Enhancing the efficacy of 5-HT uptake inhibitors in the treatment of Attention Deficit Hyperactivity Disorder

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common childhood behavioural disorders, the frontline treatments for which are drugs with abuse potential. As a consequence, there is an urgent need to develop non addictive drug treatments with equivalent efficacy. Preclinical evidence suggests that selective serotonin uptake inhibitors (SSRIs) are likely to be effective in ADHD, however clinical reports suggest that SSRIs are of limited therapeutic value for the treatment of ADHD. We propose that this disconnect can be explained by the pattern of drug administration in existing clinical trials (administration for short periods of time, or intermittently) leading to inadequate control of the autoregulatory processes which control 5-HT release, most notably at the level of inhibitory 5-HT_{1A} somatodendritic autoreceptors. These autoreceptors reduce the firing rate of 5-HT neurons (limiting release) unless they are desensitised by a long term, frequent pattern of drug administration. As such, we argue that the participants in earlier trials were not administered SSRIs in a manner which realises any potential benefits of targeting 5-HT in the pharmacotherapy of ADHD. In light of this, we hypothesise that there may be under-researched potential to exploit 5-HT transmission therapeutically in ADHD, either through changing the administration regime, or by pharmacological means. Recent pharmacological research has successfully potentiated the effects of SSRIs in acute animal preparations by antagonising inhibitory 5-HT_{1A} autoreceptors prior to the administration of the SSRI fluoxetine. We suggest that combination therapies linking SSRIs and 5-HT_{1A} antagonists are a potential way forward in the development of efficacious non-addictive pharmacotherapies for ADHD.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common childhood behavioural disorders, although estimates of its prevalence vary widely (0.6-29.2%; [1]). This suggests that there is considerable ambiguity in the interpretation of the diagnostic criteria for the disorder and how they relate to the symptoms observed. This ambiguity arises in large part because the pathophysiological basis for the disorder is poorly understood [2]. Pathophysiological uncertainty has also hindered the development of new pharmacotherapies for the disorder, the frontline treatments for which are still amphetamines or methylphenidate (e.g. in the UK, NICE Guideline NG87 [3]), both of which have abuse potential [4]. Although non-stimulant drugs such as atomoxetine are available for the treatment of ADHD, the efficacy of these drugs are poor in comparison to psychostimulants [5] and the search is on for a drug strategy that is as efficacious as psychostimulants without carrying the abuse potential.

Since the seminal work of A.A. Strauss in the 40s and 50's (e.g. [6]), besides hyperactivity, distractibility has been recognised as a core symptom of ADHD. Indeed, increased distractibility is the most frequently presenting symptom of ADHD [7], and is the symptom that shows greatest resistance to extinction with age [8]. On the basis of recent theoretical and experimental work, we have proposed that increased distractibility in ADHD is caused by a hyper-responsiveness of the superior colliculus (SC; [9]), a visual (superficial layers) and multimodal (deep layers) sensory structure in the midbrain which is intimately linked to eye movements and attentional focus (e.g. [10]). The original case for a collicular sensory hyper-responsiveness in ADHD is made fully in Overton [9], based on clinical observations by other groups and our own early preclinical work. In brief: 1. ADHD patients show increased distractibility in tasks which are sensitive to collicular function; 2. ADHD patients have a general problem inhibiting eye movements (saccades), the generation of which involves the SC; 3. Covert shifts in attention, which have been argued to involve the SC, are also impaired in

ADHD; 4. D-amphetamine, an effective pharmacotherapeutic agent in ADHD, depresses visually evoked activity in the colliculus; 5. Aberrant reward processing identified in ADHD could also reflect a collicular dysfunction, given the role played by the SC in the regulation of the dopamine systems.

More recently, we have gone on to show that two well validated animal models of ADHD, the Spontaneously Hypertensive Rat and the New Zealand Genetically Hypertensive Rat, both exhibit collicular visual hyper-responsiveness [11], [12]. We have also shown that non-clinical human participants who have higher levels of ADHD-like traits exhibit elevated levels of small amplitude saccades at fixation (micro-saccades) compared to those with lower levels of ADHD-like traits [13], a saccadic type that is particularly associated with the colliculus (e.g. [14]). Participants with higher levels of ADHD-like traits also process multisensory stimuli abnormally [15], and the SC is acknowledged to play an important role in multisensory integration (e.g. [16]).

Current pharmacotherapies for ADHD

Identifying the SC as a potential pathological locus of change in ADHD fits well with the known pharmacological actions of frontline ADHD treatments. While the pharmacodynamics of D-amphetamine are complex, there is converging evidence that it's effects are mediated by elevating synaptic levels of the monoamine neurotransmitters dopamine (DA), noradrenaline (NA)[17] and serotonin (5-HT)[18], [19]. D-amphetamine affects widespread areas of the brain [17, 18, 19], many of which may be involved in the therapeutic effects of the drug, however due to the pathophysiological uncertainty surrounding the disorder, we focus here on the SC. The SC is extensively innervated by 5-HT and NA [20], [21], and to a lesser extent by DA [22], thus expresses the appropriate neurochemistry to allow for the action of D-amphetamine (and methylphenidate, a DA/NA/5-HT uptake inhibitor [23]) to be mediated locally within the colliculus. That theoretical possibility was demonstrated to be correct by Dommett et al. [24]

using an in vitro SC preparation to probe the proximal effects of therapeutically appropriate doses of D-amphetamine or methylphenidate applied to the SC. Perfusion of either drug inhibited superficial layer collicular responses to low intensity stimulation of the optic tract, while responses to high intensity stimulation were largely preserved. The inhibitory action of the psychostimulants was blocked by the broad spectrum 5-HT antagonist metergoline, implicating 5-HT in psychostimulant-induced suppression of collicular responsiveness. This suggests that therapeutically D-amphetamine and methylphenidate may act to enhance 5-HT mediated modulation of sensory activity at the level of the SC, thereby normalising collicular hypersensitivity and reducing symptoms of distractibility. Although metergoline also interacts with dopamine receptors as well as 5-HT receptors [25] and dopamine receptors are present in the SC [26], the agonistic actions of metergoline appear to be largely confined to D2-type dopamine receptors [27], which are scarce in the superficial layers [22]. The involvement of 5-HT is additionally supported by the finding in Dommett et al. [24] that the inhibitory action of D-amphetamine and methylphenidate was mimicked by 5-HT itself. This pharmacological evidence implicating 5-HT in the effects of D-amphetamine and methylphenidate at the level of the SC, however, is contradicted by clinical reports that suggest selective serotonin uptake inhibitors (SSRIs) are of limited efficacy in the treatment of ADHD (e.g. [28]). There is therefore a clear disconnect; if collicular dysfunction underlies distractibility in ADHD, and collicular activity is effectively modulated by 5-HT and normalised by psychostimulants, why are SSRIs not more efficacious in treating ADHD?

Hypothesis

We believe that the low efficacy of SSRIs arises as a result of inadequate control of the autoregulation process that regulates the release of 5-HT, most notably at the level of inhibitory 5-HT_{1A} somatodendritic autoreceptors which limit synaptic release via a reduction in the firing rate of 5-HT neurons. As a consequence, we hypothesise that desensitisation of autoregulation

processes, either via an appropriate administration regime for the drug, or via pharmacologically controlling the autoregulatory process, will enhance the efficacy of SSRIs in the treatment of ADHD.

Serotonin based interventions for ADHD: Disconnect between theory and application

There is convergent evidence that frontline ADHD pharmacotherapies may reduce distractibility by targeting 5-HT transmission at the collicular level (e.g. [24]). However, despite this pharmacological evidence, clinical and behavioural reports assessing the efficacy of SSRIs in the treatment of ADHD have been mixed at best. Trials assessing the viability of treating ADHD with SSRIs were initially promising. In a six week preliminary open trial, ADHD patients who had been non-responsive to stimulants showed at least a moderate improvement in symptoms when treated with fluoxetine [28]. In other trials, however, SSRIs have shown little efficacy in treating ADHD. Donnelly et al. [29] showed that while D-amphetamine produced marked improvements in hyperkinetic and inattentive ADHD symptoms, the SSRI fenfluramine did not significantly alter symptom presentation relative to placebo. Similarly, in patients with comorbid ADHD and major depressive disorder, fluoxetine monotherapy produced a remission of depressive symptoms, but had no significant effect on ADHD symptoms [30]. In addition to limited efficacy as a primary treatment for ADHD [28], SSRIs may actually act to exacerbate the symptoms of ADHD. Riddle et al. [32] found that administering fluoxetine to treat children with comorbid ADHD and depression often aggravated ADHD symptoms in a dose dependant manner. Discontinuing fluoxetine treatment reversed this aggravation.

While these trials suggest that SSRIs are of inconsistent therapeutic viability in ADHD [33], it should be noted that each of these studies were comprised of small sample sizes (no trial had more than 20 participants), and that the course of SSRI treatment may have been too

short for observable clinical effects [34]. Nevertheless, these early trials have been cited by several major contributors to the field of ADHD psychopharmacology as evidence that the 5-HT system, and drugs that target this system, are of little to no relevance to the treatment of ADHD [35], [36]. This, combined with the emergence of other viable alternatives to psychostimulant medication, such as the NA reuptake inhibitor atomoxetine [37], [38], has contributed to a period of reduced interest in researching the viability of 5-HT manipulation in the psychotherapy of ADHD.

However, in recent years 5-HT transmission in ADHD has been revisited. Much of this renewed interest stems from advances in genetics, which have revealed that ADHD can be reliably predicted by polymorphisms of the 5-HT transporter (SERT; [39], [40]). Specifically, ADHD is associated with a significant over-expression of the long variant of the promoter region of the SERT gene (the 5HTTLPR; [39], [41]). The SERT is the carrier protein that is responsible for reuptake of 5-HT into presynaptic terminals, thus terminating 5-HT signalling [42]. Expression of the long allele of the 5HTTLPR is associated with an approximate two fold higher uptake of 5-HT compared to other genotype expressions [43]. As action of the SERT constitutes a fundamental mechanism for the regulation of 5-HT levels in the central nervous system, the rapid 5-HT uptake associated with the long variant of 5HTTLPR results in reduced availability of active 5-HT [44].

While genetic evidence points towards a dysfunction at the level of the SERT in ADHD, in vivo evidence for altered SERT expression and availability in ADHD patients is currently inconclusive. Early PET investigations assessing binding potentials for ligands with high specificity for SERT showed no difference in SERT availability between ADHD patients and healthy controls [45], [46]. Recently, however, Vanicek et al. [47] has argued that these studies lacked the required statistical power to detect differences between groups. Vanicek et al. [47] performed a PET interregional molecular correlational analysis to assess functional

connectivity between various regions of interest that are traditionally implicated in the neuropathology of ADHD. They found altered interregional SERT binding between various regions of ADHD patients compared to healthy controls. As SERT expression in vivo is partially regulated by 5-HT release [48], these findings point towards altered 5-HT dynamics in ADHD.

There are thus clear contradictions within the literature assessing the contribution of the serotonergic system to ADHD symptoms. Other than a single open-label trial [28], clinical reports suggest that monotherapeutic interventions targeting 5-HT in ADHD are either ineffective, or otherwise exacerbate symptoms [35], [36]. However, genetic and biological evidence point towards dysfunction at the level of the serotonergic system [39]. We have argued above that collicular dysfunction underlies distractibility in ADHD and have presented pharmacological evidence that psycho-stimulants may reduce distractibility in ADHD by targeting 5-HT transmission at the level of the SC. In light of this biological and genetic evidence, it is somewhat paradoxical that clinical reports suggest that drugs targeting 5-HT are of limited efficacy when the treating the symptoms of ADHD. One potential explanation for this disconnect is that the contribution of 5-HT to the pathology of ADHD is more complex than an overall increase or decrease in symptom presentation. In a review of serotonergic dysfunction in ADHD, Oades [49] proposed that while a widespread association of 5-HT dysfunction with a diagnosis of ADHD is unlikely, there may be a differential contribution of 5-HT to the major symptomatic domains of ADHD. Evidence reviewed showed little association between 5-HT and hyperkinetic ADHD symptoms, but did show an association between 5-HT and inattentive symptoms. In particular, Oades [49] proposed that reduced 5-HT availability in ADHD contributes to altered perceptual sensitivity and salience designation, leading to enhanced cognitive impulsivity and distractibility. If 5-HT only has relevance to attentional symptoms, this may explain the mixed results presented in the clinical trials above,

where specific symptomatic domains were not controlled for. While this proposition may contextualise why D-amphetamine affects 5-HT transmission in salience designation circuits such as the SC, it does not explain why 5-HT based interventions are not more efficacious in the treatment of ADHD, particularly for inattentive symptoms (e.g. [50]).

A more viable explanation for clinical reports suggesting that 5-HT is of limited relevance to the pharmacotherapy of ADHD relates to the regulatory mechanisms that control 5-HT neurotransmission in vivo. It has long been known in the depression literature that a minimum of 3-4 weeks of continuous daily SSRI use is required until improvements in clinical symptoms are observed [51]. Similarly, when SSRIs are used in the treatment of obsessive compulsive disorder (OCD), a minimum period 8-12 weeks of continuous daily SSRI use is required until a clinically and statistically significant improvement in symptoms is observed [34], [52] . This delay in time to response is believed to result from feedback mechanisms at the level of the raphe nuclei, the major source of ascending 5-HT projections for the central nervous system [53], [54], which act to regulate the rate of 5-HT release in target regions [51]. Consequently, it is only after chronic regular exposure to SSRIs that these regulatory feedback mechanisms are desensitised, allowing for increased levels of synaptic 5-HT and commensurate therapeutic benefits. In the trials assessing SSRI use for ADHD described above, SSRIs were prescribed either for short periods (three weeks for Findling [30]; six weeks for Barrickman et al., [25]), or were otherwise not administered daily [29], [31]. Given that up to twelve weeks of continuous daily SSRI use is required to desensitise raphe feedback mechanisms and allow for observable clinical improvements in other disorders (e.g. OCD; [52]), it is plausible that participants in the ADHD clinical trials described above were not administered SSRIs for sufficient regularity and length for any potential clinical effect on ADHD symptoms. As these trials represent a basis for which SSRIs are considered to have limited pharmacological relevance to ADHD (e.g. [35]), it is possible that by bypassing the

mechanisms that regulate 5-HT release, we may observe effects of SSRIs which have clinical relevance to the pharmacotherapy ADHD. The next section will thus consider the principal mechanism that regulates the release of 5-HT, and a potential strategy for bypassing this mechanism.

Serotonin based interventions for ADHD: Autoregulation of serotonergic activity

The delayed onset of the therapeutic benefits of SSRIs observed in both depression and OCD can be explained by regulatory mechanisms of somatodendritic autoreceptors situated on 5-HT cells in the raphe nuclei, which decrease the firing rate of 5-HT neurons in response to locally released 5-HT. Serotonergic neurons in the dorsal and medial raphe nuclei (DRN and MRN) form the majority of all 5-HT producing cells within the central nervous system, with the DRN and MRN accounting for up to 85% and 15% of all serotonergic cell bodies respectively [55]. Neurons in the DRN give rise to ascending projections to a broad range of cortical and subcortical targets, including the cerebral cortex, basal ganglia, and limbic system [56], and of particular relevance to the present discussion, the SC [57]. The firing rate of raphe neurons alters the release of 5-HT in target regions [58]. Consequently, the mechanisms that regulate the firing of these DRN neurons thus regulate 5-HT release and availability at afferent targets. The most relevant of these mechanisms to the delayed efficacy SSRIs pharmacotherapy is the down-regulation of DRN firing elicited by somatodendritic 5-HT_{1A} autoreceptors.

Under typical conditions, 5-HT neurons exhibit spontaneous firing at a rate of 1-5 action potentials per second [59]. When DRN neurons are exposed to 5-HT, either through local dendrodendritic connections or raphe-raphe projections [60], inhibitory post synaptic potentials can be observed, resulting in down-regulation of DRN activity and thus reduced central nervous system 5-HT release [61]. A major contributor to this down-regulation is negative feedback evoked by 5-HT_{1A} autoreceptors ([58], [62]. 5-HT_{1A} autoreceptors are a class of G

protein-coupled receptors which are densely expressed on somatodendritic compartments of raphe nuclei cell bodies [63]. Upon binding with 5-HT, these autoreceptors activate G protein-coupled inwardly rectifying potassium channels, thereby increasing permeability to K^+ and thus causing membrane hyperpolarisation and a consequent reduction in neural excitability [64], [65].

It has long been recognised that acute SSRI administration increases extracellular 5-HT availability in the DRN, thereby activating 5-HT_{1A} autoreceptors and reducing the firing rate of neurons mediated by these autoreceptors [66]. As a result, 5-HT release is inhibited in areas innervated by these DRN neurons [67]. Consequently, the delayed time to response observed when SSRIs are administered clinically (for e.g. in depression) can be explained by desensitisation of 5-HT_{1A} autoreceptors following consistent daily use over a number of weeks [68]. In terms of 5-HT availability at afferent DRN targets, it can be conceptualised that any initial increase in synaptic 5-HT availability caused by SSRIs occupying presynaptic 5-HT transporters is counteracted by the down-regulation of DRN firing rate by 5-HT_{1A} autoreceptors. Following desensitisation of these autoreceptors, negative feedback at the level of the raphe is reduced, thereby normalising firing rate and allowing for increased 5-HT availability in afferent target regions. This conceptualisation is supported by evidence that more rapid onset of anti-depressant effects of SSRIs can be obtained when SSRIs are administered concurrently with a 5-HT_{1A} antagonist [69]. Similarly, selective deactivation of 5-HT_{1A} autoreceptors in murine models allows for immediate anti-depressant effect following a single dose of fluoxetine [70]. This concept can be expanded to allow for the examination of effects of SSRIs in acute animal preparations. Pre-treatment with 5-HT_{1A} antagonists prior to administration of fluoxetine has allowed for the exploration of a variety of behavioural and pharmacological effects which would have otherwise been obscured by the autoregulation of DRN activity (e.g. [66], [71], [72].

One potential problem for the proposal that insufficient 5-HT_{1A} autoreceptor desensitisation might underlie the previous lack of effectiveness of SSRIs in the treatment of ADHD is that the classical psychostimulant pharmacotherapeutic agents used in the disorder, d-amphetamine and methylphenidate, do not require extended exposure before they become effective (e.g. [73], [74]) (as we have argued is likely to be the case for SSRIs), even though they too are likely to lead to elevated levels of 5-HT in the DRN, which should activate inhibitory 5-HT_{1A} receptors on the cell bodies of raphe neurons. Why might they not require a period of time to desensitise 5-HT_{1A} receptors before becoming effective? In the case of d-amphetamine, the explanation is fairly straightforward, since the drug produces the impulse-independent release of monoamine neurotransmitters (e.g. [75]), hence the elevation of forebrain 5-HT levels is still likely to occur following d-amphetamine administration even if DRN firing rate is acutely suppressed. The case for methylphenidate is a more complicated, since there is no direct evidence of impulse-independent release as far as we are aware. However, evidence from freely moving animals suggests that acute methylphenidate administration changes that activity of over half of the neurons in the DRN, in most cases increasing their firing rate [76]. Although the mechanism of action is unknown, again this means the drug is likely to produce an early increase in forebrain 5-HT levels without the need for a period of desensitisation.

We have previously presented evidence outlining the potential benefits of exploiting collicular 5-HT transmission in the treatment of ADHD. The critical role of 5-HT_{1A} auto-receptors in regulating 5-HT transmission suggests that the efficacy of SSRIs in the treatment of ADHD can be improved by combining SSRIs with the administration of 5-HT_{1A} antagonists. Antagonism of 5-HT_{1A} receptors is unlikely to directly interfere with the therapeutically desired inhibitory effects of 5-HT on collicular activity as this appears to be mediated by 5-HT_{1B} and 5-HT_{1D} and receptors [57], [77].

Summary and next steps

There is a disconnect between pre-clinical evidence, which suggests that SSRI-based therapies for ADHD are likely to be effective, and clinical reports which suggest that SSRIs are of limited therapeutic relevance to the treatment of ADHD. We propose that this disconnect can be explained by inadequate control of autoregulation processes, which paradoxically limit the availability of 5-HT when SSRIs are administered over the irregular periods used in these clinical trials [30], [31]. As such, we argue that the participants in earlier trials were not administered SSRIs with sufficient regularity or for long enough to fully realise any potential benefits of targeting 5-HT in the pharmacotherapy of ADHD. In light of this, there may be under-researched potential to exploit 5-HT transmission therapeutically in ADHD, by administering SSRIs according to a regime which desensitises 5-HT_{1A} auto-receptors. Hence, we suggest that combination therapies linking SSRIs and 5-HT_{1A} antagonists are a potential way forward in the development of efficacious non-addictive pharmacotherapies for ADHD. The need to develop new efficacious non-addictive pharmacotherapies for ADHD is made even more acute by the recent evidence that not only do ADHD symptoms persist into adulthood in up to 43% of childhood cases [78], but ADHD can also emerge de novo in adulthood [79]. Introducing a combination therapy may be relatively straightforward as the centrally-active 5-HT_{1A} partial agonist pindolol (Visken) is already in clinical use for unrelated conditions in physical medicine [80], and drugs like the 5-HT_{1A} antagonist lecozotan have been developed in the context of Alzheimer's disease [81], so their adoption in the context of ADHD would represent a repurposing of existing medications rather than the generation additional drugs. However, recent studies with SSRI-resistant depression underline the critical issue of dose when it comes to incorporating an adjunct therapy into a treatment regime alongside SSRIs [82]. It is also important to bear in mind the costs and benefits of such adjunct therapies. As a monotherapy in ADHD, very high dose pindodol (20 mg b.i.d.) has recently been shown be as

effective as a standard dose of methylphenidate against conduct problems and hyperactive behaviour at home and hyperactivity at school, although adverse effects were greater [83]. The extent to which those effects might be ameliorated via reducing the dose, and/or the combined administration of pindodol and SSRIs has yet to be determined.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Disclosures

The authors have no financial conflicts of interest to disclose.

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