Rat Models of ADHD

Terje Sagvolden and Espen Borgå Johansen

Contents

Abstract Showing that an animal is hyperactive is not sufficient for it to be accepted as a model of ADHD. Based on behavioral, genetic, and neurobiological data, the spontaneously hypertensive rat (SHR) obtained from Charles River, Germany, (SHR/NCrl) is at present the best-validated animal model of ADHD. One Wistar Kyoto substrain (WKY/NHsd), obtained from Harlan, UK, is its most appropriate control. Another WKY substrain (WKY/NCrl) obtained from Charles River, Germany, is inattentive, has distinctly different genetics and neurobiology, and provides a promising model for the predominantly inattentive subtype of ADHD (ADHD-I) if one wants to investigate categorical ADHD subtypes. In this case, also, the WKY/NHsd substrain should be used as control. Although

Note. Strain nomenclature is based on the Rat Genome Database (Twigger et al. 2007; Rat Genome Database 2008).

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other rat strains may behave like WKY/NHsd rats, neurobiological results indicate significant differences when compared to the WKY/NHsd substrain, making them less suitable as controls for the SHR/NCrl. Thus, there are no obvious behavioral differences among the various SHRs, but there are behavioral and neurobiological differences among the WKY strains. The use of WKY/NCrl, outbred Wistar, Sprague Dawley, or other rat strains as controls for SHR/NCrl may produce spurious neurobiological effects and erroneous conclusions. Finally, model data yield support to independent hyperactivity and inattention dimensions in ADHD behavior.

Keywords Animal models · Attention-deficit/hyperactivity disorder · Genetics · Neuroanatomy · Neurophysiology · Validation

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ADHD-C	Attention-deficit/hyperactivity disorder combined subtype
ADHD-H	Attention-deficit/hyperactivity disorder predominantly hyperactive-impulsive subtype
ADHD-I	Attention-deficit/hyperactivity disorder predominantly inattentive subtype
DA/OlaHsd	Inbred rats from Harlan, UK
IMAGE	International multi-center ADHD gene (project)
LEW/NHsd	Lewis rats from Harlan, UK
PVG/Mol	Inbred hooded rats from Møllegaard Breeding Centre, Denmark
RT-PCR	Real-time polymerase chain reaction
SD/MolTac	Outbred Sprague Dawley rats from Møllegaard Breeding Centre, Denmark
SD/NTac (NTac:SD)	Taconic Sprague Dawley rats
SHR	Spontaneously hypertensive rat
SHR/N	Inbred SHR from NIH
SHR/NCrl	Inbred SHR from Charles River, Germany
SHR/NMol	Inbred SHR from Møllegaard Breeding Centre, Denmark
SNP	Single nucleotide polymorphism
SSLP	Simple sequence length polymorphisms
WH/HanTac (also known as: HanTac:WH)	Outbred Wistar Hannover GALAS rats from Taconic Europe
WHHA/Edh (now WKHA/N)	Inbred rat from a cross between SHR and WKY with selection for high spontaneous activity and low systolic blood pressure at the University of Vermont College of Medicine, USA

WHHT/Edh (now WKHT/N)	Inbred rat from a cross between SHR and WKY with selection for normal spontaneous activity and high systolic blood pressure at the University of Vermont College of Medicine, USA
Wistar/Mol	Outbred from Møllegaard Breeding Centre, Denmark
WKY/N	Inbred WKY from NIH, USA
WKY/NHsd	Inbred WKY from Harlan Europe, UK
WKY/NicoCrlf	Inbred WKY from Charles River, France
WKY/NMolTac (also known as: WKY/NMol)	WKY from Møllegaard Breeding Centre, Denmark

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder where all clinical criteria are behavioral. It is a heterogeneous disorder affecting about 5% of children (Faraone and Mick 2010), and its prevalence is similar in different cultures (Dwivedi and Banhatti 2005; Meyer et al. 2004; Rohde et al. 2005). The heterogeneity may be sorted along two independent behavioral dimensions: inattention and hyperactivity impulsiveness (Lahey and Willcutt 2010). DSM-IV (American Psychiatric Association 2000) attempts to reduce the heterogeneity by subdividing ADHD into three subtypes: the predominantly inattentive subtype (ADHD-I); the predominantly hyperactive-impulsive subtype (ADHD-H); and the combined subtype (ADHD-C). ADHD places the child at increased risk of school failure, juvenile delinquency, criminality, substance abuse, and HIV/AIDS as a consequence of sexual promiscuity and disregard for preventative measures (Barkley et al. 2004; Molina et al. 2002; Kahn et al. 2002).

There have been many attempts to explain the origins of ADHD symptoms. A learning-theory perspective is gaining ground for the case of ADHD-C. The dynamic developmental theory of ADHD (Johansen et al. 2002, 2009; Sagvolden et al. 2005a; Johnson et al. 2009; Sagvolden and Archer 1989) suggests that less efficient dopamine-mediated reinforcement processes and deficient extinction of previously reinforced behavior may explain behavioral changes that are often described as either poor "executive functions" (Tannock 1998) or "response disinhibition" (Barkley 1997). This learning-theory perspective predicts specific neuronal changes related to synaptic plasticity and long-term potentiation (LTP) (Sagvolden et al. 2005a).

A reinforcer is not defined in terms of previous events, but defined in terms of the behavioral changes that follow the reinforcer. For a reinforcer to alter behavior, events need to occur within a limited time-frame, but the duration of this time-frame also depends on attentional and memory variables. This is important both in basic laboratory research, where it is often overlooked, and in analysis of ADHD, which is associated with poor attention and memory (Martinussen et al. 2005; Willcutt et al. 2005).

Animal models are helpful in medical research (Sagvolden et al. 2009). There are many putative animal models of ADHD (Roessner et al. 2010; Pardey et al. 2009; Sagvolden et al. 2009; Vendruscolo et al. 2009; Sanabria and Killeen 2008; DasBanerjee et al. 2008; Heal et al. 2008; Kostrzewa et al. 2008). However, it is important to emphasize that the DSM-IV definition of ADHD does not say "always hyperactive." Thus, although several molecular and genetic manipulations may produce hyperactive animals (Vendruscolo et al. 2009; Ruocco et al. 2009; Yan et al. 2009; Dalley et al. 2009; Kostrzewa et al. 2008), hyperactivity alone is insufficient for the animal to qualify as a model of ADHD. It is important to consider whether children with ADHD would be hyperactive in a similar test or situation (Johansen et al. 2009).

This review concentrates on the best-validated animal model of ADHD: the spontaneously hypertensive rat (SHR) obtained from Charles River, Germany (SHR/NCrl) (Rat Genome Database 2008) (see the Abbreviations section) with the Wistar Kyoto rat, obtained from Harlan, UK (WKY/NHsd), as the reference strain in an animal model for ADHD-C. However, WKY rats obtained from Charles River, Germany (WKY/NCrl), are a promising model for the predominantly inattentive subtype of ADHD (ADHD-I) when the WKY/NHsd STRAIN is used as control. Use of both substrains as models of ADHD is potentially interesting even if ADHD is not regarded as separate subtypes, but as one disorder with the severity of symptoms varying along two independent dimensions: inattentiveness and hyperactivity impulsiveness.

2 Criteria for a Valid Animal Model of ADHD

Because the diagnosis of ADHD is based on behavior, the validation of animal models must also be based on behavior. If valid animal models were to be found, one would expect many of the same fundamental genetic and neurobiological alterations to be common in the human and the animal case. Thus, an ADHD animal model should mimic the fundamental behavioral characteristics of ADHD (face validity), conform to a theoretical rationale (construct validity), and predict correlates of ADHD in humans as regards behavior, genetics, and neuronal functions not shown previously in clinical settings (predictive validity) (Sagvolden 2000; Sagvolden et al. 2009). Although a variety of rat and mouse strains exhibit hyperactivity (Russell et al. 2005), few meet the complete set of criteria for model validation.

2.1 Behavioral Differences Among Strains of Rats

The SHR displays the major symptoms of ADHD (inattention, hyperactivity, and impulsivity) that, like ADHD, develop over time when reinforcers are infrequent

(Li et al. 2007; van den Bergh et al. 2006; Sagvolden 2000; Johansen et al. 2005b; Sagvolden et al. 1998, 2005b). As in children with ADHD (Sonuga-Barke et al. 1992), SHRs are more sensitive to delayed reinforcement (Johansen and Sagvolden 2005; Johansen et al. 2005b), consistent with a steepened delay-of-reinforcement gradient found in SHR relative to controls (Johansen et al. 2007). This means that a reinforcer has to be given immediately following the correct behavior to be efficient in the SHR, while reinforcers could be delayed somewhat in controls and still affect behavior. In addition, as in children with ADHD (Castellanos et al. 2005; Aase et al. 2006), there is increased intraindividual variability and variability in the individual SHR's behavior within the task, relative to controls (Perry et al. 2010a, b).

There is systematic overactivity, impulsiveness, and sustained attention deficit in the SHRs obtained from: NIH (SHR/N), the Møllegaard Breeding Centre, Denmark (SHR/NMol); Charles River, Italy (SHR/CrlIco); and Charles River, Germany (SHR/NCrl). By contrast (to these SHRs) neither the hypertensive WHHT/Edh nor the hyperactive WHHA/Edh substrains showed any systematic overactivity, impulsiveness, or sustained attention deficit, although the WHHA/Edh does appear to be overactive in fear-provoking open-field tests (Sagvolden et al. 2009).

The development of overactivity, impulsiveness, and sustained attention deficit in the SHRs appear to be poorly correlated [see Fig. 2 in (Sagvolden et al. 2005b)]. Medication affects these behaviors differently in the SHR (Sagvolden 2006; Sagvolden and Xu 2008). Thus, it may appear that inattention and overactivity-impulsiveness are two independent behavioral dimensions in the SHR just as they may be in children with ADHD (Lahey and Willcutt 2010).

Behaviorally, the WKY/NHsd, WKY/N, and the WKY/NMolTac are all normal in which these WKY substrains may not differ behaviorally from either WH/HanTac Wistar rats; SD/MolTac; SD/NTac Sprague Dawley rats; hooded PVG/Mol rats; outbred Wistar/Mol rats; or the offspring of DA/OlaHsd females, time-mated with LEW/NHsd Lewis males (Harlan, UK) (Sagvolden 2000; Sagvolden et al. 2009). However, the WKY/NHsd substrain is the preferred control on the basis of genetic and neurobiological considerations (see below).

2.2 Genetic Differences Among Strains

To investigate whether SHR/NCrl rats show changes in expression in systems relevant to ADHD, we (DasBanerjee et al. 2008) have analyzed ADHD candidate genes identified as a part of the International Multi-center ADHD Gene project (IMAGE), and their biological neighbors (collectively referred to as IMAGE genes) (Kuntsi et al. 2006). The IMAGE gene biological neighbors are defined as any gene that was part of the same gene or protein family as an IMAGE gene, or has a well-established direct relationship with an IMAGE gene.

The SHR/NCrl rats showed significant changes in a set of IMAGE genes: a number of these genes are relevant for a learning-theory perspective of ADHD-C. The dynamic developmental theory of ADHD (Johansen et al. 2009; Sagvolden

et al. 2005a; Johnson et al. 2009; Sagvolden and Archer 1989) suggests that defective interactions between dopamine and glutamate alter synaptic plasticity and LTP. On a behavioral level, such a faulty interaction may give rise to less efficient dopamine-mediated reinforcement processes and deficient extinction of previously reinforced behavior, and these differences could explain both inattention and overactivity-impulsiveness associated with ADHD (Sagvolden et al. 2005a).

Some of these genes showed *decreased* expression across tissues in ~65-day-old SHR/NCrl rats compared with WKY/NHsd rats: these included the ionotropic glutamate NMDA-binding protein (*Grina)*, the NMDA-like 1A complex (*Grinl1a*); the NR2D subunit (*Grin2d*); the AMPA receptor subunit GluR-3 (*Gria3*); the alpha stimulating, olfactory-type guanine nucleotide-binding protein (*Gnal*/*Golf*); the norepinephrine transporter NET (*Slc6a2*); calmodulin 3 (*Calm3*); calcium/calmodulin-dependent protein kinases *Camk1*, *Camk2a*, and *Camk2g*); synaptotagmin III (*Syt3*); and syntaxin-binding protein 1 (*Stxbp1*). *Gnal* (*Golf*) is coupled to the dopamine receptor, DRD1, and plays a major role in excitatory dopamine transmission in the striatum. Significant relationships have been observed between certain SNPs in *Gnal* and symptoms of inattention and hyperactivity/impulsivity in ADHD children (Laurin et al. 2008).

In contrast, other genes showed *increased* expression (mRNA) in the SHR/NCrl rats compared to WKY/NHsd rats: these included the AMPA receptor subunit Glu-R2 subunit (*Gria2*); the NMDA subunits NR1 and NR2C (*Grin1* and *Grin2c*); calcium/calmodulin-dependent protein kinase kinase 1 (*Camkk1*); catechol-*O*-methyltransferase (*Comt*); the dopamine transporter DAT1 (*Slc6a3*); the dopamine receptor D1 interacting protein (*DRD1ip*); the 5-hydroxytryptamine (serotonin) receptor (*Htr3b*); the calmodulin-binding protein striatin (*Strn*); syntaxin 11 (*Stx11*); syntaxin 17 (*Stx17*); nicotinic cholinergic alpha polypeptide 9 receptor (*Chrna9*); mu opioid receptor 1 (*Oprm1*); hairy and enhancer of split 6 (*Hes6*); and aquaporin 3 (*Aqp3*). A complete list of significantly altered genes is available in DasBanerjee et al. (2008).

Based on blood samples, no between-strain differences in DNA were observed for either the DRD2 or the DRD4 genes, suggesting that neither gene is likely to mediate the behavioral differences between the WKY and SHR strains. In contrast, WKY/SHR differences were observed in the third exon of DAT1. While these mutations do not result in direct amino acid changes to the DAT protein, it is possible that they mediate some other process that explains the differences in DAT expression and function in the two strains (Mill et al. 2005).

The dopamine receptor (DRD1)-interacting protein (*DRD1ip*), calcyon, represents a brain-specific protein involved in DRD1/DRD5 receptor-mediated calcium signaling. In our data, the SHR/NCrl had a twofold increase in expression of calcyon mRNA compared with WKY/NHsd rats. This is in agreement with a recent study that examined calcyon mRNA expression in the frontal-striatal circuitry of 3-, 5-, and 10-week-old SHR and WKY rats (Heijtz et al. 2007). Such a changed expression of *DRD1ip* may indicate an underlying disruption of reinforcement processes mediated by dopamine (Schultz 2010).

A major function of dopaminergic transmission is to modulate fast, ionotropic synaptic transmission mediated by the neurotransmitter glutamate. Thus, the observed changes in gene expression for subunits of both AMPA and NMDA glutamatergic receptors may profoundly affect neuronal function. Electrophysiological studies revealed two potential consequences of such changes (Jensen et al. 2009). First, in male SHR/NCrl and WKY/NHsd rats, at postnatal day 28, the AMPA receptor-mediated transmission at the CA3-to-CA1 synapses was reduced in the stratum radiatum of the hippocampus. Second, the NMDAR containing *Grin2b* (aka *GluN2B*) subunits contributed substantially to induction of LTP in SHR/NCrl, but not in WKY/NHsd. In human ADHD, there is evidence for genetic polymorphism of both *Grin2a* and *Grin2b* subunits of the NMDA receptor (Turic et al. 2004; Dorval et al. 2007), which might mean that synaptic plasticity associated with learning, reinforcement, and extinction may be altered in ADHD individuals as well (Sagvolden et al. 2005a).

Human and animal data indicate that the mu opioid receptor 1 (*Oprm1*) is associated with substance abuse disorders (Berrendero et al. 2002; Zhang et al. 2006). Individuals with ADHD show strong substance dependence (Faraone et al. 2007). Thus, it is possible that substance dependence in ADHD may be modulated by *Oprm1*.

3 Applying Validity Criteria to Animal Research

A large number of studies support the use of SHR as the best animal model of ADHD. However, there are also researchers who question the validity of the SHR/NCrl model (Ferguson and Cada 2003; van den Bergh et al. 2006). This section highlights a few important factors that may have contributed to some of the inconsistencies in the literature regarding the value of SHR as an animal model of ADHD.

3.1 WKY Heterogeneity: SHR/NCrl and WKY/NCrl Versus WKY/NHsd Controls

From a genetic point of view, the best candidate for a control strain is the progenitor strain of SHR/NCrl: i.e., the WKY. However, the various WKY substrains are not equally suited to serve as controls due to genetic and behavioral differences. For instance, genome-wide analyses show that the WKY/NCrl rats are more similar to the SHR/NCrl than to the WKY/NHsd rats (Sagvolden et al. 2008). Behaviorally, WKY/NCrl rats are more similar to the WKY/NHsd strain in some tasks, but are more similar to SHR/NCrl in others. We will argue that the SHR/NCrl strain, with the WKY/NHsd substrain acting as controls, is the best animal model of ADHD-C

if this subtype really exists, or ADHD with individually highly variable dimensions of inattention and overactivity (Perry et al. 2010a, b) in a dimensional view of ADHD (Lahey and Willcutt 2010).

The newly described genetic and behavioral changes in the WKY/NCrl make this a promising model of ADHD-I (Sagvolden et al. 2008) if subtypes of ADHD exist. Both the WKY/NCrl and SHR/NCrl strains are inattentive relative to Sprague Dawley and Wistar/HanTac controls strains. However, WKY/NCrl rats are neither hyperactive nor impulsive, like the SHR/NCrl rat (Sagvolden et al. 2008). It is conceivable; however, that inattention is a phenomenon by itself and not necessarily associated with ADHD. Then, the WKY/NCrl might not be a model of ADHD, but of some other disorder mainly associated with inattention.

Independent of whether or not the WKY/NCrl is a model of ADHD, the heterogeneity between the WKY substrains makes it imperative that researchers provide information about the substrain and breeder used in their studies to enable empirical findings to be adequately evaluated by others.

3.2 ADHD: Defining Features and Situational Factors

One issue that might lead to disagreement regarding the validity of SHR/NCrl as an animal model of ADHD is how findings are interpreted and extrapolated. A defining feature of ADHD-C and of ADHD-H is hyperactivity. However, the DSM-IV definition of ADHD does not say "always hyperactive," but includes statements like "have persisted for at least 6 months to a degree that is maladaptive and inconsistent with the developmental level" or "present in more than two or more settings." Some animal researchers seem to assume that ADHD implies persistent hyperactivity. Thus, if hyperactivity is not found in the animal model (in the specific test used in the present study), it is not a valid model of ADHD. These researchers fail to ask an additional, central question: "Are children with ADHD always hyperactive?" The answer to that question is "no" based on findings reported in the research literature, clinical experience, and reports from parents and teachers.

As in people with ADHD, the degree of behavioral problems in SHR depends on the task. Thus, the conclusion that a particular animal model is not valid for studies of ADHD, based on results from one test, only, may simply be incorrect. This point emphasizes the importance of good, reliable, translational tests that can be used in the animal model as well as in children with ADHD to test the correspondence between ADHD hyperactivity and hyperactivity in the animal model.

A second, related issue is the uncritical reliance on ADHD research literature when designing animal model studies. Such studies may refer to findings that report the presence of a particular behavioral change or cognitive deficit, which is then investigated in the animal model. Researchers may sometimes conclude that the results do not support continued use of an ADHD model, because a behavioral change or cognitive deficit that has been reported in the ADHD literature is absent

in the animal model. However, many behavioral measures and cognitive concepts studied in ADHD, e.g., many aspects of "executive functions," are not defining features of the disorder. The literature on children diagnosed with ADHD is inconsistent regarding most of these cognitive or behavioral measures. Furthermore, if a clinician observes a child with all the symptoms of ADHD, but without the behavioral change or specific cognitive deficit in question, she or he would not automatically conclude that this child does not have ADHD. Thus, categorical conclusions on the validity of animal models based solely on one such measure may be erroneous.

3.3 Age and Development

The lack of a positive response to medication is a final issue that sometimes is used as an argument against the SHR/NCrl model of ADHD. As the greater majority of patients with ADHD *do* respond positively, an animal model of ADHD should do the same. However, a positive response to medication is not a defining feature of ADHD: up to one in five children diagnosed with ADHD will similarly not respond positively (Faraone and Buitelaar 2010).

Several studies find that psychostimulants improve symptoms of inattention, hyperactivity, and impulsivity in SHR/NCrl (Sagvolden et al. 1992; Wultz et al. 1990; Myers et al. 1982; Sagvolden and Xu 2008). When some researchers do not find ameliorating effects of medication in SHR/NCrl, it is important to consider whether the behavioral measures are improved by medication in children with ADHD. Furthermore, we may need to adopt a developmental perspective. The effect of psychostimulant treatment in young and adolescent individuals may not be the same as in adults; medication may interact with brain development and neuronal pruning to produce its effects (Shaw et al. 2009; Bizot et al. 2007).

In this developmental perspective, we examined the expression of genes involved in dopamine signaling and metabolism in the dorsal striatum and ventral mesencephalon of SHR/NCrl and WKY/NCrl, as well as three reference control strains (WKY/NHsd, WK/HanTac, and SD/NTac) using quantitative real-time RT-PCR. In addition, we determined striatal dopamine transporter (DAT) density, by ligand-binding assay, in the two ADHD-like strains at different developmental stages and after methylphenidate treatment. In adult rats, the mRNA expression of DAT and tyrosine hydroxylase was elevated in SHR/NCrl and WKY/NCrl rats compared to control strains: differences in DAT and tyrosine hydroxylation expression between SHR/NCrl and WKY/NCrl rats were also evident. During normal development, changes in striatal DAT densities occurred in both strains, with lower densities in WKY/NCrl than SHR/NCrl after postnatal day 25. Two weeks of methylphenidate treatment, during different developmental stages, was associated with decreased striatal DAT density in both rat strains compared to the non-treated rats with more pronounced effects followed by prepubertal treatment (Roessner et al. 2010).

Thus, use of old, hypertensive SHRs may potentially produce misleading results when studying SHR/NCrl as an animal model of ADHD. Hypertension can have deleterious effects on the brain function and produce spurious results. Studies of the SHR/NCrl model should preferably use young, prehypertensive animals to avoid this possible confound, although young adults with ADHD may be hypertensive as well as obese (Fuemmeler et al. 2010).

4 Implications for Understanding ADHD

The dynamic developmental theory of ADHD (Johansen et al. 2005a; Sagvolden et al. 2005a) suggests that reduced dopaminergic transmission changes fundamental behavioral selection mechanisms. This arises from deficient reinforcement of successful behavior, combined with deficient extinction (elimination) of unsuccessful behavior. In SHR/NCrl, neurobiological evidence for such factors is found both in the reduced dopamine efficacy (Sagvolden et al. 2009; Roessner et al. 2010) and in altered LTP in hippocampal slices (Jensen et al. 2009).

Such deficient selection mechanisms will slow the association ("chunking") of simple response units into longer, more elaborate chains of adaptive behavioral elements that function as higher-order behavioral units (Miller 1956; Aase and Sagvolden 2005; Aase et al. 2006; Perry et al. 2010a, b). Whenever behavioral units are chunked together into a chain of responses that is emitted in this context, each behavioral unit reliably precedes the next with high predictability. Consequently, deficient or slowed chunking of behavior will increase intraindividual variability. This is observed in children with ADHD and in the SHR (Aase and Sagvolden 2006; Johansen et al. 2009; Perry et al. 2010a, b).

5 Conclusions

There are no obvious behavioral differences among the various SHRs, but there are behavioral and neurobiological differences among the WKY strains. Several strains of rats may behave like WKY/NHsd rats; genetic studies indicate significant differences between various "normal" strains. Thus, Sprague Dawley rats may be a poor control for the SHR/NCrl, particularly in neurobiological studies. Given that the Wistar WH/HanTac rats and WKY/NCrl deviate both genetically and behaviorally from the WKY/NHsd, the use of these strains as controls for SHRs may produce spurious neurobiological differences. Thus, WKY/NHsd is the most appropriate control for SHR/NCrl. As a consequence, data may be misinterpreted if researchers or readers do not pay attention to the strain or substrain that was used in a study.

It is likely that lack of attention to such factors has led to erroneous conclusions in studies involving the SHR, WKY, and other comparison strains, in model studies

of ADHD. The SHR/NCrl is the best-validated animal model of ADHD. Genetic and neurobiological data strengthen such a conclusion. Recent data suggest that the WKY/NCrl is inattentive, but it is unclear whether this substrain can be used as a model of ADHD.

The availability of validated ADHD animal models has substantial implications for research. Unlike some disorders, such as schizophrenia or bipolar disorder (for which there exist brain tissue resource centers), brain tissue is not available for ADHD patients. Animal models provide a source of such tissue for studies of gene expression, epigenetics, neuroanatomy, cellular neurophysiology, and other methods. Animal models of ADHD can also be used to search for ADHD genes using linkage or association analysis and to search for gene–environment interactions by exposing susceptible animals to environmental toxins (e.g., polychlorinated biphenyls) suspected to be risk factors for ADHD (DasBanerjee et al. 2008; Holene et al. 1998; Kuehn 2010). The SHR/NCrl is clearly useful for these.

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References

Aase H, Sagvolden T (2005) Moment-to-moment dynamics of ADHD behaviour. Behav Brain Funct 1:12

Aase H, Sagvolden T (2006) Infrequent, but not frequent, reinforcers produce more variable responding and deficient sustained attention in young children with attention-deficit/hyperactivity disorder (ADHD). J Child Psychol Psychiat 47:457–471

Aase H, Meyer A, Sagvolden T (2006) Moment-to-moment dynamics of ADHD behaviour in South African children. Behav Brain Funct 2:11

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Association, Washington, DC

Barkley RA (1997) Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr 18:271–279

Barkley RA, Fischer M, Smallish L, Fletcher K (2004) Young adult follow-up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry 45:195–211

Berrendero F, Kieffer BL, Maldonado R (2002) Attenuation of nicotine-induced antinociception, rewarding effects, and dependence in mu-opioid receptor knock-out mice. J Neurosci 22:10935–10940

Bizot JC, Chenault N, Houze B, Herpin A, David S, Pothion S, Trovero F (2007) Methylphenidate reduces impulsive behaviour in juvenile Wistar rats, but not in adult Wistar, SHR and WKY rats. Psychopharmacology 193:215–223

Castellanos FX, Sonuga-Barke EJ, Scheres A, Di Martino A, Hyde C, Walters JR (2005) Varieties of attention-deficit/hyperactivity disorder-related intra-individual variability. Biol Psychiatry 57:1416–1423

Dalley JW, Fryer TD, Aigbirhio FI, Brichard L, Richards HK, Hong YT, Baron JC, Everitt BJ, Robbins TW (2009) Modelling human drug abuse and addiction with dedicated small animal positron emission tomography. Neuropharmacol 56(Suppl 1):9–17

DasBanerjee T, Middleton FA, Berger DF, Lombardo JP, Sagvolden T, Faraone SV (2008) A comparison of molecular alterations in environmental and genetic rat models of ADHD: a pilot study. Am J Medical Genet B Neuropsychiatr Genet 147B:1554–1563

Dorval KM, Wigg KG, Crosbie J, Tannock R, Kennedy JL, Ickowicz A, Pathare T, Malone M, Schachar R, Barr CL (2007) Association of the glutamate receptor subunit gene GRIN2B with attention-deficit/hyperactivity disorder. Genes Brain Behav 6:444–452

Dwivedi KN, Banhatti RG (2005) Attention deficit/hyperactivity disorder and ethnicity. Arch Dis Child 90(Suppl 1):i10–i12

Faraone SV, Buitelaar J (2010) Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 19:353–364

Faraone SV, Mick E (2010) Molecular genetics of attention deficit hyperactivity disorder. Psychiatr Clin North Am 33:159–180

Faraone SV, Biederman J, Wilens TE, Adamson J (2007) A naturalistic study of the effects of pharmacotherapy on substance use disorders among ADHD adults. Psychol Med 37:1743–1752

Ferguson SA, Cada AM (2003) A longitudinal study of short- and long-term activity levels in male and female spontaneously hypertensive, Wistar-Kyoto, and Sprague-Dawley rats. Behav Neurosci 117:271–282

Fuemmeler BF, Ostbye T, Yang C, McClernon FJ, Kollins SH (2010) Association between attention-deficit/hyperactivity disorder symptoms and obesity and hypertension in early adulthood: a population-based study. Int J Obes. Oct 26. [Epub ahead of print]

Heal DJ, Smith SL, Kulkarni RS, Rowley HL (2008) New perspectives from microdialysis studies in freely-moving, spontaneously hypertensive rats on the pharmacology of drugs for the treatment of ADHD. Pharmacol Biochem Behav 90:184–197

Heijtz RD, Alexeyenko A, Castellanos FX (2007) Calcyon mRNA expression in the frontal-striatal circuitry and its relationship to vesicular processes and ADHD. Behav Brain Funct 3:33

Holene E, Nafstad I, Skaare JU, Sagvolden T (1998) Behavioural hyperactivity in rats following postnatal exposure to sub- toxic doses of polychlorinated biphenyl congeners 153 and 126. Behav Brain Res 94:213–224

Jensen V, Rinholm JE, Johansen TJ, Medin T, Storm-Mathisen J, Sagvolden T, Hvalby O, Bergersen LH (2009) N-methyl-d-aspartate receptor subunit dysfunction at hippocampal glutamatergic synapses in an animal model of attention-deficit/hyperactivity disorder. Neuroscience 158:353–364

Johansen EB, Sagvolden T (2005) Behavioral effects of intra-cranial self-stimulation in an animal model of attention-deficit/hyperactivity disorder (ADHD). Behav Brain Res 162:32–46

Johansen EB, Aase H, Meyer A, Sagvolden T (2002) Attention-deficit/hyperactivity disorder (ADHD) behaviour explained by dysfunctioning reinforcement and extinction processes. Behav Brain Res 130:37–45

Johansen EB, Sagvolden T, Aase H, Russell VA (2005a) Authors' response: the dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD): present status and future perspectives. Behav Brain Sci 28:451–468

Johansen EB, Sagvolden T, Kvande G (2005b) Effects of delayed reinforcers on the behavior of an animal model of attention-deficit/hyperactivity disorder (ADHD). Behav Brain Res 162:47–61

Johansen EB, Killeen PR, Sagvolden T (2007) Behavioral variability, elimination of responses, and delay-of-reinforcement gradients in SHR and WKY rats. Behav Brain Funct 3:60

Johansen EB, Killeen PR, Russell VA, Tripp G, Wickens JR, Tannock R, Williams J, Sagvolden T (2009) Origins of altered reinforcement effects in ADHD. Behav Brain Funct 5:7

Johnson KA, Wiersema JR, Kuntsi J (2009) What would Karl Popper say? Are current psychological theories of ADHD falsifiable? Behav Brain Funct 5:15

Kahn JA, Kaplowitz RA, Goodman E, Emans SJ (2002) The association between impulsiveness and sexual risk behaviors in adolescent and young adult women. J Adolesc Health 30:229–232

Kostrzewa RM, Kostrzewa JP, Kostrzewa RA, Nowak P, Brus R (2008) Pharmacological models of ADHD. J Neural Transm 115:287–298

Kuehn BM (2010) Increased risk of ADHD associated with early exposure to pesticides, PCBs. J Am Med Ass 304:27–28

Kuntsi J, Neale BM, Chen W, Faraone SV, Asherson P (2006) The IMAGE project: methodological issues for the molecular genetic analysis of ADHD. Behav Brain Funct 2:27

Lahey BB, Willcutt EG (2010) Predictive validity of a continuous alternative to nominal subtypes of attention-deficit/hyperactivity disorder for DSM-V. J Clin Child Adolesc Psychol 39:761–775

Laurin N, Ickowicz A, Pathare T, Malone M, Tannock R, Schachar R, Kennedy JL, Barr CL (2008) Investigation of the G protein subunit Galphaolf gene (GNAL) in attention deficit/hyperactivity disorder. J Psychiatr Res 42:117–124

Li Q, Lu G, Antonio GE, Mak YT, Rudd JA, Fan M, Yew DT (2007) The usefulness of the spontaneously hypertensive rat to model attention-deficit/hyperactivity disorder (ADHD) may be explained by the differential expression of dopamine-related genes in the brain. Neurochem Int 50:848–857

Martinussen R, Hayden J, Hogg-Johnson S, Tannock R (2005) A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 44:377–384

Meyer A, Eilertsen DE, Sundet JM, Tshifularo JG, Sagvolden T (2004) Cross-cultural similarities in ADHD-like behaviour amongst South African primary school children. S Afr J Psychol 34:123–139

Mill J, Sagvolden T, Asherson P (2005) Sequence analysis of Drd2, Drd4, and Dat1 in SHR and WKY rat strains. Behav Brain Funct 1:24

Miller GA (1956) The magical number seven plus or minus two: some limits on our capacity for processing information. Psychol Rev 63:81–97

Molina BS, Bukstein OG, Lynch KG (2002) Attention-deficit/hyperactivity disorder and conduct disorder symptomatology in adolescents with alcohol use disorder. Psychol Addict Behav 16:161–164

Myers MM, Musty RE, Hendley ED (1982) Attenuation of hyperactivity in the spontaneously hypertensive rat by amphetamine. Behav Neural Biol 34:42–54

Pardey MC, Homewood J, Taylor A, Cornish JL (2009) Re-evaluation of an animal model for ADHD using a free-operant choice task. J Neurosci Methods 176:166–171

Perry GM, Sagvolden T, Faraone SV (2010a) Intra-individual variability in genetic and environmental models of attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 153B:1094–1101

Perry GM, Sagvolden T, Faraone SV (2010b) Intraindividual variability (IIV) in an animal model of ADHD – the Spontaneously Hypertensive Rat. Behav Brain Funct 6:56

Rat Genome Database (2008) http://rgd.mcw.edu

Roessner V, Sagvolden T, DasBanerjee T, Middleton FA, Faraone SV, Walaas SI, Becker A, Rothenberger A, Bock N (2010) Methylphenidate normalizes elevated dopamine transporter densities in an animal model of the attention-deficit/hyperactivity disorder combined type, but not to the same extent in one of the attention-deficit/hyperactivity disorder inattentive type. Neurosci 167:1183–1191

Rohde LA, Szobot C, Polanczyk G, Schmitz M, Martins S, Tramontina S (2005) Attention-deficit/hyperactivity disorder in a diverse culture: do research and clinical findings support the notion of a cultural construct for the disorder? Biol Psychiatr 57:1436–1441

Ruocco LA, Carnevale UA, Sadile AG, Sica A, Arra C, Di MA, Topo E, D'Aniello A (2009) Elevated forebrain excitatory l-glutamate, l-aspartate and d-aspartate in the Naples high-excitability rats. Behav Brain Res 198:24–28

Russell VA, Sagvolden T, Johansen EB (2005) Animal models of attention-deficit hyperactivity disorder. Behav Brain Funct 1:9

Sagvolden T (2000) Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). Neurosci Biobehav Rev 24:31–39

Sagvolden T (2006) The alpha-2A adrenoceptor agonist guanfacine improves sustained attention and reduces overactivity and impulsiveness in an animal model of Attention-Deficit/Hyperactivity Disorder (ADHD). Behav Brain Funct 2:41

Sagvolden T, Archer T (1989) Future perspectives on ADD research – an irresistible challenge. In: Sagvolden T, Archer T (eds) Attention deficit disorder: clinical and basic research. Lawrence Erlbaum Associates, Hillsdale, NJ, pp 369–389

Sagvolden T, Xu T (2008) l-Amphetamine improves poor sustained attention while d-amphetamine reduces overactivity and impulsiveness as well as improves sustained attention in an animal model of Attention-Deficit/Hyperactivity Disorder (ADHD). Behav Brain Funct 4:3

Sagvolden T, Metzger MA, Schiørbeck HK, Rugland AL, Spinnangr I, Sagvolden G (1992) The spontaneously hypertensive rat (SHR) as an animal model of childhood hyperactivity (ADHD): changed reactivity to reinforcers and to psychomotor stimulants. Behav Neural Biol 58:103–112

Sagvolden T, Aase H, Zeiner P, Berger DF (1998) Altered reinforcement mechanisms in Attention-Deficit/Hyperactivity Disorder. Behav Brain Res 94:61–71

Sagvolden T, Johansen EB, Aase H, Russell VA (2005a) A dynamic developmental theory of Attention-Deficit/Hyperactivity Disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav Brain Sci 28:397–468

Sagvolden T, Russell VA, Aase H, Johansen EB, Farshbaf M (2005b) Rodent models of attention-deficit/hyperactivity disorder. Biol Psychiatr 57:1239–1247

Sagvolden T, DasBanerjee T, Zhang-James Y, Middleton F, Faraone S (2008) Behavioral and genetic evidence for a novel animal model of Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive Subtype. Behav Brain Funct 4:56

Sagvolden T, Johansen EB, Woien G, Walaas SI, Storm-Mathisen J, Bergersen LH, Hvalby O, Jensen V, Aase H, Russell VA, Killeen PR, DasBanerjee T, Middleton FA, Faraone SV (2009) The spontaneously hypertensive rat model of ADHD–the importance of selecting the appropriate reference strain. Neuropharmacology 57:619–626

Sanabria F, Killeen PR (2008) Evidence for impulsivity in the Spontaneously Hypertensive Rat drawn from complementary response-withholding tasks. Behav Brain Funct 4:7

Schultz W (2010) Dopamine signals for reward value and risk: basic and recent data. Behav Brain Funct 6:24

Shaw P, Sharp WS, Morrison M, Eckstrand K, Greenstein DK, Clasen LS, Evans AC, Rapoport JL (2009) Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. Am J Psychiatr 166:58–63

Sonuga-Barke EJ, Taylor E, Sembi S, Smith J (1992) Hyperactivity and delay aversion–I. The effect of delay on choice. J Child Psychol Psychiatr 33:387–398

Tannock R (1998) Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatr 39:65–99

Turic D, Langley K, Mills S, Stephens M, Lawson D, Govan C, Williams N, Van den BM, Craddock N, Kent L, Owen M, O'Donovan M, Thapar A (2004) Follow-up of genetic linkage findings on chromosome 16p13: evidence of association of N-methyl-D aspartate glutamate receptor 2A gene polymorphism with ADHD. Mol Psychiatr 9:169–173

Twigger SN, Shimoyama M, Bromberg S, Kwitek AE, Jacob HJ (2007) The rat genome database, update 2007–easing the path from disease to data and back again. Nucleic Acids Res 35: D658–D662

van den Bergh FS, Bloemarts E, Chan JS, Groenink L, Olivier B, Oosting RS (2006) Spontaneously hypertensive rats do not predict symptoms of attention-deficit hyperactivity disorder. Pharmacol Biochem Behav 83:380–390

Vendruscolo LF, Izidio GS, Takahashi RN (2009) Drug reinforcement in a rat model of attention deficit/hyperactivity disorder–the Spontaneously Hypertensive Rat (SHR). Curr Drug Abuse Rev 2:177–183

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF (2005) Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatr 57:1336–1346

Wultz B, Sagvolden T, Moser EI, Moser MB (1990) The spontaneously hypertensive rat as an animal model of attention-deficit hyperactivity disorder: effects of methylphenidate on exploratory behavior. Behav Neural Biol 53:88–102

Yan TC, Hunt SP, Stanford SC (2009) Behavioural and neurochemical abnormalities in mice lacking functional tachykinin-1 (NK1) receptors: a model of attention deficit hyperactivity disorder. Neuropharmacology 57:627–635

Zhang L, Kendler KS, Chen X (2006) The mu-opioid receptor gene and smoking initiation and nicotine dependence. Behav Brain Funct 2:28