

Additional Antidepressant Pharmacotherapies According to a Neural Network

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Abstract

Major depression, a frequent psychiatric disease, is associated with neurotransmitter alterations in the midbrain, hypothalamus and hippocampus. Deficiency of postsynaptic excitatory neurotransmitters such as dopamine, noradrenaline and serotonin and a surplus of presynaptic inhibitory neurotransmitters such as GABA and glutamate (mainly a postsynaptic excitatory and partly a presynaptic inhibitory neurotransmitter), can be found in the involved brain regions. However, neuropeptide alterations (galanin, neuropeptide Y, substance P) also play an important role in its pathogenesis. A neural network is described, including the alterations of neuroactive substances at specific subreceptors. Currently, major depression is treated with monoamine reuptake inhibitors. An additional therapeutic option could be the administration of antagonists of presynaptic inhibitory neurotransmitters or the administration of agonists/antagonists of neuropeptides.

Keywords: Acetylcholine; Bupropion; Dopamine; GABA; Galanin; Glutamate; Hippocampus; Hypothalamus; Major depression; Midbrain; Neural network; Neuropeptide Y; Noradrenaline; Serotonin; Substance P

Abbreviations: CRH: Corticotropin Releasing Hormone; CRH1: Corticotropin Releasing Hormone Receptor; CSF: Cerebro Spinal Fluid; D2: Dopaminergic Subreceptor; GABA: Gamma Amino Butyric Acid; GABAA: Gamma-Aminobutyric Acid Subtype A Receptors; GABAB: Gamma-Aminobutyric Acid Subtype B Receptors; Gal2: Galanin 2; 5-HT: Serotonergic Receptor; 5-HT1A: 5-Hydroxytryptamine 1A Receptors; 5-HT7: 5-hydroxytryptamine-7 Receptor; m5GluR: Subtype 5 of Metabotropic Glutaminergic Receptor; MC4R: Melanocortin Receptor Four; nAChR: Nicotinic Cholinergic Receptor; NK1: Tachykinin Subreceptor; NMDA: N-Methyl-D-Aspartate; sDNRI: Selective Dopamine and Noradrenaline Reuptake Inhibitor; SNRI: Selective Serotonin and Noradrenaline Reuptake Inhibitor; sNRI: Selective Noradrenaline Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor

Introduction

Major depression is a frequent psychiatric disease, which can be induced by stressful life events [1]. In major depression, monoamine hypoactivity, i.e. of dopamine, noradrenaline, serotonin can be observed in the midbrain and hippocampus [1]. Presynaptic inhibitory neurotransmitters, namely gamma-aminobutyric acid (GABA) and glutamate (mainly a postsynaptic excitatory and partly a presynaptic inhibitory neurotransmitter), also play an important role in its pathogenesis. GABA and glutamate enhance noradrenaline and serotonin hypoactivity through an increased presynaptic inhibition [2,3]. The hypothalamic-adrenocortical axis regulates the alteration of neurotransmitters in the midbrain [4]. This neural relationship hints at the depressive symptoms induced by stressful life events. Major depression is currently treated with selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs) or with the selective noradrenaline and dopamine reuptake inhibitor (sDNRI), bupropion [5]. In spite of the administered antidepressant drugs, a percentage of depressive patients remain treatment-resistant. Here, neural networks are described in order to derive additional antidepressant pharmacotherapies.

The purpose of this review is to describe the alterations of classical neurotransmitters and neuropeptides in the brain areas involved

in major depression and to point out the coherence between single neuroactive substances and their corresponding subreceptors. A question should be answered, whether a multimodal pharmacotherapy with an agonistic or antagonistic effect at several subreceptors is higher than the current conventional antidepressant treatment.

Clinical Features in Major Depression

Major depression is a frequent psychiatric disorder, which concerns 5-8% of the population. The symptoms of the disease are prolonged sadness, loss of energy, interest and pleasure, changes in behavior and physical health as well in the circadian rhythm with an early awakening and an improved mood in the evening. Major depression, which is not treated sufficiently, may lead to suicide attempts [6]. In a large Swedish cohort, it has been examined the relationship between the prevalence of major depression and unemployment, and it has been found that foreign-born, unemployed women had the highest risk to develop major depressive disorders [7]. Alterations of classical neurotransmitters and neuropeptides in the hypothalamus, midbrain and hippocampus

In the hypothalamus, midbrain and hippocampus, the alteration of neurotransmitters and neuropeptides will be reviewed, and the neural relationship between the hypothalamic-adrenocortical axis and the neural networks in the midbrain will be explained.

Dysfunction of the hypothalamic-adrenocortical axis in major depression

Dysfunction of the hypothalamic-adrenocortical axis can

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be observed in depressive patients. Enhanced response in the dexamethasone (DEX)/corticotropin-releasing hormone (CRH) test can be observed in major depression, but not in schizoid or in passive-aggressive patients [4]. In the chapter of the neural networks, it will be shown that hypothalamic CRH neurons, via CRH1 receptors, transmit a strong activating impulse to glutaminergic neurons which strongly inhibit 5-HT_{1A} serotonergic neurons located in the midbrain via subtype 5 of metabotropic glutaminergic receptors (m5Glu receptors) [1].

Serotonin

Serotonin is a postsynaptic excitatory neurotransmitter, which acts at different 5-HT receptors and in major depression shows hypoactivity in the brainstem and hippocampus. In major depression, serotonin (5-HT) hypoactivity is encoded in the 5-HT transporter gene [1]. The serotonergic effect is mediated via 5-HT_{1A} receptors. SSRIs such as paroxetine, citalopram or fluoxetine and 5-HT_{1A} agonists improve depressive symptoms. In the hippocampus, an additional antidepressant effect can be achieved by an agonism at 5-HT_{2C} or an antagonism at 5-HT₇ receptors [1,8].

Noradrenaline

In major depression, noradrenaline hypoactivity is encoded in the noradrenaline transporter gene and occurs in the brainstem via a reduced activation of the alpha₁ noradrenergic receptor [9]. Patients with this gene better respond to selective noradrenaline reuptake inhibitors such as duloxetine than to SSRIs [10]. SNRIs, such as venlafaxine, are more effective in the treatment of major depression than SSRIs [11]. In a meta-analysis, it was shown that the adult antidepressant treatment with escitalopram, an SSRI, compared to the treatment with duloxetine, a 5-HT and noradrenaline reuptake inhibitor, was more effective and resulted in fewer adverse effects [12].

Dopamine

Dopamine is as well involved in the pathogenesis of major depression and shows reduced levels in the hippocampus and the extrapyramidal system. Hypoactivity of dopamine, which has a postsynaptic excitatory action via D₂ receptors, is accompanied in different brain regions by increased dopamine transporter binding and elevated monoamine oxidase levels, an enzyme degrading dopamine [9]. In major depression, dopamine hypoactivity via D₂ receptors occurs in the hippocampus. An increased GABAergic presynaptic inhibition of D₂ dopaminergic neurons can enhance dopamine hypoactivity [1]. Bupropion, a sNDRI exerts a good antidepressant effect and improves the “decreased positive effect”, i.e. the loss of energy, interest and pleasure [5].

Acetylcholine

Acetylcholine, which exerts its effect on muscarinic and nicotinic cholinergic receptors, is also involved in the pathogenesis of major depression [1]. In the dorsal hippocampus and in the medial prefrontal cortex, acetylcholine stimulates serotonin release by activating nicotinic cholinergic receptors [13]. Agonists of nicotinic cholinergic receptors (nACh agonists) could have antidepressant properties, because in the hippocampus nicotinic cholinergic neurons activate D₂ dopaminergic neurons via alpha₄beta₂ nACh receptors [14].

Gamma-aminobutyric acid (GABA)

GABA is dysfunctional in major depression. GABA exerts its presynaptic inhibitory effect via GABA_A and GABA_B receptors. GABA hypoactivity is partly due to polymorphisms of the GABA 1 transporter gene. The four neurotransmitters noradrenaline, serotonin, GABA and glutamate form a neural network in the center of the circadian

rhythm and the “mood center” [8]. In the “mood center”, GABAergic neurons could strongly inhibit alpha₁ noradrenergic neurons via GABA_B receptors and thus enhance noradrenaline deficiency [15]. The antidepressant effect of GABA_B receptor antagonists should be examined in clinical trials.

Glutamate

Glutamate is mainly an excitotoxic, postsynaptic excitatory neurotransmitter and partly a presynaptic inhibitory neurotransmitter and exerts its effect upon ionotropic glutaminergic receptors, i.e. N-methyl-D-aspartate (NMDA) receptors and on metabotropic glutaminergic receptors [1]. In major depression, an increase or decrease of glutamate can be found in certain brain regions [1]. Glutaminergic neurons could strongly inhibit 5-HT_{1A} serotonergic neurons in the brainstem via NMDA or subtype 5 of metabotropic glutaminergic receptors. Therefore, NMDA and m5GluR antagonists should be examined in clinical trials in order to know whether they exert antidepressant properties or not [16].

Galanin

Galanin is involved in hyperglycemia, nociception, memory, neuropathic pain and modulates serotonin function [17]. In an animal model of depression, galanin levels have been found to be decreased in the medial and lateral hypothalamus [18]. Paroxetine, a selective serotonin reuptake inhibitor is often prescribed and exerts a safe antidepressant effect. The effects on non-serotonergic neurotransmitters have been examined. Paroxetine exerted an effect on some neuropeptides, i.e. it increases galanin levels [19]. Galanin agonists acting at Gal₂ receptors could have an antidepressant effect, because galanin neurons located in the hypothalamus could activate, via Gal₂ receptors, serotonergic neurons located in the hippocampus [8,18].

Neuropeptide Y

Neuropeptide Y is implicated in hypertension, controls the circadian rhythm, improves memory and it is involved in sexual behaviour [20]. In major depression, neuropeptide Y levels are decreased or increased after antidepressive treatment [21]. In the hippocampus, neuropeptide Y neurons activate GABAergic neurons via NPY₁ receptors. A question arises, whether NPY₁ antagonists could have antidepressant properties or not [8]. A prophylactic treatment in stress-triggered anxiety or depressive-like behaviour has been examined. The intranasal administration of neuropeptide Y and/or the melanocortin receptor four (MC₄R) antagonist, HS014, showed anxiolytic and antidepressant effects in this clinical trial [22].

Substance P

Substance P has been found to be increased in the cerebrospinal fluid (CSF) in depressive patients and to be decreased after antidepressive pharmacotherapy [23]. Since substance P neurons activate GABAergic neurons located in the hippocampus, it should be examined whether substance P antagonists, i.e. NK₁ receptor antagonists could have an additional antidepressant effect [8]. The NK₁ receptor, through which substance P exerts its effect, is involved in wound healing, neurogenic inflammation and in tumorigenesis. Substance P exerts a neuromodulating effect in the central and peripheral nervous systems and is associated with depression, stress, anxiety, and emesis. The NK₁ receptor antagonist aprepitant is prescribed for high or moderate emesis [24].

Major Depression: Signalling Mechanisms of Different Neurotransmitters in the Hippocampus

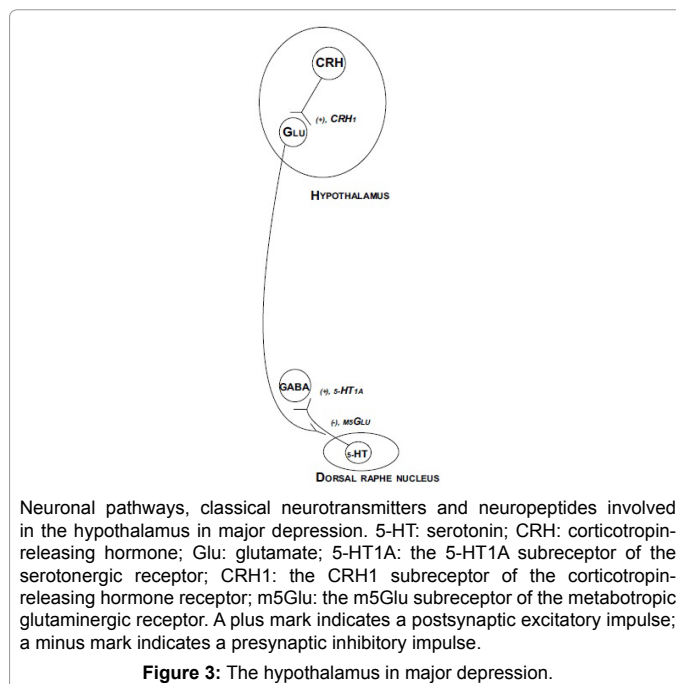
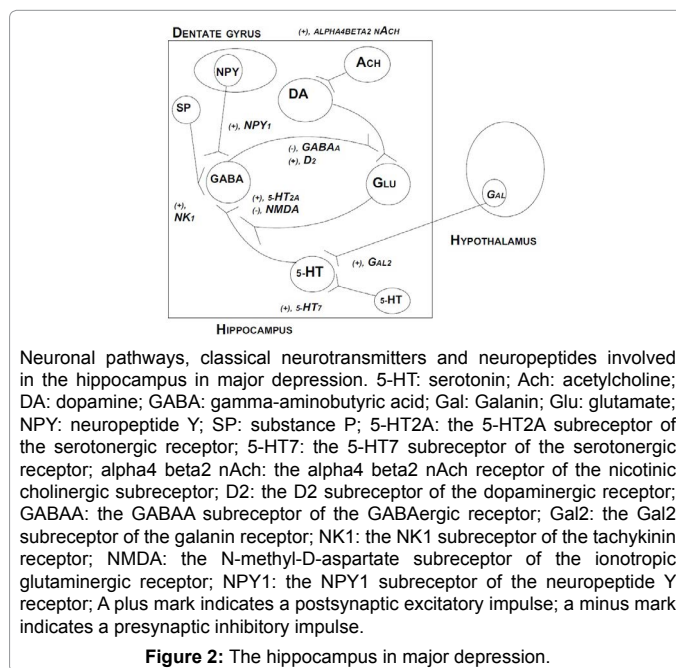
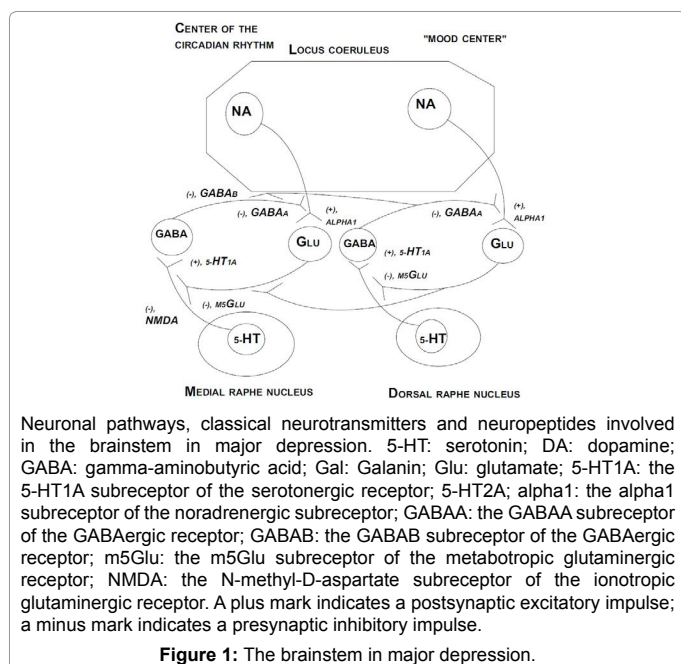
In a review about the psychological, genetic and environmental

risk factors for major depressive disorders, it was reported that some brain structures such as amygdala, hippocampus and basal ganglia are reduced in volume in major depression. In the hippocampus, the main neurotransmitters are dopamine and serotonin as well as GABA and glutamate [25]. Antidepressant drugs, which block the reuptake of serotonin, improve depressive symptoms by increasing synaptic serotonin. SSRIs reduce energy metabolism by increasing extracellular serotonin, which is restored by compensatory mechanisms. That is the reason why depressive patients suffer worsening depressive symptoms during the first weeks of the treatment with SSRIs [26].

Neural Networks in the Hypothalamus, Midbrain and Hippocampus

The neural networks in the hypothalamus, midbrain and hippocampus are shown in Figures 1-3. It can be described as follows (Figure 1): in the “mood center” of the brainstem, 5-HT1A serotonergic neurons transmit a weak postsynaptic excitatory impulse to GABAergic neurons, which via GABAB receptors inhibit alpha1 noradrenergic neurons. 5-HT1A serotonergic neurons have a weak activity due to the 5-HT transporter gene. Alpha1 noradrenergic neurons weakly activate glutaminergic neurons, which strongly inhibit 5-HT1A serotonergic neurons via m5Glu receptors. Glutaminergic neurons located in the center of the circadian rhythm. The latter glutaminergic neurons inhibit, via NMDA receptors, 5-HT1A serotonergic neurons which activate GABAergic neurons. GABAergic neurons in the “mood center” inhibit, via GABAB receptors, the GABAergic neurons located in the center of the circadian rhythm. GABAergic neurons inhibit, via GABAA receptors, alpha1 noradrenergic neurons located in the locus coeruleus which activate glutaminergic neurons. In the center of the circadian rhythm, serotonergic and noradrenergic neurons have alternating levels during the course of the day: 5-HT is preponderant during the night and noradrenaline during the day [27].

In the hippocampus (Figure 2), D2 dopaminergic neurons with a low activity activate glutaminergic neurons, which via NMDA receptors inhibit 5-HT2A serotonergic neurons. Hippocampal 5-HT2A



serotonergic neurons activate GABAergic neurons, which inhibit D2 dopaminergic neurons via GABAA receptors. In the hippocampus, nicotinic cholinergic neurons activate D2 dopaminergic neurons via alpha4 beta2 nACh receptors, and 5-HT7 serotonergic neurons activate 5-HT2A serotonergic neurons. Neuropeptide Y neurons, located in the dentate gyrus, activate GABAergic neurons via NPY1 receptors and substance P neurons also activate, via NK1 receptors, GABAergic neurons. In the hypothalamus, galanin neurons activate via Gal2 receptors hippocampal 5-HT2A serotonergic neurons. In the hypothalamus (Figure 3), CRH neurons with a high activity activate glutaminergic neurons via CRH1 receptors, and via m5Glu receptors the glutaminergic neurons strongly inhibit 5-HT1A serotonergic neurons located in the brainstem “mood center”.

Antidepressant drugs	Example of drugs	Therapeutic effects	Adverse effects	References
SSRIs: selective serotonin reuptake inhibitors	Citalopram, fluoxetine, paroxetine	Antidepressant effect, sedating effect to a small extent	Arrhythmias, constipation, increased intraocular pressure, decreased sexual activity, hypotension, weight gain	[31,32]
Tricyclic antidepressant drugs	Amitriptyline	Antidepressant and sedating effects	Arrhythmias, constipation, increased intraocular pressure, decreased sexual activity, hypotension, sedation, weight gain	[31,32]
SNRIs: selective serotonin and noradrenaline reuptake inhibitors	Venlafaxine	Good antidepressant effect	Arrhythmias, hypertension, insomnia, increased intraocular pressure, weight gain and loss	[31,32]
sNRIs: selective noradrenaline reuptake inhibitors	Reboxetine	Treat the "decreased positive effect", the lack of energy, interest and pleasure	Insomnia, dry mouth, constipation, nausea, excessive sweating, tachycardia, hypotension and hypertension	[31,32]
sDNRI: selective dopamine and noradrenaline reuptake inhibitors	Bupropion	Treat the "decreased positive effect", the lack of energy, interest and pleasure	Arrhythmias, hypertension, insomnia, increased intraocular pressure, weight loss	[31,32]

Table 1: Therapeutic and adverse effects of antidepressant drugs.

Current Antidepressant Pharmacotherapies

Major depression is currently treated with monoamine reuptake inhibitors. The different therapeutic effects of the different antidepressant drugs will be pointed out in the subsequent chapters.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs, for example fluoxetine, paroxetine or citalopram have a good therapeutic effect in depressive patients. Adverse effects of the SSRIs are constipation, increased intraocular pressure, ECG abnormalities and sexual dysfunction. All antidepressant drugs except bupropion, mirtazapine and vortioxetine, which blocks the 5-HT transporter and the 5-HT₇ receptor, cause these side effects [28,29].

Selective serotonin and noradrenaline reuptake inhibitors (SNRIs)

The sSNRI venlafaxine can be used to treat major depression. In a clinical trial, venlafaxine had a better therapeutic effect than SSRIs [11].

Selective noradrenaline and dopamine reuptake inhibitor (sDNRI)

The sDNRI bupropion can be administered to treat the "decreased positive effect", i.e. the loss of energy, interest and pleasure. Frequent adverse effects are hypertension, insomnia, constipation, however no sexual dysfunction has been reported [30]. An overview of the therapeutic and adverse effects of the different approved antidepressant drugs is given in Table 1 [31,32].

Additional antidepressant pharmacotherapies

In agreement with the neural networks described above, the following drugs can be administered for the treatment of major depression:

- GABAB antagonists which increase noradrenaline levels through a decreased presynaptic inhibition [15],
- m5GluR and NMDA antagonists which increase 5-HT levels [16],
- CRH1 receptor antagonists which increase 5-HT levels through a reduced presynaptic inhibition via m5GluR receptors [8],
- GAL2 agonists which enhance 5-HT neurotransmission [18],
- 5-HT₇ antagonists [11],
- NK1 receptors antagonists which enhance GABAergic neurotransmission and NPY1 receptor antagonists [21,23].

Prevention of Major Depression

Major depression can be triggered by stressful events. Therefore

psychohygiene, i.e. alternating professional and leisure-time and social activities are of great importance. In a social working place, a good communication between the colleagues and supervision could stabilize the mental health. In preventive examinations, physicians should focus on symptoms hinting at major depression, for example sleep disturbances.

Conclusion

In major depression, we have summarized the alterations of classical neurotransmitters and neuropeptides in the hippocampus, midbrain and hypothalamus. Hypoactivity of the monoamines dopamine, noradrenaline and 5-HT and hyperactivity of GABA and glutamate at specific subreceptors have been reported in the involved brain regions. In most cases, depressive patients are treated with monoamine reuptake inhibitors; it has been reported that bupropion (a sDNRI) and venlafaxine (a SNRI) exert a higher antidepressant effect than SSRIs. We described neural networks in the hippocampus, midbrain and hypothalamus. It is important to include the hypothalamus in the neural networks, because the neural relationship between the CRH neurons and the decreased activity of the brainstem 5-HT_{1A} serotonergic neurons of the "mood center" could be explained. We suggest a multimodal antidepressant pharmacotherapy in order to enhance the antidepressant effect. We point out some additional subreceptors in the brain regions involved in major depression, on which new antidepressant drugs could exert an agonistic or antagonistic effect. The development of the new antidepressant drug vortioxetine, which blocks the 5-HT transporter and antagonizes the 5-HT₇ receptor, shows that a multimodal antidepressant pharmacotherapy can achieve progress in the patients' treatment.

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