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Validation of Animal Models of ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder of childhood onset that is characterized by inattentiveness, hyperactivity, and impulsiveness. All clinical criteria are behavioural. Inattentiveness, overactivity, and impulsiveness are presently regarded as the main clinical symptoms.

The dynamic developmental behavioural theory (DDT) is based on the hypothesis that altered dopaminergic function plays a pivotal role by failing to modulate nondopaminergic (primarily glutamate and GABA) signal transmission appropriately (Johansen, Sagvolden, Aase, & Russell, 2005; Sagvolden, Johansen, Aase, & Russell, 2005a).

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A hypofunctioning mesolimbic dopamine branch produces altered reinforcement of behaviour and deficient extinction of previously reinforced behaviour (Figure 1). This gives rise to delay aversion, development of hyperactivity in novel situations, impulsiveness, deficient sustained attention, increased behavioural variability, and failure to "inhibit" responses ("disinhibition").

A hypofunctioning mesocortical dopamine branch will cause attention response deficiencies (deficient orienting responses, impaired saccadic eye movements, and poorer attention responses toward a target) and poor behavioural planning (poor executive functions).

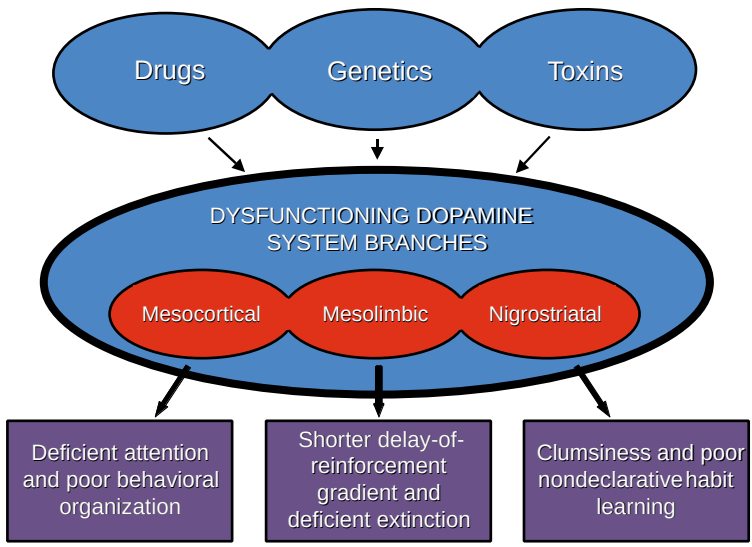

Figure 1. Dysfunction of dopaminergic systems resulting from drug abuse, genetic transmission, or environmental pollutants may cause ADHD symptoms by interacting with frontostriatal circuits (not shown) (Sagvolden et al., 2005a).

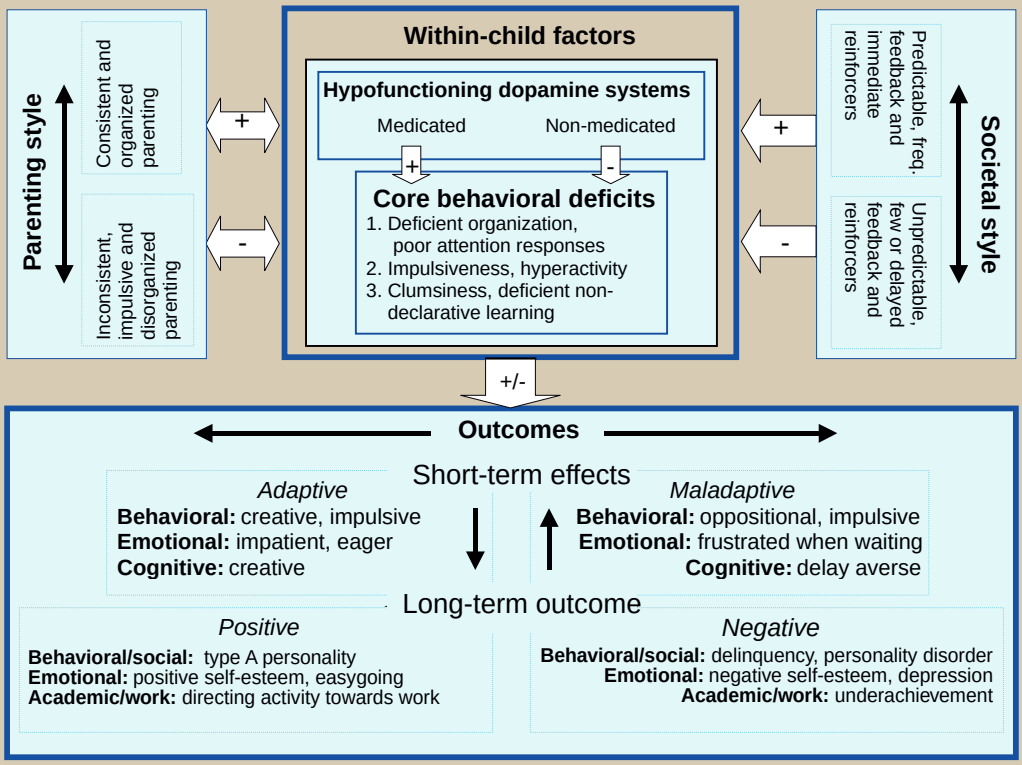

Figure 2. The dynamic developmental theory (DDT) predicts adaptive as well as maladaptive behavioural outcomes of the core deficits in interaction with medication, parenting, and societal styles. A plus sign (+) within an arrow means a beneficial interaction or influence, a minus sign (–) denotes an unfavourable interaction or influence. Parenting and societal styles and the behavioural outcomes are regarded as vectors, not as discrete categories in order to stress the dynamic and developmental aspects of ADHD behaviour (Sagvolden et al., 2005a).

A hypofunctioning nigrostriatal dopamine branch will cause impaired modulation of motor functions and deficient nondeclarative habit learning and memory. These impairments will give rise to apparent developmental delay, clumsiness, neurological "soft signs," and a "failure to inhibit" responses when quick reactions are required.

Hypofunctioning dopamine branches represent the main individual predispositions in the DDT theory (Sagvolden et al., 2005a). DDT predicts that behaviour and symptoms in ADHD result from the interplay between individual predispositions and the surroundings. The exact ADHD symptoms at a particular time in life will vary and be influenced by factors having positive or negative effects on symptom development (Figure 2). Altered or deficient learning and motor functions will produce special needs for optimal parenting and societal styles. Medication will to some degree normalize the underlying dopamine dysfunction and reduce the special needs of these children. DDT describes how individual predispositions interact with these conditions and produce behavioural, emotional, and cognitive effects that can turn into relatively stable behavioural patterns.

Animal models

Although animals cannot be used to study complex human behaviour such as language, they do have similar basic functions. In fact, human disorders that have animal models are better understood than disorders that do not. An ideal animal model should be similar to the disorder it models in terms of aetiology, biochemistry, symptomatology, and treatment. Animal models provide several advantages over clinical research: simpler nervous systems, easily interpreted behaviours, genetic homo-

geneity, easily controlled environment, and a greater variety of interventions (Johansen, Aase, Meyer, & Sagvolden, 2002; Johansen & Sagvolden, 2004; Johansen & Sagvolden, 2005a; Johansen & Sagvolden, 2005b; Johansen, Sagvolden, & Kvande, 2005; Russell, Sagvolden, & Johansen, 2005; Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005b).

The ADHD diagnosis is behaviourally based; therefore, the validation of an ADHD model must be based in behaviour. An ADHD model must mimic the fundamental behavioural characteristics of ADHD (face validity), conform to a theoretical rationale for ADHD (construct validity), and predict aspects of ADHD behaviour, genetics, and neurobiology previously uncharted in clinical settings (predictive validity).

Spontaneously hypertensive rat (SHR)

SHR fulfil many of the validation criteria and compare well with clinical cases of ADHD (Figure 3) (Sagvolden, 2000; Sagvolden, Aase, Zeiner, & Berger, 1998; Sagvolden et al., 2005b). Poor performers in the five-choice serial reaction time task and Naples high-excitability rats (NHE) are useful models for attention-deficit disorder (Sagvolden et al., 2005b). 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 behaviour is displayed.

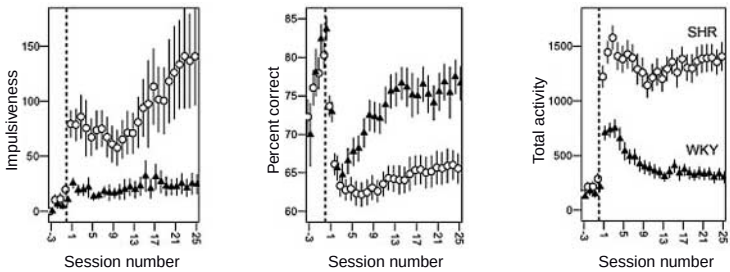

Figure 3. Correct responding in operant chambers was reinforced according to intermittent schedules of reinforcement. During the four initial sessions (session numbers -3 to 0), practically every correct response was reinforced; the average interval ranged between .1 and 15 s. From session 1 (at the vertical dotted line), responses were reinforced intermittently, with the average interval being 3 min. Rats were tested every day. Impulsiveness (premature responses with interresponse times less than .67 s) (A), sustained attention (percent correct lever choices) (B), and total activity (C) were measured. Results are mean ± SEM of 83 spontaneously hypertensive rats (SHR, open circles) and 67 Wistar Kyoto rats (WKY, filled triangles (Sagvolden et al., 2005b).

ADHD is a heterogeneous disorder. The relatively simple nervous systems of rodent models have enabled identification of neurobiological changes that underlie certain aspects of ADHD behaviour. Several animal models of ADHD suggest that the dopaminergic system is functionally impaired (Russell et al., 2005). Some animal models have decreased extracellular dopamine concentrations and upregulated postsynaptic dopamine D1 receptors (DRD1, Figure 4) while others have increased extracellular dopamine concentrations. In the latter case, dopamine pathways are suggested to be hyperactive. However, stimulus-evoked release of dopamine is often decreased in these models, which is consistent with impaired dopamine transmission. It is possible that the behavioural char-

acteristics of ADHD result from impaired dopamine modulation of neurotransmission in cortico-striato-thalamo-cortical circuits (Figure 1). There is considerable evidence to suggest that the noradrenergic system is poorly controlled by hypofunctional ·2-autoreceptors in some models, giving rise to inappropriately increased release of norepinephrine. Aspects of ADHD behaviour may result from an imbalance between increased noradrenergic and decreased dopaminergic regulation of neural circuits that involve the prefrontal cortex. Animal models of ADHD also suggest that neural circuits may be altered in the brains of children with ADHD. In neurobiological and pharmacological studies it is therefore of particular importance to study animal models of the disorder and not normal animals.

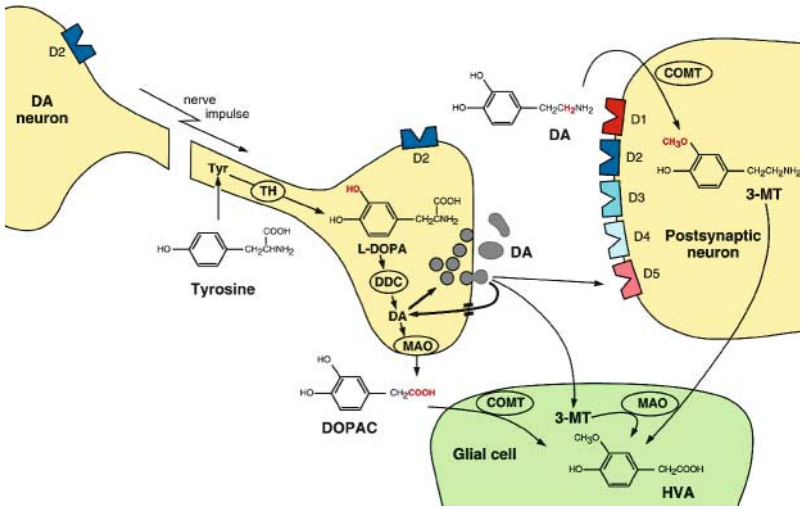

Figure 4. Neurons and glial cell showing dopamine synthesis, metabolism, and typical positions of dopamine receptors. Note that D1/5 and D2/3/4 receptors are not generally colocalized on the same neuron as they have opposite effects. Abbreviations: 3MT = 3-methoxytyramine, COMT = catechol-O-methyl transferase, D1–D5 = dopamine receptors 1 through 5, DA = dopamine, DDC = DOPA decarboxylase, HVA = homovanillic acid, MAO = monoamine oxidase, TH = tyrosine hydroxylase, Tyr = tyrosine. (Modified after (Waters, 1995)).

Evidence obtained from animal models suggests that psychostimulants may not be acting on the dopamine transporter to produce the expected increase in extracellular dopamine concentration in ADHD. There is evidence to suggest that psychostimulants may decrease motor activity by increasing serotonin levels. In addition to providing unique insights into the neurobiology of ADHD, animal models are also being used to test new drugs that can be used to alleviate the symptoms of ADHD (Russell et al., 2005).

Conclusions

ADHD is a heterogeneous disorder, suggested to result from combinations of genetic and environmental factors. Animal models can mimic only certain aspects of the complex symptomatology of ADHD, but may still provide feasible hypotheses regarding the underlying causes of specific

aspects of ADHD behaviour. These hypotheses can then be tested in the clinic. Animal models can also be used to test potential drugs for the treatment of ADHD.

Future research on animal models of human disorders will undoubtedly promote a better understanding of the contribution of specific neurobiological factors to behavioural components like attention, reinforcement and extinction that seem to be important for understanding ADHD.

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