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Genetically Based Animal Models of Attention Deficit Hyperactivity Disorder

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Attention deficit hyperactivity disorder (ADHD) affects children, adolescents, and adults. Research suggests ADHD has a heritable component. The present article presents and assesses several genetic animal models of ADHD. The paper reviews the literature involving the following genetic animal models of ADHD: the spontaneously hypertensive rat (SHR); the Wistar–Kyoto hyperactive rat; the coloboma mouse; the fast kindling rat; the acallosal mouse; the whirler mouse; and the genetically hypertensive (GH) rat. Research investigating animal models of ADHD has concentrated on hyperactivity, but impulsiveness, learning, and attention are also being examined. The use of animal models allows for the control of possibly confounding variables and has proven very useful in the screening of new therapies. These models have not been shown to be the equivalent of the human disorder, and no model encompasses all of the symptoms of the human disorder, but they are useful nevertheless.

Keywords: animal models, behavior, genetics, ADHD

Attention deficit hyperactivity disorder (ADHD) is a diagnosis based on behavioral symptoms. The Diagnostic and Statistical Manual fourth edition (DSM-IV) (American Psychiatric Association, 1994) lists eighteen behavioral symptoms of ADHD. Nine of these are symptoms of inattention and nine are symptoms of hyperactivity and impulsiveness. There are three subtypes of ADHD. Six symptoms of inattention are required for a diagnosis of ADHD, predominantly inattentive subtype. Six symptoms of hyperactivity and/or impulsiveness are required for a diagnosis of ADHD, predominantly hyperactive-impulsive subtype. Six symptoms from each category of symptom are required for a diagnosis of ADHD, combined subtype (American Psychiatric Association, 1994). It should

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be noted that the DSM-V is in development and the criteria for ADHD are under review (American Psychiatric Association, 2010).

There is some question as to whether the three subtypes of ADHD are the same disorder with the same etiology (Lahey, Schaughency, Strauss, and Frame, 1984). There is also evidence to suggest that individuals with the combined subtype are more severely affected academically and socially than are individuals with the other two subtypes (Faraone, Biederman, Weber, and Russell, 1998; Gaub and Carlson, 1997). It is likely that there is a multifactorial basis to the origin of ADHD which would explain the heterogeneity of symptoms.

There has been a great deal of research investigating the etiology of ADHD. There is strong evidence that the disorder has a heritable component as demonstrated by family-genetic studies and twin studies (Biederman, Faraone, Keenan, Knee, and Tsuang, 1990; Faraone, Biederman, Keenan, and Tsuang, 1992; Gilger, Pennington, and DeFries, 1992; Goodman and Stevenson, 1985). The mode of inheritance, however, is unknown. The disorder is certainly not inherited in a Mendelian manner. It is likely that multiple genes are involved in a complex inheritance pattern.

Although there has been much research conducted on the possible anatomical and neurological bases for ADHD, diagnosis is still based on behavior (American Psychiatric Association, 1994). Animal models should also follow this protocol. Related to this, it is circular reasoning, and not proper, to argue that if drugs used to treat ADHD in children improve behavior in an animal model, then the animal model must be a true representation of ADHD. Individuals should not be diagnosed according to medication response.

Animal models are widely used in psychiatry research. Animal models may be of many different types and a complete review is beyond the scope of this paper. There are tests that may be administered to normal animals that are said to elicit emotions and behaviors comparable to those that occur in humans. For example, the Morris water maze (Morris, 1981) is used to study learning in rodents, and the elevated plus maze is a rodent model of anxiety (Walf and Frye, 2007). Animal models may also be genetically based or induced by trauma. A number of transgenic animal models of Alzheimer's disease have been reviewed by Götz et al. (2004). Marcotti, Pearson, and Srivastava (2001) have reviewed pharmacologic and lesion models of schizophrenia.

Animal models are useful because they allow for the control of environmental conditions that are completely uncontrollable in a human population. They also allow for the testing of new therapies to treat a condition. For example, new medications must first be tested in animal models. The Porsolt test (Porsolt, Anton, Blavet, and Jalfre, 1978; Porsolt, Le Pichon, and Jalfre, 1977), also called the forced swim test, is widely viewed as a model for depression and is used to screen for new antidepressants (Ali, Bashir, and Tanira, 1998; Einat, Karbovski, Korik, Tsalah, and Belmaker, 1999; Kroczka, Branski, Palucha, Pilc, and Nowak, 2001).

A number of models of ADHD have been proposed (Anisman and McIntyre, 2002; Magara, Ricceri, Wolfer, and Lipp, 2000; Sackler and Weltman, 1985; Sagvolden, Pettersen, and Larsen, 1993; Wilson, 2000). Each of these models has its strengths and weaknesses (which will be discussed later) and none captures all aspects of the disorder. It is of no surprise that a definitive animal model of ADHD has not been found given the heterogeneity of symptoms in humans and the complexity of the neurological findings. Several genetic strains of rat that have been discussed in the literature as possible animal models for ADHD are presented in this paper. The paper discusses the history of a number of older genetic models and cites recent research involving these models. Several newer models (the fast kindling rat and genetically hypertensive rat) are also discussed.

Animal Models

The Spontaneously Hypertensive Rat (SHR)

The spontaneously hypertensive rat strain was introduced by Okamoto and Aoki (1963). It is the most extensively studied of the animal models of ADHD. The SHR was developed by mating a male rat of the Wistar–Kyoto (WKY) strain showing spontaneous hypertension with a female of the same strain with a blood pressure slightly above average. Succeeding generations resulted in 100% recurrence of the spontaneously hypertensive trait. These rats show increasing blood pressure with age. The SHR has a shorter lifespan (approximately 18 months) than a normal rat (Linz et al., 1999) and is prone to brain damage, which begins at the age of four months (Sabbatini, Strocchi, Vitaioli, and Amenta, 2000). While the SHR was developed to study hypertension and stroke, Okamoto and Aoki (1963) noted certain behavioral abnormalities and reported them anecdotally. These abnormalities include aggressiveness, irritability, hyperkinesis or hypokinesis, and hyporesponsiveness. Since then, the behavioral traits of this strain have been studied extensively.

Activity level is the variable most often studied in the SHR. Research has produced conflicting data regarding this variable, but generally, the SHR has been found to be more active than other strains. This was first reported by Sasagawa and Yamori (1975), although their statistical analyses were not reported.

Knardahl and Sagvolden (1979) allowed rats to acclimatize to their home cage and then placed the cage in an open field. The door to the cage was left open, and the rats were allowed to freely explore for 15 minutes. The SHRs were found to be slightly less active than normal rats on first exposure to an open field but to show a gradual increase in activity in subsequent sessions in the open field. The SHRs were also found to have a shorter latency to leave the home cage. The gradual development of increased activity in the SHRs was suggested to demonstrate faster habituation and/or rapid sensitization. Generally

speaking, however, the term habituation is used to refer to the decrease in activity level seen with repeated exposures to an open field (Bert, Fink, Huston, and Voits, 2002; Dai, Krost, and Carey, 1995; Stam, Croiset, Akkerman, and Wiegant, 1997).

In a second experiment, Knardahl and Sagvolden (1979) found that if a novel object was placed in the open field, activity level increased, and decreased upon the removal of the novel object. The authors concluded that the SHR is more motivated by novelty than are normal rats and are, therefore, more active when confronted with novelty.

Sagvolden, Hendley, and Knardahl (1992) tested the activity level of the SHR against that of three other types of rat: (1) the normal Wistar–Kyoto (WKY), (2) a strain of Wistar–Kyoto bred to be hypertensive but not hyperactive (WKHT), and (3) a strain of Wistar–Kyoto bred to be hyperactive but not hypertensive (WKHA). In open field tests lasting 15 minutes, the SHR was found to be the most active strain.

McCarty and Kopin (1979) also found a higher activity level in SHRs than in Wistar–Kyoto rats and stroke prone (SP) SHRs when the groups were tested in a novel environment for 60 minutes. The SP SHRs had an intermediate activity level. As the authors also found that this higher activity level was not present when the animals were tested in their home cage, they speculated that this high activity level is related to heightened reactivity to environmental change. They also suggested that the higher activity level found in the SHRs was not related to blood pressure as the SP SHRs were not as active as the SHRs.

In a later experiment, Sagvolden, Pettersen, and Larsen (1993) compared the activity level of the SHR to that of four strains of normotensive rat. This experiment differed from earlier experiments in that a shorter period of testing (five sessions of 1.5 minutes each) in the open field was employed. In this research, the SHR was not found to be the most active strain.

Other types of tests have been employed to measure locomotory activity. Sagvolden, Metzger, Schiorbeck, Rugland, Spinnangr, and Sagvolden (1992) conducted an experiment involving operant conditioning to measure activity level. Water deprived SHRs and controls were trained to bar press for water drops. Fixed-interval trials in which water was available and extinction trials in which water was not available were alternated. In both the fixed interval trials and the extinction trials, the SHRs were found to lever press more than the controls. The researchers also conducted trials in which the subjects were not water deprived. The lever pressing behavior of the SHRs normalized under this condition. It is a matter of interpretation as to whether this experiment demonstrates hyperactivity in the SHR or some other type of behavior, such as impulsiveness.

Impulsiveness is a symptom of ADHD. Adriani, Capriolo, Granstrem, Carli, and Laviola (2003) measured impulsiveness in the SHR and the Wistar–Kyoto

rat. In this research, food deprived subjects were given the chance to poke their nose into one of two holes for a food reward. Nose-poking in the first hole (H1) resulted in an immediate small reward. Nose-poking in the second hole (H5) resulted in a larger reward after delay, which was progressively increased (0–100 seconds). All animals switched their preference from H5 to H1 with an increasing delay of reward. Impulsiveness was defined as speed in switching from H5 to H1. Several interesting results were obtained. Although there were no individual differences found in the WKY groups, there were very large individual differences in the SHR group. The SHRs seemed to divide into impulsive and non-impulsive subgroups. This work, again, was conducted in young rats, before the onset of hypertension.

Research has demonstrated that SHRs are more sensitive than controls to delays in reinforcement (Pardey, Homewood, Taylor, and Cornish, 2009; Sutherland et al., 2009) much like children with ADHD are more sensitive to delays in gratification (Marco et al., 2009; Sonuga–Barke, Taylor, Sembi, and Smith, 1992). Research has found SHRs to be more likely than control strains to choose a small immediate food reinforcement over a larger delayed reinforcement (Pardey et al., 2009; Sutherland et al., 2009).

Other findings obtained from research with the SHR are many, varied, and often conflicting. These findings include the following: superior (Ferguson and Cada, 2004; Widy–Tyszkiewicz, Scheel–Kruger, and Christensen, 1993) and inferior (Gattu, Pauly, Bass, Summer, and Buccafusco, 1997; Gattu, Terry Jr., Pauly, and Buccafusco, 1997) performance in the Morris water maze compared to normal controls; enhanced (Randich and Maixner, 1982) or reduced (Ledoux, Sakaguchi, and Reis, 1982) suppression of ongoing activity by fear-arousing stimuli; greater reactivity to footshock than normal controls as evidenced by a faster escape response (Leaton, Cassella, and Whitehorn, 1983); and a decreased rate of inhibition compared to normal controls (Johansen and Sagvolden, 2004).

The SHR shows utility as a screening model for potential treatments for ADHD. Stimulants decrease hyperactivity, and increase cognitive performance in these animals (Myers, Musty, and Hendley, 1982; Sagvolden, Metzer et al., 1992). How these findings relate to human ADHD is very open to interpretation. As a mechanistic model, the SHR is useful, but care must be taken not to interpret the data to fit the observations made of children.

The possible effect of hypertension on behavior in the SHR must be considered. Hypertension and hyperactivity in the SHR seem to be separable in some instances. Hyperactivity in the open field has been found in young animals before the onset of hypertension (Knardahl and Sagvolden, 1979; McCarty and Kopin, 1979). Researchers have also attempted to develop a strain of hyperactive and hyperreactive, but not hypertensive, rat (Hendley, 2000; Sagvolden, Metzger et al., 1992).

Wistar–Kyoto Hyperactive Rat (WKHA)

Two new inbred rat strains were developed in the 1970s by crossing the SHR with the normotensive Wistar–Kyoto (WKY) [Hendley, 2000]. Crossbreeding was used to produce a separation of the hyperactive and hypertensive traits of the SHR. The products of this crossbreeding are the WKHA, which is said to be normotensive but hyperactive and the WKHT, which is said to be hypertensive but not hyperactive (Hendley and Ohlsson, 1991; Hendley, Wessel, and Van Houten, 1986). Research has been conducted to determine the behavioral attributes of these strains (Hendley, 2000; Hendley et al., 1986; Hendley and Ohlsson, 1991; Sagvolden, Metzger et al., 1992). There are some areas where the data are open to interpretation. There are similarities, but also differences in the behavior of the SHR, WKHA, and WKHT.

The WKHA rat, like the SHR, has been reported to be more active than normal controls (Castanon, Hendley, Fan, and Mormede, 1993; Hendley et al., 1986; Hendley and Ohlsson, 1991; Sagvolden, Metzer et al., 1992) using a number of methods of measuring activity level. Sagvolden and colleagues have found the SHR and WKHA to be more active than the WKY and WKHT in a forced-exploration paradigm. In this paradigm the animal is placed in an open field with no opportunity to retreat to a home cage. However, in a free-exploration paradigm, where the animal can choose to enter an open field or stay in the home cage, the WKHA was found to spend less time than the SHR or WKHT in exploration of the open field. The SHR was the most active and most exploratory of the four groups in this test. The WKHT spent more time in the open field than the WKHA, but there was no difference in time spent in ambulation between these two groups.

The SHR and WKHA exhibit different patterns of habituation. Hendley and Ohlsson (1991) found that while the SHR seems to habituate poorly, showing little decrease in activity level with repeated exposure to an environment, the WKHA decreases activity level with successive trials in the open field.

The WKHA and the WKHT differ in aggressiveness (Hendley, Ohlsson, and Musty, 1992) with the WKHT being the more aggressive strain. The WKHA seems to have a different reaction to stress than other strains of normotensive rat. Henry et al. (1993) found that overcrowding for over four months created an increase in blood pressure in Long–Evans and Sprague–Dawley rats but not in WKHA rats. It is not clear how this latter finding fits in with previous research in which physiological measurements suggest that the WKHA is more reactive to stress than the WKY or the WKHT rat (as is the SHR) (Hendley, Cierpial, and McCarty, 1988; Knardahl and Hendley, 1990). It might be noted that conduct disorder and antisocial personality disorder are often comorbid with ADHD (Biederman et al., 1993; Mannuzza, Klein, Bessler, Malloy, and LaPadula, 1998; Rommelse et al., 2009).

Coloboma Mouse

The coloboma mutant mouse has a deletion within mouse chromosome 2 which spans the gene for the synaptosomal-associated protein (SNAP-25). The Cm mutation is semidominant. The homozygous Cm/Cm mouse is not viable and the mutation is lethal during embryogenesis. The heterozygous Cm/+ is viable. The phenotypic expression of Cm/+ includes head bobbing, opthalmic malformation, and extreme levels of hyperactivity. These traits are shown to cosegregate consistently with the coloboma mutation (Hess, Jinnah, Kozak, and Wilson, 1992; Wilson, 2000).

Hess et al. (1992) compared the 24-hour activity patterns of the coloboma mutant mouse (Cm/+) to that of control littermates (+/+) using infrared beam detectors. The coloboma mice spent more time in spontaneous locomotion than did the controls. Hess at al., however, reported no group difference in time spent quiescent, which was defined as the number of 15-minute intervals per mouse during which no photocells were tripped. The authors concluded that while extraordinarily active, the Cm/+ demonstrates normal sleep/wake patterns. There have been several studies, however, which show abnormal sleep patterns in children with ADHD (LeBourgeois, Avis, Mixon, Olmi, and Harsh, 2004; Ramos Platon, Vela Bueno, Espinar Sierra, and Kales, 1990).

Bruno, Freet, Twining, Egami, Grigson, and Hess (2007) assessed attention in the coloboma mouse. Latent inhibition was used as a measure of attention. A conditioned aversion taste paradigm was used to test latent inhibition, a phenomenon that occurs when a subject is preexposed to a stimulus later used as a conditioned stimulus (CS). In normal animals, preexposure to the CS results in a slower acquisition of the CS and unconditioned stimulus (US) association. The coloboma mice acquired the association between the CS and US faster than the control animals, indicating a deficit in latent inhibition. The authors suggested that this finding reflects impairment in selective attention.

Bruno et al. (2007) also investigated impulsiveness in the coloboma mouse using a delayed reinforcement paradigm. Coloboma mice and normal controls were tested to determine ability to delay an immediate, less preferred reward in order to obtain a preferred reward. The coloboma mice were found to have a deficit in this ability compared to control mice.

Few other aspects of the behavior of the coloboma mouse have been studied. It has been reported that the coloboma mouse shows delays in reaching developmental milestones (Heyser, Wilson, and Gold, 1995). The research, however, suggests that the coloboma mouse exhibits several important aspects of ADHD.

Fast Kindling Rat

Anisman and McIntyre (2002) proposed an animal model for ADHD based on level of amygdala excitability. Kindling of the amygdala in rats is used as a

model for temporal lobe epilepsy with secondary generalization (Albright and Burnham, 1980; Loscher, Jackel, and Czuczwar, 1986; McNamara, 1986). Kindling is a process involving repeated electrical stimulation of a brain site, often the amygdala, via an implanted electrode. At first, a focal seizure at the site of implantation is elicited, but with repeated stimulation, the seizure spreads until a behavioral seizure results (Goddard, McIntyre, and Leech, 1969; Racine, 1972). Rats are often the subjects of kindling experiments, and seizure thresholds vary among individuals. Anisman and McIntyre (2002) have produced strains of fast and slow kindling rats and propose fast kindling rats (those that require fewer stimulations to produce full behavioral seizures) as a model for ADHD.

Mohapel and McIntyre (1998) reported that fast kindling male rats have a higher ratio of open to closed arm entries in the elevated plus maze than do slow kindling rats, suggesting that fast kindling rats are less anxious than the slow kindling animals. They also report that fast kindling rats have a higher activity level than slow kindling rats, exhibit less freezing in an inhibitory avoidance task, and demonstrate faster acquisition and better retention in a one-way avoidance task. In a later experiment, female fast kindling rats were also found to be more anxious than slow kindling rats (Runke and McIntyre, 2008). Although high anxiety level is not a criterion for the diagnosis of ADHD, it is often a cormorbidity (American Psychiatric Association, 1994; Rommelse et al., 2009).

Anisman and McIntyre (2002) later studied learning using the Morris water maze and obtained somewhat different results. Fast kindling rats were found to perform more poorly than slow kindling rats in the Morris water maze under several different conditions. Of interest, however, is the result that in a forced swimming test of three trials (in which no platform was present), the swimming activity of the fast kindling rats remained unchanged while the swimming activity of the slow kindling rats declined over the three trials and was replaced with floating.

It is important to note that although differences were found in behavior between a strain of rat bred to be slow kindling and a strain of rat bred to be fast kindling, no normal rat strain was used as a control. It is, therefore, difficult to tell whether the fast kindling rats were more active than normal, or the slow kindling rats less active. A comparison between normal rats and these specially bred strains should be conducted.

The fast kindling rats in this research had low seizure thresholds. Children, adolescents, and adults with epilepsy have a higher incidence of psychiatric disorders, including ADHD, than do individuals in the general population (Ounstead, 1955; Semrud–Clikeman and Wical, 1999; Smith, Craft, Collins, Mattson, and Cramer, 1986; Stores, 1978). The reasons for this are not clear. The seizure disorder and the psychiatric disorder may have the same underlying cause. Some evidence suggests that the seizures themselves may drive behavioral

change and cause symptoms of psychiatric disorders (Murphy and Burnham, 2003). In addition, environmental factors cannot be ruled out. ADHD does not appear to be a risk factor for epilepsy (Williams, Schultz, and Griebel, 2001).

Acallosal Mouse Strain I/LnJ

An animal model with callosal agenesis has been suggested as an animal model for ADHD (Magara, Ricceri, Wolfer, and Lipp, 2000). In the I/LnJ strain, callosal agenesis is total and seems to have a complete penetrance. Callosal agenesis of varying degrees also occurs in other mouse strains (Lipp and Wahlsten, 1992). There seem to be no other neurological deficits associated with the callosal agenesis seen in mice (Lipp and Wahlsten, 1992).

Although there seems to be a great deal of inter-individual variability in activity level in this strain, on the whole, the acallosal I/LnJ mouse is more active in the open-field than are normal mice and in a study by Magara et al., showed a higher rate of spontaneous activity in an avoidance test. The I/LnJ mouse also appears to be dominant over other strains (Magara et al., 2000).

More work on the acallosal mouse strain I/LnJ is needed before its usefulness as a model for ADHD can be assessed. However, there does not seem to be a great deal of interest in this model.

Whirler Mouse

The whirler mouse is the result of a recessive mutation. Differences between mutant animals (wi/wi) and their littermates become evident early in development. At postnatal day 9 or 10, mutant animals are more active and slower to recover when placed on their backs than are normal mice. They also adopt a distinctive posture when suspended by the tail; whirlers clasp their hind feet together and bring the head toward the belly. At 14 to 16 days of age, the whirler mouse develops head-shaking and circling behavior (Lane, 1963). Whirler animals have been described as hyperactive, unsteady on their feet, restless, nervous, excitable, and irritable (Lane, 1963; Sackler and Weltman, 1985; Sidman, Green, and Appel, 1965). All adult whirler mice are deaf, and Sidman et al. (1965) reported that they cannot swim, as they cannot stay on the surface of the water.

There has been little work conducted on validating the whirler mouse as a model of ADHD and none conducted recently. Sackler and Weltman (1985), however, conducted two studies demonstrating the usefulness of animal models even if the models do not meet all criteria for the disorder in question. These authors found that methylphenidate in single, low doses increased circling behavior in the whirler mouse while higher, repeated doses of the drug inhibited circling behavior and hyperactivity significantly. This decrease in circling behavior

and activity level reversed with cessation of drug administration. Sackler and Weltman (1985) stated in their article that it would be inappropriate to conclude that the behavior of the whirler mouse and the behavior of ADHD children are closely allied and that the response of the whirler mouse to stimulant medication indicates that it may be useful for screening new therapeutic agents.

Genetically Hypertensive Rat (GH)

The genetically hypertensive rat (GH) has been proposed as a model for ADHD. The GH is a strain of inbred rat derived from the Wistar rat (WI). Sutherland et al. (2009) investigated sensitivity to reinforcement delay in the SHR and its control, the WKY, and the GH rat and its control, the WI. The rats had a choice between two levers, one delivering an immediate reward and one delivering a delayed reward. The authors reported that the GH rat and SHR preferred an immediate reward to a delayed reward to a greater degree than did the WKY and WI rats. Further, the GH rats showed a preference for the immediate reward whether or not an immediate reward was obtained in the preceding trial. The preferences of the SHR, WKY, and WI rats for an immediate reward were smaller if an immediate reward was obtained in the preceding trial. The authors concluded that the GH rat may be more homogeneous genetically than the SHR and could be of great value in investigating the genetic basis of reward sensitivity.

Discussion

All of the animal models discussed have something to offer in the study of ADHD. Although finding the exact equivalent of ADHD in the animal kingdom would be of great interest, it is not necessary for an animal model to fulfill all of the criteria of a human disorder to be useful. There is some controversy, for example, about whether the Porsolt test is really a measure of depression. In this two-part test, the subject is placed in an inescapable container of water. At first, the animal tries to escape but eventually gives up and adopts a characteristic floating posture. This part of the test is used to induce "behavioral despair." The second part of the test is used in the screening of potential antidepressants. Rodents given antidepressants spend more time trying to escape from the situation in the second part of the test than do controls (Porsolt et al., 1977, 1978). The Porsolt test is very useful as a test for potential antidepressant treatments whether or not the behavior it induces truly represents a state of depression.

There are pitfalls in trying to develop a true model of ADHD in animals. Animal behavior is not always easily interpreted. A poor performance in the Morris water maze, for example, may be due to many things. In addition, the behavior of children with ADHD is not homogeneous, and the core symptoms

within the disorder are not unique to ADHD. For example, the DSM-IV (American Psychiatric Association, 1994) includes hyperactivity as a clinical feature of bipolar disorder. Impulsiveness is inherent within disorders such as bulimia, mania, addictions, and intermittent explosive rage. The cause of ADHD and the brain chemistry involved are still puzzles. Animal models, however, have proven to be extremely useful in psychiatric research whether or not they are really an animal equivalent of the human disorder under investigation. As stated earlier, animal models allow for environmental influences to be controlled; it is not possible to control the environment of human participants so closely. New treatments that cannot be administered to humans without further testing can be investigated. For example the ketogenic diet (a high fat, low protein and low carbohydrate diet used to treat intractable epilepsy) has been found to improve symptoms of ADHD in individuals with epilepsy (MacCracken and Scalisi, 1999; Pulsifer, Gordon, Brandt, Vining, and Freeman, 2001; Sirven et al., 1999). The findings of these researchers led to the testing of the ketogenic diet in an animal model. The ketogenic diet decreases activity level in rats (Murphy and Burnham, 2006; Murphy, Likhodii, Hatamian, and Burnham, 2005). The ketogenic diet is unpalatable and may have health consequences (Katyal, Koehler, McGhee, Foley, and Crumrine, 2000; Sirven, et al., 1999), and testing in normal children, adolescents, or adults is problematic. The effects of the diet, independent of seizure activity, can be studied in normal rats.

Different animal models display different aspects of ADHD. No model has been developed that displays all aspects of ADHD. The existence of so many animal models of ADHD allows different aspects of the disorder to be examined.

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