REVIEW

Transgenic mouse models for ADHD

Damiana Leo · Raul R. Gainetdinov

Abstract Attention-deficit hyperactivity disorder (ADHD) is a developmental disorder characterized by symptoms of inattention, impulsivity and hyperactivity that adversely affect many aspects of life. Whereas the etiology of ADHD remains unknown, growing evidence indicates a genetic involvement in the development of this disorder. The brain circuits associated with ADHD are rich in monoamines, which are involved in the mechanism of action of psychostimulants and other medications used to treat this disorder. Dopamine (DA) is believed to play a major role in ADHD but other neurotransmitters are certainly also involved. Genetically modified mice have become an indispensable tool used to analyze the contribution of genetic factors in the pathogenesis of human disorders. Although rodent models cannot fully recapitulate complex human psychiatric disorders such as ADHD, transgenic mice offer an opportunity to directly investigate in vivo the specific roles of novel candidate genes identified in ADHD patients. Several knock-out and transgenic mouse models have been proposed as ADHD models, mostly based on targeting genes involved in DA transmission, including the gene encoding the dopamine transporter (*DAT1*). These mutant models provided an opportunity to evaluate the contribution of dopamine-related processes to brain pathology, to dissect the neuronal circuitry and molecular mechanisms involved in the antihyperkinetic action of psychostimulants and to evaluate novel treatments for ADHD. New transgenic models mouse models targeting other genes have recently been proposed for ADHD. Here, we discuss the recent advances and pitfalls in modeling ADHD endophenotypes in genetically altered animals.

Keywords Attention-deficit hyperactivity disorder (ADHD) · Dopamine · Transgenic mice · Hyperactivity · Dopamine transporter · DAT knock-out

Abbreviations
ADHD   Attention deficit hyperactive disorder
DA   Dopamine
DAT   Dopamine transporter
NE   Norepinephrine
MPH   Methylphenidate
AMPH   Amphetamine

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Introduction

Attention deficit hyperactive disorder (ADHD) is a clinically heterogeneous disorder presenting as various combinations of impulsivity, hyperactivity and inattention symptoms. ADHD is among the most common neuropsychiatric disorders in children, affecting 5%–7% of children worldwide (Polanczyk et al. 2007; Faraone et al. 2003; Faraone and Mick 2010; Willcutt 2012) and often leads to adverse consequences in adult life including drug abuse, delinquency, anxiety and depression and social rejection (Barkley et al. 2004; Biederman 2005; Bernardi et al. 2012). ADHD creates a significant financial burden involving the cost of medical care and work loss for patients and family members. Causative mechanisms for ADHD have not yet been identified and at present, no objective biomarkers are available to support the diagnosis, which is based on symptom descriptions in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association 2000). However, a diversity of ADHD clinical forms might result in a revision of the diagnosis, classification and segregation of the distinct nosologies of ADHD in a new DSM-V edition.

Although the exact molecular mechanisms involved in the etiology of ADHD have yet to be uncovered, clinical studies clearly indicate that ADHD has a significant genetic component (Lasky-Su et al. 2007; Faraone et al. 2005; Purper-Ouakil et al. 2011), most likely involving several genes with each determining the severity of particular symptoms. Environmental components that have been implicated as risk factors include brain traumas during infancy and alcohol or drug abuse during pregnancy (Sinopoli et al. 2011; Mick et al. 2002a, b; Biederman et al. 1995). Thus, genetic, developmental and environmental factors influence the severity of symptoms observed in affected individuals, leading to a "spectrum" of abnormal behaviors (Dick et al. 2010). Nevertheless, some ADHD patients present some brain abnormalities (e.g., a reduction in total brain volume; Valera et al. 2007), especially in the basal ganglia, prefrontal cortex and cerebellum (Giedd et al. 2001; Cortese and Castellanos 2012) and alterations in neural networks (Rubia et al. 2010; Konrad and Eickhoff 2010). The circuits associated with ADHD are rich in monoamines, which are involved in the mechanism of action of the psychostimulants and antidepressants used to treat this disorder. Neuropharmacological studies provide evidence that ADHD involves the dysregulation of complex interactions between the dopamine (DA), norepinephrine (NE) and 5-hydroxytryptamine (serotonin) neurotransmitter systems (Pliszka 2005; Himelstein et al. 2000; Heal et al. 2009). For more than 70 years, ADHD treatment has been dominated by the use of monoaminergic psychostimulants (Bradley 1937), mostly methylphenidate (MPH) and amphetamine (AMPH), plus the catecholaminergic nonstimulant atomoxetine (ATX). These medications are generally believed to exert their therapeutic effects by increasing the availability of monoamines in the synapse by reducing their uptake rates or promoting reverse efflux as a result of interactions with monoamine transporters on the plasma membrane. Notably, not all patients respond to these treatments and both responders and non-responders to amphetamine and methylphenidate therapy in the clinic have been documented (Heal et al. 2009; Krause et al. 2005).

The involvement of monoamines in ADHD is also supported by candidate gene association studies that show positive associations with various DA (dopamine receptor 4, DR4; dopamine receptor 5, DR5; dopamine transporter, DAT; Faraone et al. 2005; Li et al. 2006; Gizer et al. 2009; Brookes et al. 2006), NE (norepinephrine transporter, NET; Yang et al. 2004; Kim et al. 2008) and serotonergic (serotonin transporter, SERT; serotonin receptor subtype 1B gene, HTR1B; Faraone and Khan 2006) genes. However, monoamines in general act as modulators of fast neurotransmission mediated by glutamate and gamma aminobutyric acid (GABA) suggesting that many other mechanisms beyond those involved exclusively in monoaminergic transmission could be important for the pathogenesis of ADHD and the targeting of these mechanisms could provide

more specific pharmacological and cognitive therapies for this disorder (Carlsson et al. 2001; Greengard 2001; Gainetdinov et al. 2001). These findings suggest that ADHD is likely to be based on several specific neurobiological dysfunctions and involves many genes, each with small effect sizes (Faraone et al. 2005).

Some specific endophenotypes of ADHD can be relatively easily modeled by targeted genetic manipulations in experimental animals, as is in the case with other neuropsychiatric disorders with a significant genetic component. An ideal model needs to recapitulate all the key endophenotypes of ADHD: inattention, impulsivity and hyperactivity. However, one single model is unlikely to be able to mimic all ADHD symptoms. At the same time, a model that recapitulates some key endophenotypes of the disorder could be useful for understanding the biological basis of the particular aspects of the disease and for predicting the clinical efficacy of potential therapeutic agents in specific clinical forms of the disorder. Thus, an ADHD animal model should mimic the fundamental behavioral characteristics of ADHD (face validity), involve a similar etiology and/or underlying pathophysiological mechanism (construct validity) and predict responses to medications that could be used in ADHD treatment with regard to behavior, molecular mechanisms and neuronal functions that have not previously been shown in clinical settings (predictive validity; Sagvolden and Johansen 2012; Gainetdinov 2010). Whereas nonhuman primate brains are closer to human brains, rodent models of ADHD have the advantage of being genetically more homogeneous, less expensive to maintain and more thoroughly characterized neurobiologically in comparison with primates (Russell et al. 2005). Thus, mouse models are invaluable tools for directly testing hypotheses on the underlying pathologies and finding new pharmacological therapies for human disorders in a relatively short period of time. Because ADHD is a heterogeneous disorder, a number of animal models have unsurprisingly been proposed that mimic symptoms of ADHD. Here, we review only transgenic rodent models with defined genetic causes that have been proposed to be useful tools for understanding ADHD neurobiology (Table 1). We do not discuss rodent models with unknown genetic origins or those that are based on environmental interventions or chemical lesions, such as the inbred spontaneously hypertensive rat (SHR), the Naples high-excitability rat (NHE), or neonatal 6-hydroxydopamine (6-OHDA) lesioned mice, which are by far the most widely studied rodent models of ADHD and subjects of a number of excellent reviews (Russell 2011; Sagvolden et al. 2009; Bari and Robbins 2011).

Transgenic models: dopamine transmission-related genes

The widespread use of rodents, especially mice, in preclinical research has been steadily growing since the

Table 1 Mutant mice with relevance to ADHD discussed in this review

Mutant mice	Mutation	References
Dopamine transmission-related genes		
• DAT-KO	Knock-out of dopamine transporter gene	Giros et al. 1996; Gainetdinov and Caron 2000; Trinh et al. 2003
• DAT-KD	Knock-down of dopamine transporter gene	Zhuang et al. 2001; Tilley et al. 2007
• DAT-CI	Triple point-mutation in the cocaine-binding site of DAT	Napolitano et al. 2010; Tilley and Gu 2008a
• BAC DAT-tg	Overexpression of dopamine transporter	Salahpour et al. 2008
• D4R-KO	Knock-out of dopamine receptor 4	Rubinstein et al. 1997; Helms et al. 2008
Other genes		
• NK1R-KO	Knock-out of tachykinin-1 receptor	De Felipe et al. 1998; Yan et al. 2009
• TRβPV-KI	Knock-in of human thyroid hormone β receptor gene	Kaneshige et al. 2000; Siesser et al. 2006
• 39 X^yO mice	End-to-end fusion of the X and Y chromosome resulting in steroid sulfatase deficiency	Davies et al. 2007, 2009
• Coloboma mice/SNAP25 (synaptosomal-associated protein 25) mutant mice	Mutation on chromosome 2 with approximately 20 genes disrupted including SNAP-25	Searle 1966; Bruno et al. 2007
• nAChR β2-KO	Knock-out of β2-subunit of the nicotinic acetylcholine receptor	Granon et al. 2003; Granon and Changeux 2006
• CK1δ mice	Over-expression of the subunit δ of casein kinase1	Zhou et al. 2010
• Git1-KO	Knock-out of G-protein-coupled receptor kinase-interacting protein-1	Won et al. 2011; Schmalzigaug et al. 2009
• CdK5-KO	Knock-out of Cdk5-activating cofactor p35	Drerup et al. 2010
• Gβ5-KO	Knock-out of type 5 G protein beta subunit	Xie et al. 2012
• DGKβ KO	Knock-out of diacylglycerol kinase β	Ishisaka et al. 2012

development of transgenic knock-out techniques in the 1980s (Smithies 1993) and the publication of the mouse genome in 2002 (Mouse Genome Sequencing Consortium et al. 2002). Rodents provide relatively easy targets for genome manipulation in order to create disease models by targeting candidate genes and by analyzing the related dysfunctions on a controlled genetic background. Use of the candidate ADHD gene approach in a recent meta-analysis of studies performed over the past 15 years has revealed consistent evidence of significant associations between ADHD and polymorphisms in several candidate genes, almost all of which are involved in the regulation of dopaminergic and serotonergic transmission (Gizer et al. 2009; Wu et al. 2012). The generation of knock-out, knock-in, or transgenic over-expressing animals has become a novel approach to investigating the neuronal and biochemical basis of ADHD. These transgenic mouse models representing bottom-up approaches (from gene to behavior) have provided an opportunity to link a specific gene to specific endophenotypes of the disease, thus complementing alternative top-down approaches (i.e., from behavior to the genes) based, for instance, on the selective breeding of animals demonstrating ADHD-related behavioral phenotypes of unknown origin (Russell 2011; Sagvolden et al. 2009; Bari and Robbins 2011).

Like all rodent models, transgenic mice certainly have some limitations. First, given that ADHD appears to be a complex and multifactorial disease with no reliable genetic or biochemical markers, such mouse mutants can obviously have only limited construct validity. Moreover, the deletion of certain genes might produce different phenotypes in humans and animals and transgenic animal models might not be powerful enough to mimic gene epistasis, effects of "small mutations", adaptive functional compensation and abnormal neuronal system development. Nevertheless, transgenic animals are the most reliable and simple models used to study gene-function relationships and to investigate the effects of novel pharmacological approaches.

DAT knock-out mice

Several lines of evidence suggest that abnormal DAT function is important in ADHD. Both increased and decreased DAT expression have been reported in small cohorts of ADHD patients (Sakrikar et al. 2012; Madras et al. 2005; Volkow et al. 2002) and genetic studies have demonstrated the associations of DAT gene variants with unknown functional consequences with ADHD (Spencer et al. 2012). A link between DAT function and ADHD is further suggested by the therapeutic utility of the psychostimulants methylphenidate (Ritalin) and AMPH, which exert a significant part of their action via an interaction with DAT (Sakrikar et al. 2012). Thus, several transgenic animal models of ADHD have been developed based on the postulated role of DA, particularly DAT, in this disorder.

DAT is a member of the family of Na^+/Cl^--dependent transporters that have the general structure of 12 transmembrane domains with intracytoplasmic carboxy- and amino-terminals (Giros and Caron 1993; Kristensen et al. 2011; Torres et al. 2003). The DAT protein is expressed selectively in DA cell bodies and terminals and can be used as a selective marker of DA neurons (Eriksen et al. 2010). In the central nervous system, DAT is mainly expressed in the striatum and nucleus accumbens, whereas in the periphery, it is present in the retina, lung, kidney and pancreas (Ciliax et al. 1995). In the striatum, DAT is exclusively presynaptic and is localized to the plasma membranes of axonal varicosities and axon terminals (Nirenberg et al. 1996). The major function of DAT is the reuptake of DA from the synaptic cleft into presynaptic nerve terminals, making DAT essential in controlling the half-life of extracellular DA. The psychostimulatory actions of MPH, cocaine and AMPH are primarily dependent on a direct interaction of these compounds with DAT, leading to attenuated DA clearance and thus elevated DA tone (Chen et al. 2006; Pifl et al. 1996; Thomsen et al. 2009; Fumagalli et al. 1998). These drugs generally exert inhibitory and/or specific reversing actions on the function of the monoamine transporters DAT, NET and SERT, thereby disrupting the normal reuptake of neurotransmitters from the synaptic cleft and causing an elevation in the extracellular monoamine levels. Although the debate continues as to whether ADHD is a hypo- or hyper-dopaminergic condition, numerous clinical genetic studies have provided evidence that alterations in DAT-mediated processes significantly contribute to the pathogenesis of ADHD (Gainetdinov 2010). DAT knock-out mice (Giros et al. 1996; DAT-KO mice) have provided important information concerning the neurobiological consequences of impaired DAT function. DAT-KO mice are considered ADHD models for many reasons, including their spontaneous hyperactivity and impaired learning and memory (Gainetdinov and Caron 2000, 2001; Trinh et al. 2003). Recent studies have also demonstrated an impaired cliff-avoidance reaction in DAT-KO mice, indicating increased impulsivity in these mutants (Yamashita et al. 2013). Unlike wild-type or heterozygous mice, DAT-KO mice are significantly more active in novel and home-cage environments and show remarkable deficits in learning and memory in the 8-arm maze, novel object recognition and social food preference transmission tests (Gainetdinov et al. 1999a; Wong et al. 2012). In DAT-KO animals, DA clearance is approximately 300 times slower than in controls (Gainetdinov et al. 1999b; Jones et al. 1998, 1999). However, the increase in the basal extracellular levels of DA is only approximately five-fold (two-fold in the DAT heterozygous mice), because of several compensatory mechanisms (Gainetdinov and Caron 2000, 2001; Trinh et al. 2003). Intriguingly, electrically stimulated DA release is reduced and a marked

depletion of reuptake-dependent intraneuronal DA stores (20-fold) is observed in these mutants (Gainetdinov et al. 1999b; Jones et al. 1998). Thus, we can speculate that the steady-state "tonic" extracellular DA levels are increased but that "phasic" DA release might, in fact, be diminished because of depleted storage pools (Gainetdinov 2010). Importantly, the lack of DAT-mediated recycling makes DA levels in the striatum of these mice totally dependent on the rate of the ongoing synthesis of DA (Jones et al. 1998; Sotnikova et al. 2005). Notably, DAT-KO mice have disrupted DA autoreceptor function and significantly reduced tyrosine hydroxylase (TH) protein expression, despite only minor alterations in the number of TH-positive neurons (Giros et al. 1996; Jaber et al. 1999). Indeed, unlike the normal situation in which the predominant mode of DA transmission in the striatum can be defined as a point-to-point wired transmission, this mode in DAT-KO mice can be defined as "volume transmission" in which released molecules can diffuse over longer distances in the extracellular space, thus affecting larger volumes of postsynaptic receptors and structures (Jones et al. 1998). Volume transmission is believed to occur in situations in which DAT-mediated DA reuptake is low, as in the frontal cortex or following dopaminergic degeneration in the striatum; this causes a reduction in the number of DA terminals and re-uptake sites (Zoli et al. 1999). Similar situations might occur in another commonly used model of ADHD, i.e., neonatal 6-hydroxydopamine (6-OHDA)-treated rodents. In this neurotoxic ADHD model, which is used to support the hypodopaminergic theory of this disorder, the neonatal administration of the neurotoxin 6-OHDA exerts selective dopaminergic neurotoxicity by entering terminals via DAT that causes transient hyperactivity and cognitive deficits that last approximately 2 weeks in 40%–50% of the animals (Kostrzewa et al. 2008). Because DAT function in rodents is relatively low in the early neonatal period (Gordon et al. 1995; Patel et al. 1994), one might expect that only neurons with sufficient DAT function would be affected by 6-OHDA, leaving neurons with delayed maturation of DAT intact and thus causing a transient state of low DAT-mediated re-uptake and "volume transmission".

As in ADHD patients, MPH and AMPH are able to reduce hyperactivity in DAT-KO animals (Gainetdinov et al. 1999a). Therefore, these mice have face and predictive validity as a model of ADHD. The "calming" effect of psychostimulants suggests the involvement of a DAT-independent mechanism of action, possibly involving other monoamine transporters. The administration of inhibitors of the serotonin transporter (SERT) or of several serotonin receptor agonists and antagonists (non-selective agonists quipazine and 5-carboxamidotryptamine or the selective 5HT2A antagonist M10090) dramatically reduces the hyperactivity in DAT-KO mice (Gainetdinov et al. 1999a; Barr

et al. 2004; Beaulieu et al. 2006) indicating an involvement of serotonergic mechanisms. At the same time, the specific NET inhibitor nisoxetine does not suppress the hyperactivity of DAT-KO animals (Gainetdinov et al. 1999a; Gainetdinov and Caron 2000) but reverses the manifestations of impulsivity in the cliff-avoidance test (Yamashita et al. 2013) and sensorimotor gating deficits in the pre-pulse inhibition test (Arime et al. 2012). The involvement of both SERT- and NET-mediated effects of psychostimulants in these models is not surprising because both SERT-KO and NET-KO mice are hypoactive (Kalueff et al. 2007; Xu et al. 2000) and, as is well established, the serotonin and NE systems closely interact at many levels, with alterations in one neurotransmitter system causing significant changes in the other (Bortolozzi and Artigas 2003).

Glutamatergic transmission might also be an intermediate in the inhibitory action of psychostimulants and serotonergic drugs on the hyperactivity of DAT-KO mice. The blockade of N-methyl-D-aspartate (NMDA) receptors causes a remarkable potentiation of hyperactivity in DAT-KO mice and prevents the antihyperkinetic effects of psychostimulants and serotonergic drugs suggesting the involvement of cortico-striatal glutamatergic pathways in the effects of these drugs. Importantly, whereas the psychomotor stimulatory effect of psychostimulants is correlated with the well-known rise in extracellular DA levels in major DA brain areas in normal mice, psychostimulants inhibit activity without causing a decrease in elevated DA levels in DAT-KO mice. These findings give further support to the idea that, in these mutants, psychostimulants do not affect the striatal DA system directly but instead exert their antihyperkinetic effects by modulating different neurotransmitter systems in other brain regions (Gainetdinov et al. 1999a). These observations particularly highlight the processes occurring in the frontal cortex in regulating striatal mechanisms. In general, DA transmission in the striatum and frontal cortex might be differentially involved in the control of certain behaviors, with striatal mechanisms mostly contributing to the regulation of locomotor activity and cortical mechanisms regulating predominantly cognitive processes such as attention and impulsivity. Whereas extracellular DA levels in the frontal cortex of DAT-KO mice are elevated as in the striatum (Xu et al. 2009), NET is known also to contribute to the clearance of DA in this brain region. Thus, either the modulation of cortical DA dynamics via NET inhibition or the direct serotonin-mediated modulation of the frontostriatal glutamatergic pathway might potently affect the aberrant behaviors caused by an enhanced striatal DA transmission in these mutants.

In summary, this mouse model shows face and predictive validity because of behavioral similarities, alterations in the catecholaminergic system and the effectiveness of psychostimulants. However, since no clear indications are yet available that the DAT level or function is altered in

patients with ADHD, the construct validity of DAT-KO is only partial. Human studies on the role of DAT in ADHD etiology are still controversial, although recent brain imaging studies have shown a decrease in DAT levels in several brain areas of ADHD patients (Volkow et al. 2007, 2009a). Intriguingly, recent studies have found two novel DAT-coding variants: A559V, which has been identified in two male siblings with ADHD displaying increased DAT channel activity and spontaneous non-vesicular DA release that can be greatly enhanced by membrane depolarization (Mazei-Robison et al. 2008; Bowton et al. 2010) and a second rare ADHD-associated DAT-coding variant, R615C, in which amino acid substitution results in significant regulatory alterations in DAT function (Sakrikar et al. 2012).

Other DAT mutant models

Another model of mild DAT deficiency has been developed by the local injection of small interfering RNA (siRNA) against DAT into the midbrain of adult mice (Salahpour et al. 2007). However, despite a decrease of approximately 40% in DAT levels, no alterations in spontaneous locomotor activity have been found. At the same time, decreased levels of DAT have been functionally revealed by the lower level of hyperactivity induced by AMPH in siRNA-treated animals (Salahpour et al. 2007). Whereas these DAT siRNA-treated mice and DAT heterozygous mice displaying a 50% reduction in DAT levels do not show phenotypes that are relevant to ADHD, mice with more severe DAT functional deficits, e.g., DAT knock-down mice (DAT-KD) and DAT cocaine-insensitive (DAT-CI) mice, represent useful models for understanding the role of DAT in ADHD. Hyperdopaminergic DAT-KD mice were created by reducing the expression of DAT to 10% of wild-type levels (Zhuang et al. 2001). Similar to DAT-KO mice, DAT-KD mice display a reduced rate of DA reuptake and a higher extracellular DA concentration (approximately two-fold higher than controls). DAT-KD mice display normal home cage activity but significant hyperactivity and impaired response habituation in novel environments. These mutants also demonstrate an increased motivation for food reward but do not show significant alterations in learning abilities. Notably, as in DAT-KO mice, AMPH exerts a pronounced inhibitory effect on locomotor activity in the DAT-KD mouse; in contrast, the normal stimulatory effects of cocaine have been reported (Tilley et al. 2007).

An additional strain of DAT-deficient mice, i.e., DAT-CI (Cocaine Insensitive) mice, were obtained by introducing a triple point-mutation in the cocaine-binding site of DAT (Napolitano et al. 2010; Chen et al. 2006). In these animals, DAT is partially functional but insensitive to cocaine. Because of their significantly reduced DAT function (estimated to be in the range of 60%–80%, based on a comparative analysis of various neurochemical parameters), DAT-CI mice exhibit

severe alterations of DA signaling in the striatum, such as elevated extracellular DA levels, decreased total striatal DA content, enhanced DA turnover and reduced D2 dopamine receptor-mediated autoreceptor function (Napolitano et al. 2010). DAT-CI mice also lack cocaine-induced extracellular DA elevation and cocaine- and MPH-induced conditioned place preference (Tilley and Gu 2008a, b). As might be expected, DAT-CI mutants display significant spontaneous hyperactivity (Napolitano et al. 2010). Whereas the cognitive phenotype of these mutants has not yet been characterized, not only cocaine but also several other psychostimulants, including AMPH, MPH, nomifensine and bupropion, exert antihyperkinetic action in DAT-CI mice (Napolitano et al. 2010). Similarly, a NET inhibitor has been able to induce a moderate decrease in the activity of these hyperdopaminergic mutants (Napolitano et al. 2010). Taken together, the observations of DAT-KD and DAT-CI mice support the major findings observed in DAT-KO mice. However, neither DAT-KD nor DAT-CI mice show all of the cardinal phenotypes of an ADHD mouse model, thereby displaying only partial face validity. Conversely, several attempts have been made to evaluate the effects of increased DAT expression in animal models. Although many of the DAT-deficient mice described above have phenotypes that are at least partially relevant for ADHD, the behaviors displayed by mice with increased DAT expression lack such validity. The transgenic over-expression of DAT in TH-expressing neurons by approximately 30% results in spontaneous locomotor hypoactivity in a new environment (Donovan et al. 1999). Adriani et al. (2009) have used a lentivirus to over-express or silence the DAT gene by infusing a DAT gene enhancer/silencer into the nucleus accumbens of adult Wistar rats. In the absence of general locomotor effects, DAT over-expressing rats show a somewhat increased impulsivity but they do not demonstrate a significant preference for a novel environment. The authors suggested that altered accumbal DAT function might serve a sensation-seeking phenotype and a vulnerability to impulse-control disorders. Salahpour and colleagues (2008) have generated, via the pronuclear injection of a bacterial artificial chromosome, DAT transgenic mice (DAT-tg) that significantly overexpress the transporter. In DAT-tg mice, a three-fold increase in the level of total transporter has been achieved, which results in a 50% increase in the rate of DA uptake and a 40% decrease in DA extracellular levels. Behaviorally, these mice display normal levels of spontaneous locomotor activity but markedly increased locomotor responses to AMPH and reduced operant responses to a natural reward. These studies indicate that increased DAT expression does not recapitulate the major endophenotypes related to ADHD (no face or predictive validity), such as hyperactivity and the paradoxical inhibitory responses to AMPH (Salahpour et al. 2008). In contrast, the behavioral phenotype and the responses to psychostimulants in various strains of DAT-deficient mice generally support the

clinical observations of decreased (Volkow et al. 2009b, 2007), rather than increased (Madras et al. 2005) DAT expression found in some ADHD patients, although these alterations might represent secondary adaptive changes but not causative factors of the disease. Intriguingly, DAT expression and function in normal rodents has been found to be relatively low at birth, with significant maturation of DAT occurring over an extended period of postnatal development (Gordon et al. 1995; Patel et al. 1994). If a similar developmental maturation of DAT occurs in humans, the relatively low DAT function during childhood could explain the preferential appearance of ADHD in children. Furthermore, one might expect that deficiencies in processes that are critical for DAT maturation will contribute to the etiology of this developmental disorder.

D4 dopamine receptor KO mice

Mice lacking the D1, D2, D3, D4 and D5 receptors, or some combination thereof, have been produced but all have failed to show ADHD-related phenotypes. Among all DA receptors, the most studied receptor has been D4R. Whereas alleles of the human D4R gene have repeatedly been associated with ADHD (Grady et al. 2003), D4R knock-out (D4R-KO; Rubinstein et al. 1997) mice have failed to become a valid ADHD model. These mutants demonstrate hypoactivity and have similar levels of impulsivity compared with control animals, suggesting that D4R-mediated signaling does not affect impulsivity (Helms et al. 2008). At the same time, D4R-KO mice are supersensitive to alcohol, cocaine and methamphetamine. DA synthesis and its conversion to DOPAC are elevated in the dorsal striatum of D4R-KO mice (Rubinstein et al. 1997). Taken together, these observations provide little support to consider D4R-KO mice a relevant model in ADHD research.

Transgenic models: other genes

Tachykinin-1 (NK1) receptor

The tachykinin-1 (NK1) receptor is a receptor for substance P, which is a member of the tackyinin family of neuropeptides (Maggi 1995). Substance P levels are high in monoaminergic nuclei, especially in the substantia nigra and ventral tegmental area (Ljungdahl et al. 1978; Ribeiro-da-Silva and Hökfelt 2000). Substance P preferentially activates NK1 receptors (NK1R), which are the product of the *tacr1* gene. Another subtype of substance P receptor, NK2, has lower binding affinity than NK1R and has only limited expression in the rat or human brain (McLean and Lowe 1994). NK1R is a member of the family of G protein-coupled receptors and is mainly expressed in subcortical regions (i.e., amygdala/hippocampus and striatum; Yan et al. 2009). When NK1R-KO animals were generated in 1998 (De Felipe et al.

1998), the discovery of an important modulatory influence of tachykinin-1 (now known as TACR1 in humans or NK1R in rodents) on monoaminergic transmission attracted interest with regard to this factor being a novel target for antidepressants (Yan et al. 2009). In NK1R-KO mice, the serotonergic (Froger et al. 2001), norepinephrinergic (Fisher et al. 2007; Herpfer et al. 2005) and dopaminergic systems are affected (Murtra et al. 2000). The serendipitous discovery that NK1R-KO mice express core features of ADHD arose from the observation that NK1R-KO mice express minor locomotor hyperactivity corrected by psychostimulants (AMPH or MPH). Moreover, hyperactivity is induced in wild-type mice by treating them with an NK1R antagonist at doses that have no effect on the behavior of NK1R-KO mice; this hyperactivity is prevented by AMPH, as occurs in NK1R-KO mice (Yan et al. 2009). These mutants also display other abnormalities that might be relevant to ADHD, such as reduced DA efflux in the frontal cortex, a lack of an increase in DA efflux in the dorsal striatum following systemic administration of AMPH and a lack of development of AMPH or morphine-induced conditioned place preference (Yan et al. 2009, 2010). NK1R-KO mice have been reported to express inattentiveness and impulsivity in five-choice serial reaction-time task tests (5-CSRTT) but AMPH does not correct these deficits (Yan et al. 2011). In a case–control study of 450 ADHD patients and 600 screened normal controls, four single-nucleotide polymorphisms at the TACR1 gene, previously known to be associated with bipolar disorder or alcoholism, were strongly associated with ADHD (Yan et al. 2010). Thus, NK1R-KO animals display some face and predictive validity as a model of ADHD and, with further validation, might become an interesting new model of the disease.

Thyroid hormone receptor

Resistance to the thyroid hormone (RTH) has long been known to be often associated with symptoms of hyperactivity (Hauser et al. 1993; Magner et al. 1986). RTH is linked to mutations in exons 9 and 10 of the human thyroid hormone β receptor gene (TRβ). It is characterized by a normal or elevated level of the thyroid-stimulating hormone (TSH) in the presence of high levels of serum triiodothyronine (T3) and thyroxine (T4) and by the resistance of pituitary or peripheral tissues to the actions of the thyroid hormone attributable to a decreased affinity of TRβ for T3 (McDonald et al. 1998). In two studies, 50%–70% of RTH patients met the diagnostic criteria for ADHD (Hauser et al. 1993; Brucker-Davis et al. 1995) supporting the idea that this gene might be involved in ADHD pathogenesis. A model of knock-out mice lacking the TRβ gene was generated by Forrest and colleagues (1996). These animals had elevated TSH and free T3 and T4 but they were not hyperactive. However, male transgenic mice bearing the human

PV (the acronym for the patient name) mutant $TR\beta$ gene (RTH mutants) tested for horizontal activity displayed some hyperactivity and a moderate deficit in learning, showing normal performance after training for a reaction time task that measured sustained attention (McDonald et al. 1998). The TRβPV knock-in (KI) mice seemed to be more promising as a model of ADHD (Kaneshige et al. 2000), as they displayed the characteristic endophenotypes of ADHD: inattention manifesting as slow reaction times and inaccuracy in an operant task, moderate hyperactivity that was not evident in a novel environment but developed gradually after repeated exposure to the environment and impulsivity observed by indirect measures (Siesser et al. 2005, 2006). TRβPV-KI mice show increased striatal DA turnover but the response to MPH does not differ between genders or between transgenic and wild-type animals; an initial transient decrease of activity is followed by normalization up to baseline values within 1 h (Siesser et al. 2006). Hence, these mice seem to have some face validity as an ADHD model but limited construct validity. Ambiguous face and predictive validity (the ambiguous response to MPH) detract from the validity of this model, as demonstrated by the absence of recent reports concerning TRβPV-KI mice utility to model ADHD.

Steroid sulfatase

Steroid sulfatase (STS) is an enzyme encoded by the X-linked gene STS (Xp22.3) in humans and by the pseudoautosomal Sts gene in mice. It catalyzes the desulfation of steroid hormones, such as the neurosteroid dehydroepiandrosterone sulfate (DHEAS) to DHEA. DHEAS and DHEA have important effects on neuronal functions, including cognition, by acting on various neurotransmitter receptors (GABA-A, NMDA; Davies et al. 2009; Reddy 2010). Both DHEAS and its non-sulfated form DHEA are negative modulators of the GABA-A receptor and positive modulators of the NMDA receptor (Yadid et al. 2010). STS is expressed in key regions of the developing brain critical for attention and impulsivity, including the frontal cortex, thalamus and basal ganglia, i.e., regions whose structure/function is expected to be perturbed in ADHD (Stergiakouli et al. 2011). Several lines of evidence have suggested a role of STS in ADHD: males with cytogenetic deletions encompassing the gene (or with inactivating mutations within it) show an enhanced vulnerability to the disorder (Brookes et al. 2010; Kent et al. 2008). DHEA(S) levels are inversely correlated with ADHD symptomatology (Strous et al. 2001) and can be elevated by MPH treatment (Maayan et al. 2003; Lee et al. 2008). Moreover, the total or partial loss of the X chromosome in Turner syndrome results in attention deficits. In 1997, Davies and colleagues reported that, in 39 X^yO mice with an end-to-end fusion of the X and Y chromosome, haploinsufficiency for STS

accounted for attentional deficits (see Davies et al. 2009, 2007) by limiting the conversion of DHEAS to DHEA. Furthermore, DHEAS administration improved the attentional deficits in 39 X^{y}O mice, suggesting that STS deletion is a possible model for the inattentive subtype of ADHD. Further characterizations of this mouse model have shown similarities with ADHD endophenotypes such as hyperactivity, heightened emotional reactivity and aggression and lowered serum DHEA levels (Trent et al. 2012a, b). The authors propose that these deficits are related to increased tissue serotonin levels in the striatum and hippocampus as a result of reduced DHEA levels (Trent et al. 2012a). The putative role of the STS gene in ADHD is also supported by the results of the pharmacological blockade of the activity of the enzyme in normal animals. This treatment produces visuo-spatial attentional deficits, perseverations, aggression and increased locomotor activity comparable with those observed in 39 X^{y}O mice. Thus, 39 X^{y}O mice have partial construct validity as an ADHD model and exhibit a reasonable degree of face validity. However, as with other "new" ADHD models, further investigations are needed to understand the neurobiological underpinnings of the behavioral endophenotypes caused by this mutation.

Other mutant mice that are relevant for ADHD

In 1966, a mutant mouse strain resulting from neutron irradiation, the coloboma mutant mouse, was described (Searle 1966). These mutants bear a mutation on chromosome 2 with approximately 20 genes being disrupted (e.g., PCLB-1 [phospholipase c beta-1] and Jag1 [Jagged 1]). Among these genes, the synaptosomal-associated protein 25 (SNAP-25), which is a key protein in synaptic vesicle docking and fusion with the presynaptic membrane, has attracted the most interest. These mice display delayed neurodevelopment and behavioral deficits that might recapitulate to some degree the developmental deficits in ADHD patients. The mice exhibit pronounced hyperactivity, impulsivity and impaired inhibition in a delayed reinforcement task (Bruno et al. 2007; Wilson 2000; Hess et al. 1994, 1996). Coloboma mice also have disrupted latent inhibition, thus indicating "inattentive" behavior (Bruno et al. 2007). The hyperkinetic behavior is corrected to a certain extent by AMPH but not at all by MPH (Hess et al. 1996; Wilson 2000) and so the mice respond only partially to classical ADHD treatments. Catecholamine metabolism is indeed altered in coloboma mice: DA release is almost completely disrupted in the dorsal striatum, whereas it is augmented in the cerebral cortex (Raber et al. 1997; Jones et al. 2001) and DA metabolite concentrations are decreased in the ventral striatum. Likewise, NE is increased in the striatum and nucleus accumbens of mutants (Jones et al. 2001). The experimental depletion of NE in this model with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4) reduces hyperactivity and restores latent inhibition but does not ameliorate impulsivity (Bruno et al. 2007; Jones and Hess 2003). This has led to the idea that the hyperlocomotor activity is caused by a hyperactive norepinephrinergic system; however, the finding that hyperlocomotion is not completely abolished by NE depletion suggests that additional factors contribute to the mutant phenotype. The deletion of SNAP25 might be related to some of the behavioral deficits of these animals but SNAP25 heterozygous mice (SNAP25 homozygous KO mice are perinatally lethal) notably show no apparent phenotype (Washbourne et al. 2002). Thus, the behavioral phenotype of coloboma mice probably depends on the loss of genes other than SNAP25 within the deleted region (Jeans et al. 2007; Oliver and Davies 2009). Therefore, coloboma mice have only limited construct validity as a model of ADHD.

Among the other transgenic animals used as ADHD models, knock-out animals for the β2-subunit of the nicotinic acetylcholine receptor are noteworthy. They display some of the key ADHD symptoms: inattention, lack of inhibitory control and hyperactivity (Granon et al. 2003; Granon and Changeux 2006). The polymorphisms of nicotinic receptor subunits in ADHD patients and the deregulation of nicotinic pathways in other ADHD models (i.e., DAT-KO mice; Weiss et al. 2007) suggest that further investigations of this model as regard to ADHD related behaviors are warranted.

Equally intriguing is the over-expression of the subunit δ of casein kinase1 (CK1δ) in the forebrain. CK1δ is highly expressed in the brain and regulates the phosphorylation of DARPP-32 (dopamine and cAMP-regulated phosphoprotein MW 32 kDa), which is an important, striatally expressed, protein phosphatase inhibitor that integrates synaptic inputs from DA and glutamatergic afferents. The overexpression of CK1δ causes a decrease in DA receptor levels and mutant mice exhibit hyperactivity, reduced anxiety and nesting behavior deficiencies (Zhou et al. 2010). CK1δ mice also show paradoxical responses to psychostimulants, displaying hypoactivity following the injection of AMPH and MPH, indicating that CK1 activity has a profound effect on DA signaling in vivo. Thus, despite lacking construct validity, CK1δ over-expressing mice might have some face and predictive validity as an ADHD model.

Another mouse model with partial construct validity is based on the association between the gene encoding G-protein-coupled receptor kinase-interacting protein-1 (GIT1) and ADHD. Git1-KO mice developed by a gene trap approach show, at younger ages, a transient hyperactivity that can be inhibited by AMPH and MPH (Won et al. 2011). Furthermore, these mutants display impaired learning and memory. However, another strain of Git1-KO mice developed by homologous recombination do not demonstrate hyperactivity or altered responses to psychostimulants during adulthood (Schmalzigaug et al. 2009) or during development (R.T. Premont, personal communication).

Recent reports have indicated that mice deficient in Cdk5-activating cofactor p35 (Drerup et al. 2010), type 5 G protein beta subunit (Gβ5; Xie et al. 2012), or diacylglycerol kinase β (Ishisaka et al. 2012) demonstrate some phenotypes relevant to ADHD but only limited information is available on these mutants at this time. Further detailed investigations are necessary to validate their potential utility as putative models of ADHD.

Concluding remarks

The opportunity to perform targeted genetic manipulations in mice has tremendously increased our ability to evaluate the contribution of candidate genes to the pathology of ADHD. An ideal animal model of ADHD should display unambiguous construct, face and predictive validity. The major disadvantage in modeling ADHD in animals is the absence of a commonly accepted theory on its causes and pathogenesis. Thus, until the molecular mechanisms involved in the etiology and pathology of ADHD are deciphered, the construct validity of any animal model of ADHD will remain limited. Under these circumstances, the best animal models are largely based on the ability of the model to recapitulate major endophenotypes and to demonstrate the efficacy of the medications used in clinical practice. The growing understanding that ADHD represents a heterogeneous disorder, with many genetic and environmental factors contributing to it, should lead to the generation of many new animal models that might be instrumental in modeling specific ADHD endophenotypes. Thus, each single model has certain strengths and limitations that must be recognized in using the model to address specific scientific questions. Moreover, although the development of novel transgenic animal models is critically dependent on the identification of contributing genetic factors, the development of reliable approaches to investigate complex behaviors in animals is clearly also important (Markou et al. 2009). Unfortunately, such reliability is still lacking for the approaches used to study behavioral characteristics that are critical for ADHD, such as attention and impulsivity, in mice. New opportunities are emerging with the recent ability to develop transgenic rat models, for example, through zinc-finger nuclease technology (Geurts et al. 2010). Rats are the preferred rodent models for cognitive research, because a well-accepted repertoire of behavioral approaches exists to assess complex behaviors such as impulsivity and attention. With increasing knowledge of the etiology and pathology of ADHD and the development of more reliable approaches to model endophenotypes of this disorder in rodents, the translational value of these studies should increase, eventually bringing a new generation of safer and more effective medications.

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