Adrenoceptors: a focus on psychiatric disorders and their treatments

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Abstract Research into the involvement of adrenoceptor subtypes in the cause(s) of psychiatric disorders is particularly challenging. This is partly because of difficulties in developing animal models that recapitulate the human condition but also because no evidence for any causal links has emerged from studies of patients. These, and other obstacles, are outlined in this chapter. Nevertheless, many drugs that are used to treat psychiatric disorders bind to adrenoceptors to some extent. Direct or indirect modulation of the function of specific adrenoceptor subtypes mediates all or part of the therapeutic actions of drugs in various psychiatric disorders. On the other hand, interactions with central or peripheral adrenoceptors can also explain their side-effects. This review discusses both aspects of the field, focusing on disorders that are prevalent: depression, schizophrenia, anxiety, attention-deficit hyperactivity disorder, binge-eating disorder and substance use disorder. In so doing, we highlight some unanswered questions that need to be resolved before it will be feasible to explain how changes in the function of any adrenoceptor subtype affects mood and behavior in humans and other animals.

Key words Adrenoceptor subtypes ● Anxiety ● Attention-deficit hyperactivity disorder ● Binge-eating disorder ● Cognition ● Depression ● Neurogenesis ● Opiate/opioid withdrawal syndrome ● Schizophrenia

Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention-deficit hyperactivity disorder
BED	Binge-eating disorder
cAMP	Cyclic adenosine monophosphate
CHO	Chinese hamster ovary
CNS	Central nervous system
DAT	Dopamine reuptake transporter
DMN	default mode network
EN	Executive network
LTP	Long-term potentiation
NARI	Norepinephrine reuptake inhibitor
NET	Norepinephrine reuptake transporter
NK1	Neurokinin-1 (receptor)
PET	Positron emission tomography
PFC	Prefrontal cortex
SN	Salience network
SNP	Single nucleotide polymorphism
SSRI	Selective serotonin reuptake inhibitor
vPFC	Ventral prefrontal cortex

Introduction

The possibility that norepinephrine might influence brain function directly, rather than merely regulating the intracranial vasculature, was highly controversial until the 1960s (Vogt 1954). However, the development of fluorescence histochemistry enabled mapping of norepinephrine-releasing ('noradrenergic') neurones in the brain, which revealed clusters of their cell bodies in the brainstem and a diffuse distribution of their terminal fibres to nearly all brain regions; the majority of these terminals derive from neurones with cell bodies within nucleus locus coeruleus (Dahlström and Fuxe, 1984; Ungerstedt, 1971; Szabadi 2013).

The subsequent development of radioligand binding enabled quantitation of α- and β-adrenoceptors in different regions of the brain, albeit initially using fairly non-selective ligands to study large brain regions of large animals (U'Prichard and Snyder 1977). The discovery of subtypes of α_1- (α_{1A}, α_{1B} and α_{1D}), α_2- (α_{2A}, α_{2B}- and α_{2C}) and β- (β_1, β_2 and β_3) adrenoceptors then led to a plethora of research that has produced evidence, in progressively finer detail, that has helped to refine our knowledge of the distribution of adrenoceptors in the brain.

The rationale for the classification of these nine subtypes is described, in detail, elsewhere in this volume. Here, we shall discuss the evidence that has informed our understanding of the extent to which they are implicated in the cause(s) of, and/or treatments for, prevalent psychiatric disorders: anxiety, depression, schizophrenia, attention-deficit hyperactivity disorder (ADHD), binge-eating disorder and opiate / opioid withdrawal syndrome.

Experimental approaches and their limitations

As with other neurotransmitter systems, research of the role of adrenoceptors in psychiatric disorders has followed three main approaches. One is to study humans suffering from a disorder and to hunt for biomarkers that could offer clues to its cause. So far, none has come to light as a causal factor for any disorder, but there are many candidates that might increase vulnerability. However, these studies are subject to many potential confounds, including: the limitations of what can be sampled in patients; the influence of any medication; and uncertainty about whether findings relate to the primary disorder or its comorbidities. Additional problems are that the expression of symptoms and signs that are used to diagnose psychiatric disorders can vary between patients, change with time and, for most disorders, rely on patients' self-reporting of symptoms, which cannot be evaluated objectively.

Another approach is to characterize the pharmacodynamics of drugs that are used to treat the disorder of interest. However, it has to be acknowledged that drug treatments for a disorder might not cure the cause(s) of the illness but might simply recruit different brain mechanisms that mask its consequences. Also, as will become evident below, psychotropic drugs are promiscuous in their binding to adrenoceptors (as well as receptors for other neurotransmitters) and so it has not been possible to attribute dedicated functionality to any adrenoceptor subtype.

A third approach is to develop animal models of the disorder, using experimental interventions, such as a genetic mutation, neuronal lesioning or drug administration, and to look for parallel changes in the underlying neurobiology and behavioral phenotype. However, there is growing scepticism about the extent to which such experimental interventions can produce animal models that recapitulate the diagnostic criteria for any full-blown human psychiatric disorder. Instead, a more circumspect interpretation of behavioral abnormalities as being plausibly analogous to specific aspects (symptom domains or endophenotypes) of the human disorder is more likely (see Stanford 2017; Stanford 2020; Pratt et al. 2022).

Regarding studies of the different adrenoceptor subtypes, each successive technological development (radioligand binding, immunoblotting, in situ hybridisation….) has prompted a new wave of efforts to map their distribution and role in the brain. Although much has been learned from these different approaches, they all have limitations, for instance: almost none of the ligands binds exclusively to only one receptor family, still less one adrenoceptor subtype; their binding to membrane homogenates does not detect intracellular receptors under most experimental conditions; the rate of receptor internalisation depends on both the activating ligand and receptor subtype (see Akinaga et al. 2019); and weak affinity and cross-reactivity of binding of antibodies to their target.

The use of *in situ* hybridisation to quantify mRNA for each of the receptor subtypes avoids some of these problems, but mismatches between the intensity of a given mRNA signal and expression of its protein product have been problematic. A notable example is the concentration of mRNA for the β_3-adrenoceptor subtype, which is high in the cortex, hippocampus and striatum (Summers et al. 1995) but, with the possible exception of cerebellar Purkinje cells (Lippiello et al. 2020), the expression of this subtype has not been detected in the brain (*e.g.*, Sugama et al. 2019). A similar discrepancy has been reported for α_{1D}-adrenoceptors (Yang et al. 1997).

Mapping individual adrenoceptor subtypes in the human brain, using positron emission tomography (PET), is even more challenging on account of the need for safe, selective, high-affinity ligands that cross the blood-brain barrier: many candidates have been tested, but with limited success (Alluri et al. 2020).

All these factors need to be considered when appraising the evidence discussed in the following sections.

Adrenoceptor subtypes in the brain

3.1 The distribution of adrenoceptors in the brain

Evidence suggests that about 55% of α_1-receptors are the α_{1A}- subtype, 35% are α_{1B}-adrenoceptors, but only 10% are α_{1D}-adrenoceptors (see refs in Perez 2021). Important progress was made by studies of transgenic mice expressing human α_{1A}- or α_{1B}-adrenoceptors (Papay et al. 2004; 2006). Their findings broadly, but not invariably, confirmed those from studies using pre-existing techniques. In respect of their distribution in brain regions of particular interest in research of psychiatric disorders, both subtypes are prominent in the amygdala, but are relatively scarce in the basal ganglia and thalamus (see Table 1). α_{1A}-Adrenoceptors, have a high concentration in the hippocampus and brainstem, unlike α_{1B}-adrenoceptors, and are expressed by many different types of neurones, including glutamatergic and GABAergic interneurons (Papay et al. 2006). There have been no equivalent studies for mapping α_{1D}-adrenoceptors, which appear to be almost exclusively intracellular.

No studies to date have used transgenic mice expressing human α_2-subtypes but the majority are α_{2A}-adrenoceptors, which are ubiquitous in the brain. Between 11- 44% are α_{2B}-adrenoceptors, most of which are in the cerebellum and thalamus. α_{2C}-Adrenoceptors are mainly in the striatum and hippocampus. The majority of α_{2A}-adrenoceptors are postsynaptic, but α_{2C}-adrenoceptors are more evenly expressed on both pre- and postsynaptic membranes (Erdozain et al. 2019) where they function as autoreceptors, on noradrenergic neurons, and heteroceptors on other neuronal phenotypes, both of which blunt neurotransmitter release (Scheibner et al. 2001).

Using radioligand binding to map the distribution of β-adrenoceptors is problematic because most ligands also bind to 5-HT_{1A}-receptors and their lipophilicity affects their binding. However, evidence suggests that the densities of β_1- and β_2-adrenoceptors are similar in many brain regions, but they differ in respect of their membrane *versus*

intracellular distribution (Guo and Li 2007). The majority of β_1-adrenoceptors are postsynaptic, but some are presynaptic (Gereau and Conn 1994), expressed by catecholaminergic neurones (Levin and Biegon 1984; Aoki et al. 1989). β_2-adrenoceptors are mainly in the cerebellum and thalamus. Although no β_3-adrenoceptor binding has been detected in the brain, there is pharmacological evidence that they modulate metabolism in the frontal cortex (Mirbolooki et al. 2015) and the firing-rate of noradrenergic neurons in the locus coeruleus (Claustre et al. 2008).

Adrenoceptors are also expressed by glial cells, which is interesting because this will affect neuronal signalling indirectly. There is a good deal of evidence that α_1- and α_2-adrenoceptors on astrocytes promote glutamate uptake, glycogen synthesis and glucose metabolism (see: Hertz et al. 2010; O'Donnell et al. 2012). Some β-adrenoceptors are similarly expressed by glial cells (Hertz et al. 2010; Milner et al. 2000) and promote glycogenolysis (O'Donnell et al. 2012). This has profound implications for neuronal function in the light of the evidence that lactate, produced by astrocytes, influences neuronal signalling (e.g., Magistretti and Allaman 2018). A recent study of mixed cultures of neurons and astrocytes from the mouse cerebral cortex further suggests that β_3-adrenoceptors promote glutathione release from astrocytes, which could have a neuroprotective effect (Yoshioka et al. 2021).

Further interesting possibilities for the complex functional interplay between neuronal and glial adrenoceptors have been discussed elsewhere (e.g., O'Donnell et al 2012; Wahis and Holt 2021).

3.2 Functional implications for psychiatric disorders of the regional distribution of adrenoceptors

Norepinephrine is only one of a family of catecholamine neurotransmitters. Dopamine, another catecholamine, is prevalent in the brain, but has negligible affinity for α_1-adrenoceptors. However, its affinity for α_{2A}- and α_{2C}-adrenoceptors is similar to that for dopamine D_2 receptors (Sánchez-Soto et al. 2018), which makes it likely that these adrenoceptor subtypes contribute to dopaminergic transmission, especially in brain regions with both a dense dopaminergic innervation and a high density of these subtypes. Such regions include the dorsal striatum (which is one of the few brain regions to lack a noradrenergic innervation) and the (medial prefrontal) cortex. Dopaminergic activation of these subtypes in these brain regions has important implications for the causes of, and

treatments for, several psychiatric disorders, such as depression, schizophrenia, and attention-deficit hyperactivity disorder, which are thought to involve abnormal dopaminergic transmission.

There is also evidence for neurons in the brain that express the enzyme, phenylethanolamine-*N*-methyl transferase, especially in the amygdala, hypothalamus and brainstem regions (Mefford 1988; Howe et al. 1980; Bochorishvili et al. 2014). Although this suggests that these neurones have an epinephrine-releasing phenotype, their release of that catecholamine has not been confirmed. Nevertheless, the affinity of epinephrine for binding to α_{1D}-adrenoceptors is similar to that of norepinephrine and is even higher for binding to the α_{1A}-subtype (Proudman and Baker 2021), which is densely expressed in the brainstem. Likewise, the affinity of epinephrine for binding to α_2-adrenoceptors is similar to that of norepinephrine (Audinot et al. 2002). The functional implications of a role for epinephrine in the brain, mediated by adrenoceptors, merits more consideration.

Another key variable is the location of different receptor subtypes within the brain matrix: those that are close to the norepinephrine release sites (the active zone) will be exposed to higher concentrations of neurotransmitter than receptors that are activated by norepinephrine that has diffused through the extracellular space to remote targets ('volume transmission'; see, for example: Fuxe et al. 2015). As a consequence, low affinity adrenoceptor antagonists are likely to have a proportionally greater influence on extrasynaptic receptors than on receptors that lie close to the release sites. Unfortunately, the mapping of the synaptic *versus* extrasynaptic location of different adrenoceptor subtypes and the pharmacokinetic modelling of these variables are not sufficiently refined to ascertain how this affects the overall noradrenergic response. Nevertheless, this variable is highly relevant to understanding the contribution of different subtypes to the overall effects of systemic administration of drugs that affect mood and behavior (see below).

In summary, the extent to which different adrenoceptor subtypes are physiologically activated *in vivo* will depend on both their neurotransmitter environment and the extent to which the released neurotransmitter escapes neuronal reuptake to reach extrasynaptic receptors. This will be especially relevant to the actions of psychotropic drugs because the majority, if not all, modify norepinephrine release and/or its reuptake. Because these compounds also bind to adrenoceptors directly, to varying extents, it follows that their overall

effects will depend not only on their receptor binding affinity (which is measured *in vitro),* but also on the location of their target receptors: *i.e.*, synaptic or extrasynaptic.

Adrenoceptor subtypes and behavior

Owing to all the variables discussed above, it is difficult to assign specific roles to each of the adrenoceptor subtypes, on the basis of findings from studies using pharmacological tools. Studies of the effects of how gene-knockout for each of the adrenoceptor subtypes affects animals' behavioral phenotype avoids many such confounders and some examples are included in Table 1. Although compensatory adaptive changes could mask the effect of the gene loss of function, that factor is also likely to be the case in humans with genetic mutations that impair the function of the receptor. However, none of the changes in Table 1 links any adrenoceptor subtype with phenotypic abnormalities that could qualify as a model of any psychiatric disorder in humans.

Depression and antidepressants

5.1 Adrenoceptors and depression

Drawing on observations of the side-effects of drugs on the mood of patients being treated for hypertension or tuberculosis, it was inferred that depression was explained by a deficit in catecholamine transmission in the brain, especially that of norepinephrine (Schildkraut 1965). That proposal, which was later refined to include serotonin and rebranded as the 'monoamine theory of depression', has been deprecated for decades, mainly because no consistent supporting evidence has emerged, still less a biomarker (e.g., McTavish et al. 2005; Strawbridge et al. 2022).

By contrast, the corollary of the monoamine theory (*i.e.*, drugs that augment noradrenergic neurotransmission are effective antidepressants) is borne out by clinical experience. This is further supported by evidence that norepinephrine makes a vital contribution to the *relief* of depression in patients who have responded to antidepressants that augment noradrenergic transmission (*e.g.*, Booij et al. 2003).

5.2 Adrenoceptors and antidepressants

Antidepressants can augment noradrenergic transmission in three different ways. One is to expand the vesicular neurotransmitter store, so that more noradrenaline is released when the neurons are active (as in the case of monoamine oxidase inhibitors). Another is to block

neuronal uptake of noradrenaline, which blunts its clearance from the extracellular fluid (as do tricyclic antidepressants and selective norepinephrine reuptake inhibitors). Both these processes will increase activation of adrenoceptors indirectly. The third is to block presynaptic α_2-autoreceptors, which are responsible for feedback inhibition of impulse-evoked neurotransmitter release (see Starke 1977).

However, the lag of several weeks before any beneficial effects of antidepressants become apparent, makes it clear that none of these mechanisms explains the therapeutic response, directly. Instead, evidence that prolonged, but not acute, administration of monoamine oxidase inhibitors (see Mobley and Sulser 1981) or tricyclic antidepressants (Banerjee et al. 1977) caused a long-latency downregulation β-adrenoceptors in the rat brain, and a reduction in the production of their intracellular second messenger, cAMP (cyclic adenosine monophosphate: Vetulani and Sulser 1975; Mishra et al. 1983), suggested an alternative explanation for the therapeutic lag. That tranche of research turned out to be a red-herring, mainly because β-adrenoceptor down-regulation was not found after treatment with antidepressants that were developed subsequently: *e.g.*, the selective serotonin reuptake inhibitors ('SSRI's; Maggi et al. 1980; Mobley and Sulser 1981). Despite exhaustive research other adrenoceptor subtypes, no changes in any neurotransmitter receptors have been found that are shared by all antidepressants.

5.3 Binding of antidepressants to adrenoceptors

As well as increasing the activation of adrenoceptors by norepinephrine, indirectly, almost all antidepressants bind to adrenoceptors directly, albeit to different extents. As discussed below, this binding accounts for some of their side-effects and could help to ameliorate certain aspects of depression.

The chance discovery in the 1950s that the dibenzazepine, imipramine, was an effective treatment for depression led to the development of the family of tricyclic antidepressants, which block neuronal reuptake of extracellular norepinephrine and serotonin. However, their binding to α_1-adrenoceptors, as antagonists, attracted attention because this causes orthostatic hypotension, which is one of the problematic side-effects of this class of drugs. All tricyclic antidepressants have a K_D of less than 100 nM for binding to α_1-adrenoceptors in homogenates of human brain tissue *postmortem* (Richelson and Nelson 1984). As a consequence, drug development of antidepressants aimed to produce compounds

with a lower affinity for binding to this receptor. With the exception of mianserin, maprotiline and trazodone, that strategy was broadly successful (Richelson and Nelson 1984).

A recent and comprehensive study compared the binding of antidepressants from a wide range of mechanistic categories to all three subtypes of human α_1-adrenoceptors. These were expressed by transfected Chinese hamster ovary (CHO) cells, with each cell-line expressing one of the human α_1-adrenoceptor subtypes (Proudman et al. 2020). Importantly, the binding assays were carried out under conditions that should enable comparisons of the binding parameters across the entire range of compounds and different classes of antidepressants.

That study confirmed that the affinity of binding of tricyclic antidepressants to all α_1-adrenoceptor subtypes was typically considerably higher than that of more recent compounds, apart from mirtazapine, trazodone and vortioxetine. Reboxetine and venlafaxine showed particularly low affinity for all α_1-adrenoceptor subtypes (Table 2). The full dataset is published in Proudman et al. (2020)

In a different study, Proudman et al. (2022) compared the binding of antidepressants to the three human α_2-adrenoceptor subtypes, using the same CHO expression system as before. The binding affinity of tricyclic antidepressants for all α_2-adrenoceptor subtypes was considerably higher than for the majority of antidepressants that were developed subsequently (e.g., reboxetine and venlafaxine), but mirtazapine and trazodone were again exceptions, together with vortioxetine. Apart from sertraline (K_D in the low μM range), the binding of selective serotonin reuptake inhibitors (SSRIs) to any of the α_2-adrenoceptor subtypes was either low or negligible.

It must be acknowledged that such comparisons do not take into account the possibility that active metabolites of these drugs might have a different binding profile. However, insofar as these two separate studies can be compared (*c.f.*, Proudman et al. 2020, 2022), the binding affinity of the majority of antidepressants to α_1-adrenoceptor subtypes remains considerably higher than for α_2-adrenoceptors, but mirtazapine, duloxetine and the SSRIs are exceptions.

Despite the lower affinity of antidepressants for α_2-adrenoceptors, it should be borne in mind that antagonism of any α_1-adrenoceptors that are close to the site of release will need much higher concentrations of an antagonist than would blockade of any extrasynaptic α_2-adrenoceptors that are recruited through volume transmission. This is likely to be

particularly important for antidepressants because they all increase the concentration of extracellular norepinephrine and so will amplify the activation of extrasynaptic adrenoceptors. For this reason, it should not be assumed that the lower K_D of antidepressants for α_2-adrenoceptors indicates that their interaction with these receptors makes a negligible contribution to the therapeutic response.

Finally, apart from vortioxetine, none of a wide range of antidepressants show any appreciable binding to β_1- or β_2-adrenoceptors (Proudman et al. 2022).

5.4 The binding profile of antidepressants and the therapeutic response

No selective adrenoceptor agonist or antagonist is an effective antidepressant but, on the grounds that antagonism of α_2-adrenoceptors blocks feedback inhibition of release of norepinephrine (and other neurotransmitters) and so increases noradrenergic transmission, any antagonism of these receptors by antidepressants could be therapeutically advantageous. Also, α_2-adrenoceptor antagonism would tend to mask any orthostatic hypotension caused by their α_1-adrenoceptor antagonism (Shibao et al. 2010; Jones et al. 2015).

It is striking that all the tricyclic antidepressants have a higher binding affinity for α_{2B}- than α_{2A}- or α_{2C}-adrenoceptors, especially amitriptyline; only mirtazapine has a lower affinity for this subtype than for other α_2-subtypes. This makes the high density of α_B-adrenoceptors in the thalamus particularly interesting in the light of emerging evidence that adjusting neurotransmission within the lateral habenula (in the epithalamus) is an effective treatment for depression (Webster et al. 2021). Given the evidence that α_{2B}-adrenoceptors have a role in negative emotional processing, which is apparent in depression (Gibbs et al. 2013), the contribution of this receptor subtype to the therapeutic response of antidepressants clearly needs further investigation.

Comparison of the *relative affinities* (selectivity) of antidepressants across all adrenoceptor subtypes, which is a variable that will determine their net effect on noradrenergic transmission, points to another interesting possibility. By preferentially blunting activation of α_1- (and α_2-adrenoceptors to some extent), antidepressants will increase the relative influence of β-adrenoceptors, for which they have negligible affinity. The possibility that such a shift in the receptor profile of noradrenergic transmission is a component of antidepression is interesting because the opposite shift, from activation of β- to α_1-adrenceptors (i.e., activation of G_s and inhibition of $G_{q/11}$ G protein-coupled receptors) seems to happen after a bout of chronic stress (Stanford 1995). The possibility of such a shift

is supported by evidence, albeit controversial, that β-adrenoceptor antagonists can exacerbate depression (Luijendijk et al. 2011; Andrade 2021) and that the newest antidepressant, vortioxetine, increases activation of β-adrenoceptors (Todorovic et al. 2022).

In short, the important components of the therapeutic actions of antidepressants could depend on the relative contributions of their effects on neurotransmission mediated by synaptic *versus* extrasynaptic adrenoceptors, together with a reduction the contribution of α_1-adrenoceptor mediated transmission, *in combination with* an increase in the relative contribution of β-adrenoceptor activation.

Schizophrenia and antipsychotics

6.1 Adrenoceptors and schizophrenia

The neurotransmitters, dopamine, serotonin and glutamate, have been investigated extensively for their involvement in schizophrenia, especially in respect of the positive symptoms of this disorder. By contrast, there have been comparatively few studies of noradrenergic transmission in this context. Although there are isolated reports of abnormalities in adrenoceptors in schizophrenic patients, no consistent findings have come to light to suggest that dysfunctional noradrenergic transmission is a causal factor in schizophrenia (e.g., Bennett et al. 1979; Dean 2003; Clark et al. 2006; Brocos-Mosquera et al. 2021). Nevertheless, this does not rule out the possibility that modifying noradrenergic transmission might be beneficial when treating this disorder.

6.2 Adrenoceptors and antipsychotics

It should be noted that both the first-generation antipsychotics (phenothiazines) and the tricyclic antidepressants (dibenzazepines) derive from the same parent molecule (promazine) and so it is not surprising that they have similar receptor-binding profiles. This doubtless contributes to the cardiovascular side-effects, partly mediated by α_1-adrenoceptor antagonism, that can be problematic with antipsychotics as well as antidepressants.

An early report that chronic administration of antipsychotics caused upregulation of α_1-adrenoceptors suggested that antagonism of these receptors might have a crucial role in the therapeutic response of these drugs (Cohen and Lipinski 1986). This finding was largely ignored for many years. An influential proposal for the involvement of α_1- and α_2-adrenoceptors in the actions of antipsychotics was that antagonism of α-adrenoceptors blunts dopaminergic transmission by neurones that project from the ventral tegmentum to the

ventral striatum and so relieves the positive symptoms of schizophrenia. Furthermore, antagonism of α_2-adrenoceptors is thought to disinhibit noradrenergic release by neurones projecting from the locus coeruleus, which augments dopamine release in the prefrontal cortex (PFC) and so relieves the negative symptoms and cognitive deficits of schizophrenia (Svensson 2003). This explanation for the beneficial pharmacology of antipsychotics still prevails.

Interest in these receptors increased following the development of the first of a new class of (atypical) antipsychotics, clozapine. Unlike its predecessors, this compound turned out to have comparatively low D_2 dopamine receptor binding, which hitherto had been thought to explain the efficacy of antipsychotic drugs. In addition to a reduced incidence and severity of extrapyramidal side-effects, another notable ('atypical') feature of clozapine was that it was the first antipsychotic to show any appreciable improvement in both the Type 2 (negative) symptoms of schizophrenia, which include symptoms that resemble depression, and cognitive deficits (Hagger et al. 1993). This also turned out to be the case with atypical antipsychotics that were developed subsequently. The role of different adrenoceptors in cognition is discussed in Section 7, below.

6.3 Binding of antipsychotics to adrenoceptors

Studies of the binding of antipsychotics to a wide range of neurotransmitter receptors in homogenates of human brain tissue *postmortem* revealed that, for compounds that are licensed for use in the UK or USA, their K_D for binding to α_1-adrenoceptors was consistently in the low nM range. However, apart from ziprasidone and zotepine, the binding affinity of atypical antipsychotics for α_1-adrenoceptors was similar that for α_2-adrenoceptors (*i.e.*, a difference in the K_D of less than 10-fold) (Richelson and Souder 2000).

The binding of antipsychotics to α_1-adrenoceptors was also measured by Proudman et al. (Proudman et al. 2020), using CHO cells transfected with the human gene for each of the subtypes. These studies confirmed the high affinity of antipsychotics for this subgroup, especially the α_{1A}-subtype. For all licensed compounds, the K_D for binding to these receptors was consistently higher than for α_{1B}-adrenoceptors, but the difference reached the criterion for selectivity (10-fold difference) only with ziprasidone and paliperidone (Table 3). Apart from lurasidone, another consistent finding was that binding to α_{1A}-adrenoceptors was higher than to the α_{1D}-subtype, but none of the compounds showed any α_{1B}- / α_{1D}-adrenoceptor selectivity (Table 3).

Data from a later study (Proudman et al. 2022) indicate that the K_D for binding of these antipsychotics to α_{2A}-adrenoceptors was in the μM range but, apart from clozapine, none showed any selectivity for any of the α_2-adrenoceptor subtypes (Table 3). These findings broadly confirm an earlier radioligand meta-analysis in which binding affinities were compared with that of haloperidol, as a standard (Minzenberg and Yoon 2011).

As with the antidepressants, neither the first- or second-generation antipsychotics bind appreciably to either the β_1- or β_2-adrenoceptors, but the lead compound for the third generation of antipsychotics, aripiprazole, is an interesting exception (with μM affinity for both subtypes: Proudman et al. 2022); his compound shares the benefits of the atypical antipsychotics on Type 2 symptoms and cognitive impairment, but carries an appreciably lower risk of obesity and its co-morbidities.

6.4 The binding profile of antipsychotics and the therapeutic response

It is not surprising that the K_Ds for binding of antipsychotics to α_{1A}-adrenoceptors is higher than for other subtypes, as is the case for antidepressants, because they have a similar molecular heritage. However, it is striking that, whereas the rank order for antipsychotics is typically $\alpha_{1A} > \alpha_{1B} > \alpha_{1D}$, that for antidepressants is usually $\alpha_{1A} > \alpha_{1D} \geq \alpha_{1B}$. Also, whereas the rank order of binding of antidepressants to α_2-subtypes is not consistent (but often $\alpha_{2C} \geq \alpha_{2A} \geq \alpha_{2B}$), this is not the case with antipsychotics, for which there is little difference in binding these three subtypes. Whether (and, if so, how) these different rank profiles affect overall noradrenergic transmission in ways that could contribute to the different therapeutic applications of antidepressants and antipsychotics merits consideration.

Although, like the tricyclics, all antipsychotics have cardiovascular side-effects, for the "atypicals", these have been eclipsed by the incidence of harmful weight gain and metabolic syndrome (see: Heal et al, 2012; Bernardo et al. 2021). There is some evidence that this is associated with polymorphism of α_{2A}- and β_3-adrenoceptor genes, *ADRA2A* and *ADRB3* (Sickert et al. 2009; Zhang et al. 2016, but see Tsai et al 2004), which would be consistent with evidence that activation of α_{2A}-adrenoceptors inhibits lipolysis, glycolysis and thermogenesis, whereas activation of β_3-adrenoceptor has the opposite effect. It is tempting to speculate that the exceptional binding of the third generation (atypical) antipsychotic, aripiprazole, to β-adrenoceptors has some bearing on the lower incidence of weight gain and other metabolic side-effects associated with this compound, compared with its predecessors.

Unfortunately, binding of antipsychotics to β_3-adrenoceptors was not included in the Proudman study (Proudman et al. 2022), but this is an obvious candidate for future research. The relative affinities of antipsychotics for α- and β-adrenoceptor subtypes could be an important factor in determining their overall effect on body weight.

Adrenoceptors, neurogenesis and cognition in treatment of depression and schizophrenia

Following reports that depression is associated with reduced hippocampal volume (Sheline et al. 1996; Bremner et al. 2000) and that prolonged, but not acute, administration of antidepressants promotes hippocampal neurogenesis in rats (Malberg et al. 2000), this response has been investigated extensively as an explanation for the therapeutic response. However, the functional consequences of an increase in neurogenesis are uncertain. The undisputed role of the hippocampus in cognition gives rise to the possibility that increased neurogenesis helps to resolve the cognitive impairment that is prominent in depression, which has been therapeutically challenging. A recent suggestion is that neurogenesis augments cognitive flexibility and that this has beneficial effects on stress resilience and mood (see: Anacker and Hen 2017; Tartt et al. 2022).

However, cognitive impairment is also a prominent feature of schizophrenia, Given the similar chemical provenance of antidepressant and antipsychotic drugs, it is surprising that comparatively little research has focussed on the effects of antipsychotics on neurogenesis (but see, for example; Kusumi et al. 2014; Carli et al. 2021), not least because atypical antipsychotics, unlike their predecessors, are noted for their beneficial effects on cognitive impairment in schizophrenia (but see: Clissold and Crowe 2019). Isolated preclinical studies have suggested that atypical antipsychotics, like antidepressants, increase hippocampal neurogenesis (e.g., Chikama et al. 2017; Chen and Nasrallah 2019), but there has been little research of the role of adrenoceptors in this response.

Extensive evidence has accumulated to suggest that noradrenergic transmission in the brain, influences long-term potentiation (LTP) (Maity et al. 2020), cognition (Perez 2021), focussed attention (see: Vazey et al. 2018) and neurogenesis (Kulkarni et al. 2002). There is also evidence that neurogenesis is required for expression of the effects of antidepressants in preclinical screens using rats (Santarelli et al. 2003). Furthermore, activation of α_1-adrenoceptors (particularly the α_{1A}-subtype, but not the α_{1B}-subtype (reviewed by Perez 2021) improves cognitive performance and augments LTP and neurogenesis (e.g., Doze et al.

2011). This is interesting because, as discussed above, antidepressants and antipsychotics bind to the former subtype (Tables 1 and 2), but as antagonists, which gives cause to question their contribution to the beneficial effects of antidepressants and antipsychotics on cognition.

A role for α_2-adrenoceptors in the effects of antidepressants and antipsychotics on neurogenesis is also uncertain. There are reports that the α_2-adrenoceptor antagonist, yohimbine, accelerates neurogenesis (Yanpellawar et al. 2010), but another study did not find any change in proliferation of neural precursor cells from the dentate gyrus after treatment with either yohimbine (Jhaveri et al. 2014) or a range of antidepressants (Masuda et al. 2012). Yet another study, using the more selective α_2-adrenoceptor antagonist, idazoxan, concluded that α_2-adrenoceptor activation promotes proliferation (Bortolotto et al. 2021). The explanation for these disparate findings is unknown, but it is possible that antagonism of α_2-adrenoceptors by either antidepressants or antipsychotics promotes neurogenesis.

An early finding was that norepinephrine has a direct effect on proliferation *in vitro* of neurosphere cultures derived from the hippocampus (Jhaveri et al. 2010): this response was attributed to activation of β_3-adrencoceptors on pluripotent neural precursors from the hippocampal subgranular zone and could be replicated by administration of noradrenaline reuptake inhibitors, but not serotonin or SSRIs, *in vivo.* This is an interesting finding because, as noted above, there is little, if any, detectable β_3-adrenoceptor protein in the brain (Sugama et al. 2019), but their mRNA is denser in the hippocampus than elsewhere (Summers et al. 1995). There is also conflicting evidence regarding the effects of other β-adrenoceptor subtypes on neurogenesis: whereas one study found no change (Jhaveri et al. 2010), more recent evidence suggests that activation of β_2-adrenoceptors promotes neurogenesis of adult hippocampal progenitor cells (Masudo et al. 2012; Bortolotto et al., 2019, 2021).

Clearly, more research is needed to improve our understanding of the role of different adrenoceptor subtypes in neurogenesis and whether this response is relevant to the actions of antidepressants and antipsychotics on cognition, or other aspects of depression and schizophrenia.

Anxiety

8.1 Norepinephrine and anxiety

Because some of the symptoms and signs of anxiety resemble the sympathoadrenal stress response, an obvious explanation for the cause of anxiety is excessive noradrenergic transmission in the brain. Evidence apparently supporting that proposal emerged from

experiments in which the locus coeruleus in non-human primates was stimulated directly. The behavioral changes that ensued were ethologically similar to those expressed when these animals experience threatening stimuli and so were interpreted as an indication that they were anxious (Redmond and Huang 1979). Despite evidence that direct stimulation of the locus coeruleus in humans caused a sensation of relaxation, not anxiety or even fear, in human subjects (Libet and Gleason 1994), the theory that excessive noradrenergic transmission in the brain causes anxiety has dominated the field ever since (e.g., Morris et al. 2020). However, a complicating factor is that anxiety comprises a family of heterogenous disorders. Although they all share features of an inappropriate stress response (sympathetic hyperarousal), the subjective symptoms and diagnostic criteria differ markedly from one to another, as do their treatment strategies.

8.2 Do adrenoceptor agonists and antagonists induce or prevent anxiety?

There is now a great deal of evidence that undermines the proposal that excessive noradrenergic transmission in the brain causes anxiety. One line of research has been to study the response of humans who have been given the α_2-adrenoceptor antagonist, yohimbine, which binds with high affinity to all α_2-adrenoceptor subtypes (Proudman et al. 2022). Although this compound causes sympathetic arousal and exacerbates anxiety in patients with a pre-existing anxiety disorder, evidence that this drug induces anxiety in healthy subjects is equivocal (*e.g.*, Charney et al 1982; 1983). Similarly, the more selective α_2-adrenoceptor antagonist, idazoxan, which binds to all three subtypes, does not induce anxiety in healthy human subjects (Glue et al. 1991), with the possible exception of a transient increase in anxiety after a high dose of this drug (Schmidt et al. 1997). However, in both cases, it should be borne in mind that antagonism of presynaptic α_2-adrenoceptors will not only increase release of norepinephrine (and other neurotransmitters) but will also block transmission mediated by postysynaptic α_2-adrenoceptors and so the net effect of this drug on noradrenergic transmission is hard to predict.

By contrast, α_2-adrenoceptor agonists have established anxiolytic effects, but only at doses that also induce sedation. The α_2-adrenoceptor partial agonist, clonidine, is used to treat anxiety in the context of supervised alcohol and opiate withdrawal: this drug is not a viable for routine treatment of anxiety on account of its profound hypotensive and sedative effects. Both clonidine and the more selective, full agonist, dexmedetomidine, are also used preoperatively because, in this context, the sedation is beneficial. A sedative dose of guanfacine has been used off-label to treat anxiety in post-operative critical care (Srour et al.

2018) and an extended-release formulation has been used to treat paediatric anxiety (Strawn et al. 2017).

There is evidence that activation of presynaptic α_2-adrenoceptors, which will blunt norepinephrine release and the firing-rate of neurones in the locus coeruleus, contributes to the sedative effects of these drugs (Heal 1990). This is most likely because neurones project from this nucleus to the ventral preoptic area of the hypothalamus, which governs arousal state. However, the extent to which activation of α_2-heteroceptors, which blunt release of the many other transmitters that influence arousal, is unknown.

The proposal that excessive noradrenergic transmission is a cause of anxiety has been used as a rationale for using the β-adrenoceptor antagonists to treat anxiety in humans. It is clear that these compounds blunt the peripheral sympathoadrenal hyperarousal during a stressful experience ('situational anxiety' /' competition nerves': see: Anon 1985), which could serve as an interoceptive, anxiogenic cue, but whether or not β-adrenoceptor antagonists prevent the subjective elements of anxiety is controversial and their long-term use is not recommended. For instance, recent metanalyses advise that propranolol should not be used to treat any anxiety disorder on the grounds of lack of clear efficacy (Steenan et al. 2016; Raut et al. 2022)

In summary, there is plenty of evidence that challenges the theory that excessive noradrenergic transmission, mediated by adrenoceptor activation, in the brain causes anxiety. It is also clear that blockade of any adrenoceptor subtype is not an effective strategy for treating this family of disorders. For all these reasons, evidence gathered from preclinical studies in which adrenoceptor ligands have been used to study the neurobiology of anxiety and its treatment should be interpreted with caution.

Attention-deficit hyperactivity disorder (ADHD)

Attention-deficit hyperactivity disorder is a common developmental disorder that is characterized by its core symptoms of inattentiveness, distractibility, impulsiveness and hyperactivity. ADHD is a heterogeneous disorder, but it is currently broadly classified as either "Predominantly inattentive" subtype (low level of hyperactivity) or "Combined predominantly hyperactive-impulsive" subtype. As a developmental disorder, ADHD should strictly be supported by a diagnosis in childhood (before the age of 7 years). However, because ADHD is considerably under-diagnosed, many cases go unrecognized leading to an ADHD diagnosis later in life.

It was originally believed that ADHD was exclusively a disorder of childhood and adolescence that gradually resolved as individuals reached adulthood. It is now recognized that in many instances ADHD persists in adults. Although the symptoms may reduce in adulthood and be partly mitigated by individuals developing coping strategies for the disorder, nonetheless, persistent ADHD symptoms have a substantial negative impact on the mental health, wellbeing, and life opportunities of adult sufferers. The clinical case for continued treatment has now been accepted and many ADHD drugs are approved for adults in addition to children and adolescents.

Although it widely believed that an imbalance between noradrenergic and dopaminergic neurotransmission in the PFC plays an important role in the psychopathology of ADHD (Heal & Pierce, 2006; Arnsten, 2006; Heal et al., 2008; 2009; 2012; 2022), no evidence has so far emerged from brain imaging experiments in humans to suggest that alterations in adrenoceptor density or function are responsible for this imbalance. Yet, despite a lack of any evidence that ADHD can be ascribed to an abnormality in the number or function of any adrenoceptor subtype(s), the α_{2A}-adrenoceptor has been unequivocally implicated in the therapeutic effect of ADHD drugs.

The history of pharmacotherapy in ADHD started with racemic amphetamine in the 1930s, followed by methylphenidate in the 1950s; these drugs are catecholaminergic stimulants. Their powerful effect on dopaminergic neurotransmission has led to a persistent erroneous belief that dopamine is the primary mediator of efficacy in ADHD with norepinephrine relegated to a minor supporting role (Volkow et al. 2012; del Campo et al. 2011; 2013; Aarts et al. 2015). The introduction of the selective norepinephrine reuptake inhibitor (NARI), atomoxetine, in 2002 failed to resolve the matter because it potentiates both noradrenergic and dopaminergic neurotransmission in the PFC (Bymaster et al. 2002), which is the primary site of action for ADHD drugs (Heal et al. 2008; 2009; 2012; 2022; Arnsten 2009; Arnsten and Pliszka 2011; Berridge and Devilbiss 2011). The PFC has highly unusual neuroanatomy with a low density of dopamine reuptake transporter (DAT) sites in the PFC (Hitri et al. 1991; Sesack et al. 1998). For this reason, a substantial proportion of released dopamine is transported into noradrenergic neurones via norepinephrine reuptake transporters (NET) (Morón et al. 2002; Stahl 2003) and, as a consequence, selective NARIs increase the synaptic concentrations of norepinephrine and dopamine (Bymaster et al. 2002; Yu et al. 2020) thereby potentiating signalling of both catecholamines.

A selective role for norepinephrine, and α_2-adrenoceptors specifically, came to light with the 1985 report by Hunt et al. (1985) of the therapeutic benefit of clonidine in treating children with ADHD. Later, the ability of α_2-adrenoceptor agonists to improve cognitive function was demonstrated in primates by Arnsten and colleagues (Arnsten et al. 1988; Cai et al. 1993), which ultimately led to the conduct of several small, open-label, clinical trials that provided preliminary proof of efficacy for guanfacine in ADHD (reviewed by Arnsten et al. 2007). These initial findings for positive effects of α_{2A}-adrenoceptor agonists on cortical level cognitive function in primates have been replicated in subjects with ADHD (Schulz et al. 2013; Logemann et al, 2013; Bédard et al, 2015). Moreover, when tested in the 5-choice serial reaction-time (5-CSRT) test, the attention deficit of mice with functional ablation of neurokinin-1 receptors (NK1R), which express all core features of ADHD, is ameliorated by low (non-sedative) doses of guanfacine (Pillidge et al. 2014a).

A long-acting formulation of guanfacine (guanfacine-XR) has been shown to reduce ADHD symptoms in pivotal clinical trials in children and adolescents and adults (Biederman et al. 2008; Sallee et al. 2009; Wilens et al. 2012; Iwanami et al. 2020) and it was approved for use in this psychiatric indication in 2010. Although the potential value of clonidine as an ADHD treatment had been reported many years earlier, it was only in approximately 2005 that development of a long-acting formulation of clonidine (clonidine-XR) in ADHD was initiated. The results of these studies have not been published, but the FDA approval of clonidine-XR was supported by efficacy demonstrated in two pivotal trials, one as monotherapy and one as an adjunct to stimulant therapy (FDA Clonicel® Clinical Review. 2010).

Evidence from animal experiments (Arnsten and Leslie. 1991; Arnsten and Cai. 1993) supports the hypothesis that the α_2-adrenoceptor agonists produce their primary therapeutic effect on ADHD symptoms by activating postsynaptic α_2-adrenoceptors in the PFC. Unlike the NARIs and stimulants that increase synaptic concentrations of both dopamine and norepinephrine in the PFC, the α_2-adrenoceptor agonists actually decrease exocytotic (impulse-dependent) release of both these catecholamines (Gresch et al. 1995; Tanda et al. 1996) via their inhibitory and autoreceptor actions. Nonetheless, the α_2-agonists are unquestionably efficacious in ADHD providing clear evidence that dopamine is not a critical effector of efficacy in ADHD. This point is further illustrated by the moderate efficacy of the DAT inhibitor, bupropion, in ADHD trials (see Heal et al. 2012) and discontinuation of several drug-candidates that preferentially enhance dopaminergic neurotransmission (see Heal et al. 2012; 2022).

These findings demonstrate a role for α_2-adrenoceptors as a mediator of efficacy in ADHD, but they do not identify which subtype is responsible. Although there can be no absolute certainty on this point, it is highly likely to be the α_{2A}-subtype because almost all of the key effects of α_2-adrenoceptor agonists in the central nervous system (CNS) (e.g., monoamine turnover, locomotion, sedation and analgesia) are abolished in animals lacking functional α_{2A}-adrenoceptors (MacMillan et al. 1998; Lähdesmäki et al. 2002; 2003). Also, the affinity of guanfacine for this (human) subtype is higher than that for α_{2B}- or α_{2C}-adrenoceptors (Audinot et al. 2003; Table 4)

One key question with respect to efficacy is whether or not the α_2-adrenoceptor agonists genuinely modulate PFC function to improve cognitive control or merely dampen aberrant behavior as a result of their powerful sedative properties? Huss et al. (2019) addressed this question by stratifying patient populations from pooled trials with guanfacine-XR and showed that efficacy was significantly greater in subjects without sedative side-effects than in those with them and, moreover, the drug was equally effective in treating the combined/predominantly hyperactive-impulsive and predominantly inattentive (non-hyperactive) forms of ADHD. Together, these findings clearly support the hypothesis that activation of central α_2-adrenoceptors rectifies the psychopathological symptoms of ADHD.

On the basis of what has been learned about the α_2-adrenoceptor agonists, it is safe to assume that the activation of post-synaptic α_{2A}-adrenoceptors also mediates a substantial part of ADHD effects of the NARIs, atomoxetine and viloxazine, and also the catecholaminergic stimulants, methylphenidate and the amphetamines (*d*-amphetamine, lisdexamfetamine, and enantiomer-mixed salts of amphetamine) (see Figure 1). The involvement of other adrenergic subtypes in the actions of these indirect agonists is unclear. It has been suggested that activation of β_1- and α_1-adrenoceptors in the PFC impairs cognitive function (Arnsten and Jentsch 1997; Arnsten and Dudley 2005; Arnsten 2006), but the evidence is based on experiments in normal rats and, therefore, has debatable translational relevance to humans with ADHD. Given that the α_2-agonists are considered to be no more effective as ADHD treatments than the NARIs, and to have weaker efficacy than the catecholaminergic stimulants (Taylor and Russo 2001; Bilder et al. 2016), the clinical evidence indicates that non-selective activation of central adrenoceptors has no deleterious outcome, and as discussed later, may contribute to the benefits of atomoxetine.

Atomoxetine, which is a selective NARI, is often considered to be a less effective in ADHD than the stimulants, but this opinion is open to debate. For example, a comparison against methylphenidate revealed that although it was superior to atomoxetine in some trials

(Kemner et al. 2005; Starr and Kemner 2005), it showed no advantage over atomoxetine in others (Kratochvil et al. 2002; Wang et al. 2007). The picture may also be distorted by the short duration of many ADHD trials which favours drugs with a rapid trajectory of efficacy. A significant proportion of patients prescribed atomoxetine have a notably gradual rate of clinical improvement (Sobanski et al. 2015) putting it at a disadvantage in such comparisons. A meta-analysis of trials ≥12-weeks in duration showed no superiority of methylphenidate over atomoxetine (Bushe et al. 2016; Elliott et al. 2020).

Atomoxetine not only differs from the stimulants by virtue of its slower onset of action, but it also maintains efficacy for much longer after discontinuation. Terminating treatment with amphetamine- or methylphenidate-based stimulants results in a rapid relapse to pre-medication status (e.g., Arnold et al. 2004; Brams et al. 2012; Matthijssen et al. 2019). A similarly rapid relapse has also been reported after guanfacine-XR discontinuation (Newcorn 2016). In contrast, efficacy after discontinuing atomoxetine is maintained at high levels for many weeks or months (Michelson et al. 2004; Upadhyaya et al. 2013; Buitelaar et al. 2015; Tanaka et al. 2017). Following 6-month open-label treatment, adults randomised to placebo showed >90% maintenance of efficacy for the following 6 months (Upadhyaya et al. 2013).

NET inhibition by atomoxetine produces sustained activation of all subtypes of adrenoceptor in the brain. Although this pharmacological mechanism generally requires 2-3 months of treatment to achieve maximum efficacy, the benefit is maintained for many months after discontinuation. It raises the intriguing possibility that atomoxetine works through a neuro-adaption mechanism to produce a more permanent resetting of catecholaminergic function in the brain leading to remission in patients for substantial periods. In contrast, the efficacy produced by the stimulants or α_2-agonists is directly driven by the concentration of drug in plasma and brain: i.e., these drugs merely provide daily symptom relief that rapidly dissipates when treatment is discontinued.

Interestingly, despite all blunting reuptake of catecholamines, atomoxetine, methylphenidate and amphetamine have strikingly different effects on the performance of neurokinin-1 receptor (NK1R) knockout mice in 5-CSRT test. Whereas atomoxetine reduced their excessive expression of premature responses (an index of motor impulsivity), but not inattention or perseveration (Pillidge et al. 2014b), both d-amphetamine and methylphenidate reduced perseveration, but did not reduce inattention or premature responses (Yan et al. 2011; Pillidge et al. 2016; reviewed by Stanford 2022). These findings support the view that direct activation of α_2-adrenoceptors accounts for the beneficial effect of guanfacine on attention but suggest that activation of different adrenoceptor subtypes is needed to effect a reduction in

impulsivity and perseveration. The disparate responses to drugs with confirmed efficacy in treating ADHD further suggest that, although all these compounds increase noradrenergic transmission indirectly, they have different effects on each of the core diagnostic elements of ADHD, likely through activation of different combinations of catecholamine receptors.

Although the focus has been on cortical mechanisms, numerous studies have implicated abnormal reward processing in sub-cortical brain regions and dysregulated dopaminergic connectivity with the PFC (Teicher et al. 2000; Paloyelis et al. 2010; Costa Dias et al. 2013) in the psychopathology of ADHD. It is this secondary dopaminergic mechanism which pharmacologically differentiates the catecholaminergic stimulants from the NARIs and α_2-adrenergic agonists (see Figure 1).

The α_2-adrenoceptor agonists have also gained a role as adjunctive treatments in ADHD to augment the efficacy of stimulant drugs, particularly in situations when ADHD coexists with other conditions: e.g., oppositional-defiant disorder, autism and tics. Clonidine-XR and guanfacine-XR are both approved for use in ADHD as either monotherapy or as adjunctive therapy with stimulant medications (Clonidine-XR - US Product Label; Intuniv® - US Product Label). These drugs have been clinically evaluated in combination with methylphenidate- or amphetamine-based stimulants in which the combinations were shown to be significantly superior in reducing ADHD severity than treatment with stimulants alone (FDA Clonicel® Clinical Review, 2010; Wilens et al, 2012; McCracken et al, 2016).

The pharmacological mechanism responsible for the increased efficacy of the α_2-adrenergic agonists + stimulant combination has not been elucidated. Based on our knowledge of the pharmacology of these drugs, the former would be predicted to decrease the exocytotic release of catecholamines in the PFC (Gresch et al. 1995; Tanda et al. 1996; Devoto et al. 2003) and also the release of monoamines in many other regions, including dopamine in the striatum (Devoto et al. 2003; Sood et al, 2012). The result would be to increase α_2-adrenoceptor-mediated transmission in the PFC while simultaneously attenuating the effect of the stimulant on dopaminergic transmission in sub-cortical regions, such as the striatum. A supplementary therapeutic effect derived from activation of α_2-adrenoceptors in other areas modulating the function of the striato-thalamo-cortical pathway also cannot be discounted.

All of the drugs used to treat ADHD illustrated in Figure 1 are “clean” molecules with no potential to cause side-effects due to off-target interactions. Therefore, the pharmacology that delivers efficacy is the same as the one producing side-effects and adverse events. From a prescribing perspective, it means that the selection of drug dose in ADHD will often be a

balance between optimizing efficacy whilst maintaining an acceptable level of safety and tolerability.

Side-effects and adverse events resulting from activation of α_{2A}-adrenoceptor and other CNS and peripheral adrenergic receptor subtypes stated in the "Warnings and Precautions" sections of the Product Labels include sedation, hypotension and bradycardia, syncope, and rebound hypertension on discontinuation (Clonidine-XR - US Product Label; Intuniv® - US Product Label); all of which are α_{2A}-adrenoceptor-mediated CNS adverse events (MacMillan et al, 1998; Lähdesmäki et al. 2002, 2003). Their impact on patients can be mitigated by staged, dose-titration. In addition, tolerance to the sedative and cardiovascular effects of the α_{2A}-adrenergic agonists develops within a few weeks; hence, the warning about rebound hypertension.

The NARIs activate all adrenoceptor subtypes indirectly and have a spectrum of adverse events that differs from the α_{2A}-adrenergic agonists. They are non-sedative, but their use comes with the risk of hypertension and tachycardia, aggression and hostility, mania/hypomania, and they carry a Black Box Warning for inducing suicidal ideation (Strattera® - US Product Label; Qelbree® - US Product Label). In addition, atomoxetine carries a specific warning for causing sudden death and pre-existing structural cardiac abnormalities or other serious heart problems (Strattera® - US Product Label). With the exception of sudden death, these adverse events are consistent with the sympathomimetic effects of the NARIs.

The side-effect profiles of the stimulants reflect their sympathomimetic properties with Warnings and Precautions for hypertension, stroke and myocardial infarction in adults, and sudden death in children and adolescents (Concerta® [methylphenidate] - US Product Label; Adderall-XR® [mixed enantiomer-mixed salts amphetamine] - US Product Label; Vyvanse® [lisdexamfetamine] - US Product Label). It is their powerful dopaminergic effects that are associated with the emergence of psychotic or manic symptoms, seizures, and the Black Box Warning for drug dependence (Concerta® [methylphenidate] - US Product Label; Adderall-XR® [mixed enantiomer-mixed salts amphetamine] - US Product Label; Vyvanse® [lisdexamfetamine] - US Product Label).

In summary, central adrenoceptors have an important role in mediating the therapeutic effects of drugs used to treat ADHD. Agonism of central α_{2A}-adrenoceptors is, of itself, sufficient to ameliorate the severity of ADHD systems not only for the α_2-adrenergic agonists but also for the NARIs and stimulants. However, caution should be exercised when prescribing

these drugs because indirect or indirect activation of these receptors is also responsible for many of their CNS and cardiovascular side-effects.

Binge-eating Disorder

Binge-eating disorder (BED) is characterized by loss of control leading to frequent, compulsive episodes of excessive eating (binges). It is now recognized that, like ADHD, BED is an impulse-control disorder (Kessler et al. 2016; Reinblatt. 2015; Ural et al. 2017; Heal and Smith 2022; Heal and Gosden 2022). BED can be differentiated from bulimia nervosa (BN) or anorexia nervosa (AN) because individuals do not indulge in compensatory behavior such as purging, fasting or excessive exercising. BED is the commonest eating disorder with a lifetime prevalence rate in young individuals >1% versus 0.3% and ~1% for AN and BN, respectively (Hoek and van Hoeken 2003). Although BED is a predisposing factor for the development of obesity (Goldschmidt et al. 2011; Kessler et al. 2013; Micali et al. 2015), it is a psychiatric disorder, not a metabolic disease, and BED is unresponsive to treatment with appetite suppressants or anti-obesity drugs (Heal and Gosden 2022). The efficacy goal for drug treatment in BED is to enable the individual to regain self-control, reduce the impulsive, compulsive and perseverative drive to binge-eat, and to decrease the frequency and severity of binge-eating episodes.

The similarities between BED and ADHD extend to drug treatments where the only two pharmacological interventions to have demonstrated efficacy in pivotal, clinical trials are lisdexamfetamine and dasotraline (Heal and Gosden 2022). Both these drugs are effective in ADHD (Heal et al. 2022). In the USA and some other countries, lisdexamfetamine has been approved to treat BED as well as ADHD. After showing efficacy in phase 3 trials in BED and ADHD, development of dasotraline was discontinued in both indications after the Food and Drug Administration declined to approve it without additional clinical studies to support its safety for human use (Sunovion Press Release 2020).

Allowing female rats repeated, intermittent, limited access to palatable food over a period of weeks induces a binge-eating phenotype that mimics many of the core psychopathological symptoms of BED (Vickers et al. 2015; 2017; Heal et al. 2016, 2017; Heal et al. 2022). The clinically effective drugs, lisdexamfetamine and dasotraline, reduce binge-eating in these rats (Vickers et al. 2015; Heal et al. 2018, Heal and Smith 2022). In addition, lisdexamfetamine has been shown to decrease their compulsive, perseverative and impulsive responding to the presentation of palatable foods (Heal et al. 2016, Vickers et al. 2017). In translationally valid rat models of BED, single-unit, electrophysiological activity

recorded in the locus coeruleus showed no differences in spontaneous or tonic activity compared with normal chow-fed controls, but significantly reduced locus coeruleus discharge rates in response to sciatic nerve stimulation (Bello et al. 2019).

In a previous study, Bello et al. (2014) observed that binge-eating rats showed greater neuronal activation in the medial PFC (mPFC) and paraventricular nucleus (PVN) in response to immobilization stress than chow-fed controls. Both studies suggest that the binge-eating phenotype is associated with dysregulation of noradrenergic neurotransmission in the CNS.

Experiments with selective antagonists revealed the reduction of binge-eating produced by lisdexamfetamine was partially reversed by prazosin (α_1-adrenoceptor antagonist) and SCH23390 (a D_1 dopamine receptor antagonist) but was unaffected by RX821002 (α_2-adrenoceptor antagonist) or raclopride (a D_2 dopamine receptor antagonist) (Vickers et al. 2015). Consistent with the non-involvement of α_2-adrenoceptors as efficacy mediators, prolonged administration of guanfacine not only failed to decrease palatable food consumption by binge-eating rats, but it significantly increased it (Bello et al. 2014). The latter effect may be explained by the observation that activation of α_2-adrenoceptors in the PVN stimulates food intake (Wellman, 2000).

Ascending fibres from the locus coeruleus innervate the neocortex and thalamus, and dysregulation of the striato-thalamo-cortical pathway regulating cognitive control and reward processing is implicated in both BED and ADHD (see Heal and Smith 2022; Heal et al. 2022). We have reported that the density of D_1 dopamine receptors was substantially decreased, and μ-opioid receptors increased, in the striata of binge-eating rats (Heal et al. 2017). There were no changes D_1- or μ-opioid receptors in the PFC, or D_1 dopamine receptors nucleus accumbens or D_2 dopamine receptors in PFC and striatum (Heal et al. 2017). Unfortunately, we could find no published investigations on noradrenergic function or adrenoceptors in the brains of binge-eating rats.

When the totality of non-clinical evidence is considered, it points to BED being linked to a deficit in cognitive control at the PFC level resulting from reduced α_1-adrenergic and D_1 dopamine receptor-mediated neurotransmission. At the sub-cortical level, reward processing deficits due to D_1 and μ-opioid receptors are likely to be an important secondary driver of BED psychopathology.

A number of brain imaging studies have been performed in individuals with BED. Although there are subtle differences between the findings, there is a broad consensus that PFC executive function is significantly attenuated in BED and it exerts diminished control

over reward processing at the striatal level which, in turn, is abnormally under-functional (Balodis et al. 2013; Stopyra et al. 2019; Fleck et al. 2019; see reviews by Steward et al. 2018; Heal and Smith 2022). Balodis et al. (2013) conducted fMRI scans on groups of subjects who were performing a monetary reward/loss task. Subject cohorts were BED/obese individuals, obese individuals without BED, and lean controls. Compared with BMI-matched controls, the BED/obese group exhibited a generalized pattern of diminished fronto-striatal processing of both rewards and losses revealing a psychopathology specific to BED that is unrelated to the metabolic condition of obesity.

It is important to emphasize that abnormal brain functioning in BED is not only not linked to obesity, but is also different from the psychopathology of BN, which is another binge-related eating disorder. Stopyra et al. (2019) conducted resting-state fMRI experiments to compare functional connectivity in the default mode network (DMN), salience network (SN), and executive network (EN) in groups of subjects with BED, BN and normal-weight controls. Compared with normal-weight controls, the eating disorder groups showed aberrant functional connectivity in the dorsal anterior cingulate cortex (dACC) within the SN, as well as in the mPFC within the DMN. Within each of these networks, the aberrant functional connectivity differed between the BED and BN groups. The BN group also exhibited stronger synchronous dACC-retrosplenial cortex activity than the BED group.

Having identified the deficits in cognitive control and reward processing in the striato-thalamo-cortical network in individuals with BED, Fleck et al. (2019) took the next logical step to investigate whether lisdexamfetamine alleviated these abnormalities. BED/obese women were treated with lisdexamfetamine for 12 weeks; the obese control group received no pharmacological intervention. fMRI scans focusing on the ventral PFC (vPFC) and striatum were taken at baseline and at the end of treatment. At baseline, the BED/obese women with moderate/severe BED symptoms showed greater activation of vPFC and globus pallidus than the obese controls when presented with pictures of palatable food.

Lisdexamfetamine, which produced remission from BED in 87% of the subjects, significantly reduced these exaggerated responses. Treatment-associated decreases in binge-eating scores correlated with reductions in vPFC activity, while decreases in obsessive-compulsive symptoms correlated with reductions in thalamus activation. The effect-sizes of lisdexamfetamine in different brain regions suggest it exerts a greater influence on cortical control than in sub-cortical regions. The findings indicate that exaggerated vPFC-subcortical brain response to palatable foods may be a causal factor in BED and this abnormality is at least partially prevented by lisdexamfetamine treatment.

The non-clinical and clinical evidence consistently supports the hypothesis that BED is due to deficits of α_1-adrenergic and D_1 signaling in PFC and hypoactive dopaminergic neurotransmission in the striatum. A comprehensive re-evaluation of the results from drug trials in BED revealed the catecholamine reuptake inhibitors and releasing agents are the only pharmacological classes with clinically proven efficacy in BED; drugs acting on other neurotransmitters were ineffective or showed equivocal efficacy (Heal and Gosden 2022).

To date, the pharmacology of efficacious drugs to treat BED and ADHD is highly specific and almost identical. Lisdexamfetamine (a norepinephrine + dopamine releasing agent) and dasotraline (norepinephrine + dopamine reuptake inhibitor) have been clinically proven to be effective treatments for BED and ADHD (see reviews by Heal and Smith 2022; Heal et al. 2022) but what about other ADHD drugs? The non-clinical evidence predicts that the α_2-adrenoceptor agonists will not be effective BED treatments, but it should be emphasized there are no clinical data to support that prediction. NARIs would increase α_1-adrenergic and D_1 receptor-mediated signaling in the PFC but would not alleviate diminished dopamine signaling in sub-cortical regions: e.g., the striatum.

Atomoxetine was investigated in a small, double-blind, placebo-controlled trial in subjects with moderate/severe BED (McElroy et al. 2007). The results were confounded by high drop-out rates in both arms (Atomoxetine = 30%; Placebo = 45%) and a very high placebo response rate. With this *caveat*, the results suggested that atomoxetine reduced binge-eating frequency and severity and decreased YBOCS-BE scores. Reboxetine has been investigated in a small open-trial in BED where it showed substantial efficacy (Silveira et al. 2005); however, given the high rate of placebo responding in BED trials, this result carries little weight. Solriamfetol (Sunosi®) is a weak micromolar potency dopamine and norepinephrine reuptake inhibitor (IC_{50}s: Dopamine = 2.9 µM; Norepinephrine = 4.4 µM) (Baladi et al. 2018) that is approved to treat excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (Sunosi® - US Product Label). A clinical trial of solriamfetol in BED was planned (Guerdjikova et al. 2021) but at this time no results are available. The preliminary evidence suggests that NARIs might be effective treatments in BED. What also emerges is the efficacy of NARIs appears to be substantially lower than lisdexamfetamine or dasotraline indicating the secondary dopaminergic actions of the latter drugs are an important contributor to efficacy.

In summary, adrenoceptors have an important role in the therapeutic actions of drugs used to treat BED. Although catecholaminergic stimulants are effective in both BED and ADHD, in the former, it is the α_1-adrenoceptor rather than the α_2-adrenoceptor that is the

mediator of efficacy. Increasing dopaminergic neurotransmission in the PFC is almost certainly therapeutically essential. The ability of drugs to alleviate deficits in striatal dopaminergic neurotransmission appears to be more important in BED than ADHD.

Opiate/opioid withdrawal and detoxification

It is an established fact that tolerance rapidly develops to the pharmacological effects of opiates (naturally occurring compounds derived from opium) and opioids (synthetic opioid agonists). Attempts to maintain the pharmacological effects of μ-opioid receptor agonists can lead to dose-escalation by patients when prescribed as analgesics, and by abusers when self-administering these drugs to experience their euphoriant "highs". In both situations, the result is the establishment of opiate/opioid dependence and terminating μ-opioid agonists produces a withdrawal syndrome involving craving and physical signs including restlessness, aching, cramps, fever, hyperventilation, hypertension, seizures and even hallucinations. The physical withdrawal symptoms last for 5 to 7 days and peak around the second or third day of abstinence. The psychological effects of withdrawal such as anhedonia, anxiety and drug craving, can persist for many weeks or months after quitting opiate/opioid abuse.

Experiments in animals and humans have demonstrated that many of these withdrawal symptoms are mediated by hyperactivity of sympathetic drive in the peripheral and central nervous systems (Chang and Dixon 1990; Delle et al. 1990; Milanés et al. 2001; Hoffman et al. 1998; McDonald et al. 1999). α_2-Adrenoceptors are located presynaptically on sympathetic neurons where they regulate neurotransmitter release, and postsynaptically in the CNS where they play an important role in emotional and cognitive function and central regulation of blood pressure and heart-rate.

Although clonidine and dexmedetomidine have been used off-label to alleviate the severity of withdrawal symptoms, or as an adjunct to opioid antagonist detoxification (Spencer and Gregory, 1989; Cuthill et al. 1990; Senft 1991; Upadhyay et al. 2011; Nasr et al. 2011), lofexidine has shown greater therapeutic potential because of its reduced propensity to cause cardiovascular side-effects (Kahn et al. 1997; Lin et al. 1997; Carnwath and Hardman 1998; Gerra et al. 2001). In the UK, lofexidine was approved to treat opiate/opioid withdrawal in 1992, but it is no longer marketed in this territory. In the USA, a collaborative development program between US WorldMeds and the National Institute of Drug Abuse (NIDA) led to the approval of lofexidine to mitigate opioid withdrawal symptoms and facilitate abrupt opioid discontinuation in adults (Lucemyra® - US Product Label).

This partnership investigated the efficacy and safety of lofexidine in treating opiate/opioid withdrawal in three multi-site, pivotal, clinical trials (Yu et al. 2008; Gorodetzky et al. 2017; Fishman et al. 2019). The initial trial to study the efficacy and safety of lofexidine on withdrawal symptoms in 68 heavy opiate/opioid abusers was relatively small (Yu et al. 2008). It was followed by two very large trials using the same inclusion/exclusion criteria; the second involving 264 subjects (Gorodetzky et al, 2017) and the third in 603 subjects (Fishman et al. 2019) which evaluated lofexidine at two different doses. Lofexidine met its primary efficacy endpoint in all of these trials and the results consistently demonstrated that lofexidine markedly reduced the withdrawal symptoms at their peak and accelerated their disappearance.

Opiate/opioid withdrawal is an exceptionally unpleasant physical and psychological experience and the very high discontinuation rates are testament to this fact; drop-out rates ranged between 72-83% in the placebo groups and 59-65% in the lofexidine groups (Yu et al. 2008; Gorodetzky et al. 2017; Fishman et al. 2019). When there are high drop-out rates, the intention to treat/last observation carried forward (LOCF-ITT) analysis can be misleading and discontinuation for lack of efficacy can provide a more realistic perspective on the efficacy of the intervention. Discontinuations for lack of efficacy in the lofexidine and placebo arms were 15% and 30%, respectively (Yu et al. 2008) and 22%, 33% for the two lofexidine dose groups and 49% for placebo (Fishman et al. 2019).

Overall, lofexidine effectively reduces the severity of opiate/opioid withdrawal symptoms in a significant proportion of opiate/opioid dependent individuals and is a useful aid to detoxification. The findings also reveal that, despite successfully undergoing detoxification, many individuals relapse to opiate/opioid abuse; this high rate of relapse highlights the negative effect of psychological dependence, which usually persists for months after the physical symptoms of opiate/opioid dependence have resolved.

Lofexidine has also been evaluated as an adjunct to naltrexone therapy to maintain abstinence in a 12-week, placebo-controlled trial in 69 detoxified previously opiate/opioid dependent subjects (Hermes et al. 2019). Although lofexidine did not meet the co-primary efficacy endpoints of increasing the number of naltrexone treatment-compliant days, opioid craving, or days of opiate/opioid use, the sub-group of lofexidine/naltrexone subjects who completed the trial reported greater naltrexone compliance, and a lower number of positive urine tests than the placebo/naltrexone group. Drop-out rates were ~40% in both groups.

When assessing the efficacy of lofexidine as an aid to detoxification or as an adjunct to abstinence therapy, it is important to appreciate not only the grip of opiate/opioid dependence, but also the challenges of other comorbid psychiatric disorders. Using the subjects from the trial by Hermes et al. (2019) as an example, at the time of entry into the trial 15% were suffering anxiety, 2% had PTSD, 20% were cannabis dependent and 7% alcohol dependent; therefore, any positive outcome in such challenging treatment population should be regarded as a major success.

The adverse cardiovascular (increased blood pressure and heart-rate) and physical effects of opiate/opioid withdrawal result from central and peripheral sympathetic hyperactivity. The attenuation of these effects by the α_2-adrenoceptor agonists is most probably mediated by activation of the α_{2A}-adrenoceptor subtype (MacMillan et al. 1998; Lähdesmäki et al. 2002; 2003). The most common adverse effects of lofexidine and clonidine reported in these trials were tiredness/fatigue, lightheadedness/dizziness and decreased blood pressure and heart-rate; these side-effects are also mediated by α_{2A}-adrenoceptor agonism (MacMillan et al. 1998; Lähdesmäki et al. 2002; 2003). Therefore, the efficacy and adverse effects of the α_2-adrenoceptor agonists are predominantly mediated by the same pharmacological mechanism.

Lofexidine is a potent agonist of the α_{2A}- and α_{2C}-adrenoceptor subtypes whereas clonidine is a moderately potent agonist at all three α_2-adrenoceptor subtypes (Table 4). Experiments in mice showed that the ability of clonidine and dexmedetomidine to attenuate naloxone-precipitated morphine withdrawal was absent in the α_{2A}-adrenoceptor knock-out genotype (Özdoğan et al. 2004). Other research has revealed that α_{2C}-adrenoceptor agonism has no effect on blood pressure or heart-rate (Link et al. 1995), and co-agonism of α_{2A}- and α_{2C}-subtypes produced greater inhibition of CNS monoamine turnover than selective α_{2A}-adrenoceptor activation (Bücheler et al. 2002). Activation of α_{2B}-adrenoceptors increases blood pressure, which partly counteracts the hypotensive effect of α_{2A}-adrenoceptor agonism (Link et al 1995). These results are, therefore, difficult to reconcile with the clinical observation that clonidine produced more cardiovascular adverse events than lofexidine. One possible explanation is potent α_{2A}/α_{2C}-adrenoceptor co-agonism by lofexidine leads to profound inhibition of peripheral and central sympathetic drive before its postsynaptic α_{2A}-adrenoceptor-mediated central hypotensive and bradycardic effects reach a problematic level.

In summary, sympathetic hyperactivity is an important driver of opiate/opioid withdrawal symptoms, which can be substantially reduced by administration of α_2-adrenoceptor agonists. In this pharmacological class, lofexidine has the best therapeutic profile. Experimental evidence indicates that its efficacy in mitigating withdrawal symptoms is probably mediated by α_{2A}/α_{2C}-adrenoceptor co-agonism, while its side-effects predominantly result from α_{2A}-adrenoceptor agonism.

Concluding remarks

Given that the acceptance of norepinephrine as a neurotransmitter in the CNS was still a subject of debate until the 1960s, there has been dramatic transition over the last 60 years, not only to ascribing a role for this catecholamine in the neurobiology of many psychiatric disorders, but also in the therapeutic actions of drugs used in their treatment.

Adrenoceptors are the molecular effectors of norepinephrine signaling with specific adrenoceptor subtypes in the central and peripheral nervous systems responsible for a wide spectrum of behavioral, emotional, cognitive, and physiological functions. We now know that the most, or all, drugs used in psychiatry interact with adrenoceptors to some extent. Direct or indirect activators of specific adrenoceptor subtypes have been exploited as therapeutic strategies to treat disorders such as depression, ADHD, BED and opiate/opioid withdrawal. The interaction of drugs with various adrenoceptor subtypes is also a probable contributor to enhancing their therapeutic efficacy and mitigating side-effects in other disorders:, e.g., schizophrenia and anxiety. However, drug/adrenoceptor interactions are not always beneficial; they are unequivocally implicated as mediators of the cardiovascular and CNS side-effects of drugs used in psychiatry and they limit the clinically tolerated doses of others: e.g., α_2-adrenoceptor agonists.

The substantial progress that has been achieved in basic and clinical research on central adrenoceptors has addressed many of these problems. However, the task is not complete and there are still unanswered questions that need to be resolved before it will be feasible to explain how changes in the function of any adrenoceptor subtype affects mood and behavior in humans and other animals.

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