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Brain, networks, depression, and more

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Abstract
Depression is a heterogeneous disorder with a highly variable course. Individual responses to treatment are inconsistent, and an established mechanism remains elusive. The classical hypothesis of depression posits that mood disorders are caused by a chemical imbalance in the brain that can be corrected with antidepressant drugs. However, recent evidence indicates that information-processing dysfunction within neural networks might underlie depression, and antidepressant drugs induce plastic changes in neuronal connectivity that gradually lead to improvements in neuronal information processing and recovery. This review presents the major current approaches to understanding the biological mechanisms of major depression, with a focus on complex brain networks.

1. Introduction

Depression is a syndrome related to the normal emotions of sadness and affliction. However, its mood symptoms are disproportionate and do not remit when the external cause ceases. Indeed, the classical severe states of depression often have no external precipitating cause such as psychosocial events (endogenous depression) (Wakefield et al., 2007; Belmaker and Agam, 2008).

A diagnosis of a major depressive disorder (MDD) requires a distinct mood modification characterized by sadness or irritability and accompanied by at least several psychophysiological changes, such as disturbances in sleep, appetite, or libido, constipation, weight loss and/or gain, the loss of the ability to experience pleasure during work or with friends (anhedonia), crying, suicidal thoughts, and the slowing of speech and actions. These changes must persist a minimum of 2 weeks and interfere considerably with work and family relations. Based on this broad definition, the lifetime incidence of depression is more than 12% in men and 20% in women (Kessler et al., 2003). Some have advocated a much narrower definition of severe depression, which is termed melancholia or vital depression (Van Praag, 1987; Belmaker and Agam, 2008).

Despite the prevalence and considerable impact of depression, knowledge about its pathophysiology is rudimentary compared to other common, chronic, and multifactorial conditions, such as type-2 diabetes. There are mainly two major explanations for this discrepancy. First and foremost, observing pathological changes within the living brain remains markedly more difficult compared to other organs. The available techniques to document aberrant brain circuit function are *post mortem* studies, which have numerous limitations, and neuroimaging techniques, which rely on detecting neuronal activity differences by

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using indirect markers of activation. Although these approaches have provided important insights into candidate brain regions, simple increases or decreases in regional brain activity most likely are insufficient for explaining the complex array of depressive symptoms. Several animal models have also been used to explore the neural circuitry of depression, but there are important challenges regarding how the information gained from these models should be interpreted (Bouchard, 1994; Belmaker and Agam, 2008; Krishnan and Nestler, 2008).

Second, most depression is idiopathic. The limited understanding of its etiology is reflected by the list of risk factors associated with depression, such as stressful life events, endocrine abnormalities (hypothyroidism and hypercortisolism), cancers (pancreatic adenocarcinoma and breast tumors), and drug side effects (e.g., isotretinoin for acne and interferon-α for hepatitis C), and many others (Nestler et al., 2002; Evans et al., 2005). Genetic association studies have not uncovered strong or consistent genetic risk modifiers (Lopez-Leon et al., 2007), perhaps because of the sheer heterogeneity of depressive syndromes (Nestler et al., 2002; Rush, 2007). Thus, 'depression genes' that could be used to generate rodent disease models have not yet been identified. Genetic predispositions are thought to interact with environmental risk factors, such as stressful life events, which can initiate depressive episodes in some patients (Kendler et al., 1999). Still, the tendency to live in a high-stress environment might also be partly heritable (as is the case for 'risk- or sensation-seekers') (Mill and Petronis, 2007), emphasizing the strong genetic contribution to all depressive episodes, even those that are 'environmentally precipitated' (Krishnan and Nestler, 2008).

Diagnosing depression is subjective and rests on the documentation of a certain number of symptoms that significantly impair function for a given duration (Kessler et al., 2003; Belmaker and Agam, 2008). These diagnostic criteria overlap with anxiety disorders, which have substantial comorbidities with depression (Caspi et al., 2003). Therefore, two 'depressed' patients might have only one symptom in common, and a manic episode in one patient, even later in life, switches the diagnosis to bipolar disorder, which is presumably a distinct pathophysiological entity. This symptom-based diagnostic approach clouds the interpretation of genome-wide association studies and neuroimaging and *post mortem* investigations (Kendler et al., 2006; Belmaker and Agam, 2008; Krishnan and Nestler, 2008).

Thus, depression is a heterogeneous disorder with a highly variable course, an inconsistent response to treatment, and no established mechanism.

This review summarizes the current understanding of the neural and molecular mechanisms of depression, focusing on the leading hypotheses related to brain network theories, and critically examines their strengths and weaknesses in light of recent preclinical and translational studies. Finally, this review highlights new insights garnered from network theories that promise to extend the understanding of depression and improve its treatment.

2. The monoamine-deficiency hypothesis

The 'monoamine hypothesis' of depression originated from the early clinical observations and posits that depression is caused by decreased monoamine levels in the brain (Berton and Nestler, 2006; Pittenger and Duman, 2008). Historically, two structurally unrelated compounds developed for non-psychiatric conditions, iproniazid and imipramine, had potent antidepressant effects in humans and were later shown to enhance central serotonergic or noradrenergic transmission. At the opposite, Reserpine, an old antihypertensive agent that depletes monoamine stores, produced depressive symptoms in a subset of patients. Today's antidepressant agents offer a superior therapeutic index and lower rates of side effects in most patients, but they are still designed to acutely increase monoamine transmission, either by (i) inhibiting neuronal reuptake (e.g., selective serotonin reuptake inhibitors [SSRIs] such as fluoxetine) or by (ii) inhibiting degradation (e.g., monoamine oxidase inhibitors [MAOIs], such as moclobemide). Although these monoamine-based agents are potent antidepressants and alterations in central monoamine function might contribute marginally to genetic vulnerability, the cause of depression is not a simple central monoamine deficiency (Berton and Nestler, 2006; Lopez-Leon et al., 2007; Krishnan and Nestler, 2008).

In fact, MAOIs and SSRIs produce immediate increases in monoamine transmission, but their mood-enhancing properties require several weeks of treatment. Conversely, experimental depletion of monoamines can produce a mild worsening of mood in unmedicated depressed patients, but such manipulations do not alter mood in healthy controls (Ruhe et al., 2007). Moreover, rodent stress models have shown that enhancing dopaminergic and noradrenergic transmission can have maladaptive roles in stress-related disorders by strengthening the memories of aversive life events (Krishnan et al., 2007).

It is now thought that the acute increases in synaptic monoamine levels induced by antidepressants produce secondary neuroplastic changes that are on a longer timescale and involve transcriptional and translational changes that mediate molecular and cellular plasticity (Nestler et al., 2002; Pittenger and Duman, 2008). For example, the serotonin 5-HT1B receptor interacts with a calcium-binding protein (p11) that was upregulated in cerebral cortex upon chronic treatment with SSRIs and was also found to be downregulated in *post mortem* cingulate cortex samples from depressed individuals (Nestler et al., 2002). Brain-specific transgenic overexpression of p11 produced an antidepressant phenotype, implicating this SSRI-mediated upregulation of p11 as an important mechanism downstream of serotonin receptor activation. Chronically administered antidepressants have also been shown to upregulate the transcription factor CREB (cyclic AMP response element-binding protein), which is downstream of several serotonin and other stimulatory G-protein-coupled receptors in the hippocampus; this effect has been validated in *post mortem* human tissue and directly linked to antidepressant-like responses in animal models (Nestler et al., 2002; Svenningsson et al., 2006; Pittenger and Duman, 2008; Krishnan and Nestler, 2008). In contrast, stress activation of CREB in the nucleus accumbens (NAc) triggers depression-like responses, which underscores the crucial region-specific actions of neurotransmitters and their downstream effectors that have not been incorporated into simplistic deficiency models (Nestler and Carlezon, 2006; Krishnan and Nestler, 2008).