Rat Models of ADHD

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Running title: ADHD – Rat Models

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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 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 amongst the various SHRs, but there are behavioral and neurobiological differences amongst the WKY strains. Finally, 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.

Key words Animal models; Attention Deficit Disorder; Validation; Genetics, Neurophysiology; Neuroanatomy

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
Wistar/Mol	Outbred from Møllegaard Breeding Centre, Denmark
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, US.

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, US.

WKY/NHsd: inbred WKY from Harlan Europe, UK

WKY/N: inbred WKY from NIH, US

WKY/NicoCrlf: inbred WKY from Charles River, France

WKY/NMolTac (also known as: WKY/NMol): WKY from Møllegaard Breeding Centre, Denmark

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

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 of ADHD (ADHD-I); the predominantly hyperactive-impulsive subtype (ADHD-H) and the combined subtype of Attention Deficit/Hyperactivity Disorder (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; Johansen et al. 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 as '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 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. 2005b; Sagvolden et al. 1998). 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 in order 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 intra-individual variability and variability in the individual SHR ‘s behavior within the task, relative to controls (Perry et al. 2010a; Perry et al. 2010b).

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 from 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 Figure 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 that 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 long-term potentiation (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. (DasBanerjee et al. 2008).

Based on blood samples, no between-strain differences in DNA were observed for either the DRD2 or 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 3rd exon of DAT1. Whilst 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 two-fold increase in expression of calcyon mRNA compared with WKY/NHsd rats. This is in agreement with a recent study which 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). Firstly, 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. Secondly, the NMDAR containing *Grin2b* (aka *GluN2B*) subunits contributed substantially to induction of long-term potentiation 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; Perry et al. 2010b) 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 is characterized by 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. Further, if a clinician observes a child with all the symptoms of ADHD, but without the behavioral change or specific cognitive deficit in question, (s)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. Further, 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 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 long-term potentiation 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; Perry et al. 2010b). 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 intra-individual variability. This is observed in children with ADHD and in the SHR (Aase and Sagvolden 2006; Johansen et al. 2009; Perry et al. 2010a; Perry et al. 2010b).

5 Conclusions

There are no obvious behavioral differences amongst the various SHRs, but there are behavioral and neurobiological differences amongst 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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