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Invited review

Neurobiology of animal models of attention-deficit hyperactivity disorder

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous, highly heritable, disorder resulting from complex gene–gene and gene–environment interactions. The defining symptoms of hyperactivity, impulsivity and impaired sustained attention are not unique to ADHD. It is therefore not surprising that animals with distinctly different neural defects model the behavioural characteristics of the disorder. Consistent with ADHD being a developmental disorder, animal models are either genetic (spontaneously hypertensive rats (SHR), dopamine transporter (DAT) knock-out mice, SNAP-25 mutant mice, mice expressing a mutant thyroid receptor) or have suffered an insult to the central nervous system during the early stages of development (anoxia, 6-hydroxydopamine). It appears that neural transmission is impaired by either direct disruption of dopaminergic transmission or a more general impairment of neurotransmission that gives rise to compensatory changes in monoaminergic systems that are not sufficient to completely normalize neural function. In general, results obtained with animal studies suggest that dopamine neurons are functionally impaired. However, evidence obtained from some animal models suggests that the noradrenergic and serotonergic neurotransmitter systems may be the target of drugs that ameliorate ADHD symptoms.

Keywords: Norepinephrine; Dopamine; Attention; Hyperactivity; SHR; Thyroid hormone

Contents

1. Attention-deficit/hyperactivity disorder

Development of the human brain follows a precise genetically determined programme that is subject to modification by the environment (Toga et al., 2006). During the first 3–4 years of life, stimulation and experience produce an initial increase

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in dendritic branching and synaptic contacts on neurons (Toga et al., 2006). This is followed by dendritic pruning and synapse elimination which occurs over several years into late adolescence to produce more efficient neural circuits that continue to be remodeled throughout life (Toga et al., 2006). Any disruption of this process can result in impaired brain function. Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous but nevertheless highly heritable disorder resulting from complex gene-gene and gene-environment interactions (Faraone, 2004; Thapar et al., 2005). Meta-analyses suggest that polymorphisms in the genes that encode the D4 and D5 subtypes of the dopamine receptor (DRD4 and DRD5), the dopamine transporter (DAT), SNAP-25 (a protein required for neurotransmitter release as well as transfer of glutamate NMDA receptor subunits to the plasma membrane), and the serotonin transporter, are associated with ADHD (Thapar et al., 2005). Environmental risk factors include prenatal exposure to drugs such as alcohol and nicotine, obstetric complications, head injury, and psychosocial adversity (Biederman and Faraone, 2005; Romano et al., 2006). ADHD is a behavioural disorder characterized by difficulty in sustaining attention, impulsivity and hyperactivity (American Academy of Pediatrics, 2000). It affects 5–10% of children worldwide and persists through adolescence into adulthood in about half of the affected individuals (Faraone et al., 2003).

2. Animal models of ADHD

Diagnosis of ADHD depends on behavioural criteria and so animal models of the disorder should mimic the major symptoms of hyperactivity, impulsivity and impaired sustained attention. Very few animal models have been as extensively studied as the spontaneously hypertensive rat (SHR) and so much of this review will focus on SHR. However, each of the animal models of ADHD provides unique insight into possible gene defects and environmental conditions that might predispose an individual to ADHD, and so these will be considered as well. ADHD itself is a heterogeneous disorder, no two children with ADHD are identical, and so it is not surprising that many different animal models with distinctly different neural defects model the behavioural characteristics of the disorder.

In general, results obtained with animal studies suggest that monoaminergic systems, particularly the dopaminergic systems are functionally altered in ADHD (for review see Russell et al., 2005). Consistent with ADHD being a developmental disorder, animal models are either genetic (e.g. DAT knock-out, SNAP-25 mutant mice) or have suffered an insult to the central nervous system during the early stages of development (e.g. anoxia, 6-hydroxydopamine), whereas exposure to toxins in adulthood does not produce the characteristic ADHD-like behaviour (for review see Russell et al., 2005). It appears that there are several different ways in which neural transmission is impaired in animal models of ADHD which involve either direct disruption of dopaminergic transmission or a more general impairment of neurotransmission, such as impaired calcium signaling in SHR or SNAP-25 in the coloboma mutant mouse, that 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) but there have been interesting new data that provide novel insights that will be reviewed in this paper.

2.1. Transgenic mice expressing mutant 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 behaviour (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-knockout mouse) and is suggestive of DAT dysfunction (Jones et al., 1998; Siesser et al., 2006; Zhuang et al., 2001). 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, amongst others, dopaminergic transmission as well as the behavioural symptoms that define ADHD. This is a novel finding which adds to the increasing number of potential models for ADHD and also shows how general and diverse the possible causes are that can give rise to the ADHD phenotype.

2.2. ADHD symptoms are not unique to ADHD: in utero exposure to alcohol

ADHD symptoms are not unique to ADHD but are found in other disorders such as phenylketonuria (Realmuto et al., 1986;

Sullivan and Chang, 1999) and fetal alcohol syndrome (Nash et al., 2006; Riikonen et al., 2005). Phenylketonuria results from high concentrations of phenylalanine that arise from an inability to convert it into tyrosine, and which inhibit the transport of neutral amino acids such as tyrosine and tryptophan across the blood brain barrier, thereby limiting the synthesis of the three principle monoamine transmitters. Prenatal exposure to ethanol affects mainly dopaminergic transmission and causes hyperactivity (Gibson et al., 2000). 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). Prenatal ethanol exposure produced a persistent reduction in the number of spontaneously active dopamine neurons in the ventral tegmental area of the midbrain (VTA). Acute *d*-amphetamine treatment normalized the activity of dopamine neurons after prenatal ethanol exposure, it increased the number of spontaneously active VTA neurons and reduced their firing rate (Xu and Shen, 2001). Similarly, repeated methylphenidate treatment normalized VTA dopamine neuron activity in rats exposed to ethanol prenatally whereas repeated methylphenidate treatment of control rats increased the excitability of VTA dopamine neurons causing a transient increase in activity followed by a decrease in spontaneous activity lasting more than 30 days (Shen and Choong, 2006). These results suggest that dopamine transmission is impaired in rats exposed to ethanol prenatally, similar to animal models of ADHD.

2.3. *In utero exposure to nicotine*

Epidemiological evidence reveals that ADHD is associated with prenatal exposure to nicotine (Mick et al., 2002; Milberger et al., 1998; Thapar et al., 2003). Prenatal nicotine increased spontaneous locomotion in mice (Paz et al., 2006). 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 behaviour in the mouse model (Granon and Changeux, 2006). 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., 2002a).

2.4. *Anoxia in neonatal rat*

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, 1999; Dell'Anna et al., 1993; Iuvone et al., 1996). 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 ischaemia (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. Dopamine D1 receptor (DRD1) and D2 receptor (DRD2) mRNA levels were increased in the striatum suggesting altered 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.

2.5. *Coloboma mutant mouse*

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 impulsivity and impaired inhibition in a delayed reinforcement task (Bruno et al., 2006) as well as spontaneous hyperactivity that 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 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 (Jones et al., 2001a; Raber et al., 1997) suggesting that the coloboma mouse has a hypofunctional dopaminergic system, similar to SHR (Russell et al., 2005). 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 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, restored latent inhibition but did not ameliorate impulsivity of the coloboma mice (Bruno et al., 2006; Jones and Hess, 2003). 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 noradren-

ergic system but 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).

2.6. 6-OHDA-lesioned rat

Neonatal 6-OHDA-lesioned rats have also 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 (Davids et al., 2002, 2003; Luthman et al., 1989; Shaywitz et al., 1978). Rat pups lesioned on postnatal day 1 displayed hyperactivity in adulthood (Luthman et al., 1989). They showed an initial decrease in spontaneous motor behaviour 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 straitum, 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 (Davids et al., 2002, 2003; Zhang et al., 2001, 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.

2.7. DAT-knock-out mouse

DAT-knock-out (DAT-KO) mice have been suggested to model ADHD because they are hyperactive (Gainetdinov and Caron, 2000, 2001; Trinh et al., 2003), demonstrate impaired extinction of responses in operant food reinforcement tasks (Hironaka et al., 2004) and impaired learning and memory (Gainetdinov and Caron, 2001; Trinh et al., 2003). Impulsivity has not been systematically investigated in DAT-KO mice. The absence of DAT in the DAT-KO mouse provides an extreme model of reduced midbrain DAT binding in adolescents with ADHD (Jucaite et al., 2005) and contrasts with several studies that found increased DAT in the striatum of children and adults with ADHD (Cheon et al., 2003; Dougherty et al., 1999; Krause et al., 2000). The DAT-KO mouse nevertheless provides useful information concerning the neurobiological consequences of impaired DAT function.

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

Inhibitors of the serotonin transporter as well as drugs that activate the serotonergic system dramatically reduced the hyperactivity of DAT-KO mice whereas specific inhibitors of the norepinephrine transporter or DAT were ineffective (Gainetdinov and Caron, 2001). Results obtained with DAT-KO mice suggest that hyperactivity induced by high extracellular levels of dopamine can be reduced by enhancing serotonergic tone (Gainetdinov and Caron, 2001). Antagonists of the 5-HT_{2A} receptor reversed the behavioural deficits of DAT-KO mice (Barr et al., 2004). Polymorphisms of the 5-HT_{2A} receptor gene have been associated with ADHD (Levitan et al., 2002; Quist et al., 2000) suggesting that specific antagonists of the 5-HT_{2A} receptor may be useful in the treatment of ADHD. However, the relevance of this finding to ADHD is questionable since serotonin reuptake inhibitors are not effective in treating ADHD and serotonin uptake inhibitors increase motor activity (Biederman et al., 2004; Gainetdinov and Caron, 2001).

The DAT-KO mouse has been criticized as a model for ADHD because DAT-knockdown mice (expressing 10% of wild-type DAT) displayed excessive sequential stereotypy reflected as a complex serial pattern of grooming actions becoming more sequentially rigid and persistent (Berridge et al., 2005; Russell et al., 2005). This type of behaviour is not characteristic of ADHD but may serve as a model for Tourette's syndrome and obsessive compulsive disorder (Berridge et al., 2005). DAT-knockdown mice tended to be hyperactive, to walk in perseverative straight paths, and to over-pursue certain incentive stimuli, consistent with obsessive compulsive disorder (Berridge et al., 2005).

2.8. Selection of poor performers in the 5-CSRT test

Rats that are selected for poor performance in a 5-choice serial reaction time (5-CSRT) test provide a useful model of the inattentive subtype of ADHD in that they are selected for deficient sustained attention, they show poor choice accuracy towards the end of testing sessions, they demonstrate impulsiveness (premature responding) and they are not hyperactive (Barbelivien et al., 2001; Puumala et al., 1996). Han:Wistar rats were food-deprived for 16 h 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). Responses recorded during the intertrial interval were considered premature and provided a measure of impulsivity. Methylphenidate treatment improved accuracy and reduced impulsiveness (at low doses) in poor performers (Puumala et al., 1996). Activation of 5-HT_{2A} receptors increased the number of premature responses in normal animals (Koskinen et al., 2000) which suggests that 5-HT_{2A} receptor antagonists may be useful in treating symptoms of ADHD and is consistent with 5-HT_{2A} receptor antagonists reducing ADHD-like behaviour in DAT-KO mice (Barr et al., 2004).

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 at which correct responses were made (Granon et al., 2000). These results suggest that dopamine function is reduced in poor performers of the 5-CRST task and that 5-HT_{2A} antagonists may be beneficial in the treatment of ADHD. This finding once again 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.

2.9. SHR

The SHR exhibits all of the behavioural characteristics of ADHD when compared to its normotensive Wistar–Kyoto (WKY) control rat. Inattention is seen as increased percentage of errors in operant tasks, hyperactivity that is not present in novel, non-threatening situations, develops over time when reinforcers are infrequent (Sagvolden, 2000; Sagvolden et al., 2005a,b; Wiersema et al., 2005). Impulsivity also develops over time and is seen 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 (Bull et al., 2000; Sagvolden, 2000; van den Bergh et al., 2006). However, both SHR and WKY have been criticized (Bull et al., 2000; van den Bergh et al., 2006). The WKY rat does not perform as well as other rat strains in certain behavioural tasks and is often less active than other rat strains (Bull et al., 2000; van den Bergh et al., 2006). The results of behavioural studies are unfortunately inconsistent and depend on the demands of the task. Sagvolden et al. (2005a,b) showed that SHR learn as quickly as WKY 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 behavioural 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., 2005a,b). Similar results were obtained by Hand and coworkers (Hand et al., 2006) who showed that SHR took longer than WKY to learn a novel response when reinforcement was delayed but not when reinforcer delivery was immediate.

Different levels of arousal can be confounding factors in behavioural 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, they also failed to show improvement in a win-shift version of the water radial arm maze compared to WKY and Sprague–Dawley controls (Clements and Wainwright, 2006; Hernandez et al., 2003; Nakamura-Palacios et al., 1996; Prediger et al., 2005; Wyss et al., 1992). 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, 2001; Russell and Wiggins, 2000; Russell et al., 2000a,b). 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, 2001; Russell and Wiggins, 2000; Russell et al., 2000a,b; Howells and Russell, unpublished). 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 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-CSRT task (van den Bergh et al., 2006) which argues against the suggestion that poor performers of the 5-CSRT task may serve as a potential rodent model for the inattentive subtype of ADHD (Barbelivien et al., 2001; Puumala et al., 1996; Russell et al., 2005). SHR were also criticized for lack of response to methylphenidate in several behavioural 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 behaviour if one considers the complexity of human behaviour 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 behaviour 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 appropriate behaviour.

SHR is a genetic model of ADHD bred from progenitor Wistar–Kyoto rats (Okamoto and Aoki, 1963). A 160 bp insertion was found in the non-coding region upstream of exon 3 of the DAT gene of SHR (Mill et al., 2005) which is of significance since variable number tandem repeats in the 3′-untranslated region of the DAT gene has been associated with ADHD in several family studies (Bobb et al., 2005; Cook et al., 1995; Dougherty et al., 1999; Kirley et al., 2003; Krause et al., 2000). 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 SHR midbrain during the first postnatal month and increased in adult SHR compared to controls (Leo et al., 2003; Watanabe et al., 1997). 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).

In addition to the hypothesis that dopaminergic systems are hypofunctional in ADHD, noradrenergic neurons have been suggested to be poorly regulated and hyperfunctional in the prefrontal cortex of children with ADHD (Arnsten, 1998; Russell, 2002; Solanto, 1998). Normally, noradrenergic neurons enhance the signal-to-noise ratio in prefrontal and parietal cortices, amplify responses to attended stimuli, and reduce responses to irrelevant stimuli (Aston-Jones et al., 1994; Himelstein et al., 2000). These functions are defective in ADHD (Himelstein et al., 2000).

The locus coeruleus noradrenergic neurons innervate the entire cerebral cortex, various subcortical areas, cerebellum and spinal cord. They play an important role in attention, arousal, orienting, and vigilance (Solanto, 1998). Locus coeruleus neurons respond selectively to attended (target) stimuli, tonic locus coeruleus activity corresponds to arousal state, and both very low and very high locus coeruleus activity are associated with impaired vigilance (Arnsten, 1998; Aston-Jones et al., 1994). Noradrenergic neurons that project from the locus coeruleus to the prefrontal cortex release norepinephrine which guides behaviour by modulating the transfer of information through neuronal circuits that are responsible for selective and sustained attention (Solanto, 1998). Methylphenidate increases norepinephrine release and suppresses long-latency sensory responses in the primary somatosensory cortex of freely behaving rats (Drouin et al., 2006). Methylphenidate may improve sensory attention by increasing norepinephrine release in somatosensory cortex and suppressing "noise" (Drouin et al., 2006). Methylphenidate was suggested to have both direct effects in the somatosensory cortex as well as indirect effects through top–down (prefrontal cortex) influences on primary somatosensory cortex responsivity (Arnsten, 2006).

Disturbances in norepinephrine metabolism in SHR are suggested by the finding that tyrosine hydroxylase gene expression is higher in the ventrolateral medulla oblongata of SHR than WKY (Reja et al., 2002a), consistent with elevated norepinephrine concentration in several brain areas of SHR including locus coeruleus, substantia nigra and prefrontal cortex (de Villiers et al., 1995). Increased norepinephrine concentrations in SHR brain is consistent with downregulation of β-adrenoceptors in cerebral cortex of SHR (Myers et al., 1981).

Evidence suggests that there is 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. The noradrenergic system appears to be hyperactive as a result of impaired α_2-autoreceptor regulation (Russell, 2002).

Stimulus-evoked (electrically stimulated or K^+-evoked) release of norepinephrine from prefrontal cortex slices of SHR was no different from that of WKY (Russell et al., 2000a,b). However, α_{2A}-adrenoceptor mRNA levels were decreased in SHR compared to WKY and α_2-autoreceptor-mediated inhibition of norepinephrine release was less efficient in SHR than in WKY suggesting that α_2-adrenoceptor function is impaired (Reja et al., 2002b; Russell et al., 2000a,b; Tsuda et al., 1990). α_{2A}-Adrenoceptors are the subtype specifically expressed in the prefrontal cortex, so impaired α_{2A}-adrenoceptor function would be expected to impair cognition (Arnsten, 1998; Franowicz et al., 2002).

Decreased α_2-autoreceptor-mediated regulation of norepinephrine neurons and impaired inhibition of norepinephrine release 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. Repeatedly increased release of norepinephrine from sympathetic nerve terminals could give rise to stress-dependent development of hypertension in SHR (Printz et al., 2003). Expression of the gene encoding $G_{i\alpha}$ (the G-protein subunit that inhibits cAMP formation from ATP by adenylyl cyclise) is increased in SHR aorta at 2 weeks of age, possibly reflecting an attempt by a target organ to decrease the effect of increased norepinephrine release from sympathetic nerve endings. Poorly controlled norepinephrine release could also give rise to excessive activation of α_1-adrenoceptors in the prefrontal cortex, impairing its function. Other noradrenergic terminal areas in the central nervous system may be similarly affected. These findings suggest that the noradrenergic system is hyperactive in SHR, par-

ticularly in response to stress, and supports the hypothesis that there is an imbalance between norepinephrine hyperfunction and dopamine hypofunction in ADHD.

The underlying defect in SHR appears to be a disturbance in calcium metabolism not only in brain but also in other tissues including vascular smooth muscle (Fellner and Arendshorst, 2002; Horn et al., 1995; Lehohla et al., 2001; Ohno et al., 1996, 1997; Oshima et al., 1991; 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, 2005).

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). One possible consequence of the elevated intracellular calcium concentration is that calcium-dependent potassium channels are constitutively open in SHR, causing the cell membrane to be hyperpolarized and therefore refractory to α_2-adrenoceptor-mediated inhibition (Fauaz et al., 2003). A neuron will only fire if the cell membrane is sufficiently depolarized to reach threshold for generation of an action potential at the axon hillock. If the membrane is hyperpolarized it will require greater excitatory input to reach the threshold for firing. Similarly, hyperpolarization of the axon terminal will cause less neurotransmitter to be released because the membrane potential will be more negative and hence the duration of opening of voltage-gated calcium channels will be reduced. If the membrane is hyperpolarized then α_2-adrenoceptor activation is less likely to have an effect on the membrane (because its inhibitory action depends on hyperpolarization of the membrane) which could explain impaired α_2-autoreceptor-mediated feedback inhibition of norepinephrine release observed in prefrontal cortex and brain stem of SHR (Russell et al., 2000a,b; Tsuda et al., 1990).

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. A summary of the most important findings with SHR is presented in Table 1.

Recently, the ADHD symptom of increased intra-individual variability during performance of high energy demanding cognitive tasks, was attributed to insufficient energy (lactate) supply by astrocytes to neurons at times of rapid and/or continuous firing (Russell et al., 2006). This ubiquitous finding is not unique to ADHD but occurs in several disorders and may be attributed to inefficient information processing. Energy supply is a limiting factor in brain function (Attwell and Gibb, 2005). Inefficient neural transmission due to impaired learning in ADHD would place abnormally high demands on local energy resources and lead to intra-individual variability in responses to externally paced cognitive tasks. This aspect has not been tested in animal models of ADHD, however, consistent with impaired energy production, the synthesis rate of ATP is much lower in mitochondria of SHR brains than WKY (Doroshchuk et al., 2004). Impaired mitochondrial function was attributed to calcium overload, as a result of Ca^{2+}ATPase not being able to pump Ca^{2+} efficiently into the endoplasmic reticulum and across the cell membrane into the extracellular space. Deficient endoplasmic reticular stores of Ca^{2+} would also impair the function of neurotransmitters acting on receptors that stimulate inositol triphosphate (IP_3) formation and release of calcium from intracellular stores [e.g. α_1-adrenoceptors and metabotropic glutamate receptors that regulate astrocyte function, Biber et al., 1999; Glowinski et al., 1994]. Astrocytes provide lactate as a source of energy to rapidly and/or continuously firing neurons. Increased intra-individual variability in performance of tasks that require continual responses to rapid, externally-paced stimuli observed in subjects with ADHD as well as SHR has been attributed to inability of astrocytes to provide sufficient lactate at times of high energy demand (Russell et al., 2006).

2.10. Non-human 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 cortex 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 non-human primates selected for poor performance in attentional tasks may serve as a useful model for

Table 1
Summary of most important findings with SHR

Reference	Test	Differences between SHR and control rats
Knardahl and Sagvolden (1979)	Open-field exploration	SHR gradually became more active than WKY
Myers et al. (1981)	Uptake and receptor binding studies	SHR have greater rates of norepinephrine uptake, decreased dopamine uptake and decreased β-adrenergic receptor density in the frontal cortex compared to WKY
Linthorst et al. (1990)	*In vitro* superfusion	Decreased electrically stimulated release of [^{3}H]dopamine from SHR caudate slices compared to WKY. Nomifensine did not influence the difference in release between the two strains
Tsuda et al. (1990)	*In vitro* superfusion	Inhibitory effect of α_2-adrenoceptor agonist on [^{3}H]norepinephrine release from SHR medulla oblongata significantly less than WKY
Linthorst et al. (1991)	Trans-striatal brain dialysis	Extracellular striatal dopamine concentration lower in SHR than WKY. DRD2 inhibition of dopamine release was greater in SHR than WKY
Sagvolden et al. (1992a,b)	Open-field, multiple fixed-interval extinction schedules of reinforcement	SHR were more active than WKY in the open field. SHR emitted more lever presses during the extinction component of the schedule than WKY. SHR became more active towards the end of the session
Wultz and Sagvolden (1992)	Differentially reinforced immobility	SHR received more reinforcers than WKY as long as the schedule did not require long periods of immobility. The total number of movements on target of SHR increased as the schedule requirements increased
Sagvolden et al. (1992a,b)	Multiple fixed-interval extinction schedules of reinforcement	Psychomotor stimulants weakened control by immediate reinforcers and strengthened control by delayed reinforcers
Wyss et al. (1992)	8-Arm radial maze	SHR took longer than Sprague–Dawley rats to learn a spatial memory task and made nearly twice as many errors at 12 months of age. Three-month-old SHR learned the task faster and with fewer errors than other rat strains
Mook et al. (1993)	12-Arm radial maze	SHR varied their choices, making fewer repetition errors than WKY
Sagvolden et al. (1993)	Multiple schedules of reinforcement with a 2 min fixed interval and a 5 min extinction period	SHR were more active than WKY in free exploration and forced exploration open field tests. SHR were not overactive initially but activity increased towards the end of the extinction period in a two-component multiple reinforcement schedule
Kirouac and Ganguly (1993)	DRD1 and DRD2 receptor autoradiography	Increased SHR striatal DRD1 density at 5 and 15 weeks of age, increased DRD2 density at 5 weeks of age
Linthorst et al. (1994)	High performance liquid chromatography (HPLC)	Homovanillic acid (HVA) and the ratios of DOPAC/dopamine and HVA/dopamine were lower in SHR than in WKY
De Jong et al. (1995)	*In vitro* and *in vivo* release of dopamine	No difference between SHR and WKY in blood pressure at 4 weeks of age. Decreased release of [^{3}H]dopamine from caudate slices of 4-week-old SHR compared to WKY. Decreased extracellular concentration of dopamine in caudate of 8-week-old SHR
Russell et al. (1995)	*In vitro* superfusion	Electrically stimulated [^{3}H]dopamine release was lower in caudate-putamen and prefrontal cortex slices of SHR compared to WKY. DRD2 agonist caused greater inhibition of [^{3}H]dopamine release from SHR caudate-putamen slices. DRD2 antagonist caused greater increase in [^{3}H]dopamine release in SHR nucleus accumbens slices
de Villiers et al. (1995)	High performance liquid chromatography (HPLC)	Decreased homovanillic acid, decreased homovanillic acid/dopamine ratio, and increased norepinephrine in brainstem and prefrontal cortex of SHR
Horn et al. (1995)	$^{45}Ca^{2+}$ uptake into plasma membrane vesicles	Diminished $^{45}Ca^{2+}$ uptake into synaptic plasma membrane vesicles prepared from cerebrum of SHR compared to WKY
Papa et al. (1996)	Immunocytochemistry	Reduced Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) in nucleus accumbens shell of SHR compared to WKY
Nakamura-Palacios et al. (1996)	8-Arm radial maze	SHR made more errors than Wistar rats during execution of a working memory task which was more pronounced after a delay of 1 h than after a 5 s delay
Watanabe et al. (1997)	DAT, DRD1 and DRD2 autoradiography	Increased DAT in SHR caudate-putamen at 2 and 15 weeks and increased DRD1 density at 15 weeks compared to WKY
Marcil et al. (1997)	$G_{i\alpha}$ expression	Increased expression of G_i-protein in SHR heart at 2 weeks and older, compared to WKY
Papa et al. (1997)	Immunohistochemistry	Decreased c-fos and zif/268 in nucleus accumbens core and shell of SHR compared to WKY
Russell et al. (1998)	*In vitro* superfusion	Methylphenidate released less [^{3}H]dopamine in nucleus accumbens slices of SHR than WKY. *d*-Amphetamine released more [^{3}H]dopamine from SHR caudate-putamen, nucleus accumbens and prefrontal cortex slices. Methylphenidate-induced increase in electrically stimulated [^{3}H]dopamine release in caudate-putamen, nucleus accumbens and prefrontal cortex slices of SHR was not different from WKY
Berger and Sagvolden (1998)	Multiple 2 min fixed interval, 5 min extinction schedule of water reinforcement	SHR were more active and displayed extinction deficit towards the end of the extinction component of an operant discrimination task compared to WKY

Table 1 (*Continued*)

Reference	Test	Differences between SHR and control rats
Carey et al. (1998)	DRD1 and DRD2 receptor autoradiography	SHR have a higher DRD1 density than WKY in caudate-putamen, nucleus accumbens and olfactory tubercle which was reversed by methylphenidate treatment (3 mg/kg i.p., for 2 weeks). Methylphenidate also down-regulated DRD2 in these brain areas
Russell et al. (2000a,b)	*In vitro* superfusion	Depolarization evoked by electrical stimulation or exposure to high K^+ released similar [^{3}H]norepinephrine from SHR and WKY prefrontal cortex. α_2-Adrenoceptor-mediated inhibition of [^{3}H]norepinephrine release was decreased in SHR prefrontal cortex compared to WKY
Russell and Wiggins (2000)	*In vitro* superfusion	Increased glutamate-stimulated release of [^{3}H]norepinephrine from SHR prefrontal cortex slices compared to WKY
Russell et al. (2000a,b)	*In vitro* superfusion	Methylphenidate (3 mg/kg for 2 weeks) did not normalize the decreased electrically stimulated release of [^{3}H]dopamine in SHR caudate-putamen. Methylphenidate increased endogenous dopamine activation of DRD2 in WKY but did not alter DRD2 function in SHR striatum
Sagvolden (2000)	Reanalysis of data	ADHD-like overactivity, motor impulsiveness, and deficient sustained attention in SHR compared to several rat strains
Bull et al. (2000)	Differential reinforcement of low rate responding in an operant task	WKY performed better than SHR and Sprague–Dawley rats when low rates of responding were required but performed poorly compared with the other rat strains in those parts of training that required high response rates
Russell (2001)	*In vitro* superfusion	Increased glutamate-stimulated release of [^{3}H]norepinephrine from SHR prefrontal cortex slices is antagonized by AMPA antagonist, CNQX
Lehohla et al. (2001)	NMDA-stimulated uptake of $^{45}Ca^{2+}$	Decreased *In vitro* $^{45}Ca^{2+}$ uptake into barrel cortex slices of SHR
Fellner and Arendshorst (2002)	Cytosolic Ca^{2+} measured with fura-2 fluorescence	Store-operated calcium entry into vascular smooth muscle cells was greater in SHR than WKY. L-channel calcium entry was greater in SHR
Christiansen et al. (2002)	Blood pressure measurement	SHR and WKY have similar body weight. Mean arterial blood pressure was not different at 2 weeks but increased from 4 to 10 weeks of age
Ueno et al. (2002b)	Open-field exploration	Methylphenidate (0.01–1 mg/kg, i.p.) significantly attenuated locomotor hyperactivity at low doses
Ueno et al. (2002a)	Spontaneous alternation requiring attention and working memory in a Y-maze	Spontaneous alternation was lower and total arm entries higher in juvenile stroke-prone SHR than in WKY. Nicotine (0.1–1 mg/kg, s.c.) dose dependently improved the spontaneous alternation deficit without affecting total arm entries in SHR via activation of $\alpha4\beta2$, but not $\alpha7$, nAChR
Reja et al. (2002b)	Total RNA was reverse-transcribed into cDNA and quantified by real time polymerase chain reaction	α_{2A}-Adrenoceptor mRNA was lower in brainstem and spinal cord of SHR than WKY or Sprague–Dawley rats. Phenylethanolamine-*N*-methyltransferase, noradrenaline transporter, and α_{1A}-adrenoceptor mRNA levels were positively correlated and α_{2A}-adrenoceptor mRNA levels were negatively correlated with systolic blood pressure
Reja et al. (2002a)	Total RNA was reverse-transcribed into cDNA and quantified by real time polymerase chain reaction	Increased tyrosine hydroxylase gene expression in the rostral and caudal ventrolateral medulla oblongata of the brainstem of SHR compared to WKY. There was a positive relationship between systolic blood pressure and tyrosine hydroxylase gene expression
Leo et al. (2003)	RNA extraction, reverse transcriptase PCR	Tyrosine hydroxylase and DAT gene expression was transiently reduced in the SHR midbrain during the first month of postnatal development compared to WKY. High-affinity dopamine uptake activity was reduced in synaptosomes of the striatum of 1-month-old SHR compared to WKY
Yang et al. (2003)	Automated activity monitoring system, total distance travelled, rearing, stereotypic movements	Repeated administration of 2.5 mg/kg methylphenidate elicited locomotor sensitization in Sprague–Dawley and WKY rats but not in SHR. Repeated administration of 10 mg/kg methylphenidate induced locomotor tolerance in Sprague–Dawley and WKY rats but variable response in SHR
Hernandez et al. (2003)	Radial arm maze	SHR performance in a working memory task was impaired relative to Wistar and WKY rats
Calzavara et al. (2004)	Elevated plus-maze, discriminative avoidance task	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
Ferguson and Cada (2004)	Morris water maze, acoustic startle, elevated plus maze	SHR performed better than WKY and Sprague–Dawley rats in spatial memory tasks. Acoustic startle and prepulse inhibition were less in SHR than WKY or Sprague–Dawley rats. SHR and WKY displayed less anxiety-related behaviour in the elevated plus maze than Sprague–Dawley
Van den Buuse (2004)	Acoustic startle and prepulse inhibition	SHR displayed lower acoustic startle amplitude than WKY and Sprague–Dawley rats, but no difference in startle habituation. Baseline percentage prepulse inhibition was higher in SHR and WKY rats than in Sprague–Dawley rats
Doroshchuk et al. (2004)	ATP synthesis	Mitochondria prepared from SHR brain have 30% decreased ATP synthesis compared to WKY

Table 1 (*Continued*)

Reference	Test	Differences between SHR and control rats
Tabet et al. (2004)	Calcium measurement by fura-2 fluorescence, real-time PCR, immunoblotting	H_2O_2 caused greater increase in intracellular calcium of SHR vascular smooth muscle cells than WKY. L-type and T-type Ca^{2+} channels were expressed (mRNA and protein) in greater abundance in SHR
Sagvolden et al. (2005a,b)	Operant tasks reinforced according to intermittent schedules of reinforcement	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 when the reinforcer was presented within a few seconds after a correct behavioural response. SHR failed to learn a new rule when correct responses were reinforced intermittently after a delay of approximately 3 min
Prediger et al. (2005)	Morris water maze	Adult female SHR displayed impaired acquisition in a spatial memory task compared to Wistar rats. Pre-training administration of caffeine (1–10 mg/kg i.p.) improved SHR spatial learning deficit
Mill et al. (2005)	Gene sequencing	Several differences between SHR and WKY were found in the DAT1 gene, no between-strain sequence differences were found in DRD2 or DRD4
Hand et al. (2006)	Response acquisition with delayed reinforcement	SHR took longer than WKY to learn a novel response when reinforcement was delayed but not when reinforcer delivery was immediate
Clements and Wainwright (2006)	Win-shift version of the water radial arm maze	SHR performance failed to improve over time, the number of incomplete arm entries into reference memory arms decreased over weeks in WKY and Sprague–Dawley rats, but increased in SHR, suggesting increased impulsivity in the later stages of testing
Vendruscolo et al. (2006)	Acoustic startle and prepulse inhibition	SHR rats displayed decreased acoustic startle and prepulse inhibition compared to Lewis rats
van den Bergh et al. (2006)	Open-field, differential reinforcement of low-rate responding, 5-CSRT test	In the open-field, young SHR were hyperactive compared to Wistar and WKY. SHR performed worse than WKY but not Wistar in the differential reinforcement task. SHR performed as well as WKY and Sprague–Dawley rats in the 5-CSRT test. Methylphenidate did not affect SHR behaviour
Chan et al. (2006)	Gene expression, enzyme activity	Reduced mRNA, protein expression (and enzyme activity) of superoxide dismutase, catalase, but not glutathione peroxidase, in rostral ventrolateral medulla of SHR compared to WKY

ADHD (Roeltgen and Schneider, 1994). Perhaps non-human primates could be selected using a multi-choice 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.

Experiments with non-human primates have shown that the prefrontal cortex is essential for keeping information in mind (i.e. sustaining attention over a delay), inhibiting distraction and dividing attention, while the parietal cortex is essential for perception and the allocation of attentional resources (Arnsten, 2006). Lesions to the prefrontal cortex produce symptoms characteristic of ADHD; distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity (Arnsten, 2006). Optimal levels of norepinephrine and dopamine have been shown to be required for efficient functioning of the prefrontal cortex (Arnsten, 2006). Stimulant medication has been suggested to increase endogenous stimulation of α_{2A}-adrenoceptors and DRD1 receptors in the prefrontal cortex, optimizing prefrontal cortical regulation of behaviour and attention (Arnsten, 2006). Electrophysiological studies 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 produces 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, strengthening prefrontal cortex regulatory output to parietal association areas, thereby inhibiting responses to irrelevant sensory stimuli and improving cognitive function (Arnsten and Dudley, 2005).

Although children with ADHD have smaller cerebellar volumes and psychostimulant drugs increase activity of the human cerebral vermis, no evidence has been found of a physiological role for dopamine in cerebellar function in non-human primates (Glaser et al., 2006) arguing against the hypothesis that dopamine hypofunction is the primary disturbance in ADHD. The smaller cerebellar volume reflects a much greater problem in neural transmission and/or glial function.

3. Conclusion

ADHD is a heterogeneous disorder and so it is not surprising that different animal models mimic different aspects of ADHD-like behaviour. Diagnosis of ADHD is dependent on behavioural criteria. Animal models of the disorder must therefore not only mimic the fundamental behavioural characteristics of the disorder (face validity), they must also conform to a theoretical rationale for ADHD (construct validity) and predict aspects of ADHD behaviour, genetics, and neurobiology (predictive validity). SHR fulfill these validation criteria but other animal models have not been fully characterized in this respect. Primate models still need to develop their full potential and it has been suggested that selection based on poor performance of appropriate cognitive tasks could provide a model that is closest to the human disorder.

Nevertheless, the existing animal models of ADHD have provided unique insights into ADHD neurobiology. They 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 behaviour. All of the animal models of ADHD result from disturbances of neural function (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 in ADHD. Stimulus-evoked release of dopamine is decreased in several animal models including transgenic mice expressing mutant thyroid hormone receptor, the coloboma mutant mouse, 6-OHDA lesioned rat, DAT-KO mouse, 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 behavioural consequences which could explain many of the symptoms of ADHD (Sagvolden et al., 2005a,b). 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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