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Review Article

The Role of Dopaminergic System in the Pathogenesis and Treatment of Depression

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Abstract

Dopamine plays an important role in the pathophysiology of depression and therapeutic effects of antidepressants. Impaired neurotransmission of dopamine within the mesolimbic system may cause anhedonia, loss of motivation and psychomotor retardation in patients with severe depression. Some drugs, such as desipramine, amineptine and nomifensine exert their antidepressants effects through enhancement of synaptic availability of dopamine. Alterations in the density and binding brain levels of dopamine receptors and dopamine transporter have been implicated in the pathophysiology of major depression. The present review will summarize the evidence for a role of dopaminergic system in pathogenesis of depression and therapeutic effects of antidepressants.

Keywords: *Depression; Dopamine, Antidepressant Drugs*

Introduction

Major depressive disorder (MDD) as an important clinical problem is the principal reason of worldwide disability and has a lifetime risk of between 15% and 20% of the general population [1]. MDD in DSM-IV characterized by the presence of loss of pleasure or interest in usually pleasurable activities (anhedonia), anergia, changes in sleep and appetite, sadness, and suicidal ideation [2]. Depression has been related to the Monoamine neurotransmitter system abnormalities, including norepinephrine and serotonin [3,4]. It has suggested that dopamine also play a key role in the pathophysiology of depression and in the mechanism of action of antidepressants [5,6]. Treatment of major depressive disorder is usually based on antidepressants that enhance levels of the monoamines serotonin, norepinephrine, and dopamine [3]. Anhedonia or decreased experience of pleasure or interest in previously enjoyed activities is a core symptom of MDD that is accompanied by decreased motivation [7]. It has demonstrated that mesolimbic dopaminergic system is involved in the control of motivation and rewarding experiences [8]. In addition, hypofunction of the dopamine system has proposed as an underlying brain mechanism of the loss of pleasure/interest experienced in MDD [9]. It is thought that disturbance to the monoamine system can be a direct risk factor for MDD pathogenesis or may be an secondary factor that has a causal relationship with the other MDD risk factors [4].

The objective of this review is to examine the evidence supporting the role of the brain dopaminergic system in the pathogenesis of depression as well as the relevance of dopamine receptors and dopamine transporter (DAT) as pharmacological targets for the treatment of depression.

Dysfunction of dopaminergic system in depression

Neurotransmitter dopamine plays an important role in the central nervous system and four dopaminergic pathways have been discovered in the brain including mesolimbic dopamine pathway, mesocortical dopaminergic pathway, nigrostriatal dopaminergic pathway and tuberoinfundibular dopaminergic pathway [10]. Dopaminergic mesocortical and mesolimbic systems are involved in two core symptoms of depression including anhedonia and loss of motivation [11]. Mesolimbic dopamine system has constituted from nucleus accumbens (NAc; ventral striatum) and its dopaminergic input from the ventral tegmental area (VTA), and have potential role in the pathophysiol-

ogy and etiology of depression [12]. It has suggested that NAc and VTA cause the symptomatology of depression particularly anhedonia, reduced motivation, and decreased energy level [12]. Brain circuits containing dopamine plays a role in regulation of motivation, psychomotor speed, concentration, and the ability to experience pleasure and disturbances in these functions are core features of depressive symptoms [13]. The strongest finding connecting the role of dopamine in depression has resulted from this observation that concentrations of homovanillic acid, a metabolite of dopamine, in the cerebrospinal fluid of depressed patients is low [14]. Particularly, it has been reported that anhedonic symptoms in depressed subjects have been associated to changed mesolimbic dopamine transmission and may be improved by dopaminergic therapies [15,16]. In addition, decreased density of dopamine transporter (DAT) and increased binding of D2/D3 dopamine receptor have reported in the central and basal nuclei of the postmortem amygdala of patients with depression as compared to healthy subjects [17]. Similarly, several neuroimaging studies have revealed elevated binding levels of striatal D2 receptor and increased temporal cortex D2/3 binding; however some studies failed to show D2 density alterations in depressed patients [11,18]. In addition, depressive subjects have shown upregulated binding sensitivity of dopamine D2/D3 receptors and reduced activity of DAT, suggesting possibly compensatory alterations following deficiency of the mesolimbic dopaminergic system in patients with depression [19,20]. The nucleus accumbens that receive input from mesolimbic dopaminergic neurons probably through enhancing dopaminergic function in the mesolimbic system by increasing both expression of dopamine D2 and D3 receptors and dopamine release could be also involved in the pathophysiology of depression and mechanisms of actions of some antidepressant drugs [21-23]. Impaired dopaminergic neurotransmission within the mesolimbic system has proposed as pathogenesis of "core" symptoms of severe depression including anhedonia, loss of motivation and psychomotor retardation [10]. Conflicting findings have reported about the association between the D4 receptor alleles and symptomatology of depression [24,25].

Role of dopamine in antidepressant action

Previous studies through examining behavioral responses to dopamine agonists after chronic treatment with antidepressants and via research on effects of selective dopamine receptor antagonists on the ability of antidepressants to elicit their behavioral responses have suggested that dopamine plays a role in the mechanism of action of antidepressants [26]. Pharmacological treatments that antagonize dopamine receptors or reduce release of dopamine are related to the generation and developing of depression [27,28]. Evidence from animal models of depression demonstrated that the mesolimbic dopamine system plays a crucial role for the therapeutic effect of antidepressants and drugs that act directly on the dopaminergic system have shown antidepressant-like effects [29]. Dysphoria and many symptoms similar to those of endogenous depression have observed by administration of dopamine receptor antagonists, or drugs that reduce dopamine levels such as reserpine [30,31]. Conversely, dopamine receptor agonists and also drugs that increase dopamine function, have shown antidepressant-like profiles in animal models of depression and have been reported to have efficacy in the treatment of patients with MDD [32-35]. It has revealed that desipramine via enhancement of dopamine levels in the frontal cortex, amineptine via selective inhibition of dopamine reuptake and bupropion and nomifensine by blocking the dopaminergic transporter (DAT) exert their antidepressants effects [36-41]. There are two families of Dopamine receptors including the D1-like receptors (D1 and D5) and the D2-like receptors (D2, D3, and D4 receptor subtypes) [26]. Drugs with agonistic properties on D2-like receptors such as Bromocriptine, piribedil and pramipexole and other dopamimetic drugs that enhance synaptic availability of dopamine such as nomifensine, a selective dopamine reuptake inhibitor, and methylphenidate that stimulate release of dopamine have shown antidepressant effects [27,33,42,43]. Conversely, it has shown that dopamine receptor antagonists may intensify depression-like symptoms [16].

Conclusions

In this article we focused on the crucial role of the dopaminergic brain system in symptomatology of depression and antidepressant properties of dopaminergic drugs. Dysfunctions of mesocortical and mesolimbic dopaminergic pathways have been implicated in the pathogenesis of symptomatology of depression, particularly anhedonia, loss of motivation and psychomotor retardation. The present study reviewed evidence supporting the hypothesis that dysfunction of dopaminergic system, particularly VTA-NAc brain circuit implicated in the etiology of depression and in the mechanism of action of antidepressants. Agonists of dopamine D2-like receptors such as Bromocriptine and drugs that enhance release of dopamine such as methylphenidate have been reported to have antidepressant properties. Further research on the impact of dopaminergic system on the pathophysiology of depression is warranted to improve outcomes for patients with depression.

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