

Themed Issue: Translational Neuropharmacology – Using Appropriate
Animal Models to Guide Clinical Drug Development

REVIEW

Animal models to guide clinical drug development in ADHD: lost in translation?

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We review strategies for developing animal models for examining and selecting compounds with potential therapeutic benefit in attention-deficit hyperactivity disorder (ADHD). ADHD is a behavioural disorder of unknown aetiology and pathophysiology. Current understanding suggests that genetic factors play an important role in the aetiology of ADHD. The involvement of dopaminergic and noradrenergic systems in the pathophysiology of ADHD is probable. We review the clinical features of ADHD including inattention, hyperactivity and impulsivity and how these are operationalized for laboratory study. Measures of temporal discounting (but not premature responding) appear to predict known drug effects well (treatment validity). Open-field measures of overactivity commonly used do not have treatment validity in human populations. A number of animal models have been proposed that simulate the symptoms of ADHD. The most commonly used are the spontaneously hypertensive rat (SHR) and the 6-hydroxydopamine-lesioned (6-OHDA) animals. To date, however, the SHR lacks treatment validity, and the effects of drugs on symptoms of impulsivity and inattention have not been studied extensively in 6-OHDA-lesioned animals. At the present stage of development, there are no *in vivo* models of proven effectiveness for examining and selecting compounds with potential therapeutic benefit in ADHD. However, temporal discounting is an emerging theme in theories of ADHD, and there is good evidence of increased value of delayed reward following treatment with stimulant drugs. Therefore, operant behaviour paradigms that measure the effects of drugs in situations of delayed reinforcement, whether in normal rats or selected models, show promise for the future.

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Abbreviations

5-CSRT, 5-choice serial reaction time; 6-OHDA, 6-hydroxydopamine; ADHD, attention-deficit hyperactivity disorder; CPT, Continuous Performance Task; DAT1, Dopamine transporter; DRL, Differential reinforcement of low rates; EXT, Extinction; FI, Fixed-Interval; GH, Genetically Hypertensive; NET, norepinephrine transporter; SHR, Spontaneously Hypertensive Rat; SSRT, stop-signal reaction time

Introduction

Animal models of attention-deficit hyperactivity disorder (ADHD) should ultimately make predictions of future therapies. In the following sections, we will first discuss the clinical features of ADHD and briefly summarize current thinking about the aetiology and pathophysiological mechanisms. The current treatments will be outlined. We will then consider the requirements of an animal model of the disorder. In the absence of known pathophysiology, there are three main

strategies for development of an animal model. The first is to select animals that exhibit the core behavioural characteristics or specific components. The second is to simulate the postulated pathology by making lesions. The third strategy is to use genetic manipulation of candidate genes to produce transgenic animal models. All three strategies depend critically on a behavioural assay of the therapeutic effects. We consider existing models that exemplify the three different strategies for defining an animal model for drug development and evaluate them with respect to their potential to guide

clinical drug development in ADHD. Finally, we speculate on future approaches.

An overview of ADHD

ADHD is a prevalent and debilitating disorder diagnosed on the basis of persistent and developmentally inappropriate levels of overactivity, inattention and impulsivity (American Psychiatric Association, 1994). Underlying neurobiological causes have been proposed on the basis of strong heritability, anatomical and genetic associations, and the effectiveness of treatment with psychostimulant drugs. However, causative pathophysiological mechanisms for ADHD have not yet been identified, and at present, there is no biomedical laboratory test that is diagnostic for ADHD. The diagnosis is based on the observation of a number of behavioural symptoms of inattention, impulsivity and hyperactivity in different settings and over a certain period of time. The lack of a demonstrable physical cause for ADHD is problematic for the development of an animal model to guide clinical drug development.

The symptoms used in the diagnosis of ADHD are not unique to this disorder. Inattention, impulsivity and hyperactivity exist in the normal population and may be normal at earlier developmental stages. The symptom descriptions in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) (American Psychiatric Association, 1994) include relative terms such as 'excessive', 'inappropriate' or 'expected'. This means that to produce an animal model of the disorder *per se*, it is not simply a matter of producing the symptoms but also includes quantitative assumptions about what is relatively excessive. Abnormality is relative, and the selection of appropriate controls for an animal model is as important as the selection of the model. For example, if a control is constitutively inactive, it might appear that the model is hyperactive. There is an argument for not trying to model the disease in such a categorical way but rather identifying the range of component behavioural characteristics in a population and investigating the factors that influence their degree of expression. For example, the ability of a drug to reduce impulsivity in a normal rat may be as predictive of therapeutic potential as the ability to normalize impulsivity in an animal model relative to a control.

In reviewing the literature on ADHD from both clinical and basic science perspectives, it is clear that the clinical definition of the terms used to describe symptoms of ADHD are necessarily different from the operational definitions used by basic science researchers. For example, the clinical symptoms of impulsivity include 'often blurts out answers before question have been completed', 'often has difficulty awaiting turn' and 'often interrupts or intrudes on others'. Animal experimental measures of impulsivity include 'an abnormally high preference for small, immediate rewards over larger delayed rewards' in a delay discounting task (Cardinal *et al.*, 2004), 'bursts of responses with short interresponse intervals' in a compound fixed-interval schedule (Sagvolden *et al.*, 1998) and 'nose pokes occurring within the inter-trial interval, prior to the presentation of the visual stimulus' in a reaction time task (Robbins, 2002). The connections are sometimes tenuous. In theory, laboratory measures used in clinical studies of children with ADHD provide a bridge, but

not all such measures are responsive to drug treatment (Barkley, 1991). There is a danger that the core behavioural characteristics of ADHD may be lost in translation to the animal models.

The following sections consider the clinical features of ADHD as defined by DSM-IV criteria and laboratory methods of measurement. The effects of the existing drugs on these measures will be reviewed. This will be followed by a discussion of putative pathophysiological mechanisms and aetiology of ADHD. Animal models of the disorder will then be considered, starting with laboratory measures relevant to ADHD and then reviewing models based on behavioural characteristics, lesions and genetic manipulation. To date, these models have not been useful in predicting new drugs. To the contrary, drug effects on the models are used as an important step in validation. We conclude with a summary of the findings and some suggestions for future research.

Clinical features of ADHD

The DSM-IV criteria include descriptions of nine symptoms in each of two domains (inattention and hyperactivity/impulsivity). In clinical work, not all symptoms have to be present for the diagnosis to be made: it is sufficient to have six from one or both domains. There are many different ways of obtaining these six symptoms. Defined in this way, the ADHD research population is, inevitably, heterogeneous.

It is unrealistic to expect a single experimental model to simulate all the symptoms listed in the description of the disorder. Such a model would not represent a clinical situation that occurs in practice. On the other hand, there is considerable merit in models that simulate a specific component of the disorder. The component by itself may not be sufficient to establish a diagnosis of ADHD but may have an important impact on functioning. Even if that component is not unique to ADHD, a model that simulates a core component of the disorder can be useful to predict the clinical efficacy of potential therapeutic agents.

To go from the clinical definition to an animal model requires a definition of the clinical symptoms and some interpretation. The key words 'inattention', 'hyperactivity' and 'impulsivity' have certain meanings to clinicians who work with children. The meaning of these words for researchers developing animal models can be different.

Inattention

The DSM-IV criteria for the diagnosis of ADHD include nine symptoms of inattention, such as 'often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities'; 'often has difficulty sustaining attention in tasks or play activities' and 'is often easily distracted by extraneous stimuli'. In addition, there are symptoms related to organizing and finishing tasks, exerting mental effort, ignoring extraneous stimuli and remembering things. The symptom 'is often easily distracted by extraneous stimuli' could be construed as a deficit in selective attention, which is the ability to focus resources on a restricted number

of sensory channels and ignore the rest. The symptom 'often has difficulty sustaining attention in tasks or play activities' refers to sustained allocation of sensory or motor resources to a particular task.

Other forms of attention such as having to monitor simultaneously several different sensory channels do not seem to be included in the criteria. However, some studies suggest that divided attention is often compromised (Tucha *et al.*, 2008; 2009; Kaufmann *et al.*, 2010) and is often sensitive to methylphenidate (Pietrzak *et al.*, 2006).

It is important to note that the presence of these symptoms does not necessarily mean an *inability* to attend selectively, as is sometimes assumed. To the contrary, children with ADHD are able to focus attention during tasks that involve a high rate of immediate reinforcement. Apparent attention deficits can be reduced or eliminated when playing video games or performing tasks for large amounts of money immediately on completion (Barkley, 1990). However, when the intensity of reinforcement is decreased, behaviour becomes readily distinguishable from children without ADHD (Barkley *et al.*, 1980). Such observations may suggest that ADHD is not a primary deficit in attention mechanisms, but rather more a problem of the manner in which behaviour is regulated by its effects or consequences (Prior *et al.*, 1984; Draeger *et al.*, 1986; Haenlein and Caul, 1987). Alternatively, there may be non-contingent effects of reinforcers that provide additional stimulation.

In making the translation from the clinical disorder to animal models, an operational definition of the symptoms of interest is needed. Laboratory methods used in clinical studies provide a helpful link, and we will consider these methods in relation to different groups of symptoms. As an objective measure, the Continuous Performance Task (CPT) has been used to examine the possibility of sustained attention deficits in children with ADHD. This task was originally developed to examine the performance of radar operators (Mackworth and Taylor, 1963). Initial studies found that children with ADHD have impaired performance on the CPT compared with children without ADHD (O'Dougherty *et al.*, 1984; Losier *et al.*, 1996). The Conners's CPT shares some variance with other measures of attention and impulsivity and is moderately correlated with parent and teacher ratings of inattention and overactivity (Barkley, 1991). Stimulants improve performance on the CPT (Riccio *et al.*, 2001; Solanto *et al.*, 2009). Although CPT measures are widely used for assessing attention in ADHD, they have not been consistent in distinguishing ADHD children from other clinical groups (Werry *et al.*, 1987; Schachar *et al.*, 1988; McGee *et al.*, 2000). It is thus unclear whether CPT performance differentiates ADHD from other psychopathology (Barkley *et al.*, 1990; Koelega, 1995). Some have gone further and argued that that there was no compelling evidence at all for a sustained attention deficit in children with ADHD (Corkum and Siegel, 1993). Koelega (1995), while critical of the methodology used in Corkum and Siegel's review, also concludes that impaired performance of children with ADHD on vigilance tasks probably has multiple causes, including motivation and IQ. Koelega (1995), moreover, also notes that 'attention' *per se* may play a minor role, and that 'an attention deficit in ADHD children cannot be inferred from poor performance on a CPT alone'. On the other hand, vigilance tasks are sensitive in

detection of drug effects and a combination with physiological measures is a promising area for future research. These limitations of the CPT should be taken into account in evaluating animal paradigms derived from the CPT in translational research on ADHD (Robbins, 2002).

Hyperactivity

The symptoms of hyperactivity in DSM-IV mostly reflect a lack of control over activity by the situation rather than unmotivated and involuntary motor overactivity. For example, the symptoms include 'often leaves seat in classroom or in other situations *in which remaining seated is expected*', 'often runs about or climbs excessively *in situations in which it is inappropriate*' or 'often talks excessively'. These symptoms are all qualified by a measure of appropriateness (*italics*). It is not so much the absolute level of activity as its occurrence in a situation where children of a given age would be expected to be less active. On the other hand, there are also some symptoms such as 'is often "on the go" or often acts as if "driven by a motor"' and 'markedly excessive fidgeting and wriggling during spontaneous activities', which are more consistent with a constant or semiconstant involuntary activity.

Among the laboratory methods used to measure hyperactivity, actometers (acceleration-sensitive devices) have been used to objectively measure the activity level of children with ADHD. Studies using these measures can determine whether the activity level of children with ADHD differs quantitatively from children without ADHD, and whether it changes when children are taking stimulant medication. These studies show that children with ADHD are more active overall than normal children in natural situations (Porrino *et al.*, 1983b). Objective activity measures have also shown, however, that hyperactivity is sensitive to context.

Hyperactivity, like inattention, is modulated by situational variables and may be indistinguishable from normal when there is sufficient stimulation. While watching television, there is little difference in activity levels between children with and without ADHD, but differences become evident during reading and math classes at school (Porrino *et al.*, 1983a). During a dental visit, behaviour ratings of children with and without ADHD are not statistically different (Felicetti and Julliard, 2000). In such situations, children with ADHD may show no hyperactive behaviour during an initial clinical examination but show increased levels of activity after an extended visit (Dane *et al.*, 2000). On the other hand, hyperactivity is commonly seen in more familiar situations at home or at school (Sleator and Ullmann, 1981). Thus, children with ADHD are not particularly 'hyperactive' in novel or unfamiliar surroundings, but activity increases as familiarity with the setting increases. This influence of degree of novelty of a situation on activity levels argues against a constant, involuntary overactivity in ADHD. This is extremely important when considering the face validity of animal models, many of which focus on achieving high levels of spontaneous background activity under all conditions.

Consistent with this, it has been repeatedly shown that stimulation reduces symptoms of hyperactivity (Antrop *et al.*, 2000; 2002; 2005; 2006). In waiting situations where no

stimulus is present, ADHD children show heightened activity compared with controls, whereas if stimulation is provided through the use of a video, ADHD children display no significant differences in their activity compared to controls (Antrop *et al.*, 2000). As with inattention, high reinforcement rates can reduce hyperactivity (Douglas and Parry, 1994; Iaboni *et al.*, 1995; Carlson and Tamm, 2000). These findings also suggest that ADHD is not a primary deficit in motor mechanisms but rather more a problem of the manner in which behaviour is regulated by its effects or consequences (Prior *et al.*, 1984; Draeger *et al.*, 1986; Haenlein and Caul, 1987).

Impulsivity

Impulsivity is not a unitary concept, and there are several definitions emphasizing different aspects (Evenden, 1999a). Some definitions refer to hasty or poorly conceived decisions, prematurely expressed without regard to consequences. These place lack of inhibitory control at the core of impulsivity (Quay, 1997). Others emphasize intolerance to delay of reinforcement (Logue, 1988). These two aspects may be independent, but they are also interrelated, in that a greater preference for immediate gratification may aggravate difficulty withholding a response. Evenden (1999b) concluded that multiple neurochemical mechanisms interact to modulate impulsivity. The concepts of intolerance to delay of reinforcement and lack of inhibitory control are both important in ADHD and will be considered in more detail below.

Symptoms of impulsivity listed for ADHD in DSM-IV include 'often blurts out answers before question have been completed', 'often has difficulty awaiting turn' and 'often interrupts or intrudes on others'. Although these symptoms provide a narrow definition of impulsivity, this definition arguably includes the two aspects referred to above: preference for immediate reinforcement ('difficulty waiting') and difficulty withholding responses ('blurts out'). It is important to note that normal children are impulsive in some degree and may exhibit such behaviour at different times and at different stages of development. Normal children and adolescents often choose immediate gratification in preference to a delayed benefit (Mischel *et al.*, 1989). The diagnosis of impulsivity is thus based not only on the presence of these symptoms but also on their expression to an abnormally persistent and developmentally inappropriate extent.

An altered response to reinforcement has been demonstrated in children with ADHD and has been proposed by many authors as a mechanism underlying particular symptoms of ADHD (Sonuga-Barke, 2003; Sagvolden *et al.*, 2005a; Tripp and Wickens, 2008). Historically, children with ADHD have been described as less able to delay gratification and as failing to respond to discipline (Wender, 1971; 1972; 1974; Haenlein and Caul, 1987). As a group, children with ADHD have been reported to perform less well under partial reinforcement schedules (Freibergs and Douglas, 1969; Parry and Douglas, 1983) and to respond more impulsively to reinforcements, that is, to choose small immediate reinforcers over larger delayed reinforcers (Firestone and Douglas, 1975).

Experimental tests have supported the hypothesis that children with ADHD exhibit a greater than normal tendency

to prefer immediate reinforcers (Tripp and Alsop, 2001), or related to this, a tendency to choose smaller immediate rewards over larger delayed rewards (Sonuga-Barke *et al.*, 1992; Antrop *et al.*, 2006; Hoerger and Mace, 2006). In some protocols, the effects of delay of the reinforcer depend on whether the reinforcers are real or abstract. Barkley *et al.* (2001) found no effect of diagnostic group using a temporal discounting task with hypothetical choices in adolescents with ADHD and healthy controls. However, using real choices for monetary rewards, Scheres *et al.* (2008) found that ADHD symptoms, specifically hyperactivity-impulsivity, were associated with steep discounting. With respect to the association with symptoms of ADHD, a recent general population study found an association between inattention symptom ratings and behavioural measures of choice impulsivity and delay aversion (Paloyelis *et al.*, 2009), and Hoerger and Mace (2006) found that preference for immediacy correlated with measures of activity and attention in the classroom.

Lack of inhibitory control over behaviour is another aspect of impulsivity of relevance to symptoms such as 'often blurts out answers before question have been completed', 'often has difficulty awaiting turn' and 'often interrupts or intrudes on others'. Laboratory methods with face validity for measuring lack of inhibitory control include versions of the CPT, stop-signal paradigms, go/no go tasks and differential reinforcement of low rates (DRL).

The CPT is widely used in ADHD research because it has been shown in a number of studies to differentiate between ADHD and normal control groups (although not from other pathology). Errors of commission on the CPT have been assumed to measure impulsivity because they are responses that occur when no response is required (Epstein *et al.*, 2003). However, despite apparent face validity, commission errors have a low correlation with other measures of impulsivity and in fact correlate better with hyperactivity (Barkley, 1991).

An ability to interrupt an ongoing response and withhold responding to pre-potent stimuli is theoretically related to the concept of behavioural inhibition (Barkley, 1997a,b). In the stop-signal paradigm (Logan *et al.*, 1984), a subject is required to inhibit an already prepared motor action in response to a stop signal immediately after a go signal, in the context of a series of go signals (Alderson *et al.*, 2007). The stop-signal reaction time (SSRT) is the time taken to inhibit an already initiated motor response in response to a signal and is used as a measure of behavioural inhibition processes. In population-based samples, measures derived from this task are associated with teacher ratings of inattention (Tillman *et al.*, 2008). Kenemans *et al.* (2005) also referred to the contribution of attentional processes in ADHD, based on neurophysiological evidence.

Group differences in SSRT exist between children with and without ADHD (Oosterlaan *et al.*, 1998), although like the CPT, this measure does not distinguish children with ADHD from children with conduct disorders, and the nature of the differences suggests a more generalized deficit (Alderson *et al.*, 2007; de Zeeuw *et al.*, 2008).

Performance on a DRL schedule has been used as a laboratory measure of inhibitory control in children with ADHD. This schedule requires low rates of responding, and premature responses reset the waiting time. Performance requires

the ability to inhibit responding. The DRL task has been found to discriminate ADHD from normal children in some studies (Gordon, 1979; McClure and Gordon, 1984) but not others (Daugherty and Quay, 1991). However, it correlates better with parent and teacher ratings of hyperactivity than impulsivity (Gordon, 1979; McClure and Gordon, 1984).

Implications of clinical features for animal models

Not knowing the cause of ADHD is problematic for the development of animal models while at the same time being a major motivation to develop them for pathophysiological investigation. In the absence of known pathology, there is an emphasis on similarity in behavioural characteristics or face validity of animal models. It is important to ensure that psychological constructs used in animal research match those derived from clinical observation and measurement. The criteria for ADHD do not define a homogeneous clinical population, leaving open the possibility of multiple types of ADHD. The presence of all major symptoms in the normal population implies that pathology is a matter of degree of expression in relation to developmental stage. Creating a model is not simply a matter of generating symptoms but has quantitative aspects. Terms such as 'excessive', 'inappropriate' or 'expected' indicate that symptoms are relative, not absolute, measures. This relativity implies that choice of control or comparison group is as important as the choice of the model.

Translation of the clinical symptoms into animal behaviour should not assume that terms such as impulsivity, hyperactivity and inattention mean the same thing to those observing in a classroom as in a laboratory setting with humans. Human laboratory methods with apparent face validity are not necessarily good predictors of a correlation with parent or teacher ratings, and abnormal measures obtained in humans are not specific to ADHD. Even when laboratory measures identify differences between groups of children with and without ADHD, the differences are not always in the predicted symptom domains. For example, measures of inhibitory control correlate better with hyperactivity than impulsivity. Some measures do show a response to treatment with psychostimulants and translations of these measures may be useful in predicting drug effects.

Open-field testing in humans has not produced clear results. However, measures of motor overactivity based on actometer records seem to have good predictive power. These methods have also shown that there is not an incessant and involuntary motor overactivity but rather altered regulation of behaviour by its consequences. Sensitivity to delay of reinforcement is a reliable measure, but it is not yet known how well this measure correlates with parent or teacher ratings. However, it lends itself to translation into well-understood animal behaviour schedules.

Aetiology

The aetiology of ADHD is unknown at present, but genetic factors are thought play an important role because family

studies have consistently indicated a strong familial genetic contribution (Biederman *et al.*, 1990; 1992; Faraone and Doyle, 2001). Twin studies have shown high heritability (Biederman *et al.*, 1990; Kieling *et al.*, 2008). However, genetic factors in ADHD probably involve multiple genes of moderate effect. To date, no single gene has been discovered to play a major role, though several gene associations have been found. The most studied are genetic variations in the dopamine D4 receptor (Swanson *et al.*, 1998; 2000) and the dopamine transporter (DAT1) (Gill *et al.*, 1997). Both of these findings have been replicated (Brookes *et al.*, 2006b), but individually, they exert only weak effects, and neither is necessary or sufficient for ADHD. For example, in one study, DAT1 polymorphism accounted for a small fraction of the variance in symptoms in ADHD: specifically, 1.1% of variance for inattentive symptoms and 3.6% of the variance in hyperactive-impulsive symptoms (Waldman *et al.*, 1998).

A recent review of all molecular genetic studies of ADHD from 1991 to 2004 concluded there were significant associations for four genes in ADHD: the dopamine D4 and D5 receptors and the dopamine and serotonin transporters (Bobb *et al.*, 2006). Since 2004, this list has grown with statistically significant evidence of association with DBH, HTR1B and SNAP-25 genes (Faraone *et al.*, 2005; Gizer *et al.*, 2009). Genome-wide association studies, as opposed to candidate gene studies, have so far not reported any associations that are significant after correction for multiple testing (Franke *et al.*, 2009).

Environmental factors have also been identified that increase the risk for ADHD (Banerjee *et al.*, 2007), such as exposure to lead or polychlorinated biphenyls (PCBs) during early childhood. However, the effects of lead and PCBs are not specific to ADHD (Williams and Ross, 2007), and it is unlikely that such factors can alone account for ADHD cases. Rather, there is increasing recognition of the importance of complex interaction of genetic and environmental risk factors (Swanson *et al.*, 2007; Kieling *et al.*, 2008). For example, in one study, children exposed to prenatal smoking and homozygous for the DAT1 10-repeat allele were at significantly increased risk of hyperactivity, impulsivity and oppositional symptoms, while neither factor alone was associated significantly (Kahn *et al.*, 2003). A similar interaction between prenatal alcohol exposure and the DAT1 gene has been linked to an increased risk for ADHD (Brookes *et al.*, 2006a).

Studies of genetic association, toxin exposure and gene by environment interactions can identify risk factors, but further steps are needed to explain how the symptoms arise. Integration of such findings with additional information about the pathophysiology, and with current understanding of the neurobiology relevant to symptoms, is also required. In bridging between gene and behaviour, we need to include an understanding of how different gene variants alter the function of cells and systems of the brain.

Pathophysiology

There are many correlates of ADHD, but correlation does not necessarily mean cause. It is also necessary to develop theories that link the pathological changes to the symptoms. However, the first step is to look for changes in the brain

structure and function. Strong findings include a reduction in total brain size that persists into adolescence (Castellanos *et al.*, 2002) and reduced dimensions of several brain regions (Hynd *et al.*, 1990; 1991; 1993), including the caudate nucleus, prefrontal cortex white matter, corpus callosum and the cerebellar vermis (Valera *et al.*, 2007; Tremols *et al.*, 2008). A decrease in cortical thickness has been reported, which is apparent in childhood and largely resolves during adolescence (Shaw *et al.*, 2007). Alterations within the frontal and cerebellar white matter have been measured in children and adolescents with ADHD (Ashtari *et al.*, 2005). Recently, Carmona *et al.* (2009) reported significant reductions in the right ventral striatum that were correlated with maternal ratings of child hyperactivity/impulsivity.

The anatomical correlates of ADHD are complemented by functional studies that show differences in activation of specific regions during task performance. Studies of dopamine release are particularly relevant to the mechanisms of action of therapeutic drugs in ADHD. The dopamine hypothesis is supported by many pieces of evidence, including gene linkages to transporter and receptors, the actions of stimulant medication on dopamine release and reuptake mechanisms at the synaptic level (Swanson *et al.*, 2007); a reduction in dopamine synaptic markers associated with symptoms of inattention in ADHD (Volkow *et al.*, 2009) and evidence from functional imaging of hypoactivity of the dopamine system. In normal subjects, an increase in local fMRI signals has been observed in the striatum in relation to specific aspects of reward processing, as predicted by experimental studies in rodents and non-human primates. The fMRI signal probably represents activation of postsynaptic neurons following dopamine-mediated potentiation of corticostriatal synapses (Knutson and Gibbs, 2007). Imaging studies in humans have shown that activation of the ventral striatum occurs in relation to anticipation of reinforcement (Galvan *et al.*, 2005). The magnitude of ventral striatal activity is related to preference for immediate over-delayed reinforcement (Hariri *et al.*, 2006).

Consistent with hypothesized alterations in reward mechanisms, reduced activation of the ventral striatum in reward anticipation has been measured in adolescents with ADHD relative to controls (Scheres *et al.*, 2007). Similarly, Plichta *et al.* (2009) found reduced responsiveness of the ventral striatum to rewards in ADHD patients during a series of choices between two monetary reward options that varied by delay to delivery. The association of ADHD with alterations in the activation of brain reward circuitry in relation to reward anticipation and delay of reward is consistent with altered reinforcement mechanisms and suggests that these mechanisms may be an important target of treatment.

Pharmacological treatment of ADHD

Animal models are traditionally assessed on the basis of face, construct and predictive validation (Willner, 1984; Sagvolden *et al.*, 2005b) (see Table 1). The purpose of this review is to focus on animal models that have the potential to guide clinical drug development for ADHD. Therefore, we focus on treatment validation, that is, the ability to predict response to new treatments. Validation against established treatments

Table 1

Contrasting aims of models

Traditional aim of animal model	Aim of animal model in this review
Face validity: mimics the fundamental behavioural characteristics	Treatment validity: predicts the clinical effectiveness of a new compound.
Construct validity: expresses the known aetiology and pathophysiology	May or may not have face validity
Predictive validity: Predicts novel biology or clinical observations	May or may not have construct validity
	May or may not display expected effects of proven treatments.

may be important of drugs working by the same mechanism. In ADHD, psychostimulants are the gold standard at present. Understanding the actions of these drugs is very relevant to further development of psychostimulant variants. However, new treatments may work by novel mechanisms, so the ability to predict known treatment effects should not be overstressed.

Currently, three major classes of drugs are used in the treatment of ADHD: amphetamine enantiomers (usually supplied as 3:1 mixture of d- and l- isomers, Adderall), threo-methylphenidate enantiomers (supplied as dl-threo-methylphenidate, Ritalin; or as a slow release preparation, Concerta) and atomoxetine (selective norepinephrine reuptake inhibitor, Strattera). Amphetamine and methylphenidate are commonly referred to as psychostimulants. Treatment of ADHD with the psychostimulants has been shown to be very effective in reducing symptoms during exposure to the drug (Carlson *et al.*, 1992; Pelham *et al.*, 2000; Brown *et al.*, 2005); however they have no enduring therapeutic effects that outlast drug exposure (Solanto, 2000).

Atomoxetine (Strattera) is a relatively new, non-stimulant drug used to treat ADHD (Kratovich *et al.*, 2003; 2006; Perwien *et al.*, 2006). It is a non-stimulant and acts by a different mechanism from the psychostimulants, as a presynaptic blocker of norepinephrine reuptake (Swanson *et al.*, 2006). Unlike other medications used in ADHD, such as amphetamine and methylphenidate, atomoxetine has no appreciable affinity for dopamine receptors or the dopamine transporter. Although the non-dopaminergic action of atomoxetine appears at first sight to contradict the dopamine hypothesis, it actually increases dopamine concentration specifically in the prefrontal cortex, because the norepinephrine transporter (NET) plays an important role in clearance of dopamine in this region (Bymaster *et al.*, 2002; Swanson *et al.*, 2006). This regional specificity on DA function, plus a lower affinity for the serotonin (5-HT) transporter than methylphenidate (Bymaster *et al.*, 2002) may account for differences in clinical effects.

Psychostimulants: theory of action

The therapeutic effect of psychostimulants was discovered serendipitously by Bradley (1937), after administering Benzedrine to 30 children as part of a clinical trial for treatment of headaches arising from a lumbar puncture. The drug did not relieve the headaches but caused a dramatic change in school activities, with increased interest in schoolwork, better work habits and a significant reduction in disruptive behaviour. The effect was not limited to children with a particular disorder. Bradley noted, 'It appears paradoxical that a drug known to be a stimulant should produce subdued behaviour'.

It is important to note that the widely quoted idea that the calming effect of psychostimulants is 'paradoxical' is misleading. According to Sahakian and Robbins (1977), the improvement in attention in children with ADHD brought about by amphetamine-like compounds is related to a normal focusing action of these drugs, namely to increase activity in more limited categories of behaviour. The benefit is not unique to children with ADHD and is seen in normal children and adults. Rapoport *et al.* (1980; 1978) found that D-amphetamine has the same effects in normal children: decreasing total activity, decreasing impulsivity and increasing attentiveness. The few other studies in normal children support this finding. For instance, the performance of children without ADHD on the CPT is enhanced by methylphenidate (Werry and Aman, 1984; Peloquin and Klorman, 1986), and in normal adults, D-amphetamine and methylphenidate have similar performance enhancing effects (Rapoport *et al.*, 1980; Aman *et al.*, 1984; Strauss *et al.*, 1984). The idea that an improvement in focusing activity is paradoxical arises from an assumption that amphetamine and related drugs should have an overall effect to increase movement, which in turn may simply relate to the pervasive use of the term 'stimulant' to refer to these drugs. The conclusions of these human studies seem to have been ignored in the animal literature, however, and a 'paradoxical effect' of stimulant drugs is often cited as the *sine qua non* of animal models for hyperactivity (Gainetdinov *et al.*, 1999; Avale *et al.*, 2004b; Tsuchida *et al.*, 2009; Drerup *et al.*, 2010; Krapacher *et al.*, 2010; Napolitano *et al.*, 2010).

A separate issue is that hyperactivity in humans with ADHD is context-dependent. This means that focusing on activity measures in isolation in animal models, which is very common, may be ignoring important factors. Activity in an open field is not a good model, unless this is modified by the context. People investigating drug effects in animals have focused on unconditional motor activation. An alternative focus in analysis of stimulant effect in animals may be to investigate the effects of drugs on the sensitivity to context (occasion-setting).

The precise mechanisms by which psychostimulants exert their therapeutic effects are not known, although there are a number of theories with some support (Solanto, 2002; Oades *et al.*, 2005; Arnsten, 2006). It is known that at therapeutic dose D-amphetamine is a dopamine reuptake inhibitor and also a norepinephrine reuptake inhibitor but only a very weak inhibitor of 5-HT reuptake (Heal *et al.*, 2008). At higher doses, amphetamine also evokes the release of dopamine, norepinephrine and 5-HT. Similarly, methylphenidate (dl-

threo-methylphenidate) is a reuptake inhibitor for dopamine and norepinephrine, while it is inactive for 5-HT. The hypothesis that psychostimulant actions on the dopamine transporter are important for their therapeutic actions in ADHD has strong support, though there are also strong alternative hypotheses based on its effects on norepinephrine, and both will be considered.

Many theories of the pathophysiology of ADHD focus on the actions of psychostimulants on the dopamine transporter or, more recently, the norepinephrine transporter. Levy (1991) proposed that psychostimulant treatment corrects an underlying dopamine deficiency, increasing the effect of impulse-associated release of dopamine (Suaud-Chagny *et al.*, 1989). Others proposed that psychostimulants function as antagonists (Solanto, 2002) by raising background levels of dopamine, which then suppresses release of dopamine by acting on autoreceptors (Seeman and Madras, 1998). An alternative theory is that the therapeutic effects of psychostimulants are mediated by norepinephrine (Pliszka *et al.*, 1996; Arnsten, 2006). A key argument for the norepinephrine theory is that plasma concentrations in the therapeutic range in humans have little effect on dopamine levels when measured in preclinical studies (Kuczenski and Segal, 2001; Berridge *et al.*, 2006). Indeed, guanfacin, an agonist of noradrenalin receptors, has therapeutic effects in ADHD (Sallee *et al.*, 2009).

In support of the role of dopamine in the therapeutic effects of psychostimulants, Volkow *et al.* (1998) showed that a standard clinical dose of 0.5 mg·kg⁻¹ methylphenidate would block about 60% or more of DAT. Positron emission tomography imaging using [(11)C]raclopride showed, indirectly, an increase of extracellular dopamine suggesting that clinically relevant doses of methylphenidate produce their therapeutic effects by increasing extracellular dopamine (Volkow *et al.*, 1999; 2002a; Rosa Neto *et al.*, 2002). Consistent with this, a significant association was found between extracellular brain dopamine levels and the motivation to undertake a mathematical task (Volkow *et al.*, 2004), leading the authors to postulate that methylphenidate's therapeutic effects may be 'secondary to its ability to enhance stimulus-induced dopamine increases, thus making them more motivationally salient and thereby improving performance'.

Psychostimulant effects on inattention

The cognitive effects of stimulant medication on children with ADHD were recently reviewed by Pietrzak *et al.* (2006) and Swanson *et al.* (2011). Methylphenidate reliably improves performance on vigilance tasks in children with ADHD (Rappoport *et al.*, 1993). The SSRT is also improved by stimulants (Tannock *et al.*, 1989; Bedard *et al.*, 2003), but the effects may be selective for children with slow SSRTs (Boonstra *et al.*, 2005). Since motivational factors play a role in scores on attentional tasks, it is possible that psychostimulants work by altering motivation. Another possibility is that, as suggested by Sahakian and Robbins (1977) and Robbins and Sahakian (1979), stimulants increase stereotypic behaviour, thereby improving performance on tasks that require sustained attention. Since the initial studies, the literature has grown

exponentially, and a full treatment is beyond the scope of the present review.

Psychostimulant effects on impulsivity

The effects of psychostimulants on impulsivity, whether in children with ADHD, normal children and adults, or animal models, are relevant to understanding their therapeutic actions in children with ADHD. In normal adults, amphetamine decreases impulsivity. de Wit *et al.* (2002) showed that amphetamine decreased impulsive responding on a delay discounting measure, which measured the ability to withhold a response for a small actual monetary reward for a period of time, in order to obtain a larger reward. Similarly, Pietras *et al.* (2003) showed that in normal adults methylphenidate decreased the number of impulsive choices on a procedure in which subjects were presented with repeated choices between a small amount of money delivered after a short delay and a larger amount of money delivered after a delay that adjusted as a function of previous choices.

In children with ADHD, methylphenidate has been shown to increase the effort they will expend to obtain reward on a progressive ratio schedule (Wilkison *et al.*, 1995). In this schedule, children with ADHD were required to make a progressively increasing number of button presses to earn a fixed monetary reward. The 'breaking point' above which the child was unwilling to continue with the task was significantly higher during drug than placebo trials. This could be due either to higher response rate or increased value of reinforcement. Using a measure of delay discounting, Shiels *et al.* (2009) found that stimulant medication reduced delay discounting in children with ADHD. The effect depended on whether the task was hypothetical or involved real experience of the outcome; only the task in which the outcomes were experienced was sensitive to the effects of stimulant medication.

These findings show that methylphenidate alters delay discounting in both normal adults and in children with ADHD, in the direction of decreasing the impact of the delay. This is possibly due to increasing the value of delayed rewards, or somehow modifying the experienced cost of the delay. In contrast, methylphenidate does not increase the value of immediate rewards to the same degree. This difference is a fascinating clue to the therapeutic actions of methylphenidate that should be explored further in animal models. In terms of the mechanism of action at the synaptic level, it is unclear why the effects of methylphenidate should differentiate between immediate and delayed rewards. We may speculate that this is mediated by an effect on eligibility traces (Pan *et al.*, 2005) or on cue-evoked dopamine responses (Tripp and Wickens, 2008; 2009). This is a promising area for further research.

Psychostimulant effects on hyperactivity

Psychostimulant effects on activity levels have been extensively studied. Porrino *et al.* (1983a) measured motor activity

in boys with ADHD and found that D-amphetamine caused decreased motor activity for about 8 h after drug administration. However, as discussed above, this does not reflect a calming effect but rather improved focusing of activity. D-amphetamine decreased activity most strikingly during structured classroom activity; in contrast, during physical education, where movement is appropriate and expected, there was a significant drug-induced increase in motor activity. Borcharding *et al.* (1989) found that methylphenidate significantly lowered activity measurements in a morning-structured classroom and in less structured activities in the afternoon. However, plasma drug concentrations did not correlate with decrements in activity. Swanson *et al.* (2002) found that methylphenidate produced large, significant reductions in activity and inappropriate behaviour in the classroom. Again, however, the effects were situation-dependent, being smaller for the playground than for the classroom settings. Thus, most data point to very selective effects of stimulants on behaviour, dependent on the demands of the environment.

This situation dependence of the effects psychostimulants in humans, together with the earlier comments about the situation dependence of hyperactivity, has important implications for animal models for drug development in ADHD. Unconditional effects of drugs may be less important than modulation of sensitivity to situational variables.

Pharmacodynamics of psychostimulants

In developing an animal model to predict therapeutic effects, calibration with existing treatments should be done using therapeutically relevant doses. One approach is to use doses that result in plasma drug levels in the animal model comparable with levels obtained with therapeutically effective doses in humans.

Estimates of the plasma drug levels obtained with therapeutic doses of psychostimulants are available for children with ADHD. The effective dose range in children is 0.3–1.0 mg·kg⁻¹ for methylphenidate and 0.2–0.5 mg·kg⁻¹ for D-amphetamine. After oral doses of methylphenidate, based on pharmacokinetic and pharmacodynamic studies, Swanson and Volkow (2002) report that peak brain levels of methylphenidate occur between 1 and 2 h after dosing, which is about the same time as peak serum concentration and peak behavioural effects of clinical doses. With oral administration, the therapeutic effects have a rapid onset (30 min), peak 2 h after dosing and last about 5 h (Wargin *et al.*, 1983). The mean maximal concentration in plasma for MPH is 7.8 ± 0.8 ng·mL⁻¹ after 0.3 mg·kg⁻¹ (Wargin *et al.*, 1983). Based on PET studies in adult volunteers, the maximum MPH blockade of DAT (about 80% occupancy) occurs at serum concentrations of about 8–10 ng·mL⁻¹, suggesting that higher concentrations are not likely to be very effective in further blocking DAT or increasing efficacy due to this site of action (Swanson and Volkow, 2002; Volkow *et al.*, 2002b).

Aiming for the same plasma concentration in animals as is achieved with therapeutic doses in humans appears logical but does not guarantee equivalent effects. Borcharding *et al.*

(1989) found that drug plasma levels were *not* correlated with the effectiveness of methylphenidate in lowering activity. Furthermore, a reduction in locomotor activity can occur at a subclinical dose that does not improve vigilance (Solanto, 1986). One review concluded that effect sizes are apparently larger for behavioural than for cognitive changes in response to stimulants, and there are differential dose effects for both behavioural and cognitive tasks of different complexities (Solanto, 2002). This is consistent with clinical experience that some subjects require low doses, and others require higher doses for optimal efficacy. While it is sound practice to use drug doses that produce a serum level in the range produced by therapeutic doses in humans, this should not be the sole and overriding consideration. Doses should be chosen for their ability to produce the targeted behavioural effects in the animal model, as these effects might occur at different plasma levels.

Non-stimulant medication

Atomoxetine is a selective inhibitor of norepinephrine reuptake and increases norepinephrine levels in the prefrontal cortex, where NET is expressed. Its therapeutic effects are sometimes cited as a refutation of the dopamine hypothesis. However, in the prefrontal cortex atomoxetine increases both dopamine as well as norepinephrine (Bymaster *et al.*, 2002; Swanson *et al.*, 2006) because the NET plays an important role in dopamine clearance in this region (Swanson *et al.*, 2006). Atomoxetine can thus be considered as potentiating the effect of dopamine specifically in the prefrontal cortex, as well as potentiating the effects of norepinephrine.

Summary of psychostimulant pharmacology and implications for animal models

In summary, psychostimulants have been shown to reduce inattention, motor activity and impulsivity in children both with and without ADHD. Models based on the assumption that children with and without ADHD have the opposite response to methylphenidate are based on a fallacy. Since normal subjects show similar responses, an animal model may not have to simulate abnormality to predict drug effects, provided appropriate measures are used. Animal studies should not only use doses that produce plasma levels that are produced by therapeutic doses in humans but should also investigate mechanisms using the doses required to produce relevant behavioural effects in animals.

Animal models

It has been suggested in the literature that the ideal animal model would be similar to the human disorder it models in terms of pathology, symptoms and response to drugs. However, this is not straightforward in the case of animal

models for ADHD for a number of reasons. First, the diagnostic criteria do not define a homogeneous population; in other words, there may be multiple causes of ADHD, and different models may be required for each. Second, the pathology is unknown, and the pathological associations that have been found do not prove a causal relationship between the symptoms and the pathologies. Third, the symptoms are all present in some degree in the normal population, so there is the problem of what to consider abnormal in the animal model and what to use as a control.

These difficulties aside, for the present purpose, the essential requirement is that the model should predict therapeutic effects of drugs based on clinically relevant doses. For the purpose of predicting drug effects, it is not necessary for the symptoms to be the same as those exhibited in humans with the disorder. A primary requirement is that the model's response to a treatment predicts therapeutic efficacy. Face validity is of secondary importance to the predictive power of the model. Many examples exist of models that do not closely resemble the condition they model but are useful for predicting drug effects, such as the hemiparkinsonian rat, which has relatively subtle movement deficits and does not show strong tremor such as often seen in Parkinson's Disease and responds to treatment by rotation in circles. However, to date, animal models of ADHD have not been useful in predicting drug effects. Rather, the response to known therapeutic agents has been studied with the aim of validating putative models. Until now, most models have been developed with a view to better understanding of the basic science and not primarily as an assay for therapeutic effects of novel compounds.

A demonstration of the effects on the model of an existing drug does not mean that the model is good for identifying a new drug, unless it works by a similar mechanism. A new drug might work by a mechanism that is not expressed in the model, giving rise to a false negative. Alternatively, a drug might be effective in the model, but only because of pathology that is peculiar to the model, giving rise to a false positive.

Despite these difficulties, some progress has been made using the approaches reviewed in the following sections. Developing measures of the behavioural characteristics relevant to ADHD and studying them in normal animals is a promising direction, and such measures are essential for progress with other models. Selecting for behavioural characteristics by selective breeding or selection of phenotypes from the natural variation is a closely related approach. Mimicking presumed pathology by making brain lesions has a long history and may capture some aspects of disorder but has tended to focus on the motor symptoms. Finally, manipulation of candidate genes and the production of transgenic animals is another approach deriving from etiological hypotheses. These approaches are considered in the following sections. We do not attempt to evaluate every claim for a model of ADHD but focus on those that have been extensively studied and on the tasks that measure the components identified as important on the basis of clinical associations, as reviewed in the preceding sections. For comprehensive reviews of the range of models that exist, see Davids *et al.* (2003) and Russell (2007) and (2011).

Behavioural paradigms used to model ADHD and drug actions

In the previous sections, we commented that the symptoms of ADHD are present in some degree in the normal population. Furthermore, stimulants have beneficial effects on the symptoms of inattention, impulsivity and hyperactivity in people whether or not they have ADHD. Therefore, it may be reasonable to use 'normal' rats to investigate drug actions. We summarize below the behavioural paradigms used most frequently and the effects of drugs on those measures. These same measures can be used to select animals from extremes of the normal range for use in acute experiments investigating pathophysiology, or for inbreeding to produce congenic strains. A number of excellent reviews of behavioural models are available (Evenden, 1999a,b; Winstanley *et al.*, 2006).

Delay discounting paradigm

Impulsive choice is often measured in the delay-discounting paradigm where impulsivity is defined by a greater tendency to choose an earlier, smaller reinforcer in preference to a larger, later reinforcer. The effects of varying the delay and amount of a reinforcer have been studied by forcing animals to choose among alternatives varying in the amount and delay of the reinforcer. Such studies show organisms sharply discount future rewards as a function of the delay from the time of choice (Ainslie, 1975), resulting in choice of smaller immediate reinforcer even if it results in fewer total reinforcers (Evenden, 1999b).

Bizot *et al.* (2011) trained rats in a T-maze to choose between a small immediate reward and a larger but 30 s delayed reward. Methylphenidate (3 mg·kg⁻¹), atomoxetine (1 mg·kg⁻¹), D-amphetamine (1 and 2 mg·kg⁻¹) and desipramine (8 and 16 mg·kg⁻¹) increased the number of choices of the large-but-delayed reward, that is decreased impulsivity. They suggest that the T-maze procedure in juvenile animals may be suitable for testing the therapeutic potential of drugs for treatment of ADHD (Bizot *et al.*, 2011).

5-Choice serial reaction time test

The 5-choice serial reaction time test (5-CSRT) originated from the CPT in humans (Robbins, 2002). It requires the animals to learn to nose poke into one of five apertures following presentation of a brief visual stimulus in that aperture in order to obtain a food reward. The short duration of the stimulus requires the rat to attend closely, and the test is regarded as a measure of vigilance and impulsivity. Elevations in the frequency of premature responses reflect higher levels of impulsivity. Nose pokes occurring prior to the presentation of the visual stimulus are premature responses and provide a measure of behavioural inhibition.

Rats with a deficit in selective attention accompanied by impulsivity can be identified within a 'normal' population using a 5-CSRT (Day *et al.*, 2007). Rats selected for high levels of impulsivity on a 5-CSRT task exhibited correspondingly

high levels of impulsive decision making on a delay-of-reward task. The same rats, however, were unimpaired on a stop-signal task requiring inhibition of an already initiated motor response (Robinson *et al.*, 2009). These animals have been proposed as a rodent model of ADHD.

Puumala *et al.* (1996) used a 5-CSRT to assess sustained attention, measured by choice accuracy, and motor hyperactivity, measured by percentage of premature responses. Methylphenidate slightly improved sustained attention performance of poorly performing animals but at higher doses (1 mg·kg⁻¹) increased the number of premature responses. Similarly, Navarra *et al.* (2008) found that treatment with methylphenidate at therapeutic doses improved sustained attention as measured by the 5-CSRT. At higher doses, methylphenidate increases impulsivity as measured by increased premature responding on the 5-CSRT (Cole and Robbins, 1987; 1989). In contrast, the same authors found that atomoxetine induced a marked decrease in impulsivity and overall improvement in attention. The different effects of DAT and NET inhibitors may suggest differential involvement of dopamine and norepinephrine systems, or differential involvement of prefrontal and striatal regions.

Stop-signal reaction time task

In humans, stop-signal reaction time tasks measure impulsivity in terms of ability to withhold or inhibit an already initiated or pre-potent motor response (Alderson *et al.*, 2007). In the standard SSRT, a go signal triggers a response, and then on some trials, a stop signal is presented after the go signal to indicate trials requiring inhibition (stop trials). A failure to withhold or inhibit on the stop trials is a measure of increased impulsivity. A related paradigm is the 'go/no go' task, in which the stop signal is presented before or simultaneously with the go signal. Behavioural paradigms for both SSRT and 'go/no go' have been developed for use in animal studies (Harrison *et al.*, 1999; Eagle *et al.*, 2008b). Serotonin (5-HT) is strongly implicated in inhibitory control on the go/no go but not the stop-signal task, whereas the stop-signal reaction time appears more sensitive to the action of noradrenaline. The effects of psychostimulants on these paradigms were recently reviewed (Eagle *et al.*, 2008a). Stimulants and atomoxetine decrease impulsivity on the SSRT (Robinson *et al.*, 2008), suggesting this task may be useful in animal studies of potential therapeutic agents.

Differential reinforcement of low rates of responding

The DRL schedule provides another measure of impulsivity. On a DRL schedule, reinforcement is only available at certain inter-response intervals, and the interval between responses is reset if there is a premature movement. Monterosso and Ainslie (1999) argue that temporal discounting underlies DRL performance, as premature responses in DRL are not rewarded). A failure to inhibit premature responding is considered increased impulsivity. However, in boys with ADHD, DRL response rates were not significantly affected by meth-

ylphenidate (Weber, 1985). Furthermore, in animals, D-amphetamine impairs performance on DRL schedules, increasing response rate and decreasing reinforcement rate (Bizot, 1998). Therefore, measures of DRL performance do not provide a useful marker for therapeutic efficacy.

Summary of behavioural paradigms

This short overview indicates some of the behavioural paradigms used to measure drug effects in 'normal' rat populations. Many of these measures have a strong theoretical basis as measures of impulsivity or inattention and may be useful in predicting the therapeutic effects of drugs. In the following section, the use of these and other paradigm in animal models will be reviewed.

The spontaneously hyperactive rat model

The SHR is an extensively studied animal model of ADHD (Sagvolden *et al.*, 1992b; 1993b; 2005b; 2009; Sagvolden and Berger, 1996; Sagvolden, 2000), although it has not been used in drug development. The SHR is an inbred strain developed by selecting for the hypertensive phenotype in outbred Wistar rats and brother-sister mating (Okamoto and Aoki, 1963). As well as creating a strain that exhibited spontaneous hypertension, inbreeding also fixed some distinctive behavioural characteristics in the SHR genome (McCarty and Kopin, 1979; Schaefer, 1980). These behavioural characteristics have led to extensive use of the SHR as a model for ADHD. In this case, the hyperactive phenotype was selected unintentionally, as an unintended consequence of selecting for hypertension.

A control strain for the SHR, the Wistar-Kyoto (WKY), was developed by inbreeding normotensive rats from the original WI strain (Louis and Howes, 1990; Johnson *et al.*, 1992) as a genetic control strain in studies on blood pressure. The WKY has also been used as a control in studies of hyperactivity because it does not exhibit the hyperactivity characteristics of the SHR. However, when the WKY is compared with Sprague-Dawley rats or to Wistar rats, it appears to be abnormally inactive and may be unsuitable as a control (Bull *et al.*, 2000; Diana, 2002).

A very high degree of genetic similarity is required for a control strain, but the SHR and WKY genomes are not highly similar (Festing and Bender, 1984; Kurtz *et al.*, 1989; Johnson *et al.*, 1992; St Lezin *et al.*, 1992). Also, genetic heterogeneity between animals obtained from different breeding facilities has been reported in the WKY (Kurtz *et al.*, 1989; Nabika *et al.*, 1991). Substrains of the WKY have been suggested to model the inattentive subtype of ADHD (DasBanerjee *et al.*, 2008) or anxiety (Pardon *et al.*, 2002) and childhood depression (Malkesman and Weller, 2009). To complicate matters, DNA fingerprinting techniques have shown differences between colonies of SHR maintained in the USA and Japan (Nabika *et al.*, 1991), although there is no evidence of sub-strain differentiation among SHR stocks from the major suppliers in the USA (Twigger *et al.*, 2007; Dwinell *et al.*, 2009).

Despite these caveats, in other respects, the genetically determined behavioural characteristics of the SHR are a good fit to the requirements for modelling ADHD symptoms.

A number of different schedules have been used to investigate the behavioural characteristics of the SHR. The SHR have been reported to be hyperactive in an open field (Knardahl and Sagvolden, 1979; McCarty and Kopin, 1979). However, this characteristic has not been reliably reproduced (Ferguson and Cada, 2003). Moreover, open-field behaviour is arguably not a good measure of the ADHD phenotype: the locomotor activity of children measured in a clinical playroom in terms of grid line crossings has not correlated significantly with parent ratings of hyperactivity (Barkley and Ullman, 1975; Routh and Schroeder, 1976), or clinical diagnosis (Schroeder *et al.*, 1980). Therefore, the open-field test has poor reliability as a measure of hyperactivity in the SHR, and the face validity of the open field test for ADHD is questionable.

Of greater interest, the SHR displays impulsive behaviour that has several features in common with ADHD behaviour characteristics. An abnormal response to reward in the SHR has been described. This has been extensively studied on a compound schedule of reinforcement that includes a fixed-interval (FI) component followed by an extinction (EXT) component (Sagvolden *et al.*, 1992a; 1992b; 1993a). Both SHR and control rats on this FI-EXT schedule show the typical 'FI scallop', which is an increase in response rate over the later segments of the FI component. However, the rate increase is greater in the SHR than in control strains, with a greater terminal response rate (Sagvolden *et al.*, 1992a; 1993b). This characteristic pattern of responding is also present in children with ADHD, relative to controls, when tested on similar FI-EXT schedules (Sagvolden *et al.*, 1998), providing face validity, although correlation with clinical measures of symptoms of this measure has not been tested.

Based largely on the FI-EXT schedule, the Sagvolden group has argued that the SHR models a steeper than normal delay of reinforcement gradient that is a characteristic of children with ADHD (Sagvolden *et al.*, 1998; 2005a; Sagvolden, 2000; Johansen *et al.*, 2002; 2005; 2007; 2009). The interpretation of responding on a compound FI-EXT schedule in terms of delay gradients is complex and requires a number of theoretical assumptions (Catania *et al.*, 1988; Catania, 2005). In a more direct test of the delay gradient hypothesis, the delay of reinforcement was increased on a variable interval schedule. On this schedule, the SHR showed decreased responding relative to WKY controls (Johansen *et al.*, 2005). However, the SHR had a higher baseline response rate at the shortest reinforcement delays. It has been argued that when the higher baseline response rate is corrected for, there is less difference in the effect of delays (Alsop, 2007), suggesting that more direct measures of the effect of delays may be useful in confirming this interpretation of FI-EXT behaviour.

The SHR also show abnormal responses to reward (Wultz *et al.*, 1990; Hendley and Ohlsson, 1991; Wultz and Sagvolden, 1992; Sagvolden *et al.*, 1993b), which are similar, in several respects, to the altered reward sensitivity seen in children with ADHD. Like children with ADHD (Sagvolden *et al.*, 1998; Castellanos and Tannock, 2002; Johansen *et al.*, 2002), behaviour in the SHR is said to be more sensitive to

immediate reinforcement and proportionately less sensitive to delayed reinforcement (Sagvolden *et al.*, 1992b). Also, like children with ADHD, more frequent reinforcement reduces the differences between the SHR and controls (Sagvolden *et al.*, 1993a).

In direct measures of the effect of delay of reinforcement, SHRs are more impulsive than the WKYs as defined by preference for smaller, immediate reinforcers over larger, delayed ones. Bizot *et al.* (2007) found that adult SHR exhibit a more impulsive behaviour than WKY or WI in a T-maze, in which rats had to choose between a small-but-immediate and a large-but delayed reward procedure. Fox *et al.* (2008) used a procedure in which rats made repeated choices between a single food pellet delivered immediately and three food pellets delivered after a delay. The SHRs chose more small/immediate reinforcers than the WKYs at the longest delays (Fox *et al.*, 2008). In our laboratory, Sutherland *et al.* (2009), using a signal detection task that had been developed from a task used with children with ADHD, found that SHR were more sensitive to delay of reinforcement than control strains. These findings collectively support the SHR as a model for impulsive behaviour; however, the comparisons are against various control strains, and as discussed above, the normality of the control strain can be difficult to establish.

There have been relatively few studies of the effects of stimulants on the SHR. As might be expected from the variability of open-field measures in the SHR, tests of psychostimulant action using open-field testing have not produced reliable results. Early reports that D-amphetamine ($1.25\text{--}3.5\text{ mg}\cdot\text{kg}^{-1}$) decreased activity in the SHR (Myers *et al.*, 1982) and methylphenidate reduced hyperactivity in the stroke-prone SHR (Ueno *et al.*, 2002) have not been replicated in subsequent studies. Methylphenidate ($1\text{ mg}\cdot\text{kg}^{-1}$) did not attenuate hyperactivity of SHR in an open-field test (van den Bergh *et al.*, 2006a). Higher doses (2.5 and $10.0\text{ mg}\cdot\text{kg}^{-1}$) increased activity in the adolescent and the adult rats (Barron *et al.*, 2009). Yang *et al.* (2006) and Amini *et al.* (2004) found that methylphenidate increased open-field activity of SHR and WKY. Warton *et al.* (2009) found that SHR were more active in the open field than WKY; however, neither strain showed any effect of treatment with methylphenidate. These findings show that drug effects on open-field behaviour in the SHR are not reliable indicators of therapeutic effectiveness. Most researchers would agree, however, that the open-field test is a poor measure because it is not sensitive to context in the same way as hyperactivity in children ADHD.

In testing drug effects on the SHR in the multiple FI-EXT schedule, the effects of methylphenidate and D-amphetamine were complex (Sagvolden *et al.*, 1992b). There was an increase in responses earlier in the interval, leading to a flatter fixed interval and less obvious scallop. These effects were more pronounced in WKY than in SHR. The authors suggested that the psychomotor stimulants weakened the control by immediate reinforcers and strengthened the control by delayed reinforcers (Sagvolden *et al.*, 1992b). However, treatment with psychostimulants did not make the SHR more like the WKY or other control strains. Thus, the subtlety of this effect of psychostimulants on SHR performance in the FI-EXT suggests it has limited predictive value for treatments of ADHD.

The T-maze task described earlier, in which rats had to choose between a small-but-immediate and a large-but

delayed reward procedure (Bizot *et al.*, 2007), is a more direct measure differentiating control by immediate and delayed reinforcers. On this task, the SHR exhibits more impulsive behaviour. Bizot *et al.* (2007) found that methylphenidate $3\text{ mg}\cdot\text{kg}^{-1}$ did not reduce impulsivity in the SHR.

Kantak *et al.* (2008) investigated the effects of oral methylphenidate ($1.5\text{ mg}\cdot\text{kg}^{-1}$) on three tasks chosen to measure prefrontal cortical or dorsal striatum function: odour-delayed win-shift (non-spatial working and reference memory), win-stay (habit learning) and attentional set-shifting (attention and behavioural flexibility) tasks. On all three tasks, the SHR made significantly more errors than the WKY. Treating the SHR with methylphenidate eliminated strain differences in all three tasks. Liu *et al.* (2008) investigated the effects of atomoxetine on the behaviour of the SHR in the Morris water maze. Maze learning was improved after atomoxetine administration. However, the relevance of the foregoing tasks to ADHD is unclear at present. The performance of the SHR has also been tested in the 5-CSRT paradigm but was not abnormal. Methylphenidate ($0.1\text{--}1.0\text{ mg}\cdot\text{kg}^{-1}$) did not improve performance of SHR in this task (van den Bergh *et al.*, 2006b).

In summary, while the SHR has face validity, drug studies in the SHR have produced inconsistent results. Currently available evidence does not support the predictive validity of this rat strain as a test of the efficacy for drugs to treat ADHD. It may be argued that children with ADHD may have different neurochemistry or physiology that would lead to specific drug effects due to ceiling effects, chronic adaptations, metabolic differences or receptor hypersensitivity. Thus, it is important to take the potential for strain-by-drug interactions into account. However, there is no guarantee that the differences between the SHR and reference strains are the same as the differences between children with and without ADHD at the physiological/biochemical level.

New Zealand genetically hypertensive rats

At about the same time as the development of the SHR, a second, genetically independent, hypertensive rat strain, known as the genetically hypertensive rat (GH), was developed in New Zealand by selective breeding of Wistar (WI) rats for hypertension (Smirk and Hall, 1958; Phelan, 1968; Simpson *et al.*, 1973). The GH showed no evidence of hyperactivity within an open field in comparison with its parent strain, the Wistar (McCarty and Kopin, 1979; McCarty and Kirby, 1982; McCarty, 1983). Wickens *et al.* (2004) tested the GH strain using the FI-EXT task that has been used extensively in studies with the SHR. Like the SHR, the GH showed higher terminal response rates and response bursts, and a greater level of continued responding during EXT, in comparison with both the WI and WKY strains. In an F-2 hybrid strain obtained by crossbreeding of GH and WI rats, response rates were uncorrelated with blood pressure, providing evidence for dissociation between hyperactivity and hypertension in the GH (Wickens *et al.*, 2004).

Recently, Sutherland *et al.* (2009) measured sensitivity to delay of reinforcement in the SHR and GH strains using a task adapted from one previously used to measure effects of delay

of reinforcement in children with ADHD (Tripp and Alsop, 2001). The experimental task required pressing one of two available levers each trial. One lever delivered an immediate reinforcement, and the other lever a delayed reinforcement. Both the SHR and GH strains allocated significantly more responses to the immediately reinforced lever than their genetic control strains. These findings support the use of both SHR and GH rat to model altered response to the immediacy of reinforcement. In addition, as in children with ADHD, individual instances of reinforcement affected response allocation in the GH so that responses on the immediate lever were not less likely following immediate reinforcement on the previous trial. In contrast, SHR, like control strains, tended to change their response after immediate reinforcement. This suggests that the GH strain may have particular value as a model of the effects of individual instances of reinforcement seen in children with ADHD.

The GH provides an interesting complement to the SHR, in that in both strains the hyperactivity has arisen from selection for high blood pressure, though it is not related to blood pressure *per se*. This convergence across strains suggests that the relevant genes may be physically close but are not identical to those for hypertension. However, further work is needed to analyse the behavioural characteristics of the GH. For example, the effects of methylphenidate have not been tested in the GH rat.

Mice selectively bred for high voluntary wheel-running activity

Rhodes *et al.* (2001) have recently described mouse lines that have been selectively bred (23–24 generations) for increased running-wheel activity. Basal activity in animals deprived of wheels (quantified using photobeam breaks) was significantly higher in selected than control lines on the second day of testing. The DAT inhibitors cocaine and GBR 12909 decreased wheel running in hyperactive lines, suggesting an association between genetically determined hyperactive wheel-running behaviour and dysfunction in the dopamine system. Methylphenidate (15 and 30 mg·kg⁻¹) increased wheel running in control lines but decreased running in selected lines (Rhodes and Garland, 2003). Mice selectively bred for high voluntary wheel-running activity may be a useful genetic model for ADHD, though the doses of methylphenidate reported are about 100-fold higher than the clinically relevant dose, and as noted previously, simple increases in activity are not a good marker of ADHD.

Dopamine-depleted animals

Neurochemically selective lesions of the dopamine neurons by administration of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) to neonatal rats leads to locomotor hyperactivity during development that persists until adulthood (Shaywitz *et al.*, 1976a; Kostrzewa *et al.*, 2008). A 6-OHDA mouse model has also been developed, which shows increased activity levels and a reduction in activity following treatment with psychomotor stimulants (Avale *et al.*, 2004a;

2004b). In most cases, the lesion is made using desipramine pretreatment to prevent loss of norepinephrine-containing neurons. The locomotor hyperactivity caused by dopamine depletion in neonates is in contrast to that seen when the lesion is made in adult rats, which causes Parkinsonism. In neonates, the effects of the lesions vary according to specific details of the protocols, such as the age of the rat at treatment, the dose, the age of animal at testing and the degree of subsequent hyperactivity is correlated with the extent of the dopamine depletion (Miller *et al.*, 1981). However, the hyperactivity in this model is not necessarily a primary effect of low dopamine levels but possibly a secondary effect due to compensatory overgrowth of another neurochemical pathway, such as 5-HT.

The hyperactivity induced by neonatal 6-OHDA lesions is reduced by amphetamine (Shaywitz *et al.*, 1976b) and methylphenidate (Heffner and Seiden, 1982; Davids *et al.*, 2002b). Kuczenski and Segal (2002) established stimulant doses and conditions that approximated clinically relevant conditions. They found that low, oral doses of methylphenidate that produce blood levels similar to those in ADHD patients decrease locomotor activity in juvenile rats (Kuczenski and Segal, 2001; 2002). These low doses have a preferential effect on the norepinephrine transporter and increase norepinephrine levels in the prefrontal cortex (Berridge *et al.*, 2006).

Although norepinephrine neurons are spared in the standard dopamine-depleting protocols, there is evidence that the effects of stimulants on hyperactivity in the 6-OHDA-lesioned animals are mediated by actions on the norepinephrine transporter (NET) rather than DAT. For example, Davids *et al.* (2002a) found that although methylphenidate reduced locomotion in a novel environment, these effects were not mimicked by selective DAT inhibitors, but they were mimicked by NET and serotonin transporter inhibitors. Consistent with these findings, administration of the NET-inhibitor atomoxetine strongly antagonized motor hyperactivity in 6-OHDA-lesioned juvenile rats (Moran-Gates *et al.*, 2005). These findings suggest that NET and DAT mediate the stimulant effects on locomotor hyperactivity in 6-OHDA-lesioned rats.

What are the implications of these findings for the power of the 6-OHDA-lesioned animal model to predict therapeutic response? As a measure of ADHD symptoms in children, open-field activity measures have not been very successful in the sense of correlating with teacher or parent reports of hyperactivity (Barkley, 1991). On the other hand, 6-OHDA-lesioned rats have not been tested on tasks that measure impulsivity. Some learning deficits have been reported in the 6-OHDA model. These include poor maze performance (Shaywitz *et al.*, 1978) and impaired active avoidance (Takasuna and Iwasaki, 1996). However, the neonatal 6-OHDA-lesioned animal model has not yet been validated using tasks that measure behavioural characteristics such as impulsivity.

Dopamine transporter knockout mouse

Several pieces of evidence suggest that abnormal DAT function may be important in ADHD. The dopamine transporter

plays a critical role in terminating the dopamine signal after a release event and in regulating the ongoing extracellular concentration of dopamine. As previously discussed, overexpression of DAT has been found in human ADHD, and one of the major actions of the psychostimulants is to block DAT, so DAT over-function has been proposed. On the other hand, under-expression of DAT has been also been reported in human ADHD. Hence, mice with genetically engineered reduction or even elimination of DAT function have been proposed as models for use in ADHD research (Drago *et al.*, 1998; Gainetdinov and Caron, 2003; Gainetdinov, 2008).

The behavioural characteristics of the genetically engineered DAT knockout mice have some distinct features. DAT knockout mice show high levels of spontaneous locomotion activity compared with wild-type controls (Spielewoy *et al.*, 2000). They are easily aroused by novelty and respond with hyperlocomotion, which interferes with habituation to the testing environment and with exploratory behaviour in an open field (Spielewoy *et al.*, 2000). While the wild-type mice exhibit a mixture of straight, meandering and circumscribed movements around a testing enclosure, the DAT knockout mouse is more active and engages almost exclusively in repetitive straight movements around the perimeter of the enclosure (Ralph *et al.*, 2001). The hyperactivity is attenuated by the dopamine antagonist haloperidol. This suggests that the hyperactivity might be mediated by dopamine, although dopamine antagonists may also reduce activity by different mechanisms. In the open-field environment, high doses of methylphenidate (30 mg·kg⁻¹) increased locomotion in wild-type mice and decreased locomotion in DAT knockout mice. The effects in knockout mice were mediated by increases in serotonin, suggesting that therapies directed at serotonin may be useful in ADHD (Gainetdinov *et al.*, 1999).

Although genetic engineering offers powerful approaches to develop models, there are some limitations. First, the role of DAT in ADHD is unclear. Genetic studies show only small fraction of variance is accounted for by variation in dopamine transporter. Second, the cause of altered DAT expression in ADHD could be secondary to changes in dopaminergic innervation as well as changes in the amount of DAT per cell. If the reason for lower DAT expression is less innervation, then approaches that depend on higher dopamine levels lack construct validity. Third, measuring activity in an open-field situation lacks face validity when the nature of the activity in humans is compared with that seen in the knockout.

Conclusions

As a behaviourally defined disorder of unknown aetiology and pathophysiology, ADHD presents special problems for the development of animal models for examining and selecting compounds with potential therapeutic benefit. At the present stage of development, although there are some promising candidates, there are no *in vivo* models of proven effectiveness for examining and selecting compounds with potential therapeutic benefit in ADHD. In terms of animal models that simulate the symptoms of ADHD, the most commonly used are the SHR and the 6-OHDA-lesioned animals. Behavioural characteristics of the SHR have been extensively studied. To date, however, impulsivity and inhibitory control

have not been studied extensively in 6-OHDA-lesioned animals.

Our review of the human studies indicates that hyperactivity in humans with ADHD is context-dependent. Therefore, animals with high activity in all situations do not adequately model this aspect. Similarly, the situation dependence of the effects psychostimulants in humans should be taken into account. Drugs may, for example, modulate sensitivity to reinforcement or novelty and secondarily affect activity levels depending on context. A better approach may be to focus on the effects of drugs on the sensitivity to the contingencies that set the occasion and modulate activity levels.

Because the symptoms of ADHD are present in some degree in the normal population, and stimulants have beneficial effects on inattention, impulsivity and hyperactivity in people with and without ADHD, it is reasonable to use 'normal' rats to investigate drug actions. A number of behavioural paradigms of relevance have been tested and shown to be sensitive to existing drug treatments. Many of these measures have a strong theoretical basis as measures of impulsivity or inattention and can therefore be used in predicting the therapeutic effects of drugs. These behavioural paradigms can also be used to select animals from extremes of the normal range for use in drug development. In particular, temporal discounting is an emerging theme in theories of ADHD, and there is good evidence of increased value of delayed reward following treatment with stimulant drugs. Therefore, operant behaviour paradigms that measure the effects of drugs in situations of delayed reinforcement, whether in normal rats or selected models, show promise for the future.

Future progress requires close interaction of clinical and basic science perspectives to prevent the core behavioural characteristics of ADHD from being lost in translation to animal models. On the one hand, the clinical features of the disorder need to be communicated to animal researchers in a manner that recognizes that symptoms such as hyperactivity are context-specific. On the other hand, animal researchers need to appreciate that they are dealing with a disorder that has no known pathology and no specific combination of features that can be considered necessary and sufficient to define ADHD.

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Conflict of interest

Nothing to report.

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