CellPress

The ceramide system as a novel antidepressant target

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Major depression is a systems disorder which impairs not only central nervous system aspects of mood and behavior but also peripheral organ systems. Current views on the pathogenesis and treatment of depression are predominantly based on proteins and transmitters and thus are difficult to reconcile central with peripheral pathomechanisms. Recent research showed that there is also a lipid-based pathway involved in the pathology of depression, which is activated by psychosocial stress, oxidative stress, or inflammation. Inducible dysfunction of the ceramide pathway, which is abundant in the brain as well as in peripheral organs, may account for mood disorder, behavioral symptoms, and further promote inflammation and oxidative stress in peripheral systems. As such, the lipid ceramide pathway may provide the missing link between brain dysfunction and somatic symptoms of depression. Pharmacological interventions that reduce ceramide abundance also show antidepressant action and may promise a better treatment of major depression.

Depression as a systems disorder

Major depressive disorder (MDD) is a severe mood disorder with a lifetime prevalence of more than 10% [1]. Patients often show a marked loss of interest or pleasure in activities that are normally pleasurable, a lack of emotional reactions, early waking in the morning, marked psychomotor retardation or agitation, and a marked loss of appetite, weight, and libido. The circadian rhythm of mood is more variable compared to unaffected individuals. The clinical presentation of MDD is heterogeneous with melancholic depression occurring most frequently. However, atypical depression affects approximately 15–30% of depressed cases and is characterized by fatigue and hypersomnia, increased appetite, and weight gain [2,3]. The distinction between these two subtypes is relatively stable over long periods [3]. MDD currently ranks fourth in the global burden of disease and is expected to rise to second place by 2030 worldwide and to first place in high-income countries [4]. The suicide risk is several-fold increased in

MDD compared to the general population [5]. There is a substantial heritability of MDD [6]. However, specific genetic loci have not yet been convincingly identified [7]. Hippocampal volume is reduced in first episode depression and is smaller during depressive episodes than during remission [8]. Besides the subjective suffering and behavioral impairments, there are also multiple peripheral organ systems impaired in MDD (Box 1). Overall, MDD is a highly prevalent systems disorder with psychological and peripheral manifestations that together result in significantly reduced quality of life.

The best known 'pharmaco' treatments of depression are based on their interaction with transporter or receptor proteins in the brain, but a substantial proportion of patients do not respond adequately. Nevertheless, this has shaped a picture of depression as a predominantly protein-driven brain disorder, which has faced problems in explaining the somatic symptoms such as inflammation or coronary dysfunction. Here, we review recent evidence which suggests a major pathway into and out of depression mediated by lipids, which may well capture the somatic side of the disorder.

Neurobiological theories of depression

The neuroplasticity hypothesis states that intracellular mechanisms mediate a stress-induced reduction of neurotrophic factors, which are necessary for survival of certain neurons [9]. This results in a disturbed proapoptotic and antiapoptotic balance, as well as a disrupted neurogenetic balance. Adult neurogenesis, which occurs in the dentate gyrus of the hippocampus [10], is inhibited by stressful experiences and by corticosteroids [11]. Patients suffering from depression and anxiety usually develop hippocampal atrophy [8]. Antidepressant therapies such as tricyclic antidepressant drugs, lithium, electroconvulsive therapy, and physical activity increase adult neurogenesis [11]. It was shown that adult hippocampal neurogenesis buffers stress responses [12], a finding linking the neuroplasticity hypothesis to the hypothalamus–pituitary–adrenal (HPA)/stress hypothesis. An inhibition of adult neurogenesis blocks the behavioral effects of antidepressants [13]. However, a blockade of hippocampal neurogenesis does not induce depression-like behavior in mice [13].

According to the HPA/stress hypothesis, genetic risk factors interact with environmental stressors, such as

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Box 1. Depression: more than a brain disorder

According to meta-analyses from longitudinal studies, MDD increases overall mortality and morbidity and enhances the risk for heart disease, hypertension, stroke, diabetes, Alzheimer's disease, obesity, and cancer with pooled risk estimates ranging from 1.8 for overall mortality to 1.3 for cancer [27]. Furthermore, according to meta-analyses and systematic reviews from cross-sectional studies, MDD is associated with additional disease constellations and dysregulation of the biological system, such as osteoporosis [55], irritable bowel syndrome [111], and metabolic syndrome [73], in particular abdominal obesity [124]. Increased levels of proinflammatory cytokines, such as IL-6, and TNF-α [23,24], oxidative stress [112], and HPA axis dysregulation with higher CRH, adrenocorticotropic hormone, and peripheral cortisol levels [113] are found in MDD. There are also abnormalities in heart rate variability [114]. Importantly, the links between MDD and inflammation [72], as well as MDD and metabolic syndrome [73], appear bidirectional. Altogether, MDD is a multisystems disorder with symptoms beyond psychological manifestations.

traumatic life events in childhood, thus contributing to the occurrence of a depressive episode. Stress is an important trigger of depressive episodes [14,15] and may be modulated by serotonergic neurotransmission [16]. According to this hypothesis, glucocorticoids triggered by stress result in downstream cellular effects leading to degeneration and dysfunction of brain areas normally inhibiting the HPA axis by negative feedback mechanisms [17]. However, corticotropin-releasing hormone (CRH) receptor antagonists show antidepressant effects in animal models, but not in humans [18]. In addition, many patients with MDD have no psychosocial stressors, and there is also no evidence for alterations of the HPA–stress axis in many patients.

The monoamine hypothesis suggests that a deficit of the neurotransmitters serotonin, norepinephrine, or dopamine is responsible for the occurrence of depressive symptoms [19]. This hypothesis rests on the fact that nearly all antidepressant drugs enhance the synaptic availability of monoamines. The hypothesis has a strong predictive power. Nearly all compounds that enhance monoamine availability show an antidepressant effect. However, the hypothesis has also several limitations. Although the effects of antidepressant treatment are influenced by a polymorphism in the serotonin transporter gene [20], there is no association between this polymorphism and the risk of depression [14]. The purported monoamine deficiency has not been reliably demonstrated in patients with MDD and a substantial proportion of MDD patients do not respond to monoamine targeting antidepressant treatment. Depletion of serotonin and norepinephrine does not induce MDD in healthy individuals, but only results in a relapse of depression in patients successfully treated with serotonin reuptake inhibitors [21]. Thus, monoamines are important for the mechanism of action of serotonin reuptake inhibitors, but additional mechanisms are required for the induction of a major depressive episode. A direct link between altered hippocampal neurogenesis and reduced monoaminergic function is currently unclear [22].

The cytokine/inflammatory hypothesis suggests that proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) are increased in patients with MDD [23,24]. Exposure to peripheral cytokine inducers prompts depressive symptoms [25] and may reduce monoamine levels in the brain [26]. However, peripheral proinflammatory markers are elevated only in a subgroup of patients with MDD.

The two major clinical subtypes of MDD tend to be associated with biological parameters: metabolic and immune inflammatory dysregulation with atypical depression and HPA axis dysregulation with melancholic depression [27]. This may suggest different etiologies and starting points converging to the syndrome of MDD. However, available biological theories of MDD are so far only partially related to each other. Disturbed neuroplasticity and reduced hippocampal neurogenesis may explain the buffered stress response [12], but not monoamine deficiency [22]. In particular, the relationship between the peripheral proinflammatory cytokines and central dysregulation is insufficiently understood.

Here, we suggest that ceramide might be the missing link between peripheral immune inflammatory–oxidative stress dysregulation and central mechanisms of MDD by providing initially independent starting points for interlinked pathological mechanisms. Ceramide induces the generation of reactive oxygen species and is important for full cytokine response to infection. Proinflammatory cytokines and oxidative stress, in turn, independently stimulate acid sphingomyelinase (ASM)/ceramide in the immune system. In peripheral organ systems, a local ceramide increase may cause metabolic syndrome, heart disease, and other organ dysfunctions. The HPA axis dysregulation in MDD may indirectly be explained by increased abundance of ceramide in the brain. Ceramide results in reduced hippocampal neurogenesis. As a result, the negative hippocampal control of the HPA axis is reduced and monoamine systems become dysregulated. MDD may, thus, be conceptualized as a ceramide overload or 'ceramidose'. Depending on the organ system or cell type, where ceramide abundance particularly increases, the corresponding clinical manifestations may occur (Figure 1).

Ceramide in organ systems

Ceramide is the central molecule of the sphingolipid pathway [28]. It can be generated either by *de novo* synthesis starting from palmitoyl-CoA and serine or by the reacylation of its degradation product sphingosine. Alternatively, ceramide can be formed by the hydrolysis of sphingomyelin or glycosphingolipids (Figure 2). The ASM/ceramide system has a major function in infection and inflammation of peripheral organs [29,30]. Infection with bacteria or viruses results in activation of the ASM and a concomitant release of ceramide. Ceramide has been shown to function in several forms of cellular stress. Activation of ASM and the concomitant increase in the cellular ceramide concentration is triggered by diverse receptors including those for CD95L, TNF-α, IL-1, and platelet-activating factor (PAF), and by cellular stress induced by ischemia, radiation, oxidative stress, or chemotherapeutic agents [28,31–34] (Box 2). Psychological stress induces oxidative stress in humans [35,36], as well as experimental animals [37,38], in the periphery and central nervous systems [37,38]. Reactive oxygen species and oxidative stress increase