Antidepressants and brain monoaminergic systems: a dimensional approach to understanding their behavioural effects in depression and anxiety disorders

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Abstract

There is extensive comorbidity between depression and anxiety disorders. Dimensional psychiatric and psychometric approaches have suggested that dysregulation of a limited number of behavioural dimensions that cut across diagnostic categories can account for both the shared and unique symptoms of depression and anxiety disorders. Such an approach recognizes that anxiety, the emotional response to stress, is a key element of depression as well as the defining feature of anxiety disorders, and many antidepressants appear to be effective in the treatment of anxiety disorders as well as depression. Therefore, the pharmacological actions of these drugs must account for their efficacy in both. Brain noradrenergic and serotonergic systems, and perhaps to a more limited extent the dopaminergic system, regulate or modulate many of the same behavioural dimensions (e.g. negative or positive affect) that are affected in depression and anxiety disorders, and that are ameliorated by drug treatment. Whereas much recent research has focused on the regulatory effects of antidepressants on synaptic function and cellular proteins, less emphasis has been placed on monoaminergic regulation at a more global systemic level, or how such systemic alterations in monoaminergic function might alleviate the behavioural, cognitive, emotional and physiological manifestations of depression and anxiety disorders. In this review, we discuss how chronic antidepressant treatment might regulate the tonic activity and/or phasic reactivity of brain monoaminergic systems to account for their ability to effectively modify the behavioural dimensions underlying improvement in both depression and anxiety disorders.

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Introduction

Early studies of the acute pharmacological actions of antidepressant drugs (ADs) revealed potent effects on central noradrenergic and serotonergic systems and, for monoamine oxidase inhibitors (MAOIs), dopaminergic systems as well. At the same time, preclinical research began to reveal important behavioural roles for these biogenic amine systems. The integration of such research led to the ideas that (1) antidepressants act by enhancing central biogenic amine function, and (2) reduced functioning of central noradrenergic and/or serotonergic systems may contribute to the development of Major Depressive Disorder (MDD) (Coppen, 1967; Prange, 1964; Schildkraut, 1965). Many effective antidepressants have been developed, almost all of which are known to potently affect central noradrenergic and/or serotonergic neurons (Frazer, 2001). In addition to the early generation of MAOIs and tricyclic antidepressants (TCAs), other classes of antidepressants include selective serotonin (5-HT) reuptake inhibitors (SSRIs), selective norepinephrine (NE) reuptake inhibitors (NRIs), dual serotonin/norepinephrine reuptake inhibitors (SNRIs), and other drugs with a different pharmacology, such as mirtazapine. Although there is no conclusive evidence that any of these drugs are better substantially than any other from the perspective of antidepressant efficacy,
the improved tolerability and toxicity of the newer antidepressants encouraged the evaluation of their efficacy in psychiatric disorders other than depression (Schatzberg, 2000), most notably in anxiety disorders. In addition, the recognition that a degree of neurobiological commonality may exist between depressive and anxiety disorders, implied by their high degree of comorbidity (Mineka et al., 1998; Nemeroff, 2002; Rouillon, 1999; Zimmerman et al., 2002), has stimulated further the evaluation of the efficacy of ADs in anxiety disorders. Indeed, the comorbidity and symptomatic overlap between depressive and anxiety disorders, along with the anxiolytic efficacy of antidepressants, raises the central questions to be addressed in this review: Are there behavioural dimensions that are dysregulated in common in depressive and anxiety disorders, accounting for the high degree of comorbidity and overlapping symptomatology, as well as the similar efficacy achieved by ADs in both? Can we relate the behavioural dimensions regulated by brain monoamines to the behavioural and therapeutic effects of ADs in these disorders?

Clinical efficacy of antidepressants

MDD

Given the typically accepted definition of ‘response’ as at least a 50% reduction in the severity of depression, TCAs produce response in about two-thirds of patients (Klerman and Cole, 1965). TCAs that block the reuptake of both NE and 5-HT have equivalent efficacy to those that block NE reuptake selectively. In randomized clinical trials (RCTs) carried out since 1980, approx. 50–60% of patients studied were ‘responders’, significantly higher than the 30–35% who responded to placebo (Janicak et al., 1997). Further, reviews and meta-analyses of the effectiveness of SSRIs and other drugs such as venlafaxine, mirtazapine, bupropion, nefazodone and reboxetine have generally found the newer drugs to have equivalent efficacy to the older TCAs (Mace and Taylor, 2000; Nelson, 1999; Olver et al., 2001; Williams et al., 2000). Based on this definition, then, there is no evidence to suggest that one class of antidepressant, let alone any specific drug, has superior efficacy to any other class, even in more severe depression (Sonawalla and Fava, 2001).

Emphasis has shifted recently from the above criterion for clinical response to a higher threshold, often referred to as ‘remission’, defined as a minimal level of symptomatology on a standardized rating scale that is considered within the range of normal functioning. It is as yet unclear if drug classes or specific drugs may differ from one another in their ability to elicit remission. Two large-scale studies found significantly more remission in endogenous depressives treated with the TCA clomipramine than with either citalopram or paroxetine (DUAG, 1986, 1990). By contrast, Beasley et al. (1993) found no significant differences in either response or remission rates between depressed in-patients treated with imipramine or high-dose fluoxetine. Thase et al. (2001) analysed data from eight RCTs comparing venlafaxine to several SSRIs or placebo. The remission rate for patients on venlafaxine was 45% compared to 35% for SSRIs and 25% for placebo. The superior efficacy of venlafaxine was seen in both men and women and over a wide age range (Entsuah et al., 2001). This result awaits confirmation in prospective head-to-head studies.

Anxiety disorders

There is considerable comorbidity of all anxiety disorders with MDD (Mineka et al., 1998), with 50–60% of patients with anxiety disorders having at least one other psychiatric diagnosis, often MDD (Lenze et al., 2001; Mineka et al., 1998). Substantial evidence suggests that SSRIs and dual SNRIs (including many TCAs) are effective in treating many anxiety disorders. As will become obvious, however, the evidence is less substantial for selective NRIs, in part because there are far fewer RCTs examining the efficacy of these drugs in anxiety disorders.

Panic disorder (PD)

Kasper and Resinger (2001) reviewed studies of SSRIs in PD involving more than 4000 patients and found SSRIs to be superior to placebo. Direct comparisons have shown SSRIs to be more effective than desipramine or maprotiline in reducing panic-attack frequency (den Boer and Westenberg, 1988; Johnson et al., 1995; Sasson et al., 1999). However, desipramine improved other anxiety measures not specifically related to PD, whereas maprotiline appeared to be less effective in this regard. In another open trial, desipramine also improved non-panic-attack anxiety symptoms (Kalus et al., 1991). In a comparison of the selective NRI lofepramine with clomipramine in PD, neither drug was superior to placebo in reducing panic-attack frequency; although both drugs were comparably superior to placebo in improving anxiety on a number of standard rating scales after 6 wk of treatment, the magnitude of these effects was not great (Fahy et al., 1992). Another selective NRI, nortriptyline, significantly reduced depressive symptoms in PD patients,
and there was a strong trend for it to reduce panic-attack frequency as well (Munjack et al., 1988). Thus, whereas selective NRIs appear to be less effective than SSRIs with respect to specific anti-panic effects, it appears they may reduce other anxiety-related symptomatology in PD patients. In a more recent study, the newer selective NRI, reboxetine, was shown to improve PD symptomatology and frequency of attacks significantly more than placebo (Versiani et al., 2002). However, since there was no comparator SSRI in this study, further research is warranted to compare reboxetine to SSRIs in PD as well as in other anxiety disorders. If it is shown to be effective, it may be due to its ‘cleaner’ pharmacological profile, in comparison to that of desipramine or maprotiline. By contrast, bupropion has not shown much promise in PD (Sheehan et al., 1983).

**Generalized Anxiety Disorder (GAD)**

Extended-release venlafaxine (venlafaxine XR) and the SSRI paroxetine have been approved by the FDA to treat GAD. Venlafaxine XR, the best evaluated antidepressant in GAD to date (Brawman-Mintzer, 2001; Sheehan, 2001), has been found to be superior to placebo in several large RCTs involving either fixed or flexible dosing schedules, and in short- (8 wk) or long-term (up to 28 wk) studies. Venlafaxine XR is effective at a fixed dose of 75 mg, at which it is likely to act as an SSRI (Frazer, 2001), but there is somewhat greater efficacy at higher doses (Sheehan, 2001), at which it is also likely to inhibit NE reuptake (Frazer, 2001). We have been unable to find any controlled trials of the efficacy of selective NRIs in GAD.

**Social Anxiety Disorder (SAD)**

TCAs do not appear, in general, to be effective in SAD (Liebowitz et al., 1985), but SSRIs have been shown to be effective, and SAD is accepted as a drug indication by the FDA. Reviews of the pharmacotherapy of SAD have appeared recently (Van Ameringen et al., 2000; den Boer, 2000; Sareen and Stein, 2000; Schneier, 2001). Among SSRIs, paroxetine is the best studied, but efficacy has been demonstrated also for fluvoxamine and sertraline. In these studies, response rates for the SSRIs vary from 46–66%, significantly greater than the 7–32% seen with placebo. In a recent 8-wk open-label trial, reboxetine was found to be effective in SAD (Atmaca et al., 2003), as was bupropion in a 12-wk open label trial with a small group of SAD patients (Emmanuel et al., 2000). These results obviously require further investigation.

**Obsessive–Compulsive Disorder (OCD)**

OCD is currently classified as an anxiety disorder. However, there are substantial data from genetic studies as well as dimensional analyses suggesting that OCD is quite distinct from all other anxiety disorders, as well as from MDD (Kendler et al., 1995; Mineka et al., 1998). Moreover, the treatment parameters required for effective therapeutic response, as well as the time-course of response, also differentiate OCD from the other anxiety disorders. The selective NRI desipramine is not effective in OCD (Fernandez-Cordoba and Lopez-Ibor, 1967; Goodman et al., 1990; Leonard et al., 1988). Although clomipramine and SSRIs are both efficacious in OCD (Gorman and Kent, 1999), and individual SSRIs appear to have equivalent efficacy (Vythilingum et al., 2000), higher doses and a longer course of treatment are required for these drugs to

**Post-Traumatic Stress Disorder (PTSD)**

There have been considerably fewer RCTs of antidepressants in PTSD, only about a dozen, than in most other anxiety disorders. A review by Solomon et al. (1992) found only four such pharmacotherapy trials using an antidepressant in which diagnosis was made using DSM-III or DSM-III-R criteria. In these patients, all of whom were male combat veterans, there was at best minimal evidence for efficacy of the MAOI or TCAs, whether dual reuptake inhibitors or selective NRIs (Dow and Kline, 1997; Reist et al., 1989). Since then, two RCTs with fluoxetine, each with approx. 50 outpatients, have been carried out (Brunello et al., 2001; H�名an et al., 2001; Pearlstein, 2000); fluoxetine was superior to placebo, with efficacy seen in civilians but not in combat veterans. Recently, two multi-centre trials, involving almost 400 outpatients, compared sertraline to placebo (Brady et al., 2000; Davidson et al., 2001). In both studies, approx. 75% of the patients were female and only 5% of the patients had been in war or combat. By far, the most frequent traumatic event was physical or sexual assault. Both studies had essentially identical results, with 53–65% responding to sertraline vs. 32–38% for placebo after 12 wk. Paroxetine has been approved by the FDA for treatment of PTSD (Wagstaff et al., 2002). Recently, mirtazapine was reported to be more effective than placebo in PTSD (Davidson et al., 2003). More studies with mirtazapine are needed before definitive conclusions can be reached. In conclusion, it appears that SSRI treatment is effective in civilians with PTSD, particularly women experiencing physical or sexual trauma. However, these drugs have little-to-no efficacy in male combat veterans with PTSD.
produce optimal efficacy in OCD than in other disorders (Hollander et al., 2000). For these reasons, we have elected not to consider OCD together with the other anxiety disorders in the remainder of this review.

Comment

The foregoing establishes that antidepressants, including tertiary amine TCAs, SSRIs and many newer drugs such as venlafaxine are not only efficacious in treating MDD, but anxiety disorders as well. The temporal pattern of response to antidepressant treatment is also similar in MDD and most anxiety disorders. Onset of behavioural improvement, however that may be defined (Katz et al., 1996/1997), is gradual, and maximal improvement can take months. Although not studied extensively, the limited data available also suggest that maintaining patients on these drugs prevents relapse or recurrence of anxiety disorders as well as MDD (Brawman-Mintzer, 2001; Frank et al., 1990; Gorman and Kent, 1999; Hidalgo et al., 2001; Hirschfeld, 2001; Kasper and Resinger, 2001). The continuation and maintenance data would imply that antidepressant treatment does not ‘fix’, in any permanent way, the neurobiological abnormalities that underlie these disorders. Rather, the continued presence of drug, perhaps indefinitely in some patients, is necessary to maintain whatever alterations they induce in neurotransmitter function to produce their beneficial effects.

With respect to their efficacy in anxiety disorders, the data are much more limited for the secondary amine TCAs, such as desipramine, that selectively block NE reuptake. Although an initial report that the new selective NRI, reboxetine, is effective in PD is promising, more research is needed before definitive statements can be made about its efficacy in PD or other anxiety disorders. Overall, evidence collected to date would seem to indicate that most selective NRIs have little effect on anxiety symptoms associated specifically with disorders such as PD.

However, in addition to being a defining characteristic of anxiety disorders, anxiety is also both a prominent and prevalent symptom in depression (Fawcett and Barkin, 1998; Gorman, 1996/1997; Katz et al., 1984). Although not listed in DSM-IV as a diagnostic criterion for MDD, it has been estimated that as many as 85% of adults with depression have significant symptoms of anxiety (Gorman, 1996/1997). In this context, it is clear that all existing antidepressants successfully ameliorate anxiety as a component of depression, including those that selectively block NE reuptake (Ferguson et al., 2002; Kleber, 1979; Nelson, 1999; Nystrom and Hallstrom, 1985; Stahl et al., 2002; Szegedi et al., 1997), as well as bupropion (Trivedi et al., 2001) and mirtazapine (Fawcett and Barkin, 1998), which has a prominent noradrenergic component to its complex pharmacology (Frazer, 1997). Later in this review, with respect to the specific behavioural dimensions that may be affected by drugs regulating noradrenergic and serotonergic function, we will discuss how it may be that SSRIs can be effective in both MDD and the various anxiety disorders, whereas selective NRIs seem to improve non-specific symptoms of anxiety, but are less effective against other symptoms, e.g. panic attacks or agoraphobia, that are associated specifically with anxiety disorders such as PD or SAD.

The suggestion that ADs act by regulating monoaminergic neurotransmission is hardly a radical view. It has been much more elusive and controversial, however, to try to understand how drug-induced alterations in monoaminergic function could produce behavioural improvement in depression and anxiety disorders. Implicit in the present attempt is the idea, presented in the next section, that these disorders share some common underlying behavioural dimensions, and that the same dimensions that are dysregulated in these disorders are also related to the behavioural dimensions normally regulated and modulated by noradrenergic and serotonergic neurotransmission.

Behavioural dimensions of MDD and anxiety disorders

Comorbidity of MDD with most if not all anxiety disorders, and among the anxiety disorders themselves, is the rule rather than the exception. The overlapping symptomatology has been recognized clinically for decades (Maser and Cloninger, 1990; Mineka et al., 1998; Nemeroff, 2002), and is evident in the symptoms indicated in the DSM-IV diagnostic criteria for MDD and anxiety disorders (APA, 2000). Table 1 shows a list of symptoms manifest in common in MDD and anxiety disorders, as well as among the various anxiety disorders.

To account for this symptomatic overlap and comorbidity, a number of theoretical schemata have been formulated in an attempt to define the behavioural dimensions shared by depression and anxiety disorders (Brown et al., 1998; Clark and Watson, 1991; Krueger, 1999; Mineka et al., 1998). Although several such formulations may differ in the details of the structural relationships that they postulate and in the
interpretation of specific dimensions that are revealed, they nonetheless share many commonalities, and the overall dimensional structure that they suggest is remarkably similar. Such behavioural models may thus offer a theoretical framework within which we can begin to identify neurobiological substrates underlying these dimensions, as opposed to syndromes, and in so doing, to understand the regulatory processes affected by antidepressant drug administration that are involved in alleviating the symptoms of both depressive and anxiety disorders. Specifically, such a dimensional approach to understanding these disorders may allow us to hypothesize how regulation of brain monoaminergic neurotransmission by ADs may explain their therapeutic efficacy.

As an illustrative example of one of the most extensive and robust formulations, the ‘tripartite’ model was based on reviews and meta-analyses, including factor analyses, measures of convergent and discriminant validity and inter-rater reliability, of a number of psychometric instruments, with data derived from both patient and non-patient samples (Brown et al., 1998; Clark and Watson, 1991; Mineka et al., 1998; Watson et al., 1995). Three independent factors were derived to account for both the common and unique symptoms and manifestations of MDD and anxiety disorders, which the authors termed Negative Affect, Positive Affect and Physiologic Hyperarousal.

**Negative affect**

Dysregulation of this dimension was found to be manifest in common in both depression and all of the anxiety disorders, accounting for much of the symptom overlap (Mineka et al., 1998). This factor, resembling in general other higher order factors such as ‘internalization’, ‘general distress’ or ‘neuroticism’ that have been described in similar models (see e.g. Krueger, 1999; Watson et al., 1995), is defined by negative mood states that are seen in both MDD and anxiety disorders, such as agitation, anger, anxiety, fatigue, irritability and hostility; and also includes a number of more cognitive symptoms such as poor concentration and a sense of loss of control. Some components of Negative Affect, such as sadness, hopelessness, guilt, worthlessness, and suicidal ideation are more prominent in MDD; others, such as fear and helplessness, are associated primarily with anxiety disorders, but many are present in both.

**Positive affect**

Includes positive feelings such as pleasure, joy, energy, arousal, alertness and interest in activities that are pleasurable or rewarding. This dimension is most closely related, in an inverse manner, to MDD, and comprises a more limited number of symptoms, such as anhedonia, lack of interest in or engagement with the external environment, and psychomotor retardation.

**Physiologic hyperarousal**

Originally called ‘Anxious Arousal’. We prefer the term Physiologic Hyperarousal to distinguish it from the behavioural and cognitive arousal that is more a component of Positive Affect. Symptoms related to this dimension are characterized by autonomic and somatic manifestations such as somatic tension, shortness of breath, light-headedness, choking or smothering sensations, chest pangs or palpitations, nausea, etc. Although somatic manifestations of anxiety may occur in many disorders, Physiologic Hyperarousal as an independent factor has been most prominently and specifically associated with PD (Brown et al., 1998; Mineka et al., 1998). Indeed, in subsequent analyses and validation of the tripartite model, Negative Affect and Positive Affect were identified as higher-order personality traits influencing the structure and relations of all the disorders, whereas Physiologic Hyperarousal was identified specifically as a subordinate, non-trait factor associated with PD and agoraphobia (Brown et al., 1998). Importantly, some somatic symptoms may also be associated with anxiety as a component of Negative Affect, for instance in GAD, but these manifestations of anxiety can be differentiated from the Physiologic Hyperarousal emerging specifically in patients with PD or agoraphobia (Brown et al., 1998; see also Watson et al., 1995). Given the diagnostic criteria specified in DSM-IV, dysregulation of Physiologic Hyperarousal seems likely to be associated with SAD as well as PD.

Based on these analyses, Table 2 ascribes symptoms associated with the diagnosis and classification of MDD and anxiety disorders, as specified in DSM-IV, to the behavioural dimensions defined in the tripartite model. In this table, which is admittedly a
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Table 2. Summary of behavioural dimensions and associated symptoms

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A noteworthy aspect of this model is the recognition that anxiety, as a component of the common dimension of Negative Affect, is a key element of depression as well as a defining feature of all the anxiety disorders. Indeed, depression without anxiety is much more rare than anxiety without depression (Mineka et al., 1998). An independent second-order factor analysis of the behavioural components of depression has also found that a dimension including anxiety, agitation, somatization and sleep disorder was as much a component of depression as was the dimension involving depressed mood itself, along with retardation of movement and speech (Katz et al., 1984). Because anxiety is such a prominent component of Negative Affect, it would seem to be necessary, but not sufficient, that a drug be anxiolytic in order to be an effective antidepressant. Anxiolytic activity alone would not suffice, because ADs must also resolve the deficit in Positive Affect in depression. This is borne out by the fact that benzodiazepines are anxiolytic, but do not alleviate the core symptoms of depression, and are not effective antidepressants (Birkenhager et al., 1995).

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and Hagan, 1992). By contrast, cognition in depressed patients is driven by themes of loss, personal deficiency, worthlessness and hopelessness. Based on these ideas, we have also included these cognitive components of depression and anxiety disorders, namely loss of control, distress (the cognitive response to stress), helplessness and hopelessness within the three dimensions outlined in Table 2.

The similarity of therapeutic effects and the shared behavioural dimensions in MDD and anxiety disorders raise the possibility that these may represent dysregulation of similar if not identical neurobiological substrates. This is not to suggest that MDD and the various anxiety disorders are identical diseases, nor that all anxiety disorders are identical. Rather, the same neural systems may be dysregulated, with the specific clinical manifestation in each case determined by the nature, context, and degree of dysregulation. Genetic data consistent with this view suggest neither that anxiety disorders and MDD arise from a single set of genes, nor that each specific disorder arises from discrete genes, but that both common and specific genes may account, at least in part, for both their shared and unique dimensions (Kendler, 1996; Kendler et al., 1995; Mineka et al., 1998).

Comment

A number of complementary approaches have suggested that a higher-order factor, resembling the dimension of Negative Affect in the tripartite model, is dysregulated in both depressive and anxiety disorders. Anxiety is a prominent component of this dimension, along with other manifestations of negative mood. Other factors that are relatively unique to each type of disorder include a Positive Affect dimension that is inversely related to depression, and a Physiologic Hyperarousal dimension that is most prominently associated with PD, and perhaps also with SAD. Human as well as basic animal studies may offer further support for these models, and such studies may also begin to suggest possible neural substrates associated with the dysregulation of these behavioural dimensions or, more relevant to this review, to their alleviation by ADs. For example, individuals with elevated levels of Negative Affect also display an exaggerated baseline startle response (Lang et al., 1993). The startle response is a stress-related behavioural response thought to reflect anxiety-related processes mediated in the bed nucleus of the stria terminalis (Davis and Shi, 1999). It has also been shown that stress-induced NE release in this same brain region facilitates acute anxiety-like behavioural reactivity to stress (Cecchi et al., 2002a), providing one possible site where neural systems modulating the behavioural response to stress may converge with those involved in regulating the behavioural dimensions of depression and anxiety. In the following section, we discuss how the function and activity of brain noradrenergic and serotonergic systems may relate to the behavioural dimensions that are affected in depression and anxiety disorders, in an attempt to understand how drug-induced regulation of monoaminergic function can account for behavioural improvement.

Behavioural dimensions modulated by NE and 5-HT

The noradrenergic and serotonergic systems originate from relatively few cells in the pons and medulla, yet both project widely throughout the brain, exerting effects that are correspondingly widespread. Their activity appears to be important in regulating or facilitating many of the changes in neural function that underlie or enable shifts in behavioural ‘states’, such as arousal, attention, motivation, etc. Although these modulatory effects may be widespread and exerted in a global fashion when the systems as a whole are activated, it is nonetheless possible to investigate experimentally specific responses and effects of 5-HT and NE in specific brain regions where their modulatory functions may influence most directly some of the key behavioural components of the dimensions that are dysregulated in depression and anxiety disorders. Thus, understanding how the modulatory influence of 5-HT and NE in regions such as the bed nucleus of the stria terminalis, the extended amygdala, or the medial prefrontal cortex (mPFC) (discussed below) can influence the behaviour of the organism is essential to understanding how alterations in those functions can contribute to the efficacy of ADs in the treatment of depression and anxiety disorders.

NE

Noradrenergic neurons project widely throughout the brain, innervating many regions involved in stress and affect (Moore and Bloom, 1979). Relatively few noradrenergic neurons, located in a few small clusters in the brainstem, innervate the entire neuraxis, positioning this system ideally to enact global ‘state-change’ functions that may influence the operating characteristics of the entire nervous system under conditions of elevated noradrenergic activity. At a cellular level, the effect of NE on target neurons is modulatory in nature. Rather than inducing simple inhibition or excitation,
NE alters the ‘signal-to-noise’ ratio of evoked activity, both excitatory and inhibitory, making synaptic transmission in target circuits more effective (Woodward et al., 1991b). Such modulatory effects are mediated by both β- (Woodward et al., 1991a), and α1-adrenergic receptors (Aghajanian and Rogawski, 1983; Waterhouse et al., 1990). Presumably, such modulation serves to enhance an array of response capabilities mediated throughout the brain when noradrenergic activity is elevated.

To understand the behavioural function of the brain noradrenergic system at such a global level, it is useful to differentiate between tonic or steady-state noradrenergic activity on one hand, and phasic or stimulus-evoked reactivity on the other. The cellular effects, and perhaps even the overt behavioural effects of NE may be similar in these two modes of activity, but the pattern, duration and context in which these effects are exerted are quite different. Tonic noradrenergic activity is most closely related to the overall state of behavioural arousal, which may be conceptualized as the degree to which an organism is ‘engaged’ with or responsive to its external environment (Aston-Jones et al., 1991; Jacobs et al., 1991). In electrophysiological studies, tonic noradrenergic activity was highest during an active, alert waking state, and decreased steadily through states of decreasing arousal from quiet waking to drowsy to slow-wave sleep, until these neurons were silent during REM sleep (Aston-Jones et al., 1991; reviewed in Jacobs et al., 1991). Brain noradrenergic activity is closely associated with behavioural and physiological indices of arousal (Berridge and Foote, 1991; Page et al., 1993; Rasmussen et al., 1986; Rosario and Abercrombie, 1999); by contrast, α1-adrenergic receptor blockade induces a state of sedation and behavioural inactivity (Hilakivi and Leppavuori, 1984; Hilakivi-Clarke et al., 1991).

Phasic activation of the noradrenergic system to even higher levels of activity in response to temporally defined environmental stimuli may facilitate acute behavioural reactivity to subsequent stimuli. Noradrenergic neurons are excited briefly by punctate sensory stimuli of several modalities (Aston-Jones et al., 1991; Rasmussen et al., 1986). Notably, as animals habituate behaviourally to the stimuli, so does the response of the noradrenergic system (Rasmussen et al., 1986), suggesting that the ‘salience’ of the stimulus is important in evoking a noradrenergic response. This has been further elaborated in a recent series of experiments by Aston-Jones and colleagues, aimed at investigating in primates a potential role for NE in facilitating processes involved in ‘vigilance’, or selective attention to salient, meaningful stimuli, a cognitive component of arousal (Aston-Jones et al., 1999, 2000). In these studies, noradrenergic neurons were shown to respond most robustly to stimuli that had been conditioned to signal a meaningful reward. Further, in correlating the tonic level of activity of noradrenergic neurons with accuracy in responding to target stimuli in the presence of distracting non-reward stimuli, an inverted U-shaped relationship was described (Aston-Jones et al., 1999). At low levels of tonic noradrenergic activity, arousal was low, and selective attention was accordingly low. At higher levels of noradrenergic activity, arousal and alertness were higher, and the ability to attend to meaningful stimuli and appropriately filter out distracting stimuli was better. However, at very high levels of tonic noradrenergic activity, arousal was so high as to interfere with attentional focus, distractibility was increased, accuracy in responding to salient stimuli was reduced, and electrical activation of noradrenergic neurons by the target stimulus was masked by the elevated level of tonic activity.

In experiments testing the performance of rats on a five-choice serial reaction time task, the pattern and nature of errors made by the test animals after selective neurochemical lesions of the monoaminergic innervation of prefrontal cortex were used to assess changes in cognitive capabilities such as perceptual sensitivity, attention, motivation, and accuracy of working memory (Robbins, 2000). Lesions of the noradrenergic innervation specifically decreased response accuracy under conditions of distractibility and increased attentional demands, consistent with the role suggested above for NE in facilitating responsivity to salient stimuli. Thus, many of the modulatory effects of NE on attention and arousal may be mediated in part by facilitation of neuronal processes in the mPFC that underlie cognitive functions involving attention, working memory, motivation, processing causal relations, and other complex operations (Robbins, 2000). The mPFC is important in guiding behaviour using working memory, inhibiting inappropriate responses, suppressing distractions, organizing purposeful behaviour, and integrating cognition with emotion (Arnsten, 2000; Robbins, 2000). Damage to this region can induce behavioural and cognitive changes that resemble many of the symptoms of depression and anxiety disorders (Arnsten, 2000; Rajkowska, 2000).

In contrast to the relationship of tonic noradrenergic activity to arousal, widespread acute modulatory effects of the brain noradrenergic system are most likely to be evoked phasically in the context of stress, as this system has been shown to be powerfully...
activated by a diverse array of acute stressors (Jacobs et al., 1991; Pacak et al., 1995; Svensson, 1987; Valentino et al., 1993). Phasic activation of the noradrenergic system by acutely stressful stimuli can last in the order of seconds to minutes or more, depending on the stimulus. In such contexts, stress-induced noradrenergic activation enhances sensorimotor reflex responses (Morilak and Jacobs, 1985; Stafford and Jacobs, 1990) and more complex behavioural responses such as the acoustic startle reflex (Davis et al., 1984). Elevated noradrenergic transmission specifically reduces immobility and facilitates active escape behaviours, such as struggling and climbing in the forced swim test in rats (Detke et al., 1995; Kitada et al., 1983), a behavioural assay that is particularly useful for detecting antidepressant drug activity.

Selective blockade of adrenergic receptors in the lateral bed nucleus of the stria terminalis and central nucleus of the amygdala of rats immediately prior to acute immobilization stress showed that NE release in these limbic forebrain regions facilitates a number of autonomic, neuroendocrine and behavioural measures of stress reactivity (Cecchi et al., 2002a,b). These observations, together with many others investigating a variety of specific response parameters, indicate that activation of the noradrenergic system by stress, and the consequent release of NE throughout the brain, facilitates several behavioural-affective, autonomic and neuroendocrine components of the organismic response to stress. Although specific responses, such as those described above, may be modulated in a region- and receptor-specific fashion, it is important to recognize that in the context of stress, it appears that the noradrenergic system as a whole is recruited into action. Its divergent anatomical organization and multimodal response characteristics, and the fact that most if not all of its components seem to be activated similarly in contexts of stress, suggest that the brain noradrenergic system not only facilitates an array of specific responses to acute stressors, but it also enacts global changes in brain function in more tonic behavioural states such as arousal. Thus, dysregulation of this function could contribute to the dimensional features of anxiety disorders and depression, and drug-induced alterations in this same function could contribute to their treatment.

5-HT

It has been stated that 5-HT is implicated in many behavioural and physiological functions, but does not appear to be essential to any of them (Jacobs and Azmitia, 1992), a reflection of its presumed modulatory influence, widespread and divergent anatomical organization, and the tonic steady-state nature of serotonergic neurotransmission. Similar to the noradrenergic system, the brain serotonergic system, originating in the raphe nuclei clustered along the midline of the brainstem, projects widely throughout the central nervous system (Jacobs and Azmitia, 1992). Serotonergic innervation of the forebrain, including prefrontal cortex, arises from the dorsal and median raphe nuclei in the rostral pons. The electrical activity of serotonergic neurons in these regions has been shown to be closely related to the state of behavioural arousal and the level of locomotor activity. Similar to noradrenergic neurons, the average firing rate of serotonergic neurons shows a steady decline as the animals proceed from a state of active waking, through quiet waking, drowsy, slow-wave sleep, and finally REM sleep, when serotonergic neurons in the rostral raphe are completely silent (Jacobs and Azmitia, 1992).

The activity of serotonergic neurons differs from that of noradrenergic neurons, however, in that they exhibit a much more regular, almost pacemaker-like pattern of activity at all levels, with very little phasic activation or burst-like activity. This steady, tonic rate of firing has been shown to be elevated by stress, commensurate with stress-induced increases in behavioural arousal and activity, but no more so than with non-stressful stimuli producing the same degree of arousal or behavioural activity, and with no specificity as to the modality, nature or intensity of the arousing stimulus (reviewed in Chaouloff et al., 1999). It has been suggested that the steady firing rate of 5-HT neurons in the midbrain raphe may provide a constant ‘tone’, driving a continuous level of serotonergic neurotransmission throughout the brain, but that local modulation of 5-HT release, perhaps via presynaptic heteroreceptors located on serotonergic terminals, may confer a degree of region- or stimulus-specificity to serotonergic responses. Consistent with this, stressor-specific alterations in 5-HT efflux have been demonstrated using microdialysis (Kirby et al., 1997), and qualitatively different changes in 5-HT efflux have been measured in response to the same stimulus in different brain regions, even in regions innervated by the same serotonergic cell groups (Kirby et al., 1995). However, in another study arguing against this, a series of behavioural and environmental stimuli incorporating varying degrees of pain, stress, feeding, motor activity, arousal and behavioural activation, were each found to induce changes in 5-HT release to a similar extent in several forebrain sites (Rueter and Jacobs, 1996). Differences in the magnitude of 5-HT release were not specific to the stimuli eliciting the
response, but were more related to the degree to which behavioural activation and arousal were induced. These results, consistent with the electrophysiological studies, suggest that 5-HT may function mainly in a tonic steady-state mode of activity related primarily to behavioural arousal. That is not to say, however, that this relationship cannot be modified. For example, chronic stress has been shown to increase 5-HT synthetic capacity through activation or induction of tryptophan hydroxylase and to modulate sensitivity or expression of post-synaptic 5-HT receptors (Chaouloff et al., 1999), thus potentially modifying the functional relationship between arousal and effective serotonergic ‘tone’.

5-HT has long been hypothesized to play a role in anxiety and emotional reactivity (reviewed in Griebel, 1995, and Handley, 1995). In general, acute administration of drugs that elevate serotonergic neurotransmission, including SSRIs, facilitate fear-induced anxiety-like responses, but elevating serotonergic transmission in the absence of a fearful context does not in and of itself promote anxiety-like behaviour (Handley, 1995), reflecting the modulatory nature of serotonergic effects (Jacobs and Azmitia, 1992). However, an extensive review of many pharmacological studies using a variety of drugs that inhibit, block, promote or mimic serotonergic neurotransmission with acute or chronic treatment has revealed contradictory, inconclusive and inconsistent results on a number of behavioural measures (Griebel, 1995). Part of the inconsistency may result from the different conditions under which tests have been conducted. For example, it has been demonstrated that 5-HT-1A receptor agonists can be anxiolytic when tested under conditions that elicit high levels of baseline anxiety, but they are anxiogenic under conditions producing low baseline anxiety (Handley and McBlane, 1993; Handley, 1995). Part of the inconsistency may also arise from the fact that the organismic response to stress or fearful stimuli is a complex amalgam of both activation and inhibitory processes, impacting several behavioural and physiological dimensions. Different behavioural tests used to measure fear responses in animal models may access different dimensions of behavioural reactivity and anxiety, and may, therefore, reveal different modulatory effects.

Indeed, it has been suggested that fear engages two qualitatively different behavioural response systems in the brain (reviewed in Handley, 1995). The first, a behaviourally activating Defense System, initiates overt behavioural and autonomic responses serving to eliminate or escape from a threat (e.g. fight-or-flight response). The second, a Behavioural Inhibition System, invokes responses (e.g. freezing), that suppress ongoing behaviours in situations in which the continuation of such behaviour may itself represent a threat. The ultimate response to a threatening stimulus represents a coordination and balance of these distinct systems that will depend on the context and nature of the stimulus. Handley (1995) proposed that serotonergic transmission primarily facilitates responses mediated by the Behavioural Inhibition System. Thus, the close relationship of serotonergic tone to arousal and locomotor activity suggests that serotonergic transmission would be highest when ongoing behaviour of the organism is most likely to bring it into a threatening or potentially dangerous situation. The widespread, tonic modulatory influence of 5-HT may thereby promote a shift in brain state, biasing the brain towards a pattern of impulse control rather than fight-or-flight responding, during periods of high arousal and locomotor activity. Thus, in any animal model of anxiety, the effects of serotonergic drugs can differ depending on whether a particular test measures anxiety as a suppression of behaviour or as an active response, and whether the baseline level of arousal is high or low.

It has been suggested more generally that 5-HT plays a role in behavioural constraint that is independent of anxiety- or fear-induced behavioural suppression (Soubrie, 1986; Spoont, 1992). Reducing serotonergic function by lesioning or depleting brain 5-HT, or by blocking serotonergic receptors, releases behaviours that are inhibited by punishment, which is a model of anxiety, but also releases behaviours that are suppressed by novelty, by extinction of non-rewarded responses, or where reinforcement is contingent upon response restraint and behavioural suppression (Soubrie, 1986). In experiments testing the performance of rats on a five-choice serial reaction time task, lesioning the serotonergic innervation of the prefrontal cortex induced spontaneous or premature responding, interpreted as a failure to inhibit inappropriate behaviours (Robbins, 2000), akin to experimental ‘impulsivity’. This is quite different from the result seen on the same test after NE depletion, as described earlier. Soubrie (1986) suggested that when there is a conflict between active responding (‘Go’) and response suppression (‘No-Go’), 5-HT promotes response suppression, and Spoont (1992) proposed that 5-HT plays a more general role in impulse control and blunting of behavioural reactivity. It has been shown recently that reducing serotonergic function in rats disrupts prepulse inhibition, a process related to sensorimotor gating and filtering (Prinssen et al., 2002). It is perhaps significant that patients with PD...
exhibit a deficit of prepulse inhibition (Ludewig et al., 2002). Thus, in the context of antidepressant drug effects in depression and anxiety disorders, enhancing serotonergic tone could conceivably diminish impulsivity, aggression or even suicide (Soubrie, 1986; Spoont, 1992), as well as attenuating excessive emotional reactivity to fearful or stressful stimuli.

Comment

We have presented a broad and purposely general description of the behavioural functions of the brain noradrenergic and serotonergic systems. Just as the trend in psychiatry has been to reduce the depressive and anxiety disorders into component symptoms for purposes of categorization and diagnosis, the trend in preclinical research has also been towards a reductionist approach. The prevalent strategy has been to isolate and study specific behavioural responses, cellular responses, even biochemical and molecular responses for purposes of experimental access, controllability and interpretation. In so doing, although our analytic capacity may be greatly improved, it has become easy to lose sight of the ‘big picture’, of the fact that these specific responses never occur in such isolation. Rather, these responses represent continuously changing and integrated processes of homeostatic regulation, occurring in complex systems in complex organisms and complex situations. Although it is possible to dissect them into their components, the monoamines in particular appear to function as whole systems, the functions of which are greater than the sum of their individual parts.

Perhaps a useful analogy can be drawn with the peripheral sympathetic nervous system, the activation of which elicits a myriad of specific responses, mediated by specific receptors and effectors. Any one of these responses can be understood in terms of its specific effect, e.g. mydriasis increases visual sensitivity, cardiovascular changes (tachycardia, vasoconstriction and hindlimb vasodilation) divert blood to skeletal muscle and increase aerobic capacity, whereas other changes lead to energy mobilization and increased catabolic activity. However, the adaptational significance and the essential role of all of these individual responses to the survival of the individual and the survival of the species are not appreciated unless one considers the system as a whole. It has long been appreciated that the sympathetic nervous system functions as an integrated entity, mediating the now well-understood ‘fight-or-flight’ response to stress (Cannon, 1929). We view the synergistic functions of the brain monoaminergic systems in much the same way. Understanding the specific responses mediated by specific projections to specific brain regions utilizing specific receptor subtypes and effectors is important to understanding how the system does what it does. But recognizing the true significance of these responses lies in the fact that together they comprise the components of a higher order, integrated and systematic modulatory function. Such an integrated view is key to understanding not only the ‘normal’ adaptive functions of the monoamines, but also to understanding how pharmacological regulation of these functions by ADs contributes to normalization or compensation for the neurobiological deficits underlying the dimensional features of depression and anxiety disorders.

Our purpose in attempting to relate the shared behavioural dimensions of MDD and anxiety disorders to the behavioural dimensions modulated by NE and 5-HT is to understand better how antidepressant-induced alterations in the function and activity of these systems might account for their therapeutic effects, and it is entirely possible that alterations in monoamine function could counteract or compensate for a primary dysfunction in other systems. In other words, the presumption that drug-induced regulation of monoamines contributes to the alleviation of the symptoms of these disorders neither requires nor implies that dysregulation of the monoamines is causative in their development or manifestation. However, it is also possible that dysregulation of noradrenergic or serotonergic function could contribute to the aetiology of these illnesses.

Excellent reviews of the clinical evidence surrounding this issue, much of which has been inconsistent, contradictory or inconclusive, have appeared recently (Delgado, 2000; Ressler and Nemeroff, 1999, 2000), and a detailed discussion of that literature is beyond the scope of this review. One of the more consistent observations, relevant to our discussion below of drug-induced changes in the noradrenergic system, suggests an increased density or sensitivity of adrenergic receptors in depression, typically interpreted to reflect an adaptive response to reduced noradrenergic transmission. However, as pointed out by Ressler and Nemeroff (2000), even if this elevated receptor expression is a result of reduced NE levels, it could render the system potentially hyper-responsive to any stimulus that subsequently activates NE release. Thus, given the role of NE in both arousal and phasic stress reactivity, a reduction of tonic noradrenergic transmission but hyper-responsiveness to phasically activating stimuli could contribute to both a reduction in arousal and an increase in anxiety.
Indeed, increased ‘volatility’ of the noradrenergic system has been reported particularly in anxiety disorders (Sullivan et al., 1999). Other results, however, fail to support a direct aetiological role for the monoamines in depression or anxiety. Studies examining the effects of transient 5-HT or NE depletion have demonstrated that the therapeutic efficacy of SSRIs and selective NRIs are dependent upon intact serotonergic and noradrenergic systems, respectively (Delgado, 2000). However, such transient depletion has little effect on mood in healthy individuals, and the effects of tryptophan depletion in unmedicated, recovered depressives are less clear. Based on a ‘mega’-analysis of five studies, Booij et al. (2002) concluded that recurrent depressive episodes, female gender, history of suicidal thoughts and attempts, as well as previous treatment with an SSRI were all predictors of mood lowering in response to tryptophan depletion. Variability in such factors may account for some of the discrepancies among studies, and for the fact that only approx. 50% of depressives who show a beneficial response to SSRI treatment relapse with tryptophan depletion (Moore et al., 2000). Nonetheless, it seems clear that a simple, acute disruption of monoamine function is not sufficient to induce illness by itself, nor is it likely to be the primary cause (Delgado, 2000). It may be that the factors which render individuals vulnerable to depression can also make them susceptible to the mood-lowering effects of monoamine depletion, perhaps by compromising some compensatory capability. Alternatively, given their global modulatory functions, if dysregulation of NE or 5-HT has any aetiological role at all, it seems most likely to contribute to a predisposition or vulnerability to develop MDD or anxiety disorders in the face of other causative or precipitating factors.

One such precipitating factor may be stress, as it has become increasingly clear that there is an important link between stress and both depression and anxiety disorders (Anisman and Zacharko, 1982; Charney et al., 1995; Harris, 2001; Heim and Nemeroff, 2001; Kendler et al., 1998, 1999; Vaidya and Duman, 2001; Yehuda et al., 1995). Anisman and Zacharko (1982, 1986), in one of the most ambitious attempts yet to integrate basic research on the neurobiology of stress with clinical observations relating stressful life events to depression, suggested that when behavioural and physiological coping strategies that comprise the stress response fail to mitigate the impact of environmental stressors, the capacity of brain monoaminergic systems may fail to meet the resulting excessive or prolonged demand, resulting in further loss of coping ability and increased vulnerability to subsequent stress, ultimately leading to depression. Also, continued activation of the monoamine systems can induce compensatory increases in synthetic capacity, cell responsivity, and receptor number or effector sensitivity (Anisman and Zacharko, 1986). Although these compensatory alterations may be adaptive in the face of persistent stress, they can themselves produce conditions that are maladaptive in other contexts or, if prolonged, may result in neuropathology such as that associated with depression or anxiety disorders (McEwen, 2000b). Thus, monoaminergic dysregulation could contribute to stress vulnerability as a factor in the development of MDD and anxiety disorders.

**Effects of antidepressants on brain monoaminergic systems**

Regardless of an aetiological role, if any, for NE or 5-HT in depression and anxiety, regulation of the modulatory functions of these monoamine neurotransmitters by ADs is essential to their therapeutic efficacy. Many antidepressants potently block the transporters mediating reuptake of 5-HT or NE, but not dopamine (DA). In addition, uptake inhibition elicits both rapid and delayed compensatory effects on the NE and 5-HT systems. Based on the temporal course of treatment response, many current theories attribute the behavioural improvement caused by these drugs to such compensatory effects rather than the acute alterations in extracellular transmitter levels (Artigas et al., 2001; Duman et al., 1999; Jacobs et al., 2000; Lenox and Frazer, 2002). However, the cascade of delayed regulatory processes occurring after long-term treatment are nonetheless thought to be initiated specifically by the acute blockade of serotonergic and/or noradrenergic reuptake. Although it has been argued that compensatory effects may actually decrease noradrenergic transmission (Mongeau et al., 1997), the bulk of evidence suggests a tonic enhancement of both serotonergic and noradrenergic activity. Most convincing are clinical studies showing that depletion of brain NE or 5-HT causes relapse in depressed patients who improved substantially following treatment with selective NRIs or SSRIs respectively (Booij et al., 2002; Delgado, 2000). Furthermore, such data imply that selective NRIs require the availability of NE, but not 5-HT, for their beneficial effects, and the converse is true for SSRIs. It appears, then, that selective serotonergic or noradrenergic drugs produce their beneficial effects through separate and distinct systems that can either achieve the same effects independently, or converge to affect common downstream processes (Eriksson, 2000; Frazer, 2000).
Much exciting research has emerged in recent years characterizing the effects of antidepressants on intra-cellular signalling pathways linked to noradrenergic or serotonergic receptors. In particular, attention has focused on antidepressant-induced effects on second-messenger-regulated protein kinases, transcription factors such as CREB, or growth regulatory factors such as BDNF (Duman et al., 2001). Such research has led to fundamentally new hypotheses suggesting that depression may result from neuronal death or deficiency in specific brain regions such as the hippocampus, and that antidepressants induce neuroprotective mechanisms and even neurogenesis to resolve such deficits (Duman et al., 2001; McEwen, 2000a). This body of research, of profound importance for understanding the cellular and molecular mechanisms of antidepressant action, has been reviewed extensively (Duman et al., 1999, 2001; McEwen and Magarinos, 2001; Popoli et al., 2000).

We have elected, however, to consider the function of the monoamines at a more systemic level. In this section, we will consider how the behavioural effects of ADs may be a result of regulatory alterations in monoaminergic neurotransmission and modulation of the many target circuits throughout the brain that these systems innervate. In particular, we suggest that because serotonergic and noradrenergic autoreceptors may be regulated differently, that antidepressants may produce differential effects on the tonic vs. phasic activity of these two systems. Whereas the tonic activity of both may be enhanced, the phasic reactivity or volatility of the noradrenergic system may be diminished selectively by chronic antidepressant treatment.

Regulatory effects on serotonergic and noradrenergic autoreceptors

One important way in which the serotonergic and noradrenergic systems appear to differ is in the degree to which their inhibitory autoreceptors are desensitized in response to chronic reuptake blockade. As extracellular levels of a transmitter increase, it acts not only on post-synaptic receptors, but also on somatodendritic autoreceptors, decreasing the firing rate and excitability of the cell, as well as autoreceptors located on nerve terminals, inhibiting the subsequent release of transmitter in response to electrical activity in the cell. This mechanism is thought to account for the inhibition of electrical activity of both serotonergic and noradrenergic neurons observed after acute administration of SSRIs or selective NRIs respectively, counteracting in part the elevated transmitter concentration caused by acute reuptake blockade. However, with chronic SSRI treatment, the elevated 5-HT levels appear over time to desensitize the inhibitory somatodendritic 5-HT-1A autoreceptors, leading to a gradual restoration of tonic baseline firing rate (Mongeau et al., 1997; Píñeyro and Blier, 1999). This time-dependent desensitization of somatodendritic autoreceptors is thought to be necessary for SSRIs to enhance tonic serotonergic transmission (Artigas et al., 2001).

In the noradrenergic system, there is also evidence that chronic NE-reuptake blockade may induce some degree of desensitization of α2 autoreceptors (Sacchetti et al., 2001), and attenuate the inhibitory influence of the autoreceptor agonist clonidine (Svensson, 1980). However, it appears that, unlike the serotonergic system, α2 adrenergic autoreceptors remain largely functional after chronic reuptake blockade. Indeed, it has been suggested that the reduced effect of clonidine on noradrenergic activity after chronic reuptake blockade may result not from desensitization (Szabo et al., 2000), but may be due instead to a direct pharmacological interaction of certain TCAs with the α2 autoreceptor (Svensson, 1980). After chronic NE-reuptake blockade, tonic electrical activity of noradrenergic neurons remains inhibited (Béjague et al., 2000; Huang et al., 1980; Linnér et al., 1999; Rueter et al., 1998; Svensson, 1980; Szabo et al., 2000; Szabo and Blier, 2001), and phasic excitation of noradrenergic activity, for instance by acute hypotensive stress, is attenuated (Valentino et al., 1990). Further evidence that noradrenergic autoreceptor activity is maintained after chronic reuptake blockade is seen after acute autoreceptor antagonist administration. If autoreceptors were desensitized, not only would agonist effects be diminished, but so would the effects of antagonists that block endogenous transmitter activity (Meana et al., 1997). However, it has been shown in rats treated chronically with an NE reuptake inhibitor that acute autoreceptor blockade elevates the firing rate of NE neurons, increases cortical NE release, and induces behavioural activation as much as, or even more than it does in vehicle-treated rats (Garcia et al., 2003; Linnér et al., 1999; Svensson, 2000).

Thus, chronic reuptake blockade may exert a dual influence on noradrenergic neurotransmission. Whereas tonic noradrenergic transmission is enhanced, with an elevation of steady-state extracellular NE levels, the persistent inhibitory influence exerted by that elevated extracellular NE on its autoreceptors can attenuate the phasic stimulus-evoked reactivity of the noradrenergic system (Figure 1). In effect, chronic antidepressant treatment may ‘clamp’ NE at an elevated level of tonic activity, but reduce acute ‘volatility’,...
and this dual effect may be key to the ability of NRIs to exert both antidepressant and anxiolytic effects.

By contrast with effects of selective NRIs on phasic reactivity of the noradrenergic system, the desensitization of serotonergic autoreceptors seen after chronic SSRI treatment makes it unlikely that phasic reactivity of the serotonergic system would be similarly attenuated. Indeed, it is not even clear whether the serotonergic system exhibits phasic reactivity (Jacobs and Azmitia, 1992), making this perhaps a less important mechanism for altering serotonergic function after chronic reuptake blockade. However, even in the serotonergic system, recent observations using microdialysis suggest that, despite electrophysiological evidence of somatodendritic autoreceptor desensitization, inhibitory autoreceptors continue to effectively restrain the release of 5-HT in terminal regions such as the frontal cortex and hippocampus after chronic SSRI treatment (reviewed in Hjorth et al., 2000). Thus, the regulatory alterations of serotonergic transmission and noradrenergic transmission induced by chronic reuptake blockade may be, ultimately,
more notable for their similarities than for their differences.

Is regulation of dopamine neurotransmission involved in antidepressant effects?

Some of the symptoms of MDD and anxiety disorders that are ameliorated by antidepressant drug treatment, for instance anhedonia, seem related more to dopaminergic function than to either serotonergic or noradrenergic modulatory function. Yet none of the antidepressants, including bupropion, potently block the dopamine transporter (Frazer, 1997), and except for MAOIs, antidepressants have typically not been thought to influence dopaminergic function directly. However, DA is a substrate for reuptake by the NE transporter (Povlock and Amara, 1997). It has been estimated that DA can diffuse at least 10 μm from its release sites in brain within one half-life, which may permit DA not only to act on extrasynaptic receptors, but also to contact other nerve terminals (Bunin and Wightman, 1998; Garris et al., 1994). Thus, the transport of DA into noradrenergic terminals may play a significant role in DA clearance in regions such as the mPFC, where dopaminergic and noradrenergic terminals overlap with comparable density (Cass and Gerhardt, 1995; Levitt et al., 1984). Indeed, the NE transporter may be the primary mechanism for DA reuptake in the frontal cortex (Morón et al., 2002), and drugs that block the NE transporter, such as desipramine, may also prevent the uptake of extracellular DA into noradrenergic terminals (Pozi et al., 1994). Preclinical studies have shown that NE uptake inhibitors elevate extracellular concentrations of DA in areas such as mPFC, but not in the nucleus accumbens (Carbini et al., 1990; Linnér et al., 2001; Millan et al., 2000; Tanda et al., 1994).

Chronic administration of NRIs also potentiates behaviours typically associated with pharmacological activation of mesolimbic dopaminergic neurotransmission in the nucleus accumbens (e.g. self-stimulation, locomotor activity; see Bonhomme and Esposito, 1998). The mechanism of this effect is not well-understood, and may be related to a variety of regulatory factors, including changes in DA receptor sensitivity or sensitization of the excitability of DA neurons in the VTA (Ainsworth et al., 1998; Stewart and Rajabi, 1996; see also Bonhomme and Esposito, 1998). The mechanism for this is apparently distinct from that involved in elevating DA neurotransmission in the mPFC, as baseline levels of extracellular DA are not increased in the nucleus accumbens by antidepressant treatment (Reith et al., 1997; Stewart and Rajabi, 1996; Tanda et al., 1994). Nonetheless, these effects may be important in the behavioural response to antidepressants. Exposing rats to variable chronic mild stress, a model for depression, reduces preference for a sweet substance (suggested to model anhedonia), and reduces sensitivity to the locomotor effects of stimulants and the rewarding effects of dopaminergic agonists (Willner, 1997). These effects are reversed by chronic administration of NRIs (Bonhomme and Esposito, 1998). Thus, enhancement of DA activity in cortical and limbic areas by NRIs may contribute to improvement of certain deficits in Positive Affect, increasing motivation and the ability to experience pleasure and reward.

It is unclear whether acute treatment of rats with SSRIs increases extracellular DA in the mPFC (Clark et al., 1996; Ichikawa and Meltzer, 1995; Millan et al., 2000; Tanda et al., 1994). Fluoxetine may be unique in producing this effect acutely (Bymaster et al., 2002), but extracellular DA is not elevated in mPFC after chronic fluoxetine treatment (Tanda et al., 1996). By contrast, chronic treatment of rats with SSRIs, as with NRIs, enhances reward-related behavioural effects of DA in the nucleus accumbens, possibly through effects on mesolimbic DA neuronal activity (Bonhomme and Esposito, 1998), and chronic SSRI treatment reverses DA-related behavioural deficits produced by chronic mild stress (Bonhomme and Esposito, 1998; Willner, 1997). Thus, changes in mesolimbic DA function may contribute to the beneficial effects of SSRIs on Positive Affect. However, it is unclear to what extent the role played by DA in the effects of SSRIs that have been observed in animals may extend to the clinical situation. Transient depletion of catecholamines by administration of AMPT to patients who had responded to treatment with SSRIs did not cause a relapse of depressive symptoms, including items such as loss of pleasure or loss of interest, as it did in patients who had responded to selective NRI treatment (Miller et al., 1996). The differential effects of selective NRIs and SSRIs on dopaminergic function in the prefrontal cortex would, however, make it still informative to determine, both preclinically and in patients, if these drug classes induce different effects on behavioural and cognitive processes mediated by DA specifically in this brain region.

Antidepressant effects on behavioural dimensions

In view of the preceding, and in an effort to speculate how antidepressant-induced effects on the activity and modulatory function of brain monoaminergic systems might improve the behavioural-cognitive dimensions
that are dysregulated in anxiety and depressive disorders, a number of specific questions may be addressed. For instance, how can drugs that selectively enhance the tonic activity of the serotonergic system, thought to exert a primarily inhibitory influence on behavioural reactivity, produce the same therapeutic effects as drugs that selectively enhance the tonic activity of the noradrenergic system, thought to exert a facilitatory effect on behavioural reactivity? Indeed, if NE facilitates behavioural reactivity and arousal, how can drugs that selectively enhance neurotransmission in this system improve anxiety, at least as they do when it occurs in concert with depression?

As described earlier, the Negative Affect dimension that is dysregulated in MDD and anxiety disorders may be seen to comprise symptoms that fall into two broad categories, those that have an ‘activated’ component (e.g. agitation, irritability, anxiety) and those that are more ‘inhibitory’ or withdrawal-related (e.g. sadness, worthlessness, helplessness, etc.). Given the close relationship that has been demonstrated between tonic noradrenergic activity and attention, alertness, behavioural activation and arousal, it seems likely that the tonic elevation of extracellular NE levels produced by many antidepressants contributes to an alleviation of the inhibitory or withdrawal-related symptoms of depression. Similarly, this might also improve several manifestations of the deficit of Positive Affect seen in depression, including symptoms such as psychomotor retardation and lack of interest in or engagement with the external environment, as well as alleviating the fatigue/languor and avoidance/withdrawal that are characteristic of both anxiety disorders and depression.

However, as discussed previously, it has also been demonstrated that phasic activation of the noradrenergic system facilitates many of the affective and cognitive components of the stress response, including acute fear- or anxiety-like behavioural responses. Thus, how can selective NRIs also alleviate the anxiety that is an essential component of depression? Preclinical as well as clinical studies have suggested that it may not simply be an absolute elevation of NE levels per se, but rather an increased ‘volatility’ or reactivity of the noradrenergic system that is most closely associated with stress-induced anxiety-like behaviours (Cecchi et al., 2002a,b; Pardon et al., 2002), and with clinical anxiety disorders (Sullivan et al., 1999). Further, as described in the preceding section, it is likely that the tonic elevation of extracellular NE levels obtained with chronic reuptake blockade is accompanied by a decrease in excitability and electrical activity of noradrenergic neurons, and in the phasic activation of NE release. Preclinical research has shown that a reduction or antagonism of the phasic reactivity of the noradrenergic system attenuates the acute stimulus-evoked induction of anxiety-like behavioural reactivity (Cecchi et al., 2002a,b; Pardon et al., 2002). It may be, then, that elevating tonic noradrenergic activity improves the inhibitory withdrawal-like symptoms of depression that are associated with Negative Affect and the loss of Positive Affect, and that a concurrent decrease in phasic noradrenergic reactivity can improve a different set of Negative Affect symptoms, including those related to anxiety as a component of depression.

Although the data addressing the efficacy of selective NRIs in anxiety disorders are surprisingly limited, what little there is would seem to indicate that they are at best partially effective in PD, and perhaps also in SAD, and in these cases they appear to be less effective than SSRIs. Thus, a dimensional model such as the tripartite model might suggest that SSRIs alleviate symptoms related to all three dimensions, but that selective NRIs, while effective in alleviating symptoms associated with Negative Affect and loss of Positive Affect, are not effective in those symptoms related to Physiologic Hyperarousal, which are most prominent in the anxiety disorders in which these drugs are least effective (e.g. PD, SAD). It has been suggested that GAD may be differentiated from other anxiety disorders, and especially from PD, by a lack of association with the Physiologic Hyperarousal dimension (Brown et al., 1998). Unfortunately, as mentioned previously, we have been unable to find any controlled studies describing the efficacy of selective NRIs, such as desipramine, reboxetine or lofexidine, in GAD, which could be an important test of this dimensional model.

In addition, as discussed above, selective NRIs can enhance the function of the mesocortical and mesolimbic dopaminergic systems, which have been most implicated as playing a role in reward (Schultz, 1998; Wise and Rompre, 1989). ‘Rewards’ are stimuli that elicit and reinforce approach behaviour, inducing subjective feelings of pleasure and positive emotional states (i.e. Positive Affect). A recent refinement of the role of DA in reward, based on the phasic electrical responses of dopaminergic neurons to the conditioning of reward-predicting stimuli, suggests that DA may be involved specifically in the association between a stimulus and a reward that guides approach behaviour to that stimulus (Schultz, 1998). Thus, enhancing such a function could contribute to the alleviation of several symptoms related to a deficit of Positive Affect, including anhedonia, loss of motivation, lack of interest in pleasurable activities, psychomotor retardation,
avoidance and social withdrawal. Indeed, enhancing both dopaminergic and noradrenergic function together could have beneficial effects on distinct aspects of Positive Affect, increasing attention and arousal, thus facilitating interaction with the environment, while at the same time enhancing motivation and reward processes that increase the subjective feelings of pleasure derived from that interaction.

As described above, a prominent role for 5-HT in the brain appears to be to bias the behavioural repertoire of an organism away from a pattern of activation of responses, and to promote instead a pattern of impulse-control and behavioural constraint. Enhancing such an effect may suppress certain symptoms of Negative Affect reflecting a loss of control, excessive reactivity or impulsivity that are associated with depression and anxiety disorders, including sleep disturbances, agitation, distractibility, fear, anxiety, irritability, anger, hostility and aggression, and suicidal thoughts or acts. This is consistent with the fact that SSRIs, whose only direct pharmacological action is to block 5-HT reuptake, are effective anxiolytics. It is possible that some symptoms of Negative Affect could be largely resolved solely by enhancing serotonergic tone, but it seems doubtful that an exclusive effect on serotonergic transmission could account for the full spectrum of symptomatic relief produced by SSRIs. Moreover, SSRIs and other antidepressant classes that block uptake of both 5-HT and NE or NE alone have similar clinical effects without, in general, discriminating between preferentially responsive patient subpopulations or symptoms, and with similar efficacy in terms of response rate, response magnitude, or clinical outcome. These observations suggest that the changes in serotonergic transmission induced by chronic SSRI treatment might interact in some way with the noradrenergic and dopaminergic systems, altering their activity to contribute to the clinical effects of these drugs.

One such interaction may involve the complementary roles played by 5-HT and NE in establishing the level of behavioural reactivity during changes in arousal. Serotonergic neurons exhibit a tonic pattern of activity that, like the noradrenergic system, exhibits a close correlation with behavioural arousal. Under conditions of increased arousal, the elevation of tonic noradrenergic function would facilitate active behavioural responding to environmental stimuli, but this would normally be balanced by a concurrent elevation of serotonergic tone that promotes behavioural constraint. By suppressing inappropriate behavioural responses to non-salient stimuli, this serotonergic ‘balance’ may enhance the overall impact of those stimuli that are of sufficient salience to elicit a behaviourally activating noradrenergic response, effectively increasing behavioural ‘signal-to-noise’ ratio. Low serotonergic tone could cause exaggerated behavioural reactivity or volatility (Spoont, 1992), and elevating serotonergic tone by SSRI treatment could attenuate behavioural reactivity, exerting an anxiolytic influence similar to that discussed above for NE reuptake blockade.

Whereas this interaction with NE may be important in the anxiolytic effects of SSRIs, they are also effective antidepressants. Given that 5-HT generally acts to inhibit, counteract or balance the activational influence of NE, it is unlikely that such a reciprocal interaction could also account for the efficacy of SSRIs in depression. Our limited understanding of serotonergic function in the brain leaves it unclear as to how an elevation of serotonergic tone alone, and an enhancement of its behaviourally inhibitory role, might resolve the dysregulation of Positive Affect that is characteristic of MDD.

Indeed, few, if any, clinical studies have been conducted with the purpose of clarifying the effects of ADs specifically on behavioural dimensions such as these. Symptomatic improvement is typically measured at a predetermined ‘end-point’ of treatment, by which time a variety of effects secondary to the initial actions on neurotransmitter systems may also have come into play (Katz et al., 1987, 1996/1997), and symptomatic assessment is typically performed globally, using rating scales such as the HAM-D or HAM-A, which were not developed with the purpose of either defining or differentiating the underlying dimensions accounting for symptomatic improvement. A few studies have been carried out in which either improvement in certain symptom clusters was examined in patients at the earliest onset of detectable behavioural effects of antidepressants, or in which early effects were measured in healthy volunteers (Davidson et al., 2002; Katz et al., In Press; Knutson et al., 1998). In a study of PTSD patients, sertraline produced initial improvement on a subset of symptoms including anger, anhedonia, and emotional distress to reminders, whereas by 12 wk, essentially all symptoms of the disorder had been affected (Davidson et al., 2002). In healthy volunteers the SSRI, paroxetine, reduced indices of hostility (Knutson et al., 1998), and in another study of depressed patients, paroxetine also was found to have its earliest effects on anxiety and hostility, with improvement in other symptoms occurring later (Katz et al., In Press). By contrast, in the same study, desipramine had its earliest effects on psychomotor retardation and depressed
mood, symptoms quite distinct from those initially affected by SSRIs. Taken together, these observations may be consistent with the postulated roles of 5-HT in behavioural constraint and of NE in behavioural activation, as derived from the preclinical research described above.

**Summary and implications**

To summarize the primary points made in this review: (1) dysregulation of a limited number of behavioural dimensions can account for both the shared and unique symptoms of MDD and anxiety disorders; (2) therefore, the neurobiology of ADs must account not only for their efficacy in MDD, but also for their ability to alleviate anxiety as a component of depression, as well as their efficacy in anxiety disorders; and (3) chronic antidepressant drug administration elicits regulatory alterations, directly or indirectly, in the activity of the noradrenergic, serotonergic and, perhaps to a more limited extent, dopaminergic neurotransmitter systems that can modify these behavioural dimensions so as to improve the symptoms of MDD and anxiety disorders. In this final section, we address some implications of these hypotheses, and identify some issues that remain unaddressed or unresolved.

Specific hypotheses pertaining to the ideas presented in this review are offered in Table 3.

More research and carefully conducted clinical studies are needed to more conclusively establish the effectiveness of selective NRIs, particularly the newer non-TCA drugs (e.g. reboxetine), in GAD and other anxiety disorders. Such studies could contribute to a more refined characterization of Negative Affect, including the suggestion that the constellation of symptoms related to Negative Affect may be further differentiated into two broad categories, those that are ‘activated’ in nature and those that are more inhibitory. Further, we have suggested that selective NRIs may not only alleviate some of the inhibitory symptoms of Negative Affect, as well as restoring some behaviours associated with loss of Positive Affect, by elevating tonic noradrenergic transmission, but at the same time, these drugs could also alleviate the activated symptoms of Negative Affect by attenuating phasic noradrenergic reactivity, thus eliciting both antidepressant and anxiolytic effects. Finally, if it is true that GAD is differentiated from other anxiety disorders (e.g. PD) by a lack of association with the Physiologic Hyperarousal dimension, and that selective NRIs are effective in alleviating anxiety-related symptoms of Negative Affect, but not those associated with...
with Physiologic Hyperarousal, then it would be predicted that selective NRIs should be as effective in treating GAD as they are in MDD.

Indeed, the idea that selective NE-reuptake blockade can induce differential regulation of tonic noradrenergic activity and phasic noradrenergic reactivity is one of the more novel mechanistic hypotheses presented in this review, and the key elements of this hypothesis are testable. Tonic elevation of extracellular NE levels with chronic NE-reuptake blockade should produce changes in baseline behavioural activity indicative of an elevation in arousal, attention or vigilance. By contrast, activation of inhibitory adrenergic autoreceptors mediated by the tonic elevation of extracellular NE should at the same time attenuate acute behavioural reactions to stress, indicative of an attenuation of phasic noradrenergic reactivity. Preclinical research aimed at testing these hypotheses will provide a better understanding of the regulatory changes induced in the noradrenergic system to account for its behavioural and cognitive role in the effects of antidepressant drug treatment. Even if true, it remains unclear whether this dual regulatory effect is capable of alleviating the activated symptoms prevalent in anxiety disorders, in the absence of the inhibitory symptoms associated with depression. It is less likely that attenuation of phasic serotonergic reactivity would be important in antidepressant drug action, given the desensitization of 5-HT autoreceptors seen with chronic SSRI treatment, as well as the question that remains whether the serotonergic system exhibits phasic reactivity (Jacobs and Azmitia, 1992). The results of such studies may also suggest ways to address other issues of clinical relevance, such as the mechanisms underlying the temporal relationship between the emergence, as well as the treatment, of ‘anxiety-related’ and ‘depression-related’ symptoms.

Along these same lines, too few functional studies at either the preclinical or clinical level have addressed the potential role played by DA in antidepressant drug efficacy. Basic research has suggested that, although both SSRIs and selective NRIs can increase limbic DA transmission, cortical dopaminergic function may be preferentially enhanced by NE-reuptake blockade. It would, therefore, be useful to develop measures of specific cognitive parameters in patients suffering from MDD or anxiety disorders that could serve as valid and reliable indices of cortical dopaminergic function, in order to reveal any potential differences in the ability of the different antidepressant drug classes to resolve symptoms related specifically to changes in cortical dopaminergic transmission.

Another important implication arising from the current discussion is the possible use of adjunct therapies to hasten or enhance the response to antidepressants. The prevailing theory regarding serotonergic autoreceptor desensitization has led to the idea that concurrent treatment with a 5-HT-1A autoreceptor antagonist along with an SSRI might be beneficial (Artigas et al., 2001). However, if the sensitivity of noradrenergic autoreceptors is maintained during antidepressant treatment, and if this persistent sensitivity represents a mechanism for the anxiolytic efficacy of NE-reuptake blockade in depression, we might predict that similar adjunct treatment with a noradrenergic autoreceptor antagonist would not only fail to be beneficial, but could in fact exacerbate anxiety and other activational symptoms related to noradrenergic reactivity.

In conclusion, behaviour, whether normal or pathological, is sufficiently complex that no individual discipline will provide a full understanding of its regulation and dysregulation. In this review, we have tried to stimulate a reappraisal of the global integrative functions that are modulated by brain NE and 5-HT, and how regulation of these functions may participate in the clinical efficacy of ADs. In so doing, we have attempted to integrate psychological, psychiatric and...
neurobiological ideas and findings. Only through such an integration and mutual appreciation of complementary, though often disparate, fields of study can we make real strides towards improving the treatment of diseases such as depression and anxiety disorders.

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Statement of Interest

None.

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