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Ever Increasing Number of the Animal Model Systems for Attention Deficit/Hyperactivity Disorder: Attention, Please.

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Abstract – Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, inattention, and impulsiveness. Current estimates suggest that 4-12% of school age children are affected by ADHD, which hampers proper social relationship and achievements in school. Even though the exact etiology of the disorder is still in the middle of active investigation, the availability of pharmacological treatments for the disorder suggest that at least the symptoms of ADHD are manageable. To develop drugs with higher efficacy and fewer side effects, it is essential to have appropriate animal models for *in vivo* drug screening processes. Good animal models can also provide the chances to improve our understanding of the disease processes as well as the underlying etiology of the disorder. In this review, we summarized current animal models used for ADHD research and discussed the point of concerns about using specific animal models.

Keywords: Genetic models, Acquired animal models, Hyperactivity, Inattention, Impusivity

INTRODUCTION

Even though the pharmacological treatments of ADHD is feasible by using CNS stimulants such as methylphenidate and recently launched nonstimulant atomoxetine, not much details are known about the ADHD. For example, three core symptoms of ADHD such as inattention, hyperactivity, and impulsiveness themselves often found in other neuropsychiatrical disorders, and this make it difficult to correctly diagnose ADHD. ADHD is categorized into three subtypes: predominantly inattentive subtype, predominantly hyperactive/impulsive subtype, and combined subtype (Taylor *et al*., 1998).

In most of the cases, ADHD prevalence reach up to 4-12% depending on epidemiological studies conducted (American Academy of Pediatrics, 2008). The outbreak of ADHD is observed predominantly in children under age 7, and sometimes it persists into adolescence and adult period. Majority of ADHD affected children have memory problems and behave aggressively, which makes them subject to peer rejection and poor performance in school. In addition, affected children often have substance abuse problem (Barkley, 1997) and can not adjust themselves, and this occasionally leads to alienation of their family members from the society. Although it is getting clear that ADHD is a neurodevelopmental disorder in which genetic and environmental factors are involved, the molecular basis of ADHD is still unclear. Development of appropriate animal models is essential for the diagnosis and intervention of ADHD as well as for the development of new therapeutical agents. The drug market for ADHD currently reaches 20-30 billion dollars per year, which is comparable to that of Alzheimer's disease. The number of currently available animal models for ADHD counts more than 20, which are developed by genetic manipulation or acquired by nature. They have pros and cons in their applications. The characteristics of those animal models are summarized as follows.

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KEY SYMPTOMS OF ADHD

ADHD is characterized with three core symptoms listed

below, although subtypes of disorder exist with one or two core symptoms are missing. The definition and characteristics of the three core symptoms are as follows:

1) Hyperactivity

Hyperactivity is not evident in novel environment but becomes predominant after repeated exposure to same environment. Hyperactivity is relatively easy symptoms to detect. In human patient, actigraph can be used to determine the level of activity over sustained period of time. In animal studies, activity can be monitored using an open-field activity chamber.

2) Inattention

Attention is the cognitive process of selectively concentrating on one aspect of the environment while ignoring other things. Several mode of attention has been described including focused attention, sustained attention and selective attention etc. In ADHD patients, sustained attention deficit is evident when the inter-stimuli interval is long. In preclinical test, inattention is often tested as a slow reaction times and inaccurate reaction in an operant tasks.

3) Impulsivity

The impulsivity is commonly defined as acting before forethought, which is usually consists either "impulsive action" or "delay aversion". These two categories of impulsivity are interpreted as the lack of inhibition of behavior or the intolerance to delayed reward. The impulsivity usually determined by experimental paradigms like 5-choice serial reaction time task (5-CSRT) or delayed reinforcement tasks.

ANIMAL MODELS OF ADHD

Spontaneously Hypertensive rats

Spontaneously hypertensive rats (SHR) have been regarded one of the best model for human ADHD. Albeit the different opinion in the extent of the validity of the model (van den Bergh *et al*., 2006), SHR shows hyperactivity in familiar places when reinforcers are infrequent, inattentive behavior, which exemplifies with the decreased learning ability in operant tasks as well as impulsivity, which means that they can not wait for larger reward and inhibit a response during the extinction phase of an operant tasks (Sagvolden, 2000). One of the drawbacks using SHR is that SHR develops hypertension, which may compound the interpretation of the experimental data. However, hypertension usually develops later in life, typically after 6 weeks, which make it possible to use SHR in 3-5 weeks of age, which corresponds to child and adolescent period of human. Another criticism is that the mother strain of SHR, Wistar Kyoto Rats (WKY), which is used as a control when using SHR, has reduced ability to learn a new task in behavioral tests. These reports suggest that SHR is a good but not perfect model for ADHD, which makes the need for new model development for ADHD study as a still ongoing demands.

To be a good animal model, the genetic basis of the disorder should be recapitulated in the animal model of ADHD. In ADHD patients, genetic differences in dopamine system, including D1 and D5 receptors as well as dopamine transporter (DAT) has been suggested. In imaging studies, DAT has been observed to be increased in the striatum of ADHD patients even though controversy still exist in the DAT changes in human brain. Interestingly, reduced DAT1 expression in the midbrain during the 1st postnatal month and increased expression in adult SHR midrain has been observed suggesting possible DAT involvement in the development of ADHD symptoms in SHR (Watanabe *et al*., 1997; Leo *et al*., 2003). In the forebrain of adolescent SHR, it was observed that DAT protein expression is slightly increased (our unpublished results), which also support the DAT involvement in ADHD both in human and SHR. For extended reading, a recent thorough review describing the neurochemical and neurobiological features of SHR is available (Russell, 2007).

Coloboma mice

The coloboma mice (cm−/−) is another model system of ADHD. Coloboma mice has 'synaptosome-associated protein of 25000 daltons' (SNAP-25) deficiency, which is involved in the regulation of neurotransmitters as well as membrane trafficking of receptors including N-methyl-D-aspartic acid (NMDA) receptors. It has been suggested that Human ADHD also displays polymorphism of SNAP-25 (Mill *et al*., 2002). In general, coloboma mice has been regarded to reflect hyperactivity form of ADHD but not inattentive or impulsive behavior, although it has been argued recently that these mice showed impulsivity and impaired inhibition in a delayed reinforcement task (Bruno *et al*., 2006). In addition, SNAP-25 should affect the release of several different kinds of neurotransmitters all at the same time. Why it shows ADHD behavior is a still unanswered question.

Dopamine transporter knockout mice

DAT knockout mice shows hyperactivity (Trinh *et al*.,

2003), although human ADHD usually shows increased DAT level in the striatum (Cheon *et al*., 2003). It is still enigmatic why these mice shows hyperactivity. Even with the increased extracellular concentration of dopamine (DA) in DAT knockout mice, the phasic release of DA is decreased in these mice (Gainetdinov *et al*., 1999) and postsynaptic density of dopamine receptor D1 (DRD1) and D2 (DRD2) is decreased, which may indicate hypofunctional DA system. The imbalance of norepinephrine (NE)/DA system, i.e. increased NE and decreased DA function has been suggested as a definitive parameters of ADHD-like behavior in SHR (Russell *et al*., 2005). The hyperactivity of DAT knockout mice is reduced by serotonin transporter (SERT1) inhibitor as well as serotonergic agonists, while SSRI has only marginal effect, if any, in human ADHD symptoms. Making the story more complex, an antagonist against serotonin receptor 2A (5-HT2A receptor) improves hyperactivity of DAT knockout mice. Further studies should be ensued to investigate the possible role of serotonergic system in the regulation of ADHD phenotypes.

Mutant thyroid hormone mice

Mice expressing mutant form of human thyroid receptor β1 (TRβ1) shows transient increase in TSH during early phase of life, after which thyroid hormone (TH) level was normalized when they reach adulthood (Siesser *et al*., 2006). Because TH has been implicated in the development of nervous system including DA system, it is not surprising to see the TH mutant mice develops all three symptoms of ADHD, i.e. hyperactivity, inattention and impulsivity. In human, children with elevated thyroid stimulating hormone (TSH) and resistance to TH show signs of ADHD (Burd *et al*., 2003). Obviously, mutant TH mice model is among the growing list of animal models for ADHD and further study should follow to prove the validity of this animal model for the study of ADHD.

Brain derived neurotrophic factor (BDNF) knockout mice

Largely based on the fact that ADHD is one of the neurodevelopmental disorder, many researchers focused on the role of neurotrophic factors in the pathogenesis of ADHD. It has been suggested that BDNF may play important role in ADHD (Tsai *et al*., 2007) based on several genetic and experimental observations such as hyperactivity of BDNF knockout animals. There is comorbidity between ADHD and major depression, which may imply that they have common etiological basis including reduced BDNF. When it proved real, it may provide a new direction for the development of new therapeutic reagents against ADHD.

Neuropeptide Y (NPY) Y2 receptor knockout mice

NPY Y2 receptors play an important role in anxiety-related behaviors, which may affect cognitive functions including attention. In a study designed to investigate the role of NPY Y2 receptor deletion in mice on visual attention and response control using 5-choice serial reaction time (5-CSRT) task, it has been suggested that these mice show reduced attention as well as higher level of impulsivity (Greco and Carli, 2006). Considering the adverse behavior is improved by anti-anxiolytic drugs, it may be possible to use this animal model for ADHD especially with anxiety co-morbidity, which awaits further investigation.

Wiggling (WIG) rats

WIG rats has been suggested to be a model of ADHD because it showed hyperactivity. Kamimura *et al*. found spontaneously hyperactive animals designated as "wiggling," in a strain of the Long-Evans Cinnamon (LEC) rats, and established a congenic WIG rat (Kamimura *et al*., 2001). Although the usefulness of the model has been challenged (Sagvolden *et al*., 2005), the same group recently reported interesting omics results, which may need further attention (Hirano *et al*., 2008).

Naples high-excitability rats

These animals are selectively bred for high activity and have higher DAT and tyrosine hydroxylase level in prefrontal cortex. It has been suggested as a good model for inattentive suptypes of ADHD because it did not show impulsivity and hyperactivity (Viggiano *et al*., 2002).

Wistar-Kyoto hyperactive rats

These animals were bred-out for the isolation of hyperactivity from hypertension (Hendley and Ohlsson, 1991). It is not an ideal model for ADHD in that it shows hyperactivity in novel situation and is without impulsive behavior. It has been suggested that these animals have abnormalities in attentional processing (Chess *et al*., 2005).

Poor 5-CSRT performers

5-CSRT quantify attentional deficits in ADHD and schizophrenia and assesses sustained attention over a 30 min or so test session (for a methodological and theoretical reviews, see Robbins, 2002). In this test, rats are placed in an apparatus with five holes, each equipped

with light and small size food is dropped when the animal pokes its nose to the hole after stimulus light is on. The animal should wait until the light's on and any premature trial to gain the food droplet is considered as a "premature response", which indicates impulsive behavior. Poor performers of this task may provide useful model for ADHD, especially inattentive subtype, because it showed inattention, impulsivity but not hyperactivity. The animal of choice for the selection of poor performers is rat although mice can be used for 5-CSRT (Greco and Carli, 2006)

Phenylketonuria

Children with phenylketonuria shows characteristic ADHD behavior. Phenylketonuria patients have elevated level of phenylalanine in the blood and reduced tyrosine and tryptophan level, which impairs normal supply of several amine neurotransmitters. BTBR *Pah*^{enu2} (PKU) mouse has been shown to closely mimic the anatomical, neurochemical and metabolic phenotypes of human phenylketonuria (Sarkissian *et al*., 2000). It is remained to be examined whether these animal can be used as a model of ADHD.

Neurofibromatosis-1

Neurofibromatosis type 1 (NF1) is a genetic disorder associated with cognitive deficits, learning problems with other medical complications. Clinical observations have linked NF1 and ADHD. NF1 is caused by mutations in the NF1 gene and it would be of interest to find out whether NF1 mutant mice show similar characteristics of ADHD. Recent reports that a 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor, lovastatin, decreased the enhanced brain p21Ras-MAPK activity of the nf1+/- mice, rescued their long term potentiation (LTP) deficits, and reversed their spatial learning and attention impairments (Li *et al*., 2005), may provide additional motivation to study these animal models.

In utero exposure to alcohol

Many factors other than genetic alteration may results in ADHD-like phenotypes. Rats received fetal alcohol exposure displays ADHD-like symptoms similar to human fetal alcohol syndrome (Hausknecht *et al*., 2005). It is assumed that dopamine transmission is impaired in this model of ADHD.

In utero exposure to nicotine and nicotinic acetylcholine (nAch) receptor knockout mice

Prenatal exposure to nicotine is one of the epidemiological risk factors of ADHD. Deletion mutant of the β2-nAch receptor produces ADHD symptoms in mice and it has been suggested that an agonist (RJR-2403 (N-methyl-4-(3-pyridinyl)-3-butene-1-amine), 1-10 mg/kg, s.c.) against α4β2-nAch receptor can prevent ADHD symptom (Ueno *et al*., 2002).

Lead intoxication

Lead intoxication has long been acknowledged as an environmental factor mediating human symptoms similar to ADHD (Nigg, 2008). Lead toxicity is especially important in young animals because of the irreversible damage during neural development. Among three core symptoms of ADHD, hyperactivity is most common and reliably observed in lead-exposed animals

Polychlorinated biphenyl (PCB)-exposed rats

It is still controversial whether environmental pollutants like PCBs can cause ADHD-like symptoms in human. Nevertheless, rats administered PCBs showed impulsive behavior with hyperactivity but not defects in attention. Recently, it was shown that ontogenetic treatments with PCB congeners cause alterations in cerebellar Purkinje cell development (Kimura-Kuroda *et al*., 2007). More data is needed to use PCS-exposed rats as a reliable model for ADHD.

Hyposexual rats

It has been suggested that hyposexual male rats have problems in selective attention and show hyperactivity (Kohlert and Bloch, 1993). Considering ADHD is diagnosed before age 7 and the hyperactivity was not reversed by d-amphetamine, the validity of the model is questionable.

Rats reared in social isolation

Although it has been almost disputed that ADHD is induced by abnormal social interaction with other peoples surrounding the affected child, rats reared in isolation after weaning showed hyperactivity (Dalley *et al*., 2002) although there is no direct evidence that these animals also demonstrate inattention and impulsivity. Many reports suggest that neural development is affected by environmental enrichments. In many animal models reviewed above, it would be interesting to examine the effects of environmental enrichments on hyperactivity, impulsive behavior and inattention. In an experiment using SHR and WKY, rats were reared in an enriched environment or in isolation. Although there is no dramatic differences between groups, there is some differences in response kinetics and individual variation. Peer rejection

is commonly observed among ADHD children and the issues raised with this animal model may be useful to understand the effect of social interaction in modulating ADHD symptoms.

Neonatal hypoxia

Neonatal hypoxia in rats (postnatal day 1-3) may mimics premature human brain insults. Neonatal hypoxia in rats has been suggested to demonstrate hyperactivity and anatomical and neurochemical abnormalities (Dell'Anna, 1999), which may underlie the hyperactivity. Repeated hypoxia early in neonatal periods produced hyperactivity but not inattention (Oorschot *et al*., 2007). In contrast, it was observed that rats subjected to subneurotoxic doses of anoxia during the early post-natal life develop behavioral symptoms that are frequently encountered in the inattentive subtype of the ADHD (Casolini *et al*., 2005), These authors also found that group-I metabotropic glutamate receptor (mGluR) may be involved in the pathophysiology of these symptoms, which might have some importance considering the role of mGluR in dendritic and neural development as well as the regulation of synaptic plasticity including LTP. Neurochemical changes include dopamine, norepinephrine and serotonergic nervous system with emphasis on DA system. Recently, it has been suggested that an antioxidant treatment reversed hyperactivity in hypoxic rats suggesting oxidative insults may underlie the observed neurochemical and neuroanatomical abnormalities (Ujhazy *et al*., 2006).

6-Hydroxydopamine (6-OHDA)-lesioned rats

Neonatal 6-OHDA-induced damage to rats has long been used as an useful model for ADHD. Neonatal injection of 6-OHDA induced more than 50% decrease in DA contents at 5 weeks with behavioral hyperactivity (Shaywitz *et al*., 1976), which is reversed by d-amphetamine treatment as in ADHD patients. One of the best thing using this model in ADHD research is that the animals do not show hyperactive behavior in novel environment but develops hyperactivity by repeated testing, which is consistent with human ADHD cases. Not only catecholamines but also serotonergic system was altered by 6-OHDA-induced damage. Serotonin and serotonin transporter binding was increased in striatum (Zhang *et al*., 2002) and an inhibitor of serotonin transporter or norepinephrine transporter attenuated hyperactivity (Davids *et al*., 2002). These results suggest that not only DA system but also serotonergic system is involved in the regulation of hyperactivie behavior either directly or indirectly via DA system and should be given more attention in developing anti-hyperactive agents for ADHD. In general, this model is considered not showing impulsive behavior, which limits the usefulness of the model. In addition, 6-OHDA-lesioned animal showed almost complete destruction of DA varicosities, while there is no obvious and massive destruction of any nervous system in human ADHD patients. In this sense, it is noteworthy that activation of 5-HT system is observed in 6-OHDA treated animals, especially in the neostriatum (Molina-Holgado, 1994), which again suggest that serotonergic nervous system could be the target of the hyperactivity intervention. Interestingly, destruction of serotonergic nervous system using 5,7-dihydroxytryptamine (5,7-DHT) in 6-OHDA-lesioned rats produced robust increase in locomoter activity, which was attenuated by amphetamine treatment (Kostrzewa *et al*., 1994). However, selective serotonin reuptake inhibitor like fluoxetine has only marginal effects in human ADHD while it reduced hyperlocomoter activity in 6-OHDA-lesioned animal (Davids *et al*., 2002). These results suggest that ther is still longway to go before any generalized conclusion is drawn.

5,7-DHT lesion model

Stereotaxic microinjection of the serotonin neurotoxin 5,7-DHT into the median raphe nucleus showed marked enhancement of a psychotic drug (phencyclidine)-induced locomotor hyperactivity and a disruption of prepulse inhibition in rats (Adams *et al*., 2008). In addition, although 5,7-DHT (i.c.v.) itself did not affect choice behaviour, it prevented amphetamine-induced decrease in impulsivity, particularly in animals showing a high level of impulsive choice (Winstanley *et al*., 2004). Even though 5,7-DHT injection destroys more than 85% of serotonergic terminal, it did not produce hyperactivity or impulsiveness per se, which limits the usefulness of the model. However, it should be remembered that different serotonin receptors are involved in subtype selective manners in the regulation of impulsive behavior (which is nicely reviewed in a recent article, Pattij and Vanderschuren, 2008) and the lack of impulsivity in 5,7-DHT model doesn't necessarily mean that serotonergic system is not involved in impulsivity control.

Cerebellar damage

Reductions in the volume of the cerebellum (Mostofsky *et al*., 1998) and impairments in cerebellar-dependent eyeblink conditioning have been observed in ADHD, which also observed in SHR. Children and adolescents with ADHD have smaller cerebellar volumes, particularly in the posterior-inferior cerebellar vermis (lobules VIII-X).

Altered baseline activity (Zang *et al*., 2007) and functional activation of the human cerebellar vermis following stimulant administration has also been demonstrated. Even though basal release is not evident, d-amphetamine-induced dopamine release in rat cerebellar vermis was also reported (Glaser *et al*., 2006). Recently, it has been reported that hemicerebellectomy in rats delays but does not prevent visuo-locomotor associative learning (Mandolesi *et al*., 2007). Several drugs administered to experimental animals early in life produced ADHD like-symptoms. The antimitotic drug methylazoxymethanol as well as a steroid, dexamethasone, produced mild hyperactivity (Ferguson *et al*., 1996, Fergusson, 2001). Similarly, cerebellar injury produced by P.O. treatment of trans-retinoic acid for three consecutive days at E11°©13 results in hyperactivity of the offsprings (Holson *et al*., 1997). The report of Kimura-Kuroda (2007) showing that ontogenic exposure to PCB elicit cerebellar damage, which replicates some aspects of ADHD symptoms, needs further attention.

Similar lesion study also has been reported for other targets. X-radiation of rats at 2°©15 days after birth produces neuronal damage in hippocampus accompanied by hyperactivity, which can be reduced by d-amphetamine treatment (Highfield *et al*., 1998). Damage to the nucleus accumbens produces hyperactivity and impulsivity without causing inattention. In addition, lesions to subthalamic nucleus caused impairments in visual attention. Simply because these models do not reflect human ADHD etiology, they are not in widespread use.

Acallosal mouse

Human ADHD patients show functional and anatomical abnormalities in the communication of two hemisphere (Kayl *et al*., 2000). It has been suggested that the inbred mouse strain I/LnJ shows total callosal agenesis with complete penetrance, and behavioral features which resemble ADHD (for a review, see Magara *et al*., 2000). These mice was considered to be impulsive compared to C57BL/6 at the start of the test based on their reduced latency to enter Y-maze in discriminative tasks but unlikey ADHD, the latency increased over time. The hyperactive behavior was also observed during the beginning of the session (Magara *et al*., 2000).

CONCLUDING REMARKS

Currently, SHR is the most well-accepted animal model of ADHD with many genetic, anatomical and neurochamical features appearing in common with human cases of ADHD. However, obvious discrepancies also exist in this model, not to mention other animal models for ADHD. To minimize misinterpretation of the data, it should be remembered that multiple systems should be examined during the drug screening process as well as investigation of etiology of ADHD using these animal models. Finally, emerging concepts including the involvement of cerebellum in the regulation of ADHD symptoms and the role of serotonergic system in impulsivity and hyperactivity are awaiting new and better animal models, with which we can obtain more detailed information to handle with the debilitating disorder.

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REFERENCES

Adams, W., Kusljic, S. and van den Buuse, M. (2008). Serotonin depletion in the dorsal and ventral hippocampus: Effects on locomotor hyperactivity, prepulse inhibition and learning and memory. *Neuropharmacology*. doi:10.1016/j.neuropharm. 2008.06.035.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychol. Bull*. **121**, 65-94.

Bruno, K. J., Freet, C. S., Twining, R. C., Egami, K., Grigson, P. S. and Hess, E. J. (2006). Abnormal latent inhibition and impulsivity in coloboma mice, a model of ADHD. *Neurobiol. Dis*. **25**, 206-216.

Burd, L., Klug, M. G., Coumbe, M. J. and Kerbeshian, J. (2003). Children and adolescents with attention deficit-hyperactivity disorder. 1. Prevalence and cost of care. *J. Child. Neurol*. **18**, 555-561.

Casolini, P., Zuena, A. R., Cinque, C., Matteucci, P., Alema, G. S., Adriani, W., Carpinelli, G., Santoro, F., Alleva, E., Bosco, P., Nicoletti, F., Laviola, G. and Catalani, A. (2005). Sub-neurotoxic neonatal anoxia induces subtle behavioural changes and specific abnormalities in brain group-I metabotropic glutamate receptors in rats. *J. Neurochem*. **95**, 137-145.

Cheon, K. A., Ryu, Y. H., Kim, Y. K., Namkoong, K., Kim, C. H. and Lee, J. D. (2003). Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. *Eur. J. Nucl. Med*. **30**, 306-311.

Chess, A. C., Keene, C. S., Wyzik, E. C. and Bucci, D. J. (2005). Stimulus processing and associative learning in Wistar and WKHA rats. *Behav. Neurosci*. **119**, 772-780.

Dalley, J. W., Theobald, D. E., Pereira, E. A., Li, P. M. and Robbins, T. W. (2002). Specific abnormalities in serotonin release in the prefrontal cortex of isolation-reared rats measured during behavioral performance of a task assessing visuospatial attention and impulsivity. *Psychopharmacology* (Berl). **164**,

329-340.

Davids, E., Zhang, K., Kula, N. S., Tarazi, F. I. and Baldessarini, R. J. (2002). Effects of norepinephrine and serotonin transporterer inhibitors on hyperactivity induced by neonatal 6-hydroxydopamine lesioning in rats. *J. Pharmacol. Exp. Ther.* **301**, 1097-1102.

Dell'Anna, M. E. (1999). Neonatal anoxia induces transitory hyperactivity, permanent spatial memory deficits and CA1 cell density reduction in developing rats. *Behav. Brain. Res*. **45**, 125-134.

Ferguson, S. A. (2001). A review of rodent models of ADHD. In: Solano, M. V., Arnsten, A. F. T. and Castellanos, F. X. (eds) Stimulant Drugs adnd ADHD, *Basic and Clinical Neuroscience*. University Press, Oxford. pp 209-220.

Ferguson, S. A., Paule, M. G. and Holson, R. R. (1996). Functional effects of ethylazoxymethanol-induced cerebellar hypoplasia in rats. *Neurotoxicol. Teratol*. **18**, 529-537.

Gainetdinov, R. R., Jones, S. R. and Caron, M. G. (1999). Functional hyperdopaminergia in dopamine transporter knock-out mice. *Biol. Psychiatr.* **46**, 303-311.

Glaser, P. E., Surgener, S. P., Grondin, R., Gash, C. R., Palmer, M., Castellanos, F. X. and Gerhardt, G. A. (2006). Cerebellar neurotransmission in attention-deficit/hyperactivity disorder: does dopamine neurotransmission occur in the cerebellar vermis? *J. Neurosci. Methods*. **151**, 62-67.

Greco, B. and Carli, M. (2006). Reduced attention and increased impulsivity in mice lacking NPY Y2 receptors: relation to anxiolytic-like phenotype. *Behav. Brain. Res*. **169**, 325-334.

Hausknecht, K. A., Acheson, A., Farrar, A. M., Kieres, A. K., Shen, R. Y., Richards, J. B. and Sabol, K. E. (2005). Prenatal alcohol exposure causes attention deficits in male rats. *Behav. Neurosci*. **119**, 302-310.

Hendley, E. D. and Ohlsson, W. G. (1991). Two new inbred rat strains derived from SHR: WKHA, hyperactive, and WKHT, hypertensive rats. *Am. J. Physiol. (Heart Circ Physiol)*. **261**, H583-H589.

Highfield, D. A., Hu, D. and Amsel, A. (1998). Alleviation of x-irradiation-based deficit in memory-based learning by D-amphetamine: Suggestions for attention deficit/ hyperactivity disorder. *Proc. Natl. Acad. Sci. USA.* **95**, 5785-5788.

Hirano, M., Rakwal, R., Shibato, J., Sawa, H., Nagashima, K., Ogawa, Y., Yoshida, Y., Iwahashi, H., Niki, E. and Masuo, Y. (2008). Proteomics- and transcriptomics-based screening of differentially expressed proteins and genes in brain of Wig rat: a model for attention deficit hyperactivity disorder (ADHD) research. *J. Proteome. Res*. **7**, 2471-2489.

Holson, R. R., Gazzara, R. A., Ferguson, S. A. and Adams, J. (1997). Behavioral effects of low-dose gestational day 11-13 retinoic acid exposure. *Neurotoxicol. Teratol*. **19**, 355-362.

Hunziker, M. H., Saldana, R. L. and Neuringer, A. (1996). Behavioral variability in SHR and WKY rats as a function of rearing environment and reinforcement contingency. *J. Exp. Anal. Behav.* **65**, 129-144.

Kamimura, E., Ueno, Y., Tanaka, S., Sawa, H., Yoshioka, M., Ueno, K. I., Inoue, T., Li, X., Koyama, T., Ishikawa, R. and Nagashima, K. (2001). New rat model for attention deficit hyperactive disorder (ADHD). *Comp. Med.* **51**, 245-251.

Kayl, A. E., Moore, B. D. 3rd., Slopis, J. M., Jackson, E. F. and Leeds, N. E. (2000). Quantitative morphology of the corpus callosum in children with neurofibromatosis and attention-deficit hyperactivity disorder. *J. Child. Neurol*. **15**, 90-96.

Kohlert, J. G. and Bloch, G. J. (1993). A rat model for attention deficit-hyperactivity disorder. *Physiol. Behav.* **53**, 1215-1218.

Kimura-Kuroda, J., Nagata, I. and Kuroda, Y. (2007). Disrupting effects of hydroxy-polychlorinated biphenyl (PCB) congeners on neuronal development of cerebellar Purkinje cells: a possible causal factor for developmental brain disorders? *Chemosphere* **67**, S412-S420.

Kostrzewa, R. M., Brus, R., Kalbfleisch, J. H., Perry, K. W. and Fuller, R. W. (1994). Proposed animal model of attention deficit hyperactivity disorder. *Brain Res. Bull*. **34**, 161-167.

Leo, D., Sorrentino, E., Volpicelli, F., Eyman, M., Greco, D., Viggiano, D., di. P. U. and Perrone-Capano, C. (2003). Altered midbrain dopaminergic neurotransmission during development in an animal model of ADHD. *Neurosci. Biobehav. Rev.* **27**, 661-669.

Li, W., Cui, Y., Kushner, S. A., Brown, R. A., Jentsch, J. D., Frankland, P. W., Cannon, T. D. and Silva, A. J. (2005). The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. *Curr. Biol*. **15**, 1961-1967.

Magara, F., Ricceri, L., Wolfer, D. P. and Lipp, H. P. (2000). The acallosal mouse strain I/LnJ: A putative model of ADHD? *Neurosci. Biobehav. Rev.* **24**, 45-50.

Mandolesi, L., Leggio, M. G., Spirito, F., Federico, F. and Petrosini, L. (2007). Is the cerebellum involved in the visuolocomotor associative learning? *Behav. Brain. Res*. **184**, 47-56.

Mill, J., Curran, S., Kent, L., Gould, A., Huckett, L., Richards, S., Taylor, E. and Asherson, P. (2002). Association study of a SNAP-25 microsatellite and attention deficit hyperactivity disorder. *Am. J. Med. Genet*. **114**, 269-271.

Molina-Holgado, E., Dewar, K., Descarries, L. and Reader, T. A. (1994). Altered dopamine and serotonin metabolism in the dopamine-denervated and serotonin-hyperinnervated neostriatum of adult rat after neonatal 6-hydroxydopamine. *J. Pharmacol. Exp. Ther.* **270**, 713-721.

Mostofsky, S. H., Reiss, A. L., Lockhart, P. and Denckla, M. B. (1998). Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *J. Child. Neurol*. **13**, 434-439.

Nigg, J. T. (2008). ADHD, lead exposure and prevention: how much lead or how much evidence is needed? *Expert. Rev. Neurother.* **8**, 519-521.

Oorschot, D. E., Voss, L., Covey, M. V., Bilkey, D. K. and Saunders, S. E. (2007). ADHD-like hyperactivity, with no attention deficit, in adult rats after repeated hypoxia during the equivalent of extreme prematurity. *J. Neurosci. Methods* **166**, 315-322.

Pattij, T. and Vanderschuren, L. J. (2008). The neuropharmacology of impulsive behaviour. *Trends Pharmacol. Sci.* **29**, 192-199.

Russell, V. A., Sagvolden, T. and Johansen, E. B. A. (2005). Animal models of attention-deficit hyperactivity disorder. *Behav. Brain Funct.* 1, 9.

Sagvolden, T. (2000). Behavioral validation of the spontane-

ously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). *Neurosci. Biobehav. Rev.* **24**, 31-39.

Sarkissian, C. N., Boulais, D. M., McDonald, J. D. and Scriver, C. R. (2000). A heteroallelic mutant mouse model: a new orthologue for human hyperphenylalaninemia. *Mol. Genet. Metabol*. **69**, 188-194.

Shaywitz, B. A., Yager, R. D., Klopper, J. H. (1976). Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. *Science* **191**, 305-308.

Siesser, W. B., Zhao, J., Miller, L. R., Cheng, S. Y. and McDonald, M. P. (2006). Transgenic mice expressing a human mutant beta1 thyroid receptor are hyperactive, impulsive, and inattentive. *Genes. Brain Behav.* **5**, 282-297.

Taylor, E. (1998). Clinical foundations of hyperactivity research. *Behav. Brain Res*. **94**, 11-24.

Trinh J. V, Nehrenberg D. L, Jacobsen J. P, Caron M. G. and Wetsel W. C. (2003) Differential psychostimulant-induced activation of neural circuits in dopamine transporter knockout and wild type mice. *Neuroscience* **118**, 297-310.

Tsai, S. J. (2007). Attention-deficit hyperactivity disorder may be associated with decreased central brain-derived neurotrophic factor activity: clinical and therapeutic implications. *Med. Hypotheses* **68**, 896-899.

Ueno, K., Togashi, H., Matsumoto, M,, Ohashi, S., Saito, H. and Yoshioka, M. (2002). Alpha4beta2 nicotinic acetylcholine receptor activation ameliorates impairment of spontaneous alternation behavior in stroke-prone spontaneously hypertensive rats, an animal model of attention deficit hyperactivity disorder. *J. Pharmacol. Exp. Ther.* **302**, 95-100.

Ujhzy, E., Schmidtov, M., Dubovick, M., Navarova, J., Bucknerov, I. and Mach, M. (2006). Neurobehavioural changes in rats after neonatal anoxia: effect of antioxidant stobadine pretreatment. *Neuro. Endocrinol. Lett*. 27 Suppl **2**, 82-85.

van den Bergh, F. S., Bloemarts, E., Chan, J. S., Groenink, L., Olivier, B. and Oosting, R. S. (2006). Spontaneously hypertensive rats do not predict symptoms of attention-deficit hyperactivity disorder. *Pharmacol. Biochem. Behav.* **83**, 380-390.

Viggiano, D., Vallone, D., Welzl, H. and Sadile, A. G. (2002). The Naples High- and Low-Excitability rats: Selective breeding, behavioral profile, morphometry, and molecular biology of the mesocortical dopamine system. *Behav. Genet*. **32**, 315-333.

Winstanley, C. A., Dalley, J. W., Theobald, D. E. and Robbins, T. W. (2003). Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology (Berl)*. **170**, 320-331.

Watanabe, Y., Fujita, M., Ito, Y., Okada, T., Kusuoka, H. and Nishimura, T. (1997). Brain dopamine transporter in spontaneously hypertensive rats. *J. Nucl. Med*. **38**, 470-474.

Zang, Y. F., He, Y., Zhu, C. Z., Cao, Q. J., Suim M. Q., Liang, M., Tian, L. X., Jiang, T. Z. and Wang, Y. F. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain. Dev.* **29**, 83-91.

Zhang, K., Davids, E., Tarazi, F. I. and Baldessarini, R. J. (2002). Effects of dopamine D4 receptor-selective antagonists on motor hyperactivity in rats with neonatal 6-hydroxydopamine lesions. *Psychopharmacology (Berl)* **161**, 100-106.