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APPROACHES TO MODELING AUTISM IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Abstract. Among neurodevelopmental disorders in children, the most common and socially significant are attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD). It has already been proven that ASD and ADHD have a number of common components of pathogenesis and are characterized by some common clinical features, but the factors that would lead to the development of ADHD, ASD or ADHD + ASD have not yet been described, which necessitates the development of animal models of this condition. Many research groups consider ASD and ADHD as polygenic diseases. However, the identification of more and more new candidate genes does not bring us closer to understanding the etiology. According to modern concepts, the development of AS + ADHD requires a combined effect of at least a genetic and cerebro-organic factor, therefore, to model the main symptoms of this condition, it is optimal to use drugs that cause organic brain damage in animals with genetically determined disorders. In these diseases, genetically determined disorders should mainly affect monoaminergic neurotransmitter systems, because they determine the course of all fundamental processes for the CNS. This review argues that rats with knockout of the dopamine transporter gene (genetic factor) and developed valproate syndrome (cerebral-organic factor) can be used to study the pathogenesis of ASD combined with ADHD.

Key words: autism spectrum disorders; attention deficit hyperactivity disorder; dopamine transporter knockout rats; sodium valproate.

ПОДХОДЫ К МОДЕЛИРОВАНИЮ АУТИЗМА ПРИ СИНДРОМЕ ДЕФИЦИТА ВНИМАНИЯ С ГИПЕРАКТИВНОСТЬЮ

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Резюме. Среди психических расстройств у детей наиболее распространенными и социально значимыми являются синдром дефицита внимания с гиперактивностью (СДВГ) и расстройства аутистического спектра (РАС). Уже доказано, что РАС и СДВГ имеют ряд общих звеньев патогенеза и характеризуются некоторыми общими клиническими особенностями, но факторы, действие которых приводило бы к развитию СДВГ, РАС или СДВГ + РАС, еще не описаны, что обусловливает необходимость разработки животных моделей такого

состояния. Многие исследовательские группы рассматривают РАС и СДВГ как полигенные заболевания. Однако выявление все новых и новых генов-кандидатов не приближает нас к пониманию вопроса их этиологии. Согласно современным представлениям, для развития РАС + СДВГ необходимо сочетанное действие, как минимум, генетического и церебрально-органического факторов, поэтому для моделирования основных симптомов данного состояния оптимально использовать препараты, вызывающие органическое поражение головного мозга у животных с генетически детерминированными нарушениями. При данных заболеваниях генетически детерминированные нарушения, главным образом, должны затрагивать моноаминергические нейромедиаторные системы, потому что именно они определяют течение всех фундаментальных для ЦНС процессов. В данном обзоре приводятся доводы в пользу того, что крысы с нокаутом гена — транспортера дофамина (генетический фактор) и развившимся вальпроатным синдромом (церебрально-органический фактор) могут быть использованы для изучения патогенеза РАС в сочетании с СДВГ.

Ключевые слова: расстройства аутистического спектра; синдром дефицита внимания с гиперактивностью; DAT-KO крысы; вальпроат натрия.

In children, the most common and socially significant psychiatric disorders are attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) [26, 37]. ADHD is a complex behaviour disorder [32] with high level of inheritance [41]. It is characterised by inattention, increased mobility and impulsiveness [32]. According to the 5th edition of Diagnostic and Statistical Manual of Mental Disorders, symptoms of ADHD appear before the age of 12 years, and cause significant impairment in social, academic, and occupational functioning throughout life [7]. Prevalence of ADHD in the world is 5–12 % [25]. It occurs 2–7 times more often in boys [41]. ASD is heterogeneous group of psychiatric diseases and disorders with similar symptoms, such as of a violation of the ability for social interaction, verbal and non-verbal communication, stereotypical behaviour [3, 6]. In recent years, the prevalence of ASD in the world increased 7–8 times, and currently is observed in 0.7–2.6 % of humans of all populations, regardless of racial, ethnic and socioeconomic states [1, 27]. ASD, like ADHD, are more common in boys [2, 21].

The most unfavourable prognosis is observed in case of ASD and ADHD combination [11, 12]. In children with both disorders, there are a lot of problems with education and socialisation, than, e.g., in children who have just ASD. In 12.5 % patients with ADHD, ASD is diagnosed, that is more common than in general population [60]. Despite its great social significance and prevalence of ASD and ADHD, etiology and pathogenesis of these disorders is still unknown. High frequency of ADHD and ASD combination shows some common links in etiology and pathogenesis. For example, in the study on genetic linkage of several groups of polymorphic markers located at loci 16p13, 2q24, 16p1, 17p11, 5p13 and 15q, it was shown, that such loci linked to ASD and ADHD [4, 20]. However, finding of new genes linked to ASD and ADHD does not bring us any closer to understanding the etiology of these disorders.

In these diseases, genetically determined disorders must affect monoaminergic neurotransmitter systems, because the systems determine the course of all fundamental processes for central nervous system (CNS). For example, dopamine has regulatory impact on motor activity, motivation, cognitive functions, reinforcement learning systems, excitation processes, and the development of addictions [23, 35, 55]. At the same time, serotonin is primarily involved in psychomotor inhibition, regulation of emotions and mood, cognitive activity, and adaptation to stressful influences [9, 10]. Of course, associations between severity of the disease and mutations in genes encoding dopamine transporter (DAT1), D_4-dopamine receptor, D_5-dopamine receptor, dopamine beta-hydroxylase, alpha-2A adrenergic receptor, serotonin transporter, tryptophan hydroxylase-2, monoamine oxidase-A, etc. [28]. However, there was no specific mutations for the diseases. In children with ADHS, decrease in dopamine transporter (DTA) level in basal ganglia and thalamus was found [40, 47, 57]. Also, several studies have shown the presence of amino acid substitutions in DAT sequence associated with ASD [13, 19, 24]. For the one of such substitutions, DAT T356M, it was proven that the mutation leads to an increase in the level of extracellular dopamine. Assumptions, that ASD development is linked with disorders of the dopaminergic system (DE-system), are also supported by the widespread clinical use of neuroleptics (D2 dopamine receptor antagonists) in the symptomatic treatment of ASD [53]. D2 receptors are metabotropic receptors whose mechanism of action is associated with the inhibition of cyclic adenosine monophosphate (cAMP) production via Gi/Go proteins [42]. The receptors are widespread in striatum (corpus striatum), and in temporal, frontal, occipital, prefrontal and anterior cingulate cortex, i.e. in areas involved in processing emotional and sensorimotor modalities. Receptors are localised both pre- and postsynaptically [42]. In ASD and ADHD or combination, changes in the expression

of D2 receptors are observed, which correlates with the severity of symptoms of these mental disorders [42].

In recent years, microRNAs have been considered as potential "participants" in the pathogenesis of ASD and ADHD. MicroRNAs modulate gene expression and encode brain-derived neurotrophic factor, DAT1, serotonin 2C receptor, 5-hydroxytryptamine receptor 1B [45]. It is not unbelievable, because around 70 % of all studied microRNAs are in brain and play key role in regulation of synaptogenesis and synaptic plasticity [54]. Nowadays, decrease in the level of six microRNAs ((miR-19a-3p, miR-361-5p, miR-3613-3p, miR-150-5p, miR-126-3p и miR-499a-5p) in blood was observed in children with ASD and their healthy relatives compared to the controls [49]. There were five microRNAs (miR-181b-5p, miR-320a, miR-572, miR-130a-3p и miR-19b-3p) with high predictive power for the diagnosis of ASD [43]. In children with ASD and ADHD, decreased level of microRNAs 18a-5p, 22-3p, 24-3p, 106b-5p, 107 was found compared to controls. At the same time the level of microRNA-107 had high predictive role in ASD diagnosis [31].

So, ADHD and ASD have some similar links in pathogenesis and are characterised by some similar symptoms, but the factors, which effect would inevitably lead to the development of ADHD, ASD or ADHD + ASD have not been described. In this regard, research aimed at identifying the nature of relationship between ASD and ADHD is of great importance. Discovery of new pathogenesis links common to these diseases will undoubtedly contribute to the development of reliable diagnostic ways, effective treatment, and correction approaches.

Since the range of possible clinical trial designs, especially involving minors, is very limited, solution to the problem described above requires the development of adequate animal models of ASD + ADHD. However, it is currently impossible to obtain a similar clinical picture of psychopathology in animals. This problem may be solved only partially by modelling only limited set of characteristics observed in both patients and laboratory animals. Known data on the etiology and pathogenesis of the disease should be taken into account. There must be methods for objectively assessing these characteristics.

Due to modern point of view, combination of genetic and cerebral organic factors is necessary for development of ASD+ADHD [29, 33, 37]. So, to model common symptoms of such disorder, it is better to use medicines causing organic brain damage in animals with genetically determined disorders, such as dopamine metabolism disorders. One of such medicine is valproic acid, a short chain fatty acid which is used as anti-epileptic drug. Mechanism of action of the valproic acid is realised due to changes in neurotransmitters, inhibition of histone deacetylase activity and gamma-aminobutyric acid catabolism, activation of β-catenin-Ras-ERK-p21 signalling pathway, inhibition of glycogen synthase 3β-kinase [46]. However, valproic acid in pregnant women penetrates the placental barrier and accumulates in the fetal bloodstream [56], where the acid anion forms covalent bonds with negatively charged molecules, such as antioxidant enzymes, disrupting their function. Accumulation of free radicals leads to damage in nucleic acids (including mitochondrial DNA), lipids and proteins [48], which leads to neural tube defects [17]. Valproic acid also inhibits enzymes of folic acid metabolism, which is reflected in a decrease in its content and/or a decrease in the rate of conversion of the inactive form of folic acid into a biologically active one [38]. So, the valproic acid has a pronounced teratogenic effect, which has been confirmed in multicentre clinical researches [14, 59]. Based on the described data, valproic acid began to be used to model some symptoms of autism [39]. So, it was shown, that in rats, who were treated with valproic acid in utero, decreased pain sensitivity, hyperactivity, stereotypical actions, increased anxiety and decreased social interaction were observed [52]. These manifestations phenomenologically correspond to common symptoms of ASD (triad of autistic impairments). It is worth noting that disturbances in social adaptation and behaviour are characteristic features of all forms of ASD, as well as one of the symptoms of ADHD.

Several studies on mice and rats have demonstrated anatomical changes in cerebral cortex and cerebellum induced by valproic acid (VPA) administration: a decrease in number of Purkinje cells, damage to cranial nerve nuclei, and synaptic changes in cerebral cortex [2, 3, 24], accompanied by ASD-like behaviour. Thus, modelling of ASD with valproic acid administration has etiological basis [51, 52]. However, ASD may appear in children born to mothers who have not received valproic acid. Nevertheless, it was shown, that teratogenic impact of the valproic acid is similar in male, and female rats. At the same time, ASD is 4 times more common in boys, than in girls [22]. The damaging effects of the valproic acid are not directly related to modulation of monoaminergic neurotransmitter systems. There is only one study demonstrating an increase in serotonin levels in the hippocampus and a decrease in dopamine in the prefrontal cortex in rats after the administration of valproates on the 9th day of embryonic development [44]. The most interesting thing is that when valproate acted on dopaminergic neurons in culture (line N27), a 3-10-fold increase in mRNA production and two-fold increase in DAT protein content were observed [30], which does not correspond to clinical observations. That is why validity of such model is very limited. There is a possibility that an introduction of low valproate doses in combination with a genetically determined disorder of dopamine metabolism, set by knockout

of the dat-gene will allow us to remove the limitations of the model described above. Rats and mice of an DAT-KO line have already been considered as models for studying the etiology and pathogenesis of ADHD.

Already established phenotypic manifestations of DAT gene knockout in mice are hyperactivity and cognitive impairment. The hyperactivity of DAT-KO mice has been observed in many studies, in particular in Open Field test, beam-break test, and test of locomotor activity in a novel environment (Loco). The distance covered in the tests in such mice was significantly greater, their average speed was higher, and the time of immobility was shorter than in wild-type animals [23, 50]. In addition, the average turning angle of DAT-KO mice and tortuosity of their trajectory in the Open Field test were lower, as the level of interaction with novel objects in Loco. It can be concluded that their exploratory activity was reduced [22].

Cognitive impairments in KO mice were demonstrated in the Y-maze and H-maze tests. In the H-maze, these mice performed worse in learning rules, although the olfactory functions necessary for successful rule memorisation were not impaired [18]. In the Y-maze, KO mice showed a decrease in spontaneous alternation of sleeves [36]. In addition, KO mice had worth results in Morris water maze [58]. In general, these data indicate an impairment of working memory functions.

Anxiety in KO mice was assessed using an elevated plus maze and light-dark preference assays [15]. In the elevated plus maze, a decrease in anxiety was observed in KO mice compared to wild-type mice, which was manifested by an increase in the time spent in the open (light) sleeve of the maze and increase in the number of hangings in the open sleeves. The anxiolytic phenotype (reduced anxiety) was confirmed in the light-dark preference assays, where KO mice spent significantly more time in the light compartment of the chamber compared to wild-type mice.

The phenotypic manifestations of *dat* gene knockout in rats are largely similar to those in DAT-KO mice. Hyperactivity in DAT-KO rats has been confirmed in many studies [5, 8, 16, 34]. For example, in the in the active avoidance conditioned reflex test, DAT-KO rats demonstrated a high level of locomotor activity even after receiving an electric shock [5]. In the Open Field test, DAT-KO rats travelled a distance several times longer than controls, but they moved in one direction along the periphery of the arena. Cognitive impairments in DAT-KO rats have been demonstrated in tests such as the Y-maze, marble burying tests, and Intolerance-to-Delay Task [5, 16, 34]. In the Y-maze, such rats had a reduced level of spontaneous alternation compared to wild-type animals, which may indicate a deterioration in working memory [34]. The results of the marble burying test and Intolerance of Delay test suggest compulsive behaviour in DAT-KO rats [5, 16]. Such rats spend significantly more time interacting with the balls and also prefer a larger reward, even if it is presented at a suboptimal time (large and late reward).

Contradictory results were obtained when analysing the anxiety level of DAT-KO rats. While in the elevated plus maze test DAT-KO rats demonstrated increased exploratory activity, indicating a low level of anxiety, in the light-dark preference assays their activity in the light part of the box was reduced (long freezing was observed) [5, 8]. So, it can be assumed that the level of anxiety of DAT-KO rats is reduced (similar to mice), but they show short-term anxiety under certain conditions.

Thus, ASD and ADHD have common pathogenesis links, are accompanied by dopamine metabolism disorders. The ASD + ADHD combination is the most unfavourable. The changes observed in ASD + ADHD can be set in an experiment using intrauterine exposure to low doses of valproates as an additional cerebral organic factor in DAT-KO rats. Modelling ASD + ADHD will allow us to expand our understanding of the pathogenesis of such diseases and increase the possibility of developing targeted pharmacotherapy.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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REFERENCES

1. Makarov I.V., Avtenuk A.S. Diagnostika detskogo autizma: oshibki i trudnosti [Diagnostics of childhood autism: mistakes and difficulties]. Sotsial'naya i klinicheskaya psikhiatriya. 2018; 28 (3): 74–81. (in Russian).

2. Rasstroystva autisticheskogo spektra v detskom vozraste: diagnostika, terapiya, profilaktika, reabilitatsiya [Autism spectrum disorders in childhood: diagnosis, therapy, prevention, rehabilitation]. Klinicheskie rekomendatsii. Moscow; 2020. (in Russian).
3. Simashkovoy N.V., Makushkina E.V., eds. Rasstroystva autisticheskogo spektra: diagnostika, lechenie, nablyudenie [Autism Spectrum Disorders: Diagnosis, Treatment, Monitoring]. Klinicheskie rekomendatsii (protokol lecheniya). Moscow; 2015. (in Russian).
4. Ronal'd A., Simonov E., Kuntsi Dzh., Asherson P., Plomin R. Dokazatel'stva perekryvayushchikhsya geneticheskikh vliyaniy na povedenie autistov i SDVG v vyborke bliznetsov iz soobshchestva [Evidence for overlapping genetic influences on autistic and ADHD behavior in community twin selection]. Detskaya psikhologicheskaya psikhiatriya. 2008; 49 (5): 535–542. (in Russian).
5. Adinolfi A., Zelli S., Leo D. et al. Behavioral characterization of DAT-KO rats and evidence of asocial-like phenotypes in DAT-HET rats: The potential involvement of norepinephrine system. Behavioural Brain Research. 2019; 359: 516–27. DOI: 10.1016/j.bbr.2018.11.028.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. American Psychiatric Association; 2013.
7. Anand D., Colpo G.D., Zeni G. et al. Attention-Deficit/Hyperactivity Disorder And Inflammation: What Does Current Knowledge Tell Us? A Systematic Review. Front Psychiatry. 2017; 8: 228. DOI: 10.3389/fpsyt.2017.00228.
8. Apryatin S.A., Shipelin V.A., Trusov N.V. et al. Comparative analysis of the influence of a high-fat/high-carbohydrate diet on the level of anxiety and neuromotor and cognitive functions in Wistar and DAT-KO rats. Physiological Reports. 2019; 7(4): e13987. DOI: 10.14814/phy2.13987.
9. Bacqué-Cazenave J., Bharatiya R., Barrière G. et al. Serotonin in Animal Cognition and Behavior. Int J Mol Sci. 2020; 21(5): 1649. DOI: 10.3390/ijms21051649.
10. Bamalan O.A., Khalili Y.Al. Physiology, Serotonin. Stat Pearls Publishing; 2019.
11. Berenguer C., Roselló B., Colomer C. et al. Children with autism and attention deficit hyperactivity disorder. Relationships between symptoms and executive function, theory of mind, and behavioral problems. Research in Developmental Disabilities. 2018; 83: 260–9. DOI: 10.1016/j.ridd.2018.10.001.
12. Berenguer-Forner C., Miranda-Casas A., Pastor-Cerezuela G., Roselló-Miranda R. Comorbilidad del trastorno del espectro autista y el déficit de atención con hiperactividad. Estudio de revisión [Comorbidity of autism spectrum disorder and attention deficit with hyperactivity. A review study]. Rev Neurol. 2015; 60(1): 37–43. (in Spanish).
13. Bowton E., Saunders C., Reddy I.A. et al. SLC6A3 coding variant Ala-559Val found in two autism probands alters dopamine transporter function and trafficking. Translational psychiatry. 2014; 10 (4): e464. DOI: 10.1038/tp.2014.90.
14. Bromley R.L., Mawer G., Love J. et al. Liverpool and Manchester Neurodevelopment Group. Early cognitive development in children born to women with epilepsy: A prospective report. Epilepsia. 2010; 10 (51): 2058–65. DOI: 10.1111/j.1528-1167.2010.02668.x.
15. Carpenter A.C., Saborido T.P., Stanwood G.D. Development of hyperactivity and anxiety responses in dopamine transporter-deficient mice. Developmental Neuroscience. 2012; 2–3 (34): 250–7. DOI: 10.1159/000336824.
16. Cinque S., Zoratto F., Poleggi A. et al. Behavioral phenotyping of dopamine transporter knockout rats: Compulsive traits, motor stereotypies, and anhedonia. Frontiers in Psychiatry. 2018; 9: 43. DOI: 10.3389/fpsyt.2018.00043.
17. Copp A.J., Greene N.D., Murdoch J.N. The genetic basis of mammalian neurulation. NatRev Genet. 2003; 4: 784–93. DOI: 10.1038/nrg1181.
18. Del'Guidice T., Lemasson M., Etiévant A. et al. Dissociations between cognitive and motor effects of psychostimulants and atomoxetine in hyperactive DAT-KO mice. Psychopharmacology. 2014; 1 (231): 109–22. DOI: 10.1007/s00213-013-3212-8.
19. DiCarlo G.E., Aguilar J.I., Matthies H.J. et al. Autism-linked dopamine transporter mutation alters striatal dopamine neurotransmission and dopamine-dependent behaviors. Journal of Clinical Investigation. 2019; 8 (129): 3407–19. DOI: 10.1172/JCI127411.
20. Fisher S.E., Francks C., McCracken J.T. et al. A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. Am J Hum Genet. 2002; 70(5): 1183–96. DOI: 10.1086/340112.
21. Fombonne E. Epidemiological trends in rates of autism. Molecular Psychiatry. 2002; 7: 4–6. DOI: 10.1038/sj.mp.4001162.
22. Fox M.A., Panessiti M.G., Hall F.S. et al. An evaluation of the serotonin system and perseverative, compulsive, stereotypical, and hyperactive behaviors in dopamine transporter (DAT) knockout mice. Psychopharmacology (Berl). 2013; 227(4): 685–95. DOI: 10.1007/s00213-013-2988-x.
23. Franco R., Reyes-Resina I., Navarro G. Dopamine in health and disease: Much more than a neurotransmitter. Biomedicines. 2021; 9(2): 1–13. DOI: 10.3390/biomedicines9020109.
24. Gadow K.D., Roohi J., DeVincent C.J., Hatchwell E. Association of ADHD, tics, and anxiety with dopamine transporter (DAT1) genotype in autism spectrum disorder. J Child Psychol Psychiatry. 2008; 49(12): 1331–8. DOI: 10.1111/j.1469-7610.2008.01952.x.
25. Garcia-Martínez I., Sánchez-Mora C., Pagerols M. et al. Preliminary evidence for association of genetic variants in pri-miR-34b/c and abnormal miR-34c expression with attention deficit and hyperactivity disorder. Transl Psychiatry. 2016; 6(8): e879. DOI: 10.1038/tp.2016.151.
26. Genovese A., Butler M.G. Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). Int J Mol Sci. 2020; 21(13): 4726. DOI: 10.3390/ijms21134726.
27. Gesundheit B., Rosenzweig J.P., Naor D. et al. Immunological and autoimmune considerations of Autism Spectrum Disorders. J Autoimmun. 2013; 44: 1–7. DOI: 10.1016/j.jaut.2013.05.005.
28. Giros B., Jaber M., Jones S.R. et al. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature. 1996; 379(6566): 606–12. DOI: 10.1038/379606a0.
29. Gizer I.R., Ficks C., Waldman I.D. Candidate gene studies of ADHD: A meta-analytic review. Human Genetics. 2009; 126(1): 51–90. DOI: 10.1007/s00439-009-0694-x.

30. Green A.L., Zhan L., Eid A. et al. Valproate increases dopamine transporter expression through histone acetylation and enhanced promoter binding of Nurr1. Neuropharmacology. 2017; 125: 189–96. DOI: 10.1016/j.neuropharm.2017.07.020.
31. Kandemir H., Erdal M.E., Selek S. et al. Evaluation of several micro RNA (miRNA) levels in children and adolescents with attention deficit hyperactivity disorder. Neurosci Lett. 2014; 580: 158–62. DOI: 10.1016/j.neulet.2014.07.060.
32. Klassen L.J., Blackwood C.M., Reaume C.J. et al. A survey of adult referrals to specialist attention-deficit/hyperactivity disorder clinics in Canada. Int J Gen Med. 2017; 11: 1–10. DOI: 10.2147/IJGM.S145269.
33. Korkmaz B. Theory of mind and neurodevelopmental disorders of childhood. Pediatric Research. 2011; 5(2): 69. DOI: 10.1203/PDR.0b013e318212c177.
34. Leo D., Sukhanov I., Zoratto F. et al. Pronounced Hyperactivity, Cognitive Dysfunctions, and BDNF Dysregulation in Dopamine Transporter Knock-out Rats. J Neurosci. 2018; 38(8): 1959–72. DOI: 10.1523/JNEUROSCI.1931-17.2018.
35. Lerner T.N., Holloway A.L., Seiler J.L. Dopamine, Updated: Reward Prediction Error and Beyond. Current Opinion in Neurobiology. 2021; 67: 123–30. DOI: 10.1016/j.conb.2020.10.012.
36. Li B., Arime Y., Hall F.S. et al. Impaired spatial working memory and decreased frontal cortex BDNF protein level in dopamine transporter knockout mice. Eur J Pharmacol. 2010; 628(1-3): 104–7. DOI: 10.1016/j.ejphar.2009.11.036.
37. Liu L., Zhang D., Rodzinka-Pasko J.K., Li Y.M. Environmental risk factors for autism spectrum disorders. Nervenarzt. 2016; 87(2): 55–61. DOI: 10.1007/s00115-016-0172-3.
38. Lloyd K.A. A scientific review: mechanisms of valproate-mediated teratogenesis. Biosci Horiz. 2013; 6: 1–10. DOI: 10.1093/biohorizons/hzt003.
39. Markram K., Rinaldi T., La Mendola D. et al. Abnormal fear conditioning and amygdala processing in an animal model of autism. Neuropsychopharmacology. 2008; 33(4): 901–12. DOI: 10.1038/sj.npp.1301453.
40. Marotta R., Risoleo M.C., Messina G. et al. The Neurochemistry of Autism. Brain Sci. 2020; 10(3): 163. DOI: 10.3390/brainsci10030163.
41. Martin J., Walters R.K., Demontis D. et al. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2018; 83(12): 1044–53. DOI: 10.1016/j.biopsych.2017.11.026.
42. Millan M.J., Dekeyne A., Gobert A. et al. Dual-acting agents for improving cognition and real-world function in Alzheimer's disease: Focus on 5-HT6 and D3 receptors as hubs. Neuropharmacology. 2020; 177: 108099. DOI: 10.1016/j.neuropharm.2020.108099.
43. Mundalil Vasu M., Anitha A., Thanseem I. et al. Serum microRNA profiles in children with autism. Molecular autism. 2014; 5: 40. DOI: 10.1186/2040-2392-5-40.
44. Narita N., Kato M., Tazoe M. et al. Increased monoamine concentration in the brain and blood of fetal thalidomide- and valproic acid-exposed rat: putative animal models for autism. Pediatr Res. 2002; 52(4): 576–9. DOI: 10.1203/00006450-200210000-00018.
45. Németh N., Kovács-Nagy R., Székely A. et al. Association of impulsivity and polymorphic microRNA-641 target sites in the SNAP-25 gene. PLoS One. 2013; 8(12): e84207. DOI: 10.1371/journal.pone.0084207.
46. Nicolini C., Fahnestock M. The valproic acid-induced rodent model of autism. Experimental Neurology. 2018; 299(A): 217–27. DOI: 10.1016/j.expneurol.2017.04.017.
47. Oades R.D. Dopamine-serotonin interactions in attention-deficit hyperactivity disorder (ADHD). Progress in Brain Research. 2008; 172: 543–65. DOI: 10.1016/S0079-6123(08)00926-6.
48. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol. 2009; 28(1): 1–10. DOI: 10.1016/j.reprotox.2009.02.014.
49. Ozkul Y., Taheri S., Bayram K.K. et al. A heritable profile of six miRNAs in autistic patients and mouse models. Sci Rep. 2020; 10(1): 9011. DOI: 10.1038/s41598-020-65847-8.
50. Perona M.T., Waters S., Hall F.S. et al. Animal models of depression in dopamine, serotonin, and norepinephrine transporter knockout mice: prominent effects of dopamine transporter deletions. Behav Pharmacol. 2008; 19(5-6): 566–74. DOI: 10.1097/FBP.0b013e32830cd80f.
51. Rodier P.M., Ingram J.L., Tisdale B. et al. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. J Comp Neurol. 1996; 370(2): 247–61. DOI: 10.1002/(SICI)1096-9861(19960624)370:2<247::AID-CNE8>3.0.CO;2-2.
52. Schneider T., Przewłocki R. Behavioral alterations in rats prenatally to valproic acid: Animal model of autism. Neuropsychopharmacology. 2005; 1(30): 80–9. DOI: 10.1038/sj.npp.1300518.
53. Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. Clin Schizophr Relat Psychoses. 2010; 4(1): 56–73. DOI: 10.3371/CSRP.4.1.5.
54. Stranger B.E., Nica A.C., Forrest M.S. et al. Population genomics of human gene expression. Nat Genet. 2007; 39(10): 1217–24. DOI: 10.1038/ng2142.
55. Torrisi S.A., Laudani S., Contarini G. et al. Dopamine, Cognitive Impairments and Second-Generation Antipsychotics: From Mechanistic Advances to More Personalized Treatments. Pharmaceuticals (Basel). 2020; 13(11): 365. DOI: 10.3390/ph13110365.
56. Vajda F. Dose issues in antiepileptic therapy. J Clin Neurosci. 2012; 19: 1475–7. DOI: 10.1016/j.jocn.2012.05.003.
57. Volkow N.D., Wang G.J., Newcorn J. et al. Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. Neuroimage. 2007; 34(3): 1182–90. DOI: 10.1016/j.neuroimage.2006.10.014.
58. Vorhees C.V., Williams M.T. Morris water maze: Procedures for assessing spatial and related forms of learning and memory. Nature Protocols. 2006; 2(1): 848–58. DOI: 10.1038/nprot.2006.116.
59. Wiggs K.K., Rickert M.E., Sujan A.C. et al. Antiseizure medication use during pregnancy and risk of ASD and ADHD in children. Neurology. 2020; 95(24): e3232–40. DOI: 10.1212/WNL.0000000000010993.
60. Zablotsky B., Bramlett M.D., Blumberg S.J. The Co-Occurrence of Autism Spectrum Disorder in Children With ADHD. J Atten Disord. 2020; 24(1): 94–103. DOI: 10.1177/1087054717713638.

ЛИТЕРАТУРА

1. Макаров И.В., Автенюк А.С. Диагностика детского аутизма: ошибки и трудности. Социальная и клиническая психиатрия. 2018; 28(3): 74–81.
2. Расстройства аутистического спектра в детском возрасте: диагностика, терапия, профилактика, реабилитация. Клинические рекомендации. М.; 2020.
3. Симашковой Н.В., Макушкина Е.В., ред. Расстройства аутистического спектра: диагностика, лечение, наблюдение. Клинические рекомендации (протокол лечения). М.; 2015.
4. Рональд А., Симонов Э., Кунци Дж. и др. Доказательства перекрывающихся генетических влияний на поведение аутистов и СДВГ в выборке близнецов из сообщества. Детская психологическая психиатрия. 2008; 49(5): 535–42.
5. Adinolfi A., Zelli S., Leo D. et al. Behavioral characterization of DAT-KO rats and evidence of asocial-like phenotypes in DAT-HET rats: The potential involvement of norepinephrine system. Behavioural Brain Research. 2019; 359: 516–27. DOI: 10.1016/j.bbr.2018.11.028.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. American Psychiatric Association; 2013.
7. Anand D., Colpo G.D., Zeni G. et al. Attention-Deficit/Hyperactivity Disorder And Inflammation: What Does Current Knowledge Tell Us? A Systematic Review. Front Psychiatry. 2017; 8: 228. DOI: 10.3389/fpsyt.2017.00228.
8. Apryatin S.A., Shipelin V.A., Trusov N.V. et al. Comparative analysis of the influence of a high-fat/high-carbohydrate diet on the level of anxiety and neuromotor and cognitive functions in Wistar and DAT-KO rats. Physiological Reports. 2019; 7(4): e13987. DOI: 10.14814/phy2.13987.
9. Bacqué-Cazenave J., Bharatiya R., Barrière G. et al. Serotonin in Animal Cognition and Behavior. Int J Mol Sci. 2020; 21(5): 1649. DOI: 10.3390/ijms21051649.
10. Bamalan O.A., Khalili Y.Al. Physiology, Serotonin. Stat Pearls Publishing; 2019.
11. Berenguer C., Roselló B., Colomer C. et al. Children with autism and attention deficit hyperactivity disorder. Relationships between symptoms and executive function, theory of mind, and behavioral problems. Research in Developmental Disabilities. 2018; 83: 260–9. DOI: 10.1016/j.ridd.2018.10.001.
12. Berenguer-Forner C., Miranda-Casas A., Pastor-Cerezuela G., Roselló-Miranda R. Comorbilidad del trastorno del espectro autista y el déficit de atención con hiperactividad. Estudio de revisión [Comorbidity of autism spectrum disorder and attention deficit with hyperactivity. A review study]. Rev Neurol. 2015; 60(1): 37–43. (in Spanish).
13. Bowton E., Saunders C., Reddy I.A. et al. SLC6A3 coding variant Ala559Val found in two autism probands alters dopamine transporter function and trafficking. Translational psychiatry. 2014; 10 (4): e464. DOI: 10.1038/tp.2014.90.
14. Bromley R.L., Mawer G., Love J. et al. Liverpool and Manchester Neurodevelopment Group. Early cognitive development in children born to women with epilepsy: A prospective report. Epilepsia. 2010; 10 (51): 2058–65. DOI: 10.1111/j.1528-1167.2010.02668.x.
15. Carpenter A.C., Saborido T.P., Stanwood G.D. Development of hyperactivity and anxiety responses in dopamine transporter-deficient mice. Developmental Neuroscience. 2012; 2–3 (34): 250–7. DOI: 10.1159/000336824.
16. Cinque S., Zoratto F., Poleggi A. et al. Behavioral phenotyping of dopamine transporter knockout rats: Compulsive traits, motor stereotypies, and anhedonia. Frontiers in Psychiatry. 2018; 9: 43. DOI: 10.3389/fpsyt.2018.00043.
17. Copp A.J., Greene N.D., Murdoch J.N. The genetic basis of mammalian neurulation. NatRev Genet. 2003; 4: 784–93. DOI: 10.1038/nrg1181.
18. Del'Guidice T., Lemasson M., Etiévant A. et al. Dissociations between cognitive and motor effects of psychostimulants and atomoxetine in hyperactive DAT-KO mice. Psychopharmacology. 2014; 1 (231): 109–22. DOI: 10.1007/s00213-013-3212-8.
19. DiCarlo G.E., Aguilar J.I., Matthies H.J. et al. Autism-linked dopamine transporter mutation alters striatal dopamine neurotransmission and dopamine-dependent behaviors. Journal of Clinical Investigation. 2019; 8 (129): 3407–19. DOI: 10.1172/JCI127411.
20. Fisher S.E., Francks C., McCracken J.T. et al. A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. Am J Hum Genet. 2002; 70(5): 1183–96. DOI: 10.1086/340112.
21. Fombonne E. Epidemiological trends in rates of autism. Molecular Psychiatry. 2002; 7: 4–6. DOI: 10.1038/sj.mp.4001162.
22. Fox M.A., Panessiti M.G., Hall F.S. et al. An evaluation of the serotonin system and perseverative, compulsive, stereotypical, and hyperactive behaviors in dopamine transporter (DAT) knockout mice. Psychopharmacology (Berl). 2013; 227(4): 685–95. DOI: 10.1007/s00213-013-2988-x.
23. Franco R., Reyes-Resina I., Navarro G. Dopamine in health and disease: Much more than a neurotransmitter. Biomedicines. 2021; 9(2): 1–13. DOI: 10.3390/biomedicines9020109.
24. Gadow K.D., Roohi J., DeVincent C.J., Hatchwell E. Association of ADHD, tics, and anxiety with dopamine transporter (DAT1) genotype in autism spectrum disorder. J Child Psychol Psychiatry. 2008; 49(12): 1331–8. DOI: 10.1111/j.1469-7610.2008.01952.x.
25. Garcia-Martínez I., Sánchez-Mora C., Pagerols M. et al. Preliminary evidence for association of genetic variants in pri-miR-34b/c and abnormal miR-34c expression with attention deficit and hyperactivity disorder. Transl Psychiatry. 2016; 6(8): e879. DOI: 10.1038/tp.2016.151.
26. Genovese A., Butler M.G. Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). Int J Mol Sci. 2020; 21(13): 4726. DOI: 10.3390/ijms21134726.
27. Gesundheit B., Rosenzweig J.P., Naor D. et al. Immunological and autoimmune considerations of Autism Spectrum Disorders. J Autoimmun. 2013; 44: 1–7. DOI: 10.1016/j.jaut.2013.05.005.
28. Giros B., Jaber M., Jones S.R. et al. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. Nature. 1996; 379(6566): 606–12. DOI: 10.1038/379606a0.

29. Gizer I.R., Ficks C., Waldman I.D. Candidate gene studies of ADHD: A meta-analytic review. Human Genetics. 2009; 126(1): 51–90. DOI: 10.1007/s00439-009-0694-x.
30. Green A.L., Zhan L., Eid A. et al. Valproate increases dopamine transporter expression through histone acetylation and enhanced promoter binding of Nurr1. Neuropharmacology. 2017; 125: 189–96. DOI: 10.1016/j.neuropharm.2017.07.020.
31. Kandemir H., Erdal M.E., Selek S. et al. Evaluation of several micro RNA (miRNA) levels in children and adolescents with attention deficit hyperactivity disorder. Neurosci Lett. 2014; 580: 158–62. DOI: 10.1016/j.neulet.2014.07.060.
32. Klassen L.J., Blackwood C.M., Reaume C.J. et al. A survey of adult referrals to specialist attention-deficit/hyperactivity disorder clinics in Canada. Int J Gen Med. 2017; 11: 1–10. DOI: 10.2147/IJGM.S145269.
33. Korkmaz B. Theory of mind and neurodevelopmental disorders of childhood. Pediatric Research. 2011; 5(2): 69. DOI: 10.1203/PDR.0b013e318212c177.
34. Leo D., Sukhanov I., Zoratto F. et al. Pronounced Hyperactivity, Cognitive Dysfunctions, and BDNF Dysregulation in Dopamine Transporter Knock-out Rats. J Neurosci. 2018; 38(8): 1959–72. DOI: 10.1523/JNEUROSCI.1931-17.2018.
35. Lerner T.N., Holloway A.L., Seiler J.L. Dopamine, Updated: Reward Prediction Error and Beyond. Current Opinion in Neurobiology. 2021; 67: 123–30. DOI: 10.1016/j.conb.2020.10.012.
36. Li B., Arime Y., Hall F.S. et al. Impaired spatial working memory and decreased frontal cortex BDNF protein level in dopamine transporter knockout mice. Eur J Pharmacol. 2010; 628(1-3): 104–7. DOI: 10.1016/j.ejphar.2009.11.036.
37. Liu L., Zhang D., Rodzinka-Pasko J.K., Li Y.M. Environmental risk factors for autism spectrum disorders. Nervenarzt. 2016; 87(2): 55–61. DOI: 10.1007/s00115-016-0172-3.
38. Lloyd K.A. A scientific review: mechanisms of valproate-mediated teratogenesis. Biosci Horiz. 2013; 6: 1–10. DOI: 10.1093/biohorizons/hzt003.
39. Markram K., Rinaldi T., La Mendola D. et al. Abnormal fear conditioning and amygdala processing in an animal model of autism. Neuropsychopharmacology. 2008; 33(4): 901–12. DOI: 10.1038/sj.npp.1301453.
40. Marotta R., Risoleo M.C., Messina G. et al. The Neurochemistry of Autism. Brain Sci. 2020; 10(3): 163. DOI: 10.3390/brainsci10030163.
41. Martin J., Walters R.K., Demontis D. et al. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2018; 83(12): 1044–53. DOI: 10.1016/j.biopsych.2017.11.026.
42. Millan M.J., Dekeyne A., Gobert A. et al. Dual-acting agents for improving cognition and real-world function in Alzheimer's disease: Focus on 5-HT6 and D3 receptors as hubs. Neuropharmacology. 2020; 177: 108099. DOI: 10.1016/j.neuropharm.2020.108099.
43. Mundalil Vasu M., Anitha A., Thanseem I. et al. Serum microRNA profiles in children with autism. Molecular autism. 2014; 5: 40. DOI: 10.1186/2040-2392-5-40.
44. Narita N., Kato M., Tazoe M. et al. Increased monoamine concentration in the brain and blood of fetal thalidomide- and valproic acid-exposed rat: putative animal models for autism. Pediatr Res. 2002; 52(4): 576–9. DOI: 10.1203/00006450-200210000-00018.
45. Németh N., Kovács-Nagy R., Székely A. et al. Association of impulsivity and polymorphic microRNA-641 target sites in the SNAP-25 gene. PLoS One. 2013; 8(12): e84207. DOI: 10.1371/journal.pone.0084207.
46. Nicolini C., Fahnestock M. The valproic acid-induced rodent model of autism. Experimental Neurology. 2018; 299(A): 217–27. DOI: 10.1016/j.expneurol.2017.04.017.
47. Oades R.D. Dopamine-serotonin interactions in attention-deficit hyperactivity disorder (ADHD). Progress in Brain Research. 2008; 172: 543–65. DOI: 10.1016/S0079-6123(08)00926-6.
48. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol. 2009; 28(1): 1–10. DOI: 10.1016/j.reprotox.2009.02.014.
49. Ozkul Y., Taheri S., Bayram K.K. et al. A heritable profile of six miRNAs in autistic patients and mouse models. Sci Rep. 2020; 10(1): 9011. DOI: 10.1038/s41598-020-65847-8.
50. Perona M.T., Waters S., Hall F.S. et al. Animal models of depression in dopamine, serotonin, and norepinephrine transporter knockout mice: prominent effects of dopamine transporter deletions. Behav Pharmacol. 2008; 19(5-6): 566–74. DOI: 10.1097/FBP.0b013e32830cd80f.
51. Rodier P.M., Ingram J.L., Tisdale B. et al. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. J Comp Neurol. 1996; 370(2): 247–61. DOI: 10.1002/(SICI)1096-9861(19960624)370:2<247::AID-CNE8>3.0.CO;2-2.
52. Schneider T., Przewłocki R. Behavioral alterations in rats prenatally to valproic acid: Animal model of autism. Neuropsychopharmacology. 2005; 1(30): 80–9. DOI: 10.1038/sj.npp.1300518.
53. Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. Clin Schizophr Relat Psychoses. 2010; 4(1): 56–73. DOI: 10.3371/CSRP.4.1.5.
54. Stranger B.E., Nica A.C., Forrest M.S. et al. Population genomics of human gene expression. Nat Genet. 2007; 39(10): 1217–24. DOI: 10.1038/ng2142.
55. Torrisi S.A., Laudani S., Contarini G. et al. Dopamine, Cognitive Impairments and Second-Generation Antipsychotics: From Mechanistic Advances to More Personalized Treatments. Pharmaceuticals (Basel). 2020; 13(11): 365. DOI: 10.3390/ph13110365.
56. Vajda F. Dose issues in antiepileptic therapy. J Clin Neurosci. 2012; 19: 1475–7. DOI: 10.1016/j.jocn.2012.05.003.
57. Volkow N.D., Wang G.J., Newcorn J. et al. Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. Neuroimage. 2007; 34(3): 1182–90. DOI: 10.1016/j.neuroimage.2006.10.014.
58. Vorhees C.V., Williams M.T. Morris water maze: Procedures for assessing spatial and related forms of learning and memory. Nature Protocols. 2006; 2(1): 848–58. DOI: 10.1038/nprot.2006.116.
59. Wiggs K.K., Rickert M.E., Sujan A.C. et al. Antiseizure medication use during pregnancy and risk of ASD and ADHD in children. Neurology. 2020; 95(24): e3232–40. DOI: 10.1212/WNL.0000000000010993.
60. Zablotsky B., Bramlett M.D., Blumberg S.J. The Co-Occurrence of Autism Spectrum Disorder in Children With ADHD. J Atten Disord. 2020; 24(1): 94–103. DOI: 10.1177/1087054717713638.