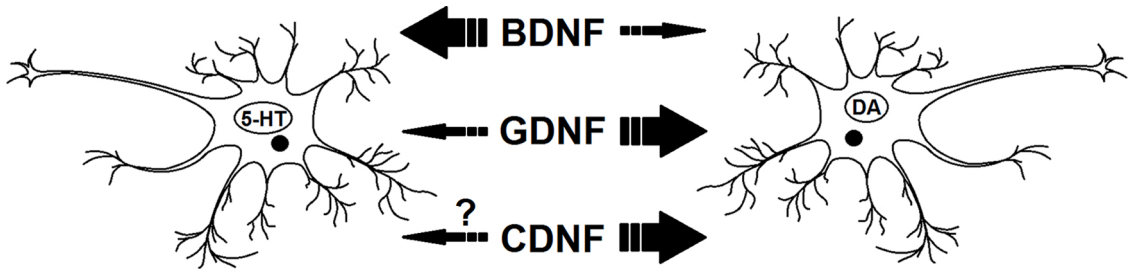

Fig. 4. Neurotrophic factors BDNF, GDNF and CDNF affect 5-HT and DA neurons. Bold arrow – major effect; thin arrow – alternative effect; arrow with question mark – non-documented assumed effect.

3.1. BDNF

Keen interest to widely distributed in the brain (Yan et al., 1997) BDNF is linked to its remarkable property of stimulating growth of neurons, axons and dendrites, synaptic formation, and other processes of neuroplasticity (Benarroch, 2015; Cohen-Cory et al., 2010; Gibon and Barker, 2017; Gulyaeva, 2017; Hoyng et al., 2011; Lu and Figurov, 1997). The deficiency of BDNF is considered to play an important role in the pathogenesis of depressive disorders (Carlino et al., 2013; Mondal and Fatima, 2019; Pittenger and Duman, 2008; Schmidt et al., 2008). It is known that mature BDNF promotes the neurogenesis via TrkB (tropomyosin receptor kinase B) receptor, whereas BDNF precursor proBDNF initiates apoptosis via p75 receptor (Ichim et al., 2012). An interaction between BDNF and the 5-HT system in adult brain was well demonstrated (Homberg et al., 2014; Popova and Naumenko, 2019). *Bdnf*+/- heterozygous mice with the two-fold lowered BDNF level show an early decline of the brain 5-HT functional activity, a reduction in the 5-HTT protein level, 5-HT_{1A} receptor functional activity (Homberg et al., 2014; Lyons et al., 1999) and elevation in the 5-HT_{2A} receptor protein level (Trajkovska et al., 2009). In contrast, BDNF overexpression in striatum induced local 5-HT fiber sprouting (Tronci et al., 2017). Chronic administration of 5-HT-related antidepressants increases the expression of BDNF and TrkB receptors (Castren and Rantamaki, 2010).

Hypergravity exposure affects NGF and BDNF levels in the developmental brain of rat (Sajdel-Sulkowska et al., 2009) and mice (Santucci et al., 2000, 2009). At the same time, no effect of microgravity on the level and expression of these neurotrophins was observed. In the experiment carried out on mice that returned after a 91-day-long space mission on the board of International Space Station (ISS) showed no effect of actual spaceflight on BDNF and NGF protein levels in cortex, hippocampus and cerebellum (Santucci et al., 2012). More detailed investigation of the effect of spaceflight on the BDNF system also did not reveal significant changes in the BDNF system as well (Naumenko et al., 2015). Long-term spaceflight on Bion-M1 did not alter the expression of BDNF gene as well as genes encoding both the BDNF receptor TrkB and the proBDNF receptor p75 in frontal cortex, visual cortex, hippocampus, striatum, hypothalamus, midbrain and substantia nigra. These data indicate the resistance of genes encoding BDNF, TrkB and p75 receptors to the spaceflight microgravity and environmental stress and allow to suggest that long-term spaceflight does not affect the BDNF-mediated neurogenesis.

3.2. GDNF and CDNF

In contrast to BDNF, long-term spaceflight produced significant effect on GDNF and CDNF (Fig. 5). GDNF was originally identified as a factor for survival of DA neurons (Lin et al., 1993). It is produced by striatal glial cells, astrocytes, and is necessary for the maintenance of the adult nigrostriatal DA circuit (Andressoo and Saarma, 2008). In rodent and primate models of Parkinson's disease, GDNF administration to striatum or substantia nigra protected nigrostriatal neurons from neurotoxins and rescued previously damaged neurons, promoting recovery of motor function (Pascual et al., 2011; Rangasamy et al., 2010).

CDNF is another neurotrophic factor regulating the DA system functioning. It is a member of a novel evolutionarily conserved protein family showing neurotrophic activities (Lindholm and Saarma, 2010). In the mouse brain, CDNF protein is detected mostly in striatum, substantia nigra, cortex, hippocampus, and cerebellum (Lindholm et al., 2008). Since CDNF recovers the motor function and prevents the loss of DA neurons in the 6-OHDA-lesioned nigrostriatal system, and in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease (Airavaara et al., 2012), it was suggested that CDNF prevents further degeneration of DA neurons and maintains or increases the functionality of remaining neurons (Cordero-Llana et al., 2015; Lindholm et al., 2007; Nadella et al., 2014; Voutilainen et al., 2011). Presumably, CDNF also induces DA neurite growth and axonal sprouting (Lindholm et al., 2008, 2007).

One-month spaceflight on the board of biosatellite Bion-M1 produced a considerable reduction in GDNF gene expression in striatum and hypothalamus, and reduced the expression of the gene encoding CDNF in substantia nigra. At the same time, actual spaceflight increased the expression of the genes encoding GDNF and CDNF in the raphe nuclei area of midbrain (Tsybko et al., 2015). All these alterations seem to be caused by microgravity, since one month shuttle cabin housing under normal gravity does not affect GDNF and CDNF expression in these brain structures.

Spaceflight-induced decrease in GDNF gene expression in striatum and hypothalamus, and CDNF gene in substantia nigra can aggravate the damaging effect of microgravity on the DA system. At least one known mechanism of GDNF-dependent regulation of the DA function is associated with the TH mRNA level (Pascual et al., 2008) and TH phosphorylation in striatum and especially in substantia nigra (Salvatore et al., 2004). There is an evidence that GDNF is transported from striatum to dopaminergic cell bodies in substantia nigra, suggesting that in the nigrostriatal system GDNF acts as a target-derived factor for dopaminergic neurons (Saavedra et al., 2008).

In contrast to uniform negative effect of spaceflight on the expression of 5-HT- and DA-related genes in different brain areas, the response of GDNF and CDNF genes depends on the brain area, and, along with suppressed genes (GDNF in striatum and hypothalamus; CDNF in substantia nigra), the substantial increase in GDNF and CDNF gene expression was found in midbrain raphe nuclei (GDNF and CDNF) and frontal cortex (GDNF).

It is interesting that GDNF and CDNF responded synergistically both in the nigrostriatal DA system (decrease in GDNF gene expression in striatum accompanied by the decrease in CDNF expression in substantia nigra) and in the 5-HT system (increase in GDNF and CDNF expression in the midbrain raphe nuclei area) (Tsybko et al., 2015). These intriguing findings arise many questions that remain to be answered. Firstly, what is the molecular mechanism underlying remarkable regional diversity in response of GDNF and CDNF genes to spaceflight? GDNF and CDNF are predominantly expressed in glial cells, astrocytes, notable by structural, morphological and functional heterogeneity. Astrocytes represent populations of complex and morphologically and functionally diverse cell

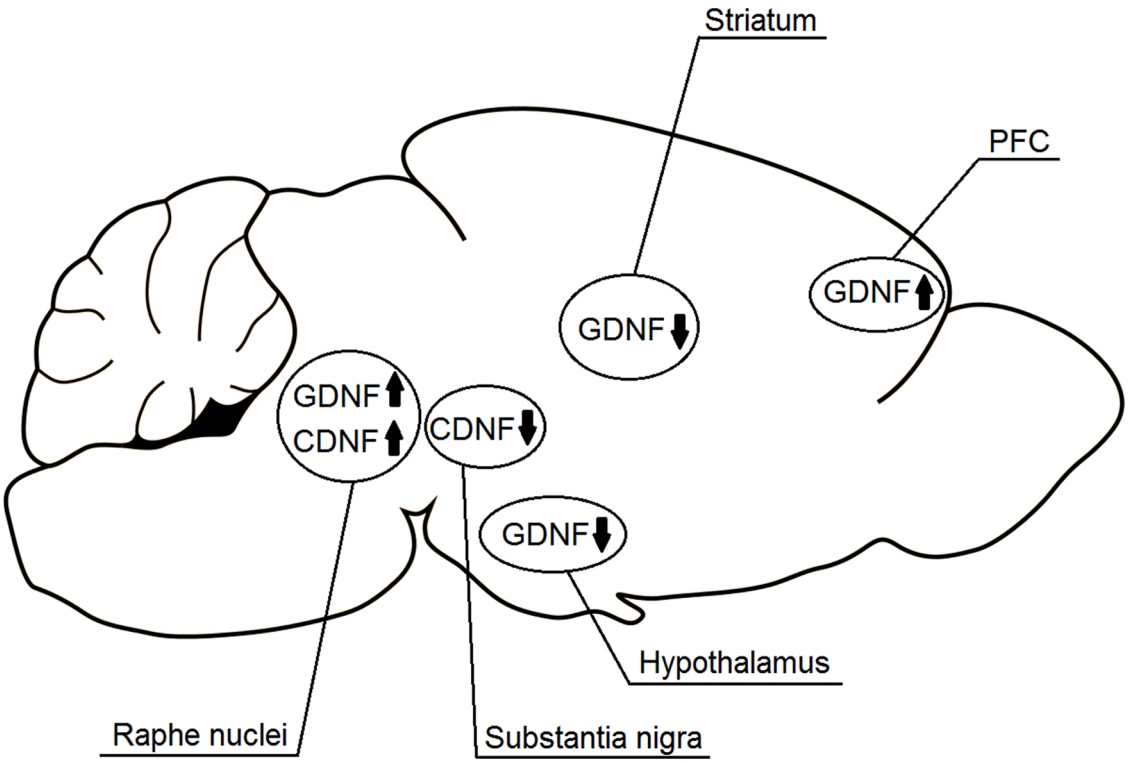

Fig. 5. Long-term spaceflight-induced changes in the expression of GDNF and CDNF. PFC – prefrontal cortex; Up arrow – spaceflight-induced increase of the gene expression; down arrow - spaceflight-decrease of the gene expression.

that mediate neural circuit-specific roles in health and disease. They respond to all forms of brain damage by undergoing cellular, molecular and functional changes (Gomazkov, 2018; Khakh and Sofroniew, 2015; Matyash and Kettenmann, 2010; Neal and Richardson, 2018). We hypothesize that regional heterogeneity in morphology and physiology of astrocytes may be at least one of the factors underlying region specificity in GDNF and CDNF response to microgravity.

4. Conclusion

Long-term spaceflight affected genetic control of both neurotransmitters and neurotrophic factors, although the sensitivity of various systems is different. Evidently, key genes of BDNF system belong to spaceflight-resistant neurogenes. The risk neurogenes for long-term spaceflight are DA system-related genes, the 5-HT_{2A} receptor and CDNF and GDNF genes. Long-term spaceflight decreased the expression of genes encoding enzymes for both DA biosynthesis and degradation. The expression of the gene encoding TH, a key enzyme in DA synthesis, in substantia nigra, the main area of DA synthesis in the brain, was reduced. DA catabolism in the brain occurs via two pathways: oxidative deamination by MAO A and MAO B, and O-methylation by COMT. MAO A gene expression in frontal cortex and COMT gene expression in striatum were decreased followed by spaceflight. Taken together with the decrease in the expression of dopamine D1 receptor gene in striatum and hypothalamus, these data indicate a substantial attenuating effect of long-term spaceflight on the genetic control of the brain DA system.

Noteworthy, the changes were found in the nigrostriatal DA system, which is considered to be the center of sensomotor integration (Onn et al., 2000), regulating the tone and contraction of skeletal muscle (Korchounov et al., 2010). The deleterious effect of microgravity on skeletal muscle is one of the major problems of space travel. One of the direct effects of microgravity is related to mechanical and proprioceptive changes during the execution of movements, leading to a disruption of usual relationships among efferent and afferent signals (Clement and Reschke, 2008). Studies of the effect of microgravity on both rats and humans have demonstrated increased rate of fatigue, severe atonia, rapid loss of muscle and fiber mass, muscle atrophy, impaired postural and locomotor activity (Kozlovskaya et al., 1981; Layne et al., 2001; LeBlanc et al., 2000; Roy et al., 1996; Shenkman et al., 2003). Decreased genetic control of the DA system may contribute to the spaceflight-induced locomotor impairment and dyskinesia. The damaging effects of space travel on skeletal muscle, as well as increased rates of fatigue, can be attributed not only to local changes in the substrates for muscle fiber metabolism and defective microcirculation (Fitts et al., 2001; Riley et al., 1992), but also to decreased nigrostriatal DA-ergic control (Popova et al., 2015).

Long-lasting spaceflight reduced the mRNA level of the gene encoding TH, a key enzyme in DA biosynthesis, in the main area of DA synthesis in the brain, substantia nigra (Popova et al., 2015). It is known that the mRNA level does not always fully correlate with the protein level as well as with the protein function. However, increased TH expression has been shown to be a good predictor of increased DA synthesis (Elsworth and Roth, 1997; Foley and Fleshner, 2008). In contrast, the reduction of DA neurotransmission in substantia nigra could impair activation of the basal ganglia and reduce stimulation of motor cortex leading to central fatigue and disruption in a wide spectrum of reward-related behavior including deficit of motivation to initiate physical activity (Foley and Fleshner, 2008). The negative effect of spaceflight on the genetic control of DA circuits could be aggravated by decreased expression of DA-protecting neurotrophines, CDNF gene in substantia nigra and GDNF gene in striatum and hypothalamus (Tsybko et al., 2015).

The effect of long-term spaceflight is region-specific. Substantia nigra, striatum and hypothalamus occurred to be risk brain areas highly sensitive to the microgravity and spaceflight. In these regions, both neurotransmitter and neurotrophic factor systems were affected. Spaceflight produced a decrease in the expression of genes encoding: (i) D1 receptor, COMT and GDNF in the striatum; (ii) D1 receptor, 5-HT_{2A} receptor and GDNF in the hypothalamus, (iii) TH and CDNF in substantia nigra. Substantia nigra represents the brain area of DA synthesis.

Striatum has been involved in complex behaviors such as motor control, and reward-related behavior (Soares-Cunha et al., 2016). Hypothalamus is involved in the mechanisms of stress-response, stress-induced depression (Ge et al., 2013; Tennison et al., 2010), psychotic depression (Goekoop et al., 2012) and major depressive disorders (Carvalho Fernando et al., 2012).

Enormous amount of literature linked DA to reward-related behavior - learning, decision-making, reward and aversion (Cohen et al., 2012; Fujii and Patten, 1992; Guzman-Ramos et al., 2012). In long-lasting spaceflight, DA deficiency-induced impairments of motivation and decision-making are of great importance. After landing however, ataxia, neuromuscular weakness and fatigue play significant roles in astronauts' health and retardation in adaptation to terrestrial environments (Fujii and Patten, 1992).

In contrast to dopamine, the effect of the spaceflight on genes of the 5-HT system was more limited. There were no changes in the expression of the genes encoding key regulators of the 5-HT functional activity: (a) rate limiting enzyme for 5-HT synthesis in the brain, TPH2, (b) 5-HT transporter (c), MAO B, (d) 5-HT_{1A} receptor, (e) 5-HT_3 receptor. Moreover, spaceflight did not alter the expression of 5-HT protecting BDNF. There were no changes in the mRNA level of BDNF gene as well as genes encoding both BDNF receptors - TrkB and p75, in all investigated brain structures (Naumenko et al., 2015). One can suggest that BDNF system persistence contributes to relative stability of the 5-HT circuit.

The only specific 5-HT system effect of spaceflight was decreased expression of common with DA metabolic enzyme, MAO A, in the frontal cortex and the expression of 5-HT_{2A} genes in the hypothalamus. The functional significance of this effect of spaceflight is not clear, but taking into account that 5-HT_{2A} receptors are involved in the regulation of a wide range of physiological functions, including sleep (Atkin et al., 2018; Jones, 2005; Oikonomou et al., 2019; Popa et al., 2005; Ursin, 2002), stress response (Hanley and Van de Kar, 2003; Heisler et al., 2007; Jorgensen, 2007), cognition, and memory (Williams et al., 2002; Wilson and Argyropoulos, 2005), the 5-HT_{2A} receptor should be investigated further.

Long-lasting space travel produced significant changes in genetic control of DA and 5-HT circuits and in neurotrophic factors, but which of these are adaptive, compensatory or damaging should still be determined. The question concerns: (I) the decrease in the expression of genes encoding two pathways of DA metabolism – MAO A and COMT, which can play a compensatory role directed to ameliorate the deleterious effect of spaceflight-induced decrease in DA synthesis, and (II) the increase in CDNF and GDNF genes expression in the midbrain raphe nuclei, main area of 5-HT neurons location. GDNF, which are considered to be predominantly regulators of the DA system, also interact with the brain 5-HT system (Popova et al., 2017) (Fig. 4). A single central administration of GDNF produced significant change in the expression of key genes of the 5-HT system leading to increase in expression of the genes encoding the TPH2 in the midbrain and 5-HT_{2A} receptor in frontal cortex (Naumenko et al., 2013). These data allow suggesting the adaptive and beneficial character of spaceflight-induced increase in GDNF gene expression in the midbrain raphe nuclei of mice. Although there is no data on the effect of CDNF on the brain 5-HT system, the results on the CDNF gene expression increase in the midbrain raphe nuclei followed spaceflight gives the ground to assume the role of CDNF in the regulation of the brain 5-HT system.

Taken together, these data indicate a substantial and complex effect of long-term spaceflight on the genetic control of the brain DA and 5-HT circuits and neurotrophic factor systems. This is new and important information that attracts attention of spaceflight neurophysiologists to the brain neurotransmitters and neurotrophic factors, GDNF and CDNF. Since the mRNA level does not always fully correlate with the protein level and function, the exact role of produced by long-term spaceflight dysregulation in the genetic control of DA and 5-HT circuits and neurotrophic factors remains to be elucidated. We can anticipate that genetic and functional studies of other individual genes will provide insight into the effect of long-term space travel on the brain of astronauts. After further detailed investigations the information concerning risk neurogenes will undoubtedly one day lead to new methods and pharmaceuticals that help to prevent the damaging effect of space travel on health of astronauts.

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