Rodent Models of Attention-Deficit/Hyperactivity Disorder

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An ideal animal model should be similar to the disorder it models in terms of etiology, biochemistry, symptomatology, and treatment. Animal models provide several advantages over clinical research: simpler nervous systems, easily interpreted behaviors, genetic homogeneity, easily controlled environment, and a greater variety of interventions. Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder of childhood onset that is characterized by inattentiveness, hyperactivity, and impulsiveness. Its diagnosis is behaviorally based; therefore, the validation of an ADHD model must be based in behavior. An ADHD model must mimic the fundamental behavioral characteristics of ADHD (face validity), conform to a theoretical rationale for ADHD (construct validity), and predict aspects of ADHD behavior, genetics, and neurobiology previously uncharted in clinical settings (predictive validity). Spontaneously hypertensive rats (SHR) fulfill many of the validation criteria and compare well with clinical cases of ADHD. Poor performers in the five-choice serial reaction time task and Naples high-excitability rats (NHE) are useful models for attention-deficit disorder. Other animal models either focus on the less important symptom of hyperactivity and might be of limited value in ADHD research or are produced in ways that would not lead to a clinical diagnosis of ADHD in humans, even if ADHD-like behavior is displayed.

Key Words: Attention-deficit/hyperactivity disorder, animal model, spontaneously hypertensive rat, inattentive, impulsive, dopamine

Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioral disorder affecting 2%–12% of children. It typically manifests by age 7 years and is most prevalent among boys (American Academy of Pediatrics 2000). Three core clinical symptoms define ADHD: inattentiveness, hyperactivity, and impulsiveness (American Psychiatric Association 1994). Psychostimulants (e.g., methylphenidate, d-amphetamine, and pemoline) are the most common treatments for ADHD (Solanto 1998).

Diagnostic criteria have evolved to include three ADHD subtypes: predominantly inattentive subtype (most prevalent in girls), predominantly hyperactive/impulsive subtype (most prevalent in boys), and combined subtype (Taylor et al 1998). Predominantly inattentive children appear dreamy and inert; inattention is nonspecific and related to poorly focused attention and less accurate information processing. Predominantly hyperactive/impulsive children have inattention specifically related to distractibility and reduced persistence (Taylor et al 1991). They often have memory retrieval problems, exhibit aggressive, oppositional behavior leading to adolescent delinquency and substance abuse, and suffer peer rejection (Barkley 1997).

Attention-deficit/hyperactivity disorder might be two separate disorders of different etiologies: attention-deficit disorder (ADD), characterized by inattention without hyperactivity/impulsiveness; and ADHD, characterized by impulsiveness, poorly sustained attention, and hyperactivity in familiar situations with few reinforcers (Johansen et al 2002; Sagvolden et al, in press). The ADHD syndrome describes clusters of symptoms; however, inattention and hyperactivity are nonspecific symptoms found in many psychiatric disorders and might not by themselves be good markers for ADHD.

Animal models help to simplify and promote the understanding of disorders. This article will discuss criteria required to validate animal models for ADD and ADHD.

Advantages of Animal Models

Optimal animal models should be similar to clinical cases in terms of etiology, biochemistry, symptomatology, and treatment (McKinney and Bunney 1969). Models usually have simpler nervous systems, and their behaviors are easier to interpret than clinical cases. Additionally, models are often more genetically homogeneous, their environment is easy to control, and more interventions are possible than in clinical cases.

General Validation Criteria for Animal Models

Sarter et al (1992) developed validation criteria for animal models of human disorders. Recently, criteria for assessing models for ADD and ADHD were proposed (Sagvolden 2000). An ADHD model must conform to three validation criteria: face validity, construct validity, and predictive validity. Face validity is the ability to fundamentally mimic the behavioral clinical characteristics of the disorder. Construct validity conforms to a theoretical rationale for the disorder. Predictive validity is the ability to predict previously unknown aspects of behavior, genetics, and neurobiology of the disorder from the model.

Face and predictive validity represent the empirical status of a model, whereas construct validity represents the model's theoretical status (Willner 1986). A model can be valid if some face or predictive validities are not met, although it cannot be valid if construct validity is violated; this is problematic in poorly understood disorders such as ADD and ADHD. Nonetheless, data from all validity criteria should be considered.

Specific Criteria for Animal Models of ADHD

Criteria for Face Validity

Children with ADHD and control subjects react differently to reinforcers. The major behavioral characteristics of children with

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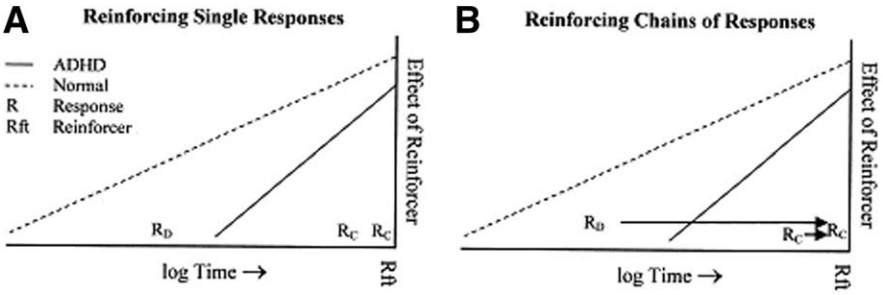

Figure 1. Different types of responses are reinforced and maintained by reinforcers ("rewards"): theoretical plot of single responses **(A)** and chains of responses **(B)**. A shorter delay-of-reinforcement gradient will reinforce fewer immediate correct responses (R_C), no delayed responses (R_D) **(A)**, and only short interresponse times **(B)**.

ADHD can be demonstrated with multiple fixed-interval/extinction schedules of reinforcement (FI/Ext schedules) with two or more components that operate in alternation, each in the presence of a different stimulus (Sagvolden et al 1998). The fixed-interval component delivers reinforcers at fixed time intervals when the required response is performed (e.g., a lever is pressed). The efficacy of the reinforcer (the delay-of-reinforcement gradient, Figure 1) and the maximum attainable response rate are measured (Sagvolden et al 1992b, 1993). The schedule also enables measurements of motor impulsiveness, that is, premature responses. In this particular case, impulsiveness is measured as responses with short interresponse times (IRTs). The extinction component measures sensitivity to stimulus change and the ability to sustain attention. When the extinction component is in effect, no reinforcer is delivered.

Motor Impulsiveness. Impulsiveness might be the most significant ADHD symptom (Johansen et al 2002; Sagvolden and Sergeant 1998; Taylor 1998). Motor impulsiveness is operationalized as bursts of responses with short IRTs (Johansen et al 2002; Sagvolden et al, in press). This response pattern is inefficient in FI/Ext schedules because the behavior does not result in an increased number of reinforcers. Children with ADHD do not exhibit motor impulsiveness in novel situations; impulsiveness develops gradually over time (Sagvolden et al 1998). This is an important criterion for any animal model of ADHD.

Deficient Sustained Attention. In clinical settings, sustained attention deficit occurs when stimuli are widely spaced in time (van der Meere 1996) or the task is unwelcome or uninteresting (Taylor 1998). In the extinction component of FI/Ext schedules, children with ADHD had normal sustained attention at initiation of testing, but it markedly decreased with repeated testing over time. Furthermore, at the start of every extinction component, both ADHD and normal children noticed the onset of the extinction component (a light signal) and stopped responding, but children with ADHD resumed responding after a short time (Sagvolden et al 1998).

Hyperactivity. Hyperactivity, like impulsiveness, is absent in novel situations, including test initiation (Sagvolden et al 1998; Sleator and Ullmann 1981). In FI/Ext schedules, children with and without ADHD had similar activity levels at initiation of testing. Hyperactivity developed gradually in children with ADHD as the test proceeded (Sagvolden et al 1998).

Conclusion. The optimal animal model for ADHD should ideally mimic ADHD in all respects: 1) impulsiveness should be absent initially and develop gradually over time; 2) sustained attention-deficit should be demonstrated only when stimuli are widely spaced in time; and 3) like ADHD children, the model should not display hyperactivity in a novel environment—hyperactivity should develop over time.

Criteria for Construct Validity

Genetics. Attention-deficit/hyperactivity disorder is a genetic disorder, most likely caused by multiple genes with small effect size (Sagvolden et al, in press). Optimal animal models should therefore be neurodevelopmental, preferably genetic models. Genetic studies link ADHD to the human dopamine receptor 4 gene (DRD4) mapped to chromosome 11p15.5 (Cook et al 1995) and allelic variations of the gene for the plasma-membrane dopamine transporter (DAT-1) (Kuntsi and Stevenson 2000), which is responsible for synaptic dopamine uptake.

Neuropathology. In addition to behavioral criteria, an animal model should display the structural and functional neuropathology of ADHD (i.e., reduced frontal lobe activity, increased somatosensory cortical blood flow, abnormal caudate, and reduced brain volumes; Castellanos et al 2002; Lou et al 1989; Paule et al 2000).

Neurotransmitter Dysfunction. A role for dysfunction of dopamine and other monoamine systems in ADHD has been suspected because the most effective drugs used to treat ADHD are psychostimulants that block dopamine and norepinephrine transporters. Animal models should have similar neurotransmitter dysfunction and provide insight into the neural disturbances of the disorder.

Delay-of-Reinforcement Gradient. Reinforcers act retroactively on past responses by increasing the probability of future responses of the same operant class (Catania et al 1988). The reinforcing effect is largest when the reinforcer is delivered immediately after the response and wanes when reinforcer delivery is delayed (Figure 1). This relationship between the effect of the reinforcer and the interval between response and reinforcer is called the "delay-of-reinforcement gradient" or the "delay gradient" (Catania et al 1988; Johansen et al 2002; Sagvolden et al, in press). It has been argued that ADHD symptoms are caused by steeper and shorter delay gradients and slower extinction of previously reinforced behavior (Johansen et al 2002; Sagvolden et al, in press). The behavior of animal models should be consistent with a steeper delay gradient.

Motor Impulsiveness. Not only single responses (e.g., R_C in Figure 1), but also the relationships between responses (e.g., IRTs; see Figure 1, right panel) are conditioned and maintained by reinforcers (Catania 1971; Catania et al 1988; Sagvolden et al 1998). In contrast to the normal delay gradient, the steeper delay gradient of children with ADHD is too short to reinforce the long IRT involved in the sequence R_D–R_C, (Figure 1, right panel). This reinforcement process explains why motor impulsiveness, responses emitted with short IRTs, is not present in a novel situation but develops gradually (Sagvolden et al 1998).

Impaired Sustained Attention. The three-term contingency—stimulus–response–consequence relationship (Catania 1998)—is important to understand the impaired sustained attention in