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**Review**

# Sphingolipids in Major Depression

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**Abstract**
Major depression is one of the most common and severe diseases affecting the world's population. However, the pathogenesis of the disease remains inadequately defined. Previously, a lack of monoaminergic neurotransmitters was the focus of pathophysiological concepts; however, recent concepts focus on a alteration of neurogenesis in the hippocampus. This concept suggests that neurogenesis is decreased in major depression with a rarefication of neuronal networks and a lack of new, immature neurons in the hippocampus, events that may result in the clinical symptoms of major depression. However, molecular targets involved in the pathogenesis of major depression and, in particular, a reduction of neurogenesis, are largely unknown. We have recently discovered that an inhibition of the acid sphingomyelinase/ceramide system mediates the effects of tri- and tetracyclic antidepressants. Moreover, an accumulation of ceramide in the hippocampus results in depression-like symptoms. This suggests the acid sphingomyelinase/ceramide system is very important in the pathogenesis of major depression.



## Pathophysiological models of major depression

With a lifetime prevalence of more than 10% in the overall population and an estimated suicide rate of 10%, major depressive disorder is one of the most severe chronic illnesses [1]. Patients with major depression suffer not only from depressed mood, loss of interest, anhedonia, fear, feelings of worthlessness, weight loss, insomnia, and concentration deficits,

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but also from cardiovascular symptoms, osteoporosis, adrenocortical activation and a general pro-inflammatory status [2-9].

Although major depression is a very common disease, the pathogenesis is presently still unknown. Many patients show high plasma concentrations of cortisol and dysfunction of the hypothalamic-pituitary-adrenal axis [1]. However, the molecular mechanisms causing this increase as well as the pathophysiological consequences of these changes are still poorly characterized. A recent concept indicated a lack of neurogenesis in the hippocampus [10-20], a concept that will be discussed in more detail below. Surprisingly, even the molecular targets of antidepressants are as of yet unclear. Most antidepressants regulate the concentrations of monoaminergic transmitters in the synaptic space, and the effect of antidepressants on the monoaminergic transporters in the synpatic membrane has been considered the active mechanism of these drugs [21]. However, this hypothesis has been questioned since (i) some antidepressants, in particular tianeptine, promote serotonin reuptake rather than block it [22, 23], (ii) the regulation of synaptic uptake of monoamines is very rapid after treatment, while the clinical effect of antidepressants is usually delayed by 2 to 4 weeks and (iii) anti-inflammatory therapies also show therapeutic effects in major depression, which is difficult to explain with the monoaminergic neurotransmitter hypothesis of antidepressants [4, 5, 24].

In particular the delay of 2-4 weeks in therapeutic effects of many antidepressants suggests a trophic effect of antidepressants and, therefore, recent concepts of the pathogenesis of major depression have focused on a defect in neurogenesis and the correct function of neuronal networks in the hippocampus to explain the pathophysiology of major depressive disorder. The hypothesis that hippocampal neurogenesis is reduced in major depression is also supported by the finding that at least in some cases major depression also leads to hippocampal atrophy [25]. The atrophy seems to be primarily caused by a reduction in the number of glial cells rather than in the number of neurons [26]. The role of glial cells in the genesis of major depression is largely unknown. However, a concept of an imbalance between neurogenesis and possibly glial cell genesis and apoptotic events in the hippocampus has become very attractive to explain many of the pathophysiological findings. It should be noted that the molecular cause for the defect of neuro- and gliagenesis is also still unknown.

Mammalian brains show two hotspots of neurogenesis- the subventricular zone of the lateral ventricles and the hippocampal dentate gyrus [27-33]. However, newborn neurons are able to migrate, for instance into the olfactory bulb [29-31] or the striatum [34]. In the hippocampus, the newborn, immature neurons migrate to and differentiate in the granular cell layer, a process that requires 3 to 4 weeks. This time frame is very similar to the delayed action of many antidepressants and supports the notion that reconstitution of neurogenesis and correct integration and/or formation of neuronal networks is required to treat major depression [30, 35-38]. The molecular mechanisms mediating proliferation of neuronal and glial stem cells are largely unknown. Thus, it was shown that low doses of reactive oxygen species, a reduction of cellular ceramide by inhibition of the acid sphingomyelinase and an activation of phosphatidylinositol-3-kinase (PI3K), Akt, Erk1/2, Wnt3a, Notch molecules and cAMP response element-binding protein (CREB) trigger neurogenesis [39-47], but the molecular details of these signaling molecules and pathways in neurogenesis warrant further research.

Consistent with the hypothesis that hippocampal neurogenesis is impaired in major depression, it was demonstrated that antidepressants such as fluoxetine, desipramine, imipramine, and amitriptyline induce neurogenesis of cultured neurons *in vitro*, but more importantly also *in vivo* in the hippocampus [10-12,15, 16, 18, 19]. The latency of antidepressant-induced neurogenesis is consistent with the delayed action of these drugs. Neurogenesis correlated with the improvement of depressive-like behavior in mouse models which was blocked by irradiation of the hippocampus [19], suggesting that neuronal proliferation is not just a simple readout of changes in the brain during major depression, but rather causative in the pathogenesis of the disease.

On the other hand, clinical experience indicates that irradiation of the brain or general chemotherapy blocking proliferation of stem cells does not necessarily result in major depression. Further, treatment of major depression with sleep deprivation or electroconvulsive therapy shows fast effects that are inconsistent with neurogenesis, maturation and integration into or even the formation of neuronal networks of newly formed neurons. Thus while neurogenesis may be required for the effects of antidepressants, it may not be sufficient to overcome major depression. Thus, there are likely unknown mechanisms that are disturbed and must be targeted by antidepressants. However, massive formation of immature neurons, for instance after electroconvulsive therapy [48] may change the excitability of the hippocampus and the limbic system [49]. In addition newborn neurons might negatively regulate the hypothalamic-pituitary-adrenal axis, which seems to be overactive in many patients with major depression [50, 51]. Such a negative feedback system between immature neurons in the hippocampus and the hypothalamic-pituitary-adrenal axis may allow an adequate response to stress and therefore be important for the treatment of major depression [51, 52].

Finally, stress and glucocorticoids reduce, and antidepressants as well as electroconvulsive therapy induce, the production of a variety of growth factors, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF), which act on neurons and on vascular endothelial cells and thereby induce neurogenesis and angiogenesis [26, 53, 54]. An improved coupling of neuronal stem cells and the vascular cells in the stem cell niche might promote neurogenesis and thereby reduce symptoms of major depression.

As discussed below, antidepressants and many growth factors inhibit the acid sphingomyelinase/ceramide system. It might be possible that antidepressants have a relatively weak effect on that system, while growth factors released by electroconvulsive therapy might exhibit a strong inhibition of the acid sphingomyelinase/ceramide system. If inhibition of the hippocampal ceramide concentrations under a certain critical level is required for treatment of major depression, the strong effects of electroconvulsive therapy have a fast therapeutic effect, while the lower potency of antidepressants to inhibit the acid sphingomyelinase only slowly reduces the concentration of hippocampal ceramide explaining the delayed onset of the action of these drugs. If ceramide-levels are too high to be reduced by antidepressants under that critical level, the patient would fail to respond to therapy. This model is certainly speculative, and has to be proven *in vivo*, but it may explain many of the discrepancies between the fast action of electroconvulsive therapy and the slow onset of action of antidepressants.

## Role of the acid sphingomyelinase/ceramide system in major depression

We have previously shown an important role of the acid sphingomyelinase (EC 3.1.4.12, sphingomyelin phosphodiesterase, optimum pH 5.0; gene symbol, *Smpd1)* and ceramide system in major depression. Acid sphingomyelinase is a glycoprotein that functions as a lysosomal hydrolase, catalyzing the degradation of sphingomyelin to phosphorylcholine and ceramide at acidic pH [55]. Acid sphingomyelinase is present in lysosomes but also on small acidic domains of the outer leaflet of the plasma membrane [56]. The latter form was shown to have important signaling functions [56]. In addition, acid sphingomyelinase is also present in mitochondria, but the function of the mitochondrial form is unknown [57]. Depending on its glycosylation, acid sphingomyelinase is also secreted into the extracellular space [58].

Ceramide is formed by hydrolysis of sphingomyelin by the activity of acid, neutral, and alkaline sphingomyelinases depending on the pH optimum of the enzyme activity [59], by de novo synthesis [60], by degradation of complex (glyco)sphingolipids [61] and even from sphingosine by a reverse ceramidase activity [62]. Ceramide generated by acid sphingomyelinase has been shown to play a pivotal role in the mediation of stress and apoptotic stimuli including CD95, CD40, DR5/TRAIL, FcγRII, CD5, LFA-1, CD28, TNFα, Interleukin-1 receptor,

PAF-receptor, infection with *P. aeruginosa*, *S. aureus*, *N. gonorrhoeae,* Sindbis-Virus, measles virus, Rhinovirus, γ-irradiation, UV-light, $Cu^{2+}$, cisplatin or gemcitabine [56, 63-84].

Mechanistically, surface acid sphingomyelinase releases ceramide in the outer leaflet of the cell membrane [56]. Ceramide molecules spontaneously form small ceramide-enriched membrane domains that fuse to large ceramide-enriched membrane platforms. These platforms serve to trap and cluster receptor molecules and to initiate stress signals by mechanisms that still require definition. However, ceramide also directly regulates molecules, in particular ceramide released within multilamellar bodies or lysosomes binds to and activates cathepsin D, which translocates into the cytoplasm and causes cell death by activating Bid [85]. Other proteins that bind to ceramide include: kinase supressor of Ras (KSR), which mediates cell death via Bad [86]; LCIIIB, which mediates autophagy [87]; $PLA_2$; which mediates the release of arachidonic acid; several protein kinase C (PKC) isoforms [88, 89]; and additional metabolites that may be important not only for apoptosis but also for the generation of inflammatory responses [88]. Finally, ceramide was shown to regulate important cellular ion channels, in particular calcium-release activated calcium channels (CRAC) and the potassium channel Kv1.3 [90, 91].

Although the regulation of acid sphingomyelinase is not well characterized, the enzyme seems to be regulated by redox mechanisms [92], in particular via a redox sensitive cysteine at position 629 (Cys629) [93]. As mentioned above some growth factors, for instance VEGF, inhibit acid sphingomyelinase [94].

The first link between the acid sphingomyelinase and major depression came from the observation that many tricyclic and tetracyclic antidepressant drugs, such as desipramine, imipramine or amitriptyline, functionally inhibit the activity of acid sphingomyelinase [95, 96]. Tri- and tetracyclic antidepressants interfere with the binding of the enzyme to the lysosomal and possibly also outer plasma membrane surface, displace the enzyme from the surface and induce a proteolytic degradation of the enzyme within lysosomes or the release of the enzyme from the surface and thereby mediate a functional inhibition of the acid sphingomyelinase [97-102]. While it was assumed that this effect of antidepressants is a side effect, we have shown that therapeutic concentrations of the antidepressants amitriptyline and fluoxetine also reduce acid sphingomyelinase activity and ceramide concentrations in the hippocampus. This action mediates the therapeutic effects of antidepressants, in particular increased neuronal proliferation, maturation, and survival and improved behavior in models of stress-induced depression [12]. These studies employed genetically-modified animals that either lacked or overexpressed the acid sphingomyelinase to prove that the effects of antidepressants are in fact mediated by targeting the acid sphingomyelinase [12]. Moreover, micro-injection of C16-ceramide (a natural ceramide) into the hippocampus PDMP-induced increased abundance of ceramide, or accumulation of ceramide within the hippocampus by genetic heterozygosity of the acid ceramidase or transgenic overexpression of the acid sphingomyelinase decreased neuronal proliferation, maturation, and survival, and resulted in a depression-like behavior in mice even in the absence of stress [12]. This indicates that increased levels of ceramide are able to trigger symptoms of major depression even without stress, and that antidepressants act, at least partially, via a reduction of ceramide levels in the hippocampus. Chronic unpredictable stress resulted in increased hippocampal ceramide abundance [12]. It is presently unknown whether patients with major depression exhibit increased ceramide levels in the hippocampus. In blood samples, increased acid sphingomyelinase activity and ceramide concentrations have been found in major depressive disorder, depressive syndromes and in posttraumatic stress disorder [94, 103-106]. Endogenous changes in ceramide metabolism may result in at least some forms of major depression. At present, neither the molecular mechanisms of the regulation nor the targets of ceramide in major depression are known.

In summary, studies in recent years provide evidence that neurogenesis, neuronal maturation, and the function of immature neurons in the hippocampus are novel cellular pathophysiological systems that may be altered in major depression, and that these are in-

teresting novel targets for treatment. Mechanistically, the acid sphingomyelinase/ceramide system does not only serve as target for antidepressants but an accumulation of ceramide also directly induces major depression. It will be very exciting to explore how ceramide mediates major depression, whether this is a specific effect restricted to experimental systems or whether such a role of ceramide applies to many forms of major depression, and whether certain levels of ceramide in the hippocampus are involved on the range of major depression from mild to severe cases.

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## Disclosure Statement

The authors declare to have no conflict of interest.

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