ANIMAL PATHOLOGY, MORPHOLOGY, PHYSIOLOGY, PHARMACOLOGY AND TOXICOLOGY

ПАТОЛОГИЯ ЖИВОТНЫХ, МОРФОЛОГИЯ, ФИЗИОЛОГИЯ, ФАРМАКОЛОГИЯ И ТОКСИКОЛОГИЯ

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Literature Review

DAT Knockout Rat Models: Dopamine Dysfunction, Epigenetic Mechanisms, and Approaches to Gene Therapy: A Literature Review

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Abstract

Introduction. Dopamine transporter gene knockout (DAT-KO) animal model is a valuable experimental tool for studying the pathophysiology of diseases associated with dopamine dysfunction, such as attention-deficit/hyperactivity disorder, schizophrenia, and Parkinson's disease. The aim of the present review is to systematize the scientific data on using the DAT-KO rat models for studying dopaminergic dysfunction, epigenetic mechanisms, and gene therapy approaches.

Materials and Methods. Literary sources were searched for in PubMed, Scopus, Web of Science, and Google Scholar scientific citation databases. The original studies (n=49) on the structure and function of DAT, knockout models, epigenetic mechanisms, and gene therapy published from 1991 to 2025 in English language only were included into the review. The results have been presented in a PRISMA flow chart and in the illustrations.

Results. DAT knockout rat models exhibit a 5–7-fold increase of extracellular dopamine level, hyperactivity and structural changes in the basal ganglia, which indicates dopamine dysfunction. Homozygous knockout animals are found to completely lack functional DAT protein, whereas animals with heterozygous knockout retain approximately half of its function and exhibit intermediate phenotypes. Epigenetic regulation of SLC6A3 gene expression is mediated by DNA methylation, histone modifications (including H3K9/K14 acetylation and H3K27 methylation) and microRNA modifications. Moreover, the DAT promoter remains hypomethylated during postnatal ontogenesis in rats, resulting in its age-related expression increase. Gene therapy using viral vectors has demonstrated the potential to restore DAT function.

Discussion and Conclusion. The DAT-KO rat models reliably reproduce the key neurochemical and morphological features of dopaminergic dysfunction. However, the picture seems much incomplete due to the fragmentary character of data on the dynamics of epigenetic regulation of dopamine transporter expression during disease progression and insufficient evidence base on dose-dependent effects and long-term safety of gene therapy. The epigenetic mechanisms open the new tracks for biomarker search and personalization of therapy. Gene therapy using adeno-associated viral and lentiviral vectors demonstrates the potential to restore DAT function in the preclinical models, however, further clarification on dose-dependent effects and minimization of the immune response is required. The integration of epigenetic markers into the clinical protocols, development of combinatory strategies, and validation of the DAT-KO models for comorbid conditions continue to be the promising tracks for further research.

Keywords*:* literature review, dopamine (dopaminergic) dysfunction, dopamine transporter, DAT, DAT gene knockout, rats, mice, DAT-KO, SLC6A3, epigenetic regulation, gene therapy, viral vectors

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Обзор научной литературы

Модель крыс с нокаутом гена DAT: дофаминовая дисфункция, эпигенетические механизмы и подходы к генной терапии. Обзор научной литературы

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Аннотация

Введение. Модель животных с нокаутом кодирующего гена (DAT-KO) представляет собой ценный экспериментальный инструмент для изучения патофизиологии заболеваний, связанных с нарушением дофаминовой функции, таких как синдром дефицита внимания и гиперактивности, шизофрения, болезнь Паркинсона. Целью обзора является систематизация научных данных о дофаминергической дисфункции, эпигенетических механизмах и подходах к генной терапии на модели крыс с нокаутом гена DAT (DAT-KO).

Материалы и методы. Поиск литературных источников проводился в базах данных PubMed, Scopus, Web of Science и Google Scholar. В обзор включены оригинальные исследования только на английском языке (n=49), опубликованные в период с 1991 по 2025 гг. и посвященные структуре и функциям DAT, моделям нокаута, эпигенетическим механизмам и генной терапии. Результаты представлены в виде блок-схемы PRISMA и рисунков.

Результаты исследования. В моделях нокаута DAT у крыс наблюдается 5–7-кратное повышение внеклеточного уровня дофамина, гиперактивность и структурные изменения в базальных ганглиях, что отражает дофаминовую дисфункцию. Гомозиготные нокаутные животные полностью лишены функционального белка DAT, тогда как гетерозиготы сохраняют около половины его активности и демонстрируют промежуточные фенотипы. Эпигенетическая регуляция экспрессии гена *Slc6a3* осуществляется через метилирование ДНК, модификации гистонов (включая ацетилирование H3K9/K14 и метилирование H3K27) и микроРНК, причем в постнатальном онтогенезе крыс промотор DAT остается гипометилированным, что обеспечивает возрастное повышение его экспрессии. Генная терапия с использованием вирусных векторов демонстрирует потенциал восстановления функции DAT.

Обсуждение и заключение. Модель DAT-KO у крыс достоверно воспроизводит ключевые нейрохимические и морфологические особенности дофаминергической дисфункции. Полнота картины, однако, во многом ограничена фрагментарностью данных о динамике эпигенетической регуляции экспрессии дофаминового транспортера в ходе прогрессирования заболеваний и недостаточной доказательной базой по дозозависимым эффектам и долгосрочной безопасности генной терапии. Эпигенетические механизмы открывают новые направления для поиска биомаркеров и персонализированной терапии. Применение генной терапии с использованием аденоассоциированных и лентивирусных векторов демонстрирует потенциал восстановления функции DAT в доклинических моделях, однако требует дальнейшего уточнения дозозависимых эффектов и минимизации иммунного ответа. Перспективными направлениями остаются интеграция эпигенетических маркеров в клинические протоколы, разработка комбинированных стратегий и валидация модели DAT-KO при коморбидных состояниях.

Ключевые слова: обзор научной литературы, дофаминовая (дофаминергическая) дисфункция, дофаминовый транспортер, DAT, нокаут гена DAT, крысы, мыши, DAT-KO, *SLC6A3*, эпигенетическая регуляция, генная терапия, вирусные векторы

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Introduction. Rats and mice with knockout of dopamine transporter (DAT) protein encoded by SLC6A3 gene, represent a valuable experimental DAT-KO model for studying the pathophysiology of diseases associated with dopamine dysfunction. The dopamine transporter plays a key role in regulation of the dopaminergic neurotransmission, ensuring reuptake of dopamine from the synaptic cleft into presynaptic neurons, which controls the intensity and duration of signals on dopamine receptors [1, 2]. DAT is expressed predominantly in dopaminergic neurons of the

substantia nigra and ventral tegmental area, with the highest degree of expression in the striatum and nucleus accumbens, where it regulates up to 80% of dopaminergic signaling [1]. In the prefrontal cortex, crusial for higher cognitive control and social interactions, DAT, in conjunction with the norepinephrine transporter, modulates dopamine activity influencing social behavior [2, 3]. Dysregulation in DAT-mediated dopamine homeostasis is associated with depression, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, and Parkinson's disease. Due to DAT being a target for psychostimulants such as cocaine and methylphenidate, it is associated with disorders caused by the use of psychoactive substances [1, 4].

The DAT-KO animal model is characterized by a complete absence of functional protein, which induces a hyperdopaminergic condition characterised by a 5–7-fold increase of extracellular dopamine level and a decrease in presynaptic dopamine [5]. This results in hyperactivity, motor stereotypies, cognitive deficits and disorders of diminished motivation, as well as in neuroanatomical changes including reduced striatal volume, increased volume of prefrontal cortex and cerebellum, decreased GABAergic interneuron density and dysfunctions in the serotonergic system [2, 4, 6]. With regard to physiology, DAT-KO rats exhibit reduction of body weight and impaired motor coordination, making the model relevant for studying ADHD and schizophrenia [1, 2]. Heterozygous DAT-KO rats with partial reduction in DAT activity, also exhibit patterns of altered behavior. Therefore, even partial loss of DAT function can cause significant neurochemical and behavioral changes [6].

The aim of the present review is to systematize scientific data on using the DAT knockout (DAT-KO) rat models for studying the dopamine dysregulation, epigenetic mechanisms, and gene therapy approaches.

Materials and Methods. Search for literature was performed in PubMed, Scopus, Web of Science, and Google Scholar science citation databases by the keywords: dopamine transporter, DAT-KO, SLC6A3, dopamine dysregulation, epigenetic regulation, gene therapy, dopamine signaling, DAT knockout rats, DAT knockout mice, neurotransmitter transporters. The latest search was performed on October 5, 2025. The following publications were included in the analysis: the original studies, reviews, and meta-analyses in the English language only, published from 1991 to 2025. The sample included publications (n=49) containing data on: dopamine dysregulation (neurochemical and behavioral phenotypes) in DAT-KO rat models; epigenetic mechanisms of dopamine transporter regulation; gene therapy approaches to DAT deficiency using viral vectors. The results have been systematized and presented in the PRISMA flow chart and in the figures.

Research Results

Selection of references. As a result of the search across all scientific citation databases and other sources, 253 publications were found. After removal of 43 duplicates, 210 articles were selected for further analysis. After screening titles and abstracts, 115 articles were excluded. Potentially eligible full texts (n=95) were uploaded to cloud storage and reviewed by a wide range of experts to assess their relevance. At this stage, another 46 publications were excluded as they did not contain information on methodology, results, or interpretation thereof in the context of dopaminergic dysfunction. Thus, 49 articles were eventually selected to undergo the review. A summary of the literary sources' verification process for inclusion into the review is presented in the PRISMA flowchart (Fig. 1).

The SLC6A3 gene and its role in dopamine dysfunction. The SLC6A3 gene encoding DAT belongs to the family of Na^+- and Cl^--dependent neurotransmitter transporters (Fig. 2). In humans, it is localized on the chromosome 5p15.33 and covers approximately 52.5 kbp, including 15 coding exons [7, 8]. The DAT protein consists of 620 amino acids, has a molecular mass of approximately 69 kDa, and includes 12 transmembrane domains. The N-terminus and C-terminus are oriented toward the cytoplasm, and a large extracellular loop with N-glycosylation sites is located between the third and fourth domains [9].

In mice, the SLC6A3 gene is localized on chromosome 13 and has a highly conserved gene sequence: the gene also consists of 15 exons, and the boundaries of the intron-exon junctions in the coding regions are completely identical to those in humans [10]. The size of the mouse gene is significantly smaller—approximately 24.5 kbp—and the nucleotide sequences are 85% identic with that of human DAT (amino acid sequences are 93% identic). However, mice lack the Variable Number Tandem Repeat (VNTR) in the 3'-untranslated region characteristic of humans, and their full-length mRNA is 10% shorter [10, 11].

The rat SLC6A3 gene also contains 15 exons, and its cDNA was cloned and sequenced in the early 1990s [12, 13]. The amino acid sequence of rat DAT exhibits 97% identity with the human protein within the transmembrane domains

and 87% — in the extramembrane regions [11]. The rat protein, like the mouse protein, consists of 619 amino acids (one less than the human protein due to the absence of the CAG codon encoding glycine at position 198) and has a molecular mass of approximately 69 kDa [11].

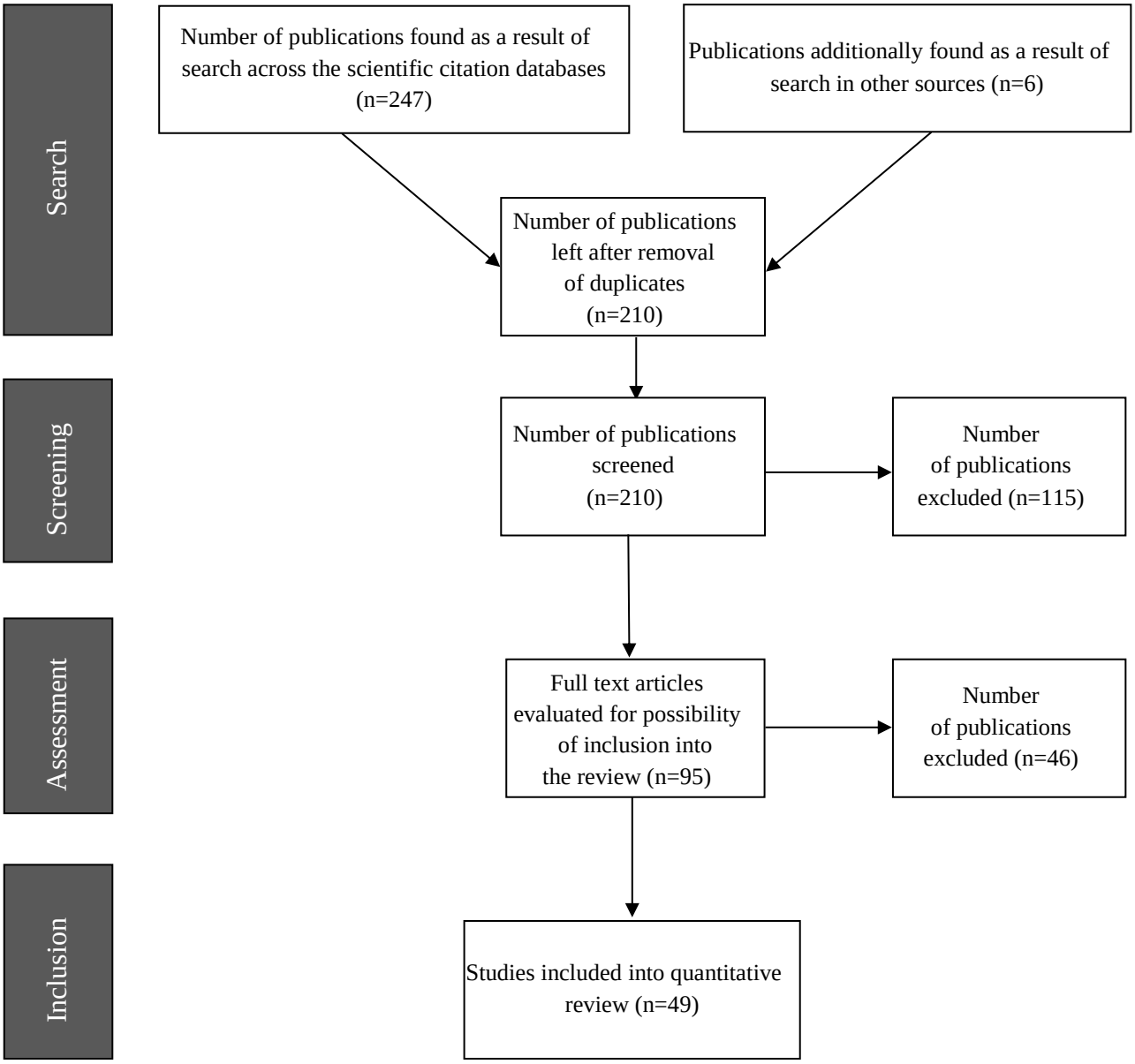

Fig. 1. Flow chart for selecting the publications in compliance with the PRISMA guidelines

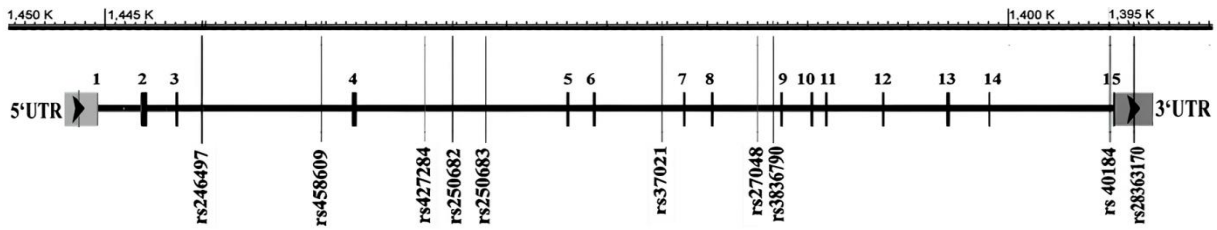

Fig. 2. Schematic representation of the human SLC6A3 gene sequence. Dark vertical blocks represent exons (1–15), with introns located between them. The positions of polymorphic markers (rs-numbers) are indicated along the gene sequence. The grey arrow indicates the 5'-untranslated region (5'UTR), and the black arrow indicates the 3'-untranslated region (3'UTR). The scale bar at the top corresponds to the gene localization on the chromosome [14]

The main function of DAT is the Na^+- and Cl^--dependent reuptake of dopamine from the synaptic cleft back to the presynaptic terminal (Fig. 3). It is less efficient in transporting norepinephrine [15, 16]. The highest expression is observed in dopaminergic neurons of the

substantia nigra and ventral tegmental area [1], whereas the highest protein density is observed in axonal terminals of the striatum and nucleus accumbens [17, 18]. In the prefrontal cortex, the amount of DAT is significantly lower, and its functions are partially compensated by the norepinephrine transporter [19].

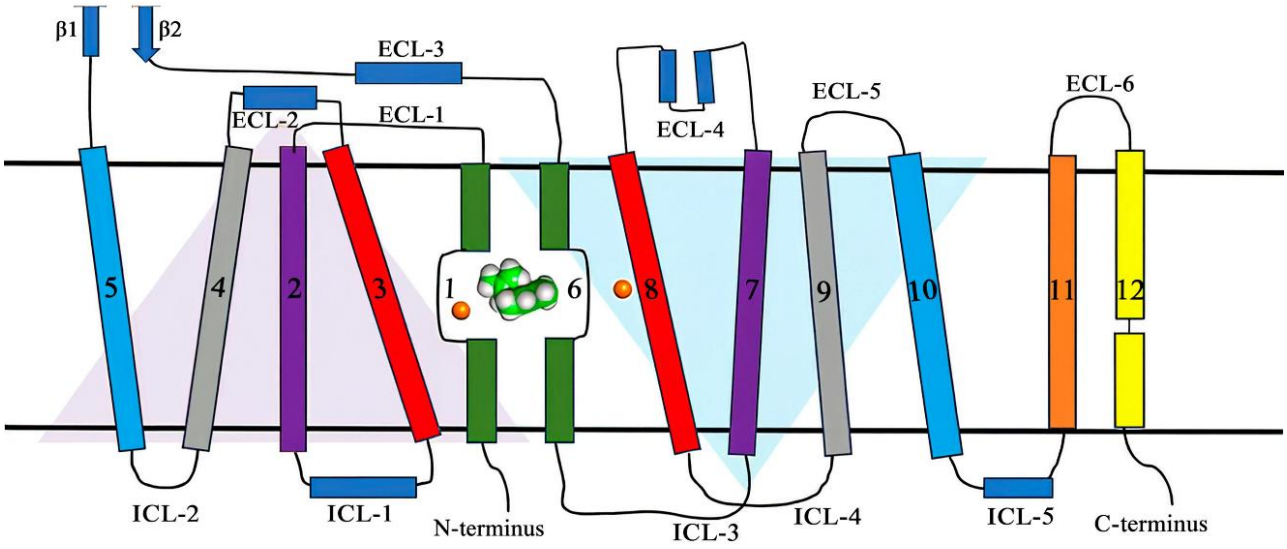

Fig. 3. Topological structure of DAT. Rectangles represent transmembrane domains (1–12) connected by intracellular (ICL) and extracellular (ECL) loops. The N-terminus and C-terminus are located in the cytoplasm. Orange-colour spheres correspond to Na^+ ions, and the green-and-white model corresponds to the substrate molecule in the binding site. Two domains with an inverted symmetry axis form the substrate binding site [15].

The functional activity of the protein is regulated by post-translational modifications. Phosphorylation of serine residues in the C-terminus affects intracellular transport and the rate of dopamine reuptake [20]. Cysteine palmitoylation in the second and fifth transmembrane domains promotes oligomer formation [21]. Lysine ubiquitination in the C-terminus determines the rate of protein degradation [22], and N-glycosylation of asparagines in the extracellular loop stabilizes the structure of DAT and regulates its expression on the membrane [23].

Genetic variants of SLC6A3 include a 40-bp VNTR polymorphism in the 3'-untranslated region. The number of repeats can vary from three to eleven, with the most common allele having ten repeats, occurring in approximately 70% of the population [24, 25]. Shorter variants, such as the 9R allele, are associated with an increased risk of schizophrenia, as well as with the development of cocaine and alcohol dependences. The 10R allele, on the contrary, is more often associated with Parkinson's disease and ADHD, as well as a lower susceptibility to nicotine dependence [8].

Alongside, the pathogenic mutations, including missense substitutions (e.g., p.Leu368GIn) and splicing abnormalities (c.1269+1G→A), which lead to the development of DAT deficiency syndrome, also known as infantile parkinsonism-dystonia 1, were found to be described [26]. This condition is characterized by a complete loss of protein function and pronounced hyperdopaminergia [26, 27]. The gene damage tolerance assessment (GDI=0.90) indicates its moderate sensitivity to mutations [28]. Among the known protein partners of DAT, the following ones have been described: PRKCABP and TGFB1I1 [29], involved in the regulation of phosphorylation; SYNGR3, binding to the N-terminus [30]; and TOR1A, affecting intracellular localization [31].

Animal models with knockout of DAT-encoding gene. The homology between human SLC6A3 and its rat ortholog is high. The coding sequence of nucleotide sequence is approximately 85% convergent, and the amino acid sequence of DAT is 92% convergent [32]. This proximity ensures preservation of key structural and functional properties of the protein across species. Therefore, gene knockout in rats replicates the key manifestations of DAT deficiency in humans, including hyperdopaminergia and motor impairments. Thus, the DAT-KO rats represent the robust models for studying the pathogenetic mechanisms associated with DAT dysfunction.

The study of the physiological role of DAT began with the creation of the first animal models with the respective gene being knocked out. Among the first such models were DAT knockout mice genetically engineered by homologous recombination *in vivo*. To construct a targeting vector, dopamine transporter cDNA was used: a 2.0 kbp region including exons 6–8 was replaced with the PGK-Neo cassette. The vector was administered into embryonic stem cells by electroporation, and homologous recombinants were selected by

double selection and confirmed by Southern blotting. Embryonic cells with correct integration were used to engineer the chimeric individuals, from which the heterozygous $DAT^{+/-}$ and homozygous $DAT^{-/-}$ mice were reared—the first experimental models with DAT deficiency [33].

Rat SLC6A3 knockout was obtained using targeted mutagenesis. This model was first engineered in 2018 in Wistar-Han rats using the "zinc fingers" method. Removal of five base pairs in the second exon resulted in the premature formation of a stop codon and the absence of DAT mRNA in the striatum [5].

In 2022, an alternative Sprague-Dawley rat strain was engineered with the identical mutation obtained by CRISPR/Cas9 method. In homozygous animals the protein was completely absent, extracellular dopamine level was 5–7 times higher, the tyrosine hydroxylase expression was observed to increase in the substantia nigra, whereas normal regulation of other genes of dopamine system was maintained [34]. Heterozygous animals preserved approximately half of the DAT function and exhibited intermediate behavioral phenotypes [35].

Epigenetic mechanisms of dopamine transporter gene regulation. Expression is regulated by epigenetic mechanisms, including DNA methylation, histone modifications, and activity of non-coding RNAs [36]. These processes determine the level of transcription in dopaminergic neurons and thereby influence dopamine reuptake and DAT endocytosis. Disruptions in these mechanisms are likely to be the factors of neurodegenerative and psychiatric disease pathogeneses.

DNA methylation is performed by DNA methyltransferase enzymes and usually reduces promoter function due to the incorporation of 5-methylcytosine into CpG islands [37]. In the brains of patients with Parkinson's disease, hypermethylation of the SLC6A3 gene promoter has been observed, which leads to reduced DAT expression and reduced efficiency of its endocytosis, increasing dopamine deficiency. The use of demethylating agents, such as 5-Aza-2'-deoxycytidine, fosters the restoration of expression and stimulates the differentiation of dopaminergic neurons [36]. In the norm, in rats in early postnatal development, DAT promoter remains hypomethylated, which ensures an age-related increase of mRNA levels in the midbrain and reflects the dynamics of the dopaminergic system maturation [38].

Histone modifications also regulate DNA accessibility for transcription factors. Acetylation of H3K9/K14 residues increases significantly by 56th postnatal day, which is accompanied by an increase in DAT mRNA levels in the midbrain and striatum. A 71.3% decrease in Dnmt1 expression and 84.3% decrease in Dnmt3a expression by 56th postnatal day are accompanied by an increase in DAT level. During the same period, the Nurr1 and Pitx3 transcription factors enhance binding to the gene promoter region, with 6- and 8-fold increase of activity, respectively. These interactions with epigenetic markers ensure age-related regulation of DAT expression [38]. Histone deacetylases HDAC1 and HDAC2 supress the transcription, whereas their inhibitors, such as vorinostat, increase acetylation and enhance protein endocytosis [36]. H3K27 methylation by EZH2 inhibits DAT expression in Parkinson's disease and reduces the levels of genes involved in endocytosis, such as clathrin and dynamin. Changes in methylation levels of H3K4 and H3K27 histones in this disease are associated with activation of neuroinflammation and death of neurons [39].

MicroRNAs and long non-coding RNAs regulate post-transcriptional DAT expression. An additional level of control is provided by mRNA modifications, such as N6-methyladenine. These modifications determine the stability and efficiency of mRNA translation and influence endocytosis via signaling pathways mediated by protein kinase C and dopamine D2 receptors [36, 40]. Demethylases reduce DAT expression and foster α-synuclein accumulation in Parkinson's disease. Moreover, RNA editing by ADAR enzymes and pseudouridylation affect the function of endocytic proteins and, consequently, dopamine reuptake processes [36].

Disruption of these mechanisms is likely to be associated with ADHD, schizophrenia, and Parkinson's disease. Whereas, according to some data, the epigenetic inhibitors, such as GSK126 and STM2457, may be considered as potential therapeutic agents [36, 41, 42].

Gene therapy for DAT deficiency. Research into gene therapy for DAT deficiency has begun relatively recently. Therapy is based on the administration of a functional copy of the SLC6A3 gene using viral vectors—mostly adeno-associated viruses (AAV) and lentiviruses (LV) [26].

Administration of AAV2 or AAV9 with the synapsin promoter into the substantia nigra or intraventricularly ensures expression of human DAT in dopaminergic neurons, followed by protein transport to the striatum. During experiments in DAT-KO mice, the therapy demonstrated distinct dose dependence: administration of 2×10^{10} vg per mouse ensured complete restoration of motor function, normalized the descent time along the vertical pole and

other motor activity indices, and resulted in 100% survival by 12th week. Similar results were obtained after administration of AAV9 on 0 postnatal day. However, excess of the therapeutic dose by an order of magnitude caused toxicity with tremor and bradykinesia in half of the animals [43].

In adult mice, administration of AAV2 or AAV2/10 with different constructs (hSyn1-hDAT, TH-iCre/CMV-DIO-mDAT) also resulted in dose-dependent recovery: walking distance and time spent in the central zone during the open field test were observed to normalize, motor skills in the vertical pole test — to improve, gait parameters — to restore and hyperlocomotion — to reduce [44].

Combinatory approaches to DAT deficiency gene therapy involve the use of multiple vectors to ensure selective expression in dopaminergic neurons or the combination of viral delivery with pharmacological agents. In the DAT-KO mouse models, combined delivery of two AAV vectors was performed: AAV2/10 packaged with Cre-recombinase under the control of the tyrosine hydroxylase (TH) promoter and AAV2/10 packaged with Cre-dependent rat DAT expression cassette were administered into the substantia nigra. This approach ensured DAT expression only in TH-positive neurons. By 48th day after injection, a decrease in hyperlocomotion in the open field test, normalization of performance in the vertical pole test, and restoration of gait parameters were observed. Biochemical analysis showed partial restoration of dopamine uptake and normalization of the ratio of metabolites of the dopaminergic and serotonergic systems [44].

Similar therapy with a dual-AAV-vector-system administered to adult mice confirmed reaching the stable effect. Tyrosine hydroxylase expression was maintained without undesirable activation in other structures, such as the locus coeruleus [44, 45].

Lentiviral vectors (LV) are used in DAT deficiency gene therapy primarily in *in vitro* models based on iPSCs differentiated into midbrain dopaminergic neurons. In such systems, LV is used to correct mutations in the target gene that cause loss of DAT function. LV transduction restores dopamine uptake, reduces apoptosis, and increases the survival of TH-positive cells. The combination of LVs with an Hsp70 protein inhibitor enhances the effect, increasing dopamine uptake by 50–100% and reducing apoptosis to 20–30% of the control level. However, for some mutations, the effect is determined predominantly by viral transduction [43]. Therapy with LV is less commonly used in *in vivo* models, including DAT-KO mice, but LVs demonstrate the potential for selective expression in dopaminergic neurons and restoration of motor function [45].

Compared to AAV systems, lentiviral vectors provide more stable integration into the host genome but are associated with a risk of insertional mutagenesis, which limits their clinical application [46]. At the same time, analysis of available data shows that the main track of research is targeted at AAV due to their low immunogenicity and high efficacy of certain serotypes (AAV2, AAV5, AAV8, AAV9) for the central nervous system [47, 48]. Studies using other viral platforms (in particular, adenovirus or herpesvirus) for the correction of DAT deficiency are not available yet, which highlights the limitations of the current experimental database.

Discussion and Conclusion. A significant amount of data on studying the dopamine dysfunction, epigenetic mechanisms, and gene therapy approaches in the DAT-KO rat models is accumulated in the scientific literature and has been systematized by the authors. However, the completeness of this dataset is limited by several factors: homozygous models are used quite oftener in research than the heterozygous ones, which limits the understanding of the full range of consequences of partial DAT dysfunction. Data on the dynamics in epigenetic regulation of the dopamine transporter remain fragmented [32, 34], and preclinical gene therapy studies are not supported by a sufficient number of studies on long-term safety [39, 42].

The literature review has shown that homozygous DAT gene knockout models can replicate certain aspects of dopaminergic transmission dysregulation [1, 5]. The complete absence of the transporter functions represents an extreme form of pathology, whereas heterozygous specimens exhibit intermediate phenotypic manifestations, and therefore their parallel study is increasingly valuable.

In addition, neuroanatomical and behavioral changes in knockout models may reflect both direct consequences of DAT deficiency and secondary conditions in other neurotransmitter networks [49]. Therefore, multimodal approaches are required to separate primary and secondary effects: high-field MRI for quantitative morphometry, targeted transcriptomic and proteomic analyses to identify cascades of compensatory changes, and time-related assessment of phenotypes at different ages. Epigenetic data on SLC6A3 regulation provide an important but still fragmentary addition to the understanding of dopaminergic dysfunction. Single studies indicate

hypermethylation of the SLC6A3 promoter in Parkinson's disease and age-dependent changes in histone methylation and modifications in rodent models [38, 39]. However, these scattered data do not allow building a comprehensive picture, since this requires establishing an exact correspondence between epigenetic markers, DAT expression and the clinical picture.

At the same time, the prospects for therapeutic correction of DAT deficiency appear encouraging. AAV-mediated delivery of SLC6A3 has shown dose-dependent restoration of motor parameters in animal models [43, 44, 45]. However, the use of AAV vectors has certain difficulties due to a narrow therapeutic index in terms of time and dose [46], which requires precision of the parameters of administration and spatiotemporal control of transgene expression.

Alongside, two-vector approaches ensuring selective expression in TH neurons and LV strategies for *in vitro* correction in iPSCs demonstrate functional efficacy [43]. But LV vectors are a priori less safe compared to AAV [48]. Therefore, research priority should be given to optimising targeting, control of expression levels and long-term monitoring of side effects.

Thus, the SLC6A3 gene knockout rat model represents a valuable experimental model for studying the pathophysiology of dopaminergic dysfunctions. Its high homology to the human SLC6A3 gene ensures the replicability of key phenotypes, including hyperdopaminergia, motor and cognitive disorders, and makes it relevant for studying ADHD, schizophrenia, Parkinson's disease, and DAT deficiency syndrome.

Advanced gene therapy strategies based on AAV and LV vectors demonstrate high efficacy in restoring DAT function and correcting motor and behavioral disorders in experimental models. However, the specific nature of gene therapy using viral vectors, particularly the narrow therapeutic dose range and the need to prevent side effects, as well as the limited available data, emphasise the importance of further research.

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