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Neurobiological Background of Affective Disorders

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1. Introduction

Affective disorders, including major depression, mania and bipolar disorder, represent a spectrum of severe psychiatric diseases reflecting a continuum of psychopathological symptoms. Starting in young adulthood and often leading to suicidal ideation, affective disorders are ranking among the most disabling diseases worldwide in terms of the WHO global burden of disease, are socio-economically relevant, severe and prevalent. These diseases lead to enormous social disabilities due to affective and cognitive symptoms [1]. Depression, for example, has a lifetime risk of about 20-25% [2] and, besides suicide, a higher prevalence of the metabolic syndrome including coronary heart disease and diabetes increase mortality [3]. Bipolar disorder with manic episodes, in contrast, has a lifetime prevalence of about 1-5% [4]. However, due to the occurrence of depressive symptoms, the disease may be misdiagnosed - Goldberg et al. [5] could show a hypo-manic or manic episode in 46% in patients with depression.

Despite tremendous efforts, the neurobiological background of affective disorders remains elusive, and due to lacking biomarkers an early diagnosis and reliable prognosis is difficult. Undisputed is a multifactorial etiology with genetic and psychosocial factors such as stress, emotional trauma and viral infections during the vulnerable episodes of brain development. They possibly interact in inducing disease symptoms. Beside neuroendocrinological factors, neurotransmitter disturbances and alterations of signal transduction constitute the basis of structural and functional alterations in neuronal circuits of the brain.

2. Neuroimaging studies in affective diseases

Since the description of the limbic “Papez-circuit of emotion” in the 1930s involving hippocampus, cingulated gyrus, anterior thalamus and hypothalamus, magnetic resonance

imaging [6] studies in patients revealed volume deficits in regions relevant for emotion processing, be it amygdala, hippocampus, anterior cingulate gyrus, prefrontal, or orbitofrontal cortex as well as basal ganglia. In bipolar disorder, affective and psychotic symptoms are related to a dysfunction in the prefrontal-subcortical network interacting with limbic regions [7]. Meta-analyses in bipolar disorder indeed show gray matter reductions in the paralimbic regions anterior cingulate cortex and insula, partially overlapping with decreased volumes in schizophrenia and indicating a continuum of the neurobiological background of psychoses [8, 9]. Anterior cingulate dysfunction in bipolar disorder has been strengthened by functional MRI studies, which revealed functional attenuation in the anterior cingulate cortex in patients with bipolar disorder performing cognitive and emotional tasks [10, 11]. Recent meta-analyses of fMRI studies in bipolar disorder show decreased activation of the inferior frontal cortex corresponding to frontal hypoactivity and overactivated hippocampus plus amygdala (limbic hyperactivity), which was consistent across emotional and cognitive tasks and related to the state of mania [12, 13]. Reduced fractional anisotropy nearby the parahippocampal gyrus and anterior cingulate cortex have been identified in diffusion-tensor imaging studies in bipolar disorder and speak for impaired limbic connectivity in neuronal networks [14]. With respect to amygdala size, decreased volumes have only been detected in younger patients and a respective correlation between volume and age has been reported [15, 16]. Contrastingly, schizophrenia patients showed larger ventricles and smaller amygdala volumes compared to bipolar disorder, pointing to a continuum of neurobiological alterations [8].

Compared to patients with bipolar disorder, those with major depressive disorders present decreased rates of white matter hyperintensity, smaller hippocampal and basal ganglia volumes and a decreased corpus callosum area [17, 18]. Along with increased lateral ventricles, smaller volumes of the basal ganglia, hippocampus, thalamus, frontal lobe, orbitofrontal gyrus and gyrus rectus have been detected in major depression [19]. This especially pertained patients during depressive episodes with smaller hippocampal volumes compared to remittend patients [18]. Reduced hippocampal volumes have consistently been reported in patients with major depression and are prominent in patients with recurrent and chronic depression [20]. Shape analysis revealed deformations in the subiculum, CA1 and CA2-3 subfields in the tail of the right hippocampus of patients with first episode of depression [21]. The presence of alterations in first-episode depression is consistent with a neurodevelopmental hypothesis of early stress experience, especially since this region plays a major role in inhibiting stress response [22], providing inhibitory feedback to the hypothalamic-pituitary-adrenal (HPA) axis [23].

3. Synaptic plasticity and stress mediation

Post-mortem investigations reveal reduced density and size of interneurons in cornu ammonis (CA) 2/3 subfield of the hippocampus in bipolar disorder [24]. In the hippocampal subiculum, a decreased density of neuronal dendrites leading to disturbances of microconnectivity and probably representing the basis of the reported volume deficit in

bipolar patients has been found [25]. However, the finding of decreased neuropil (dendrites and axons) seems not to be specific for bipolar disorder, as it has also been reported in all hippocampal subfields of patients with major depression showing increased density of neurons and glia cells as a sign of increased packing of the cells. Additionally, in line with the hypothesis of a degenerative process, soma size of pyramidal neurons was decreased [26]. In the prefrontal cortex of patients with major depression, a decrease in cortical thickness goes along with lower densities of neurons and glia cells [27]. In the anterior cingulate cortex, in familial depression and bipolar disorder, decreased glia number has been detected [28]. In both regions, decrease of glia density and neuronal size has been reported [29]. Decreased glia density has also been found in the amygdala of patients with major depression [30]. In animal studies again, chronic stress or repeated administration of glucocorticoids interestingly results in degeneration of hippocampal neurons with decreased soma size and atrophy of dendrites [31, 32]. Stress possibly also influences synaptic plasticity in the prefrontal cortex [33]. Thus the volume loss in brain regions like the hippocampus reported in affective disorders may indeed be mediated by stress-induced glucocorticoid neurotoxicity [34, 35].

Division and differentiation of stem cells to neurons and their migration to the granule cell layer has been demonstrated in the hippocampal dentate gyrus of both humans and adult rodents [36]. Some factors influence this neurogenesis: While blockade of the glutamatergic N-methyl-D-aspartate (NMDA) receptor and adrenalectomy results in increased production of granule neurons, adrenal steroids and NMDA receptor activation diminished neurogenesis [37]. Acute, chronic or prenatal stress, all of them implicated in the pathophysiology of depression [38], have been shown to inhibit proliferation of subgranular neurons [39-42]. Because both, circulating adrenal steroids and glutamate-induced excitatory input to the hippocampus, are enhanced by stress [43, 44], the influence of stressful events on cell proliferation and survival of newly generated neurons may be mediated by these mechanisms [40, 45]. In an animal model of learned helplessness, inescapable stress is leading to downregulation of neurogenesis [46]. Accordingly, antidepressants are known to induce cell proliferation and neurogenesis [46-49].

4. Neurotrophins and the HPA axis

Neurotrophic factors, particularly Brain-Derived Neurotrophic Factor (BDNF) are expressed in the hippocampus and cortex and are involved in neurogenesis and synaptic plasticity such as promotion of survival and differentiation as well as branching of axons and dendrites [50]. In patients with bipolar disorder, reduced hippocampal expression of BDNF has been reported [51] while antidepressants reversed this effect [52]. In blood of depressed patients, including patients with bipolar disorder, BDNF levels have been found to be decreased and correlated to higher depression evaluation scores [53, 54]. Post-mortem studies of the hippocampus in major depression revealed a reduced BDNF immunohistochemistry [51].

To date, beside a genetic vulnerability, stress is widely accepted as risk factor for depression. In animal models, acute or chronic stress decreased BDNF levels in the hippocampus

inclusive the dentate gyrus [52]. Along with this hypothesis, stress is known to reduce the branching of hippocampal dendrites [55]. It additionally increases plasma and adrenal corticosterone levels and application of this hormone induces reduced hippocampal BDNF levels, mimicking stress reaction [52]. The major stress system of the body is the HPA axis, a neuroendocrine system involved in the production of the stress hormone cortisol by adrenal glands. In more than 50% of patients with major depression, a dysfunction of the HPA axis with increased basal cortisol levels and dexamethasone non-suppression of cortisol was detected, suggesting abnormal negative feedback system of the HPA axis. Additionally, the production of corticotrophin-releasing hormone (CRH) production is abnormal while pituitary and adrenal sensitivity seem to be intact [56] (figure 1). CRH is produced in the paraventricular nucleus of the hypothalamus in response to psychosocial stress and activates the HPA axis. It is binding in the pituitary gland to induce release of adrenocorticotropine hormone (ACTH), which in turn stimulates the release of cortisol from the adrenal gland. In a negative feedback loop, cortisol binding inhibits CRH and ACTH release, inhibiting the HPA axis [57], but this hormonal feedback is known to be abnormal in depression. In animal models, CRH administration and overexpression induce depression-like behavior, while CRH antagonists have antidepressant properties [58, 59]. Depressed patients with history of childhood abuse have enhanced HPA axis response to psychosocial stress and attenuated adrenocorticotrophin and cortisol response to application of the synthetic corticosteroid dexamethasone [60]. However, individual genetic background influences the incidence of depression in response to psychosocial stress and only a minority of persons exposed to common stressors develops depression [61]. Thus, genes may modulate the association between environmental factors like stress and risk of illness.

5. Genetic findings

Twin, family and adoption studies have shown that major depression is a moderate heritable disease. During the last years, candidate gene and genome-wide association studies (GWAS) have linked common DNA sequence variation, called polymorphisms, to major depression [62-64] and identified novel candidate loci [65]. However, single nucleotide polymorphisms (SNPs) only slightly affect the pathophysiology, and affective disorders seem to be of complex polygenetic origin. With respect to CRH dysfunction, a genetic variation of the corticotropin releasing hormone type 1 receptor (CRHR1) has been found to be associated with decreased HPA axis response to CRH infusion, suggesting to influence this pathophysiology of depression [66]. In addition, negative feedback control on CRH secretion may be impaired due to altered glucocorticoid receptor (GR) function on hippocampal level [67]. A GR polymorphism has also been found to be associated with vulnerability to depression [68]. According to the neurotrophin hypothesis, in patients with depression and healthy controls, smaller hippocampal volumes have been detected in carriers of the BDNF Met66 allele compared to Val/Val homozygotes [69]. These results suggest that a Val66Met polymorphism may possibly predispose to smaller hippocampal volumes and depression, although this topic currently is under debate [70]. An interaction between a 5-HTTLPR serotonin transporter polymorphism and Val66Met BDNF gene

variant has been shown to be associated to stress-induced depression [71-73]. Furthermore, depression has been associated with polymorphisms in the glucocorticoid receptor gene NR3C1, the monoamine oxidase A gene, and genes for glycogen synthase kinase-3 β , a neuron-specific neutral amino acid transporter (SLC6A15) as well as group-2 metabotropic glutamate receptor (GRM3) [74, 75].

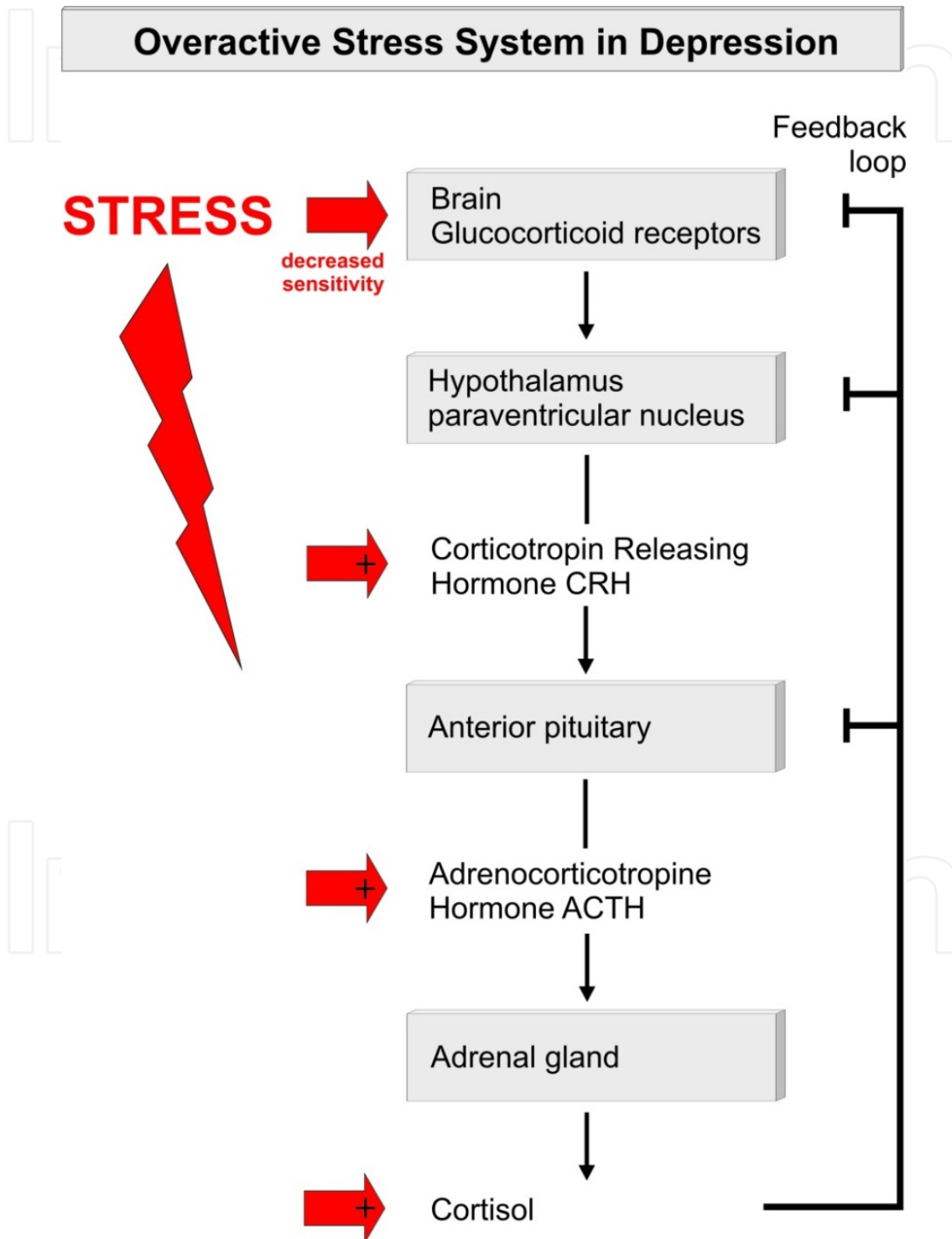


Figure 1.

Several other genes are associated with bipolar disorder inclusive brain-derived neurotrophic factor (BDNF), D-amino acid oxidase activator (DAOA, G72), disrupted in schizophrenia 1 (DISC1), solute carrier family 6 (SLC6A4), tryptophan hydroxylase 2 (TPH2), catechol-O-methyltransferase (COMT), serotonin transporter (5-HTT) [76-81], but there is a large overlap with schizophrenia-associated genes, pointing to a continuum between affective disorders and psychosis. Among the risk variants for bipolar disorder, to date G72 is the most supported locus [76, 82-84]. However, there is also evidence for an association with depression and panic disorder [78, 85]. Additionally, G72 possibly influences a predisposition for affective symptoms in schizophrenia [83]. A further risk gene for bipolar disorder and depression is diacylglycerol kinase (DGKH), showing 10 SNPs to be associated with bipolar disorder while 7 SNPs are associated with unipolar depression and four SNPs with ADHD, thus influencing mood instability [86]. Additionally, a region of both ankyrin 3 (ANK3) and neurocan (NCAN) has been found to be associated with bipolar disorder [65, 87]. A recent meta-analysis revealed association of two SNPs in the serotonin 1A receptor gene with major depression and bipolar disorder and supports the hypothesis of disturbed serotonin neurotransmission in mood disorder [88].

Altogether, the heritability of major depression seems to be meager compared to bipolar disorder and schizophrenia, which show heritability rates of up to 80%. To date, GWAS studies could not identify many reproducible individual gene loci associated with affective disorders [89], but SNPs near exons exhibit a greater probability of replication, supporting an enrichment of reproducible associations near functional regions of genes [90]. However, the confirmation of some loci affords larger samples. In a GWAS study from the GWAS consortium Bipolar Disorder Working Group, in large cohorts evidence for association of CACN1C, an L-type voltage-gated calcium channel has been confirmed [91]. In order to improve methodological quality, new investigations using next-generation sequencing are under way.

Epigenetic mechanisms altering chromatin structure such as histone acetylation and DNA methylation may link effects of environmental factors such as stress to transcriptional regulation of specific genes. Depression-like behavior and antidepressant action have been found to be regulated by epigenetic mechanisms [92]. Besides downregulation of BDNF transcripts, stress increased histone methylation at their corresponding promoters. The antidepressant imipramine reversed the decrease on the mRNA level and increased histone acetylation along with downregulation of histone deacetylase, suggesting an important role in histone remodeling in the pathophysiology and treatment of depression [93]. As a consequence, new treatment strategies influencing epigenetic targets could be developed.

6. Neurotransmitter hypotheses

Selective antidepressant treatment is known to act on the serotonergic and the noradrenergic system. Traditional long-term antidepressant treatment is known to induce increased levels of serotonin from the raphe nuclei [94]. The serotonin hypothesis of depression suggests that decreased serotonin activity increases vulnerability for depression

[95]. The serotonin system originates from the dorsal and medial raphe nuclei in the brainstem infringing on limbic structures such as the hippocampus and amygdala [94]. Reducing serotonin synthesis induces depressive symptoms in healthy probands exposed to uncontrollable stress [96], and increased serotonin release in the hippocampus has been implicated in the mechanisms underlying coping with stress [97]. Serotonin (5-HT) receptors are represented by 5-HT₁ class receptors, being situated pre- and postsynaptically and inhibitory by reduction of adenylate cyclase activity. The 5-HT₂ class excitatory receptors are located predominantly postsynaptically through activation of phospholipase C [94]. 5-HT_{1A} receptors are known to mediate adaption to stress and these receptors located in the hippocampus could attenuate the emotional impact of aversive stimuli, inhibiting the consolidation of stressful memories [97]. Additionally, 5-HT_{1A} receptors are known to mediate the serotonin-based increase in neurogenesis [98] and induce release of neurotrophic factors [99]. Moreover, serotonin is involved in the regulation of the HPA axis [100]. The downregulation of 5-HT_{1A} receptors in the hippocampus by stressors is corticoid-dependent and reversed by antidepressants [101, 102]. Indeed, patients with depression have reduced 5-HT_{1A} receptor binding as revealed by positron emission tomography (PET) studies [103, 104] plus results of altered receptor number in post-mortem investigations [105, 106].

The noradrenaline system derives from the locus coeruleus and lateral tegmental nuclei. The receptors belong to the excitatory postsynaptic β -adrenergic, α_1 and inhibitory pre- and postsynaptic α_2 adrenergic categories. They have been shown to be upregulated in post-mortem brains of patients with depression [95, 107], suggesting a primary noradrenaline deficit. Stressors and glucocorticoids persistently activate the noradrenergic system in the locus coeruleus with resulting disrupted responses to brief stimuli [94]. In contrast to the posterior hippocampus, facilitation of noradrenergic transmission in the ventral hippocampus, being involved in emotion and anxiety [108, 109], seems to protect against stress effects [110]. Moreover, the noradrenaline system closely interacts with serotonin, facilitating serotonin neurotransmission in the hippocampus and amygdala [97] thus providing a therapeutic target for antidepressant drugs such as noradrenaline reuptake inhibitors [111]. Dopamine is another monoamine proposed to play a role in mood disorder since the mesolimbic dopamine reward circuit originating from the ventral tegmental area is associated with rewarding effects of food, sex and drug abuse. A dopaminergic deficit may contribute to anhedonia reduced motivation and energy level in patients with depression and may represent a target for the development of new therapeutic strategies [112]. It is expected that reuptake inhibitors for all three catecholamines (serotonin, noradrenaline, dopamine) can produce greater efficacy than traditional antidepressants [113].

It has been shown that 5-HT depletion alone does not induce mood symptoms, but an interaction with glutamate may be responsible for developing affective disorders. Additionally, noradrenaline is involved in release and uptake of glutamate [114]. Glutamate is the principal excitatory, γ -aminobutyric acid (GABA) the predominant inhibitory neurotransmitter in the brain, both occupying at least 50% of the synapses. Besides regulating synaptic plasticity, they closely interact with the HPA axis. In depression, an

overactive glutamate system and hypoactive GABA system has been suggested [115]. Elevated levels of glutamine/glutamate have been shown in MR-spectroscopy (MRS) studies in the frontal and occipital cortex as well as in basal ganglia of patients with depression. In the anterior cingulate cortex, reduced levels have been reported in depression, while in bipolar disorder with acute mania, glutamate/glutamine levels were increased [28]. These findings are consistent with glutamatergic overactivity in acute mania. However, medication effects may contribute to the findings in mood disorder. In medication-free depressed patients, GABA levels have been found to be reduced in the occipital and anterior cingulate cortex as well as prefrontal cortex [115]. In clinical studies, agonists at the glycine site of the glutamatergic N-methyl-D-aspartate (NMDA) receptor as well as inhibitors of the glycine transporter elevating glycine levels have been found to exert antidepressant properties. But also antagonists at the NMDA receptor like ketamine induce a presynaptic release of glutamate, which in turn activates glutamatergic α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors act as antidepressants [116-118]. Novel potential therapeutic drugs affecting the glutamate system are under investigation, such as modulators of AMPA receptors, NMDA receptor subunit NR2B, metabotropic glutamate receptors, glutamate transporter EAAT2, and N-acetyl-L-cysteine which is a precursor of the NMDA receptor activating antioxidant glutathione [117, 119].

7. Findings on the molecular level

The above described neurotransmitters are known to modulate gene transcription and protein synthesis [120]. Proteomic studies in the frontal cortex and nucleus accumbens of depressed patients revealed altered expression of Dihydropyrimidinase-related protein 2 (DPYSL2), regulating neuronal development, migration and differentiation as well as differential expression of aldolase C (ALDOC), which plays a major role in glucose and energy metabolism [121]. In the dorsolateral prefrontal cortex, proteomic profiles and a phosphoproteomic approach showed differences in proteins associated with synaptic transmission and cellular architecture [122] [123]. In bipolar disorder, dysregulation of DPYSL2 and glial fibrillary acid protein (GFAP) along with tubulin subunits suggest cytoskeletal dysfunction and altered brain development [121].

Genome-wide gene expression studies in bipolar disorder unearthed a high correlation of expression changes also observed in schizophrenia such as decreased oligodendrocyte and myelination related genes, as well as deregulation of mitochondrial energy metabolism, oxidative phosphorylation, synapse-related and mitochondrial genes [124, 125]. In depressed patients, alterations of genes involved in neurodevelopment, signal transduction, cell communication and myelination have been reported. Additionally, genes encoding for the glutamate and serotonin system have been found to be altered in bipolar disorder and depression [125]. Moreover, in mood disorder, alterations of BDNF and subunits of glutamate receptors and the GABA synthesizing enzyme GAD have been detected to be differentially regulated [126]. In a previous laser-capture microdissection study of the locus coeruleus, Bernard [127] found alterations of the glutamate-, astroglia- and growth factor

related genes in depression, but not in bipolar disorder, suggesting differential processes in both disorders. In the frontal cortex of patients with major depression, increased apoptosis stress and upregulation of pro-and anti-inflammatory cytokines have been detected [128] which differs from findings in schizophrenia [129]. Interestingly, in an animal study, chronic stress affected expression of genes involved in brain development, morphogenesis and synaptic transmission in the dentate gyrus of the hippocampus, which is involved in neurogenesis [130]. Modulation of these stress effects may lead to development of new therapeutic strategies for mood disorder.

8. Conclusion

Overall, mood disorder entails a broad spectrum of alterations in specific neuronal circuits. Despite overlapping findings in patients with major depression, bipolar disorder and even schizophrenia, pointing to a neurobiological continuum of the diagnostic spectrum of psychoses, specific findings can be detected on the cellular, molecular and hormonal level. Besides genetics, environmental factors like acute or chronic stress are known to account for the pathophysiology of the named disorders. New treatment strategies involving several neurotransmitter systems are under way and may improve outcome. However, preventive and cause-related treatments based on molecular findings plus animal studies of environmental and genetic factors should be developed to increase efficacy and prevent burden of severe psychiatric diseases.

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