

The control of responsiveness in ADHD by catecholamines: evidence for dopaminergic, noradrenergic, and interactive roles.

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Abstract:

We explore the neurobiological bases of Attention-Deficit/Hyperactivity Disorder (ADHD) from the viewpoint of the neurochemistry and psychopharmacology of the catecholamine-based behavioural systems. The contributions of dopamine (DA) and noradrenaline (NA) neurotransmission to the motor and cognitive symptoms of ADHD (e.g., hyperactivity, variable and impulsive responses) are studied in rodent and primate models. These models represent elements of the behavioural units observed in subjects with ADHD clinically or in laboratory settings (e.g., locomotion, changed sensitivity/responsivity to novelty/reinforcement and measures of executive processing). In particular, the models selected emphasize traits that are strongly influenced by mesocorticolimbic DA in the spontaneously hypertensive [SHR] and the Naples high excitability [NHE] rat lines. In this context the mode of action of methylphenidate treatment is discussed. We also describe current views on the altered control by mesolimbic catecholamines of appropriate and inappropriate goal-directed behaviour, and the tolerance or intolerance of a delay in achieving reinforcement in ADHD children and animal models. Recent insights into the previously underestimated role of the NA system in the control of mesocortical DA function, and the frontal role in processing information are elaborated.

Key Words:

ADHD; Attention; Dopamine; Hyperactivity; Mesocortical; Mesolimbic; NHE; Noradrenaline; SHR

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Introduction:

To discuss the role of catecholamine neurotransmitter activity in ADHD we need animal models. We cannot use invasive measures of central catecholamines in children.

At best one can rely on measures of catecholamine metabolism or drug challenges to the dopamine (DA) or noradrenaline (NA) systems (reviews Oades 2002, 2004). Animal models for the 'dissection' of the underlying

mechanisms are central to the present overview. But what are the primary features of ADHD that represent the items sought in the model?

ADHD usually arises in childhood before 6 years of age. It shows itself more frequently in boys than girls in the few years before and after puberty. Some features continue into adulthood (ca. 30% of childhood ADHD) when the incidence in women becomes more marked. The areas of dysfunction highlighted by diagnostic schemes include executive and attention-related abilities (poor concentration), increased motor activity (restlessness), cognitive and behavioural impulsivity (ill-considered responses). Frequently associated are features of low self-esteem, emotional outbreaks, and difficulties with delayed gratification (Faraone & Doyle 2001). These functional domains are reflected in selected behaviours of animals, so-called models. Examples include errors of omission on discrimination tasks (concentration) and errors of commission or the difficulty to withhold prepotent responses (impulsivity). Loco-motion in novel or familiar environments reflects both motor hyperactivity and sensitivity to environmental stimuli (hyper-reactivity). There is widespread agreement from neurophysiological and brain-imaging studies that circuits integrating frontal executive-like functions with the neostriatal organization of response strategies (Oades, 1998; Rubia et al. 2001), and their control by catecholamine transmitters function inappropriately in children with ADHD (Sagvolden & Sergeant 1998; Castellanos & Tannock 2002).

Rodent Models of Hyperactivity and Hyperreactivity: Role of Dopamine (DA)

A number of rodent models – we would list 30 - have been proposed to investigate the putative neural substrates of impulsiveness, and the varied manifestations of hyperactivity in ADHD. In these models, hyperactivity may result from genetic, pharmacologic or lesion-related interventions (Davids et al. 2003; Viggiano et al. 2003).

Current developmental explanations for ADHD (Sagvolden et al. 2004) are based on the idea that altered DA function fails to modulate excitatory glutamergic and inhibitory GABAergic signal transmission appropriately in one or all of the meso-striatal, mesolimbic and mesocortical projection regions. First we examine the DA terminals in these networks with two of the leading models.

The spontaneously hypertensive rat (SHR: selected for familial hypertension) and Naples high excitability rats (NHE: selected for increased exploration in a Låt-Maze) both feature hyperactivity, impulsivity and poor sustained attention, similar to ADHD. However, the activity of these two lines of rats is differentially sensitive to environmental stimulation. This is why we also refer to hyper-reactivity in the model (below). Hyperactivity in the open-field is also present in the home cage for the SHR (Sagvolden et al. 1993) but not for the NHE rats (Sadile et al. 1993), which increase their activity with increasing environmental complexity (Viggiano et al. 2002). While handling of the animals can reduce hyperactivity in the SHR (Ferguson et al. 2003), it influences the activity of NHE rats in a non-linear manner (Fresiello et al. 2002). Nonetheless changes in the activity of DA pathways lie close to the root of increased motor activity in both lines.

The differences between rat lines in hyper-reactivity are associated with differences in the make-up of the main components controlling DA activity (i.e., the DA transporter [DAT], and the D1-like and D2-like receptor-families). The anomaly lies with the poor function of one or another type of control, in one or more DA projection systems at an early stage of development. A consideration of the binding sites crucial for 'control' leads us to differentiate the neural systems that are predominantly concerned (i.e., the meso-limbic from the meso-cortical projections and both of these from the meso-striatal pathway). In contrast to the decreased DA release and turnover reported for the SHR mesostriatal projection, poor control in the mesocorticolimbic projections may lead to excess DA in the synapse (and perhaps beyond).

The decreased striatal DA turnover of the SHR reflects stronger D2-mediated inhibition of release (de Jong et al. 1995). This has implications for explaining impaired stop-signal inhibition in ADHD that depends on fronto-striatal not limbic circuitry in rats and humans [Aron et al. 2003; Eagle & Robbins, 2003

In contrast DA levels in the SHR mesolimbic projection are higher, reflecting a decreased storage capacity in DA terminals (Carboni et al. 2003). This is important because delayed reinforcement task-performance depends on an intact N. accumbens (Cardinal et al. 2002: cf. anomalous delayed gratification in ADHD). Further, in the DAT knockout-mouse the excess DA that cannot be taken up leads to hyper-reactive responses to novelty. The consequence of a (manipulated) absence of DAT sites is an increase of synaptic DA, and a decrease of neuronal impulse-dependent release (Gainetdinov et al. 1999). In both the SHR and NHE rat line DAT is over-expressed in the mesocortical projections (Viggiano et al. 2002; Watanabe et al. 1997).

In contrast to the DAT-knockout mouse, in the SHR and NHE lines increases of DAT sites are the consequence of the excess DA at an early stage of development. In NHE rats there are more DA synthesizing terminals, more DA and therefore appropriately more DAT sites. DA midbrain neurons are hyper-trophic with more terminals expressing the DA-synthesising enzyme tyrosine hydroxylase (TH). But in the SHR, while mesolimbic DA levels may reflect the impaired vesicular storage of DA (Russell et al. 1998), excess mesocortical DA arises through less efficient DAT uptake on the DA terminals (Viggiano et al. 2002). The up-regulation in the mesocortical pathway may be the result of compensation for DAT hypofunction. Unfortunately reports on mesostriatal and mesolimbic DAT function conflict and render any generalization premature (e.g., up-, down-regulation and no change: Leo et al. 2003; Russell et al. 1998; Watanabe et al. 1997). Nonetheless raised tonic levels of mesolimbic DA in the SHR, reflecting less DA clearance, have been reported (Carboni et al. 2003). Here,

environmental factors can also produce permanent effects on behavioural and neuronal networks (see above), with implications for parental style. Namely, handling during the 5th and 6th week of postnatal life in the SHR modifies neuronal markers to the level of the control line. These markers include DA D1 receptors, and the molecular transduction devices CAMKII and c-fos. This is likely to be due to the normalization of DA neuronal activity (Ferguson & Cada, 2003; Sadile 2000).

The expression of D1- and D2-sites provides further contrasts between the two rat lines. While D1 sites are over-expressed in the striatal and frontal regions of the SHR (Kirouac and Ganguly, 1993; Watanabe et al. 1997), there is *less* mRNA for mesocortical D1 expression in the NHE (Viggiano et al. 2002). An over-view suggests that changes in the markers for DA and related neuronal function are restricted to mesocortical regions in the NHE (Viggiano et al. 2003). Conversely, in the SHR, despite disagreement on the levels of D2 sites, only the most rostral forebrain (including the neostriatum and frontal cortex) is affected. This implies the involvement of parts of the mesocortical *and* mesolimbic projections (Sadile 2000).

On the Mechanism of Action of Methylphenidate Treatment

About two thirds of patients with ADHD improve after treatment with methylphenidate (MPH) or amphetamine: 'non-response' following consecutive treatment is rare (Elia et al. 1991). Cognitive symptoms are the most sensitive to MPH treatment. Motor and social behaviour may require, successively, slightly higher doses. MPH inhibits the re-uptake of synaptic DA by presynaptic DAT binding sites on midbrain somata and forebrain terminals. Without treatment amounts of DA released per impulse elicit less of a post-synaptic effect than expected for any given level. Treatment crudely promotes the likelihood of effective DA transmission by providing a relative increase of synaptic DA. This does not lead to hyperactive animals as the firing frequency of DA neurons is reduced (Ruskin et al. 2001). In humans, as in

the contrast between the two models, there is no simple relationship between increased motor activity (or sensitivity to reinforcement), increased DA activity and psychostimulant effects. PET studies of regional brain metabolism and D2 binding sites illustrate the complexity. (1) Treatment may increase glucose metabolism in the cortices, but decrease it in subcortical regions. (2) The direction may change between acute and repeated treatments. (3) Grey-matter glucose metabolism may be increased if subjects have numerous cortical D2 receptors, but decreased if there are relatively few of them (Volkow et al. 1998). Decreased metabolism was associated with better cognition (Mehta et al. 2000).

This scenario is based on the normal availability of DA. In fact, in the areas giving rise to the DA pathways, the basal expression of TH controlling the rate of DA synthesis is lower than normal in the young SHR and higher than normal in NHE rats (Figure 1). This result has been confirmed for young SHR (Leo et al. 2003), but TH levels may normalize in adult animals (Reja et al. 2002). Repeated treatment with MPH reverses both trends, normalizing the rates of synthesis in the SHR and NHE (Figure 1). Since more mesocortical DA is released in animal models of ADHD (Carboni et al. 2003), low doses of MPH are thought to produce an optimal reduction/normalization of DA neuronal firing rates. From recordings in normal rats a reduction of firing is predicted to result in reduced responsivity to non-salient novel stimuli (Viggiano et al. 2004).

This comparison of DA control mechanisms in NHE and SHR lines points to their modelling two separate contributions to hyper-reactivity. This supports the hypothesis of a “*dual pathway*” to the ADHD constellation of symptoms. Sonuga-Barke (2002) hypothesizes that there is a cluster of symptoms reflecting frontal “executive dysfunction” (cf. NHE) and another reflecting limbic “delay-aversion” activity (cf. SHR) incurring differential contributions from the mesocortical and mesostriatal/limbic systems, respectively. Particular support for this proposal comes from

findings of hypotrophy/hypofunction at the fronto-striatal interface in ADHD (Semrud-Clikeman et al. 2000). In the model this reduces the efficacy of the glutamate output modulating motor activity (Russell 2003) and affects the GABA inhibitory processes that modulate and are modulated by DA activity ascending from the midbrain (Grace, 2001). We now consider these two variants reflecting the “dual pathway”.

Catecholamines in Subcortical “Pathways”: Mechanisms and Functions

The developmental behavioural theory of Sagvolden and colleagues (2004) is based on the idea that ascending DA pathways are dysfunctional, perhaps hypofunctional (see above). Directly or indirectly, they do not modify appropriately the excitatory glutamatergic or inhibitory GABAergic transmission that mediates behaviour. Here we concentrate on the inadequate mesolimbic role in ADHD in the control of reinforcement of novel behaviour and extinction of previously reinforced responses. Other aspects of the theory apply these considerations to the meso-cortical role in behavioural organization and the mesostriatal role in the expression of response patterns (see below).

The neural basis may be summarised as follows. Midbrain DA neurons in monkeys respond phasically with a burst of firing when reinforcement follows a response (Schultz et al. 1993). DA release by mesolimbic fibres can be low (tonic background) or high (reflecting salience and/or reinforcement). This DA release in the N. accumbens can modify the activity of glutamate terminals, and be modified by frontal and limbic glutamate input (Moore et al. 1999). Although some uncertainty exists about the precise mechanism (e.g., role of metabotropic sites, co-release of glutamate in DA synapses, and the applicability of rodent studies to primates: Adams et al. 2002; DalBo et al. 2004), these authors argue for a “switching mechanism” permitting the further processing of certain salient inputs. This may reflect the use of facilitatory D1 and inhibitory D2 binding sites.

Thus, the integration of information about reinforcement associated with a particular event can be impaired by a dysfunctional mesolimbic DA pathway and exacerbated by a

hypoactive glutamate input from frontal sources (Grace 2001).

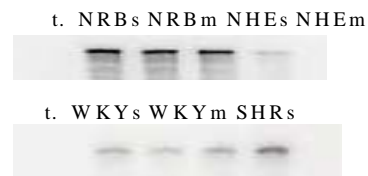


Fig. 1. RNAse protection for TH mRNA in ventral mesencephalon of NHE-NRB and SHR-WKY rats after 14-days treatment with methylphenidate (m) or vehicle (v). t: control tRNA. Note that MPH has opposite effects on TH mRNA levels in the two hyperactive lines (NHE and SHR).

It is also noteworthy that NA activity influences the acquisition and reinforcement of conditioned responses, and uniquely their extinction (Mingote et al. 2004). Indeed the DA control of responsiveness with a switching mechanism (using intra- and extra-synaptic DA receptors: Moore et al. 1999; Oades, 1985), and the involvement of NA tuning mechanisms (also impaired in the SHR Russell et al. 2000), become even more pertinent in understanding mesocortical function, below. The catecholamine-glutamate inter-actions strengthen and switch-in reinforced and adaptive behaviour. They weaken or switch-off the influences of other non-reinforced or maladaptive behaviour.

The ability to associate an event with reinforcement is constrained by a necessarily, relatively short time interval. If neuronal systems are functioning poorly in ADHD, then the time-window available for making appropriate associations is predicted to be even shorter (Sagvolden et al. 2004). This short time-window leads further to the prediction that the number of stimuli controlling behaviour will be smaller (attentional problem), and the behaviour more variable. Thus, there will be shorter response sequences that are less well-

linked to the salient features of a given situation (motor impulsivity). Indeed, Sagvolden et al. suggest that through less efficient conditioning, extinction will also be impaired. Responding will continue, as in a partial reinforcement programme. The inappropriate “excess” of responses is interpreted as “hyper-reactivity”, reflecting a failure to inhibit responses. The authors prefer not to view this as a disinhibitory process (cf. Barkley 1997), but suggest it reflects the slower acquisition of long sequences of behaviour, and the deficient extinction of previously reinforced behaviour.

ADHD children often show an aversion to the delayed delivery of reinforcement (Sonuga-Barke 2002), or a preference for immediate reinforcers (Tripp and Alsop 2001). This response pattern occurs even when the reinforcers are, by comparison, smaller. Thus, when ADHD children were asked to choose with a mouse-click between coloured rectangles on a monitor, few were prepared to wait 30 secs for twice the points-reward they could get after 2 secs (Solanto et al. 2001). This effect is modelled in the SHR. Here response rates are high for continuously reinforced responses, but fall off steeply if a fixed interval is introduced (Sagvolden et al. 1992). Intriguingly treatment

with methylphenidate increases the apparent effectiveness of the delayed reinforcer. Sagvolden's theory (2004) suggests that even short delays in reinforcement are often too long for the establishment of stimulus-control over response.

If the ADHD child requires a short delay between the sensory input and the motor output in order to perceive the reinforcement that the connection is correct, they do not have the time to think about the consequences, and alternative ways to plan and respond. At the biochemical level this is consistent with reduced "switching" among alternatives (Oades 1985; Grace 2001). Less DA activity controls the fronto-striatal-thalamic circuits and the expression of short sequences of behaviour. The result is often interpreted as poor attention and impulsive responding. Shallice (2002) describes an example from children asked to complete sentences with a word that did *not* match the sense of the sentence. Most control children quickly latched on to some object in the room. This proved far more effective than the style shown by ADHD children. They often suggested the first word that came to mind. These two examples (above), from a delayed response and a free-choice task, illustrate respectively under external and internal constraints the similar effect and outcome. We see how cognitive demands can produce both more variable responses and excess motor activity as a result of DA dysfunction. Further, this reduced "DA control" will result in a lack of regular reinforced feedback and lead to attenuated extinction of the non-adaptive responses.

These examples illustrate the concept of impulsivity that undoubtedly has a motor and a cognitive component. The motor aspect is easily observed in the delayed reinforcement paradigm where both the SHR-model and ADHD-children (Sagvolden et al. 2004) show bursts of responses with short inter-response times. Mesolimbic DA is part of the substrate of motor impulsivity in rodents (Cole and Robbins 1989), and it is currently accepted that at least an aspect of the DA system is associated with an impulsive style in ADHD children (e.g., the D4

site, Langley et al. 2004).

Cognitive impulsivity, as illustrated by decisions on matching familiar figures or solving mazes, is improved by psycho-stimulants modulating catecholamine activity (Solanto 1995). But, by concentrating on the role of DA one is omitting another part of the story. For example, in the serotonin system of ADHD children increasing and decreasing affinity of the transporter is related respectively to increasing behavioural and cognitive impulsivity (Oades et al. 2002). Indeed, the rodent models show that the psychostimulant effect on improving delay discounting also depends on an intact serotonin system (Winstanley et al. 2003).

Cognitive impulsiveness in ADHD implies that thoughts and plans concern short sequences of time. Problems lie with organizing behaviour over longer periods. This leads to risky, poorly considered decisions and highly variable reaction times (Rubia et al. 1998) viewed by some to reflect response disinhibition (Pliszka et al. 2000) and others executive dysfunction (Kooijmans et al. 2000). Sagvolden and colleagues (2004) prefer a simpler explanation in terms of the impaired timing of starting and stopping processing and the organization of response. They emphasize that this has consequences for learning appropriate sequences of behaviour, habit acquisition and memory. All of these views point towards an additional dysfunction in the mesocortical DA system. This will incur poor attention-related processing (orienting to stimulus salience and relevance, saccadic control, selection, context-appropriate retrieval of stored representations into behavioural plans). From a functional viewpoint this overlaps with altered-control in the mesostriatal projections (e.g., fine motor inhibition, clumsiness) and mesolimbic systems (integration of bottom-up processing with feedback and motivation, as seen in reinforcement gradients and extinction).

Catecholamines in the Mesocortical pathways

What are the targets of the mesocortical projections? While NA pathways project onto cortices along the entire rostro-caudal axis

(frontal to occipital lobes), DA input is more restricted to frontal regions, with (in primates) some representation in motor, parietal and temporal cortices (Williams and Goldman-Rakic 1998). The pyramidal neuron stands at the centre of interest in the prefrontal cortex (layer IV-V) with its local and long-axon input and output systems. There is a major catecholamine input to the basal dendrite region (layer V-VI). The more superficial input to the apical dendrite notably contains both DA D1 and NA alpha-2 sites. But some DA D2 binding sites lie in the deeper layers. Local interneuron, limbic and thalamic inputs innervate the soma and apical dendrite region in between (layer III-V) with depolarizing signals of glutamatergic origin. However, intra-laminar intra-cortical interactions have a more tonic hyperpolarizing action mediated by GABA. Limbic glutamatergic and mesencephalic DA inputs may converge on different parts of a single spine. The integrated response can then be disseminated to other cortices, the thalamus or striatum (Seamans et al. 2001; Goldman-Rakic 2000).

Working memory (WM) is one of the functions attributed to frontal activity and is modulated by DA activity (Williams and Goldman-Rakic 1995). The performance by rodents and primates of delayed alternation tasks requires the maintenance of a representation of what response was last executed. This can be manipulated and associated with other incoming information. Pyramidal neurons show enhanced firing during a typical "delayed-response" task. They project to both the N. accumbens and the mesencephalic source of the ascending DA pathways. DA modulates responses both directly, and via interactions with populations of GABAergic interneurons. Pyramidal activity can sharpen or block depolarizing synaptic input at the apical dendrites en route to the soma. Thus, DA can potentiate depolarizing signals arriving from neighbouring, deep layer pyramidal neurons. But, other recording studies show that D1 agonism (Seamans et al. 2001) can permit inhibition, consistent with the switching function of DA. The actions of DA on the summation of synaptic responses depends on its

concentration, the types of receptors present, the constellation of synapses (that varies between regions), the location of somato-dendritic connections, the timing of the arrival and the strength of synaptic inputs, (Williams and Goldman-Rakic, 1995, 1998; Seamans et al. 2001).

Against this background, it is useful to recall that the SHR model has an unusually high density of D1 receptors (Watanabe et al. 1997; Kirouac and Ganguly 1993), that is somewhat reduced after methylphenidate treatment (Viggiano et al. 2003). This helps us to understand the significance of a result obtained by Williams and Goldman-Rakic (1995) with non-human primates. Pharmacological D1 blockade led to an improvement of the transmission of signal vs. noise by reducing response to the noise. They also reported an improvement of WM task-performance when DA levels were increased (e.g., following psychostimulant treatment). The relevance can be seen in Russell's work (1995) with the SHR-model showing there was a lower rate of DA release in response to electrical stimulation than in controls.

Here, we again point out that by concentrating on the role of DA, one oversimplifies the more complete story. For example Russell et al. (2000) reported that autoreceptor-mediated inhibition of NA release is impaired in the SHR. Thus, NA function is also poorly regulated in the SHR's prefrontal cortex. Secondly, we should consider whether the catecholaminergic role in information processing associated with WM is relevant for the cognitive features of ADHD. Is there a WM deficit?

Recent morphological and biochemical studies suggest that prefrontal DA function could be modulated by selective manipulation of both DA and NA pathways. There is a moderate degree of mismatch between the innervation of specific layers by DA and the expression of DA binding sites. The D1 receptors are highly expressed in the superficial cortical layer where a dense plexus of NA fibres is evident. DA binding sites are frequently found

to be present extrasynaptically, away from DA terminals. Thus, two mechanisms are at work in the frontal cortex: first extrasynaptic DA will have an effect at extrasynaptic DA sites, and second, an excess of extrasynaptic DA can be cleared by NA transporters. De Montis et al. (1990) reported that chronic blockade of the NA transporter with imipramine down-regulates D1 binding and later Wayment et al. (2001) showed that indeed extrasynaptic DA can be cleared by both DA and NA transporters. Additionally, Devoto et al. (2001, 2004) showed that extrasynaptic DA levels also receive a contribution of DA from the NA terminal. This type of DA release was shown to be facilitated by the alpha-2 NA antagonists (e.g., idazoxan, mirtazepine) and prevented by the agonist clonidine in both NA innervated cortices (e.g., occipital) as well as those innervated by both catecholamines (e.g., prefrontal cortex). This effect was not seen in subcortical regions.

NA terminals are able to co-release both DA and NA. Consistent with this, methylphenidate (a DA and NA re-uptake blocker) and atomoxetine (a specific NA re-uptake blocker) show comparable clinical efficacy in ameliorating ADHD symptoms. Microdialysis studies indicate that they both elevate prefrontal levels of NA and DA, but only methylphenidate additionally increases DA levels in the mesolimbic N. accumbens (Bymaster et al. 2002).

The opportunity to alter selectively specific components of the catecholaminergic contribution to cortical information processing is now at hand. Firstly there is the possibility of specifically influencing cortical rather than subcortical contributions to ADHD dysfunction (methylphenidate vs. atomoxetine). Secondly, it is becoming possible to manipulate the NA contribution (currently the combined NA and extrasynaptic DA contribution) separately from the effects deriving from the direct mesocortical DA innervation. The relative efficacy of some antidepressants in ADHD, particularly the adult type may be noted (Maidment 2003). Thirdly, recognition of the differential contribution of extrasynaptic DA function suggests the

possibility of specifically manipulating this population. For this purpose a new class of partial DA antagonists may be considered (M. Carlsson et al. 2004). A putative differential effect is predicted from the proportionately high affinity of extra- vs. intra-synaptic binding sites and hence the sensitivity of these sites to low doses of the drug (A. Carlsson, personal communication)

Mesocortical NA/DA function

The role of NA must be considered to account for the roles of catecholamines in the cognitive domains of dysfunction in ADHD. Increasing levels of NA, decreased postsynaptic neuronal firing, and an enhanced tuning of response to signal vs. noise result from modest doses of methylphenidate and atomoxetine (Berridge & Waterhouse 2003). Modest levels of NA activity facilitate focussed attention. Impulsivity and distractibility decrease (Aston-Jones et al. 1997). Receptor affinities are such that low levels of NA act at alpha-2 sites. Here, agonists (e.g., guanfacine) can enhance WM function. (Caveat: alpha-2 antagonists increase extracellular DA rather like DA D2 antagonists.) Higher levels of NA, typical of stressful situations, bind to alpha-1 sites and interfere with WM. Indeed, stimulation of alpha-1 sites impairs DA D1 function and this also leads to poorer WM. Yet alpha-1 stimulation enhances responses to neuronal excitation (glutamate release). This may of course be adaptive under an acute stressful challenge (Oades 2004).

Enhanced WM function following alpha-2 agonism with guanfacine has been well demonstrated in studies of monkeys. Indeed, the agonists clonidine and guanfacine increased neuronal firing specifically via alpha-2 receptors during the crucial delay on delayed-learning tasks (Arnsten 2001). However, the evidence for a primary WM dysfunction, rather than impairments of other executive functions in ADHD remains equivocal (Oades 2004). In fact, Oades noted, briefly reviewing 15 studies, "A few studies have reported impairments of digit/arithmetical- and visuo-spatial span. But the WM impairments are often small (about 1 standard deviation), more of a problem for

those with comorbid reading/learning difficulties or are found only where the task loads on attentional capacity. Many of the differences disappeared after covarying for IQ and with increasing age. It is doubtful if impaired WM performance is a salient part of the neuropsychological profile of ADHD or contributes significantly to other executive functions such as planning." We suggest that, because of the role in tuning signal-to-noise ratios and in modulating mesocortical DA function, stimulation of alpha-2 NA receptors facilitates neuro-cognitive function. This occurs on the ascending side of the Yerkes-Dodson-like inverted U-curve portraying improving function with increasing stimulation. The effect is to improve signal contrast over a temporal window during which noise obscures the processing of target stimuli and interferes with behavioural planning (e.g., reduced distraction by negative primes: Slusarek unpubl. results). Indeed, guanfacine demonstrated this positive therapeutic action in both the symptom ratings and sustained attention performance of 10 year-old ADHD children with tic disorders (Scahill et al. 2001).

Perspectives:

The coupling of neural impulses to transmitter release remains to be elucidated fully. This is paramount to improve our understanding of catecholamine control mechanisms and the way they dysfunction in ADHD. The mechanisms will involve specific aspects of the pre/post-synaptic alignment of structural proteins (neuroligins), and adhesion molecules (neurexins: Missler et al. 2003) along with their reliance on docking proteins (e.g., p62Dok-1: Smith et al. 2004). Light on these issues will come from further genetic and animal model research.

The finding that the chronic accumulation of extracellular mesolimbic and mesocortical DA in development may lead to neurotoxicity and neurodegeneration, needs to be reconciled with the finding that chronic treatment with psychostimulants also leads to changes of the neuronal constitution. The development of markers to aid early detection of ADHD is

urgent. Prevention of deterioration would be the preferred strategy.

At present the altered function of DA neurons is recognised as the main predisposing factor for ADHD (Sagvolden et al. 2004). It is apparent that a 'hypofunction' is emerging from SHR studies, while the NHE and DAT-KO models point more to a 'hyperfunction'. These apparently opposed views may be explicable in terms of the 'dual pathway model' with differential involvement of cortical and subcortical mechanisms in the different expressions of ADHD (Sonuga-Barke 2002). The theory of Sagvolden and co-workers (2004) predicts that ADHD behaviour results from the interplay between individual predisposition and the environment. An individual's specific symptoms will vary over time. Environmental factors exert positive and negative effects on symptom development. Deficient learning and motor functions can produce special needs for optimal parenting and societal styles, but these can now be recognised. They, along with the underlying deficient catecholamine control, can be adjusted for the development of relatively stable behavioural patterns. Indeed, aided by pharmacotherapy, the parental style can modify the underlying bases and interactions of deficient, "canonical" DA and NA pathways.

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