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Overview

New trends in the neurobiology and pharmacology of affective disorders

Władysław Lasoń[1], Bogusława Budziszewska[1], Agnieszka Basta-Kaim[1], Marta Kubera[1], Michael Maes[2]

[1]Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

[2]Maes Clinics & TRIA, 998 Rimklongsamsen Road, Bangkok 10310, Thailand

Correspondence: Władysław Lasoń, e-mail: lason@if-pan.krakow.pl

Abstract:
Although depression is a common disorder that is often resistant to pharmacotherapy, its pathophysiology has remained elusive. Since the early 1950s, when the first antidepressants were introduced, i.e., the non-selective MAO inhibitors and tricyclic drugs, a number of hypotheses describing ethiopathogenesis of depression and antidepressant drug action have been formulated. The Institute of Pharmacology, the Polish Academy of Sciences has performed experimental and clinical research focused on the pathophysiology of depression and the mechanisms of action of antidepressant drugs for over 40 years. Our results from this period have significantly contributed to understanding the complex mechanisms of antidepressant drug actions and new pathways that underpin the pathophysiology of depression. Most of these theories are based on the finding that the chronic administration of antidepressants leads to adaptive changes in pre- and post-synaptic monoaminergic and glutamatergic neurotransmission as well as to alterations in gene transcription and immune-inflammatory and neurotrophic factors, resulting in neuroplastic changes in the brain. Taking into account the functional interdependence of the neuronal, hormonal and immunologic systems, we propose neurodevelopmental and neuroimmune theories for affective disorders. Moreover, commonalities have been documented for the pathomechanisms of depression and neurodegenerative and metabolic disorders as well as drug dependence. The aim of this special issue is to briefly present the major research contributions and the new research directions of the Institute of Pharmacology, the Polish Academy of Sciences with respect to the neurobiology of affective disorders and the mechanisms of action of marketed and new putative antidepressant drugs.

Key words:
depression, animal models, neurodevelopment, immunity, comorbidity

Introduction

Despite the enormous effort and the plethora of preclinical and clinical studies describing depression, the efficacy of the pharmacotherapy of depression is unsatisfactory and does not exceed 40–50%. This low efficacy of current antidepressants is because they were designed to act mainly on monoaminergic transmission, when it is known that other pathomechanisms, such as disorders in other neurotransmitters and immune, neurotrophic and endocrine factors, play an important role in depression. An initial theory was that the hypoactivity of monoaminergic neurotransmission is responsible for depressive disorders, whereas consecutive hypotheses pointed to an imbalance of excitatory and inhibitory neurosignaling, immune dysfunctions in the activation of immune-

inflammatory pathways, hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis, and attenuated activity of the growth and neurotrophic factors. All of these pathways, including genetic and epigenetic processes, may lead to long-term alterations in neuroplasticity. The progress in neuroimaging techniques and electrophysiological and molecular methods allowed for the detection of morphological and functional changes in the brain of depressed patients and in experimental models of depression. Moreover, recent data indicate that in depression, morphological and functional changes occur not only in neuronal cells but also in glia.

The aim of this special issue is to briefly present the major research contributions and the new directions for the research conducted at the Institute of Pharmacology, the Polish Academy of Sciences on the neurobiological basis of affective disorders and the mechanisms of action of both marketed and novel putative antidepressants. This research comprises new animal models of depression, the pathways underpinning the comorbidity of depression with other disorders, the neurodevelopmental aspects of depression and the immune-inflammatory, neurotrophic and endocrine aspects of affective disorders.

Animal models of depression

The early hypothesis regarding the putative role of the abnormal expression and function of the central adrenergic receptor in the pathophysiology of affective disorders has been recently strengthened by several lines of evidence. Recent data indicate that although all three subtypes of the α1 adrenergic receptors are important in regulating central nervous system (CNS) function, including the modulation of learning and memory processes, vulnerability to addiction and certain aspects of nociception, the α1A receptor subtype seems to be mainly involved in the mechanism of action of antidepressant drugs. A positive association was found between α1A-AR function and antidepressant-like behavior, whereas α1B adrenergic receptor hyperactivity results in a depressive-like phenotype [19].

The results obtained in the genetic models suggest that the α1 adrenergic receptor subtypes may be targeted for the treatment of mood disorders. The specific involvement of one of the α1-AR subtypes, α1A-AR, in the efficacy of antidepressants was suggested by Nalepa et al. [19], who showed that repeated imipramine and electroconvulsive shock (ECS) treatments but not citalopram elevated the α1A-AR (but not the α1B subtype) mRNA levels as well as the receptor density in the rat cerebral cortex and hippocampus. These authors, using a neurotoxin selective for noradrenergic nerve terminals, provided evidence that the noradrenergic activity of antidepressants is essential for the imipramine-induced changes in the expression of α1A adrenergic receptors.

These findings are in line with the study of Doze et al. [8], who postulated that enhanced α1A adrenergic receptor expression most likely mediates the therapeutic effects of antidepressants and electroconvulsive shock. Moreover, transgenic mice engineered to constitutively express the active mutant (CAM) form of α1A-AR (CAM-a1AAR) or α1B-AR (CAM-α1BAR) show antidepressant- or depressant-like behavior, respectively. Nalepa et al. [19] used a model of chronic mild stress and found further evidence for the involvement of α1B-AR signaling in animal depression-like behaviors, showing that this procedure increased the expression of the α1B-AR mRNA and its density in the rat hippocampus without altering the other two α1-AR subtypes. This effect was observed only in animals that developed anhedonia, suggesting the specific engagement of the α1B-AR in responsiveness to CMS. Prolonged stress induces opposite changes in the adrenergic receptor's density, pointing to time-dependent multiphasic alterations. The stress-induced α1B-AR dynamic changes may also play a role in regulating the HPA axis activity, which frequently shows abnormal activity in depressed patients. The recently discovered and intensively studied phenomenon of the heterodimerization of monoaminergic and peptidergic receptors may lead to a reevaluation of their role in the pathogenesis of depression and in the mechanism of antidepressant drug action. Heteromers can form when these receptors are expressed in the same cell and possess unique pharmacological properties. Szafran and co-workers [31] reported that antidepressant drugs promote heterodimerization of dopamine D2 and somatostatin SST5 receptors despite the lack of affinity of these drugs for the dopamine or somatostatin receptors. These results shed light on the molecular mechanism of somatostatin-induced antidepressant-like behavioral effects, which apparently engage the dopaminergic system. These authors discuss the possible significance of galanin R-5-HT1A R, dopamine D1R-D2R, dopamine – somatostatin D2R-SSTR and serotonin 5HT1A-5HT7 receptor heteromers in the pathome-

chanism of some psychiatric disorders and during antidepressant treatment [31].

An additional research development regarding antidepressant and other psychotropic drugs concerns their metabolism. Haduch et al. [12] reviewed recent research on the CYP2D-catalyzed synthesis of the monoaminergic neurotransmitters dopamine and serotonin in the brain and on the influence of psychotropic drugs on CYP2D activity in the brain. They discussed the contribution of CYP2D to the synthesis of neurotransmitters in the CNS and stressed that the effect of psychotropic drugs on brain CYP2D is structure dependent and differs from its enzymatic activity in the liver. Additionally, it has been postulated that the interaction of psychotropic drugs with brain CYP2D may alter the metabolism of endogenous biologically active substances, e.g., neurosteroids, which has a proposed role in the mechanism of action of antidepressants [12].

Sex hormones are likely to participate in the regulation of mood disorders, and the prevalence of depression is twice as common in women as in men. Nalepa et al. [19] analyzed if and how gender was taken into account in studies on genetically altered mice, which were tested for depressive-like or antidepressant behavior. This analysis showed that potentially significant gender-related differences in the responsivity to antidepressant treatments have been frequently neglected, especially in genetic models [15]. Contemporary views consider the degeneration of astrocytes and glutamate/GABA imbalance in discrete brain regions as important factors in the pathogenesis of depression. Accordingly, a new animal model of depression based on α-aminoadipic acid-induced astrocyte loss in the medial prefrontal cortex of the rat has been proposed.

The role of glial cells in the maintenance of the glutamate/GABA balance in brain tripartite glutamatergic synapses and animal models of depression based on astrocyte impairment have been reviewed by Śmiałowska et al. [33]. Regarding the glutamatergic hypothesis of depression and the possible antidepressant effects of some glutamate receptor ligands, it has been proposed that the mGlu5 receptors are promising targets for treating depression. This assumption has been supported by several experimental data and preliminary results from the clinical trials of the new mGlu5 receptor antagonist, as discussed by Pałucha-Poniewiera et al. [22].

Among the various modulators of ionotropic excitatory amino acid receptors, which have been tested in animal models for their antidepressant activity, zinc appears to be clinically relevant. Decreased blood concentrations of zinc can be considered as a biomarker for treatment-resistant depression. However, the evaluation of changes in the blood concentration of zinc should be combined with the measurements of other biochemical parameters that play a role in the pathophysiology of depression, e.g., some markers of immune activation and oxidative stress [29]. Depression has been shown to be associated with the attenuation of total anti-oxidative status, as reflected by decreased plasma concentrations of glutathione, vitamin E, coenzyme Q10 and glutathione peroxidase. Moreover, some antioxidants (zinc, N-acetylcysteine, ω-3 fatty acids) show antidepressant activity and enhance the efficacy of traditional antidepressant drugs [28].

Comorbidity of depression and other disorders

Despite intensive and long-term studies, the pathogenesis of depression is still poorly understood. One of the strategies used in research at the Institute of Pharmacology to detect important, neurobiological changes responsible for the development of depression is the search for common changes occurring in animal models of depression and models of diseases that often co-occur with depression. Depression is often accompanied by other disorders, such as Parkinson's disease, diabetes type 2, psychostimulant and alcohol addiction and chronic pain. Depression may be due to the progression of these comorbid diseases and the psychological impact of the fear of suffering from these diseases. However, recent data indicate that shared pathways may underpin the pathogenesis of depression and these comorbid disorders. It is known that in Parkinson's disease, motor symptoms occur, such as bradykinesia, rigidity, tremor and postural instability, along with psychiatric symptoms. In this disease, pathological changes occur not only in the brain areas related to motor functions but also in the limbic and cortical regions. Because depression and cognitive disturbances may occur earlier than motor signs and patients suffering from depression have increased risk of Parkinson's disease, the shared neurochemical pathways in both diseases are currently being investigated. In fact, a correlation has been found between

decreased dopamine and noradrenaline transporters in limbic structures and the severity of depression in Parkinson's disease [25]. Furthermore, higher levels of serotonin transporters in the raphe nuclei and limbic structures correlated with depressive symptoms in Parkinson's disease [24]. Although degeneration of dopamine neurons is the main change in Parkinson's disease, depressive symptoms are associated with a lower dopamine transporter in the right caudate nucleus [38]. The comorbidity of depression with Parkinson's disease is important for pharmacotherapy because some antiparkinson drugs may enhance depressive symptoms and some antidepressants may worsen motor functions. To investigate the pathways underpinning the co-existence of Parkinson's disease and depression and to develop new treatments to treat this comorbidity, new animal models reflecting depression during the preclinical and clinical phases of Parkinson disease have been developed [21]. The efficacy and mechanism of different therapeutic strategies have been examined in rats injected with 6-OHDA in the ventral part of the caudate-putamen (depression during preclinical phase) and in rats injected with 6-OHDA in the medial forebrain bundle, without desipramine pretreatment (depression during clinical phase).

In addition to Parkinson disease, diabetes type 2 is frequently associated with depression. Depression increases the risk of type 2 diabetes, and diabetes patients have a significantly increased risk of depression. The common factors/mechanisms involved in the pathogenesis of both disorders is under investigation. One of the changes observed in both diseases is the hyperactivity of hypothalamus-pituitary axis, and it is proposed that the increased levels of glucocorticoids may impair brain metabolic processes, which change the structure and function of neurons and affect neurotransmitter action. Similar dendritic and synaptic reorganizations in the hippocampus occur in an animal model of diabetes and depression [16]. Additionally, in animal models of both diseases, neurogenesis is reduced in the dentate gyrus of the hippocampus, and hippocampal-dependent memory is impaired. Glucocorticoids can also impair the action of brain insulin, a hormone that regulates the metabolism in peripheral tissues and acts as a growth factor in the brain to enhance neuronal survival as well as cognitive functions. This hypothesis is confirmed by the demonstration that chronic unpredictable mild stress reduces insulin signaling and enhances corticotropin-releasing factor (CRF) system activity [23]. In selected brain structures of rats, glucocorticoids and the diabetogenic drug streptozocin evoke similar changes in the activity of glycolytic enzymes [13]. The role of insulin and glucocorticoids on glucose brain metabolic processes is poorly understood and therefore the possible involvement of these hormones in the pathogenesis of depression is also being investigated [7]. Impairments in the brain glucose metabolism in depression have been demonstrated in clinical and functional neuroimaging studies. The hypothesis that impaired insulin signaling may contribute to the pathogenesis of depression is supported by findings that some antidepressants improve glycemic control in both non-diabetic and diabetic depressed patients.

Depression is also frequently comorbid with psychostimulant, opioid and alcohol addiction. A longtime exposure to drugs of abuse cause different neurobiological alterations within the brain, which in turn can increase the risk of depression [37]. For example, it has been found that early exposure to methylphenidate produces depression-like changes, such as increased sensitivity to stress, decreased sensitivity to natural reinforcers and a decreased threshold for helplessness in adult rats [3, 37]. Most evidence indicate that withdrawal from psychostimulants produces several depression-like symptoms and neurochemical changes. For instance, similar changes in noradrenaline, serotonin and dopamine neurotransmission and the hyperactivity of the HPA axis are observed both in the period of withdrawal from amphetamine or cocaine and in major depressive disorders [10]. Moreover, findings that antidepressant drugs attenuate psychostimulant withdrawal symptoms suggest the existence of a common pathogenetic factor between depression and the withdrawal state. Moreover, the therapeutic potential of $sigma_1$ receptor ligands for the treatment of depression induced by ethanol withdrawal is currently examined [30].

An additional research strategy used in the Institute of Pharmacology to determine the neurobiological changes in depression is to examine the mechanisms of action of currently used antidepressant drugs as well as their therapeutic effectiveness in the treatment of other diseases co-occurring with depression. As described above, research on the effectiveness of antidepressants in Parkinson's disease, diabetes and psychostimulant and alcohol addiction are currently being examined. Furthermore, antidepressant drugs have been used in the treatment of various types of chronic pain, especially neuropathic pain. It is be-

lieved that the dysfunction of the descending serotonin or noradrenaline antinociceptive pathways causes comorbid pain symptoms in patients with depression and the vulnerability to depression in individuals with pain. Current research suggests that the analgesic potency of antidepressants may result not only from their effect on monoamine reuptake but also from their actions on NMDA receptors, opioids receptors, sodium channels, uptake of adenosine or the immune system, e.g., the production of pro-inflammatory cytokines. There is some evidence that the activation of glial cells in the spinal cord and increased synthesis of pro-inflammatory cytokines, mainly IL-6 and IL-1β, play a significant role in the development of pain [17, 39]. Currently, disturbed interactions between neuronal, glial and immune cells is considered to be involved not only in chronic pain but also in the pathogenesis of depression. Thus, the examination of the mechanism of antidepressant action in animal models of neuropathic pain is important and can help identify the neurochemical targets/mechanisms for analgesic as well as antidepressant effects. Furthermore, due to the weak analgesic effects of opioids and non-steroidal anti-inflammatory drugs, antidepressants are often used in the treatment of neuropathic pain and diabetic neuropathy. Therefore, it is essential to determine their effectiveness and mechanism of action as analgesic agents [18, 41].

The strong comorbidity of depression with other diseases, which also affect brain functions, at least partially reflects that shared or overlapping environmental, genetic and neurobiological factors are involved in their pathogenesis. The use of animal models of depression comorbid with other disorders creates a new opportunity to identify pathophysiological factors of depression.

An important direction of the research conducted by the Institute of Pharmacology is to use combination treatments to increase the therapeutic efficacy of currently used antidepressants. Clinical data indicate that approximately 40% of depressed patients did not respond to antidepressant drug therapy [1]. Therefore, combination treatments of antidepressant drugs with new drugs/substances that can augment the efficacy of antidepressants have been examined. The efficacy, safety and mechanism of action of atypical antipsychotic drugs in combination with antidepressants is currently being studied because the former may augment the efficacy of the latter. The results indicate that low doses of atypical antipsychotics potentiate the action of antidepressant drugs and that they have effects on 5-HT1A, 5-HT2A and α2-adrenergic receptors [26].

Neurodevelopmental aspects of depression

Disruptions in monoamine signaling and neuroinflammation and changes in neuroplasticity or stress are some of the factors that increase the vulnerability to depression. However, most of these theories focus on the links between genetic and environmental factors, which are highly heterogeneous and complex. Starting from the perinatal period, the genetic background responsible for shaping new functions may be modified by environmental factors. Different factors affecting the maturation of brain circuits that underpin affective functions are recognized and have been observed to impair synaptic plasticity, i.e., axon branching, dendritogenesis and neurogenesis in specific areas of the CNS (such as the hippocampus, frontal cortex, amygdala), leading to the conclusion that depression may result from neurodevelopmental changes. Therefore, neurodevelopmental models of depressive disorders have been proposed.

Early life adversity (ELA) is thought to be an essential factor in the development of anxiety and mood disorders. To date, the precise mechanisms underlying adversity-associated neurobehavioral changes have not been elucidated. Studies in animal models of ELA (evidenced by adequate behavioral tests) demonstrated that stressful experiences during early life may modify both unconditioned and conditioned fear responses as well as cognitive functions and memory. Early life adversity affects behaviors dependent on the medial prefrontal cortex and the structural (i.e., morphological remodeling of dendrites and synapses turnover) and the functional synaptic plasticity of this brain structure. It should be emphasized that ELA-induced changes modulate brain functions by modifying the reactivity of the HPA axis and that these changes are regulated through epigenetic mechanisms, such as DNA methylation, histones modifications or microRNAs. Recent data indicate that the development of ELA-evoked vulnerability or resistance to future aversive events depends on three main fac-

tors: genetic predisposition and early life and later-life environment [4].

New data suggest that maternal care is one of the most important environmental factors that influences behavioral and emotional factors. It shapes emotional and psychological responses and is important in cognitive and emotional behavior. Disruptions in the relationships between the mother and her offspring may create a so-called "allostatic load", which is the repeated activation of stress mediators (e.g., glucocorticoids, catecholamines) that affects behavior and neurochemistry over the lifetime of the individual. In human beings, a lack of maternal care in the early postnatal period is a risk factor for different types of mental illnesses in later adult life, such as psychosis, depression and anxiety. There are two main types of maternal deprivation models in animals: early deprivation, where the pups are removed from the mother and transferred to a new environment, and maternal separation, where the mother is removed from the home cage. These procedures can also be modified by separating pups from their siblings. After a short period of separation, the mother rats intensify maternal behavior (grooming, licking), which explains why long-term and repeated 15 minutes neonatal isolations may attenuate stress responses in the pups. Changes in the HPA system (e.g., altered CRH gene expression, dampening and shortening of adrenocorticotropic hormone and corticosterone response in the brain) cause adult rats to show decreased behavioral and endocrine stress responses. Repeated 180 minute-long separations (MS180) result in increased stress reactivity in later life and is considered as an adequate model of depression. Apart from behavioral aspects (anxiety, depression-like syndrome, anhedonia), the rats subjected to MS180 exhibit neurochemical changes in the brain related to altered CRH, dopamine, noradrenaline and GABA transmission, along with disturbances in neurotrophic factors, e.g., brain-derived neurotrophic factor (BDNF). Because behavioral and physiological changes in adult maternally separated rats show homology with the effects of mother deprivation in humans, early maternal separation serves as a valid animal model of human depression [36].

To evaluate the effects of stress on the functions of the medial frontal cortex in rats, a behavioral test, called the attentional set-shifting task (ASST), proved to be of use. The most important element of this test is the stage called extradimensional set-shifting (ED). This stage is an indicator of cognitive flexibility and is impaired by lesions of the medial prefrontal cortex. Recent experimental data indicate that various types of chronic or acute stress have a different impact on cognitive flexibility. As a major risk factor for depression, stress causes changes connected not only with glucocorticoids but also with monoaminergic and glutaminianergic systems. It has been found that deficits in ASST induced by chronic stress can be prevented by antidepressant treatment with drugs that have different mechanisms of action (for example, selective noradrenaline reuptake inhibitors and selective serotonin reuptake inhibitors) [20].

The fact that abnormalities and disturbances in developmental neuroplasticity may lead to the occurrence of depression is supported by theories concerning the participation of adhesion molecules and neurotrophic factors in the pathogenesis of the disease. Neuroplastic changes observed in animal models of stress and depression comprise dendritic atrophy and reductions in spine density in principal neurons of the hippocampus and medial prefrontal cortex. Moreover, the examination of the morphological and metabolic brain changes in patients suffering from depression revealed significant decreases in morphological volume within the cortico-limbic circuit. In the developing nervous system, adhesion molecules, e.g., neural cell adhesion molecules (NCAM), play an important role. NCAM belongs to the family of immunoglobulins and under specific conditions undergoes polysialization (PSA-NCAM) and promotes (among other) axonal growth, synaptic reorganization and synaptogenesis. Thus, changes in PSA-NCAM expression may be relevant to the morphological changes present in the depressed brain. In fact, depressed patients exhibit decreased PSA-NCAM expression in the basolateral and basomedial amygdala [35]. T ransgenic mice lacking all three major isoforms of NCAM exhibit anhedonia along with increased levels of fear and anxiety, which makes this model useful in studies designed to determine the involvement of NCAM in depression. Furthermore, antidepressant drugs influenced PSA-NCAM expression, e.g., fluoxetine acts *via* changes in serotonergic transmission in a manner involving 5-HT3 receptors [34]. Based on these discoveries, it is proposed that the efficacy of antidepressants may be ascribed to an improvement of brain plasticity. The data also suggest that antidepressants may be effective in the treatment of brain disorders caused by abnormalities in neuroplasticity. Unfortu-

nately, due to the lack of sufficient clinical data, it cannot be presumed that NCAMs are associated with the onset of depression [40].

A new theory of depression shows that impaired neuronal plasticity associated with dysregulations in the expression and function of neurotrophic factors is involved in the pathophysiology of depression. In depression, the most extensively studied neurotrophic factor is BDNF; however, recently, the focus has been on family of Insulin-like Growth Factor-1 (IGF-1). Because IGF-1 is able to influence synaptic plasticity and adult neurogenesis, it is possible that disturbances in the IGF-1 system may be implicated in the pathogenesis of affective disorders. Apart from being a potent regulator of cell growth, survival and differentiation, IGF-1 increases the activity and synthesis of other neurotrophins, such as BDNF, and is additionally regulated by the immune system. A research strategy used in the Institute of Pharmacology determines role of IGF-1 in various animal models of affective disorders (i.e., prenatal stress, maternal separation). IGF-1 expression differs between the control and experimental animals in the brain areas associated with depression, such as the hippocampus, frontal cortex, hypothalamus and olfactory bulbs. Moreover, the central or subcutaneous administration of IGF-1 reverses depression-like behaviors in behavioral tests, such as the forced swim test and tail suspension test, whereas IGF-1 levels are affected by antidepressant drugs [32].

Immunologic and endocrine aspects of depression

Depression has been characterized as a disorder with a multifactorial etiology. Both immune system suppression and immune system activation may be associated with depression. Various populations of macrophages play a pivotal role in maintaining homeostasis; however, they also have proinflammatory properties, which may be involved in the onset of depression. Recent studies have demonstrated increased levels of proinflammatory cytokines (i.e., IL-6, TNF-α) in the serum of depressed patients. Activated immune-inflammatory pathways influence several neuronal processes, especially disturbances in neurogenesis and neurotransmitter synthesis, over-activation of the glutamatergic system and the NMDA receptors, disturbances in serotonergic transmission, decreases in the expression of trophic and growth factors (e.g., BDNF) and activation of the HPA axis. Moreover, both pharmacological and non-pharmacological anti-depressive treatments have significant effects on activated immune-inflammatory pathways, and antidepressant treatments may have anti-inflammatory properties, thereby suppressing macrophage functions [27]. Recent experimental studies have shown that antidepressants, such as fluoxetine and desipramine, are able to effectively suppress contact hypersensitivity reaction (CHS). The CHS reaction to haptens is a classic example of a cell-mediated immune response with numerous pro-inflammatory agents involved. Although the exact mechanism of the inhibitory properties of antidepressants on CHS responses is unknown, the response may be due to the inhibitory effects on T effector cell (Th1 CD4+ and CD8+ Tc1) activity or increased production of interleukin (IL)-10. These data support the theory that T-cell mediated immune responses may be a new drug target for antidepressant drugs [5].

IL-6 is a cytokine expressed during inflammatory responses in many cells. Tumor necrosis factor-α (TNF-α) and interferon γ (IFN-γ) can differentially induce IL-6 in astrocytes, microglia, neurons and endothelial cells. Increased levels of IL-6 and sIL-6R (soluble interleukin-6 receptor) are observed in depression, bipolar disorder, post-traumatic stress disorder, schizophrenia and autistic spectrum disorders. IL-6 is significantly increased in animal models of depression. Antidepressants can decrease or increase IL-6 in humans and animal models, indicating a complex role of IL-6 trans-signaling in depression.

IL-6 activates indoleamine 2,3-dioxygenase (IDO) and induces the production of tryptophan catabolites, including KYNA (kynurenic acid), QUIN (quinolinic acid) and NAD^+ (nicotinamide adenine dinucleotide). NAD^+ is an inducer of the sirtuins, which contribute to many of the processes dysregulated in depression (neurogenesis, circadian rhythm and mitochondrial regulation). Induction of IDO causes the loss of melatonin and N-acetylserotonin (NAS). Melatonin and NAS increase neurogenesis; thus, IL-6 is generally thought to decrease hippocampal neurogenesis. The efficacy of melatonin may be partially mediated by its regulation of epigenetic processes, including the induction of methyl-CpG-binding protein 2 (MeCP2). The decreased level of MeCP2 is evident in Alzheimer's disease, Parkinson's disease, and schizophrenia. All of these conditions are associated with raised levels of stress responsivity and depression.

The role of IL-6 in depression may be associated with the regulation of local inflammation (*via* interactions with macrophage and glia melatonin production and MeCP2 regulation) and tryptophan availability (*via* the IL-6 induction of IDO) [2].

Hyperactivity of HPA axis is a common clinical symptom that is evident in depression. Many patients suffering from major depression show increased secretion of corticotropin-releasing hormone (CRH) as well as elevated blood glucocorticoid levels. Moreover, both acute and chronic stress impaired the functioning of the immune system, mainly by inducing a pro-inflammatory response. One of the most important pro-inflammatory cytokines involved in HPA axis activation is interleukin-1β (IL-1β), which not only increases CRH response but is also known to mediate nitric oxide (NO) production. During stress exposure, IL-1β induces iNOS expression, which contributes to depressive-like symptoms. Recent data indicate that increased production of prostaglandins mediated by cyclooxygenases-1 and -2 (COX-1, COX-2) is part of the HPA axis response under stress conditions. Pro-inflammatory mediators seem to have a significant impact in depressed patients, especially among those showing dysregulation of HPA axis activity [11].

Prolactin (PRL) and somatostatin (SST) are "opposing" neurohormones and are involved in emotional processes, such as anxiety and depression. The most interesting results are the data obtained in rats subjected to Chronic Mild Stress, an animal model of depression. Although hyperprolactinemia is well documented in patients after treatment with neuroleptics, there are only few papers showing the same response after treatment with antidepressants. The activities of prolactin are mediated by PRL receptors (PRL), which are located in various brain regions. The highest levels of these PRL receptors are found in the choroid plexus, where the PRLR transport from blood to CSF during exposure to CMS for 2 weeks allows for the selection of stress reactive and non-reactive animals. The latter group showed an elevated level of PRL in the plasma, decreased dopamine release in the tuberoinfundibular tract and increased [^{125}I]PRL binding to PRL receptors in the choroid plexus.

SST is an inhibitor of several hormonal secretions, e.g., PRL and growth hormone. This neuropeptide acts *via* an interaction with G protein-coupled somatostatin receptors (sst1R – sst5R), which are localized in the brain cortex, striatum and limbic system, where they colocalize with the dopamine receptors. In the CMS model, the levels of SST receptors are altered by chronic stress and antidepressants. In animals that did not respond to imipramine treatment, the SST binding sites decreased in comparison with rats that responded to the drug.

These data suggest that PRL and SST play important roles in the mechanism of stress-resilience and the mechanism of action of antidepressant drugs [9].

Recent data indicate that increasing concentrations of organic pollutants in the environment, known as Endocrine Disrupting Chemicals (EDCs), are associated with neurological disorders, including depression [14]. EDCs, including dioxins, polychlorinated biphenyls, pesticides, brominated flame retardants and plasticizers (bisphenol A), are resistant to degradation and may cross the placental and blood-brain barrier because of their lipophilic properties. These compounds show affinity to some hormone receptors, mainly to estrogen receptors, and disrupt hormone-dependent processes. EDCs affect the function of the CNS by interfering with steroid hormones and thyroid signaling and acting through the aryl hydrocarbon receptor (AhR) [6]. These compounds disturb the proliferation of neural progenitor cells as well as the processes of differentiation, migration, synaptogenesis and myelination. Recent epidemiological data indicate that prenatal exposure to some EDCs may affect cognitive function and mental development in children. It seems that these compounds are also associated with the development of depression because they may alter neurotransmitter function, e.g., that of serotonin. The data show that the changes produced by EDCs in the prenatal period and infancy are responsible for the onset of depression in later life [14].

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