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Review article

Mechanisms of antidepressant action: An integrated dopaminergic perspective

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ABSTRACT

The molecular mechanisms that cause and maintain the major depressive disorder (MDD) are currently unknown. Consistently, antidepressant treatments are characterized by insufficient success rates. This causes high social costs and severe personal sufferings. In the present review we analyze some of the paradigms that are used to explain MDD, particularly from the perspective of the dopaminergic (DA) system. DA has been more classically associated with psychosis and substance abuse disorders, even though a role of DA in MDD has been proposed as well and some antidepressants with DA profile exist. In the present work, we review some of the molecular mechanisms that underpin MDD from the perspective of the dopaminergic system, in the hope of unifying some of the major theories of MDD — the monoaminergic, inflammatory, epigenetics, neurotrophin and anti-apoptotic theories. Several shared components of these theories are highlighted, partially accounted by the functions of the DA system (see supplementary video).

Contents

1. Introduction

Major depressive disorder (MDD) is a common and disabling disorder (King-Kallimanis et al., 2009; Merikangas et al., 2010; Thornicroft, 1993). An incomplete knowledge of its pathophysiology and the insufficient efficacy of the current antidepressant pharmacological treatments characterize the current therapeutic scenario (Sinyor et al., 2010). Further research is needed to better improve the treatment of MDD. We reviewed the classical monoaminergic paradigm, upon which the current antidepressant pharmacotreatments are based, with a specific interest in the functions of the dopaminergic (DA) system. Then, we reviewed the emerging paradigms on MDD, with a specific attention on the DA system.

A Copernican revolution came in the mid of fifties, from the clever clinical observation that administrating some antitubercolotics or anti-hypertensive had, amid others, unexpected outcomes on mood. This opened the era of drug treatment of depressive disorders. Those first compounds — iproniazide and reserpine — shared the property of influencing the monoamines' balance in the central nervous system, a property after which the monoaminergic theory of MDD was developed. The most part of antidepressant drugs designed ever since were engineered upon that observation, producing the high

Abbreviations: MDD, Major depressive disorder; DA, dopamine/dopaminergic; NA, noradrenaline; 5-HT, serotonin; 5-HT1A, serotonin receptor 1A; SSRI, selective serotonin reuptake inhibitor; CSF, cerebrospinal fluid; 5-HIAA, 5-Hydroxyindoleacetic acid; NGF, nerve growth factor; GDNF, glial cell line-derived neurotrophic factor; BDNF, brain-derived neurotrophic factor; DA, D2, dopamine receptor D2; FGA, first generation antipsychotic; SGA, second generation antipsychotic; INF-α, interferon α; HPA, hypothalamus-pituitary-adrenal axis; PD, Parkinson's disease; GR, glucocorticoid receptor; HDAC5, histone acetylases 5; ECS, electroconvulsive seizures; GSK3, glycogen synthase kinase 3; Wwt, wingless.

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number of drug compounds now available for the treatment of MDD. Until now the decades of research and clinical experience performed in this field leaded to an increased safety without substantial improvement on efficacy. This urged the need for new paradigms helping to identify some new antidepressant compounds. The neurotrophin, the inflammatory, the anti-apoptosis and the epigenetic hypothesis are some of the most recognized theories for MDD at the moment of writing, and will be reviewed here.

We review here the evidence supporting these hypotheses from the perspective of the dopaminergic system. The involvement of this system in MDD was suggested by pre-clinical data (Molander and Randrup, 1976; Randrup and Braestrup, 1977; Randrup and Jonas, 1967) and further elaborated by McClure (1973). In 1983, Willner and colleagues reviewed in three papers these early results about DA and MDD (Willner, 1983a,b,c). McClure described an under-activation of nigro-striatal DA system in depressed patients with psychomotor retardation and the antidepressant efficacy of DA agonism (Willner, 1983a). Willner underlined the implication of meso-limbic and nigro-striatal DA systems on responsiveness to environment (Willner, 1983b), which is classically blunted in MDD patients. He further focused on the effects of antidepressants on the brain DA turnover, suggesting an increased DA function after chronic antidepressant treatment (Willner, 1983c), as subsequently confirmed (D'Aquila et al., 2000). Despite these interesting suggestions, the DA system has not been further investigated in the field of MDD since the early nineties, when several reviews about DA involvement in MDD redirected the attention on this field by underlining that DA likely contributes to the pathophysiology of MDD (Brown and Gershon, 1993; Cabib and Puglisi-Allegra, 1996; Dunlop and Nemeroff, 2007; Fibiger, 1995). Malhi and Berk (2007) proposed a specific role for DA impairment in melancholic depression. Other authors reviewed the role of DA on the antidepressant response concluding that DA system could be a potential target for antidepressant pharmacological treatments, although not in all the forms of depression. Interestingly, it has been suggested that an excessive DA stimulation could be even detrimental for depressive patients (Dailly et al., 2004).

These data together suggested that DA system may play a role in the depressive phenotype. Consistently, DA has been associated with several function linked to depressive symptoms. Among these: 1. motivation and emotional response (classically associated with the mesocortical pathway), 2. reward (classically associated with the mesolimbic pathway) and 3. psychomotor function (classically associated with the nigro-striatal pathway).(Heinz and Schlagenhauf, 2010; Kalivas and Volkow, 2005; Nieoullon and Coquerel, 2003; Salgado-Pineda et al., 2005; Volkow et al., 2010; Wickens, 1990). All these functions are impaired during depressive episodes, supporting the direct or indirect involvement of DA system in the pathophysiology of MDD (Ruhe et al., 2007). Nonetheless, during the last decades, DA system has been more classically associated with psychosis and substance related disorders rather than affective disorders. Noradrenaline (NA) and serotonin (5-HT) on the other hand, have been classically associated with mood and anxiety disorders. It is then of considerable interest to investigate the MDD related theories through the lens of a monoamine that was somehow poorly considered in this specific field, in the hope of providing some clues that could unify the many theories in MDD. This perspective has also limits: in particular it is difficult to analyze the epigenetic related theory from the point of view of the DA, considering that research in this field is still in its very infancy. We reviewed the epigenetic theory for MDD, underlining some interesting DA related evidences that could bridge this two apparently distant systems.

2. Monoaminergic hypothesis

The monoaminergic hypothesis posits that depression is caused by a decreased monoaminergic function in the brain. The principal monoamines in the brain are 5-HT, NA and DA. The most part of available antidepressant treatments acts on the 5-HT and NA (Nutt et al., 2006). DA has been classically associated with abuse disorders and psychosis but it may play a role in MDD as well. From this point of view, the incomplete efficacy of current antidepressant treatments may depend on drug designs, mostly based on 5-HT and NA (Nutt et al., 2006).

A complex interaction between 5-HT, NA and DA exists, thus most of the activities exerted on 5-HT or NA systems affect DA release. In particular, animal studies suggested that antidepressants reshape the phasic activation of the DA system (Friedman et al., 2007). Considering that the phasic activation of the DA system is associated with motivation and hedonia (Wise, 2005), both dimensions highly impaired in MDD, this effect could represent part of the healing potential of the antidepressant molecules (see supplementary video).

The molecular basis of this pharmacological tuning may be due to the interplay among the monoaminergic systems. The DA and the NA systems' functions tend to be additive (Carboni and Silvagni, 2004 and references therein). Furthermore the NA transporter, a target of some antidepressant treatments, is able to transport DA as well (Carboni and Silvagni, 2004). On the other hand, the 5-HT and the DA system are highly interlaced: 5-HT receptors are expressed by DA neurons in the midbrain (Herve et al., 1987; Nedergaard, 1988), and in higher parts of the brain the 5-HT terminals are interconnected with the DA release by the activity of interneurons. The high number ($n = 14$ at least) and the different isoforms of the 5-HT receptors provide the 5-HT system with the flexibility required to regulate the activation of the DA tonic and phasic release. In particular, antagonizing 5-HT1A results into an increased DA tone in the deepest brain structures and inactivation of the DA system in the prefrontal cortex. These effects could support the hypothesis that desensitization of the 5-HT1A may lead to an activation of the deep DA system, which is associated with reward and motivation, typically lacking in MDD patients.

Considering this strong interplay among monoaminergic systems, it may be useful to design more antidepressant that target directly the DA system instead of using antidepressants whose activity ends with influencing the DA system through the NA and 5-HT ones. In addiction, there are some evidences that the DA based antidepressants work faster compared to other antidepressants (Amore and Jori, 2001), although buproprion — a DA antidepressant — did not show a better efficacy with regard to SSRIs (Foley et al., 2006). On the other hand, some evidences suggested that also DA antidepressant — e.g. nomifensine — act trough a modulation of 5-HT, NA and DA interplay (Katz et al., 2010), suggesting that the modulation of these interactions is a key point for antidepressant treatment. Consistently, recent studies suggested second generation antipsychotics, drugs with a DA and 5-HT profile (i.e. in other words, DA and 5-HT modulators), as potent and fast antidepressants (Thase, 2006; Weisler et al., 2008).

These lines of evidence emerge from the paradigm known as the 'monoaminergic theory of MDD' that ruled the field and research on MDD in the last decades. As stated above, it was developed in the fifties, after the clinical observation that iproniazid and imipramine had elating effect, whilst reserpine produced depressive-like symptoms (Berton and Nestler, 2006; Pittenger and Duman, 2008). These compounds shared the ability to interfere with the monoaminergic systems in the brain (Nutt et al., 2006). So far the currently available antidepressants mainly work through this paradigm, with some exceptions (e.g. agomelatine). It is therefore relevant to recollect the principles of such paradigm in order to understand the limits of the current pharmacological antidepressant treatments designed upon it, as well as the limits of any antidepressant drug only based on a DA activity (see Foley et al. (2006)). In all facts, despite its relevance, the monoaminergic theory alone cannot explain the pathophysiology of MDD. Ruhe et al. (2007) reviewed and meta-analyzed the data of the last 40 years of monoamine depletion trials, revealing that the depletion of the monoamines (data were mainly on 5-HT) did not decrease mood in healthy subjects, although it slightly decreased mood in healthy subjects with a family history of MDD. Consistently,