Stress, norepinephrine and depression

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Stress is an important precipitant factor in depression, and the changes in various body systems that occur in depression are similar to those observed in response to stress. This paper discusses the interactions among the immune, endocrine and norepinephrine systems that are evident in patients with depression, as well as those affected by stress. Many of the stress-induced changes can be reversed by antidepressants, particularly norepinephrine reuptake inhibitors.

Le stress est un important facteur catalyseur dans les cas de dépression et les changements subis par les divers systèmes corporels au cours de la dépression ressemblent à ceux qu'on observe face au stress. Cette communication porte sur les interactions entre les systèmes immunitaire, endocrinien et celui de la norépinéphrine, qui sont évidentes chez les patients atteints de dépression, ainsi que chez ceux qui sont touchés par le stress. Il est possible d'inverser un grand nombre de ces changements causés par le stress en utilisant des antidépresseurs et en particulier des inhibiteurs du recaptage de la norépinéphrine.

Introduction

Stress is an important precipitant factor in depression. A significant correlation has been found between the onset of major depression and the number of life-altering events in the previous 3 months. This is not surprising, given that chronic stress causes behavioural, endocrine, immune and neurotransmitter changes qualitatively similar to those observed in major depression.¹

The mechanisms whereby external stressors affect brain function have been the subject of extensive research over the past 60 years. The identification of specific neuropeptides in the brain that become functionally active in response to a stressful stimulus has

led to a clearer understanding of how stressful stimuli activate the central sympathetic system and the pituitary–adrenal axis. The purpose of this brief review is to summarize the evidence that links chronic stress as a causal factor of major depression and implicates a disorganization of the sympathetic system and the pituitary–adrenal axis.

Corticotropin-releasing factor (CRF), the so-called stress hormone, appears to play an important role in the regulation of the central norepinephrine (NE) system. In both animal models and humans, CRF hypersecretion occurs in depression. In addition, immunoreactivity is heightened in the cerebrospinal fluid of depressed patients.² Infusion of CRF into the locus ceruleus of rats stimulates tyrosine hydroxylase (TH),

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an enzyme responsible for NE synthesis, and thereby hastens NE turnover; these effects are blocked by CRF antagonists and NE reuptake inhibitors (NRIs).³ The rapid activation of TH also occurs in experimental models in response to foot shock or noise stress.³ In other words, CRF activates a central stress pathway involving NE. By blocking CRF receptors with the specific antagonist α -helical CRF, researchers have shown that TH changes are indeed dependent on CRF.³

One important experimental study has shown that NE reuptake inhibitors (NRIs) and selective serotonin reuptake inhibitors (SSRIs) can attenuate stress-induced changes in TH activity.⁴ Laboratory animals were treated with saline, desipramine, stress or desipramine plus stress. In animals pretreated with desipramine, the antidepressant attenuated the stress-induced TH response (Table 1).

Various types of antidepressants affect the stress response differently.⁵ Drugs that are highly selective for the NE system appear to act directly on CRF in the locus ceruleus, whereas SSRIs appear to act indirectly to modulate CRF activity in this region.

Other important factors link stress, NE and depression. TH levels in the locus ceruleus of untreated individuals who committed suicide were 108%–172% higher than levels in control subjects.⁶ Moreover, Nemeroff et al.⁷ reported a marked reduction in the number of CRF binding sites in the frontal cortices of suicide victims compared with controls, which suggests that chronic stress can cause a down regulation of central CRF function. The finding that there are 23% fewer neurons in the LC of those who have committed suicide compared with controls has led some researchers to hypothesize that altered NE transmission in severe depression may be due to the presence of fewer NE neurons.⁸

Table 1: Attenuation of stress-induced changes in tyrosine hydroxylase and neurotrophin-3 in the locus ceruleus of rats after pretreatment with desipramine, a norepinephrine reuptake inhibitor⁴

Probe	Pretreatment; enzyme activity, nmol substrate per mg protein per h			
	Saline	Desipramine	Stress	Desipramine + stress
Tyrosine hydroxylase	3880	3252*	6076*	4305†
Neurotrophin-3	213	191	350‡	295‡

* $p < 0.001$ for comparison between desipramine and stress.

† $p < 0.01$ for comparison with all other groups.

‡ $p < 0.01$ for comparison with saline and with desipramine.

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Interactions among the NE, immune and endocrine systems in depression

A close link may exist between changes in the pituitary–adrenal axis, activation of the central NE system, stress responses and depression. This link may be a factor in other pathological aspects of depression. For example, hypersecretion of cortisol occurs in the most depressed patients, an activity that cannot generally be suppressed by dexamethasone. Patients with depressive disorders, particularly those who are not treated effectively, are more prone to heart attacks, autoimmune diseases and changes in the immune system.

The central NE system innervates many vital parts of the immune system — the lymph organs, spleen, bone marrow and thymus. Lymphocytes, mast cells and other immune system cells contain adrenoreceptors that respond to the peripheral release of NE. These cells secrete a number of important cytokines, including interleukins (ILs), IL-1, IL-2 and IL-6, which stimulate neurite growth in the peripheral sympathetic nervous system.⁹

There is evidence that the sympathetic nervous, immune and endocrine systems are linked. More than 10 years ago, investigators examined lymphocyte function in depressed patients with no other illnesses. They found that lymphocyte activity was dramatically reduced in these untreated patients, but that it became normal after antidepressant therapy.¹⁰ This research suggested a biochemical link between the immune system response and the brain. We now know that immune system cells communicate with the brain by means of cytokines, and one connecting factor is clearly the NE system, as indicated above. These cells also secrete neurotransmitters, such as neuropeptides and catecholamines.¹¹

Immune system changes may indeed be influenced by depression. Increased macrophage activity hastens NE turnover in the hypothalamus, increasing CRF release and activating the hypothalamic–pituitary–adrenal axis to produce glucocorticoids (Fig. 1).¹² Under normal circumstances, the immune system is inhibited. However, in chronically depressed patients, the glucocorticoid receptors that normally switch off proinflammatory cytokines are desensitized. This explains why depressed patients do not usually respond to dexamethasone suppression, because glucocorticoid receptors in the immune system and brain are subfunctional. As a consequence, cytokine overproduction,

prostaglandin synthesis, and further activation of the hypothalamic–pituitary–adrenal axis and glucocorticoid production occur, along with other changes. This link between the sympathetic, immune and endocrine systems provides a rationale for the association of physical ill health and the depressed state.¹³

At the cellular level, immune system cytokines (e.g., IL-1 β) increase nitric oxide synthesis, stimulating CRF and guanosine monophosphate and positively affecting amine (i.e., NE) release. Simultaneously, nitric oxide stimulates prostaglandin production through cyclo-oxygenase. Prostaglandins, which are elevated in depressed patients, switch off the amine release (Fig. 2).^{14,15}

Role of TH in depression

A number of studies have examined changes in TH activity in depression, but the results have been equivocal. Ordway et al⁶ found elevated TH levels in the locus ceruleus of suicide victims, but Biegon and Fieldust¹⁶ found no such evidence. Masserano et al¹⁷ found that electroconvulsive therapy administered daily for 7 days significantly elevated TH activity in the locus ceruleus,

hippocampus, frontal cortex and adrenal axis of rats for 4–8 days. Several studies have reported that long-term treatment with a variety of antidepressants attenuates

Fig. 2: Effects of interleukins, nitric oxide and prostaglandins on central amine release. Interleukin-1 β (IL-1 β) increases nitric oxide synthesis (NOS), in turn stimulating CRF and guanosine monophosphate (GMP) and increasing the release of amines such as NE. Simultaneously, nitric oxide stimulates production of prostaglandins (PGs) through cyclo-oxygenase (COX). Prostaglandins, which are elevated in depressed patients, switch off amine release. +, stimulation, –, inhibition.

Fig. 1: Evidence that the sympathetic nervous system, through norepinephrine (NE) activity, plays a vital role in integrating the endocrine and immune systems. Immune activation hastens NE turnover in the hypothalamus, which in turn increases release of corticotropin-releasing factor (CRF) and activates the hypothalamic–pituitary–adrenal axis to produce glucocorticoids. In chronically depressed patients, the glucocorticoid receptors that normally switch off proinflammatory cytokines are desensitized, which results in cytokine over-production, prostaglandin synthesis, and further activation of the hypothalamic–pituitary–adrenal axis and glucocorticoid production. +, stimulation.

stress-induced changes in TH by 40%–70%.^{18–21} Others have also found a decrease in levels of tetrahydrobiopterin, a natural cofactor for TH, in depressed patients.^{22–25} This evidence seems to indicate that adaptive changes in TH and the onset of action of various antidepressants are linked.

Endocrine activity in depression

One of the predisposing factors in major depression is hypothyroidism, and a failure to respond to antidepressants is often associated with reduced thyroid status. In rats, thyroidectomy decreased β_1 -adrenoreceptor density in the cortex, hippocampus and hypothalamus, which in turn affected central NE function.²⁶ α_2 -Adrenoreceptor density was decreased in the amygdala, with NE uptake sites increased in the hippocampus and decreased in the hypothalamus. Long-term thyroxine replacement therapy reversed these effects, and receptor function returned to control levels. These

findings reinforce the importance of considering the patient's endocrine status when antidepressant drugs are prescribed.

Role of NE in depression

In humans, the most convincing evidence of NE abnormality in depression comes from challenge tests. Several investigators have documented a blunted growth hormone response after clonidine challenge.^{27–29} Cortisol responses to methamphetamine and desipramine challenges also suggest dysfunction of the NE system.

The bulk of the evidence suggests that metabolite changes play little or no role in the pathophysiology of depression.^{30,31} Evidence of abnormalities of NE adrenoceptors comes from untreated patients who attempt suicide. These people have a marked diminution in the mean peak response of growth hormone to clonidine challenge.

Another approach is to examine the effect of changes

Fig. 3: The role of NE in depression. The large ovals indicate factors that may cause a biochemical lesion and lead to depression. Chronic stress activates CRF, which increases TH activity in the locus ceruleus and also produces changes in NE function. Once the central sympathetic nervous system is activated, profound peripheral changes occur. Specifically, levels of cortisol, NE and adrenaline become elevated. The effects of chronic stress can be reversed by antidepressants (–).

in α_2 -adrenoreceptor function on platelets. Adrenaline or α_2 -agonist challenge in controlled, depressed and euthymic patients has been shown to blunt adrenoreceptor response, lowering the number of platelet α_2 -adrenoreceptor binding sites and decreasing platelet aggregation.^{32,33}

By and large, these findings indicate abnormalities in α_2 - and β_1 -adrenoreceptor function in depression. However, these studies are controversial. The question remains unresolved, and future research is needed to clarify the exact nature of NE dysfunction in depression. However, this evidence may suggest the presence of a biochemical lesion that involves the NE system. There are a number of possible sites for such a lesion. Depression may be caused by a presynaptic decrease in neurotransmitter production or release (e.g., changes in TH activity), an increase in presynaptic autoregulation, an increase in high-affinity α_2 -adrenoreceptors or impaired receptor function at the nerve terminal, impaired β_1 -adrenoreceptor response on the postsynaptic membrane or abnormal postsynaptic subcellular messenger activity.

Genetic abnormalities, chronic stress or other unknown factors may be responsible for the development of a biochemical lesion in depression (Fig. 3). For example, there is evidence of α_2 - and β_1 -adrenoreceptor abnormalities in depressed patients. The effects of chronic stress are reflected by activation of CRF, which produces changes in NE function in the locus ceruleus through increases in TH activity in this area. Furthermore, chronic stress and higher levels of CRF disrupt the responsiveness of the locus ceruleus to sensory stimuli.

CRF also activates, within the brain and indirectly within the peripheral systems, proinflammatory cytokines, prostaglandins and nitric oxide, thus affecting neurotransmitter function in the brain. Once the central sympathetic nervous system has been activated, profound peripheral changes occur. Specifically, levels of cortisol, NE and adrenaline are elevated. These changes undoubtedly have some impact on brain function that, in untreated patients, may prompt alterations in brain structure. For example, some evidence indicates that the hippocampus may shrink in untreated, chronically depressed patients, possibly as a consequence of cortisol hypersecretion.³⁴

The effects of chronic stress can be reversed by antidepressants, particularly NRIs. These antidepressants may shut down adverse changes by different but as-

yet-unknown mechanisms, some of which may lead to antagonism of stress-related biochemical changes.

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