Review Article

Animal Models of Attention Deficit and Hyperactivity Disorder: A Critical Overview and Suggestions

Abstract

Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopmental and neuropsychiatric disorder that appears as a subset of attention deficit and different subspecies in which both occur together and is generally observed in childhood. Pharmacological agents such as atomoxetine and methylphenidate, which are widely used against the disease, appear with different and important side effects. Since the causes of the disease are not clearly understood, many studies are carried out on various animal models in order to both understand the etiology and develop new treatment models. In this review, a holistic approach to ADHD will be presented and advances in animal models, neuroimaging, neurodevelopmental, and neurochemical conditions will be presented using different perspectives. It is very important to understand how different animal models are effective in the development of pharmacological agents. In addition, comparing ADHD with different types of disease can detect similarities and further strengthen the etiological basis. Our major proposal is to draw attention to the further development of animal models related to the importance of the thalamus, which officially sees a filter of perception. Different animal models are needed to do all this because the disease is not fully modeled, except for the symptoms of ADHD. The current review will conclude that none of the currently discussed models meet all the necessary validation criteria, but that newly created genetic models, therapeutic strategies, and the disease mechanism may be radically important points.

Keywords: *Animal models, attention deficit and hyperactivity disorder, neurochemistry, neurodevelopment, neuroimaging, pharmacology*

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Introduction

Attention deficit and hyperactivity disorder (ADHD) is classified as a heterogeneous neurodevelopmental disorder manifested by varying levels of hyperactivity, impulsivity, and inattention in humans. According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1] Although ADHD is a common and highly inherited disease, its genetic etiology is not yet fully known. Many studies have shown the genetic predisposition of ADHD but estimate that the heritability of ADHD ranges from 50% to 80% and is not known for sure.[2-6] The 1999 General Surgery Academy report on child mental health notifies "For most children with ADHD, the overall effects of these existing gene abnormalities appear negligible. This shows that these nongenetic factors are also important."[7] As our genes have not changed significantly over a thousand years, these "non-genetic factors" should explain the increased incidence of ADHD. Some of the roles that the environment can play in ADHD can be listed as follows: maternal obesity, maternal smoking, chaotic families, maternal stress during pregnancy, and inconsistent-harsh parenting.[8,9] In addition, nutrition can be classified as an environmental factor and has a critical importance for fetal development. Recent studies show a strong link between nutrition during pregnancy and the risk of having a child with neuropsychiatric diseases such as anxiety, depression, and ADHD.[10]

Patients with ADHD are generally defined in three ADHD subtypes; the first is mostly the inattentive subtype (most commonly seen in girls), the second is the predominantly hyperactive/ impulsive subtype (most commonly in boys),

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and the third is the combined subtype (i.e., includes both inattention and hyperactivity).[11] Especially psychostimulants (such as methylphenidate [MPH], atomoxetine, pemoline, and d-amphetamine) are used in their treatment.[12] There is great interest in developing specific animal models to outline specific forms of ADHD in order to develop specific therapeutic strategies outside of these treatments. ADHD is a neurobehavioral disorder of childhood and is characterized by deterioration in children's behavior. The diagnosis of this disease is based on behavior. Therefore, when validating an ADHD model, it should be based on behavior in the same way. The general characteristics of an ADHD model can be listed as follows: it must be compatible with a theoretical rationale for ADHD (construct validity), predict previously unknown aspects of ADHD behavior, genetics, and neurobiology in clinical settings (predictive validity), and simulate the basic behavioral characteristics of the disease (appearance validity).[13] The prevalence of ADHD is increasing worldwide, and although it is available for drug interventions, definitive treatment has not been found because most of the underlying etiology is still unknown[14] and underlying deficiencies include hyperactivity, attention deficit, and impaired neurocognitive events.[15]

The aim of this review is to overview ADHD animal models to show the new studies of treatment strategies, to draw attention to the lack of animal models used in the development of effective diagnosis and treatment methods for ADHD, and to provide recommendations along with critical deficiencies.

The place of developmental cognitive neuroscience in attention deficit and hyperactivity disorder

The tasks of the frontal lobe are to line up incoming information, associate current experiences with past experiences, monitor behavior, suppress inappropriate reactions and plan for future purposes. These are also called executive functions of the frontal lobe. At the core of executive functions is the ability to initiate, maintain, inhibit attention, and draw attention in another direction. Therefore, a frontal lobe dysfunction can cause disturbances in impulse control, attention, and/or cognitive activities.[16]

How are actions planned by the brain?

The prefrontal cortex (PFC) is the region where attention, perception, perceptual analysis, abstract thinking, and social behaviors are controlled and converted into behaviors; briefly, it organizes the senses from all lobes and converts them into behaviors (works in collaboration with amygdala and thalamus). As shown in Figure 1, through glutamatergic and dopaminergic activity, this information is transferred to each other by providing communication between neurons.[17,18] Primary motor cortex is the region where all calculations and decisions are made before a move is made (stop and think before doing). Then, the synaptic neurons (carrying information) are coming to the premotor cortex, then choosing the appropriate movement (the region of choosing the right move after realizing that it should stop and think). After deciding on the appropriate movement, the transition to the application to the motor motion area is the primary motor area.[19] Managerial functions are motor planning, directing attention, changing cognitive sets, monitoring, and adapting behavior through attention and process memory and are associated with the dopaminergic activity.[17]

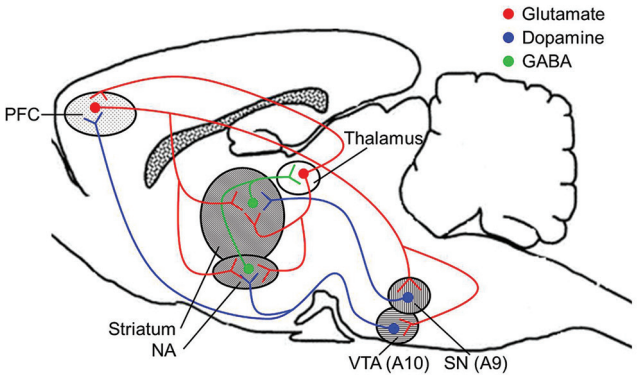

Figure 1: Relationship between dopamine transporter and growth factor. The importance of dopamine transporter in driving cellular activation in the postsynaptic membrane and the importance of working in cooperation with growth factors[18]

The importance of thalamus in attention deficit and hyperactivity disorder animal modeling

There are a number of nuclei in the thalamus, and these nuclei control the information from the surrounding lobes in the postsynaptic connections due to their ganglion feature. They act as an association region in transforming into behavior and reflect the information to the PFC in the conduct of the behavior as a motor. If neurodevelopmental nutrition disorders, especially neurochemical activity disorders with dopaminergic activity, have occurred in the PFC, symptoms that usually occur with ADHD, such as incompatibility in emotional response, inability to inhibit impulses, neglect of the consequences of their behavior, excessive mobility, restlessness and disturbance in attention occurs.[17,20] Anterior cingulate gyrus (ACG) located just above it, helps manage the organization by disabling irrelevant information and enables us to continue our attention. ACG acts as a filter for incoming data, separating and classifying information. Furthermore, ACG is the center of our brain's attention and has a connection with the hippocampus, where our long-term memory resides, through a thick fiber node called the cingulum. Moreover, the thalamus translates the information reflected from all these regions by sending to the motor activity of the behavior into the frontal cortex.[21-23]

Based on these, for the most suitable animal model of ADHD the criteria and recommendation can be made as below:

1. The model must fit a theoretical rationale for ADHD (construct validity): Two principle behavioral processes that are claimed to be major constitutive components in ADHD etiology, prereinforced behavior ought to be demonstrated
2. The model should imitate the fundamental behavioral characteristics (visual validity) of ADHD, impulsivity ought not be present at the beginning and should develop gradually over the long run, continuous attention deficit ought not be observed only when stimuli appeared at wide intervals over time, hyperactivity ought not be observed
3. The model should be neurodevelopmental, a prehereditary model
4. The model ought to anticipate new parts of ADHD conduct, hereditary qualities, and neurobiology (predictive validity).[24]

Although there is a human-like effect in the rodent brain in ADHD, this biochemical balance is different from each other since the thalamus and ACG in the human brain are more developed. In particular, dopaminergic neurons project from the ventral tegmental area and substantia nigra to the prefrontal cortex and then to the dorsal striatum. The filtering center in these projected neurons is the ACG, but in ADHD models, the models may be inadequate because this part is underestimated [Figure 2].[25]

The importance of imaging studies in animal modeling

Anatomical differences were found in people with this diagnosis in imaging studies. Among the detected findings, differences such as PFC, orbitofrontal cortex, basal ganglia, some parts of the corpus callosum, cerebellum shrinkage, and thus decreased functionality were found.[26-30] Total brain volume also decreases, especially in individuals with ADHD.[25,31] Studies are carried out to determine whether this reduced volume is due to the neuronal network, or genetically based or related to brain neurochemistry, and

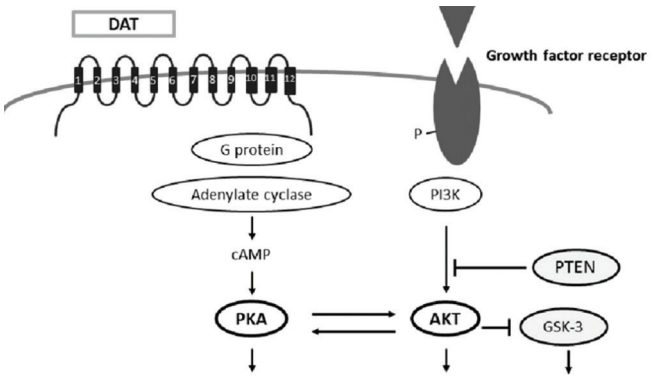

Figure 2: Molecular neurochemistry and anatomy of attention deficit and hyperactivity disorder in rodent brain. Dopaminergic neurons and glutamate neurons connect up to the prefrontal cortex. While both types of neurons have an excitatory effect from the ventral tegmental area and substantia Nigra (SN, A9) to the citriatum, GABA neurons have an inhibitory effect from the thalamus to the citriatum and nucleus accumbus[25]

animal models that are suitable for this research started to be created. Clinical proof focuses to some degree to diminished capacity of the striatum, but it is not well understood how specific genes are expressed differently and do not predispose to ADHD how they shape striatal physiology.[32] The PFC includes the anterior cingulate cortex (ACC), and this area plays major roles in learning (knowledge) and cognition.[32-35] For this reason, PFC hypoactivation and disinhibition (malfunctioning) can cause PFC-related cognition degradation.[36] Medial PFC (mPFC) and ACC are regions associated with preparatory attention in which phasic responses are both inhibitory and stimulating; this suggests that differential afferent regulation in putative PFC pyramidal cells is important for the preparation step. It also receives dopaminergic inputs from the ventral tegmental area, which is necessary for optimal cognitive function in the deep layers found in the rat PFC. Thus, the neurotransmitter dopamine (DA) is a neuromodulator of mPFC function, and it can be concluded that DA receptor transcripts are expressed more densely in the V-VI layers than other superficial or intermediate layers of the mPFC.[37,38]

DA release can activate G-protein-coupled receptors such as D2-like (D2, D3, and D4) and D1-like (D1 and D5) DA receptors. While the D1-like receptor-mediated pathway enables Gs-type G proteins, which are stimulus (s) and positively bind to adenylate cyclase (AC), to be activated; however, the D2-like receptor-mediated pathway enables inhibitor (i) and G-type G proteins that are negatively bound to AC to be activated. Briefly, activation of the DA receptor-mediated pathway provides regulation of adenosine-cyclic monophosphate (cAMP)-concentration-dependent signaling pathways. In addition, cAMP activates protein kinase A (PKA), which is known to play an important role in neuronal synaptic plasticity.[39,40] One of the basic pathophysiological models of ADHD studied to date is the hypo-dopaminergic hypothesis. In this context, it is well known that too low or too high D1 stimulation levels can impair memory and attention behaviors and lead to diseases.[36,41,42] Imaging studies can also provide us wide information about reaching the most possible result that can be achieved on comparing different animal models in different therapeutic effects. Furthermore, radiolabeling studies have showed that both cocaine and MPH share analogous forms of attachment within the dopaminergic system (e.g., nucleus accumulators, etc.) involved in repeated substance use and euphoria.[43-45]

The importance of animal modeling

The most frequently cited principles of animal models were proposed by McKinney and Bunney[46] about 50 years ago. According to what has been known since 1969, an animal model to be ideally classified should be similar to the disorder to be modeled in terms of etiology,

symptomatology, biochemistry, and treatment.[46] Animal models offer many advantages when studying diseases. A few of them are as follows: For brain-based diseases, they provide the opportunity to work on simpler nervous systems, exhibit easily interpretable behaviors, offer an easily controlled environment, provide genetic homogeneity, and allow various interventions that cannot be performed on humans. On the other hand, in animal models of ADHD, it has appeared as a crucial tool for understanding the contribution of maternal nutrition to prenatal programming, the development of three macronutrients (protein, fats, and carbohydrates), and subsequent neuropsychiatric disorders. Therefore, the importance of exposure periods reflecting the neurodevelopmental stages of human gestation in emphasizing the translational aspects of animal models is very important. Nutritional programming of neurobehavioral disorders constitutes a solid basis of preclinical studies; in addition to neurodevelopmental disorders due to neurodevelopment, synaptogenesis, and synaptic plasticity, changes in risk assessment and response have also been observed.[11] According to the findings from previous studies, several rodent models led to the emergence of ADHD-like symptoms, including DA receptor 4 (D4R)-KO mice, DA transporter (DAT)-knockout (KO) mice, and spontaneous hypertensive rats (SHR). In addition, a hyperactive mouse line was established through phenotypic selection performed over multiple generations, according to a new animal model. Consequently, the relatively simple nervous systems of rodent models enabled the identification of neurobiological changes underlying certain aspects of ADHD behavior. In this way, the formation of animal models is important and needs to be studied further.[47-51]

Pedigree differences in animal models

The results obtained in behavioral pharmacology studies with genetic interventions raised the question whether there may be differences in basal and postintervention responses in models depending on the lineage of animals, and there may also be differences in ADHD models due to lineage. As an example, the most studied ADHD model is the SHR showing inattention, hyperactivity, and impulsivity,[52] but the behaviorally SHR model known to be limited in two significant respects:

1. The animal model was bred for hypertension, so to separate the factors that result from the hyperactivity of hypertension
2. SHR does not have a suitable control type to statistically determine whether phenotypic differences between lines are associated with hyperactivity or other factors.

The control strain Wistar-Kyoto (WKY) rat, commonly used in this direction, shows activity levels below other rats, so it has been proposed and used as a model of depression.[53-56] On the other hand, studies of animal models of three different lineages compared, due to the lack of receptors shed light on the selection of the correct lineage to better treat and understand the disease. For example, comparing the ideal animal models (SHRs) for ADHD subtypes, WKY rats, and behavioral differences between Sprague-Dawley (SD) rats, the SHR model is an ideal animal model for the mixed subtypes of ADHD. Especially glucocorticoid receptor (GR) functions have an important place in ADHD models behavior. On the other hand, further studies are required to determine whether WKY rats can be used as an ideal model for ADHD. The existing GR agonist can effectively correct nonselective attention and spontaneous activity in SHR rodent models.[57]

The Animal Models of Attention Deficit and Hyperactivity Disorder

The most widely used Napoli high and low inducible rat lines have been used on the basis of behavioral arousal (Làt-maze) versus novelty since 1976.[58] The five-preferred series reaction time task (5CSRTT) is also a psychologically used laboratory behavioral test.[59] Poor performers in the five-prefer serial reaction time task and Napoli high excitability rats are more useful models for ADHD compared to other animal models which focus on less important signs of hyperactivity. Furthermore, it may have limited value due to ADHD-like behavior is shown or are manufactured in a way but that does not lead to a clinical diagnosis of ADHD in humans. This behavioral ADHD does not meet the criteria for animal models and is therefore excluded from the current review. These excluded animal models include the Napoli highly excitable rat, the WKY Hyperactive rat, the acallosal mouse, the hyposexual rat, the PCB-exposed rat, the lead-exposed mouse, and the rat reared in social isolation. With these excluded models, new models have started to be created. SHR meets most of the validation criteria and provides good comparison with clinical ADHD cases.

Model of attention deficit and hyperactivity disorder due to dopamine transporter gene deficiency

DAT carrier KO mice are important as one of the few transgenic animal models of developed ADHD disease. It is a model developed according to the suggested role of DA in ADHD. Administering the specific MPH drug to this model reduces hyperactivity and improves learning in both DAT-KO mice and patients with ADHD. This model was also created by combining heterozygous pairs of C57BL/6J strain DAT-KO mice to produce wild type and homozygous DAT-KO animals.[60]

Attention deficit and hyperactivity disorder model due to increased ataxin-7 gene expression

Ataxin-7 (Atxn7) has been proven to be a gene associated with hyperactivity. In a study, mice overexpressing an Atxn7 gene (Atxn7 OE) were created to investigate whether increased expression of Atxn7 in the brain is associated with ADHD-like behavior. When looking at the methods

used, immunofluorescence and quantitative real-time polymerase chain reaction (RT-PCR) methods confirmed the overexpression of the Atxn7 gene and protein in the PFC and striatum (STR) of Atxn7 OE mice, and Atxn7 OE mice showed hyperactivity, but did not show impulsivity. In particular, the ADHD drug atomoxetine (administered intraperitoneally 3 mg/kg) reduced ADHD disease-like behavior and Atxn7 gene expression in the PFC and STR of these modeled mice. These findings show that this drug plays a role in the pathophysiology of Atxn7. It has also been revealed that Atxn7 OE mice can be used as one of the hyperactive-impulsive phenotypes of the ADHD animal model. This study also provides valuable information on the potential genetic basis of ADHD, which is not fully known. As is known, ADHD can mostly be detected behaviorally. The emergence of genetic foundations has an important place in terms of science.[61]

Model of attention deficit and hyperactivity disorder linked to dopamine concentration and receptors

Discovering genes is important in ADHD. Studies in this direction have found several relationships between various monoaminergic genes and polymorphisms in ADHD. These include genes and polymorphisms such as DA D1, D4, and D5 receptor (DRD1, DRD4, and DRD5) genes, DA norepinephrine (NE), a2-adrenoceptor gene, and serotonin transporter (DAT1, SERT1, and NET1).[62,63] In these models, the system was functionally disrupted, and in some animal models, extracellular DA concentrations and upregulated postsynaptic DA D1 receptors (DRD1) decreased while others increased extracellular DA concentrations. DA pathways are suggested for ADHD models. However, DA release of DA stimulation is impaired in these models, which is associated with impaired DA delivery. The aspects of its behavior in ADHD models may be due to the imbalance between decreased dopaminergic and increased noradrenergic regulation of neural circuits involving PFC. The aspects of its behavior in ADHD models may be due to the imbalance between decreased dopaminergic and increased noradrenergic regulation of neural circuits involving PFC. There is evidence that psychostimulants can reduce motor activity by increasing serotonin levels, which increases the importance of these drugs in ADHD. Besides explaining the neurobiology of ADHD and its relationship with genes, these animal models can also be used to test new drugs that can be used to alleviate ADHD symptoms. These include new psychosocial additions to be found. One of the approaches that can be applied to model the symptoms of ADHD in experimental animals is to damage the dopaminergic pathways using 6-OH-DA in developing rats. The pathophysiological mechanism of ADHD is not fully known, as previously mentioned. In particular, the role of synaptic transmission systems is not fully understood. However, due to the downregulation of DA D1-like receptor pathways of GABAergic interneurons in ACC, the results obtained with the SHR animal model in the studies performed show that; dopaminergic activity stands out when looking at the differences in DA modulation of GABAergic transmission recorded from V layer pyramidal cells compared to WKY rats in the control of SHR animal models. In WKY rats, both miniature and spontaneous inhibitors increase the frequency of postsynaptic currents (for example, mIPSCs and sIPSCs, respectively), although this failure to work in SHRs brings along the inadequacy of the model. Similarly, the neuronal network amplitude of amplified IPSCs (eIPSCs) increased by DA in WKY rats comparing to SHRs. DA also increased the amplitude of unitary IPSCs (uIPSCs) that were larger than SHR patterns in WKY rats. Based on the observations made in the study, it can be concluded that D1-like receptor pathways hold promise in ADHD as potential regulators mediating these modulating effects.[64] In another study, atomoxetine's therapeutic effects on motor activity were studied. The expression of the DA D2 receptor with atomoxetine and the effects on ADHD was investigated. Young male SHR was used. As a result, it was observed that daily atomoxetine at a dose of 1 mg/kg continuously improved the motor activity. Thus, it was found that treatment with atomoxetine significantly (in a dose-dependent manner) decreased DA D2 expression in the hypothalamus of the PFC, striatum, and SHRs. In other words, hyperactivity in young SHRs can be improved by treating with the drug atomoxetine via DA D2 receptors, which is important for ADHD disease.[65] On the other hand, not only DA receptors but also other receptor mechanisms are important in ADHD modeling and many mechanisms depend on the receptors.

Sprague- Dawley acute dopamine depletion model in rats

McDougall *et al*.[66] used a protocol in 2005, 2 h apart rodents from the tyrosine hydroxylase inhibitor α-methyl-DL-p-tyrosine (AMPT) group get two intraperitoneal injections of AMPT (25 mg/kg each). After, locomotor activity was detected for 30 min to validate the animal models which placed in open-field boxes to monitor.

Due to the effects of TAT-DATNT, animals were placed in open field boxes for 15 min after induction of DA depletion. The animals were then given an intracranial injection of 40 nmol of TAT or TATT-DATNT. The rodents were returned to the open field rooms for 60-min recording session. As a result, the TAT-DATNT peptide improved spontaneous and locomotor behavior in SHR rats.[66,67]

The model of primary cortical astrocyte culture

In the DAT mutant and knock-out models in which astrocytes are cultured, the findings of neurogenesis, the importance of the GABAergic system on the nutrition of the region and neuronal networks, and the relationship between glial GABA and cortical tonic inhibition with the disease have clearly been revealed.[68]

Naples high volatility model

The Naples high volatility (NHE) model is a different model used to demonstrate ADHD. These rodents have a balanced cortical and an upgraded limbic cycle in their cerebrums. NHE rats show the distinctive roles of the dorsal (lower coding of repetitive stimulus-reward relationships to a habit) and ventral (increased value is given to true primary reward) striatum. As a result, this model has emerged as a model that can be used for gambling disease in ADHD and revealed that the dynamics in the reward system can be associated with reduced attention to pathological gambling.[69]

Model of attention deficit and hyperactivity disorder in constitutive adhesion G protein-coupled receptor L3 knockout mice

Adhesion G protein-coupled receptor L3 (LPHN3 and ADGR L3) has been associated with ADHD in several ways. In a study, the characteristics (impulsivity, gait, locomotive activity, recognition memory, sociability and visuospatial, anxiety-like behavior, and aggression) were investigated in mice with ADGRL3 deficiency in many behavioral areas related to ADHD. As a result, the combination of behavioral and transcriptomic findings has been confirmed to be an experimental animal model of ADHD in constitutive ADGRL3 KO mice. According to the data obtained, changes in gene expression in the DA system provide information to support the interspecies link between ADGRL3 inactivation and the abnormal function of the DA system. It also supports and justifies studies in ADGRL3 transgenic animals to reveal significant and biologically relevant gene expression changes in the PFC and striatum. In addition, future transgenic animal models created using more different techniques as CRISPR-Cas9 will lead to the generation of variants as ADGRL3 associated with disease. In this case, it is thought that specific noncoding polymorphisms in this gene can provide more detailed information about how the ADHD model can emerge.[70]

Other genetic factors

Other genes that are effective in ADHD etiology are in the serotonergic system: Adrenergic receptor genes such as tryptophan hydroxylase gene, dopa decarboxylase gene, alpha 1C (ADRA 1C), and alpha 2C (ADRA 2C), are the step of a third stimulus in serotonin synthesis. In addition, not only genetics but also receptor and enzyme activity encoded by genes are important. Furthermore, DA neurochemistry is very important in ADHD neurophysiology, and there are five DA receptors. The enzyme that catalyzes the D3 receptor is DA B Hydroxylase, tyrosine hydroxylase for the D4 receptor, catechol-O-methyl-transferase for the D5 receptor, and monoamine oxidase catalyzes the DAT gene, and its receptors. In addition, a relationship was found between the 5-HTT (serotonin transporter) gene and ADHD.[71,72] It has been shown that the A1 allele of the DA D2 receptor gene (DRD2) known to be located on chromosome 8 (on the long arm) may be important in ADHD. The A1 allele was detected in 46.2% of patients with ADHD, and it was stated that this gene plays a role in ADHD as a modifier rather than an etiological factor. While the D2 receptor is also observed in the striatum, it is found in moderate amounts in the hippocampus, amygdala, and thalamus. It is known that the D2 receptor is at a low level in the PFC.[73] In individuals with ADHD, it has been reported that single-photon emission computed tomography is associated with DA-carrying receptors.[74-76] An even lower than normal level of DA in humans causes various neurodegenerative disorders and ADHD.[77] When it is at a higher level than normal, it causes other disorders due to abnormal functioning brain functions, and the DRD2 gene, one of the five receptors of DA, has the effect of the Taq A1 Allele (rs1800497 polymorphism).[78] All of these genes constitute the epigenetic mechanisms of ADHD because these receptors provide mRNA stabilization and form the neurodevelopmental basis in the PFC. The production of new neurons from the mother's womb to adulthood and the epigenetic mechanisms that are integrated with dopaminergic activity are tried to be elucidated by various imaging and physiological examinations and animals are made through these models. When looking at the neuron cell, the protein and gene expressions required for the formation and development of neuronal networks can also be maintained with the help of neurochemistry by the work of these receptors and genes, and histone modifications are also required to be studied at the molecular level. The conclusion that can be drawn from this is that more animal studies are needed for ADHD on genetic factors.

Potential Therapeutics in Attention Deficit and Hyperactivity Disorder Treatment

Since ADHD is defined as a neurocognitive disease with behavioral symptoms as inattention, hyperactivity, impulsivity, and working memory defects, the neurocognitive approach in animal models makes a very important contribution to the development of treatment modulation. The most common mechanism of treatment known for this disease includes stimulant drugs (e.g., MPH and atomoxetine), and the mechanism is blocking the DAT and increases synaptic DA.[79,80] While these pharmacological agents are beneficial in this disease, they cause a variety of side effects, including risks for future substance use disorders in ADHD patients. For this reason, studies with various active substances were carried out in animal models to create new treatment options.

In a study, it was used an interfering peptide (TAT-DATNT) to cleave a protein complex composed of the interaction between DAT and the DA D2 receptor (D2R). Locomotor behavior was found to be increased in SD rats. It has been found that the degradation of D2R-DAT increases

the level of extracellular DA, especially when *in vivo* high-performance liquid chromatography and microdialysis are used. More importantly, the TAT-DATNT peptide significantly reduced hyperactivity and improved spontaneous transition behavior in the SHR model in a common ADHD animal model. A different way of regulating the activity (i.e., other than direct inhibition by a DAT inhibitor) of dopaminergic neurotransmission and DAT and a potential target site for the future development of ADHD treatments are presented in this study.[67] Given DA dysregulation and the effect of DAT on ADHD, better results can be demonstrated by comparing whether the D2R-DAT protein complex is a suitable treatment target for ADHD in different animal models. Consequently, this study investigated whether the TAT-DATNT peptide would have any beneficial effect on ADHD-like symptoms (i.e., impaired working memory and hyperactivity) in the widely used rat model of D2R-DAT disorder, ADHD SHR, and positive results were found. Likewise, studies with different proteins can be said to be promising. In another study, the SHR ADHD rat model was used and morphological changes were tried to be found during *in vitro* development of frontal cortical neurons in comparison with the control group WKY rats and the effects of adenosine A2A (A2AR and A1R), A1, and caffeine receptors signals were investigated. Cortical neurons cultured from WKY rat and SHR treated with caffeine or A1R and A2AR agonists or antagonists after analyzed by immunostaining for tau proteins (microtubule-associated protein) and protein 2.

Furthermore, the involvement of PI3K, not PKA signaling, was evaluated in this study. Importantly, frontal cortical neurons have been isolated for the first time from the ADHD model, which has been shown to cause impairments in differentiation and growth. It increases the potential of caffeine and A2AR receptors as an adjuvant for the treatment of ADHD, showing that A2AR and caffeine can act as a neuronal level capable of maintaining the growth of ADHD neurons.[81] Agents that can be used to increase the effects of different drugs that can be produced for ADHD in the future have been revealed. Furthermore, in another study, male SHRs (4 weeks old) and normal control WKY rats were used to find expression profiles of lncRNAs in the hippocampus from an ADHD model using SHRs, and rat brains were subjected to some testing. Microarray analysis technology was used to determine the expression profiles of lncRNAs and mRNAs in SHRs and WKY rats; then, the differentially expressed lncRNAs were verified by RT-PCR. Gene Ontology (GO) and pathway analysis (for expressed mRNAs or nearby genes) was used to determine the possible functions of lncRNAs in ADHD disease. In results, a total of 267 differentially expressed 311 mRNAs and lncRNAs (123 downregulated and 144 upregulated) were identified in SHRs compared to WKY rats. RT-PCR analysis was used on selected 15 lncRNAs and was confirmed. GO and Kyoto Encyclopedia of Genes and Genome pathway analyzes have shown that irregular lncRNAs in the brain play a role in neuronal function and maintenance, as well as development processes. The close relationship between differentially expressed lncRNAs and mRNAs was revealed by co-expression network analysis. In addition, the expression analysis system of disordered lncRNAs, downstream genes, and the organization of memory and learning showed that lncRNA NONRATT0006598.2 is associated with the Baiap2 gene, which may be involved in ADHD progression. The findings have the potential to contribute significantly to the advance of ADHD disease and to find possible therapeutic targets for lncRNAs and mRNAs and ADHD treatment.[82] LncRNAs (transcripts with not translated into protein and their lengths exceeding 200 nucleotides) and protein-encoding mRNAs could have a potential therapeutic effect for future ADHD therapy. In another study, the effect of catalpols (ingredient of Rehmanniae radix preparata, a Chinese medicinal herb) behavior and neurodevelopment on the ADHD SHR animal model were investigated. SHR was divided into some groups such as the SHR group, catalpol group (daily 50 mg/kg), MPH group (daily 2 mg/kg), and WKY rat group. With the findings obtained from this study, it was revealed that catalpol can effectively improve hyperactive and impulsive behavior and that catapol in ADHD can improve spatial learning and memory in SHR, which is a widely recognized animal model.[83] Hence, the Chinese traditional herb was found to be an effective therapeutic for AHDH. Studies have been conducted except for bioactive compounds found as therapeutic agents that can be used in ADHD treatment.

On the other hand, it turned out that a physical acoustic noise with the effect of external exposure can create a different effect that can treat this disease. This study was conducted on the SHR model of ADHD investigated how acoustic noise affects brain activity. Neuronal immunohistochemical staining and markers of plasticity, ΔFosB, and Ca2/calmodulin-dependent protein kinase II of Wistar rats (n = 24) and SHR (n = 16) were evaluated after the exposure to repeated ambient silence or acoustic noise. Furthermore, SHR (n = 6) was repeatedly treated with MPH. As a result, it showed that the applied acoustic noise shifts a decreased neuronal activity in the core accumulator, tuberomammillary nucleus, and dorsolateral PFC in SHR to normal activity levels in mated rats. This result can explain why noise is selectively beneficial in ADHD.[84] In this way, studies carried in animal models of ADHD, and the positive results obtained seem to have potential therapeutic properties in the future. These results should be supported by further studies and phase studies should be started.

Pharmacological Effects and Animal Models

There are many medications used to treat ADHD. These drugs are known to affect different mechanisms and the use of these drugs in different ways has been tested in experimental animals. Current drugs used for the treatment

of this disease function mostly by regulating brain DA and/or NE levels. For example, MPH, the most effective and frequently prescribed drug for ADHD, functions as a psychostimulant that stimulates DA release in the central nervous system and inhibits its reuptake, thus enhancing the temporal and spatial presence of DA at postsynaptic receptors. On the other hand, as a nonstimulant drug, atomoxetine is also widely used in ADHD and different neural diseases with its NE reuptake inhibitor function. The reduction of ADHD symptoms by atomoxetine could possibly be associated with levels of NE and DA in the PFC, as well as its effects on cognition and arousal in attention. These mechanisms may be mediated by activation of NE a-2 and/or DA D1 receptors.[34,85-89] In addition, recently, it can be said that both atomoxetine and MPH cause an increase in cortical histamine release in rats, and it was observed that MPH was more effective when these two substances were compared in this study.[84] One study found that atomoxetine supports the hypothesis that it can evolve cognitive function. The drug atomoxetine (NE reuptake inhibitor) was involved in histamine release, and it is found that it can be used for the treatment of cognitive deficits associated with neuropsychiatric disorders and ADHD.[90] There are also reports in contrast to MPH given at low doses and at high doses. SHR cannot offer the same therapeutic effects on hyperactivity behavior in rats.

Therefore, similar observations were made in SHR rats at a high dose (comparing with the other) of TAT-DATNT (4.0 nmol) by trying different dose effects, on hyperactivity a U-shaped dose-response curve was seen in SHR, but when given much higher than this dose, MPH, on the contrary, it increases excessive dopaminergic neurotransmission and fulfills the stimulating effects observed in SHR rats.[67,91,92] Although WKY rats reported higher levels of DAT in the striatum of SHR rats at 2 weeks of age compared to WKY rats when compared to a control strain for SHR rats,[93] there was no significant difference in overall D2R or DAT levels between SHR and WKY rats. TAT-DATNT administered in the same dose and had no effect on locomotor activity in WKY rats. Unlike it had dopaminergic effect on the SD rat strain. On the other hand, TAT-DATNT has been found to be dose-dependent and likewise, the effects of MPH on WKY rats are dose dependent.[94,95] On the other hand, L-threo-dihydroxyphenylserine (L-DOPS) for ADHD is a NE prodrug that increases brain NE and DA levels. A study aimed to measure the effects of this drug on ADHD-like behaviors in rats and its effects on PFC and DA neurons in the ventral tegmental region. Therefore, behavioral tests and electrophysiological tests were applied on rats. In addition to the L-DOPS drug, the peripheral amino acid decarboxylase inhibitor benserazide (BZ) also participated in the experiments in this study. In conclusion, in behavioral tests, BZ + L-DOPS improved the hyperactivity, impulsive action, and inattention of adolescent SHRs (SHR/NCrl) (well-validated animal model of combined ADHD type). BZ + L-DOPS also resulted in impulsive selection and reduction of impulsive action in Wistar rats, but did not improve inattention of Wistar Kyoto rats (WKY/NCrl) (predominantly inattentive type proposed model). It was emphasized that the L-DOPS drug has effects on PFC and DA neurons and BZ + L-DOPS can be an alternative treatment for ADHD.[96] According to positive results from the studies, it is important to understand how the drugs are effective and how they show effects with combined therapies. Therefore, more studies should be conducted, and new treatment strategies for ADHD should be investigated.

The Importance of Animal Modeling in Other Diseases That May Occur with Attention Deficit and Hyperactivity Disorder

ADHD is a disease that can be seen together in different diseases. First, it can be seen with different mental and cognitive disorders (difficult to learn, abnormal social behavior, anxiety, and depression), but on the other hand, it has been found that it may also be associated with other diseases.[97] Most of the mechanisms and causes of the different disorders in the presence of this disease are unknown. Studies have been conducted to determine these and further studies are needed. ADHD was frequently reported in children with allergic rhinitis in screenings.[98-100] A study was conducted by Suzuki *et al*.[101] after the classical model of 6 hydroxydopamine (6-OHDA) of Heffner and Seiden[102] was created.[101,102] They found that the 6-OHDA treatment treated the rats and the rat group treated with 6-OHDA had more than 6-fold higher locomotor hyperactivity on a postnasal day 46 compared with controls. They reported that they showed an increase. In this study, the impairment of hyperactivity was also observed in rats with 6-OHDA lesions.[100] In addition, it has been suggested that rats with 6-OHDA lesions have difficulty coping with sleep induction, suggesting difficulty in sleep induction in ADHD, in line with the previous reports.[103] With the application of publication therapies for ADHD in animal models, information is also obtained on whether they will cause other diseases in the future. Despite the clinical efficacy of pharmacological therapeutics, concerns remain about probable drug use and the risks, so more studies should conduct to eliminate these concerns.[104-106] It was investigated whether the function of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxaz olepropionic acid receptors (AMPARs) and expression change in ADHD SHR models; AMPAR-mediated synaptic transmission was observed in hippocampal excitatory synapses on hippocampal slices in SHR models. Immunogold labeling densities of AMPAR subunits GluA2/3 and GluA1 were measured. They showed that this reduced AMPAR-mediated synaptic transmission in stratum and stratum radiatum origins (in CA3-CA1 pyramidal cell

synapses) on SHRs compared to control rats. In result is shown, in part, that learning changes in individuals with ADHD in AMPAR dysfunction, which probably involves molecular changes in the hippocampus, and this is an important detail. Napoli high volatility (NHE) model is an animal model utilized in displaying ADHD using. These rodents have a balanced cortical and an upgraded limbic cycle in their cerebrums. ADHD and its accompanying pathological gambling include similar deficiencies of prefrontal-striatal dialogue. In one study, experiments were conducted to reveal whether NHE rats (NRB compared to normal randomly bred rats) are a useful model for the gambling vulnerability that exists in ADHD. Results obtained in NHE rats show the distinctive roles of the dorsal (lower coding of repetitive stimulus-reward relationships with a habit) and ventral (increased value to true primary reward) striatum. As a result, it has been revealed that the dynamics in the reward system can be associated with decreased attention versus pathological gambling.[69,107]

Also, Fragile X syndrome (FXS) is caused by a mutation in the X-linked gene FMR1. FMR1 encodes the fragile X mental retardation protein, an RNA binding protein that regulates protein synthesis. In FXS syndrome commonly ADHD and ADHD-related symptoms are seen. In a study of α2-agonists clonidine and clonidine witch normally used in ADHD, was tested on FXS. FMR1 KO mice (emerges as inherited form of mental retardation) were used. Findings found that clonidine is a stimulus to combine with behavioral therapies based on positive reinforcement and changes procedural behavior.[108] With different diseases, ADHD can occur and as seen in this previous study some properties that have good effects on ADHD can help recovery in other diseases.

Investigating the causes of these different disorders and deficiencies with studies conducted is an important factor in finding new treatment options. When recent studies are examined, the effects of disorders such as allergic rhinitis, AMPAR dysfunction, FXS, and pathological gambling in animal models have been examined. In this way, new treatment opportunities can be improved both for the other diseases and ADHD. For example, based on the appearance of AMPAR dysfunction, different targeted treatment models can be created for the treatment of ADHD.

Behavioral Analysis and Tests in Attention Deficit and Hyperactivity Disorder Animal Modeling

It is very important to apply behavioral tests as a complement to the experimental method in studies aimed at elucidating treatment or disease mechanism for brain diseases. The reason for this is that the brain is a part that reflects all our operational activities that make up us, unlike diseases, in other body parts, and we have the chance to analyze this reflection with the best behavior patterns. There are many tests and observations in terms of behavioral interpretation for ADHD. In order to question the accuracy of the modeling, they also offer the opportunity to comment on the clinical comparison with the patient and on the questions of whether it can treat the disease symptomatically or how it can design it to completely eradicate the disease. These tests, in the general framework of ADHD, can be measured in the animal, together with brain imaging and electroencephalography (EEG), in behavioral tests, it is possible to observe which brain region the animal has impulsivity, hyperactivity, sociality, anxiety, memory and attention disorders.[109] The passage of DA and NE, which affects PFC function, is impaired in ADHD patients. Primary drugs used in ADHD treatment increase NE and DA delivery. Existing psychostimulants (e.g., pemoline, MPH, and d-amphetamine) which is used to target dopaminergic systems, and pharmacological treatments, and these are mostly used.[110,111] The behavioral effects of these drugs on experimental animals can also be examined by various methods. Experimental animals are kept in cages with a camera system for behavioral analysis of drugs given to the model because the effect of the drug on the locomotor activity and the type and count of the movements in stereotype activity and the relationship between the disease and the drug is behaviorally clarified.[112] Behavior ethogram consists of the following types of behaviors: Upbringing (head lift raised on hind legs), sniffing upside down (nose contacting the ground), widespread movement (it can be measured with the periodicity of the transition of the home cage), face washing (forward from ears to nose and mouth), back-moving (forelimbs), grooming (cleaning itself paws or mouth), rotation (hanging from the front legs with the mouse and drawing rapid close circles on the top bars of the cage), immobility (no visible movement of the animal), stick grip (hanging from the front of the cage from the grid on the cage), circling (following a circular path at cage floor), and digging (using front legs and move the sawdust).[113] In one study, an analysis on the sum of all behavioral stereotypes observed for a measure of stereotype expressed by each strain of mice injected with d-Amphetamine and the serotoninergic agonist 2,5-dimethoxy-4-iodoamphetamine in relation to ADHD, specifically breeding and up-down, it has been reported that sniffing is common. It has also been observed that the serotonergic drug shows catatonia in animals differently. An ideal and reliable animal model should show all the symptoms present in ADHD patients in animal models and respond similarly to the same pharmacological interventions. Currently, none of the existing animal models of ADHD develop specifically to model the neurodevelopmental changes that occur in behavior initiation and progression, nor do they model various aspects of behavioral and executive functional symptoms.[114-116]

Among the ADHD animal models, the most commonly used ADHD model is defined SHR, but instead the most

classic neurodevelopmental model of ADHD, which is now more preferred by lesional brain systems and it is acquired by neonatal injection of 6-OHDA. This animal model is mostly used to study heavy symptoms of hyperactivity. Despite the existence of this model, the data in the literature on impulsive behavior or attention deficits remain uncertain and studies in this area need to be increased. Regarding the 6-OHDA Mouse Model, ADHD is known to imitate hyperactivity, which is characterized by impulsive behaviors in neurochemical pathology, with visual validity in the PFC. In the model that was lesioned with 6-OHDA in the PFC, neuron loss was also shown due to the Golgi organelles of the pyramidal neurons of the ACG, which are effective in communication between the prefrontal and the cells. The relationship between impaired filtering of information that needs attention, and its relationship is also an important finding for ADHD.[109] A better comprehension on mechanisms neurochemically in ADHD is the key to more beneficial treatments and their improvement. On the other hand, behavioral analyzes are also performed in animal models valid for the same purpose. In addition to this mouse model, sham mice (lesion in the striatum) were added, and impulsivity, hyperactivity, sociality, anxiety, memory, and attention impairment were tested and compared in these animal models. The principal component analysis that is set upon 20 factors restrained in different behavioral tests was conducted to compare all experimental groups and draw conclusions. These tests are MPH, Impulsivity, and Attention Tests (5CSRTT), respectively. As a result, impulsivity decreased and attention increased in all groups given MPH, but this change was observed less in the lesion in the striatum.[109] The 5CSRTT is a behavioral test used to evaluate motor impulsivity and visual attention in laboratory psychological research in animal models. 5CSRTT has its own impulsivity, individual attention, and reaction times. Preclinical studies conducted with 5CSRTT have enabled very useful and effective studies in ADHD diagnosis, medication, and behavioral examination (Bari, 2010; Cocker et al., 2014; Robinson & Emma, 2011[130]; Lusting, 2012 [131]; Zeeb & Fiona, 2014).[117-119]

Disruption of the five-option serial reaction time task in a mouse model created by 22q11.2 microdeletion: Growth with amphetamine

Individuals who have 22q11.2 deletion syndrome (22q11.2DS) carry a major risk for facing neurodevelopmental disorders such as ADHD and schizophrenia. These diseases are associated with general attention deficit. Effect analysis was investigated depending on the continuous performance test of modafinil and amphetamine in experimental animals with this deletion and also in the wild type model. On the other hand, modafinil knows to have more important effects on hypocretin/orexin, serotonin, glutamate, acetylcholine, and histamine functions, which shows how it affects brain activities, especially cognitively, depending on the various neurochemical activity of the brain.[120] In this test, drug discrimination is a striking element in the system because this gives us information that will enable us to relate to the reward system. On the other hand, a focused visual attention assessment was not performed in 22q11.2DS rodent models. The mice with 22q11.2 deletion carriers evaluated that clinically significant deterioration on the ability to distinguish target stimuli from nontarget stimuli (signal detection sensitivity) and the correct response rate (hit rate) (based on 5CSRTT results). Another important result is that this model provides us with various advantages in hippocampal communication with PFC and that we can establish deeper relationships between different neurochemical findings and attention. According to the results of the experiment, the selection of amphetamine instead of modafinil was more effective in deletion mice, and while amphetamine increased the responses, modafinil decreased this response.[121] Acoustic startle reflex (prepulse inhibition [PPI]) was measured in patients diagnosed with ADHD depending on MPH use. MPH has been shown to increase the pre-warning startle reflex, and it shows us that the application of tests to examine sensorimotor disorder is as important as other behavioral tests.[122] In addition, the effects of ADHD medications on this reflex on animals are shown.[123]

Careful cluster switching task: Measuring and making sense of cognitive flexibility of mice

Cognitive impairment provides the representation of the main characteristics of many neuropsychiatric and neurodevelopmental disorders, including posttraumatic stress disorder, depression, autism spectrum disorder, schizophrenia, both prepared in animal models and the disease itself, including circuit dysfunction within the human brain, particularly within the PFC. In the ADHD animal model, the cognitive impairment protocol created enables the evaluation of animal models in this respect and contributes to scientists in better modeling of the disease.[112,124]

Conclusion and Suggestions

In the latest studies, ADHD animal models are being developed through interventions with gene and gene agents. Considering the increasing practicality and widespread use of the applications, it is predicted that the studies will gradually increase in this direction, but it is expected that models with higher etiological and structural validity will be produced with these methods. Although the findings obtained with previous models and clinical studies in humans have an important role in the development of genetic models, it should be discussed how correct it is to rely only on this basis. Neurophysiological and neuropsychological studies also support that ADHD may be due to dysfunction of the frontal structures and the areas they are associated with. Findings supporting this view include executive dysfunctions, quantitative EEG, EEG

and the electrical activity of the frontal region with evoked potentials, detection of decreased blood flow in the frontal and striatal regions with functional imaging methods. In light of this information, animal models can be created based not only on pathological, physiological etiology and symptoms such as behavioral and cognitive but also on the basis of imaging results, by affecting the neuronal networks in the brain of the experimental animal with ADHD with chemical drugs.

In the future, it may be possible to reach the most accurate model home therapist to be developed, especially by a rigorous meta-analysis of studies conducted with different animal breeds, different doses, and different types of drugs, and of course combining them with experimental methods such as brain imaging and brain neurochemistry examination. Genetic-based modeling may put ADHD beyond being a consequence of this gene change. Therefore, this could be used in the future as a genetic marker rather than a disease. Different strains should be investigated in a holistic manner with gene meta-analyzes that can be used as biomarkers. Then, different pharmacological treatments can be developed by examining their neuroscientific and neural cell networks.

Naturally, using the right animal model will be a key point, and precise statements about ADHD can be used when all the right choices are in place. In the light of all this, putting the neuroanatomy of the brain on a good basis and combining it with the neurochemistry mechanism related to ADHD will bring along models that can form not only therapeutic strategies but also the best strategies in the future. It can be used in various pharmacological agents in ADHD-related regions of the brain and develop multiple neuronal networks that inhibit dopaminergic activity. The conclusion that needs to be drawn from the review is to observe that comparing similar ancestry with different ADHD and different ancestry with the same ADHD etiologies can actually provide us with many ideas, to approach them as a whole, and perhaps by combining the right parts with each other, more appropriate experimental animal models can be created. Another point is to look at the development of ADHD by combining it with different diseases. Researchers will enable us to make progress in ADHD by understanding the appropriate molecular mechanism for ADHD in the future. In particular, conducting multidisciplinary studies using the right animal models and use different disciplines (such as imaging studies) will be supportive for this purpose. Furthermore, the cortex areas in our frontal lobe responsible for behavior are very difficult to model structurally on the experimental animal because there are many differences between the experimental animal and the human behavioral mechanism. In addition, ADHD does not have a definite etiology based on sound neurobiologically evidence, and the reason is that neuronal activity transforms into behavior cognitively and the connection between it is not fully established on a solid foundation. With the information obtained from many animal model molecular studies conducted in recent years, dopaminergic and other neurochemical neuron cells, gene, and protein analyzes, cell cultures such as astrocytes, and knock-out and transgenic models that will provide the most possible reflection of these in behavior have begun to be made. Fortunately, it can be argued that a better step has been taken to replace animal models such as spontaneously hypertensive rats that do not have a strict molecular basis, but the studies need to be carried forward. When we put together all the studies we have compiled, it is clearly seen that the brain is divided into different neuron types and lobes responsible for different functions, in fact, they are characterized by cell communications and basically by different associations with other lobes. Therefore, single viewpoints and combinations of neurobiological, neurochemical and neuroimaging, behavior, and neuroanatomy will not be sufficient, and multidisciplinary studies of brain diseases by expanding into different areas can solve many brain diseases in the future. Based on the scientific competence measures of experimental animal models while developing drugs, it has been observed that many behavioral tests and animal models cannot meet the structural competence criteria. All of them have quite a lot of disadvantages. In general, drugs developed for the symptom through visual and predictive competence achieved a certain success in experimental animals with some behavioral tests on ADHD and did not have completely satisfactory results. It is also reported in the literature that drug tolerance develops as a result of taking and discontinuing drugs at regular intervals, which is supported by studies that develop addiction to DA-derived drugs.[125-128] The side effects of the symptom, rather than the treatment, can sometimes be overlooked in experimental animals and these side effects can be observed in humans when it comes to clinical studies.[129] The emergence of such adverse situations reveals that the animal models and behavioral analysis tests used are quite open to discussion and the importance of drawing attention to a good disease etiology and pathogenesis is also important. Finally, an animal model can be created, and an ADHD model can be developed, characterized by an ACG lesion in which the sensorimotor system is adversely affected by neurochemistry. By applying drugs and tests on these disease models, more therapeutic agents can be developed as well as different animal models can be developed. In addition, the PPI test can be used to measure the degree of startle, especially in accordance with this model. As a result, this review provides suggestions and ideas that will be useful to scientists while emphasizing the studies and their shortcomings in the literature about ADHD.

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Author contribution area and rate

Rümeysa Rabia Kocatürk (34%) Data collection and wrote the manuscript.

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Mesut Karahan (33%) Designed the review, data collection and supervised the article write-up. Wrote the manuscript.

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