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Neurobiological basis of depression: an update

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Abstract

The past 5 years have seen unprecedented advances in our knowledge about the neurobiology of depression. Significant breakthroughs have been made in genomics, imaging, and the identification of key neural systems involved in cognition, emotion, and behavior. In addition, novel targets have been identified for the development of new pharmacological and behavioral treatments. Genetic variations associated with most mental disorders are being identified, and reliable tests for early detection of risk and disease are now on the horizon. New neurobiological concepts have emerged, as they relate to these advances in mental health research such as the serotonin transporter receptor, a genetic variant of which doubles the risk of depression. Brain neurochemicals, including neurotropic factors (implicated in several mental disorders), and anatomical studies involving imaging of the amygdala and the hippocampus and prefrontal cortex are now at the forefront. Several brain neurotransmitters systems: glutamate, γ-aminobutyric acid, serotonin, norepinephrine, and dopamine have been implicated in depression and mania. These transmitter systems, as well as other neurochemical systems such as membrane-bound signal transduction systems and intracellular signaling systems that modulate gene transcription and protein synthesis, play an important role in the etiology of depression. This new knowledge is expected to provide important clues for the development of selective pharmacological interventions. Neuroimaging studies of depressed patients have shown several abnormalities of regional cerebral blood flow and glucose metabolism—a surrogate of neuronal function—in various brain regions, including the limbic cortex, the prefrontal cortex, the hippocampus, the amygdala, and the anterior cingulate cortex. At this time, a considerable amount of new information is converging—derived from animal models of mood disorders, genetics, basic behavioral research, and neuroscience. It is inevitable that the next step in this progression will be the integration of these basic advances in clinical management and the application of this new information in the context of the depressed patient.

1. Introduction

Mood disorders, which affect approximately 7% of the population and rank among the top 10 causes of disability [1], are a cluster of mental conditions characterized by states of depression or mania [2] beyond the normal bounds of elation and sadness. They are associated with severe morbidity and an increased mortality risk. Of the 4 major mood disorders, major depressive disorder (unipolar major depression) is the most common, affecting women twice as often as men. The other major mood disorders are bipolar disorders, dysthymia, and cyclothymia. The resulting disability and suffering are not limited to the patient; spouses, children, parents, siblings, and friends are also affected with varying degrees of severity and have to cope with guilt, frustration, anger, financial hardship, and even physical abuse [2]. Major depressive disorder differs both qualitatively and quantitatively from the usual expressions of sadness in several ways—being marked by hopelessness, loss of mood reactivity, inability to experience pleasure, suicidal thoughts, and psychotic symptoms such as delusions or hallucinations. The diagnosis of major depressive disorder is based on criteria established by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [2]. This manual is considered to be very reliable (90% agreement by independent evaluation) [2]. An untreated major depressive disorder may last an average of 9 months [2] and 80% to 90% of the patients experience an episode of remission within 2 years [3]. Dysthymia is the chronic form of depression that is characterized by its early onset, intertwining with a person's personality and following a "smoldering" course [4]. Dysthymia is often misidentified as a personality disorder and frequently occurs in combination with major depressive disorder [5]. Bipolar disorder is a recurrent mood disorder with several episodes of mania or mixed episodes of mania and depression [2,6]. The ther-

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apeutic effectiveness of lithium salts in bipolar disorder and their lack of effect in unipolar disorder provide information of pathogenic and diagnostic importance about these 2 conditions [6]. Cyclothymia is marked by low-intensity manic and depressive states [2,7], associated with a history of hypomania without prior episodes of mania or major depression [2].

Although the precise etiology of depression is not well understood, the broad forces that shape this mood disorder are well understood: they are biologic, psychological, and sociocultural. The past 5 years have seen an unprecedented advance in our knowledge about the neurobiology of depression. Significant advances have been made in genomics, imaging, and the identification of key neural systems involved in cognition, emotion, and behavior. In addition, novel targets have been identified for the development of new pharmacological and behavioral treatments. Genetic variations associated with most mental disorders are being identified [8], and reliable tests for early detection of risk and disease are now on the horizon. Neuroimaging studies of depressed patients have shown several abnormalities of regional cerebral blood flow and glucose metabolism—an important surrogate of neuronal function—in various brain regions, including the limbic cortex, the prefrontal cortex, the hippocampus, the amygdala, and the anterior cingulate cortex.

Brain neurochemicals including the neurotropic factor (implicated in several mental disorders) [9] and anatomical studies involving imaging of the amygdala [10] and the hippocampus and prefrontal cortex [11] have provided much needed evidence regarding the etiology of depression. Several brain neurotransmitter systems, glutamate, γ-aminobutyric acid, serotonin, norepinephrine, and dopamine, have been implicated in depression and mania. These transmitter systems, as well as other neurochemical systems such as membrane-bound signal transduction systems and intracellular signaling systems that modulate gene transcription and protein synthesis, play an important role. This new knowledge is expected to provide important clues in developing selective pharmacological interventions.

1.1. Monoamines

The monoamine hypothesis of affective disorders has evolved over the past 20 years and has contributed to our understanding of the cellular events leading to amine receptor-mediated signal transduction and the application of this knowledge to current antidepressant therapy [12]. The earliest clinical report of the relationship between brain monoamines and depression was published by Freis [13]. Freis reported on 5 hypertensive patients who developed mental depression after treatment with high doses of reserpine. Since then, the pharmacological discoveries that depletion of brain catecholamines and serotonin by reserpinelike drugs increased availability of norepinephrine and/or serotonin by monoamine oxidase (MAO) inhibitors and tricyclic drugs have provided ample support of the earlier clinical observations [12].

Monoamines such as dopamine, serotonin, and norepinephrine produce their effect by inducing complex biochemical changes in postsynaptic neurons in the central nervous system (CNS) by interacting with signaling proteins (G proteins) inside the postsynaptic cell membrane. These G protein–linked receptors are stimulated by monoamines (as well as certain neuropeptides) and produce a change in the way postsynaptic neurons respond to the ubiquitous (classical) neurotransmitters (glutamate and γ-aminobutyric acid) which bind to "ligand-gated" channels. It is important to note that the number of monoaminergic neurons in the CNS is very small (<1 in 200 000). These neurons send axonal branches throughout the brain forming "an intrinsic modulatory system that acts via other G protein–linked receptors to alter the overall responsiveness of the brain" [2]. It is not surprising that these modulatory neurotransmitters are targets for pharmacotherapy of mental disorders such as depression, as well as for drugs of abuse.

There is a consistent relationship between drug effects on monoamines and affective or behavioral states [12]. Drugs which cause depletion or inactivation of centrally acting norepinephrine (reserpinelike drugs) produce sedation or depression, whereas drugs which increase or potentiate brain norepinephrine (MAO inhibitors and tricyclic antidepressants) are associated with behavioral stimulation/excitement and are generally associated with an antidepressant effect [12]. Although the pharmacological and biochemical effects of the abovementioned antidepressant drugs occur within minutes, clinical practice indicated that antidepressants do not produce their mood-altering effects for at least 10 to 14 days after initiation of treatment. This observation suggests that antidepressants act via a delayed postsynaptic receptor-mediated event.

Serotonin (5-hydroxytryptamine [5-HT]) neurotransmitter systems have been implicated in the pathophysiology of affective disorders [14], and drugs which increase serotonergic activity generally exert antidepressant effects on patients. In addition, urinary and cerebrospinal fluid (CSF) 5-HT and/or its metabolites are found to be reduced in patients with affective illness. The 5-HT content in brains of suicide victims was found to be low as compared with controls [15]. In addition, there was some evidence that there was decrease in the serotonin metabolite, 5-hydroxyindole acetic acid (5-HIAA), in the suicide group [15]. There has been some interest in the finding that patients with affective disorders have low CSF 5-HIAA levels [16]. However, it was later found that low CSF 5-HIAA was a marker for impulsivity [17].

Loading depressed patients with the serotonin precursor tryptophan or 5-hydroxytryptophan, with or without standard antidepressant treatments, has been found to be beneficial in the treatment of depression [18]. In addition, 5-hydroxytryptophan has been shown to help prevent depression [19]. This response has been closely correlated with CSF 5-HIAA levels. Despite an intense effort to

correlate serotonin deficiency with depression, the findings of most studies have been inconclusive. Although serotonin deficiency alone cannot explain the pathophysiology of mood disorders, the interaction of low serotonin levels in the brain with other neurotransmitter systems in the CNS has been considered to be important in the etiology of depression and other mood disorders [18].

An important consideration of the "monoamine hypothesis" requires that it explain the discrepancy between the pharmacological/biochemical action of antidepressant drugs (a few minutes) and the clinical mood-altering response (10-15 days). Vetulani and Sulser [20] reported that chronic antidepressant treatments caused subsensitivity of the noradrenergic receptor–coupled adenylate cyclase system in the brain. This work shifted the emphasis from acute presynaptic to delayed postsynaptic receptor-mediated events in the mode of action of antidepressants. The delayed desensitization of the noradrenergic β-adrenoceptor–coupled adenylate-cylase system in the brain is an action that is common to almost all antidepressant treatments. The adrenergic and serotonergic receptors belong to the superfamily of G protein–coupled receptors which, when bound to norepinephrine or serotonin, respectively, promote the binding of guanosine-5′-O-(3-thiophosphate) (GTP) to G proteins, leading to the regulation of activities of specific effector systems that synthesize cytoplasmic second messengers or ion channels that regulate the flux of specific ions [21]. Discovery of the change that occurs in the sensitivity of the noradrenergic receptor−coupled adenylate cyclase system after chronic treatment with antidepressants has proved to be an important milestone in understanding the regulation and adaptation of the specific response involved in the etiology and treatment of affective disorders. Although the changes in receptor number or the formation of the second messenger cyclic AMP are relatively small, the receptor-coupled adenylate cyclase functions as a highly efficient kinetic amplification system, so that small changes in noradrenergic signal transduction and in formation of the second messenger cyclic AMP are greatly enhanced.

There appears to be a close correlation between electrophysiology and antidepressant-induced desensitization of the postsynaptic β-adrenoceptor system, as evidenced by a significant reduction in the sensitivity of cortical pyramidal and cerebellar Purkinje cells to noradrenaline after chronic treatment with tricyclic antidepressants and MAO inhibitors [22]. Chronic administration of antidepressants leads to an increase in the inhibitory response of forebrain neurons to microiontophoretically applied serotonin and/or dopamine [23].

1.2. Glucocorticoids and aminergic receptors

It is well known that stressful life events and vulnerability to stress are predisposing factors in the precipitation of affective disorders [24-26]. Noradrenergic receptor sensitivity is known to be altered by the level of circulating glucocorticoid hormones [26], and glucocorticoids (along with noradrenaline and serotonin) are the third physiologically important group of regulators of the β-adrenoceptor–coupled adenylate cyclase system in the brain [26] and must be considered in evaluating the etiology and treatment of affective disorders including depression. The serotonin-noradrenergic-glucocorticoid system plays an important role in the neuroanatomical, neurochemical, neurophysiological, psychopharmacological, and endocrine aspects of aminergic receptor systems in the brain which are modified by antidepressant drugs and affective disorders. This system serves to protect adaptive systems against excessive oscillation in sensory input, under normal physiological conditions. However, an impairment in this system results in maladaptation which, in turn, would trigger changes in pain perception and give rise to anhedonia and full-fledged depressive reactions. Antidepressant therapy is aimed at restoring this loss of adaptation by deamplification in the input signal, as discussed earlier in this review. Although this explanation is useful in the understanding of stress-induced depression, the role of glucocorticoid receptors in adrenergic and/or serotonergic perikarya remains to be elucidated [26]. McEwen [26] has discussed the role of disturbances in the hypothalamic-pituitary-adrenal axis in the pathophysiology of affective disorders.

2. Conclusion

Although our understanding of the underlying signal transduction mechanisms in affective disorders has been important in understanding the maladaptive processes in affective disorders, recent advances in genomics and the identification of genetic variations associated with most mental disorders offer new opportunities for design of reliable tests for early detection of risk and disease. We are now in a position to consider the possibility that abnormal behavior patterns—affective, cognitive, and somatosensory—might be caused by a disarray in gene transcription in response to internal (neurohumoral and endocrine) and external (environmental) stimuli, which makes the individual vulnerable to psychiatric disorders.

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