Noradrenaline: The forgotten neurotransmitter

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Depressive illness is a common and complex disorder. The biochemical hypothesis generated in the early 1960s simply postulated deficiencies of catecholamines (particularly noradrenaline (NA)) to be of aetiological importance.[1] Since that time, a multitude of other biochemical,[2] social[3] and psychological[4] theories have been put forward, either alone or in combination. Extension in our knowledge of cellular action has widened investigation to include 2nd messenger[5] and even nucleic acid activity.[6]

Over the last decade, serotonin (5HT) has been and continues to be the neurotransmitter most extensively studied with respect to depressive illness. The main reason for this probably relates to the development of the selective serotonin reuptake inhibitors (SSRIs), effective antidepressants with relative specificity for the serotonergic system. More recently, the use of *in-vivo* imaging has been expanded to the study of psychiatric conditions. Ligands are currently available for some serotonergic receptors, allowing demonstration of disturbances in receptor number and activity in the brain of depressed patients.[7]

Despite the emphasis on 5HT, information continues to accrue suggesting profound disturbances in noradrenergic function in depressed patients. In the absence of an *in-vivo* marker of central noradrenergic function, researchers have continued to rely on peripheral measures such as plasma NA. There are many intervening steps between activation of the locus coeruleus, its projections and activation of sympathetic neurons. It appears simplistic to suggest that activity in one can reflect activity in the other and yet recent studies examining plasma NA spill over from the brain show a clear correlation with peripheral activity, as measured by isolated sympathetic nerve firing rate in hypertensive patients.[8] Also, plasma NA correlates highly with cerebrospinal fluid NA in depressed patients[9] and controls.[10] Plasma NA appears to reflect central noradrenergic function.

The noradrenergic system is thought to play a key role in the normal functioning of learning, memory, attention and fear responses.[11] These activities have been demonstrated by a variety of experimental approaches in animals, including selective lesions; electrophysiological recording of neuronal discharge; and biochemical studies. The above physiological actions of NA suggest perturbations may be involved in the core symptoms of depression. In addition, central noradrenergic neurons have complex bi-directional interactions with the hypothalamic-pituitary-adrenal (HPA) axis and stimulate the production of corticotrophin releasing hormone (CRH) in the hypothalamus,[12] possibly explaining the overactivity of the HPA axis in some forms of depressive illness. The sympathetic nervous system derives from brainstem noradrenergic nuclei which, with the HPA axis, are fundamentally important in the human response to stress.

There is consistent evidence that plasma NA is raised during individual episodes of melancholic or psychotic depressive illness.[13] Also, several studies suggest that electroconvulsive therapy (ECT) reduces the plasma NA in these patients and this reduction may show a relationship with short-term improvement of depressive symptoms.[14,15] In addition, plasma NA (measured at index episode) is one of the few biological markers known to be associated with long-term outcome; a higher index plasma NA predicting longer time to relapse; and better global outcome.[16] These findings suggest that elevated plasma NA may reflect a more mutable or 'plastic' noradrenergic system, which may respond to physical treatment and be associated with a better long-term outcome. This hypothesis clearly requires further testing.

Stress is known to precipitate depressive illness.[17] Although the literature linking life events and neurotransmitter function is sparse, there is considerable evidence showing that laboratory stressors can alter monoamine function. The cold pressor test (which involves immersing a hand in cold water at 4°C for two minutes) can substantially elevate plasma NA.

This elevation has been shown to be blunted in patients with depressive illness when compared to controls.[18] These changes are likely to be opposed by antidepressants, though the evidence for this is mostly based on animal models.[19] Changes in noradrenergic system activity may allow an integration of social, biological and treatment factors known to occur with depressive illness.

Several studies investigating noradrenergic systems in depressed patients, using different methodologies, have also found differences compared to control groups. These findings appear more frequently when investigating melancholic/psychotic patients. Urinary NA[20] and growth hormone responses to the alpha-adrenoceptor agonist clonidine[21] have shown changes in depressed patients, specific to the melancholic form. Most recently, patients with treatment-resistant depressive illness have been shown to have altered cerebral venoarterial NA concentration gradients, in keeping with a deficit in brain noradrenergic function.[22]

Treatment differences between subtypes of depressive illness do exist. Some recent studies have suggested a differential response between melancholic and non-melancholic depressed patients to antidepressant drugs which target the 5HT system. Melancholic patients show a better

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response to drugs which have a noradrenergic or mixed action.[23,24] A recent meta-analysis suggests greater efficacy of broad-spectrum tricyclic antidepressants (TCAs) compared with SSRIs, for hospitalised inpatients with depressive illness.[25] The above findings suggest that an antidepressant's brain amine selectivity may have relevance for clinical response, at least in selected subgroups of patients with depressive illness.

Although *in vitro* selectivity for amine uptake has been clearly demonstrated between antidepressant groups, the evidence is less convincing *in vivo* in humans. The inter-dependence of serotonergic and noradrenergic systems has been known for many years but more recently the complex biochemical interactions of one system upon the other have been explored and incorporated into explanations of antidepressant action.[26] Despite these close associations, there is now clear evidence for differential physiological effects between the antidepressant classes, in platelet 5HT uptake and the pressor response to tyramine (modulated by noradrenergic systems), which mirror their *in vitro* reuptake inhibition profiles.[27] Such studies have become possible with the development of specific noradrenergic reuptake inhibitors (NARIs) and serotonin noradrenaline reuptake inhibitors (SNRIs).

Noradrenergic function is disrupted in depressive illness, alters with treatment and influences outcome, and, possibly, treatment response. The development of drugs with specific effects on noradrenergic systems should, as with the SSRIs, lead to greater exploration and interest in this neglected aspect of depressive illness.

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