Pathophysiology of depression: do we have any solid evidence of interest to clinicians?

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Due to the clinical and etiological heterogeneity of major depressive disorder, it has been difficult to elucidate its pathophysiology. Current neurobiological theories with the most valid empirical foundation and the highest clinical relevance are reviewed with respect to their strengths and weaknesses. The selected theories are based on studies investigating psychosocial stress and stress hormones, neurotransmitters such as serotonin, norepinephrine, dopamine, glutamate and gamma-aminobutyric acid (GABA), neurocircuitry, neurotrophic factors, and circadian rhythms. Because all theories of depression apply to only some types of depressed patients but not others, and because depressive pathophysiology may vary considerably across the course of illness, the current extant knowledge argues against a unified hypothesis of depression. As a consequence, antidepressant treatments, including psychological and biological approaches, should be tailored for individual patients and disease states. Individual depression hypotheses based on neurobiological knowledge are discussed in terms of their interest to both clinicians in daily practice and clinical researchers developing novel therapies.

Key words: Depression, pathophysiology, genetics, stress, serotonin, norepinephrine, dopamine, neuroimaging, glutamate, GABA

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Major depressive disorder (MDD) is a common and costly disorder which is usually associated with severe and persistent symptoms leading to important social role impairment and increased mortality (1,2). It is one of the most important causes of disability worldwide (3). The high rate of inadequate treatment of the disorder remains a serious concern (1).

This review is aimed at summarizing the solid evidence on the etiology and pathophysiology of MDD that is likely relevant for clinical psychiatry. Neurobiological findings are regarded as solid when they are consistent and convergent, i.e., they have been confirmed by several studies using the same method and fit into results from studies using different methodological approaches.

GENES AND PSYCHOSOCIAL STRESS

Family, twin, and adoption studies provide very solid and consistent evidence that MDD is a familial disorder and that this familiality is mostly or entirely due to genetic factors (4). This important finding suggests that parental social behavior and other familial environmental risk factors are not as important in the pathogenesis of MDD as previously assumed and should not be the major focus of the treatment of the disorder.

The above-mentioned studies consistently show that the influence of genetic factors is around 30-40% (4). Non-genetic factors, explaining the remaining 60-70% of the variance in susceptibility to MDD, are individual-specific environmental effects (including measurement error effects and gene-environment interactions). These effects are mostly adverse events in childhood and ongoing or recent stress due to interpersonal adversities, including childhood sexual abuse, other lifetime trauma, low social support, marital problems, and divorce (5,6).

These results suggest that there is a huge potential in the prevention of MDD by means of psychosocial interventions (e.g., in schools, at workplace). In addition, these results mirror the clinical practice of empirically validated psychotherapies to treat depression (7-9), including interpersonal, psychodynamic and cognitive behavioral psychotherapies and cognitive behavioural analysis system of psychotherapy, which all focus directly or indirectly on interpersonal difficulties and skills. This does not exclude the fact that unidentified non-genetic, non-psychosocial risk factors may also play important roles in some patients (e.g., climatic change, medical conditions).

Stress sensitivity in depression is partly gender-specific. While men and women are, in general, equally sensitive to the depressogenic effects of stressful life events, their responses vary depending upon the type of stressor. Specifically, men are more likely to have depressive episodes following divorce, separation, and work difficulties, whereas women are more sensitive to events in their proximal social network, such as difficulty getting along with an individual, serious illness, or death (10). These findings point to the importance of gender-sensitive psychosocial approaches in the prevention and treatment of MDD.

In contrast to the very solid evidence from epidemiological studies on broad risk factor domains, there is no solid evidence for specific genes and specific gene-by-environment interactions in the pathogenesis of MDD. Genome-wide association studies have indicated that many genes with small effects are involved in complex diseases, increasing the difficulty in identifying such genes (11). While there has been progress in the search for risk genes for several complex diseases despite this methodological problem (12), psychiatric conditions have turned out to be very resistant to robust gene identification. For example, based on a community-based prospective study, it has been proposed that a

specific genetic variation in the promoter region of the serotonin transporter (a target of antidepressant drugs) interacts with stressful life events in the pathogenesis of depression (13). Although there is high clinical and neurobiological plausibility of this interaction, a recent meta-analysis yielded no evidence that the serotonin transporter gene alone or in interaction with psychological stress was associated with the risk of depression (14).

The limited success of genetic studies of depression has been related to use of current classification schemas including ICD-10 and DSM-IV. These diagnostic manuals are based on clusters of symptoms and characteristics of clinical course that do not necessarily describe homogenous disorders but instead reflect common final pathways of different pathophysiolgical processes (15,16). The clinician should be aware that family history will continue to be the most solid source of information to estimate the genetic risk of MDD.

STRESS HORMONES AND CYTOKINES

Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions. This hormone induces the secretion of pituitary corticotropin, which stimulates the adrenal gland to release cortisol into the plasma. The physiologic response to stress is partly gender-specific: women show generally greater stress responsiveness than men, which is consistent with the greater incidence of major depression in women (17). Moreover, men show greater cortisol responses to achievement challenges, whereas women show greater cortisol responses to social rejection challenges (18).

Although MDD is considered as a stress disorder, most subjects treated for MDD have no evidence of dysfunctions of the hypothalamic-pituitary-adrenal axis (HPA) (19). However, some subjects with MDD do show abnormalities of that axis and of the extrahypothalamic CRH system (20). Altered stress hormone secretion appeared to be most prominent in depressed subjects with a history of childhood trauma (21). Elevated cortisol may act as a mediator between major depression and its physical long-term consequences such as coronary heart disease, type II diabetes, and osteoporosis (22).

The importance of HPA axis dysfunction for the efficacy of antidepressants is a matter of debate (23). This axis is regulated through a dual system of mineralocorticoid (MR) and glucocorticoid (GR) receptors. Decreased limbic GR receptor function (24,25) and increased functional activity of the MR system (26) suggest an imbalance in the MR/GR ratio in stress-related conditions such as MDD. Epigenetic regulation of the glucocorticoid receptors has been associated with childhood abuse (27). Such environmental programming of gene expression may represent one possible mechanism that links early life stress to abnormal HPA axis function and increased risk of MDD in adults.

While the CRH stimulation test (dex/CRH test) (28) is a sensitive measure of the HPA axis dysfunction in depression, the specificity of this test for MDD is low. However, non-suppression in the dex/CRH test has consistently predicted increased risk for depressive relapse during clinical remission (23). Additionally, the measurement of waking salivary cortisol concentration has been shown to be a simple and sensitive test for HPA axis hyperactivity in depression (29). Hypercortisolemia is almost exclusively found in subjects with severe and psychotic depression, in whom glucocorticoid antagonists may have some therapeutic effect (30).

There is convergent evidence for CRH to play a major role in the pathogenesis of certain types of depression. Levels of CRH in the cerebrospinal fluid are elevated in some depressed subjects (31). Post-mortem studies reported an increased number of CRH secreting neurons in limbic brain regions in depression (32), likely reflecting a compensatory response to increased CRH concentrations (33). In addition, CRH produces a number of physiological and behavioral alterations that resemble the symptoms of major depression, including decreased appetite, disrupted sleep, decreased libido, and psychomotor alterations (34). There is also preliminary evidence that CRH1 receptor antagonists reduce symptoms of depression and anxiety (35).

"Sickness behavior" as a result of an activation of the inflammatory response system shares many symptoms with depression, including fatigue, anhedonia, psychomotor retardation, and cognitive impairment. Sickness is mediated by pro-inflammatory cytokines such as interleukin-1α, tumor necrosis factor-α, and interleukin-6, which activate the HPA axis and impair the central serotonin system (36). The prevalence of depression as an unwanted effect of recombinant interferons is around 30% (37). In animals, blocking pro-inflammatory cytokine-mediated signaling produces antidepressant-like effects (38). Clinical data suggest that cytokines may play a role in the pathophysiology of a subgroup of depressed subjects, particularly those with comorbid physical conditions (36). The antidepressant enhancing effect of acetylsalicylic acid (39) points to the possible clinical relevance of psychoneuroimmunology in clinical depression research.

Taken together, the laboratory tests with the highest potential to be clinically useful in the care of depressed individuals are based on abnormalities of the neuroendocrine and neuroimmune systems. Despite the large amount of basic science data suggesting that the HPA axis is importantly involved in the pathophysiology of depression, the effect of pharmacological modulation of this neuroendocrine system as antidepressant therapy has been disappointing. The link between childhood trauma and a permanently altered physiologic stress system points to the use of specific psychotherapies in the treatment of depressed patients with a history of early life trauma (40).

THE MEDIATING ROLE OF MONOAMINES

Most of the serotonergic, noradren-

ergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including mood, attention, reward processing, sleep, appetite, and cognition. Almost every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant (19). Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. These observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis.

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system.

Serotonin is the most extensively studied neurotransmitter in depression. The most direct evidence for an abnormally reduced function of central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis. Such a reduction leads to the development of depressive symptoms in subjects at increased risk of depression (subjects with MDD in full remission, healthy subjects with a family history of depression) (41,42), possibly mediated by increased brain metabolism in the ventromedial prefrontal cortex and subcortical brain regions (42). Experimentally reduced central serotonin has been associated with mood congruent memory bias, altered reward-related behaviors, and disruption of inhibitory affective processing (16), all of which add to the clinical plausibility of the serotonin deficiency hypothesis. There is also evidence for abnormalities of serotonin receptors in depression, with the most solid evidence pointing to the serotonin-1A receptor, which regulates serotonin function. Decreased availability of this receptor has been found in multiple brain areas of patients with MDD (43), although this abnormality is not highly specific for MDD and has been found in patients with panic disorder (44) and temporal lobe epilepsy (45), possibly contributing to the considerable comorbidity among these conditions. However, there is no explanation for the mechanism of serotonin loss in depressed patients, and studies of serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem research on the serotonergic system in depression, have yielded inconsistent results. There is preliminary evidence that an increased availability of the brain monoamine oxidase, which metabolizes serotonin, may cause serotonin deficiency (46). In addition, loss-of-function mutations in the gene coding for the brain-specific enzyme tryptophan hydroxylase-2 may explain the loss of serotonin production as a rare risk factor for depression (47).

Dysfunction of the central noradrenergic system has been hypothesized to play a role in the pathophysiology of MDD, based upon evidence of decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase, and decreased density of norepinephrine transporter in the locus coeruleus in depressed patients (48). In addition, decreased neuronal counts in the locus coeruleus, increased alpha-2 adrenergic receptor density, and decreased alpha-1 adrenergic receptor density have been found in the brains of depressed suicide victims post-mortem (49). Since there is no method to selectively deplete central norepinephrine and no imaging tool to study the central norepinephrine system, solid evidence for abnormalities of this system in depression is lacking.

While the classical theories of the neurobiology of depression mainly focused on serotonin and norepinephrine, there is increasing interest in the role of dopamine (50). Dopamine reuptake inhibitors (e.g., nomifensine) and dopamine receptor agonists (e.g., pramipexole) had antidepressant effects in placebo-controlled studies of MDD (51). In the cerebrospinal fluid and jugular vein plasma, levels of dopamine metabolites were consistently reduced in depression, suggesting decreased dopamine turnover (52). Striatal dopamine transporter binding and dopamine uptake were reduced in MDD, consistent with a reduction in dopamine neurotransmission (53). Degeneration of dopamine projections to the striatum in Parkinson's disease was associated with a major depressive syndrome in about one half of cases, which usually preceded the appearance of motor signs (54). Experimentally reduced dopaminergic transmission into the accumbens has been associated with anhedonic symptoms and performance deficits on a reward processing task in subjects at increased risk of depression (55,56). These findings are consistent with the clinical observation that depressed patients have a blunted reaction to positive reinforcers and an abnormal response to negative feedback (57).

Almost all established antidepressants target the monoamine systems (58). However, full and partial resistance to these drugs and their delayed onset of action suggest that dysfunctions of monoaminergic neurotransmitter systems found in MDD represent the downstream effects of other, more primary abnormalities. Despite this limitation, the monoamine-deficiency hypothesis has proved to be the most clinically relevant neurobiological theory of depression. New findings on the role of dopamine in depression emphasize the scientific potential of this theory, and promising reports of antidepressant effects of drugs that modulate the dopaminergic system (e.g., pramipexole, modafinil) in difficult-to-treat depression underline its clinical relevance (51,59).

THE NEUROIMAGING OF DEPRESSION

Although many historical attempts to localize mental functions have failed, they have considerably contributed to a modern neuroscientific understanding of mental disorders (60). The development of neuroimaging techniques has opened up the potential to investigate structural and functional abnormalities in living depressed patients. Unfortunately, the diversity of imaging techniques used, the relatively small and heterogeneous study samples studied, and the limited overlap of results across imaging paradigms

(61) make it difficult to reliably identify neuronal regions or networks with consistently abnormal structure or function in MDD.

Functional imaging studies have provided the most limited overlap of findings. This may be due to methodological limitations and/or the complexity of neurocircuitry involved in MDD. A recent meta-analytic study found the best evidence for abnormal brain activity in MDD in lateral frontal and temporal cortices, insula, and cerebellum. In these brain regions activity was decreased at rest, they showed a relative lack of activation during induction of negative emotions, and an increase in activity following treatment with serotonin reuptake inhibitors. Opposite changes may exist in ventromedial frontal areas, striatum and possibly other subcortical brain regions (61).

More solid evidence has been provided by structural imaging and post-mortem studies. A recent meta-analytic study on brain volume abnormalities in MDD revealed relatively large volume reductions in the ventromedial prefrontal cortex, particularly in the left anterior cingulate and in the orbitofrontal cortex. Moderate volume reductions were found in the lateral prefrontal cortex, hippocampus and striatum (62). Post-mortem studies consistently identified a reduction in glia cell density in dorsal, orbital and subgenual prefrontal cortices, as well as in the amygdala (63,64).

Overall, functional, structural and post-mortem studies suggest that structural and functional abnormalities in the left subgenual cingulate cortex are the most solid neuroanatomical finding in MDD. Volume reduction in this region was found early in illness and in young adults at high familial risk for MDD (65), suggesting a primary neurobiological abnormality associated with the etiology of the illness. Humans with lesions that include the subgenual prefrontal cortex showed abnormal autonomic responses to social stimuli (66), and rats with left-sided lesions in this region had increased sympathetic arousal and corticosterone responses to restraint stress (67). Most importantly, chronic deep brain stimulation to reduce the potentially elevated activity in the subgenual cingulated cortex produced clinical benefits in patients with treatment-resistant depression (68).

In summary, despite the considerable heterogeneity of findings from neuroimaging studies, there is convergent evidence for the presence of abnormalities in the subgenual prefrontal cortex in some patients with MDD. Neuroanatomical research in depression is of great clinical interest, since novel antidepressant treatments such as deep brain stimulation can target specific brain regions. In addition, there are promising leads for neuroimaging findings to predict the likelihood of responses to specific treatments (69).

THE NEUROTROPHIC HYPOTHESIS OF DEPRESSION

Risk factors for depressive episodes change during the course of the illness. The first depressive episode is usually "reactive", i.e., triggered by important psychosocial stressors, while subsequent episodes become increasingly "endogenous", i.e., triggered by minor stressors or occurring spontaneously (70). There is consistent evidence that the volume loss of the hippocampus and other brain regions is related to the duration of depression (71), suggesting that untreated depression leads to hippocampal volume loss, possibly resulting in increased stress sensitivity (72) and increased risk of recurrence (73).

Glucocorticoid neurotoxicity, glutamatergic toxicity, decreased neurotrophic factors, and decreased neurogenesis have been proposed as possible mechanisms explaining brain volume loss in depression. There is no solid evidence on any of these mechanisms, since there are no imaging tools to directly examine neurotoxic and neurotrophic processes in vivo. Brain derived neurotrophic factor (BDNF) has attracted considerable interest. Specifically, preclinical studies have shown correlations between stress-induced depressive-like behaviors and decreases in hippocampal BDNF levels, as well as enhanced expression of BDNF following antidepressant treatment (74). The clinician should be aware of the potentially brain-damaging effect of depression and treat depressed patients as early and effectively as possible.

ALTERED GLUTAMATERGIC AND GABAERGIC NEUROTRANSMISSION

A series of magnetic resonance spectroscopy studies consistently showed reductions in total gamma-aminobutyric acid (GABA) concentrations in the prefrontal and occipital cortex in acute depression (75). This may reflect acute stress effects, since psychological stress seems to induce presynaptic down-regulation of prefrontal GABAergic neurotransmission (76). Alternatively, low total GABA concentration may reflect reduction in the density and size of GABAergic interneurons (77). In addition, chronic stress may reduce GABA-A receptor function, possibly through changes in neuroactive steroid synthesis (78). Contradictory evidence of the GABA hypothesis of depression includes the lack of effects of GABAergic drugs on core depressive symptoms (79) and normal prefrontal GABA concentration in subjects with remitted MDD (80).

Several lines of evidence suggest a dysfunction of the glutamate neurotransmitter system in MDD: a single dose of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine produced rapid and large antidepressant effects in patients with treatment-resistant MDD (81); inhibitors of glutamate release (e.g., lamotrigine, riluzole) demonstrated antidepressant properties (82); abnormal glutamate levels were found in depressed subjects as determined by magnetic resonance spectroscopy (75); and there is evidence for abnormal NMDA signaling in post-mortem tissue preparations (83). Since glutamate is the major excitatory neurotransmitter involved in almost every brain activity, the characterization of the specific role of glutamate in depression deserves further investigation (e.g., there are promising leads that the metabotropic glutamate receptor 5 is specifically involved in MDD (84)).

CIRCADIAN RHYTHMS

Sleep disturbances and daytime fa-

Table 1 Clinically relevant neurobiological hypotheses of major depressive disorder (MDD)

Hypothesis	Main strength	Main weakness
Genetic vulnerability	Solid evidence from twin studies that 30-40% of MDD risk is genetic	No specific MDD risk gene or gene-environment interaction has been reliably identified
Altered HPA axis activity	Plausible explanation for early and recent stress as MDD risk factor	No consistent antidepressant effects of drugs targeting the HPA axis
Deficiency of monoamines	Almost every drug that inhibits monoamine reuptake has antidepressant properties	Monoamine deficiency is likely a secondary downstream effect of other, more primary abnormalities
Dysfunction of specific brain regions	Stimulation of specific brain regions can produce antidepressant effects	Neuroimaging literature in MDD provides limited overlap of results
Neurotoxic and neurotrophic processes	Plausible explanation of "kindling" and brain volume loss during the course of depressive illness	No evidence in humans for specific neurobiological mechanisms
Reduced GABAergic activity	Converging evidence from magnetic resonance spectroscopy and post-mortem studies	No consistent antidepressant effect of drugs targeting the GABA system
Dysregulation of glutamate system	Potentially rapid and robust effects of drugs targeting the glutamate system	Questionable specificity, since glutamate is involved in almost every brain activity
Impaired circadian rhythms	Manipulation of circadian rhythms (e.g., sleep deprivation) can have antidepressant efficacy	No molecular understanding of the link between circadian rhythm disturbances and MDD

HPA – hypothalamic-pituitary-adrenal; GABA – gamma-aminobutyric acid

tigue are diagnostic criteria for MDD, suggesting impaired sleep-wake regulation in depressed patients. In addition, some depressive symptoms may show diurnal variations (mood, psychomotor activity, accessibility of memories of positive and negative experiences), and a subgroup of patients with MDD may have a circadian rhythm disorder (85). In healthy young subjects, moderate changes in the timing of the sleep-wake cycle had specific effects on subsequent mood (86). In depressed patients, manipulations of circadian rhythms (light therapy, sleep deprivation, phase advance treatment) can have antidepressant efficacy.

Based on these findings, circadian abnormalities have been hypothesized to be etiologically associated with MDD (16). The association between phase advance of the sleep-wake cycle and phase advances in nocturnal cortisol secretion; shortened REM latency in some subjects with MDD; and the effect of antidepressants on circadian rhythms of behavior, physiology, and endocrinology contribute to the biological foundation of this hypothesis (85,87,88). Despite of the many promising findings, the molecular and genetic underpinnings of this hypothesis are largely unknown. It remains to be determined whether antidepressant effects of new therapeutics such as agomelatine directly relate to normalization of circadian rhythms (87).

CONCLUSIONS

The main strengths and weaknesses of the various neurobiological hypotheses of depression are summarized in Table 1. The many theories of depression and the relatively low response rate of all available antidepressant treatments clearly argue against a "unified hypothesis of depression" and suggest that depression is a clinically and etiologically heterogeneous disorder.

This encourages research on predictors of the response to therapeutic interventions using biomarkers such as neuroimaging and neuroendocrine tests in combination with genotyping for inter-individual variability with respect to stress sensitivity and antidepressant drug action.

The identification of reliable predictors of therapeutic outcomes will allow for the development of personalized medicine that has the potential to individually tailor interventions and to open up new pathways in the evaluation of novel therapeutic approaches.

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