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What can we learn from Animal Models of ADHD?

The brain uses chemicals called neurotransmitters to transmit signals from one nerve cell to the next in pathways that control specific aspects of human behaviour. The activity of neural circuits that send rapid signals through the brain can be modulated by monoamines such as norepinephrine and dopamine. Thanks to norepinephrine's action in the brain, we learn to avoid potentially harmful situations. Norepinephrine acts by strengthening synaptic connections between nerve cells in networks that give rise to appropriate behavioural responses to arousing, potentially threatening stimuli in the external environment. Thanks to dopamine's action in the brain, we tend to repeat behaviour that leads to reward. We also tend to avoid actions that lead to unpleasant consequences. Dopamine exerts strengthening effects on neural networks that give rise to behaviour that leads to reward. These neuromodulators can also weaken synaptic connections in circuits that encode behaviour that may have been appropriate at an earlier stage but needs to be changed because the situation has changed. For example, dopamine plays an important role in extinction processes whereby learned responses to certain stimuli no longer produce reward and behaviour has to be changed.

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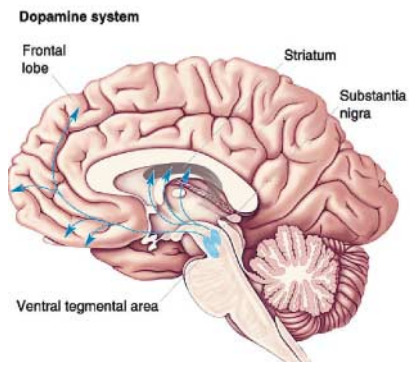
Although rodent brains cannot be used to study complex human behaviour such as language, they do have similar basic functions such as control of motor activity, response to stress, regulation of sleeping, eating, etc. We use animal models to identify changes in relatively simple nervous systems that are associated with behaviour that mimics the human disorder. Diseases that do not have animal models have made far less progress than those that do. Animal models of ADHD do not mimic ADHD. They can only mimic aspects of the complex cluster of behavioural symptoms displayed by children who are diagnosed as having ADHD. ADHD is a heterogeneous behavioural disorder caused by multiple genetic and environmental factors. Children diagnosed as having ADHD display different patterns of symptoms ranging from predominantly inattentive to the combined hyperactive/impulsive and inattentive subtype of ADHD. Genetic animal models of ADHD mimic groups of children with similar genetic predisposition and provide invaluable insight into the underlying cause of the disorder in those children. The strength of animal models of human disorders is that they permit in-depth investigation of relatively simple but dysfunctional nervous systems with associated behavioural disturbances (or other measure), that cannot be measured in humans.

Animal models offer valuable information that can be used to generate hypotheses that can be tested in the clinical situation, to determine whether similar disturbances exist in the human disorder.

Several animal models have been proposed for ADHD. These models have been generated as a result of genetic manipulation, exposure to toxins or environmental deprivation. Many of these do not meet the criteria set out in the recent review by Sagvolden et al (2005), namely (i) an animal model should mimic the fundamental behavioural characteristics of ADHD (face validity), impulsiveness should be absent initially and develop gradually over time, sustained attention-deficit should be demonstrated only when stimuli are widely spaced in time, hyperactivity should not be observed in a novel, non-threatening environment, it should develop over time; (ii) the model should conform to a theoretical rationale for ADHD (construct validity) the two main behavioural processes that are proposed to be major contributory factors in the aetiology of ADHD, altered reinforcement of novel behaviour and deficient extinction of previously reinforced behaviour, should be demonstrated; (iii) the model should predict novel aspects of ADHD behaviour, genetics, and neurobiology (predictive validity); and (iv) it should be neurodevelopmental, preferably a genetic model. Several animal models do mimic critical aspects of ADHD behaviour, either impaired sustained attention and/or hyperactivity/impulsivity that develops over time in a familiar environment (Sagvolden et al, 2005) and provide useful information concerning neurochemical changes that accompany their particular behavioural disturbances. Animal models that have provided novel insight into the mechanisms underlying the behavioural disturbances of ADHD include the spontaneously hypertensive rat (SHR, Wultz et al, 1990; Sagvolden et al 1998, 2000, 2005; Russell et al, 1995, 1998, 2002), dopamine lesioned rat (Luthman et al 1989), dopamine transporter knockout mouse (Gainetdinov and Caron, 2000), poor performers in the 5-choice serial reaction time (5-CSRT) task (Barbelivien et al, 2001), coloboma mutant mouse (SNAP-25 knockout; Jones et al, 2001), and neonatal anoxia (a risk factor for ADHD; Del'anna, 1999).

Of all the animal models of ADHD, SHR have been the most extensively investigated and provide the best model for the combined subtype of ADHD. Sagvolden and colleagues (1990, 1998, 2000) have developed sophisticated behavioural techniques to investigate specific aspects of ADHD behaviour. Using similar multiple fixed interval/extinction schedules of reinforcement but different context and nature of reinforcer (e.g., trinkets to children, water to rats), they showed that SHR behaved just like children with ADHD when compared to controls. Both displayed impaired sustained attention, and hyperactivity/impulsivity that developed gradually over time in a familiar environment (Sagvolden 2000; Sagvolden et al 2005).

Figure 1. Human right brain hemisphere, depicting dopaminergic pathways in blue. (From Baer et al., 2001, *Neuroscience – Exploring the Brain*)



The neurochemistry of ADHD has been extensively investigated and provides convincing evidence that the dopaminergic system is functionally impaired, the noradrenergic system is poorly regulated, and calcium signaling may be impaired (Lehohla et al, 2004; Russell et al, 1995, 1998, 2002). Calcium is an important second messenger and any impairment in calcium signaling would impair neurotransmitter function. It is possible that the observed changes in the neuromodulators, dopamine and norepinephrine, reflect a compensatory response to a more fundamental defect in calcium signaling in SHR. Similarly, compensatory adaptations may occur in the SNAP-25 knockout mouse. Other animal models of ADHD help to provide further insight into specific aspects of ADHD in that they mostly support the findings with SHR. All of the models display impaired learning and memory formation, but rats that have been selected for poor performance in the 5-CSRT task provide a particularly good model for the predominantly inattentive subtype of ADHD, they are selected for impaired sustained attention, and are impulsive, defined as premature responding, but they are not hyperactive. The other models display hyperactivity and reflect disturbances of the dopaminergic system or general interference with neurotransmitter release (SNAP-25) or neonatal oxygen deprivation, affecting development.

All of the animal models of ADHD display decreased function of the dopaminergic system. The dynamic developmental behavioural theory (DDT) of Sagvolden et al (2005) suggests that the dopaminergic system is hypoactive in ADHD and explains how behavioural changes associated with ADHD may result from altered reinforcement and extinction processes (Sagvolden et al, 2005). There are three major dopaminergic systems in the brain, the mesocortical, mesolimbic and nigrostriatal pathways.

Mesolimbic dopamine neurons project from the ventral tegmental area of the midbrain (VTA) to limbic areas of the brain. Activation of the projection to the ventral striatum (nucleus accumbens) is suggested to underlie the reinforcement of appropriate behaviour by signalling errors in the prediction of rewarded outcomes (Fiorillo et al, 2003). The firing rate of dopamine neurons is increased in response to unexpected reward and decreased when a fully predicted reward is omitted (Fiorillo et al, 2003; Schultz, 1998). Deficient reinforcement of appropriate behaviour and/or deficient extinction of previously reinforced behaviour can give rise to ADHD symptoms of delay aversion, hyperactivity in a familiar environment, impulsiveness, deficient sustained attention, increased behavioural variability and failure to extinguish previously acquired behaviour (Sagvolden et al, 2005).

The mesocortical dopamine system originates in the VTA and projects to cortical areas, including the prefrontal, parietal and temporal cortex. These dopamine projections modulate circuits that are known to play an important role in a variety of executive functions, including motor control, behavioural inhibition, attention, and working memory (Goldman-Rakic, 1996). Dopamine activation of D_2 receptors (DRD2) selectively modulates neural activities associated with memory-guided motor activity in delayed response tasks whereas DRD1 are responsible for memory-related persistent activation of prefrontal cortex neurons (Wang et al, 2004). Deficient dopamine-mediated modulation of prefrontal cortical circuits can cause attention response deficiencies

(impaired orienting responses, saccadic eye movements and responses towards a target) and impaired executive functions (poor behavioural planning).

Nigrostriatal dopamine neurons project from the substantia nigra pars compacta to the dorsal striatum (caudate nucleus and putamen). Impaired dopamine modulation of cortico-striato-thalamo-cortical circuits can impair motor function and cause deficient habit learning i.e. impaired nondeclarative memory formation (Sagvolden et al., 2005). These impairments can give rise to apparent developmental delay, clumsiness, neurological "soft signs" (Sagvolden et al., 2005).

Several models also suggest that the noradrenergic system is poorly regulated by hypofunctional α_2-autoreceptors and may be uncontrollably hyperactive in states of arousal, giving rise to hyperactivity of the noradrenergic system. It is possible that the behavioural characteristics of the animal models result from impaired dopamine modulation of neurotransmission in cortico-striato-thalamo-cortical circuits and in some cases behaviour may be determined by an imbalance between hyperactive noradrenergic and hypoactive dopaminergic systems in the prefrontal cortex.

Drugs that are used to treat children with ADHD, such as the psychostimulants, methylphenidate (Ritalin) and d-amphetamine, ameliorate all three major clusters of symptoms of ADHD but do not correct the underlying disturbance in neural circuits, their effects wear off within a few hours. On the other hand, drugs that target the noradrenergic system, such as atomoxetine, desipramine, and α_2-adrenoceptor agonists, take much longer to exert their effects (several weeks as opposed to half-an-hour) but their effects are enduring, lasting several months. In normal animals, desipramine causes long-term changes in noradrenergic receptors including persistent downregulation of β-adrenoceptors. Evidence from several animal models of ADHD suggests that, in addition to hypofunction of dopaminergic systems in the brain, the noradrenergic system may be hyperactive in ADHD. This is consistent with the therapeutic effect of noradrenergic drugs being dependent on downregulation of norepinephrine acting on β-adrenoceptors. Further studies using animal models of ADHD are required to determine exactly what the underlying mechanism of noradrenergic drug action is in ADHD. Once this is achieved, better drugs can be developed to target the underlying cause of the disorder.

Several important findings have emerged from studies of animal models of ADHD. Behavioural tests were designed to investigate specific aspects of ADHD behaviour in SHR, and subsequently applied to children with ADHD, enabling direct comparison of behaviour. An important contribution to the understanding of the disorder has been the identification of common neurotransmitter disturbances that are found in the brains of several different animal models, of different origins, suggesting possible fundamental causes of the behavioural disturbances of ADHD. Neurons that use dopamine as a neurotransmitter do not function normally in animal models of ADHD. All three major dopaminergic systems appear to be hypofunctional. Another important finding has been the demonstration across studies that the brains of animal models of ADHD do not react to psychostimulants in the way that brains of normal

animals do. This makes it especially important to distinguish between results obtained with ADHD children and normal controls when interpreting effects of drugs on behaviour.

In addition, animal models have generated hypotheses that can and have been tested in children with ADHD and provided unique insights into the neurophysiology of ADHD. Currently animal models are being used to test new drugs that can be used to alleviate the symptoms of ADHD.

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