Enhancing central noradrenergic function in depression: is there still a place for a new antidepressant?

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Abstract: Noradrenaline has long played a key role in the way the etiology of depression is conceptualized and in the mechanism of action of many current antidepressants. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), selective noradrenaline reuptake inhibitors (NRIs), the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, and many atypicals, like mianserin and bupropion, influence, at least in part, central noradrenergic function. Enhancement of noradrenergic function may be particularly helpful in patients with melancholia. However, while noradrenaline will continue to be a target for research into the etiology and treatment of depression, it is unlikely that antidepressants acting solely on noradrenaline will be pursued.

Keywords: alpha2-adrenoceptors, antidepressants, depression, noradrenaline, reuptake

Introduction

The notion that noradrenaline plays a key role in the etiology of depression and in the mechanism of action of antidepressants dates from the earliest days of the psychopharmacology era, and formed the basis for the catecholamine hypothesis of affective disorders (Schildkraut 1965). It was based on clinical observations that drugs that depleted noradrenaline and other brain monoamines lowered mood, while agents that enhanced the availability of brain monoamines improved mood and reversed the symptoms of depression. The original catecholamine hypothesis was soon modified to include a complementary role for serotonin as it was realized that traditional antidepressants, such as the tricyclics (TCAs) and the monoamine oxidase inhibitors (MAOIs), increased the levels of both noradrenaline and serotonin in the brain by blocking their reuptake or metabolic degradation, respectively (Coppen 1967). There are currently a large number of effective antidepressants of various classes, diverse structures, and different mechanisms of action available for clinical use (Table 1). Many of the original TCAs of the first generation were aselective in neurochemical action in that they inhibited reuptake of both monoamines, although desipramine, nortriptyline, and protriptyline were selective for noradrenaline, and clomipramine was somewhat selective for serotonin. For many years, maprotiline and viloxazine represented the last selective inhibitors of noradrenaline reuptake in an era that was dominated by research on the role of serotonin in depression and the development of selective serotonin reuptake inhibitors (SSRIs) as antidepressants (Pinder et al 1977a, 1977b). Although noradrenaline still had its place in the mechanism of action of the α_2-adrenoceptor antagonist mianserin, many of the other

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Table 1 Currently available antidepressants[a]

Group	Drug	Group	Drug
TCAs	Amitriptyline	MAOIs	Iproniazid
	Amoxapine		Isocarboxazid
	Butriptyline		Moclobemide[b]
	Clomipramine		Phenelzine
	Desipramine		Tranylcypromine
	Dibenzepin		
	Dimetacrin	SSRIs	Citalopram
	Dothiepin		Escitalopram
	Doxepin		Fluoxetine
	Imipramine		Fluvoxamine
	Iprindole		Paroxetine
	Lofepramine		Sertraline
	Maprotiline		
	Melitracen	NaSSA	Mirtazapine
	Nortriptyline		
	Opipramol	NRIs	Reboxetine
	Protriptyline		Viloxazine
	Trimipramine		
SNRIs	Duloxetine	Atypicals	Bupropion[c]
	Milnacipran		Mianserin
	Venlafaxine		Nefazodone
			Trazodone

[a] Many of these drugs are either not available in the USA or are approved for indications other than depression.
[b] Moclobemide is the only marketed example of a reversible inhibitor of the A-form of MAO (RIMA).
[c] Not currently available in Europe as antidepressants.
Abbreviations: TCAs, tricyclic antidepressants; SNRIs, serotonin-noradrenaline reuptake inhibitors; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin noradrenaline reuptake inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressant; NRIs, selective noradrenaline reuptake inhibitors.

early second generation antidepressants such as trazodone, nefazodone, and the various SSRIs were based upon serotonergic mechanisms (Pinder and Wieringa 1993). While second generation antidepressants like the SSRIs have enjoyed wide popularity due to their more selective pharmacology and consequent improved tolerability and lesser toxicity than their first generation counterparts, there have been lingering doubts about their efficacy and onset of action, particularly in the more severely depressed and melancholic patients (Anderson 2000). The introduction of newer second generation antidepressants, like the serotonin noradrenaline reuptake inhibitors (SNRIs), exemplified by venlafaxine, and the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, has demonstrated that it is possible to regain the dual pharmacological action and accompanying efficacy of the TCAs, while retaining the greater tolerability and lesser toxicity of the SSRIs (Nierenberg 2001; Smith et al 2002).

Enhancing central noradrenergic function in depression

Noradrenaline as a specific target for treating depression, as opposed to being part of a multiple target approach, has become more fashionable in recent years with the development of the selective noradrenaline reuptake inhibitors (NRIs), eg reboxetine (Brunello et al 2002). In the clinical setting, selective NRIs may be advantageous in terms of short- and long-term efficacy in both moderate and severe depression, while acting to improve energy, interest, and motivation in depressed patients. However, like earlier tricyclic examples of the genre, such as desipramine, nortriptyline, maprotiline, and lofepramine (Table 1), and unlike the dual-action SNRIs and mirtazapine, the efficacy of reboxetine is not superior to that of SSRIs (Brunello et al 2002). Reboxetine is not yet approved in the USA as a result of a series of failed clinical trials in which neither it nor the active reference antidepressant were shown to be statistically significantly different in efficacy from placebo. A similar fate befell an earlier NRI, the tetracyclic Org 4428 (Pinder and Wieringa 1993; Niklson et al 1997). Such failures have prompted proposals to improve the ways in which clinical trials are performed to evaluate the efficacy and onset of action of new antidepressants (Katz et al 2002; Montgomery et al 2002). Reboxetine is an example of the designer's approach to new antidepressants; it has a structure not dissimilar to that of the older non-tricyclic NRI viloxazine, without the structural features that are associated with classical TCA-like side effects (Pinder 1997, 2001). It may represent the last in a long line of NRIs for depression (Pinder and Wieringa 1993), since there do not appear to be any more of its ilk in clinical development at this time (Andrews and Pinder 2001). Atomoxetine, like reboxetine, is a highly selective NRI that was previously in development as tomoxetine for depression (Pinder and Wieringa 1993), and has been reincarnated as a treatment for attention deficit hyperactivity disorder (ADHD) (Allen and Michelson 2002).

In addition to inhibiting the reuptake of noradrenaline, there are other ways to enhance its synaptic availability. The most notable is by blocking the α_2-noradrenergic receptors located at the cell body, which control cell firing, or those at the synaptic terminal, which act as autoreceptors to regulate release. Two currently available antidepressants, mianserin and mirtazapine, do this as part of multiple pharmacological actions. The more potent α_2-adrenoceptor

Table 2 α_2-adrenoceptor antagonists as antidepressants

Compound	Status	Neurotransmitter affected
α_2-antagonists with multiple pharmacology		
Mianserin	Marketed	NA
Mirtazapine	Marketed	NA/5-HT
Setiptiline	Marketed in Japan	NA
Selective α_2-antagonists		
Idazoxan	Stopped	NA
Fluparoxan	Stopped	NA
Selective α_2-antagonists with additional antidepressant-like pharmacology		
Napitane	Stopped	NA
A 80426	Stopped	NA/5-HT
Napamezole	Stopped	NA/5-HT/DA
Sunepitron	Stopped	NA/5-HT

Abbreviations: NA, noradrenaline; 5-HT, serotonin; DA, dopamine.

antagonist idazoxan acts more selectively, but it has not been convincingly shown to be antidepressant (Nutt and Pinder 1996). Of these three agents, only mirtazapine additionally enhances central serotonergic function via stimulation of facilitatory α_1-adrenoceptors located on the cell bodies of raphe neurons and blockade of α_2-heteroreceptors located on serotonergic nerve terminals, thereby endowing it with the familiar dual action upon both neurotransmitters (De Boer et al 1996). As with NRIs the development of new selective α_2-adrenoceptor antagonists for depression has effectively stopped (Table 2). There is still some interest in mimicking the dual action of mirtazapine by combining α_2-antagonism with other antidepressant-like pharmacology in the same molecule, eg 5-HT_{1A}-agonism (sunepitron), and with SSRI (A 80426) or NRI (napitane) properties. Another putative antidepressant, napamezole, combines α_2-antagonism with inhibition of the reuptake of three monoamines – noradrenaline, serotonin, and dopamine. Inconclusive efficacy data have been reported for many of these compounds, and none of them seem to be in active clinical development (Nutt and Pinder 1996; Andrews and Pinder 2001).

The future for noradrenergic antidepressants

Is there a role for a pure noradrenergic drug in the treatment of depression (Montgomery 1997)? This question is particularly pertinent in an era when dual-action antidepressants affecting both noradrenergic and serotonergic systems, including the newly approved SNRI duloxetine, have demonstrated faster and more substantial effects than SSRIs on response and remission. Moreover, research on new antidepressants has largely moved away from monoamines and their receptors to focus on neurokinins, excitatory amino acids, neuronal plasticity, gene transcription factors, and the hypothalamic-pituitary-adrenal (HPA) axis (Skolnick 1997; Andrews and Pinder 2001; Pinder 2001). Furthermore, there is some evidence that combining noradrenergic agents like desipramine or mianserin with an SSRI to make a two-component dual-action treatment actually improves response (see Andrews and Pinder 2001). Nevertheless, the single-action SSRIs as a group are still very widely used, while the latest antidepressant introductions include not only duloxetine but also the SSRI escitalopram (Table 1).

There is substantial preclinical and clinical evidence that noradrenaline plays a key role in the etiology of depressive disorders (Nutt and Pinder 1996; Leonard 1997; Brunello et al 2002). Perhaps the most compelling arguments come from depletion studies in recently remitted depressed patients. Those patients who responded to, and continued to take, NRIs were more vulnerable to transient reversal of their response when given the catecholamine depleter α-methyl-para-tyrosine (AMPT). Responders to SSRIs were more vulnerable to tryptophan depletion, which reduces brain serotonin (Delgado et al 1997). The implication that there may be distinct roles for noradrenaline and serotonin in depression is not, however, entirely borne out by later observations from the same research group. Responders to the dual-action NaSSA mirtazapine were as likely to experience transient deterioration in mood when receiving either alpha-methyl-para-tyrosine (AMPT) or undergoing tryptophan depletion (Delgado et al 2002). Furthermore, the roles of the central noradrenergic and serotonergic systems may be inextricably linked in the etiology of depression, and in the mechanism of action of antidepressants both in the hippocampus (Mongeau et al 1997) and frontal cortex (Millan et al 2000). Even reboxetine seems to have an effect upon serotonergic neurotransmission in rat hippocampus, activating postsynaptic 5-HT_{1A} receptors by a desensitization of α_2-adrenergic heteroreceptors resulting from sustained inhibition of noradrenaline reuptake (Szabo and Blier 2001).

Opportunities do exist to design more specific agents to affect noradrenergic function in depression (Nutt and Pinder

1996; Potter and Schmidt 2000). Thus, the fine molecular structure of the noradrenaline transporter, which mediates reuptake of the neurotransmitter, has long been characterized as belonging to a large family of membrane proteins all having 12 hydrophobic membrane spanning domains with the amino terminal and the carboxyl terminal ends of the polypeptide located intracellularly (Amara and Kuhar 1993). The transcriptional gene for the noradrenaline transporter has also been identified (Porzgen et al 1995), and human polymorphisms are known (Zill et al 2002). Studies on chimeric dopamine-noradrenaline transporters have demonstrated that the binding domains for the tricyclic NRIs nortriptyline and desipramine are located in a different region from those for the neurotransmitter substrates (Giros et al 1994). It may well be possible to design more regioselective inhibitors of noradrenaline reuptake than have presently been evaluated as antidepressants, and it is interesting that contrary to expectations and previous experience with most psychotropic drugs, compounds lacking nitrogen in their structure are capable of inhibiting the noradrenaline transporter (Madras et al 1996).

α_2-adrenoceptors have also been cloned and characterized (Bylund et al 1994). Three human genes located on chromosomes 10, 2, and 4 encode unique α_2-adrenoceptor subtypes, which are characterized pharmacologically as α_{2A}, α_{2B}, and α_{2C}, respectively. The α_{2D}-subtype, found in the rat and other animal species but not in humans, seems to be a species variant of the human α_{2A}-adrenoceptor. It is likely that noradrenergic neurons express predominantly the same gene across all mammalian species, the $\alpha_{2A/D}$-ortholog, to control transmitter release through presynaptic autoreceptors. The α_{2A}-adrenoceptor is also the predominant subtype present in human blood platelet and cortex (see Nutt and Pinder 1996). Neither the tetracyclic antidepressants mianserin, setiptiline, and mirtazapine, nor the more potent but putative antidepressants idazoxan and fluparoxan are selective for any of the α_2-adrenoceptor subtypes, so it is entirely possible that highly selective agents could be developed (Nutt and Pinder 1996; Potter and Schmidt 2000).

Little research effort has gone into evaluating post-synaptic noradrenergic agonists as antidepressants, unlike the extensive investigations into postsynaptic 5-HT_{1A}-agonists. Two decades ago, the β_2-adrenoceptor agonist salbutamol and its more lipophilic cousin clenbuterol, which are used as bronchodilators in the treatment of asthma, enjoyed a brief vogue as putative antidepressants both in their own right and as adjuncts to TCAs: both were found wanting in efficacy and peripheral side effects (Potter and Schmidt 2000). In more recent times, modafinil, an α_1-agonist and central stimulant indicated for the treatment of narcolepsy, has become popular as an augmentation agent when standard antidepressants give an insufficient therapeutic response.

As a final note, the opportunities for finding new NRIs and ligands for the various types of noradrenergic receptors have been considerably enhanced by the modern pharmaceutical technologies of combinatorial chemistry and high-throughput screening (Pinder 2001). While such methods are potentially inhibitory to true innovation, in the sense that the biological assays are simple and usually based on known and proven technology, they are ideal for this type of opportunity. Many very large and diverse chemical libraries exist which could be screened in assays for the noradrenaline transporter and the different types of noradrenergic receptor. Any desired combination of such properties is also possible.

Conclusions

There is no doubt that some effective antidepressants act principally through central noradrenergic mechanisms, and that noradrenaline plays an important role in the etiology of depressive disorders. Antidepressants with a noradrenergic component to their pharmacology may produce superior efficacy in severely depressed patients and those with melancholia, but there is no evidence that selective NRIs are any better than SSRIs except possibly in the arena of energy, interest, and motivation. Rather, it is the older dual-action TCAs and their modern counterparts the SNRIs and mirtazapine, which seem to have set the current standard in faster onset of action and greater degrees of response and remission.

Despite the recent flurry of interest in reboxetine, and the undoubted opportunities that exist for designing new NRIs and novel agents to affect noradrenergic receptors, there are no new antidepressants on the horizon that act principally through noradrenaline. There remains a stronger interest in serotonin and its receptors than in noradrenaline. Real innovation in antidepressant research is focusing on other, non-monoamine approaches, including neurokinins, excitatory amino acids, neuronal plasticity, gene transcription factors, and the HPA axis. Whether it leads to true third generation antidepressants, which will extend our ability to treat depression more quickly in a greater proportion of patients with improved rates of response and remission, is still to be seen. Early indications are that the

first neurokinin antagonists are no faster or better than SSRIs in efficacy, and may not be developed further, but that glucocorticoid antagonists may be superior in psychotic depression, melancholia, and in those patients with disturbed cortisol. There is certainly a place in the armamentarium for new antidepressants, but it is unlikely that they will be agents that only enhance central noradrenergic function.

Declaration of Interest

At the time of writing Dr Pinder was a full-time employee of Organon International.

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