

## REVIEW ARTICLE

# Antidepressant-induced Dopamine Receptor Dysregulation: A Valid Animal Model of Manic-Depressive Illness

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**Abstract: Background:** Mania seems to be associated with an increased dopamine (DA) transmission. Antidepressant treatments can induce mania in humans and potentiated DA transmission in animals, by sensitizing DA D2 receptors in the mesolimbic system. We have suggested that the sensitization of D2 receptors may be responsible of antidepressant-induced mania. This review aims to report the experimental evidence that led to the hypothesis that antidepressant-induced DA receptors dysregulation can be considered an animal model of bipolar disorder.

**Methods:** We reviewed papers reporting preclinical and clinical studies on the role of DA in the mechanism of action of antidepressant treatments and in the patho-physiology of mood disorders.

**Results:** A number of preclinical and clinical evidence suggests that mania could be associated with an increased DA activity, while a reduced function of this neurotransmission might underlie depression. Chronic treatment with imipramine induces a sensitization of DA D2 receptors in the mesolimbic system, followed, after drug discontinuation, by a reduced sensitivity associated with an increased immobility time in forced swimming test of depression (FST). Blockade of glutamate NMDA receptors by memantine administration prevents the imipramine effect on DA receptors sensitivity and on the FST.

**Conclusion:** We suggest that chronic treatment with antidepressants induces a behavioural syndrome that mimics mania (the sensitization of DA receptors), followed by depression (desensitization of DA receptors and increased immobility time in the FST), *i.e.* an animal model of bipolar disorder. Moreover the observation that memantine prevents the “bipolar-like” behavior, suggests that the drug may have an antimanic and mood stabilizing effect. Preliminary clinical observations support this hypothesis.

*“The patients who developed continuous circularity under antidepressant drug treatment were of highly energetic temperament. The hypothesis ....these patients have latent hypomanias, which become clinically manifest under the action of antidepressants. The intensification of an underlying hypomanic process by the antidepressants would precipitate another depression and establish continuous circularity [1].”*

*Koukopoulos's group (1981)*

**Keywords:** Animal models, bipolar disorder, depression, mania, memantine, mood stabilizer.

## INTRODUCTION

Animal models of mental disorders have been widely used and play an essential role in drug discovery and in the search for the neurobiological substrate of psychiatric disorders. The majority of available animal models of mood disorders meet the Geyer and Markou [2] criteria (etiological, behavioural and neurobiological correspondence to human disorder, and sensitivity to treatments effective in the human condition) for animal model of behavioral disorders.

Face validity: animal behavior mimics that of human illness. The correspondence of neurobiological changes in the human disorder to those found in the animal model (construct). Etiological validity requires that the causes of the human condition, when etiology can be established, should be the same of the condition induced in the animal. Unfortunately, the causes of psychiatric disorders are still to be clarified. Hence, this validity subtype is limited to hypotheses regarding the possible etiology of psychiatric disorders. Finally, predictive validity regards the ability of the animal model to predict the efficacy of a drug in the corresponding human disorder (*i.e.*, a drug active in an animal model of depression should be effective in treating human depression).

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However, in spite of the availability of a great number of animal models of depression [3] and mania [4], in the last few decades, no really important therapeutic innovation has been introduced in the field of psychopharmacotherapy, but the market has been flooded with only “me too drugs”; this is particularly true for bipolar disorders [5].

Indeed, several decades after the serendipitous discovery of antidepressants, antipsychotics, and lithium, no clinically relevant innovation (as defined by Motola *et al.* [6]) has been introduced in the last 60 years.

With regard to the main aim of drug treatment of bipolar disorders, the ability to prevent both the hypomanic/manic and depressive recurrences of the manic-depressive illness has been clearly demonstrated only for lithium [5].

We have recently implemented in our laboratory an animal model of bipolar disorder that showed etiological, face, construct, and predictive validity. In fact, the condition in the model is induced by antidepressants, which can trigger mania and a rapid cycling course in human bipolar disorder. In this model, increased dopaminergic activity is followed by hypoactivity; the behavioral syndrome consists of increased sexual activity and aggression, followed by depressive-like behavior, and is prevented by NMDA receptor antagonists, including memantine. This paper will deal with this model.

#### ANTIDEPRESSANTS INDUCE MANIA

The ability of antidepressants to induce mania has been described soon after their introduction in clinical practice. The pioneers of the clinical use of both the tricyclic antidepressant (TCA), imipramine, Roland Kuhn [7] and of the monoamine oxidase inhibitor (MAOI), iproniazide, George Crane [8] recognized their mood-switching properties soon after having introduced these drugs in clinical practice. The clinical evidence accumulated in the last 60 years clearly indicates that all drugs used in the therapy of depression may produce a manic/hypomanic episode, either in patients with bipolar depression and with major depressive disorder. The frequency reported by different studies varies from 10% to 70% [9]. Recently an incidence of 12.5% has been suggested [9]. The same authors also found that mood stabilizer drugs failed to prevent the mania/hypomania in pharmacologically treated depressed patients.

Antidepressant-induced mania is considered to be the trigger leading to the malignant, continuous/rapid-cycling course of bipolar disorder. This change in the course of the disorder was first reported by Koukopoulos *et al.* in 1980 [10] and has been confirmed by a number of reports in the last few decades.

The Koukopoulos group proposed that antidepressants can induce a rapid cycle course of bipolar disorder by activating a latent hypomanic status [1, 11]. In 2008, Ghaemi [12] suggested to consider antidepressants as mood destabilizers, *i.e.*, as drugs with an opposite effect to mood stabilizers, because of their ability to induce mania and trigger a very severe course of manic-depressive illness.

#### DOPAMINE, MANIA/HYPOMANIA AND DEPRESSION

The main clinical evidence of the correlation of manic syndromes and a stimulation of dopamine activity is the observation that amphetamine, which increases dopamine transmission in the CNS, can induce euphoria, hypomania, mania without psychotic symptoms, and mania with psychotic symptoms in a dose-related manner [13]. On the other hand, antipsychotic agents, which usually block dopamine receptors, are the most potent drugs in reducing acute mania symptoms [14].

In the last 50 years many studies have demonstrated an increased dopamine transmission during mania and decreased dopamine transmission during depression [15-20].

The stimulation of dopamine receptors can induce or worsen a manic syndrome [21,22]. Drugs of abuse share the ability to induce euphoria in humans [23-25] and to increase dopamine release in the mesolimbic system [26,27]; the latter plays an essential role in the process of reward [28,29], which seems to be hyperactive in mania and hypoactive during depression [29].

Dopamine D<sub>2</sub> receptors have been shown to be increased in bipolar disorders with psychotic symptoms [30, 31]. Beyond the classical biogenic amine hypothesis of depression, which postulates reduced intrasynaptic concentration of serotonin and norepinephrine [32], a convincing complementary hypothesis has been advanced proposing dopamine hypofunction [33-36].

The supposed therapeutic mechanism of TCAs is the blockade of serotonin and norepinephrine reuptake that increases the concentrations of the two neurotransmitters in the synaptic cleft [37], but as we previously showed for imipramine and amitriptyline, but also for the tetracyclic mianserin, they also increase dopamine function through dopamine autoreceptor hyposensitization [38], whereas the prevalently norepinephrine transporter inhibitor TCA desipramine chronically supersensitized the postsynaptic dopamine receptor [39], thus potentiating dopaminergic transmission. The mechanism of MAOIs is the inhibition of monoamine oxidase, an enzyme blocking the metabolic breakdown of norepinephrine and serotonin, but also of dopamine, ensuing in an intrasynaptic elevation of the concentrations of all three biogenic amines [40]. Taken together, these data suggest that a reduction of monoaminergic activity could lead to underlying depression.

On the other hand, reserpine depletes not only noradrenaline and serotonin neurons, but also dopaminergic neurons [41, 42], and its administration results in depression [41, 42].

A number of animal models of depression are associated with decreased dopaminergic activity and anhedonia-like behavior [43-46]. Antidepressant treatments reversed both dopaminergic hypoactivity and anhedonia-like behavior [46-51], suggesting that dopamine-targeting drugs should be indicated for depressive episodes with marked anhedonia [51]. Parkinson's disease, which is caused by nigro-striatal dopaminergic neurodegeneration, is often associated (with prevalence rates ranging from 50 per cent [52] to 75 per cent

[53]) with depression. Finally, a similar condition can be observed in animals with mesolimbic dopaminergic lesions [54].

### EFFECT OF ANTIDEPRESSANT ON DOPAMINERGIC ACTIVITY

In our first report [38], we showed a reduced sensitivity of dopamine receptors mediating sedation/reduced motor activity (presynaptic or autoreceptors) after 10 days of antidepressant administration. Moreover, the stimulation of motor activity by apomorphine was potentiated. On the basis of these observations we suggested that antidepressants potentiate dopamine activity by reducing the sensitivity of autoreceptors, and that this effect may contribute either in their therapeutic action and in their ability to induce manic syndromes.

Different studies [55-63] aimed at evaluating the ability of antidepressant drugs to desensitize dopamine autoreceptors have reported contrasting data. On the other hand, a large body of studies have confirmed the ability of treatments used in the therapy of depression to induce a behavioural supersensitivity of postsynaptic dopamine receptors, particularly in the mesolimbic system [39, 64-72].

This sensitization is selective for dopamine D2 receptors, while the stimulation of D1 receptors was not influenced [67].

In keeping with these observations [65-72], the increased dopaminergic transmission secondary to D<sub>2</sub> receptor sensitization in the mesolimbic system (where conventionally we locate the reward system) induced by antidepressants, may be viewed as contributing to alleviate the symptomatology of depression, in particular that of inhibited depression [65-72]. Furthermore, the same effect may be involved in the induction of mania/hypomania and in the worsened of the bipolar disorder course [65, 67, 69, 70, 73-76]. Interesting, antidepressant-induced mania seems to be associated with increased protein kinase C (PKC) activity [77]. Finally, we observed increased sexual activity [78, 79] and aggressivity [unpublished results] in rats that may match some symptoms observed during mania in humans.

### ANTIDEPRESSANTS INDUCE BIPOLAR-LIKE BEHAVIOR

In 2003-04 we observed that the dopamine receptor sensitization obtained through chronic imipramine treatment, present during and 24h after imipramine withdrawal, was followed after 15-30 days of imipramine withdrawal by a reduction of dopamine receptor sensitivity and a behavioural syndrome similar to depression [80, 81].

Based on these results we can speculate that the increased sensitivity of dopamine receptors may be responsible for the antidepressant-induced mania [73-76, 82-84] (that has been observed in humans receiving antidepressant drugs), and that depression could be the consequence of a reduced sensitivity of these receptors [76, 81].

Thus, chronic imipramine treatment produces a bipolar-like behavior.

These findings provide a neurobiological evidence of Koukopoulos' hypothesis, that antidepressant drugs, by inducing mania, worsened the course of bipolar disorders.

### THE SENSITIZATION PHENOMENON AND THE ROLE OF NMDA RECEPTORS

Blockade of NMDA receptors prevents the sensitization of amphetamine [85-90], methylphenidate [91], cocaine [92-95], apomorphine [96, 97] and other dopamine agonists [98,99], nicotine [100], morphine [101, 102], ethanol [103-105], immobilization [88] and social defeat stress [106]. It should be remembered that behavioral sensitization to psychostimulants is an animal model of mania and psychosis [107] and is used to screen for antipsychotic/antimanic drugs.

### THE ROLE OF NMDA RECEPTORS IN ANTI-DEPRESSANT TREATMENT-INDUCED DOPAMINE RECEPTOR SENSITIZATION

We have demonstrated that the noncompetitive NMDA antagonists MK-801 (dizocilpine) or memantine [82, 108, 109] completely prevents imipramine- or electroconvulsive shock-induced dopamine receptor sensitization.

On the contrary, in keeping with clinical observations showing that conventional mood stabilizers are unable to prevent antidepressant-induced mania, the administration of lithium [110], carbamazepine [83], valproate [84], and lamotrigine (unpublished results) failed to prevent imipramine-induced dopamine receptor sensitization in rats.

Memantine prevented both the imipramine-induced sensitization and the reduced sensitivity of dopamine receptors associated with the increase of immobility time in forced swimming test [109], suggesting that it may represent a potential antimanic and mood-stabilizing agent.

On the basis of these observations, we suggested the use of memantine in the treatment of mania/hypomania and in the long-term prophylaxis of manic-depressive illness.

### MEMANTINE: A NEW ANTIMANIC AND MOOD-STABILIZING DRUG

Two 6- and 12-month clinical trials provided evidence of acute antimanic and a sustained prophylactic effect of memantine, used as augmenting agent in treatment resistant bipolar disorders [111, 112]. Keck *et al.* [113] have shown the efficacy of the drug in the treatment of mania. Furthermore, beneficial effects of memantine monotherapy have been observed in individual BD patients, including those whose lithium treatment was discontinued [114-117].

Particularly interesting are the results of our 3-year clinical trial [118]. Indeed, we found that the administration of memantine produces a statistically significant and clinically relevant improvement of treatment-resistant bipolar disorder (reduced illness episodes number, severity and duration).

Interestingly, patients without free interval showed the most marked improvement as an observation consistent with our model of bipolar disorder, which simulates a continuous

circular course of the disorder, is being resistant to available mood stabilizers.

## CONCLUSION

Antidepressant treatments can induce mania and change the natural course of manic depressive illness in humans. We have shown in rats that such treatments by inducing behavioral supersensitivity of the dopaminergic system induce mania-like behavioral responses, and this is followed by reduced sensitivity of these receptors and a behavior that mimics human depression. The antidepressant-induced dopamine receptors dysregulation represents a useful animal model of bipolar disorder with continuous/rapid cycle course, *i.e.*, a malignant course that is often resistant to currently available treatments.

The model is sensitive to memantine, which seems to be a promising drug for the treatment of mania and for the long-lasting prophylaxis of treatment-resistant manic-depressive illness.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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