Molecular Mechanisms of Depression: Perspectives on New Treatment Strategies

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Abstract
Depression is a multicausal disorder and has been associated with the risk to develop cancer, dementia, diabetes, epilepsy and stroke. As a metabolic disorder depression has been associated with obesity, diabetes, insulin sensitivity, neuropeptide Y, glucose regulation, poor glycemic control, glucagon-like peptide-1, cholecystokinin, ghrelin, leptin, the endocannabinoid system, insulin-like growth factor and gastrin-releasing peptide. As a cardiovascular disease a close relationship exists between depression and blood pressure, heart rate, norepinephrine, sympathetic tone, vascular resistance, blood viscosity, plasma volume, intima thickness and atherosclerosis. Additionally blood coagulation, fibrinolysis, D-dimers, plasminogen activator inhibitor-1 protein, platelet activation, VEGF, plasma nitric oxide and its synthase are changed in depressed patients. As an endocrinological and stress disorder depression has been connected with the concentration of free T_4, TSH, CRH, arginine vasopressin, corticotrophin, corticosteroid release and ACTH. Depression as an inflammatory disorder is mediated by pro-inflammatory cytokines, interleukin-1, interleukin-6, TNF-alpha, soluble interleukin-2 receptors, interferon-alpha, interleukin 8, interleukin-10, hs-CRP, acute phase proteins, haptoglobin, toll like receptor 4, interleukin-1beta, mammalian target of rapamycin pathway, substance P, cyclooxygenase-2, prostaglandin-E2, lipid peroxidation levels and acid sphingomyelinase. Nutritional factors might influence depression risk, i.e. the consumption of folate, omega-3 fatty acids, monounsaturated fatty acids, olive oil, fish, fruits, vegetables, nuts, legumes, vitamin B6 and vitamin B12. The neurodegenerative hypothesis of depression explains decreased hippocampal volumes in depressed patients and changes of neurotrophic support by BDNF, erythropoietin, GDNF, FGF-2, NT3, NGF and growth hormone. In this context, a fast neuroprotective and antidepressant effect has also been observed by ketamine, which acts via the glutamateergic system. Hence, GABA, AMPA, EAAT, NMDA- and metabotropic glutamate receptors (mGluR1 to mGluR8) have gained interest in depression recently. Alternative, causative or also easy available treatment strategies beyond serotonin and noradrenaline reuptake inhibition might be a major topic of future psychiatric care. In this review, an attempt is made to overview concepts of the disease and search for perspectives on antidepressant treatment strategies beyond approved medications.
Introduction

Depression is a common disorder, which occurs in all genders, ages, in all social backgrounds and also in animals. According to the World Health Organization, depression is the leading cause of disability as measured by disability adjusted live years and the 4th leading contributor to the global burden of disease in 2000, with tendency to rise up to 2020.

It presents with depressed mood, loss of interest, loss of drive and pleasure, feelings of guilt, poor concentration, low self-esteem, sleep disturbances and increased or decreased appetite. These problems can become chronic or recurrent and lead to substantial impairments in an individual’s ability to take care of his or her everyday responsibilities. At its worst, depression can lead to suicide, a tragic fatality associated with the loss of about 850,000 lives every year.

Depression is a multifaceted disorder with diverse causes and has been associated with the risk to develop severe medical disorders, i.e. depression increases the risk for cardiovascular disorders by 1.5-2 fold\(^1\), for stroke by 1.8 fold\(^2\), for Alzheimer’s Disease by 2.1 fold\(^3\), for epilepsy by 4-6 fold\(^4\), for diabetes by 60%\(^5\), for cancer by 1.3-1.8 fold\(^6\) (Fig 1).

Conventional treatment of depression with antidepressant medications and cognitive behavioral therapy can be effective in 60-80% of patients. However, fewer than 25% of those affected have access to effective treatment. Moreover, treatment resistant depression occurs in up to 40% of patients. However, antidepressant therapy has a variety of undesirable side effects such as sedation, decrease of blood pressure, increase of weight, indigestion or sexual dysfunction. This often results in patients’ poor compliance resulting in a break-up of medication with recurrence of depressive symptoms and increased suicidal risk\(^7\).

Therefore, (1) the prevention of depressive episodes by focusing on different possible physiologically relevant mechanisms beyond the neurotransmitter hypothesis and (2) the treatment of depression with alternative, causative or also easy available treatment strategies beyond serotonin and noradrenaline reuptake inhibition might be a major topic of future psychiatric care.

In this review, an attempt is made to overview new molecular concepts of the disease and search for perspectives on antidepressant treatment strategies beyond approved medications.

Depression as a metabolic disorder

The prediction is that in the US, one in three children will go on to develop Type 2 diabetes during her/his lifetime\(^8\). Research on health outcomes associated with obesity and diabetes has traditionally focussed on cardiovascular disease. However, metabolic dysregulation influences brain function and disturbances in peripheral glucose regulation might be associated with cognitive impairment and depressed mood\(^8\). Depression is highly associated with obesity, metabolic syndrome and type-2 diabetes\(^9, 10\) and it has even been discussed to classify depression as metabolic syndrome type II\(^11\). The presence of depressive symptoms is documented in 12.8–29% of males and 23.8–30.5% of females with newly diagnosed diabetes. Diabetes has in turn been shown to affect the incidence of depression\(^12\) and depressive symptoms are predictive of poor glycemic control in type 2 diabetes mellitus patients\(^13\). Vice versa depression increases the risk for diabetes by 60%\(^5\). Cross-sectional data from a population-based cohort study of 2667 residents, show depressive symptoms to be indeed associated with glucose metabolism\(^10\).

Nutrient activated gut to brain signaling pathways play a major role in the control of digestive function, appetite and energy intake. These include the modulation of gastric emptying and gastrointestinal transit and are regulated by the release of a number of signaling peptides from nutrient sensing enteroendocrine cells, glucagone-like peptide-1 and cholecystokinin\(^14\). Also ghrelin, leptin and the lipid endocannabinoid system have been
shown to signal from the gut to the brain. Interestingly, all these gastrointestinal hormones gain interest in the regulation of mood and the treatment of depressive symptoms.

A highly significant association between leptin levels, depressed mood and sleep disturbances has been shown in normal-weight women [15]. Leptin is involved in hippocampal plasticity as the functional isoform of the leptin receptor and the glucocorticoid receptor are colocalized in hippocampal neural progenitor cells [16]. Both, dexamethasone and leptin seem to converge on glycogen synthase kinase-3beta (GSK-3β) and β-catenin [16] which are key regulators in controlling hippocampal neural progenitor cell proliferation [16]. Leptin can decrease the basal secretion of dopamine as well as feeding-stimulated dopamine release within the ventral striatum of rats [17]. Furthermore, leptin receptor activation inhibits firing of VTA dopamine neurons [18], whereas long-term blockade of leptin signaling in the VTA increases locomotor activity and food intake [19, 20].

Obesity and major depression may derive, moreover, from dysregulation of ghrelin feedback at brain regions regulating feeding and mood. Ghrelin regulates central system development and mood, exerts antidepressant effects in mice and men, influences the reward behaviour [21, 22] and displays dopaminergic properties [23]. Carbohydrates appear to be the most effective macronutrients for ghrelin suppression [24]. Antidepressant effects were reported following ghrelin administration in mice and men [21, 22]. Interestingly, chronic stress, such as repeated social defeat, can elevate ghrelin levels by activation of the sympathetic nervous system and the increased ghrelin response then helps the subject cope with the stress by generating anxiolytic- and antidepressant-like behavioral adaptations [20].

Some cases of depression might result from dysfunction of the peripheral expression or the transport of insulin-like growth factor (IGF) into the brain. Also IGF increases hippocampal neurogenesis [25, 26] and a central sensitization of insulin signaling via IGF might reduce depressive symptoms [27]. IGF-1 regulates adult hippocampal neurogenesis [28], i.e. a blockade of peripheral IGF reduces exercise-induced neurogenesis [26]. Moreover, IGF produces antidepressant behavioural responses [29, 30].
Cholecystokinin is relevant to depressive-like symptoms and antidepressant therapy. Indeed, repeated social defeat triggers cortical cholecystokinin release and chronic antidepressant treatment prevents both depressive behaviour and the associated increase of cortical cholecystokinin release [31]. Blockade of cholecystokinin receptors reverses depressive behaviour in mice and prevents HPA axis hyperactivity [31]. Vice versa cholecystokinin injection leads to increased serum corticosterone. Panic induction can be experimentally carried out by a bolus injection of cholecystokinin [32] and decrease of cholecystokinin has been associated with mania, recently [33].

The mammalian bombesin-like peptide gastrin-releasing peptide (GRP) stimulates cell proliferation, displays a range of neuroendocrine activities, and acts as a growth factor in the pathogenesis of several types of human cancer [34]. GRP are distributed throughout the mammalian central nervous system. Pharmacological and genetic studies in rodents have shown that GRP in brain areas such as the hippocampus and amygdala are involved in regulating synaptic plasticity and aspects of anxious and depressive behaviour [34]. Behaviours modulated by the GRP in rodents include grooming, food intake, social behaviour and emotional-motivated learning and memory [34].

Chromium plays a crucial role in glucose and fat metabolism and improves insulin sensitivity in the hypothalamus, which enhances hypothalamic function by increasing glucose use, leading secondarily to an increased synthesis of serotonin, norepinephrine and melatonin [35, 36]. Three pilot trials of chromium indicate an antidepressant effect in patients with unipolar depression when used as adjunctive or monotherapy [37-39].

Galanin is a regulatory 29-30-amino acid peptide, widely distributed in the nervous system and gut [40]. Galanin is synthesized in the 5-hydroxytryptamine (5-HT) neurons in the dorsal raphe nucleus and in the noradrenergic neurons in the locus coeruleus and is coexpressed with various neurotransmitters and neuropeptides in other types of neurons. Converging evidence implicates the regulatory neuropeptide galanin in anxiety- and depression-related behaviors, through modulation of neuroendocrine, serotonergic, and noradrenergic systems [41].

Neuropeptide Y was initially described as a ‘co-transmitter’ of sympathetic neurons, modulating the actions of norepinephrine in the cardiovascular system [42]. Later on, many other functions of Neuropeptide Y, in particular in the CNS were discovered, connecting Neuropeptide Y with the stress response, food intake, energy balance control, sleep regulation, inflammatory processes and tissue growth and remodeling [43]. Neuropeptide Y integrates complex responses of different body systems, such as reduction of anxiety and depression, inhibition of release of Neuropeptide Y, glutamate and GABA, angiogenesis and blood pressure regulation and regulation of circadian rhythms, bone formation and feeding response [44].

BDNF is a mediator of food intake control at brain areas rich in BDNF receptors, including the hypothalamus and it is moreover involved in vagal afferent gastrointestinal impulses and thereby drives overeating and weight gain associated with increased meal size and frequency. The deletion of BDNF in the brain led to a metabolic phenotype characterized by hyperphagia, obesity, and increased abdominal white adipose tissue [45]. Brain-derived neurotrophic factor (BDNF) has been involved in vulnerability to overeating and weight gain in an obesogenic environment.

Depression as an endocrine disorder

Corticotrophin-releasing hormone and arginine vasopressin are the central drivers of the stress hormone system, elicit corticotrophin into the periphery and thereby activate the corticosteroid release from the adrenal cortex. If these stress hormones are persistently hypersecreted they can also evoke severe clinical conditions and hamper an adequate adaptation to stress. These hormones also act as neuromodulators in the brain, affecting higher mental functions including emotion, cognition, and behaviour [46].
The core hypothesis of depression as a stress-related disorder is that chronic stress-elicited corticosteroids impair corticosteroid-receptor signaling, which is a key risk factor in rendering an individual prone to stress-related disorders [46]. Indeed, glucocorticoid-activated glucocorticoid receptors are opposed by mineralocorticoid receptors which are rapidly activated and terminate humoral responses efficiently [47]. Results from open label and double-blind studies by several groups have indicated that corticosteroid synthesis inhibitors may be efficacious or of adjunctive value in some patients with depression, including those refractory to other agents; however, there is a need for more controlled studies [48].

The prevalence of depressive symptoms in hypothyroidism is near to 50% whereas in hyperthyroidism it reaches up to 28% of the cases [49, 50]. Clinical depression occurs in more than 40% of people suffering from hypothyroidism [50, 51]. Indeed, low TSH levels in healthy individuals might be linked to an increased risk of depression [52]. Vice versa, patients suffering from depression display higher than expected rates of subclinical hypothyroidism.

The concentration of free $T_4$ in the blood and cerebrospinal fluid is relatively increased during depression (at least in 30% of patients), being reduced when the clinical recovery occurs [50]. Therefore, the use of thyroid hormones to supplement antidepressants is based on evidence supporting a bidirectional connection between thyroid function and depression. Several randomized double-blind, placebo-controlled studies have shown an accelerated clinical response in patients, where a concomitant administration of thyroid hormone and antidepressant have been exerted [53]. Indeed, the augmentation of antidepressant treatment with triiodothyronine reaches the efficacy of the commonly used lithium augmentation [54]. In a recent review published by Nature, convincing evidence has been indicated that a role of type 1 iodothyronine deiodinase determines the serum $T_4:T_3$ ratio and a variant of phosphodiesterase determines TSH levels. Moreover, TSH-receptor variants, fasting glucose level, iodothyronine deiodinase variants and insulin-like growth factor production, hypertension and psychological well-being seem connected in their response to $T_3$ or $T_4$ treatment [55].

**Depression as a cardiovascular disease**

A close, bidirectional relationship exists between depression and cardiovascular disease [56]. Major depression is associated with an increased risk of coronary artery disease, myocardial infarction, congestive heart failure, and isolated systolic hypertension leading to increased mortality and morbidity in patients [56].

Blunted blood pressure reactivity, increased heart rate and altered autonomic baseline function have been observed in dysphoric individuals. Elevation in systemic arterial pressure, higher circulating levels of norepinephrine, higher sympathetic tone, increased systemic vascular resistance, elevations in blood viscosity, decreased plasma volume and extracoronary atherosclerosis are associated with a higher prevalence of depressive disorders [57, 58]. Moreover, a strong relationship has been described between severe coronary and aortic calcifications, intima thickness, osteoporosis, and depressive disorders [58-62]. Additionally in depressed patients an increased blood coagulation and fibrinolysis, D-dimer, plasminogen activator inhibitor-1 protein and platelet activation can be observed [63, 64]. Moreover, it was consistently shown that baseline levels of plasma nitric oxide, plasma nitric oxide metabolite, and platelet nitric oxide synthase activity were significantly lower in subjects with depression compared with that in healthy controls [65].

In conclusion, various pathophysiological mechanisms may underlie the risk of cardiovascular disease in patients with depression: increased inflammation, susceptibility to blood clotting, oxidative stress, hypothyroidism, hyperactivity of the sympathetic-adrenomedullary system and the hypothalamic-pituitary-adrenal axis, reductions in...
Statins have anti-inflammatory properties and accordingly, the use of statins was associated with significant reduction in the risk of depression in individuals who have had a cardiac event in a prospective clinical trial [66].

An acceleration and enhancement of the efficacy of antidepressant treatment has been associated with pindolol administered together with serotonin reuptake inhibitors, displaying a quicker and more pronounced decrease of symptoms in patients with non-resistant major depressive disorder [67].

Vascular endothelial growth factor (VEGF) is an endothelial cell mitogen and survival factor that regulates vascular function, but is also expressed in the brain and has neuroprotective and neurogenic effects [68-70]. Chronic stress exposure has been shown to decrease and antidepressant administration to increase hippocampal VEGF [71, 70]. Consistent with these results, it has been reported that VEGF expression and blood levels are increased in patients with depression and that antidepressant treatment reverses these effects [72, 73].

**Depression as an inflammatory disorder**

Clinical depression and sickness behaviour are occurring in response to nearly all physiological stressors and both are highly connected phenotypes. Sickness behaviour is characterized by malaise, hyperalgesia, pyrexia, disinterest in social interactions, lethargy, behavioural inhibition, reduction of locomotor activity, exploration and grooming, reduction of reproductive performance, anhedonia, somnolence and sleepiness, anorexia and weight loss, failure to concentrate and anxiety. This behaviour has been proved to be mediated by pro-inflammatory cytokines, such as interleukin-1, interleukin-6 and TNF-alpha [74]. Accordingly, depressive disorders could partly be based on inflammatory changes, i.e. increased interleukin-6, TNF-alpha, soluble interleukin-2 receptors, acute phase proteins, including C-reactive protein and haptoglobin [75, 76]. In a recent meta-analysis of cytokines in major depression a total of 136 studies has been identified and in 24 included studies increased concentrations of the proinflammatory cytokines TNF-alpha and interleukin-6 have been confirmed in depressed subjects when compared with healthy controls [76]. Moreover, toll like receptor 4, interleukin-1beta, cyclooxygenase-2, prostaglandin-E2 and lipid peroxidation levels are regulated by stress. These inflammatory cytokines can interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity.

From an evolutionary point of view depressive and obsessive behaviour seems senseful in the context of an infection as social withdrawal and repetitive washing might save other individuals from contamination. Moreover, depression is a state, which might save energy and thereby help an individual to overcome severe infections. Indeed, there are rare cases, where depression and obsessive compulsive behaviour could causally be linked to streptococcal infections [77]. However, depressive patients, who are using nonsteroid anti-inflammatory agents, seem to respond poorly to –mainly serotonergic– antidepressants [78]. In these conditions the inflammatory processes rather than the medication might lead to depressive behaviour [78, 79]. Indeed, both pre-clinical and clinical studies have demonstrated that newer serotonin-noradrenalin antidepressants can inhibit the production and release of pro-inflammatory cytokines and stimulate the production of anti-inflammatory cytokines [80]. Reductions in inflammation might therefore contribute to treatment response [80]. However, to our knowledge, an immunosuppressant effect of serotonergic antidepressants has not been studied systematically but might affect people with inflammatory diseases such as multiple sclerosis, cardiovascular disease, and psoriasis, who have elevated rates of depression. In this context tryptophan is an interesting example as tryptophan produces a consequent reduction in brain serotonin synthesis and release [81]. However, despite tryptophan's promising antimanic effects, the amino acid nutritional supplement has been banned by
the food and drug administration since 1989 due to rare and deadly flu-like conditions associated with its use [82].

Vice versa, many people administered inflammatory cytokines such as interferon-alpha develop depression that is indistinguishable from depression in non-medically ill populations [83]. Even completed suicides have been observed in response to treatment with interferon-alpha [83].

The importance of the inflammation hypothesis of depression lies in raising the possibility that psychotropic drugs that have a central anti-inflammatory action might provide a new generation of antidepressants. Both experimental and clinical evidence shows that a rise in glucocorticoids might lead to an increase of proinflammatory cytokines and these might in turn contribute to the behavioral changes associated with depression.

In this context, it has been suggested that the cyclooxygenase-2 inhibitor celecoxib is a potential adjunctive treatment strategy for major depression [84, 85]. Moreover, the results of this study are in line with Nery et al. who have reported that celecoxib might produce a rapid-onset antidepressant effect in bipolar patients with depressive episodes [86]. In addition, the result of a recent study indicates that celecoxib treatment reverses chronic unpredictable stress-induced depressive-like behaviour [87].

In addition, the use of gram-negative antibiotics has been discussed to offer a potential therapeutic approach for the adjuvant treatment of depression [88]. Also Sesamol, which is a potent inhibitor of cytokine production as well as an antioxidant has been shown to reverse the unpredictable chronic stress-induced behavioral, biochemical, and inflammation surge in stressed mice, i.e. sesamol may have the potential to exert antidepressant effects [89].

**Depression as a matter of darkness**

Depression has been discussed as a matter of sunshine. In contrary, light deprivation has been shown to induce depression-like behaviour and suppresses neurogenesis [90]. Environmental light influences the secretion of melatonin. Melatonin is involved in a variety of diseases, including cancer, insomnia, depression, dementia, hypertension, and diabetes; its secretion is influenced by environmental light. Agomelatine is the first melatonin analogue antidepressant drug and has therefore led to a renewed focus on the potential clinical benefits that could be derived from modulation of the circadian system [91].

Daylight exposure increases not only nocturnal melatonin secretion but also platelet 5-HT values [92] and vitamin D, which in turn has been involved in the pathophysiology of depression [93]. Season might be a possible confounding factor in reduced brain serotonin turnover following selective serotonin reuptake inhibitor therapy [94] and influences the cortisol response to awakening [95]. Serum BDNF concentrations also show strong seasonal variations and correlations with the amount of ambient sunlight [96]. However, also physical activity is higher on long days (≥ 14 hours daylight) when compared with short days [97]. In conclusion, bright light treatment seems underused in the treatment of depressive disorders.

Bright light can stimulate the suprachiasmatic nucleus and therefore improve mood, sleep, and hormonal rhythms in patients with major depressive disorder. Bright light therapy improves mood, enhances sleep efficiency, and increases the melatonin level gradient. In addition to its chronobiotic effects, melatonin also increases sleep propensity, reduces sleep latency, decreases alertness and neurocognitive functioning, lowers core body-temperature, reduces adiposity, attenuates weight gain and has anti-oxidative effects [98]. Interestingly, melatonin administration inhibits insulin release, increases insulin sensitivity and adiponectin, leptin, and ghrelin plasma levels [99]. Melatonin also increases insulin sensitivity and glucose tolerance in animals fed with either high fat or high sucrose diet [100].
In a recent study, superior response and remission rates were obtained by chronotherapeutic strategy when compared with the effects of exercise in acute depressive patients treated with duloxetine [101]. Indeed, at week 9, response was obtained in 71.4% of wake therapy patients versus 47.3% of exercise patients and remission was obtained in 45.6% of wake therapy patients and 23.1% of exercise patients [101].

**Depression as a deficiency state**

Diet may potentially influence the risk of depression. In a recent meta-analysis several nutrient variables have been inversely associated with depression risk, i.e. the consumption of folate, omega-3 fatty acids, monounsaturated fatty acids, olive oil and fish and a diet rich in fruits, vegetables, nuts and legumes [102]. However, the exact mechanisms linking mood and meal are not understood.

Interestingly, appendicular muscle mass in depressive patients is decreased [103] and creatine augmentation of SSRI treatment has been discussed to be a promising therapeutic approach as shown in a 8-week double-blind placebo-controlled clinical trial at least in women [104]. Quercetin and the organoselenium compound m-trifluoromethyl-diphenyl diselenide are flavonoids found in plant foods and herbal medicines. Both of them have been shown to be effective in the modulation of serotonergic activity by attenuating mitochondrial MAO-A activity in the brain and attenuate oxidative stress by interrupting the generation of hydrogen peroxide accompanying the MAO-A reaction [105, 106].

Several reports indicate a high prevalence of folic acid deficiency among patients suffering from psychiatric conditions such as depression, bipolar disorder and cognitive dysfunction disorders [107]. Adequate levels of folate are essential for proper brain functioning [108]. Folate, with vitamins B12 and B6 as catalysing cofactors, influences cognitive performance and mood [108]. Treatment with vitamin B6, vitamin B12, and folic acid reduces the hazard of a major depressive episode compared with placebo among survivors of a stroke and reduces the risk to re-experience a major depressive episode for 7 years about 50% [109]. Several trials have demonstrated efficacy of folic acid in the treatment of unipolar depression [110].

Epidemiologic and case-control data suggest that increased dietary intake of omega-3 long-chain polyunsaturated fatty acids may be of benefit in depression. In this context about 250 double-blind, placebo-controlled, randomized controlled trials have been performed, leading to the conclusion, that eicosapentaenoic acid might be more efficacious than docosahexaenoic acid in the treatment of depressive disorders [111]. Increased activity of acid sphingomyelinase by chronic stressors such as oxidative stress or TNFalpha could lead to the release of interleukin-1, elevated plasma corticosterone levels, the development of cardiovascular disease, increased activity of serum phospholipase A2, increase in the ratio of omega 6 fatty acids and low serum cholesterol in depressed patients [112]. S-adenosyl methionine is a naturally occurring molecule that serves as a methyl donor in human cellular metabolism. Preliminary data in 73 patients suggest that s-adenosyl methionine can be an effective, well-tolerated, and safe adjunctive treatment strategy for serotonin reuptake inhibitor nonresponders with major depressive disorder [113].

**Depression as a matter of dysregulated glutamate**

Glutamate regulates synaptic transmission and plasticity by activating ionotropic glutamate receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor) and metabotropic glutamate receptors (mGluR1 to mGluR8). The number and stability of these receptors at the synaptic membrane is an important factor in determining excitatory synaptic efficacy. Glutamate is cleared from the extracellular space by high-affinity excitatory amino acid transporters (EAATs), which are located on neighbouring glial cells (EAAT1 and EAAT2) and, to some extent, on neurons
(EAAT3 and EAAT4) [114]. In glial cells, glutamate is converted into glutamine by glutamine synthetase. Glutamine is then transported back into the glutamatergic neuron, where it is hydrolysed into glutamate by glutaminase [115]. Owing to the lack of degradative enzymes in the synapse, uptake by EAATs is the primary mechanism through which the action of extracellular glutamate is terminated.

Studies have shown that drugs, which increase glutamate clearance, can prevent or reverse the effects of chronic stress and chronic glucocorticoid exposure and exert antidepressant effects in animal models of depression [116-118].

A single subanesthetic dose (0.5 mg/kg) of the N-methyl-D-aspartate receptor antagonist ketamine causes a rapid antidepressant effect within hours in treatment-resistant patients with major depressive disorder [119]. The rapid antidepressant response after ketamine administration in treatment-resistant depressed patients suggests a possible new approach for treating mood disorders compared to the weeks or months required for standard medications [120]. As ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, which is involved also in animal models of depression, this ubiquitous protein kinase, involved in protein synthesis and synaptic plasticity, might be involved in ketamine’s rapid antidepressant effects. However, in our own study, we observed mood changes in patients using the mTOR inhibitor everolimus [121]. The NMDA receptor antagonist dextromethorphan has also been discussed as a potential rapid-acting antidepressant [122].

Then inhibition of substance P synthesis by FosB in the ventrolateral periaqueductal gray region results in reduced inhibition of escape behaviors mediated by γ-aminobutyric acid (GABA) in the nucleus accumbens [123]. Several lines of evidence suggest an antidepressant-like activity for 3-[(methyl-1,3-thiazol-4-yl)ethynyl]-pyridine, a highly selective, non-competitive antagonist of metabotropic glutamate receptors subtype 5 [124]. Recently it has been reported that the antimuscarinic agent, scopolamine, produces a rapid and robust antidepressant effect in currently depressed male and female patients with major depressive disorder or bipolar disorder [125, 126]. Antidepressants have been shown to raise brain magnesium. Zinc and magnesium are potent inhibitors of the (NMDA) receptor complex. Recent data demonstrate that both zinc and magnesium, like other NMDA receptor antagonists, exhibit antidepressant-like activity in rodent screening tests and depression models. In a randomized controlled study in elderly patients with type II diabetes mellitus magnesium led to antidepressant like effects that were comparable to those of strong antidepressant drugs (i.e. imipramine 50mg/daily) [127]. In a double-blind, randomized and placebo-controlled study, Zinc supplementation was shown to improve mood states, reduce anger-hostility score and depression-dejection score [128].

**Depression as a neurodegenerative disorder**

Decreased hippocampal volumes have been found in a series of studies in humans exposed to chronic stress leading to the hypothesis that chronic stress can inhibit neurogenesis, retract dendritic processes lead to neuronal loss in the hippocampus [129, 130]. The majority of reported volumetric findings agree with reduced hippocampal volumes in depressive subjects [131].

Brain-derived neurotrophic factor (BDNF) regulates synaptic plasticity in neuronal networks involved in depressive behaviours [132, 133]. Upregulation of BDNF may reverse stress-induced deficits in structural and synaptic plasticity in the adult brain, resulting in cognitive flexibility and an increased ability to adapt with environmental challenges that may precipitate or exacerbate depressive episodes. Recent studies demonstrate that BDNF levels are decreased in the blood of depressed patients and its levels are increased with antidepressant treatment [134-144]. Irrespective of the medication used, better treatment outcome was associated with higher BDNF plasma levels [143]. Moreover, BDNF polymorphism and serum level have been connected with anxiety, risk of depression, neuroticism and serotonergic neurotransmission [145-149]. Augmentation of antidepressants with lithium is
currently the best-evidenced augmentation therapy in the treatment of depressed patients who do not respond to antidepressants [150] and also lithium augmentation leads to a BDNF increase [143]. Neurotrophin-3 (NT-3) and nerve growth factor (NGF) also influence adult hippocampal neurogenesis and plasticity and thereby could contribute to stress-induced cellular and behavioral deficits, and antidepressant responses [151-155]. Other growth factors which have been shown to be changed in depression include glial cell line-derived neurotrophic factor (GDNF) and fibroblast growth factor-2 (FGF-2) [73, 156]. At least FGF-2 can be upregulated by antidepressant treatment [157]. It has been discussed recently, that BDNF might well signal through phosphoinositol dependent kinase 3, Akt and glycogen synthase kinase (GSK3) pathways [158], which has been supported also by our own data [159-161].

Additionally erythropoietin is involved in neuroplasticity and is a candidate for future treatment of depression. The investigators have demonstrated that a single dose of erythropoietin improves cognitive function and reduces neurocognitive processing of negative emotional information in healthy and depressed individuals similar to effects seen with conventional antidepressants [162]. Inositol as a constituent of the intracellular phosphatidylinositol second-messenger system, has shown some efficacy in small pilot studies of unipolar depression [163-165]. Finally, peripheral VGF expression is decreased in patients with MDD [166] and administration of recombinant VGF produces antidepressant behavioral responses in mice [167].

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