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The Spontaneously Hypertensive Rat model of ADHD – the importance of selecting the appropriate reference strain

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Abstract

Although several molecular and genetic manipulations may produce hyperactive animals, hyperactivity alone is insufficient for the animal to qualify as a model of ADHD. Based on a wider range of criteria — behavioral, genetic and neurobiological — the spontaneously hypertensive rat (SHR) obtained from Charles River, Germany (SHR/NCrI) at present constitutes the best validated animal model of ADHD combined subtype (ADHD-C), and the Wistar Kyoto substrain obtained from Harlan, UK (WKY/NHsd) is its most appropriate control. Although other rat strains may behave like WKY/NHsd rats, genetic results indicate significant differences when compared to the WKY/NHsd substrain, making them less suitable controls for the SHR/NCrI. The use of WKY/NCrI, outbred Wistar, Sprague Dawley or other rat strains as controls for SHRs may produce spurious neurobiological differences. Consequently, data may be misinterpreted if insufficient care is taken in the selection of the control group. It appears likely that the use of different control strains may underlie some of the discrepancies in results and interpretations in studies involving the SHR and WKY. Finally, we argue that WKY rats obtained from Charles River, Germany (WKY/NCrI) provide a promising model for the predominantly inattentive subtype of ADHD (ADHD-PI); in this case also the WKY/NHsd substrain should be used as control.

Keywords

Animal model; Attention Deficit Disorder; Validation; Genetics; Neurophysiology; Neuroanatomy

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

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a heterogeneous developmental disorder for which all clinical criteria are behavioral. It affects about 5% of children (Faraone, Sergeant et al., 2003). It typically manifests by the age of 7 years. The DSM-IV (American Psychiatric Association, 2000) identifies three subtypes of ADHD which require that symptoms must have persisted for at least six months and have caused impairment before the age of 7 years: the predominantly inattentive subtype of ADHD (ADHD-PI) requires at least six symptoms of inattention, but fewer than six symptoms of hyperactivity-impulsiveness; the predominantly hyperactive-impulsive subtype (ADHD-HI) requires at least six symptoms of hyperactivity-impulsiveness, but fewer than six symptoms of inattention; and the combined subtype (ADHD-C) is diagnosed if there are at least six symptoms both of inattention and hyperactivity-impulsiveness.

Children with ADHD-PI are non-hyperactive, inert, and rather dreamy children. Their attention problems are rather non-specific, related to deficient sensory processing, and poorly focused attention. ADHD-PI is typical amongst girls. The inattention of children with ADHD-C, which includes difficulty in sustaining attention, distractibility, lack of persistence, and disorganization, is observed more often in boys. Their hyperactivity and impulsiveness includes excessive motor activity and impulsive ('cannot wait') responding.

There have been many attempts to explain the origins of ADHD symptoms. A learning-theory perspective is, however, gaining ground for the case of ADHD-HI and ADHD-C. The dual-process theory (Johansen, Aase et al., 2002; Johansen, Killeen et al., 2009; Johnson, Wiersema et al., 2009; Sagvolden and Archer, 1989; Sagvolden, Johansen et al., 2005) suggests that less efficient dopamine-mediated reinforcement processes and deficient extinction of previously reinforced behavior may explain behavioral changes often described as poor executive functions (Tannock, 1998) or as response disinhibition (Barkley and Biederman, 1997). This learning-theory perspective predicts specific neuronal changes related to synaptic plasticity and long-term potentiation (LTP) (Sagvolden, Johansen et al., 2005). The origins of ADHD-PI symptoms may be quite different (Taylor, 1998) and may be related to systems other than dopamine (Sagvolden, Johansen et al., 2005).

Some authors have questioned the SHR as a useful model of ADHD and the WKY as an adequate control (Alsop, 2007; Bull, Reavill et al., 2000; van den Bergh, Bloemarts et al., 2006). This review summarizes data showing that the spontaneously hypertensive rat (SHR) obtained from Charles River, Germany (SHR/NCrI) (Rat Genome Database, 2008) (see the Abbreviations section) with the Wistar Kyoto rat obtained from Harlan, UK (WKY/NHsd) as the reference strain, is an excellent animal model for investigating ADHD-C. The WKY obtained from Charles River, Germany (WKY/NCrI) provides a promising model for the predominantly inattentive subtype of ADHD (ADHD-PI) when the WKY/NHsd is used as a control. Genetic and behavioral data will be presented showing that there are heterogeneous substrains of WKY that explain why some researchers, using other substrains, have failed to reproduce previously published results obtained with the SHR.

Criteria for a valid animal model of ADHD

Animal models are helpful in medical research because of their simpler nervous systems, more easily interpreted behaviors, more easily controlled environments, and the greater variety of interventions available. ADHD is a behavioural disorder. For an animal to model ADHD it must mimic the fundamental behavioral characteristics of ADHD (face validity). It must also conform to a theoretical rationale for the disorder (construct validity), and predict behavioural,

genetic and neurochemical correlates of ADHD in humans (predictive validity) (Sagvolden, 2000; Sagvolden, Russell et al., 2005; Van der Staay, Arndt et al., 2009). Although a variety of rat and mouse strains exhibit hyperactivity (Russell, 2007), few of these meet the complete set of model validation criteria.

Behavioral differences among strains

The SHR displays the major symptoms of ADHD: inattention, hyperactivity, and impulsiveness that, like ADHD, develop over time when reinforcers are infrequent (Johansen, Sagvolden et al., 2005b; Johansen, Sagvolden et al., 2005a; Li, Lu et al., 2007; Sagvolden, 2000; Sagvolden, Aase et al., 1998; Sagvolden, Russell et al., 2005; van den Bergh, Bloemarts et al., 2006). Similar to children with ADHD (Sonuga-Barke, Taylor et al., 1992), SHR have been shown to be more sensitive to delay of reinforcement (Johansen, Killeen et al., 2007; Johansen, Sagvolden et al., 2005b), consistent with a steepened delay-of-reinforcement gradient found in SHR relative to controls (Johansen, Killeen et al., 2007). In addition, similar to children with ADHD (Aase, Meyer et al., 2006; Aase and Sagvolden, 2005; Aase and Sagvolden, 2006), studies find increased intra-individual variability in SHR behavior relative to controls (Johansen, Killeen et al., 2007; Russell, Oades et al., 2006; Sagvolden, 2000; Sagvolden, Aase et al., 1998; Sagvolden, Russell et al., 2005).

Measures of activity in open field apparatuses were used in the early research (Knardahl and Sagvolden, 1979), but were discontinued because the results were sensitive to factors such as light conditions, size of the open field, and duration of testing (Sagvolden, Hendley et al., 1992; Sagvolden, Pettersen et al., 1993). These factors made it difficult to interpret the data. In addition, other aspects of ADHD like impulsiveness and poorly sustained attention are difficult to assess and model in the open field. Finally, the open field arenas used for rats, although they might seem similar to class rooms or a home, are difficult to standardize for translational research. Thus, construct and predictive validity that are critical in translational research (Sagvolden, 2000), are virtually impossible to obtain in open field apparatuses.

A more fruitful approach to meet the validation criteria was found by using either a multiple fixed-interval extinction schedule of reinforcement (Sagvolden, 2000) or a simultaneous visual discrimination task (Sagvolden, 2006; Sagvolden, DasBanerjee et al., 2008; Sagvolden, Russell et al., 2005; Sagvolden and Xu, 2008), methods that allow translational research (Aase, Meyer et al., 2006; Aase and Sagvolden, 2005; Sagvolden, Aase et al., 1998).

The two-component multiple fixed-interval extinction schedule

Both ADHD and control children (Sagvolden, Aase et al., 1998) as well as SHR and a number of other rat strains (Berger and Sagvolden, 1998; Boix, Qiao et al., 1998; Holene, Nafstad et al., 1998; Sagvolden, Hendley et al., 1992; Sagvolden, Pettersen et al., 1993) have been tested with closely similar multiple fixed-interval/extinction schedules of reinforcement. All experiments were run with the same computer programs, with the same type of interface, but of course with different manipulanda and reinforcers in children and rats. The results of these studies revealed systematic overactivity, impulsiveness and sustained attention deficit in the SHRs obtained either from NIH (SHR/N) (Sagvolden, Hendley et al., 1992) or from Møllegaard Breeding Centre, Denmark (SHR/NMol) when WKYs from NIH (WKY/N) and WKYs obtained from Møllegaard Breeding Centre, Denmark (WKY/NMolTac, aka WKY/NMol), respectively, served as controls (Berger and Sagvolden, 1998; Boix, Qiao et al., 1998; Sagvolden, Hendley et al., 1992; Sagvolden, Metzger et al., 1992; Sagvolden, Pettersen et al., 1993). Response feedback by turning on a stimulus light above the lever for the duration of the lever press, impaired the sustained attention of the SHR/N even more than in the absence of the response feedback (Sagvolden, Hendley et al., 1992).

Neither the hypertensive WHHT/Edh, nor the hyperactive WHHA/Edh substrains showed any systematic overactivity, impulsiveness or sustained attention deficit (Sagvolden, Hendley et al., 1992). The WHHA/Edh appeared to be overactive in fear-provoking open field tests.

Several other strains were also used in these studies in order to check whether the WKY/N and the WKY/NMolTac behaved normally. The results confirmed that these WKY substrains did not differ behaviorally from SD/MolTac, hooded PVG/Mol, outbred Wistar/Mol rats (all from Møllegaard Breeding Centre, Denmark) (Sagvolden, Pettersen et al., 1993), or the offspring of DA/OlaHsd females time-mated with LEW/NHsd Lewis males (Harlan, UK) (Holene, Nafstad et al., 1998; Sagvolden, 2000).

In conclusion, only the SHR/N and the SHR/Mol substrains were overactive, impulsive and exhibited a sustained attention deficit similar to that of ADHD children when children and rats were tested by equipment and schedules appropriate for translational research (Sagvolden, 2000; Sagvolden, Aase et al., 1998). In some less well-controlled experimental paradigms such as the open field, however, both the Wistar/Mol and the SD/MolTac could be as active as SHR/Mol (Sagvolden, 2000). Thus, we will argue that only carefully chosen WKY substrains are adequate controls for SHRs.

Simultaneous visual discrimination maintained by a variable-interval schedule of reinforcement

In this schedule of reinforcement, an unpredictable 180-s variable-interval schedule is in effect for 90 min on the correct lever (signaled by a constantly lit cue light above this lever). A concurrent extinction schedule (never associated with any cue light) is present on the wrong lever. The signal and the associated correct lever alternate randomly following each reinforcer delivery. Concurrent schedules of reinforcement are schedules that are simultaneously available, so that the subject or participant can respond on either schedule (Catania, 1998).

The total number of lever presses is an expression of the *general activity* level. The percent choice of the correct lever when the reinforcers are delivered infrequently is a measure of *sustained attention*: the animal must maintain attention to the light signaling which of the two levers that may produce a reinforcer when pressed. The number of responses with short inter-response times (<0.67 s) is used as a measure of degree of *impulsiveness* (“cannot hold back a response even when it is an unnecessary one”) (Sagvolden, 2006; Sagvolden, DasBanerjee et al., 2008; Sagvolden, Russell et al., 2005; Sagvolden and Xu, 2008). A translational task for children was designed and used both in Norway and South Africa (Aase, Meyer et al., 2006; Aase and Sagvolden, 2005).

Analysis of stable-state behavior on the simultaneous visual discrimination task showed that SHR/CrIco (from Charles River, Italy) and SHR/NCrI (from Charles River, Germany) were hyperactive, impulsive and performed poorly in tasks that required sustained attention (Sagvolden, 2006; Sagvolden, DasBanerjee et al., 2008; Sagvolden and Xu, 2008). The poorer sustained attention in SHR/NCrI was not due to impaired visual function or impaired working memory (Sagvolden and Xu, 2008). Several comparison groups were used in these studies: WKY/NCrI rats, WKY/NHsd rats, WKY/NicoCrlf (from Charles River, France), SD/NTac Sprague Dawley rats, and WH/HanTac (Wistar rats from Taconic Europe). The results showed that overactivity, impulsiveness and deficient sustained attention of the SHR strain were independent behaviors. Further, the WKY/NCrI substrain was inattentive without being overactive or impulsive and may therefore be considered an animal model of ADHD-PI. Thus, overactivity did not account for the deficient sustained attention in the SHR or the WKY/NCrI substrain (Sagvolden, DasBanerjee et al., 2008).

Behavioral studies of SHR/NCrI using WKY/NCrI as controls may turn out to be very valuable as they show behavioral and neurobiological differences between the ADHD-C and ADHD-PI models. Researchers have shown that both the WKY/NCrI and SHR/NCrI strains are inattentive relative to Sprague Dawley and Wistar/HanTac controls strains. However, the WKY/NCrI are neither hyperactive nor impulsive like the SHR/NCrI rat (Berger and Sagvolden, 1998; Clements and Wainwright, 2006; Fox, Hand et al., 2008; Pardey, Homewood et al., 2009; Sagvolden, DasBanerjee et al., 2008; Sanabria and Killeen, 2008). In addition, the SHR/NCrI appears to be more sensitive to reinforcer delay than WKY/NCrI (Fox, Hand et al., 2008; Pardey, Homewood et al., 2009).

Finally, the ADHD-like behavior of SHR and their neurochemistry is genetically determined and not dependent on nurturing by SHR dams (Howells, Bindewald et al., 2009).

Genetic differences among strains

Because of substantial differences in behavior of the various rat strains, it became important to investigate possible genomic differences between the animal models for ADHD and the various control strains and to compare these results to known genomic differences between children with and without ADHD.

In an ongoing project, whole genome Single Nucleotide Polymorphism (SNP) array analysis are used to investigate the total amount of genomic divergence among the SHR/NCrI, WKY/NCrI, WKY/NHsd, SD/NTac, and WH/HanTac strains (Sagvolden, DasBanerjee et al., 2008). Comparisons between WKY/NCrI and WKY/NHsd substrains revealed substantial genetic divergence, with average concordance rates of only 66.5% and large stretches of divergence on every chromosome (Sagvolden, DasBanerjee et al., 2008). Comparisons of SHR/NCrI genotyping data with those of the WKY/NHsd and WKY/NCrI substrains showed that the WKY/NCrI substrain was genetically more similar to the SHR/NCrI rats (76.6% concordance) than they were to the WKY/NHsd substrain (66.5% concordance).

Genotyping Simple Sequence Length Polymorphisms (SSLPs) that were expected to be highly polymorphic between SHR/NCrI, WKY/NHsd, WKY/NCrI, and SD/NTac rats revealed striking differences between the WKY/NCrI and WKY/NHsd SSLP product sizes. There were also differences between the SHR/NCrI and the other strains as well as between the SD/NTac Sprague Dawley and the other strains (Sagvolden, DasBanerjee et al., 2008). The results indicated that Sprague Dawley rats may be a poor control for the SHR/NCrI in neurobiological studies. Furthermore, the WH/HanTac rats and WKY/NCrI deviated both genetically as well as behaviorally from the WKY/NHsd. Thus, the use of SD/NTac, WH/HanTac or WKY/NCrI rats as controls for SHR/NCrI may produce spurious neurobiological differences. The WKY/NHsd substrain appears to be the most appropriate control for SHR/NCrI.

Gene expression differences between SHR/NCrI and WKY/NHsd

In order to investigate whether the SHR/NCrI shows changes in expression in systems relevant to ADHD, we (DasBanerjee, Middleton et al., 2008) focused our analysis on ADHD candidate genes identified by the International Multi-center ADHD Gene project (IMAGE), and their biological neighbors (collectively referred to as IMAGE genes) (Kuntsi, Neale et al., 2006). We defined IMAGE gene biological neighbors as any gene that was part of the same gene or protein family as an IMAGE gene, or had a well established direct relationship with an IMAGE gene. The gene terminology used in the following is according to the Gene Ontology project that provides a controlled vocabulary to describe gene and gene product attributes in any organism (Ashburner, Ball et al., 2000; Gene Ontology Database, 2009).

We dissected six brain regions that had been implicated in ADHD by a meta-analysis of structural imaging studies in humans (Valera, Faraone et al., 2007) — the medial prefrontal cortex, ventral striatum, dorsal striatum, hippocampal formation, cerebellar vermis, and ventral mesencephalon (including the substantia nigra and ventral tegmental area). RNA was analyzed for differences in expression of a set of 308 probe sets interrogating 218 unique genes considered highly relevant to ADHD or epigenetic gene regulation. Selected observations were confirmed by real-time quantitative RT-PCR (DasBanerjee, Middleton et al., 2008).

Gene expression alterations particularly relevant for synaptic plasticity

The SHR/NCrl 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 dual-process theory of ADHD-C (Johansen, Killeen et al., 2009; Johnson, Wiersema et al., 2009; Sagvolden and Archer, 1989; Sagvolden, Johansen et al., 2005) 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 explaining behavioral changes associated with ADHD (Sagvolden, Johansen et al., 2005).

Some of these genes showed statistically significantly *decreased* expression across tissues in ~65-day-old SHR/NCrl rats compared to WKY/NHsd rats: these included the ionotropic glutamate NMDA binding protein *Grina* and NMDA receptor subunits *Grin1a*, *Grin2d*; the ionotropic glutamate AMPA3 receptor (*Gria3*); the alpha stimulating, olfactory type guanine nucleotide binding protein (*Gnal/Golf*); the noradrenaline transporter NET (*Slc6a2*); calmodulin 3 (*Calm3*); calcium/calmodulin-dependent protein kinases *Camk1*, *Camk2a*, and *Camk2g*; synaptotagmin III (*Syt3*); syntaxin binding protein 1 (*Stxbp1*). Investigating specific brain areas, microarray data showed pronounced reductions of *Grin1a* in the dorsal striatum, the hippocampal formation, cerebellar vermis, and the ventral mesencephalon (DasBanerjee, Middleton et al., 2008).

In contrast, other genes showed statistically significant *increased* expression in the SHR/NCrl rats compared to WKY/NHsd rats: these included the ionotropic glutamate AMPA2 subunit (*Gria2*), the ionotropic glutamate NMDA subunits *Grin1* and *Grin2c*; calcium/calmodulin-dependent protein kinase 1 (*Camk1*); 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, Middleton et al., 2008).

Functional implications of gene differences between SHR/NCrl and WKY/NHsd

Gnal (*Golf*) is known to be coupled to the dopamine receptor, DRD1, and plays a major role in excitatory dopamine transmission in the striatum. This is particularly relevant since significant relationships have been observed between certain SNPs in *Gnal* and symptoms of inattention and hyperactivity/impulsiveness in ADHD children (Laurin, Ickowicz et al., 2008).

Based on blood samples, no between-strain differences were observed in either the DRD2 or DRD4 genes, suggesting that neither gene is likely to mediate the behavioral differences observed 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 observed between the two strains (Mill, Sagvolden et al., 2005).

The dopamine receptor D1 interacting protein (*DRD1ip*, calcyon) represents a brain-specific DRD1-interacting protein involved in DRD1/DRD5 receptor-mediated calcium signaling. In our data, the SHR/NCrI had two-fold increased expression of calcyon mRNA compared to WKY/NHsd rats, which 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, Alexeyenko et al., 2007).

A major dopaminergic function is to modulate fast, ionotropic synaptic transmission. The observed changes in gene expression for both AMPA receptor and NMDA receptor subunits may profoundly affect neuronal function. Electrophysiological studies revealed two potential consequences of such changes (Jensen, Rinholm et al., 2009). Firstly, in male SHR/NCrI and WKY/NHsd rats at postnatal day 28, AMPA receptor-mediated transmission at the CA3-to-CA1 synapses in stratum radiatum of the hippocampus was significantly reduced. Secondly, the NMDAR containing Grin2b (aka GluN2B) subunits contributed substantially to induction of LTP in SHR/NCrI, 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).

Human and animal data indicate that the mu opioid receptor 1 (*Oprm1*) is associated with substance abuse disorders (Berrendero, Kieffer et al., 2002; Zhang, Kendler et al., 2006). Individuals with ADHD, depending on the subtype, also show strong substance dependence (Faraone, Adamson et al., 2007; Rodriguez, Tercyak et al., 2008). Thus, it is possible that substance dependence in ADHD may be modulated by *Oprm1*.

SHR/NCrI rats also showed significant changes in the expression of Hexokinase1 (*Hk1*) and Casein kinase 1, alpha 1 (*Csnk1a1*) compared to WKY/NHsd rats. *Hk1* catalyzes the first step in glucose metabolism. Expression levels of *Hk1* in SHR/NCrI rats may be a reflection of the basal physiological glucose metabolism, and thus basal neuronal activity. The neuronal energetics aspect of these findings is supported by a common observable feature of ADHD - marked moment-to-moment fluctuation in task performance. This fluctuation may arise from deficient lactate production and supply by astrocytes to rapidly firing neurons (Russell, Oades et al., 2006).

The transcripts *Lhx1* and *Hes6* show evidence of significant modulation in SHR/NCrI. *Hes6* belongs to the basic helix-loop-helix family (bHLH) of transcription factors and is known to be involved in cortical neurogenesis. *Lhx1* plays an important role in Purkinje cell generation and differentiation (Zhao, Kwan et al., 2007). Thus, changes in the expression of these genes could affect forebrain and hindbrain circuitry in the SHR/NCrI. Although there is no known evidence connecting these genes directly to ADHD, it can be speculated that altered expression levels of these genes might affect cortical and cerebellar volumes in SHRs by influencing neurogenesis and differentiation. Such changes would be consistent with those reported in individuals with ADHD (Valera, Faraone et al., 2007).

The aquaporins are a family of water-selective membrane channels found in animals, plants, and microorganisms. *Aqp4* is the predominant water channel in the brain and has an important role in brain water homeostasis. *Aqp4* is significantly down-regulated in the SHR/NCrI (DasBanerjee, Middleton et al., 2008).

Gene expression differences between WKY/NCrI and WKY/NHsd

The genetic and behavioral changes in the WKY/NCrI make them a promising model of ADHD-PI (Sagvolden, DasBanerjee et al., 2008). There is a substantial genetic difference between the WKY/NCrI and the WKY/NHsd rat with large stretches of divergence on every chromosome (Sagvolden, DasBanerjee et al., 2008). However, compared to the SHR/NCrI and WKY/NHsd rat, little is known about the genes that differ. Among these the tyrosine hydroxylase, DAT1 and the solute carrier family 9 (sodium/hydrogen exchanger) member 9 (SLC9a9, or NHE9) (Roessner, Sagvolden et al., 2009; Zhang-James, DasBanerjee et al., 2008) genes are all upregulated in the WKY/NCrI relative to WKY/NHsd. Genome-wide association studies predicted associations between these genes (Franke, Neale et al., 2009; Lasky-Su, Neale et al., 2008). Franke and co-workers suggested the involvement of more basic processes in ADHD, such as cell division, adhesion (especially via cadherin and integrin systems), neuronal migration, neuronal plasticity, as well as related transcription, cell polarity, extracellular matrix regulation, and cytoskeletal remodeling processes.

In vitro studies of NMDA and AMPA receptor function in SHR/NCrI and WKY/NCrI obtained from Charles River USA, revealed the presence of an NMDA component in glutamate-stimulated release of norepinephrine in hippocampal slices of SHR that was not evident in WKY (Howells and Russell, 2008).

The origins of the genetic divergences

The SHR arrived at the National Institutes of Health (NIH) in 1966 at F13 from the Kyoto School of Medicine. It was bred from an outbred Wistar Kyoto male with marked elevation of blood pressure and a female with slightly elevated blood pressure followed by brother-sister mating with continued selection for spontaneous hypertension. The SHR/NCrI came to Charles River USA from NIH in 1973 at F32. There is no evidence for substrain differentiation among SHR stocks from the major commercial suppliers in the USA with respect to phenotype and DNA fingerprints (Rat Genome Database, 2008; Twigger, Shimoyama et al., 2007).

A likely explanation for the genetic divergence between the WKY/NHsd and WKY/NCrI rats is that the WKY was not fully inbred when shipped to various breeders. The NIH Animal Genetic Resource stock was obtained in 1971 as non-inbred Wistar stock from the Kyoto School of Medicine, Japan. The breeding stock was distributed by NIH before F20, possibly resulting in the emergence of a number of strains or substrains. The WKY/NCrI used in our simultaneous visual discrimination studies (Sagvolden, 2006; Sagvolden, DasBanerjee et al., 2008; Sagvolden and Xu, 2008) arrived at Charles River Laboratories USA in 1974 from NIH at F11. The WKY/NMolTac used in several of our previous multiple fixed-interval/extinction schedules of reinforcement studies (Berger and Sagvolden, 1998; Boix, Qiao et al., 1998; Sagvolden, Metzger et al., 1992; Sagvolden, Pettersen et al., 1993) arrived at the Møllegaard Breeding Centre, Denmark, from the NIH in 1975 at F13. It is unclear exactly when the Wistar Kyoto rat, later known as WKY/NHsd arrived at Harlan Sprague Dawley USA. The WKY/NCrI differs substantially from the WKY/NHsd and may be used as the phenotype and genotype of ADHD-PI. It is therefore essential that subline codes and country of origin are always used in designating the strains used in a study (Rat Genome Database, 2008; Twigger, Shimoyama et al., 2007).

SHR/NCrI and WKY/NCrI versus WKY/NHsd controls

While a large number of studies support the use of SHR as the best animal model of ADHD, there are also researchers who question the validity of SHR/NCrI as an ADHD model (Ferguson and Cada, 2003; van den Bergh, Bloemarts et al., 2006). Some of this disagreement may be caused by which WKY substrain is used as controls.

WKY heterogeneity

From a genetic point of view, the best candidate as a control strain is the progenitor strain of SHR/NCrI, the WKY. However, the various WKY substrains are not equally suited as controls due to genetic and behavioral differences (above). We will argue that the SHR/NCrI strain, with the WKY/NHsd substrain as controls, is the best animal model of ADHD-C. Compared to this control strain, the SHR/NCrI strain shows ADHD-like behavior and changes in genes shown to be altered in human ADHD research, IMAGE genes (Kuntsi, Neale et al., 2006).

The genetic and behavioral changes in the WKY/NCrI make them a promising model of ADHD-PI (Sagvolden, DasBanerjee et al., 2008). Thus, the studies of SHR/NCrI using WKY/NCrI as controls may turn out to be very valuable as they show behavioral and neurobiological differences between the ADHD-C and ADHD-PI models. Researchers have shown that both the WKY/NCrI and SHR/NCrI strains are inattentive relative to Sprague Dawley and Wistar/HanTac controls strains. However, the WKY/NCrI are neither hyperactive nor impulsive like the SHR/NCrI rat (Berger and Sagvolden, 1998; Clements and Wainwright, 2006; Fox, Hand et al., 2008; Pardey, Homewood et al., 2009; Sagvolden, DasBanerjee et al., 2008; Sanabria and Killeen, 2008). In addition, the SHR/NCrI appears to be more sensitive to reinforcer delay than WKY/NCrI (Fox, Hand et al., 2008; Pardey, Homewood et al., 2009).

The behavioral, genetic and neurobiological heterogeneity between rat substrains makes it imperative that researchers inform about substrain and breeder used in their studies so the empirical findings can be adequately evaluated by other researchers (Rat Genome Database, 2008; Twigger, Shimoyama et al., 2007).

ADHD -- defining features and situational factors

Another issue that might lead to disagreement regarding the validity of SHR/NCrI as an animal model of ADHD is how findings are interpreted and extrapolated. A defining feature of ADHD-C is hyperactivity. Some animal researchers seem to assume that ADHD is characterized by 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". Hence, when some animal researchers conclude that a substrain of rats is not valid as a model of ADHD based on the absence of hyperactivity in a particular test or setting, it is important to consider whether children with ADHD would be hyperactive in a similar test or situation.

As in children with ADHD, the severity of behavioral problems in SHR is not always the same, but 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 reliable, translational behavioral 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. Some tests, like open fields, used to study SHR behavior are vulnerable to small differences in e.g. size of the field, light conditions, and duration of testing (Sagvolden, Hendley et al., 1992; Sagvolden, Pettersen et al., 1993). Such tests do not seem to produce reliable data in several studies (Ferguson and Cada, 2003; Li, Lu et al., 2007; van den Bergh, Bloemarts et al., 2006) and should be standardized or avoided.

A second, related issue is the uncritical use of ADHD research literature when formulating research hypotheses in studies of animal models. Such studies may refer to findings that report the presence of a particular behavioral change or a specific cognitive deficit, which is then investigated in the animal model. Researchers may sometimes conclude that the results do not support the continued use of an ADHD model based on the absence of the behavioral change or cognitive deficit in the animal model that is reported in the ADHD literature. However,

many behavioral measures and cognitive concepts studied in ADHD are not defining features of the disorder. The human research literature on children diagnosed with ADHD is inconsistent regarding most of these cognitive or behavioral measures; some children with ADHD show deviant scores on these measures, but many score within the normal range. Further, if a clinician observes a child with all the symptoms of ADHD without the presence of the behavioral change or specific cognitive deficit in question, she/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.

Response to medication and developmental considerations

The lack of a positive response to medication is an issue that sometimes is used as an argument against the SHR/NCrI model of ADHD. However, positive response to medication is not a defining feature of ADHD. Almost one in five children diagnosed with ADHD does not respond positively to medication. Although some studies report that stimulant medication improves symptoms of inattention, hyperactivity, and impulsiveness in SHR (Myers, Musty et al., 1982; Sagvolden, 2006; Sagvolden, Metzger et al., 1992; Sagvolden and Xu, 2008; Wultz, Sagvolden et al., 1990) other do not find ameliorating effects of medication in SHR, leading them to question the validity of SHR as an animal model of ADHD. Our argument is that firstly, it is important to choose behavioral measures whose analogs improve symptoms following medication of children with ADHD. Secondly, we may need to take a developmental perspective on effects of psychostimulant treatment. The effect 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 (Bizot, Chenault et al., 2007; Roessner, Sagvolden et al., 2009; Shaw, Sharp et al., 2009). Thus, use of old, hypertensive SHRs may produce misleading results.

Conclusions

The SHR/NCrI is still the best validated animal model of ADHD combined subtype. Genetic and neurobiological data strengthen such a conclusion. Although SD/NTac rats may behave like WKY/NHsd rats, genetic results indicate significant differences between this strain and WKY, SHR and outbred Wistar strains. Thus, Sprague Dawley rats may be a poor control for the SHR/NCrI, particularly in neurobiological studies. Given that the WH/HanTac rats and WKY/NCrI deviated both genetically as well as behaviorally from the WKY/NHsd, we also conclude that the use of these strains as controls for SHR may produce spurious neurobiological differences. The available data show that WKY/NHsd is the most appropriate control for SHR/NCrI. Consequently, data may be misinterpreted if researchers and readers do not pay attention to which strain or substrain were used in a study. It is likely that lack of proper attention to such factors have led to erroneous conclusions in studies involving the SHR in model studies of ADHD.

Recent data suggest that the WKY/NCrI may be a suitable model for the inattentive subtype of ADHD. However, compared with what is known about the SHR/NCrI, little is known about this relatively new model. Thus, further research is needed to evaluate its validity.

The availability of validated animal models of ADHD has substantial implications for research. Unlike some disorders like 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 method of linkage or association analysis and to search for gene-environment interactions by exposing susceptible animals to toxins known to be risk factors

for ADHD. The SHR/NCrl is clearly useful for these purposes in the study of ADHD-C and the WKY/NCrl may be useful for studies of ADHD-PI.

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Abbreviations

- ADHD-C** the combined subtype of ADHD
- ADHD-HI** the hyperactive-impulsive subtype of ADHD
- ADHD-PI** the inattentive subtype of ADHD
- DA/OlaHsd** inbred rats from Harlan, UK
- IMAGE** The International Multi-center ADHD Gene Project
- LEW/NHsd** Lewis rats from Harlan, UK
- PVG/Mol** inbred hooded rats from Møllegaard Breeding Centre, Denmark
- SD/MolTac** outbred Sprague Dawley rats from Møllegaard Breeding Centre, Denmark
- SD/NTac (NTacSD)** Sprague Dawley rats
- 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 Wistar rats from Møllegaard Breeding Centre, Denmark
- WH/HanTac (HanTac:WH)** Hannover GALAS rats from Taconic Europe
- WHHA/Edh (low WKH/N)** 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. Demonstrates reactivity to stress
- WHHT/Edh (low WKH/N)** 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/NicoCrl** inbred WKY from Charles River, France
- WKY/NMolTac (low WKY/NMol)** Breeding Centre, Denmark

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