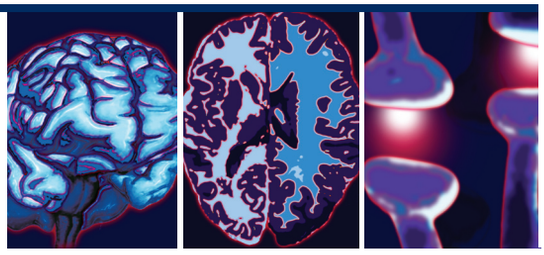
EDITORIAL



Neurobiology of depression: findings, controversies and perspectives

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"...findings give rise to hope of novel drug targets that may help to treat those depressed patients who do not reach remission from current antidepressant therapies."

Despite profound scientific efforts, the neurobiology of depression is poorly understood and the literature reveals many inconsistencies. Nevertheless, we would like to highlight the most impressive findings regarding genetics, gene expression, epigenetics, neuroanatomy, neurochemistry, neuroendocrinology and the neuroimmunology of depression, possibly directing psychiatric research towards novel antidepressant drug targets.

Genetics, epigenetics & gene expression

Consistent findings of family, twin and adoption studies indicate a familiar accumulation of affective disorders and hence suggest a genetic involvement in their pathogenesis [1]. Assuming that affective disorders are complex genetic disorders, a number of linkage and association studies were carried out for the identification of susceptibility genes. Candidate regions for affective disorders were identified on chromosomes 1, 3, 4, 9, 10, 12, 13, 16, 18, 20, 21, 22 and X. Initially, association studies of candidate genes generally focused on polymorphisms of genes whose products perform monoaminergic functions. However, the results of those studies are quite inconsistent. The meta-analytic approach considers the following susceptibility genes for unipolar depression [2]: the genes of the apoE (APOE ε2), those of subunit β3 of the guanine nucleotide binding protein (GNB3), those of the methylenetetrahydrofolate reductase (MTHFR), those of the dopamine receptor (DR)D4 and those of the serotonin transporter genes SLC6A4 and SLC6A3.

Although genome-wide association studies (GWAS) have been the gold standard for genetic testing to date, these analyses have not revealed any genome-wide significant results for unipolar depression so far. A GWAS by Shyn *et al.* using the data of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) patients reported strongly marked, but not genome-wide significant effects regarding the genes

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of a proton pump ATPase (ATP6V1B2), for the transcription factor *SP4* gene and for the gene of the metabotropic glutamate receptor GRM7 [3]. On the basis of the genes identified in GWASs and by applying the candidate gene approach, the conclusion can be drawn that not only the genes directly associated with the monoaminergic synaptic concentration contribute to the pathogenesis of affective disorders, but also genes that affect the metabolism of neurotransmitters, the signal transduction in cells and on cell surfaces, which affect the cell growth and differentiation, the organelles and axonal function of neurons and the circadian rhythm.

Numerous studies performed in recent years have examined the interaction of stressful life events and genetic predisposition with respect to the genesis of an affective disorder by outlining a gene–environment interaction. For example, it was found that a functional polymorphism in the promoter region of the serotonin transporter gene moderates the influence of stressful life events on the development of depression [4].

The most consistent results of gene expression studies are gene expression differences associated with the glutamate and the GABA system. For instance, gene expression differences concerning the VEGF and the serotonin transporter were reported in the peripheral blood cells of depressed patients [5].

Furthermore, epigenetic phenomena have been examined in patients with affective disorders as compared with healthy subjects. In general, the methylation of the DNA cytidine base, as well as histone methylation and acetylation, are among the most important epigenetic modifications. Due to various findings in depressed patients, histone deacetylase inhibitors are now discussed as possible innovative antidepressants [6].

Neuroanatomy

Owing to the increased improvement and refinement of imaging procedures and the broad availability of such methods in psychiatric research, numerous studies have demonstrated structural modifications of distinct areas of neuroanatomy in patients with affective disorders [7,8]. Today, very small anatomic areas can be investigated with the highest precision using high-resolution MRI. Neuroanatomic regions in which depressive patients show consistent MRI abnormalities include the limbic system, the hippocampus and the amygdala as well as the prefrontal cortex. These findings are attributed to both the modifications of the neurons and the modifications of the neuroglia [9]. Interestingly, volumetric MRI studies report negative correlations between the volume of the hippocampus and the duration of untreated depression. Furthermore, some studies suggest that successful therapy can lead to a normalization of the hippocampal volume [10].

Neurochemistry

In the 1960s, the so-called catecholamine deficiency hypothesis of depression was established, which was based on the antidepressant efficacy of imipramine and monoamine oxidase inhibitors [11]. This hypothesis postulates a functional deficiency of monoaminergic and catecholaminergic neurotransmitters in depression. However, recent contradictory data have been published regarding the noradrenalin, serotonin and dopamine systems.

For example, it has been consistently shown that the firing rate of noradrenergic neurons in the locus coeruleus decreases during antidepressant therapy [12]; however, according to the catecholamine deficiency hypothesis, antidepressant treatment and recovery from depression should lead to an increase in noradrenalin. Furthermore, it should be noticed that the serotonin (5-HT) reuptake enhancer tianeptin has a similar antidepressive effect as serotonin reuptake inhibitors [13]. Agomelatin, a 5-HT_{2C} antagonist, is also effective against depression. Komossa and colleagues provide evidence against the catecholamine deficiency hypothesis with respect to dopamine, by demonstrating that antipsychotics with antidopaminergic effects are applicable as a monotherapy or as an augmentation strategy in the pharmacotherapy of depressed patients [14].

A number of additional neurotransmitter and receptor systems have recently gathered interest in the scientific community. In this regard, the acetylcholinergic, the GABAergic and the glutamatergic systems have to be mentioned as examples. Additionally, the role of the modulatory neuropeptids, such as the corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), has to be discussed when thinking about future antidepressant targets.

Neuroendocrinology

Psychopathological abnormalities in endocrinopathies – such as Cushing's disease, hypothyroidism and hypogonadism – indicate a close link between endocrinal and psychiatric symptoms.

In depression, an over-activation of the hypothalamic–pituitary–adrenal (HPA) axis has been a consistent finding [15].

Contrary to the variety of neuroendocrinological studies in patients suffering from depression, relatively few studies have been conducted concerning manic patients or patients with other psychiatric disorders. One study demonstrated that acute mania also results in an over-activation of the HPA axis, which normalizes after remission [16]. Therefore, an over-activation of the HPA axis might not be specific to depression, but could also be observed in other psychiatric disorders.

Neuroimmunology

Neuroimmunological data have led to the postulation of the 'cytokine hypothesis of depression'. This theory implies that some proinflammatory cytokines – such as TNF-α – might have depressogenic effects. Possible mechanisms of action include the activation of the HPA axis, inhibition of the hypothalamic–pituitary–thyroid axis, tryptophan depletion, enhancement of the serotonin reuptake and cerebral apoptotic processes [17]. Various antidepressants reduce the production of cytokines [18], which may be owing to the increase of regulatory T cells during antidepressant therapy [19].

Conclusion

The aforementioned contradictory, or not yet replicated, findings indicate that our biological hypotheses regarding the pathophysiology of depression are preliminary and not yet proven beyond doubt. These antitheses may be derived from the heterogeneity of the depressive symptomatology and the uncertainty as to whether we really have to consider depression as one entity. In the future, the challenge will be to integrate genetic, neuroanatomical, neurochemical, neuroendocrinological and neuroimmunological information as well as data regarding the metabolism of neurotransmitters, signal transduction between and within cells, cell growth and differentiation, organelles and axonal function of neurons and the circadian rhythm as well as the interaction of the social and ecological environment with these biological systems in one model.

Despite all these inconsistencies, the aforementioned findings give rise to hope of novel drug targets that may help to treat those depressed patients who do not reach remission from current antidepressant therapies.

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