Overview of Animal Models of Attention Deficit Hyperactivity Disorder (ADHD)

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous, highly heritable, behavioral disorder that affects ∼5% to 10% of children worldwide. Although animal models cannot truly reflect human psychiatric disorders, they can provide insight into the disorder that cannot be obtained from human studies because of the limitations of available techniques. Genetic models include the spontaneously hypertensive rat (SHR), the Naples High Excitability (NHE) rat, poor performers in the 5-choice serial reaction time (5-CSRT) task, the dopamine transporter (DAT) knock-out mouse, the SNAP-25 deficient mutant coloboma mouse, mice expressing a human mutant thyroid hormone receptor, a nicotinic receptor knock-out mouse, and a tachykinin-1 (NK1) receptor knock-out mouse. Chemically induced models of ADHD include prenatal or early postnatal exposure to ethanol, nicotine, polychlorinated biphenyls, or 6-hydroxydopamine (6-OHDA). Environmentally induced models have also been suggested; these include neonatal anoxia and rat pups reared in social isolation. The major insight provided by animal models was the consistency of findings regarding the involvement of dopaminergic, noradrenergic, and sometimes also serotonergic systems, as well as more fundamental defects in neurotransmission. *Curr. Protoc. Neurosci.* 54:9.35.1-9.35.25. © 2011 by John Wiley & Sons, Inc.

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder that affects approximately 5% to 10% of children worldwide (Faraone et al., 2003; Biederman and Faraone, 2005). Individuals with ADHD generally have poor academic, occupational, and social functioning resulting from developmentally inappropriate levels of hyperactivity and impulsivity, as well as an impaired ability to maintain attention on motivationally relevant tasks (American Psychiatric Association, 1994; Abikoff et al., 2002; Biederman et al., 2004; Sagvolden et al., 2005a; Thapar et al., 2007). Hyperactivity and impulsivity develop gradually in familiar situations, manifested as overactivity, fidgeting, not sitting still, and apparently acting without thought or consideration of the consequences (American Psychiatric Association, 1994; Sagvolden et al., 2005a). ADHD is a heterogeneous disorder: no two individuals are alike. Even within subjects there is considerable variation in behavior depending on the task and motivational state of the individual. Patients are diagnosed as having either the predominantly inattentive (ADHD-PI), predominantly hyperactive-impulsive (ADHD-HI), or combined (ADHD-C) subtype of ADHD, according to their individual clusters of behavioral symptoms (American Psychiatric Association, 1994). Further subclassification into six ADHD phenotypes has also been suggested (Elia et al., 2009).

Genetics

ADHD is a heterogeneous but nevertheless highly heritable disorder resulting from complex gene-gene and gene-environment interactions (Faraone, 2004; Thapar et al., 2005). Twin and adoption studies produced estimates of heritability of about 76% (Faraone et al., 2005; Thapar et al., 2007). Associations have been found with polymorphisms in genes that encode the D4 and D5 subtypes of the dopamine receptor (DRD4 and DRD5), the dopamine transporter (DAT), the 5-hydroxytryptamine (serotonin) transporter (5HTT), the serotonin 1B receptor (HTR1B), and SNAP-25 (a protein required for neurotransmitter release as well as trafficking

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of glutamate *N*-methyl-D-aspartate (NMDA) receptor subunits to the plasma membrane) (Cook et al., 1995; LaHoste et al., 1996; Faraone et al., 2001; Maher et al., 2002; El-Faddagh et al., 2004; Manor et al., 2004; Thapar et al., 2005; Brookes et al., 2006; Genro et al., 2007; Gornick et al., 2007; Faraone and Khan, 2006; Gizer et al., 2009). Consistent with the heterogeneity of ADHD, other gene variants have been suggested to be associated with ADHD; these include genes that encode monoamine oxidase A, dopamine β-hydroxylase, the norepinephrine transporter, and the α_2-adrenoceptor (Park et al., 2005; Bobb et al., 2005a; Kim et al., 2006; Brookes et al., 2006; Faraone and Khan, 2006). The high prevalence, heterogeneity, and heritability of ADHD suggest that ADHD is the result of multiple genes with small effect size (Smalley, 1997; Faraone, 2004).

Environment

Several environmental risk factors have been identified; these include prenatal exposure to drugs, obstetric complications, head injury, and psychosocial adversity (Biederman and Faraone, 2005; Romano et al., 2006). Prenatal exposure to ethanol affects mainly dopaminergic transmission and causes hyperactivity (Gibson et al., 2000). ADHD is also associated with prenatal exposure to nicotine (Milberger et al., 1998; Mick et al., 2002; Thapar et al., 2003). Children whose mothers smoked during pregnancy had a higher incidence of ADHD than controls (Neuman et al., 2007; Schmitz et al., 2006).

Structural abnormalities

Numerous studies have reported reduced brain volume in patients with ADHD, particularly the cerebellum, corpus callosum, prefrontal cortex, and basal ganglia in the right hemisphere (Castellanos et al., 1996, 2002; Filipek et al., 1997; Hill et al., 2003; Durston et al., 2004; Valera et al., 2007). Patients with lesions of the right frontal cortex displayed ADHD-like behavior, consistent with right frontal cortex pathology in ADHD (Clark et al., 2006). Dopamine alters brain structure and function (Durston et al., 2005). The *DAT1* genotype preferentially influenced caudate volume; individuals homozygous for the 10-repeat allele which is associated with ADHD had smaller caudate volumes than individuals carrying the 9-repeat allele (Durston et al., 2005). In contrast, the *DRD4* genotype influenced prefrontal gray matter; individuals homozygous for the 4-repeat allele had smaller volumes than individuals carrying other variants of the gene (Durston et al., 2005).

Functional abnormalities

The most consistent findings in ADHD are deficits in neural activity within fronto-striatal and fronto-parietal circuits (Dickstein et al., 2006). Neuroimaging studies demonstrated functional abnormalities in dorsal and inferior frontal cortex, anterior cingulate cortex, basal ganglia, thalamus, and cerebellum of patients with ADHD (Fig. 9.35.1; Tannock, 1998; Vaidya et al., 1998; Rubia et al., 1999; Moll et al., 2000; Kim et al., 2002; Scheres et al., 2007; Bush, 2010). Functional magnetic resonance imaging (fMRI) revealed reduced ventral striatal activation in adolescents with ADHD during a reward anticipation task, suggesting impaired reward-related fronto-striatal neuronal circuits in addition to the commonly observed prefrontal executive dysfunction (Scheres et al., 2007). Ventral striatal activation was negatively correlated with parent-rated hyperactive and impulsive symptoms (Scheres et al., 2007). Increases in striatal DAT of up to 70% were found in children and adults with ADHD (Dougherty et al., 1999; Krause et al., 2000; Cheon et al., 2003), which suggests that the *DAT1* gene may be overexpressed in the striatum of ADHD subjects and that this results in reduced synaptic dopamine. However, not all studies found increased DAT (van Dyck et al., 2002; Jucaite et al., 2005), and more recent findings suggest that in some drug-naïve adults with ADHD, DAT levels in the left caudate and nucleus accumbens are reduced (Volkow et al., 2007).

Dopamine hypothesis

There is compelling evidence to suggest that ADHD symptoms may result from impaired dopamine function in the brain, specifically dopamine-mediated development and monitoring of motivated behavior and reward-related memory formation (Sagvolden et al., 2005a; Johansen et al., 2009). The most effective drugs used to treat ADHD are the psychostimulants, methylphenidate and D-amphetamine, which act by blocking DAT and the norepinephrine transporter, increasing synaptic concentrations of these neurotransmitters. Deficient dopamine release during development could impair the strengthening of reward-related synaptic connections and weaken the association of predictive cues with outcome and reward-producing behavior. As a consequence, an individual with ADHD may

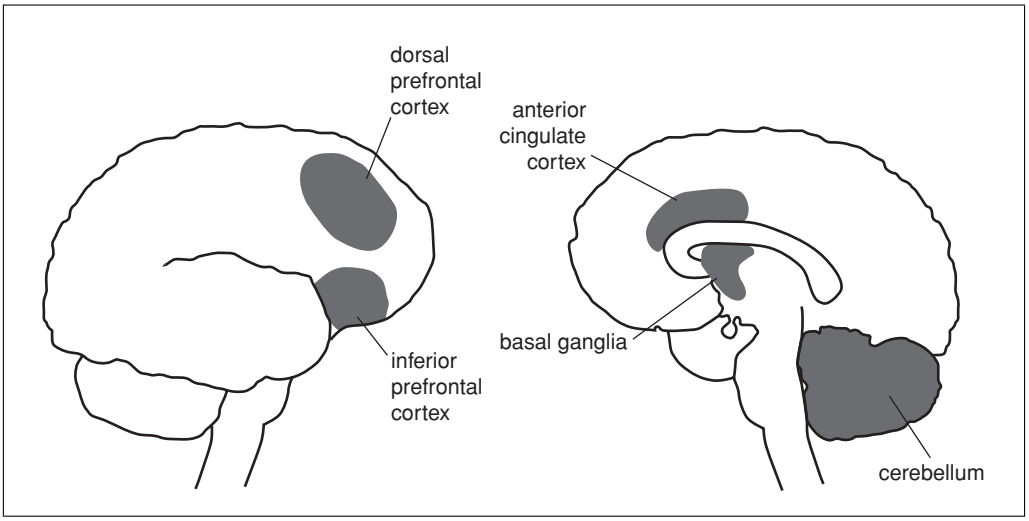

Figure 9.35.1 Brain areas that are structurally and functionally altered in ADHD.

be unable to establish long or complicated sequences of behavior in response to specific temporal patterns of presentation of reward-predicting stimuli (Sagvolden et al., 2005a; Johansen et al., 2009).

ANIMAL MODELS OF ADHD

Although animal models cannot truly reflect human psychiatric disorders, they can provide insight into the disorder that cannot be obtained from human studies because of the limitations of available techniques. While nonhuman primate brains are closer to human brains, rodent models of ADHD have the advantage that they are genetically more homogeneous, they are less expensive to maintain, greater numbers of experimental animals are available, and much more is known about their neurobiology than primates (Russell et al., 2005). The researcher also has better control over variables such as diet, environment, and learning history. Rodent models have simpler nervous systems, so they cannot be used to study complex cognitive behavior such as language, but the neural circuits that control basic behavioral function are similar to humans.

Three minimal criteria have to be met before an animal can be considered a valid model of a human disorder (Willner, 1986). Animal models are required to (i) mimic the fundamental symptoms of the human disorder (face validity), (ii) involve similar etiology and underlying pathophysiological mechanisms (construct validity), and (iii) display attenuation of symptoms by treatment that is effective in treating the human disorder, as well as provide insight into the underlying mechanisms of the disorder, predict biological and behavioral aspects of the disorder that have not been observed in clinical evaluations, and predict novel treatment strategies (predictive validity) (McKinney and Bunney, 1969; Willner, 1986; Sagvolden, 2000; Sagvolden et al., 2005b).

A diagnosis of ADHD depends on the behavioral criteria of an inability to sustain attention, hyperactivity, and impulsivity, and animal models of the disorder are required to mimic these symptoms (Sagvolden, 2000; Sagvolden et al., 2005b). ADHD is a heterogeneous disorder, and it is not surprising that many different animal models with distinctly different neural defects have been proposed to model the disorder. Consistent with ADHD being a neurodevelopmental disorder, animal models are either genetic (SHR, DAT knockout mice, SNAP-25 mutant mice, mice expressing a mutant thyroid receptor, nicotinic receptor, or tachykinin-1 receptor), or have suffered an insult to the central nervous system during the early stages of development (anoxia, 6-hydroxydopamine) (Shaywitz et al., 1978; Luthman et al., 1989; Dell'Anna et al., 1993; Jones et al., 1998; Dell'Anna, 1999; Sagvolden, 2000; Gainetdinov and Caron, 2000, 2001; Zhuang et al., 2001; Siesser et al., 2006; Bruno et al., 2007).

Not all individuals with ADHD display all of the symptoms, and individuals also differ in terms of the cluster of symptoms that they display. Thus, it may be unreasonable to expect animal models of the disorder to display all of the symptoms of ADHD. There may indeed be merit in studying animals that model specific phenotypes of ADHD rather than the full spectrum of symptoms of the disorder. The difficulty, however, lies in translating clinical descriptions of the core symptoms of ADHD

into operationally defined behaviors with clear experimental analogs (Alsop, 2007).

Attention Deficit

The attention deficit of ADHD is particularly difficult to translate into operationally defined behavior in animal models, since distractibility, carelessness, difficulty organizing tasks, losing things, failing to follow instructions, and avoiding tasks that require sustained mental attention cannot easily be measured in animals (Alsop, 2007). Sagvolden and colleagues (Sagvolden et al., 1993; Berger and Sagvolden, 1998; Boix et al., 1998; Sagvolden, 2000) designed experiments to test sustained attention in rats and humans performing multiple fixed-interval/extinction (FI/EXT) tasks or variable-interval/extinction (VI/EXT) tasks with two or more components that operate in alternation, each signaled by a different stimulus. The fixed interval (or variable-interval) component requires a fixed (or variable) time to elapse before the required response (e.g., lever press) will be reinforced. No reinforcers are delivered during the extinction component. The animal learns to associate the stimulus that signals extinction with the fact that a lever press will no longer produce a reinforcer. The extinction component measures sensitivity to stimulus change and the ability to learn the new rule/requirements of the task. The response rates are recorded during the fixed-interval (or variable-interval) and extinction phases (Sagvolden et al., 1993, 2005b), and the percentage choice of the correct lever when the reinforcers are delivered infrequently is used as a measure of sustained attention, since the animal must continue to pay attention to the cue (e.g., light) that signals the lever that may produce a reinforcer when pressed (Sagvolden et al., 2005b; Sagvolden, 2006; Sagvolden and Xu, 2008; Sagvolden et al., 2008). A translational task for children was designed and used both in Norway and South Africa (Aase and Sagvolden, 2005; Aase et al., 2006). In clinical settings, sustained attention deficit occurs when stimuli are widely spaced in time (van der Meere, 1996) or the task is unwelcome or uninteresting (Taylor et al., 1998). In the extinction component of FI/Ext schedules, children with ADHD were able to sustain attention at initiation of testing, but their ability to sustain attention decreased with repeated testing over time. At the start of every extinction component, both children with ADHD and normal children stopped responding at the onset of the extinction component (a light signal), but children with ADHD resumed responding after a short while (Sagvolden and Sergeant, 1998; Sagvolden et al., 2005b). An animal model of ADHD would be expected to behave similarly. If it is unable to sustain attention, it should respond at an increased level during the extinction phase, in the absence of a reinforcer, compared to an appropriate reference strain.

Hyperactivity

Hyperactivity may seem to be the simplest ADHD-like behavior to measure in animal models, but this is not so. Novelty and the type of apparatus used to measure behavioral activity can influence the results. Hyperactivity is reported as increased levels of activity in an open-field apparatus or increased response rates in free operant tasks. However, the conditions and time-course of the increased activity needs to mimic the disorder. Hyperactivity is reported to be absent in children with ADHD in novel situations (Sleator and Ullman, 1981; Sagvolden and Sergeant, 1998). In FI/Ext schedules, children with and without ADHD had similar activity levels at initiation of testing. Hyperactivity developed gradually in children with ADHD as the test proceeded (Sagvolden and Sergeant, 1998). The total number of lever presses was defined as an expression of the general activity level of both children and rats.

Rats will actively explore a novel, nonthreatening, open-field apparatus, either large (1 m width $\times$ 1 m length $\times$ 0.5 m height) or small (0.255 m $\times$ 0.3 m $\times$ 0.475 m) (Pardey et al., 2009). In either environment, an animal model of ADHD would be expected to have similar activity levels as controls in the initial period of testing but become more active as the surroundings become familiar, and they lose their interest in exploring the environment.

An important consideration is whether to test the rats during the light phase or dark phase of their light/dark cycle. Some researchers prefer to test the rats during the light cycle when they are rested but become active when transferred to a novel, dimly lit environment, encouraging exploratory activity (Cierpial et al., 1989), whereas others prefer to test locomotor activity during the dark cycle, when the rat is normally active (Pardey et al., 2009). However, the latter usually requires a shift in the light/dark cycle to enable researchers to test the rats' behavior during the human's normal daytime, rather than work through the night. A shift in the light/dark cycle is regarded as a stressor and can lead to long-term changes in behavior (Howells et al., 2005).

Impulsivity

Children with ADHD are not reported to exhibit motor impulsiveness in novel situations; impulsivity develops gradually over time (Sagvolden and Sergeant, 1998). Impulsivity has been defined as premature responding and recorded as bursts of responses with short inter-response times (Sagvolden, 2000; Sagvolden et al., 2005a). The number of responses with short inter-response times (<0.67 sec) has been used as a measure of the degree of impulsiveness, i.e., "cannot hold back a response even when it is an unnecessary one" (Sagvolden et al., 2005b, 2008; Sagvolden, 2006; Sagvolden and Xu, 2008). An animal model of ADHD would be expected to exhibit a greater number of bursts with short inter-response times than control rats during the extinction period of FI/EXT and VI/EXT schedules.

Sensitivity to delay of reinforcement is an important aspect of impulsive behavior. Children with ADHD have been reported to prefer small immediate reinforcers over larger reinforcers delivered after a delay (Sonuga-Barke and Taylor, 1992). An animal model of ADHD would similarly be expected to show a preference for immediate reward. The salience of the reward and motivational state of the animal would need to be carefully controlled.

GENETIC MODELS OF ADHD

Spontaneously Hypertensive Rat

By far the most widely studied model of ADHD is the inbred spontaneously hypertensive rat (SHR), which is normally compared to the normotensive Wistar-Kyoto (WKY) strain from which it was derived (Okamoto and Aoki, 1963). SHR are unique in that they have been shown to display all of the behavioral characteristics of ADHD, including poor performance in tasks requiring sustained attention, hyperactivity, and impulsivity that is not present in novel, nonthreatening environments but develops over time when reinforcers are infrequent, and sensitivity to delay and increased intra-individual variation in performance of operant tasks (Sagvolden, 2000; Wiersema et al., 2005; Sagvolden et al., 2005b; Aase and Sagvolden, 2006; Johansen et al., 2007). Impulsivity is seen in SHR as an inability to inhibit a response during the extinction phase of an operant task, as well as an inability to delay a response in order to obtain a larger reward (Sagvolden, 2000; Bull et al., 2000; van den Bergh et al., 2006).

Attention-deficit

SHR were investigated with the same visual discrimination task used for ADHD children; the computer programs and type of interface used for the multiple FI/Ext schedules were the same, but the reinforcers were different (trinkets for children, water droplets for rats previously deprived of water) (Sagvolden, 2000; Sagvolden et al., 2005b). Similar results were obtained for SHR and ADHD children, validating the use of SHR as a model of ADHD (Sagvolden et al., 1998; Sagvolden, 2000). Analogous results were obtained for SHR using a VI/EXT schedule (Sagvolden et al., 2005b, 2008). In these experiments, a light signaling the correct lever was the discriminative stimulus showing the rat which lever should be pressed in order to receive a reinforcer. A concurrent extinction schedule was present on the incorrect lever. The light was never on above the incorrect lever. During the first four 30-min sessions, reinforcers were delivered immediately after each correct lever press (Sagvolden et al., 2005b). Thereafter, reinforcers were delivered according to a 15-sec variable-interval schedule where the time between reinforcers ranged randomly between 1 and 120 sec (Sagvolden et al., 2005b). At the end of each interval, a reinforcer was delivered immediately following the first correct response. Up to this point, test and control subjects performed equally well. However, this was followed by an unpredictable 180-sec variable interval schedule where the correct lever was signaled by a constantly lit cue (Sagvolden et al., 2008). SHR rats failed to learn the new rule: their performance in this test was poorer than all other comparison strains (Sagvolden et al., 2005b, 2008). Interestingly, Sagvolden et al. (2008) showed that a WKY strain obtained from Charles River Laboratories in Germany performed as poorly as SHR in the VI/EXT task. These WKY/NCrl rats were not hyperactive and were therefore proposed as a model for ADHD-PI (Sagvolden et al., 2008). It remains to be seen whether this ADHD-like behavior will be repeated in future generations of the WKY/NCrl rat strain obtained from the breeders in Germany.

Hyperactivity

The hyperactivity of SHR has been demonstrated by several laboratories as increased response rates in free operant tasks and increased locomotor activity in an open field when compared to WKY and Sprague Dawley rats (Sagvolden et al., 1993; Berger and

Sagvolden, 1998; Johansen and Sagvolden, 2005a; Johansen et al., 2005; Pardey et al., 2009; Howells et al., 2009). The design of the operant task and dimensions of the open field vary from one laboratory to another and can determine the outcome. For example, Howells et al. (2009) used a large open-field apparatus (1 m × 1 m × 0.5 m) to demonstrate significantly increased locomotor activity in SHR during the rats' light phase compared to both WKY and Sprague Dawley rat strains within 15 min, whereas Pardey et al. (2009) did not observe any difference between SHR and WKY for the first 30 min in a small apparatus (30 cm × 25.5 cm × 47.5 cm) during the rats' dark phase. Similar to children with ADHD, SHR became more active over time in the more confined apparatus, where SHR were more active than WKY after 60 min in the smaller apparatus (Pardey et al., 2009). The behavior of SHR in the smaller apparatus mimics more closely that of children with ADHD, and is therefore recommended. However, an important aspect of ADHD-like behavior in children is its temporary amelioration by novelty and by stimulant medication (Williams et al., 2009a). One possible mechanism is an underlying drive for novelty (Williams et al., 2009a), which may be an important factor determining the behavior of SHR in the open field. The design of the experiment may have optimized testing of their drive for novelty. Howells et al. (2009) were careful to ensure that the rats were not exposed to the open field before testing during their light phase in a 50-lux room to encourage maximum exploratory behavior (Cierpial et al., 1989); the rats were transferred to the behavioral room at least 1 hr before placement in the open field. Nevertheless, it is preferable to test ADHD-like behavioral activity after the rats have become habituated to the apparatus, since children with ADHD are not hyperactive in a novel environment but become active as they habituate to the environment.

In free operant tasks, SHR are more active after richer recent reinforcement, after decelerating reinforcers and after predictable reinforcers (Williams et al., 2009b). SHR are similar in several respects to group averages of children with ADHD, except that SHR have reduced variability and perform actions faster than controls (Williams et al., 2009b). Hyperactivity in the SHR is dependent on momentary environmentally determined states, which is an important area for future investigation of ADHD (Williams et al., 2005). Using a VI/EXT schedule, Williams et al. (2009a, b) showed that SHR lack normal down-regulation of responding when reinforcers become infrequent. They suggested that SHR appear to be relearning the schedule length during the days of each calendar week (Williams et al., 2009a). They found that SHR hyperactivity was specific to the operant and developed gradually over the first 5 min of each session. Empirical within-session results were replicated by a simple simulation containing two interacting reward systems, one for water and the other for stimulation (including novelty). Enhanced sensation-seeking (or novelty-seeking) was associated with low anxiety in SHR and was suggested to provide the best account of changes in SHR activity within sessions (Williams et al., 2009a). Howells et al. (2009) also demonstrated reduced anxiety-like behavior in SHR compared to WKY and Sprague Dawley rats.

Impulsivity

Impulsivity is defined as the inability to wait for a reward or inability to delay a response in order to obtain a larger reward. SHR exhibited a greater number of bursts with short inter-response times than control rats during the extinction period following both random-interval and variable-interval schedules (Sagvolden, 2000; Sagvolden et al., 2005b, 2008).

Sensitivity to delay of reinforcement

A consistent finding across studies is that SHR and WKY differ in terms of the effects of extinction and delayed reinforcement in operant tasks in a manner similar to children with ADHD (Johansen et al., 2005; Johansen and Sagvolden, 2005b; Sagvolden et al., 2005b; Alsop, 2007). SHR reduced their response rate more slowly than WKY immediately after the introduction of the extinction phase in a VI/EXT schedule (Johansen et al., 2005; Johansen and Sagvolden, 2005b; Sagvolden et al., 2005b); their response rates were elevated at baseline, and decreased more rapidly than WKY with increasing delay of reinforcement (Johansen et al., 2005).

Sutherland et al. (2009) measured sensitivity to delay of reinforcement in two animal models of ADHD, the SHR and the genetically hypertensive (GH) rat. A task previously used to measure effects of delay of reinforcement in children with ADHD was used. Rats were required to press one of two levers on each trial. One lever delivered an immediate reinforcement, while the other lever delivered reinforcement after a delay. Both the SHR and GH

strains allocated significantly more responses to the immediately reinforced lever than their genetic control strains, WKY and Wistar rats, respectively (Sutherland et al., 2009). These findings support the use of the SHR and GH rats to model altered response to reinforcement in children with ADHD (Sutherland et al., 2009).

Genetics

SHR is a genetic model of ADHD bred from progenitor Wistar Kyoto rats (Okamoto and Aoki, 1963). A 160-bp insertion found in the noncoding region upstream of exon 3 of the DAT gene of SHR (Mill et al., 2005) is of significance since a variable number of tandem repeats in the 3′-untranslated region of the DAT gene has been associated with ADHD in several family studies (Cook et al., 1995; Dougherty et al., 1999; Krause et al., 2000; Kirley et al., 2003; Bobb et al., 2005b). A possible disturbance in the regulation of transcription of the DAT gene is in agreement with findings that DAT gene expression is transiently reduced in the SHR midbrain during the first postnatal month and increased in adult SHR compared to controls (Watanabe et al., 1997; Leo et al., 2003). Alterations in DAT gene expression can affect dopamine uptake and reutilization. Decreased expression of DAT will reduce reuptake and increase metabolism of dopamine. Differences in dopamine metabolism have been reported for children and adults with ADHD (Ernst et al., 1998, 1999), which is consistent with developmental changes in DAT expression and consequent changes in dopamine uptake. DOPA decarboxylase activity was found to be increased in the midbrain of children and decreased in prefrontal cortex of adults with ADHD compared to controls (Ernst et al., 1998, 1999). Reduced DAT expression at a young age would reduce dopamine reuptake, thereby reducing dopamine reutilization and necessitating increased synthesis of dopamine by DOPA decarboxylase. In adults, increased expression of DAT might be expected to increase reuptake of dopamine, thereby reducing the need for synthesis by DOPA decarboxylase (Russell et al., 2005).

Environment

Little is known about the involvement of environmental factors in determining SHR behavior and to what extent 'protective' nonpharmacological factors may be considered as a strategy for prevention of ADHD symptoms (Pamplona et al., 2009). Pamplona et al. (2009) investigated whether the environment in which SHR were reared may counteract later cognitive deficits in adulthood. Outbred Wistar rats were used as a control. The animals were reared in either an enriched environment or a standard environment from postnatal day 21 to 3 months of age and tested for cognitive and noncognitive phenotypes. The enriched environment improved SHR's performance in open field habituation, the spatial water maze task, social recognition task, and object recognition task, but did not affect noncognitive function, such as nociception and hypertension (Pamplona et al., 2009). The outbred Wistar rats were not affected by the enriched environment, suggesting that the poor performance of SHR in cognitive tasks may be influenced by the environment during the early stages of development, and modification of the early postnatal environment may be a putative preventive strategy for ADHD (Pamplona et al., 2009).

Howells et al. (2009) investigated the effect of the early postnatal environment on SHR neurochemistry and behavior in adolescence. SHR, WKY, and Sprague Dawley pups were cross-fostered to dams of the other two strains on postnatal day 2. Control rats remained with their birth mothers to serve as a reference for their particular strain phenotype. Behavior in the open-field and the elevated plus maze was assessed between postnatal days 29 and 33. Two days after the behavioral recordings, rats were decapitated and glutamate-stimulated release of norepinephrine was determined in prefrontal cortex and hippocampal slices. There was no significant effect of "strain of dam," but there was a significant effect of "pup strain" on all parameters investigated. SHR pups traveled a greater distance in the open field, spent a longer period of time in the inner zone and entered the inner zone of the open field more frequently than Sprague Dawley or WKY rats. Sprague Dawley rats were more active than WKY in the open field. SHR and Sprague Dawley rats entered the inner zone more rapidly than WKY. In the elevated plus maze, SHR spent less time in the closed arms and more time in the open arms, and entered the open arms more frequently than Sprague Dawley rats or WKY. There was no difference between WKY and Sprague Dawley behavior in the elevated plus maze. SHR released significantly more norepinephrine in response to glutamate than Sprague Dawley or WKY in both hippocampus and prefrontal cortex,

while Sprague Dawley prefrontal cortex released more norepinephrine than WKY. SHR were resilient; cross-fostering did not reduce their ADHD-like behavior or change their neurochemistry. Cross-fostering of Sprague Dawley pups onto SHR or WKY dams increased their exploratory behavior without altering their anxiety-like behavior. The results suggested that the ADHD-like behavior of SHR and their neurochemistry was genetically determined and not a result of being reared by SHR dams. The similarity between WKY and Sprague Dawley rats supports the continued use of WKY as a control for SHR and suggests that Sprague Dawley rats may be a useful additional reference strain for SHR. The fact that Sprague Dawley rats behaved similarly to WKY in the elevated-plus maze argued against the use of WKY as a model for anxiety-like disorders.

Structural abnormalities

In addition to behavioral and genetic similarities to ADHD, SHR exhibit brain pathology similar to ADHD. SHR brain volumes, specifically prefrontal cortex, occipital cortex, and hippocampus, are smaller than controls. There are fewer neurons in these brain areas compared to WKY (Sabbatini et al., 2000; Mignini et al., 2004; Tomassoni et al., 2004). MRI also revealed significantly increased ventricular volume in SHR compared to WKY at 3 months of age (Bendel and Eilam, 1992).

Importance of the reference strain

Although several molecular and genetic manipulations may produce hyperactive animals, hyperactivity alone is considered to be insufficient for an animal to qualify as a model of ADHD (Sagvolden et al., 2009). Based on a wider range of criteria, behavioral, genetic and neurobiological, Sagvolden et al. (2009) suggested that the SHR obtained from Charles River, Germany (SHR/NCrl) is the best validated animal model of ADHD combined subtype (ADHD-C), and that the Wistar Kyoto substrain obtained from Harlan, U.K. (WKY/NHsd) is its most appropriate control. These are the substrains that they have used for many of their recent experiments. Because of genetic heterogeneity, the use of outbred Wistar, Sprague Dawley, or other rat strains as controls for the SHR is not recommended (Sagvolden et al., 2009; Howells et al., 2009). Data may be misinterpreted if insufficient care is taken in selection of the control strain (Sagvolden et al., 2009). WKY rats obtained from Charles River, Germany (WKY/NCrl), were shown to mimic the behavioral characteristics of children with ADHD-PI, and may thus provide a promising model for this subtype of ADHD. In this case, the WKY/NHsd strain obtained from Harlan, U.K., was also recommended for use as a control (Sagvolden et al., 2008, 2009).

Limitations

Both SHR and WKY have been criticized (Bull et al., 2000; van den Bergh et al., 2006; Alsop, 2007). The WKY rat does not perform as well as other rat strains in certain behavioral tasks and is often less active than other rat strains (Bull et al., 2000; van den Bergh et al., 2006). The results of behavioral studies are unfortunately inconsistent, and depend on the demands of the task. Sagvolden and colleagues (Sagvolden et al., 2005b) showed that SHR learn as quickly as control rats, in an operant task that required the rat to learn to press a lever in order to obtain a reinforcer, only when the reinforcer was presented within a few seconds after a correct behavioral response. However, SHR failed to learn a new rule when correct responses were reinforced intermittently after a delay of approximately 3 min. Furthermore, their accuracy of performance did not improve even after 25 trials (Sagvolden et al., 2005b). Similar results were obtained by Hand and coworkers who showed that SHR took longer than WKY to learn a novel response when reinforcement was delayed, but not when reinforcer delivery was immediate (Hand et al., 2006).

Different levels of arousal can be confounding factors in behavioral testing (Calzavara et al., 2004). Young SHR performed poorly in a plus-maze discriminative avoidance task compared to WKY, but, after treatment with chlordiazepoxide, their anxiety levels were reduced and their performance improved (Calzavara et al., 2004). SHR performed poorly in tests of spatial memory—they made more errors than WKY, Wistar, and Sprague Dawley rats, and they also failed to show improvement in a win-shift version of the water radial arm maze compared to WKY and Sprague Dawley controls (Wyss et al., 1992; Nakamura-Palacios et al., 1996; Hernandez et al., 2003; Prediger et al., 2005; Clements and Wainwright, 2006). However, SHR sometimes performed as well or even better than controls (Ferguson and Cada, 2004). Inconsistencies could be due to different levels of arousal and anxiety. Increased norepinephrine release in prefrontal regions is associated with arousal and can influence

performance of cognitive tasks (Arnsten, 1998). SHR have profound alterations in the noradrenergic neurotransmitter system (Russell et al., 2000; Russell and Wiggins, 2000; Russell, 2001). Autoreceptor-mediated feedback inhibition of norepinephrine release is impaired in prefrontal cortex, and there appears to be increased release of norepinephrine in response to glutamate stimulation of AMPA receptors in prefrontal cortex and hippocampus of SHR (Russell et al., 2000; Russell and Wiggins, 2000; Russell, 2001; Howells and Russell, 2008). This could be altered by the level of arousal.

The physical requirements of the task can also produce variable results. For example, WKY took longer than SHR and Sprague-Dawley rats to acquire a task that required high response rates, but were equal to or better than the other strains when low rates of responding were required (Bull et al., 2000; van den Bergh et al., 2006). SHR displayed decreased acoustic startle response and decreased prepulse inhibition when compared to WKY, Lewis, and Sprague Dawley rats (Ferguson and Cada, 2004; Vendruscolo et al., 2006). The decreased startle response was a consistent finding across several studies, but prepulse inhibition of acoustic startle was not, SHR performed as well as WKY and better than Sprague Dawley rats in one study (Van den Buuse, 2004). SHR and WKY performed as well as Sprague Dawley rats in a 5-choice serial reaction time (5-CSRT) task (van den Bergh et al., 2006), which argues against SHR having impaired sustained attention (Puumala et al., 1996; Barbelivien et al., 2001; Russell et al., 2005; van den Bergh et al., 2006; Alsop, 2007). Operant tasks require varying degrees of food or water deprivation in order to enhance motivation for the reinforcer and require rats to be housed in isolation with minimal environmental stimulation, which can contribute to the variability in results. SHR were also criticized for lack of response to methylphenidate in several behavioral tests (van den Bergh et al., 2006). It is possible that some of the tests were not targeting SHR's impairment specifically. It may also be unrealistic to expect identical effects of the drug on rodent and human behavior if one considers the complexity of human behavior and the relatively poorly developed prefrontal cortex in rodents. Despite this criticism, a lot of useful information has been gained by comparing differences between SHR and WKY behavior in operant tasks and their neurochemistry. The strength of findings with animal models is seen when they are consistent across different laboratories and across different models of ADHD. Studies on SHR were the first to identify the importance of decreased stimulus-evoked release of dopamine, which was subsequently found in the majority of animal models of ADHD (Russell et al., 2005). This finding provides a firm basis for deficient dopamine-mediated strengthening of neural circuits, which could give rise to deficient learning and impaired reinforcement of goal-directed behavior.

Hypertension is a confounding factor in the SHR model of ADHD. However, SHR do not develop hypertension until they are adults, beginning 10 to 12 weeks of age, whereas hyperactivity is observed at 3 to 4 weeks of age before rats enter puberty (De Jong et al., 1995). In an attempt to map quantitative trait loci for complex phenotypes, SHR were crossed with a Brown Norway congenic strain to generate a set of recombinant inbred strains (Printz et al., 2003). Analysis of their behavior revealed that locomotion mapped to chromosomes 3, 8, and 18, while hypertension exhibited multigenic complexity with both environment and genetic background as contributing factors. Elevated arterial blood pressure was higher when measured by direct catheterization compared to radiotelemetry, suggesting that SHR hypertension is a product of stress-dependent trait expression (Printz et al., 2003). SHR behavior was suggested to result from an interaction between genetics and the environment (Printz et al., 2003), much like ADHD (Faraone, 2004; Sagvolden et al., 2005a).

Naples High Excitability Rat

The Naples high-excitability rat (NHE) has been selected for its higher exploratory activity in the Làt maze (Sadile et al., 1988). Novelty-induced hyperactivity increases in NHE as a function of the complexity of the environment (Sadile, 1993; Viggiano et al., 2002). Unlike SHR, NHE do not display hyperactivity in their home cage when compared to Naples low-excitability rats (NLE) (Sadile, 1993). Both NHE and NLE have impaired working memory and reference memory compared to Naples random-bred (NRB) controls. NHE have disturbances in the dopaminergic system, increased dopamine, and decreased dopamine D1 receptors (DRD1) in the prefrontal cortex. Intranasal dopamine administration improved their performance in nonreinforced spatial novelty tasks (Ruocco et al., 2009a). NHE rats also have elevated L-glutamate, D-glutamate, and L-aspartate concentrations in

various areas in the forebrain including the prefrontal cortex and have been proposed as a useful model for the study of hyperactivity, attention deficit, learning and memory disabilities, and drug abuse (Sadile, 1993; Ruocco et al., 2009b).

Poor 5-choice serial reaction time (CSRT) task performer

Rats that are selected for poor performance when trained in a visuospatial 5-CSRT task provide a useful model of ADHD-PI in that they are selected for deficient sustained attention, they show poor choice accuracy towards the end of testing sessions, they are not hyperactive, and they demonstrate impulsivity as premature responding (Puumala et al., 1996; Barbelivien et al., 2001). Rats were food-deprived for 16 hr before being trained to nose-poke an illuminated hole in order to obtain a food pellet. A nose-poke into an unlit hole or a failure to respond during the visual stimulus resulted in a punishment period of darkness (Puumala et al., 1996). Poor performers were defined as those rats that achieved less than 64% correct responses (Puumala et al., 1996). The percent accuracy provided a measure of sustained attention, since the animal had to scan the array of holes so that it could respond rapidly to the signal. Responses recorded during the inter-trial interval were considered premature and provided a measure of impulsivity. Latency to obtain the reward was used as a measure of motivation. Methylphenidate treatment improved accuracy and reduced impulsiveness (at low doses) in poor performers (Puumala et al., 1996).

Evidence supports a role for dopamine in regulating the level of performance in the 5-CSRT task. In normal animals, D-amphetamine stimulated release of dopamine in the nucleus accumbens and caused a dose-dependent increase in premature responding (Robbins, 2002). Microinfusion of a DRD1 agonist into the medial prefrontal cortex selectively impaired the accuracy of attentional performance in high performers in the 5-CSRT task (Granon et al., 2000). In contrast, microinfusion of the DRD1 agonist into the medial prefrontal cortex of poor performers enhanced the accuracy of attentional performance; a low dose increased the speed of making correct responses (Granon et al., 2000). This finding emphasizes the need to study animal models of ADHD rather than normal animals, in order to gain insight into the mechanisms that underlie the beneficial effects of drugs used to treat children with ADHD. These results suggest that dopamine function is reduced in poor performers of the 5-CRST task, a putative model for ADHD-PI.

TRANSGENIC MODELS

Dopamine Transporter (DAT)

DAT knock-out mice have been suggested to model ADHD because they are hyperactive (Gainetdinov and Caron, 2000, 2001; Trinh et al., 2003), have impaired extinction of responses in operant food reinforcement tasks (Hironaka et al., 2004), and have impaired learning and memory (Gainetdinov and Caron, 2001; Trinh et al., 2003). The absence of DAT in the DAT knock-out mouse provides an extreme model of reduced midbrain DAT binding in adolescents with ADHD (Jucaite et al., 2005) and also contrasts with several studies that found increased DAT in the striatum of ADHD children and adults (Dougherty et al., 1999; Krause et al., 2000; Cheon et al., 2003). The DAT knock-out mouse nevertheless provides useful information concerning the neurobiological consequences of impaired DAT function.

In DAT knock-out mice, dopamine is cleared very slowly from the synaptic cleft, causing a 5-fold elevation of extracellular dopamine in the striatum (i.e., a hyperdopaminergic state) (Gainetdinov et al., 1999). However, electrically stimulated release of dopamine is decreased, suggesting that phasic release of dopamine is reduced (i.e., the dopamine system is hypofunctional) (Gainetdinov et al., 1999), similar to SHR (Russell et al., 2005). Unlike SHR, striatal DRD2 autoreceptors are nonfunctional and postsynaptic DRD1 and DRD2 are down-regulated by approximately 50% in the striatum of DAT knock-out mice (Gainetdinov et al., 1999). Hyperactivity in the DAT knock-out mouse might be the result of increased dopamine tone or decreased phasic dopamine release with consequent impaired activation of postsynaptic DRD1 required for LTP (and LTD) to produce changes in synaptic strength necessary for associative learning and reinforcement of goal-directed behavior.

Inhibitors of the serotonin transporter, as well as drugs that activate the serotonergic system such as serotonin receptor agonists and serotonin precursors, dramatically reduced the hyperactivity of DAT knock-out mice, whereas specific inhibitors of the norepinephrine transporter or DAT were ineffective (Gainetdinov and Caron, 2001). These findings in DAT knock-out mice provide convincing evidence

that hyperactivity induced by high extracellular levels of dopamine can be reduced by enhancing serotonergic tone (i.e., psychostimulants do not act via DAT to reduce hyperactivity in this model) (Gainetdinov and Caron, 2001). Interestingly, antagonists of the 5-HT_{2A} receptor reversed the behavioral deficits of DAT knock-out mice (Barr et al., 2004), and polymorphisms of the 5-HT_{2A} receptor gene have been associated with ADHD (Quist et al., 2000; Levitan et al., 2002). Serotonin acts on a large number of receptor subtypes each with different spatial location and behavioral effects. Evidence obtained with the DAT knock-out mouse suggests that specific antagonists of the 5-HT_{2A} receptor warrant further investigation.

DAT knock-down mice (expressing 10% of wild-type DAT) displayed a complex serial pattern of grooming actions, becoming more sequentially rigid and persistent (Berridge et al., 2005; Russell et al., 2005). This type of behavior is not characteristic of ADHD. DAT knock-down mice tended to be hyperactive, to walk in perseverative straight paths, and to over-pursue certain incentive stimuli, consistent with Tourette's syndrome and obsessive compulsive disorder (Berridge et al., 2005).

Hewitt et al. (2009) showed that withdrawal from subchronic treatment with a potent and highly selective DAT inhibitor increased locomotor activity and impaired performance in a novel object recognition task; the rats did not discriminate a familiar object from a novel object (Hewitt et al., 2009). Adriani et al. (2009) 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 (Adriani et al., 2009). In the absence of general locomotor effects, DAT over-expressing rats showed increased impulsivity (i.e., a more marked shift of demanding from the large/delayed toward the small/immediate reward) and increased risk proneness (i.e., a less marked shift from the large/uncertain toward the small/sure reward) compared to controls (Adriani et al., 2009). Altered DAT function in the nucleus accumbens was suggested to subserve a sensation-seeker phenotype and the vulnerability to impulse-control disorders (Adriani et al., 2009).

Coloboma mutant mouse

SNAP-25 (synaptosomal-associated protein of 25 kDa) is an integral part of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor), a docking complex for synaptic vesicle exocytosis and neurotransmitter release. The SNAP-25 deficient mutant coloboma mouse provides an interesting model of ADHD, especially since SNAP-25 polymorphisms have been associated with the disorder (Barr et al., 2000; Mill et al., 2002). SNAP-25 regulates membrane trafficking; it is required presynaptically for the release of neurotransmitters, as well as postsynaptically, where it is involved in the translocation of proteins (e.g., NMDA receptor subunits) to the cell membrane. Altered expression of SNAP-25 is therefore likely to impair neuronal function. Coloboma mice displayed spontaneous hyperactivity, impulsivity, and impaired inhibition in a delayed-reinforcement task (Wilson, 2000; Bruno et al., 2007); the hyperactivity was reduced by D-amphetamine but not methylphenidate (Hess et al., 1996; Wilson, 2000). The difference in effect is likely to be due to the different actions of these two drugs. Both drugs increase the extracellular concentration of catecholamines through blockade of the dopamine and norepinephrine transporters, but D-amphetamine also increases the release of these neurotransmitters.

Glutamate release from cortical synaptosomes is reduced in the coloboma mouse (Raber et al., 1997). Depolarization-evoked release of dopamine from dorsal striatal slices is also decreased, and dopamine metabolite concentrations are decreased in the ventral striatum (Raber et al., 1997; Jones et al., 2001a), suggesting that the coloboma mouse has a hypofunctional dopaminergic system, similar to SHR and DAT knock-out mice (Russell et al., 2005). Dopamine D2 receptor (DRD2) expression is increased in the VTA and substantia nigra, consistent with increased inhibition of dopamine neuron activity (Jones et al., 2001b). Tyrosine hydroxylase expression is unaltered in the VTA and substantia nigra of the coloboma mouse (Jones et al., 2001b). Noradrenergic function appears to be increased in coloboma mice. Tyrosine hydroxylase and α_{2A}-adrenoceptor expression is increased in the locus coeruleus, and norepinephrine concentrations are increased in striatum of coloboma mice (Jones et al., 2001b). Experimental depletion of norepinephrine with *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine hydrochloride (DSP-4) reduced hyperactivity and restored latent inhibition but did not ameliorate impulsivity of the coloboma mice (Jones and Hess, 2003; Bruno et al., 2007). α_{2C}- (but not α_{2A}- or α_{2B}-) adrenergic receptor antagonists also reduced the hyperactivity of coloboma mice (Bruno

and Hess, 2006). The β-adrenergic receptor antagonist propranolol and the α_1-adrenergic receptor antagonist prazosin had little effect. This suggested that motor activity in coloboma mice is caused by a hyperactive noradrenergic system, but that the hyperactivity is not completely abolished by depletion of norepinephrine, suggesting that additional factors contribute to the mutant phenotype (Jones and Hess, 2003). An imbalance between noradrenergic hyperfunction and dopamine hypofunction may be a determining factor as suggested for SHR (Russell et al., 2005).

Thyroid Hormone Receptor

It has been known for some time that many children with elevated thyroid stimulating hormone (TSH) and resistance to thyroid hormone display symptoms of ADHD (Burd et al., 2003). Thyroid hormone directly controls the development of several brain systems associated with the regulation of attention, locomotor activity, motivation, and impulsive behavior (Siesser et al., 2006). Genes that encode proteins involved in myelination (suggested to be impaired in ADHD) (Russell et al., 2006) and the development of neurotransmitter systems that regulate attention and motor activity (cholinergic, dopaminergic, and noradrenergic neurotransmitter systems) are all regulated by thyroid hormone (Siesser et al., 2006). Consistent with ADHD being a developmental disorder, rats made transiently hyperthyroid as pups (but not as adults) are hyperactive and exhibit elevated striatal dopamine turnover (Rastogi and Singhal, 1976; Siesser et al., 2006). Male transgenic mice expressing a human mutant thyroid receptor (TRβ1, limited to the pituitary by the glycoprotein hormone α-subunit promoter) displayed all of the characteristic symptoms of ADHD: inattention seen as slow reaction times and inaccuracy in an operant task, hyperactivity that was not evident in a novel environment but developed gradually after repeated exposure to the environment, and impulsivity seen as an inability to inhibit a response during the extinction phase of an operant task (when reinforcer was no longer presented), as well as an inability to delay a response in order to obtain a larger reinforcer (Siesser et al., 2006). Striatal dopamine turnover was increased in TRβ1 transgenic mice and, similar to ADHD, their hyperactivity was reduced by methylphenidate (Siesser et al., 2006). Elevated striatal dopamine turnover has been observed in other models of ADHD (DAT knock-out mouse) and is suggestive of DAT dysfunction (Jones et al., 1998; Zhuang et al., 2001; Siesser et al., 2006). As adults, the TRβ1 transgenics had normal thyroid hormone levels. However at 33 days of age when the thyroid system is most active, male TRβ1 transgenic mice had significantly elevated TSH levels compared to wild-type controls (Siesser et al., 2006). It appears that disruption of the normal development of neural circuits in the brain by impaired thyroid hormone feedback control of TSH secretion gives rise to disturbances in, e.g., dopaminergic transmission, as well as the behavioral symptoms that define ADHD.

Nicotinic Receptor

Deletion of the gene encoding the β2-subunit of the nicotinic acetylcholine receptor caused mice to display the defining ADHD symptoms of inattention, lack of inhibitory control, and hyperactivity (Granon and Changeux, 2006). Agonists of the α4β2-nicotinic receptor reduced the ADHD-like behavior in the mouse model (Granon and Changeux, 2006). In support of a role in the cognitive dysfunction in ADHD, nicotinic agonists also reduced spontaneous alternation deficits in young stroke-prone SHR, an effect that was prevented by an α4β2-nicotinic receptor antagonist suggesting that α4β2-nicotinic agonists may be useful for the treatment of attentional deficits in ADHD (Ueno et al., 2002).

Tachykinin-1 (NK1) Receptor

Mice that lack functional substance P-preferring, tachykinin-1 receptors (NK1R), either through drug antagonism or gene ablation, display hyperactivity that is prevented by psychostimulants (D-amphetamine or methylphenidate) (Yan et al., 2009). The NK1R knock-out mice have been shown to have neurotransmitter disturbances similar to SHR in some respects—a deficit in dopaminergic transmission and increased norepinephrine release in the prefrontal cortex, lack of an increase in dopamine efflux in the dorsal striatum following systemic administration of D-amphetamine—and do not develop conditioned place preference for D-amphetamine or morphine (Yan et al., 2009). Inattention and impulsivity were not investigated in these mice. The authors suggest that the NK1R knock-out mice offer a novel model of ADHD and propose that mutations in the *NK1R* gene (tacr1 in humans) may contribute to this disorder and that drugs that activate *NK1R* could offer therapeutic relief.

CHEMICALLY INDUCED MODELS

Ethanol

Rats exposed to ethanol prenatally show attention deficits that are similar to those of children with fetal alcohol syndrome and ADHD (Hausknecht et al., 2005).

Nicotine

Animal studies also showed that prenatal nicotine exposure increased locomotor activity in mice (Paz et al., 2007).

Polychlorinated Biphenyls

Rats exposed to polychlorinated biphenyls (PCBs) around puberty displayed hyperactivity and impulsivity in adulthood, similar to children with ADHD (Berger et al., 2001). Hyperactivity, measured in a multiple FI/EXT schedule, included bursts with short (<0.6 sec) inter-response times characteristic of children with ADHD. The PCB-exposed rats were also sensitive to reinforcement by overreacting to a decrease in reinforcement density (Berger et al., 2001).

6-hydroxydopamine lesion

Neonatal 6-hydroxydopamine (6-OHDA)–lesioned rats have been suggested to be a useful model for ADHD. They display hyperactivity and impaired learning in a spatial discrimination task, which improves after methylphenidate or D-amphetamine treatment, but they are not impulsive (Shaywitz et al., 1978; Luthman et al., 1989; Davids et al., 2002, 2003). Rat pups lesioned on postnatal day 1 displayed hyperactivity in adulthood (Luthman et al., 1989). Similar to children with ADHD, they showed an initial decrease in spontaneous motor behavior when placed in a novel environment, but after repeated testing their activity was increased relative to controls (Luthman et al., 1989). Hyperactivity was accompanied by decreased dopamine in striatum, prefrontal cortex, septum, midbrain, and amygdala (Luthman et al., 1989). Serotonin and serotonin transporter binding was increased in striatum but not cerebral cortex (Luthman et al., 1989; Zhang et al., 2002b). Hyperactivity was not altered by DAT inhibitors, but was greatly reduced by DRD4 antagonists as well as inhibitors of norepinephrine and serotonin transporters (Zhang et al., 2001; Davids et al., 2002, 2003; Zhang et al., 2002a). These findings suggest that psychostimulants reduce hyperactivity of 6-OHDA lesioned rats by inhibiting norepinephrine and serotonin transporters. In addition to reducing norepinephrine uptake, inhibition of the norepinephrine transporter would reduce dopamine uptake into noradrenergic terminals in several brain areas including prefrontal cortex and nucleus accumbens, and thereby exert effects on both dopaminergic and noradrenergic function in the brain.

ENVIRONMENTALLY INDUCED MODELS

Anoxia

Anoxia increases the risk of ADHD (Lou, 1996). Neonatal anoxia caused a sequence of acute and persistent neurochemical changes in rat monoaminergic systems, as well as transient hyperactivity and spatial memory impairment that persisted into adulthood (Dell'Anna et al., 1993; Iuvone et al., 1996; Dell'Anna, 1999). Acute anoxia caused a transient decrease followed by an increase after 1 week in cerebellar norepinephrine levels (Dell'Anna et al., 1993). Dopamine and serotonin levels decreased, and then metabolite levels increased post ischemia (Dell'Anna et al., 1993). The increase in serotonin and dopamine metabolites persisted into adulthood, suggesting that dopamine turnover is increased. Tyrosine hydroxylase mRNA levels were increased in VTA and substantia nigra of perinatally asphyxiated rats, suggesting increased dopamine synthesis consistent with increased turnover. DRD1 and DRD2 mRNA levels were increased in the striatum suggesting reduced release of dopamine (Gross et al., 2000). These findings demonstrate the complex temporal sequence of compensatory changes that occur in monoaminergic systems following perinatal insult to the nervous system and implicate all three monoaminergic systems in spatial memory impairment.

Social Isolation

Rat pups reared in social isolation display a variety of behavioral changes, including hyperactivity, anxiety, impulsivity, aggression, and learning and memory deficits (Dalley et al., 2002; Koike et al., 2009). However, these rats are not impaired in measures of task acquisition in the 5-CSRT test of sustained attention. In addition, children reared in social isolation have additional disturbances and would not be diagnosed as ADHD.

NONHUMAN PRIMATES

Consistent with the hypothesis that ADHD symptoms result from impaired dopamine transmission, monkeys exposed to low

doses of the dopamine neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed attentional deficits in the absence of gross motor dysfunction (Roeltgen and Schneider, 1991, 1994). The caudate-frontal dysfunction was suggested to be consistent with the cognitive difficulties that exist in children with the inattentive subtype of ADHD and with the distribution of decreased cerebral blood flow found in children with ADHD. Monkeys given chronic low-dose MPTP displayed abnormalities in dopamine and norepinephrine metabolism (Roeltgen and Schneider, 1991). Monkeys developed deficits in maintenance of a response set as well problems in shifting attentional sets, inattentiveness, impaired ability to sustain spatial attention or to focus attention, a deficit in motor readiness and planning, and impaired time estimation (Decamp and Schneider, 2004). An attentional cue presented prior to the stimulus significantly improved performance of a modified variable delayed response task, suggesting that procedures that enhance attention may be useful in ameliorating some of the "memory" deficits associated with diminished dopamine function (Decamp et al., 2004). Monkeys classified as poor learners in delayed response tasks, which improve after treatment with methylphenidate (Schneider et al., 1994), had similar deficits in task persistence (i.e., errors of omission) as did MPTP-exposed monkeys, supporting the dopamine hypofunction hypothesis and suggesting that nonhuman primates selected for poor performance in attentional tasks may serve as a useful model for ADHD (Roeltgen and Schneider, 1994). Perhaps nonhuman primates could be selected using a multichoice serial reaction-time task similar to the 5-CSRT test used to identify rats that perform poorly in cognitive tasks, so that comparisons can be made across the different models of ADHD.

HOW HAVE ANIMAL MODELS CONTRIBUTED TO A BETTER UNDERSTANDING OF ADHD?

Initially the focus was on dopaminergic systems mainly because the drugs used to treat ADHD were psychostimulants, then animal studies revealed disturbances in the noradrenergic system which agreed with the fact that some patients with ADHD were being successfully treated with noradrenergic drugs such as desipramine and α_2-adrenoceptor agonists. However, the major insight provided by animal studies was the revelation that changes observed in the dopaminergic and noradrenergic systems were not necessarily the primary defect, but perhaps part of a compensatory mechanism. Methylphenidate and other drugs used to treat ADHD appear to function by enhancing the phasic dopamine signal and/or altering the tonic noradrenergic signal (to increase the level of arousal), in an attempt to compensate for a more generalized defect in neural transmission involving glutamate and/or GABA synapses. Some of the evidence will be reviewed below.

Results show that there are several different ways in which neural transmission can be impaired in animal models of ADHD; this involves either direct disruption of dopaminergic transmission, thereby impairing modulation of glutamate/GABA circuits, or a more general impairment of neurotransmission, such as altered calcium signaling and glutamate receptor function in SHR or SNAP-25 in coloboma mutant mice, which gives rise to compensatory changes in monoaminergic systems that are not sufficient to meet demands. The details of these models have been extensively reviewed by Russell et al. (2005). In general, results obtained with animal studies suggest that dopamine neurons are functionally impaired (Russell et al., 2005; Russell, 2007). However, evidence also suggests that the noradrenergic systems are disturbed in SHR and both noradrenergic and serotonergic neurotransmitter systems may be the target of drugs that ameliorate ADHD symptoms (Russell et al., 2005; Russell, 2007). Reduction of norepinephrine with DSP-4 restored latent inhibition and reduced the hyperactivity of coloboma mice but did not reduce their impulsivity (Bruno et al., 2007).

Since stimulant drugs inhibit both DAT and the norepinephrine transporter, they have been suggested to act by increasing endogenous stimulation of α_{2A}-adrenoceptors and DRD1 receptors in the prefrontal cortex, optimizing prefrontal cortical regulation of behavior and attention (Arnsten, 2006). Electrophysiological studies in nonhuman primates suggest that norepinephrine enhances "signals" by suppressing "noise" through postsynaptic α_{2A}-adrenoceptors in the prefrontal cortex, while dopamine decreases "noise" through DRD1 activation (Arnsten, 2006). Blockade of α_2-adrenoceptors in the monkey prefrontal cortex produced the characteristic symptoms of ADHD, impaired working memory, increased impulsivity, and increased locomotor activity. Low doses of methylphenidate increased extracellular levels of both norepinephrine

and dopamine in prefrontal cortex of rats performing a delayed alternation task, strengthening prefrontal cortex regulatory output to parietal association areas, thereby inhibiting responses to irrelevant sensory stimuli and improving cognitive function (Arnsten and Dudley, 2005). Guanfacine, an α_2-adrenoceptor agonist, improved sustained attention and reduced both impulsivity and hyperactivity in SHR (Sagvolden, 2006). MRI revealed a negative blood oxygenation level dependent (BOLD) response to guanfacine in the caudate-putamen and nucleus accumbens, and positive BOLD effects in frontal cortex of the rat brain, suggesting that guanfacine increases neuronal activity in the frontal cortex while decreasing striatal activity (Easton et al., 2006). This is consistent with activation of α_2-adrenoceptors causing inhibition of dopamine and norepinephrine release in these brain areas, as well as guanfacine acting directly on postsynaptic α_{2A}-adrenoceptors in the prefrontal cortex to enhance cognitive function (Nurse et al., 1984; Arnsten, 1998; Russell et al., 2000).

There appears to be an imbalance between dopaminergic and noradrenergic neurotransmission in the prefrontal cortex of SHR (Russell, 2002). While dopamine release is decreased in SHR prefrontal cortex, norepinephrine concentrations are elevated. This may be an attempt to increase tonic norepinephrine levels to increase arousal in an attempt to address the drive for novelty proposed by Williams et al. (2009a). The noradrenergic system appears to be poorly regulated because of impaired α_2-autoreceptor function (Russell et al., 2000; Russell, 2002). Decreased α_2-autoreceptor-mediated inhibition of norepinephrine release may increase tonic norepinephrine levels, which may be particularly disruptive to the function of target structures when the firing rate of locus coeruleus neurons is high, causing excessive spillover of norepinephrine into the extracellular space and activation of α_1-adrenoceptors in the prefrontal cortex, impairing its function (Arnsten, 1998). Other noradrenergic terminal areas in the central nervous system may be similarly affected (Howells and Russell, 2008).

A fundamental defect in SHR appears to be a disturbance in calcium metabolism not only in brain but also in other tissues including vascular smooth muscle (Oshima et al., 1991; Horn et al., 1995; Ohno et al., 1996, 1997; Lehohla et al., 2001; Fellner and Arendshorst, 2002; Tabet et al., 2004). Increased intracellular calcium concentrations have been attributed to genetic abnormalities in Ca^{2+}ATPase (Horn et al., 1995; Ohno et al., 1996; Ohno et al., 2005) but may also be the result of altered NMDA receptor function (Russell, 2001; Lehohla et al., 2001, 2004). Increased intracellular calcium levels can have several consequences: (i) reduced calcium influx into neurons in response to depolarization, due to a decreased calcium gradient across the cell membrane, would decrease neurotransmitter release; (ii) impaired calcium signaling [e.g., decreased NMDA-stimulated calcium influx into postsynaptic cells (Lehohla et al., 2001)] with subsequent derangement of calcium-dependent protein kinase and phosphatase activity [e.g., protein kinase C activity is increased in SHR (Tsuda et al., 2003)]; and (iii) impaired mitochondrial function, giving rise to increased levels of reactive oxygen species, such as the superoxide anion and hydrogen peroxide (Chan et al., 2006) and impaired ATP synthesis (Doroshchuk et al., 2004).

Attempts to compensate for impaired calcium signaling due to reduced endoplasmic reticulum Ca^{2+}ATPase function include enhanced calcium entry through L-type calcium channels and store-operated channels in vascular smooth muscle cells in SHR (Fellner and Arendshorst, 2002; Tabet et al., 2004). Impaired vascular smooth muscle contraction could influence blood flow and impair brain function at times of high energy demand.

A1 adenosine receptors inhibit neurotransmitter release. Blockade of A1 or A2A adenosine receptors were found to be as effective as methylphenidate in attenuating the discriminative learning impairments of SHR in an object-recognition task, suggesting that adenosine receptor antagonists may be potentially interesting drugs for the treatment of ADHD (Pires et al., 2009).

There is considerable evidence to suggest that NMDA receptor function is altered in SHR, perhaps due to the abovementioned disturbance in calcium homeostasis but also due to other pre- and postsynaptic factors (SNAP-25, Homer, dopamine DRD1 regulation of translocation, etc). Jensen et al. (2009) showed that synaptic transmission between hippocampal CA3 and CA1 neurons was reduced in SHR compared to WKY controls [reduced field excitatory postsynaptic potential (EPSP) in response to stimulation], whereas short-term forms of synaptic plasticity, like paired-pulse facilitation, frequency facilitation, and delayed response enhancement were comparable in the two genotypes, and long-term

potentiation (LTP) of synaptic transmission was of similar magnitude (Jensen et al., 2009). A very interesting observation was the fact that LTP in SHR was reduced by 50%, by blockade of the NR2B subunit of the NMDA receptor, while LTP in control WKY rats was not affected (Jensen et al., 2009). This indicates that the SHR may have a functional predominance of NR2B, a feature characteristic of early developmental stages in these synapses (Jensen et al., 2009). Interestingly, environmental enrichment promotes LTP induction as a result of NR2B activation of p38, a MAP kinase associated with LTD that does not normally contribute to LTP in mice housed conventionally (Li et al., 2006). These results indicate that functional impairment of glutamatergic synaptic transmission may be one of the underlying mechanisms leading to the abnormal behavior in SHR, and possibly in human ADHD (Jensen et al., 2009). Other potential factors that may affect NMDA receptor function include Homer proteins, scaffolding proteins localized at the postsynaptic density of excitatory glutamatergic synapses (Hong et al., 2009). Homer 1a and Homer 2a/b were expressed at significantly lower levels in the prefrontal cortex of SHR compared to WKY. Methylphenidate decreased the locomotor activity and nonselective attention of SHR, and up-regulated the expression of Homer 1a and Homer 2a/b in the prefrontal cortex of SHR. Homer 1a and Homer 2a/b are major signal transduction regulatory proteins in postsynaptic membranes and may play an important role in the pathogenesis of ADHD (Hong et al., 2009).

CONCLUSION

The various animal models of ADHD provide unique insights into ADHD neurobiology. They also emphasize the close interconnection between serotonergic, noradrenergic, and dopaminergic systems. Changes in any one system can alter the function of the other monoaminergic systems and alter the underlying neural circuits that control behavior. All of the animal models of ADHD result from disturbances of neural function (e.g., transient hyperthyroidism, deficient SNAP-25, impaired Ca^{2+} signaling, or disruption of the dopaminergic system) that occur during the early stages of development and give rise to compensatory changes in the monoaminergic systems.

There is convincing evidence to suggest that the activity of dopamine neurons is decreased, giving rise to decreased stimulus-evoked release of dopamine in several animal models including transgenic mice expressing mutant thyroid hormone receptor, the coloboma mutant mouse, 6-OHDA lesioned rat, *DAT* knock-out mouse (although increased extracellular dopamine may also contribute to its behavior), poor performers in the 5-CSRT task, and SHR. Evidence obtained from some animal models of ADHD suggest that the noradrenergic and serotonergic neurotransmitter systems may be the target of drugs that ameliorate ADHD symptoms.

One consequence of decreased stimulus-evoked release of dopamine would be decreased dopamine activation of DRD1 receptors on postsynaptic membranes and impaired reward-related learning of associations between predictive cues and behavioral consequences, which could explain many of the symptoms of ADHD (Sagvolden et al., 2005a). Sustained attention is also controlled by noradrenergic projections from the locus coeruleus to association areas of the parietal and prefrontal cortex. There is considerable evidence to suggest that the noradrenergic system is poorly controlled by α_2-autoreceptors in SHR, particularly at high norepinephrine release rates. This may be seen as hyperactivity of the noradrenergic system, especially when locus coeruleus neurons are stimulated in states of increased arousal. Impaired regulation of norepinephrine release in the prefrontal cortex could give rise to ADHD-like symptoms. More importantly, the balance between hypodopaminergic and hypernoradrenergic control of prefrontal cortex function appears to be a critical factor in determining ADHD symptomatology.

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