ELSEVIER

European Journal of Pharmacology 405 (2000) 365–373

ejp

www.elsevier.nl/locate/ejphar

The role of dopamine in the mechanism of action of antidepressant drugs

Paolo Stefano D'Aquila [a,*], Maria Collu [b], Gian Luigi Gessa [b], Gino Serra [a]

[a] *Dipartimento di Scienze del Farmaco, Università di Sassari, via Muroni 23 / a, 07100 Sassari, Italy*
[b] *Dipartimento di Neuroscienze "B.B. Brodie", Università di Cagliari, via Porcell 4, 09124 Cagliari, Italy*

Accepted 28 June 2000

Abstract

The present paper reviews evidence on the effect of antidepressant treatments on dopamine transmission. Chronic treatment with antidepressant drugs potentiates the behavioural stimulant responses elicited by the stimulation of dopamine receptors, including reward-related behaviours. Moreover, antidepressants affect dopamine release in several brain areas. The reviewed literature is discussed in terms of the possible mechanisms underlying antidepressant-induced supersensitivity to dopamine-mediated behavioural responses, and of the possible implications for the therapeutic effect of these drugs. It is concluded that the potentiation of dopaminergic neurotransmission induced by chronic antidepressant treatments might contribute to their therapeutic effect.

Keywords: Antidepressant drug; Dopamine; Depression; Mania; Mesolimbic dopamine system

1. Introduction

The majority of antidepressant drugs increase the availability of noradrenaline and/or serotonin in the synaptic cleft, either by blocking their reuptake by nerve terminals, or by inhibiting their catabolism by monoamine oxidase enzymes. For this reason, it has been traditionally assumed, on the one hand, that depression is caused by a decreased serotonergic and/or noradrenergic neurotransmission, and on the other hand, that the therapeutic effect of antidepressants is due to their ability to restore these deficits (Baldessarini, 1996). However, evidence for an impaired serotonergic and/or noradrenergic neurotransmission in depressive patients is inconsistent (see Schwaninger et al., 1997). Moreover, some potent antidepressants, such as mianserin and mirtazapine, do not affect the reuptake or degradation of biogenic amines (Baldessarini, 1996; Golden et al., 1998). Furthermore, the effects of antidepressant drugs on noradrenaline and/or serotonin concentration in the synaptic cleft occur immediately after a single administration, while their effect in relieving depression symptoms is not apparent before at least 2–4 weeks of treatment (Baldessarini, 1996; Schwaninger et al., 1997).

On the basis of these observations, and of the literature that has accumulated in decades of research, it is now accepted a) that the pathogenesis of depression cannot be explained only in terms of impaired noradrenaline and/or serotonin neurotransmission and b) that the mechanism of action of antidepressant drugs is due to a complex series of events, of which the acute effects of these drugs are only the first step (Hyman and Nestler, 1996; Schwaninger et al., 1997).

It has been demonstrated that chronic treatment with antidepressants influences a variety of neurotransmitter systems and induces in the brain a great number of adaptive changes. Most importantly, common long-term effects, shared by treatments with a different "acute" mechanism of action (i.e. different antidepressant drugs, but also electroconvulsive shock and REM-sleep deprivation, which exert a therapeutic effect on depressive symptoms), have been described. On the other hand, although numerous studies have produced data suggesting either an increased or a decreased activity of different neurotransmitter systems (mainly monoaminergic), the available evidence is either inconsistent or not conclusive in demonstrating that the proposed alterations are in fact either necessary or sufficient to cause a depressive state. Therefore, at present, no hypothesis based upon a single neurotransmitter system

* Corresponding author. Tel.: +39-079-228739; fax: +39-079-228712.
E-mail address: dsfpaolo@ssmain.uniss.it (P.S. D'Aquila).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00566-5

can be considered exhaustive in explaining either the therapeutic effect of antidepressant treatments, or, even less, the possible mechanisms underlying the pathophysiology of depression.

In the present paper, experimental evidence suggesting a role of dopamine in the mechanism of action of antidepressant drugs will be reviewed.

In the late seventies it has been proposed an involvement of dopamine, on the one hand, in the pathophysiology of depression and mania, and, on the other hand, in the mechanism of action of antidepressants (Randrup et al., 1975; Serra et al., 1979).

Two important lines of experimental evidence prompted the investigation on the possible role of dopamine both in the pathogenesis of depression and in the mechanism of action of antidepressant treatments. Firstly, drugs which increase dopamine levels, such as cocaine and amphetamine, produce mood elation; conversely, drugs which either reduce dopamine levels, such as reserpine, or block dopamine receptors, such as neuroleptics, can induce either dysphoria or depressed mood (Jimerson, 1987). In addition, different compounds affecting directly either dopamine levels or dopamine receptors display a demonstrated antidepressant activity (Baldessarini, 1996). Secondly, it has been demonstrated by an enormous bulk of studies, that dopaminergic neurons originating in the ventral tegmental area and projecting their nerve terminals into different telencephalic areas, amongst which are the prefrontal cortex and the nucleus accumbens, are involved in the control of reward-related behaviour and incentive motivation (Blackburn et al., 1992; Fibiger and Phillips, 1987; Wise, 1989), which are impaired in depression (American Psychiatric Association, 1994). Therefore, to demonstrate that antidepressant drugs are capable to "improve" the functioning of these neural systems, would provide a possible explanation of at least some of their therapeutic effects (i.e. the therapeutic effect on anhedonia and loss of motivation).

2. Chronic treatment with antidepressants sensitizes dopamine receptors preferentially in the mesolimbic system

The first study on the effects of chronic treatment with antidepressants on dopamine transmission was performed in 1979 in our laboratory. In particular, the effect of chronic treatment with antidepressants on the behavioural and biochemical responses to the direct dopamine receptor agonist, apomorphine (Serra et al., 1979), was studied. Direct dopamine receptor agonists display a biphasic behavioural effect: at relatively high doses they produce an increase in locomotor activity and cause stereotypies, while at smaller doses they reduce locomotor activity and cause sedation. The locomotor response to dopamine receptor agonists is mediated by the stimulation of dopamine receptors in the nucleus accumbens, which is part of the mesolimbic dopamine system. The stereotypies induced by dopamine receptor agonists are mediated by the stimulation of dopamine receptors in the corpus striatum, which is part of the extrapyramidal system (Creese and Iversen, 1975; Kelly et al., 1975). The hypomotility and sedation induced by the small doses are considered to be, at least in part, the behavioural effect of the decrease in dopamine transmission caused by the stimulation of dopamine autoreceptors, which results in the inhibition of synthesis and release of dopamine, as well as of the firing rate of dopamine neurons (Di Chiara et al., 1978). In fact, some successive studies have produced evidence suggesting that the sedative effect induced by low doses of dopamine agonists, along with other effects attributed to the stimulation of dopamine autoreceptors, might be the effect of the stimulation of a sub-population of postsynaptic receptors displaying, like dopamine autoreceptors, high affinity for dopaminergic agonists and antagonists (Morelli et al., 1986; Scheel-Krüger, 1986; Serra et al., 1986; Stahle and Ungerstedt, 1987, 1989). We observed that, after chronic treatment with antidepressants, the motor stimulant effect of apomorphine was potentiated, while the hypomotility and the inhibition of dopamine synthesis produced by the small doses of the drug were prevented (Serra et al., 1979). We interpreted these findings suggesting that chronic antidepressants potentiate dopamine transmission by inducing a subsensitivity of dopamine autoreceptors.

The first results consistent with this interpretation have been obtained by Chiodo and Antelman (1980a,b): they observed that, after chronic treatment with different antidepressant drugs or repeated electroconvulsive shock, the inhibitory effect of apomorphine on the firing rate of dopamine neurons in the substantia nigra was prevented.

Subsequent studies in the following 20 years have confirmed, with a great deal of consistency, the ability of chronic treatment with virtually all antidepressant drugs, repeated electroconvulsive shock and REM-sleep deprivation, to increase the motor stimulant effect of dopamine receptor agonists (Collu et al., 1997; D'Aquila et al., 1992a,b, 1997a,b,c; Maj et al., 1989; Serra et al., 1979, 1990a; Spyraki and Fibiger, 1981; but, for negative results, see Arnt et al., 1984a,b; Chagraoui et al., 1990; Cabib et al., 1995; Gambarana et al., 1995b). However, more conflicting results have been obtained on the ability of antidepressants to prevent the effects attributed to the stimulation of dopamine autoreceptors. While several laboratories produced results consistent with our first observation (Arnt et al., 1984b; Hasan and Leonard, 1981; Holcombe et al., 1982; Nielsen, 1985; Maj and Wedzony, 1985, 1989; Vaccheri et al., 1984), others failed to replicate the observations that antidepressant treatments prevent either the hypomotility or the decrease in firing rate of dopamine neurons induced by small doses of dopamine agonists (Diggory and Buckett, 1984; MacNeil and Gower, 1982; Spyraki and Fibiger, 1981; Welch et al., 1982). More recently, several studies have shown that chronic treatment

with some antidepressant drugs (desipramine, phenelzine and clorgyline), but not with others (e.g. clomipramine), attenuate the locomotor suppressant effect of low doses of apomorphine in rats (Allison et al., 1993, 1995). In mice, chronic treatment with amineptine or desipramine reduced the motor inhibitory effects of low doses of the dopamine D_2-like receptor agonist, quinpirole (Chagraoui et al., 1990). In our laboratory, we observed that imipramine and fluoxetine did not attenuate the locomotor suppressant effect of low doses of quinpirole (Collu et al., 1997; Serra et al., 1990a). These results are in apparent contrast with our earlier observation that chronic antidepressant treatment prevents the sedative effect of small doses of apomorphine. However, it is likely that the doses of apomorphine used in the earlier study was high enough to act postsynaptically on supersensitive dopamine D_2 receptors. Indeed, chronic treatment with imipramine prevented the sedative effect of the dose of 0.05 mg/kg of quinpirole but failed to influence the effect of smaller doses (Serra et al., 1990a).

Therefore, most of the available evidence is consistent with the hypothesis that chronic antidepressant treatments potentiate dopamine transmission, and this potentiation results from an increased sensitivity of postsynaptic dopamine receptors, as firstly suggested by Spyraki and Fibiger (1981), rather than from a decreased sensitivity of presynaptic dopamine receptors. Moreover, the potentiation of dopamine transmission as revealed by behavioural studies in normal animals occurs preferentially in the limbic system. Indeed, chronic treatment with antidepressant drugs potentiates the locomotor response to dopamine receptor agonists administered either systemically, or directly into the nucleus accumbens (Durlach Misteli and Van Ree, 1992; Maj and Wedzony, 1985), while dopamine agonist-induced stereotypies, mediated by the stimulation of striatal receptors, are not affected (Spyraki and Fibiger, 1981; Serra et al., 1990a).

The authors and others (see Serra et al., 1992), suggested that this potentiation might be responsible for the therapeutic effect of antidepressant treatments, given the involvement of dopamine in the control of reward-related behaviour and incentive motivation, which are impaired in depression. In support of this hypothesis, several studies reported a potentiation by chronic treatment with antidepressant drugs of reward-related behaviours: food- and apomorphine-induced (Papp, 1988) and cocaine-induced place preference (Collu et al., 1994, 1996), and brain stimulation reward (Fibiger and Phillips, 1981).

3. Effects of antidepressants on different dopamine receptor types

While the locomotor effect of dopamine D_2-like receptor agonists is potentiated by chronic antidepressant treatment, the behavioural effect of the administration of dopamine D_1 receptor agonists is not influenced (Serra et al., 1990a,b; Maj et al., 1989).

In spite of the behavioural evidence of supersensitivity of postsynaptic dopamine D_2-like receptors in the limbic system, the results of dopamine receptor binding have shown that the dopamine D_2-like receptor number, as measured by [^{3}H]spiperone, [^{3}H]raclopride and other radiolabelled dopamine D_2-like receptor antagonist binding, is unchanged either in the limbic system or striatum after chronic treatment with a number of different antidepressant drugs or electroconvulsive shock (Klimek and Nielsen, 1987; Martin et al., 1995; Martin-Iverson et al., 1983; Paetsch and Greenshaw, 1992). By contrast, the noradrenaline and dopamine reuptake inhibitor, nomifensine, and the monoamine oxidase inhibitor, tranylcypromine, did even decrease the number of dopamine D_2 receptors, when given for 14 days (Martin et al., 1995). However, subsequent studies have shown that, if agonists instead of antagonists are used as radioligands, an increase in the density of dopamine D_2-like receptors can be demonstrated in the limbic forebrain (Maj et al., 1996; Rogoz and Dziedicka Wasilewska, 1999).

On the contrary, although chronic antidepressants fail to modify the behavioural responses to dopamine D_1 receptor stimulation, a decrease in dopamine D_1 receptor number and sensitivity has been reported in the striatum and, even more so, in the limbic areas and prefrontal cortex after chronic treatment with antidepressants (De Montis et al., 1989; Gambarana et al., 1995a; Klimek and Nielsen, 1987; Paetsch and Greenshaw, 1992). In another study, chronic antidepressant treatments with desipramine, zimeldine, amitriptyline, tranylcypromine, mianserin, electroconvulsive shock did not alter striatal dopamine D_1 receptor sites measured as [^{3}H]SCH 23390 dopamine D_1receptor binding (Cheetham et al., 1995). The down-regulation of dopamine D_1 receptors induced by chronic antidepressant treatments appears to be species-specific. Indeed, it has been shown that chronic treatment with imipramine failed to induce a down-regulation of limbic dopamine D_1 receptors in mice, although it was effective in a model of depression, the forced swimming test (Nowak et al., 1991).

Consistent results have been reported measuring the levels of dopamine D_2 receptor mRNA. Chronic treatment with fluoxetine, desipramine and tranylcypromine induced an increase in dopamine D_2 receptor mRNA in the nucleus accumbens, mainly in the shell, but not in the striatum (Ainsworth et al., 1998). In the same study, both fluoxetine and desipramine increased dopamine D_2-like receptor binding in the nucleus accumbens shell; fluoxetine had a similar effect also in the nucleus accumbens core. Tranylcypromine, however, had no effect on dopamine D_2-like receptor binding in the nucleus accumbens but decreased binding in the striatum. The level of mRNA coding for dopamine D_2 receptors was increased both in the nucleus accumbens and in the striatum, after chronic administration of imipramine and citalopram, while (+)-oxaprotiline did

not produce any statistically significant changes (Dziedzicka Wasylewska et al., 1997).

Dopamine D_1 receptor mRNA was unaffected after chronic treatment with fluoxetine, desipramine and tranylcypromine (Ainsworth et al., 1998), while it was decreased following repeated administration of imipramine, both in the nucleus accumbens and in the striatum (Dziedzicka Wasylewska et al., 1997). In the same study, the repeated administration of citalopram, the selective inhibitor of serotonin reuptake, resulted in an increase in the level of dopamine D_1 receptor mRNA in the striatum and in the core region of nucleus accumbens.

More recently, it has been shown that chronic treatment with different antidepressant drugs (imipramine, amitriptyline, citalopram and mianserin) potentiated the locomotor response to the dopamine D_3 receptor agonist 7-OH-DPAT and increased the density of dopamine D_3 receptors in the islands of Calleja and in the shell of the nucleus accumbens, which are brain regions with highly selective expression of dopamine D_3 receptors, measured by autoradiography with [^{3}H]7-OH-DPAT as a radioligand (Maj et al., 1998).

In summary, most of the available evidence show that the increased sensitivity to dopamine receptor stimulation induced by chronic antidepressant treatments is related to an increased dopamine D_2-like (i.e. D_2 and D_3) receptor function, and a decreased dopamine D_1 receptor number and sensitivity. Moreover, these changes are most prominent in the limbic areas, i.e. those areas innervated by dopamine neurons in the ventral tegmental area, thus supporting the view that they might indeed be important in the therapeutic effect of these drugs.

4. Role of dopamine D_1 receptors in the mechanism of action of antidepressant drugs

The question arises as to whether the down-regulation of dopamine D_1 receptors might play a role in changes of dopamine D_2-like receptor function. Indeed, it is well-established that dopamine D_1 and D_2 receptors are functionally linked and that the dopamine D_1 receptors play a permissive role for the expression of postsynaptic stimulant responses mediated by dopamine D_2 receptor activation (Clark and White, 1987; Walters et al., 1987). We suggested (Serra et al., 1990a, 1992) that the imipramine-induced behavioural supersensitivity of dopamine D_2 receptors in the limbic system might be due to an overstimulation of dopamine D_1 receptors. In support of this hypothesis we found that administration of reserpine and α-methyl-tyrosine, a treatment that should eliminate endogenous dopamine, completely suppressed the behavioural effect of quinpirole in chronic imipramine-treated rats, suggesting that endogenous dopamine at the dopamine D_1 receptor is necessary for the expression of the behavioural supersensitivity (Serra et al., 1990a). In another experiment, we have shown that chronic imipramine reverses the sedative effect of B-HT 920, a selective dopamine autoreceptor agonist, into a motor stimulant response (Serra et al., 1991). A reversal of the B-HT 920 effect can be produced in normal animals also by the simultaneous stimulation of dopamine D_1 receptors with SKF 38393 (Meltzer et al., 1988), thus suggesting that chronic imipramine mimics the effect of acute stimulation of dopamine D_1 receptors. It has been shown that chronic imipramine enhance the responsiveness of adenylate cyclase, i.e. the transduction system activated by stimulation of dopamine D_1 receptors, to forskolin and to GTP, indicating an increase in the Vmax of the enzyme; these changes are restricted to within the nucleus accumbens, and are absent in the caudate nucleus (De Montis et al., 1990). Therefore, it is likely that an enhanced neurotransmission at the dopamine D_1 receptor level might depend on changes occurring downstream with respect to the recognition site rather than to an overstimulation induced by an increased dopamine release. Consistently, dopamine D_1 receptor blockade fails to antagonize the quinpirole locomotor response in rats treated with chronic imipramine (Serra et al., 1990a). However, it might contribute to this effect also an increased dopamine release in the nucleus accumbens (Ichikawa et al., 1998).

Consistent with the hypothesis that an enhanced neurotransmission at the dopamine D_1 receptor level might result in an antidepressant effect, results from our and other laboratories have shown that acute or sub-acute administration of selective dopamine D_1 receptor agonists has an antidepressant effect similar to that of chronic imipramine in two animal models of depression, the forced swimming test and the learned helplessness (D'Aquila et al., 1994; Gambarana et al., 1995a,c; Serra et al., 1988). Moreover, acute treatment with the dopamine D_1 receptor antagonist SCH 23390, but not with the dopamine D_2-like receptor antagonist L-sulpiride, suppresses the effect of chronic imipramine in the learned helplessness model of depression (Gambarana et al., 1995a), and the antidepressant-like effect of RB 101, a systemically active mixed inhibitor prodrug of the enzymes which metabolize the enkephalins (Baamonde et al., 1992).

It has been observed that there is a lower [^{11}C]SCH 23390 binding in the frontal cortex of patients with bipolar disorders (Suhara et al., 1992). In addition, we have found that acute administration of SCH 23390 is devoid of any antipsychotic effect in manic patients, suggesting that this disease might be associated with changes at the dopamine D_1 receptor level (Gessa et al., 1991a,b).

These observations provide support to the hypothesis that an enhanced dopamine transmission at the dopamine D_1 receptor level induced by chronic antidepressants might play an important role in their mechanism of action, and conversely, that changes in the sensitivity of dopamine D_1 receptors might be involved in the pathogenesis of mood disorders.

5. Antidepressants and dopamine release

Acute administration of fluoxetine, clomipramine, imipramine, desipramine, mianserin, nortryptiline and paroxetine have been reported to increase extracellular concentrations of dopamine in the rat prefrontal cortex (Carlson et al., 1996; Tanda et al., 1994, 1995, 1996a). Acute administration of fluoxetine, clomipramine, imipramine, desipramine and mianserin failed to influence dopamine release in the nucleus accumbens (Ainsworth et al., 1998; Clark et al., 1996; Tanda et al., 1994, 1996a). Acute minaprine treatment failed to influence in vivo dopamine release in the limbic part of the striatum (Imperato et al., 1994). In another study, acute fluoxetine did even produce a significant decrease in extracellular dopamine levels in both the nucleus accumbens and striatum (Ichikawa and Meltzer, 1995). Acute treatment with imipramine and clomipramine significantly increased extracellular dopamine in the striatum (Ichikawa and Meltzer, 1995). Dopamine release in the nucleus accumbens was increased in rats acutely treated with tranylcypromine (Ainsworth et al., 1998). Tianeptine, after acute administration, increased the extracellular concentrations of dopamine in the nucleus accumbens, and to a lesser extent, in the striatum (Invernizzi et al., 1992).

Chronic treatments with clomipramine and desipramine, but not fluoxetine, have been reported to increase the basal release of dopamine in the rat prefrontal cortex (Pallotta et al., 1999; Tanda et al., 1996b). Chronic tianeptine increases the extracellular concentrations of dopamine more in the nucleus accumbens than in striatum (Invernizzi et al., 1992). Basal extracellular dopamine levels in the nucleus accumbens were increased after chronic imipramine and moderately decreased after chronic fluoxetine (Ichikawa et al., 1998). Fluoxetine fails to alter dopamine level in the nucleus accumbens (Clark et al., 1996). Subchronic minaprine treatment enhanced in vivo dopamine release in the limbic part of the striatum (Imperato et al., 1994).

Chronic imipramine potentiates not only the motor stimulant effect of cocaine but also its stimulant effect on "in vivo" dopamine release in the limbic system (Rossetti et al., 1991). Moreover, also the stimulant effect of amphetamine on "in vivo" dopamine release in the nucleus accumbens, but not in the striatum, is potentiated by chronic imipramine and desipramine (Ichikawa et al., 1998; Nomikos et al., 1991). This effect is observed also when amphetamine is locally administered in the nucleus accumbens (Brown et al., 1991). However, amphetamine-induced increase in extracellular dopamine levels in the nucleus accumbens was unchanged after chronic fluoxetine (Ichikawa et al., 1998).

Either acute (a single administration) or chronic treatment with desipramine failed to influence dopamine levels in the ventral tegmental area. However, an increase in extracellular dopamine in the ventral tegmental area after 6 days of treatment and before the development of increased responsiveness to dopamine agonists, has been observed. It has been suggested that this increase in dopamine release might underlie the mechanism for the development of desipramine-induced sensitization within the midbrain dopamine system (Stewart and Rajabi, 1996).

In summary, release studies show that all antidepressants, either acutely or chronically administered, interfere with dopamine release. However, the only effect shared by all antidepressant drugs, that might be relevant for their therapeutic effect, appears to be the increase of dopamine release in the prefrontal cortex after acute administration.

6. Role of NMDA receptors in the development of dopamine receptor supersensitivity induced by chronic antidepressants

It has been suggested that the development of depression can be considered as an emotional learning process. According to this view, repeated psychosocial stress triggers depressive episodes, which eventually, in analogy to kindling, occur spontaneously (Post, 1992; Schwaninger et al., 1997).

The NMDA subtype of glutamate receptors is involved in several forms of neural and behavioural plasticity. In particular, NMDA receptors play an important role in neuronal development, long-term potentiation, kindling, learning and memory (see McDonald and Johnston, 1990). Therefore, several studies have been performed in order to investigate the effect of NMDA receptor blockade on the one hand in animal models of depression, and on the other hand, in the development of antidepressant-induced adaptive changes, including the behavioural supersensitivity of the mesolimbic dopamine system.

Chronic, but not acute, treatment with dizocilpine prevents the development of the behavioural supersensitivity to dopamine agonists induced by chronic treatment with imipramine in rats (D'Aquila et al., 1992b; De Montis et al., 1993) and by repeated electroconvulsive shock in rats (D'Aquila et al., 1997b) and mice (Nomikos et al., 1992). Moreover, chronic dizocilpine prevents the down-regulation of dopamine D_1 receptor number and the decreased response of adenylyl cyclase to dopamine stimulation in the rat limbic system induced by chronic treatment with imipramine (De Montis et al., 1993). These observations suggest that the changes induced by antidepressants on the mesolimbic dopamine system depend on the stimulation of NMDA receptors. Consistently, dizocilpine completely antagonized the effect of imipramine in the learned helplessness model in rats (Meloni et al., 1993). Thus, it would be tempting to speculate that a "learning process" might be involved not only in the pathogenesis of mood disorders, but also in the mechanism of action of antidepressants.

However, NMDA receptor antagonists display antidepressant-like activity per se in different animal models of

depression (Papp and Moryl., 1994; Trullas and Skolnick, 1990), and have been reported to potentiate the effect of different antidepressant drugs in the forced swimming test (Maj et al., 1992). In line with this evidence, acute administration of dizocilpine and desipramine displayed a synergistic effect in raising the extracellular concentration of dopamine in the rat prefrontal cortex (Wedzony and Golembiowska, 1993), an effect which appears to be a common feature of the majority of antidepressant examined so far in this respect (see above).

Regardless of the difficulty to reconcile these two apparently incompatible lines of evidence, NMDA receptor-mediated behavioural plasticity is likely to be involved both in the mechanism of action of antidepressant drugs and in the stress effects which induce depressive-like symptoms in animals.

7. Conclusions

The results of the studies we have reviewed show that the ability to potentiate behavioural stimulant responses to dopamine agonists appears to be a general characteristic of antidepressant treatments. The time course of the antidepressant effect on dopamine transmission is similar to that observed for the therapeutic effect of these drugs. In fact, the potentiating effect occurs only after chronic treatment, is present during the chronic treatment and persists after treatment withdrawal (Serra et al., 1990a,b). Among other symptoms, human depressive syndromes are characterised by a reduced capacity to experience pleasure and loss of motivation, and antidepressants preferentially potentiate dopamine transmission in the mesolimbic system, the brain system considered to be crucially involved in rewarding mechanisms and incentive motivation. Therefore, it is conceivable that the effect of antidepressants on dopamine transmission might play an important role in their therapeutic effect. In support of this hypothesis, it has been shown that in different animal models of depression (behavioural despair, learned helplessness, chronic mild stress), antidepressants seem to act by increasing dopamine transmission in the limbic system (Borsini et al., 1984, 1985, 1988; Delini-Stula et al., 1988; Muscat et al., 1990; Willner et al., 1992).

Finally, on the basis that a great deal of experimental evidence shows that manic symptoms are associated to an overactivity of dopaminergic neurotransmission, we have suggested that the potentiation of dopaminergic transmissionm induced by chronic treatment with antidepressant drugs might be responsible for the switches from depression to mania observed in bipolar patients (Gessa et al., 1995). Therefore, the increased sensitivity to dopamine agonists induced by antidepressants might provide a useful model of mania, or at least, of antidepressant-induced manic episodes.

References

Ainsworth, K., Smith, S.E., Zetterström, T.S., Pei, Q., Franklin, M., Sharp, T., 1998. Effect of antidepressant drugs on dopamine D1 and D2 receptor expression and dopamine release in the nucleus accumbens of the rat. Psychopharmacology 140, 470–477.

Allison, K., Paetsch, P.R., Baker, G.B., Greenshaw, A.J., 1993. Chronic antidepressant drug treatment attenuates motor-suppressant effects of apomorphine without changing [3H]GBR 12935 binding. Eur. J. Pharmacol. 249, 125–131.

Allison, K., Ivanová, I., Greenshaw, A.J., 1995. Behavioural response to SKF 38393 and quinpirole following chronic antidepressant treatment. Eur. J. Pharmacol. 277, 139–144.

American Psychiatric Association, 1994. DSM IV Diagnostic and Statistical Manual of Mental Disorders. 4th edn. American Psychiatric Association, Washington, DC.

Arnt, J., Hyttel, J., Overo, K.F., 1984a. Prolonged treatment with the specific 5HT uptake inhibitor citalopram: effect on dopaminergic and serotonergic functions. Pol. J. Pharmacol. Pharm. 36, 221–229.

Arnt, J., Overo, K.F., Hyttel, J., Olsen, R., 1984b. Changes in rat dopamine and serotonin function in vivo after prolonged administration of the specifie 5-HT uptake inhibitor, citalopram. Psychopharmacology 84, 457–475.

Baamonde, A., Daugé, V., Ruiz Gayo, M., Fulga, I.G., Turcaud, S., Fournié Zaluski, M.C., Roques, B.P., 1992. Antidepressant-type effects of endogenous enkephalins protected by systemic RB 101 are mediated by opioid delta and dopamine D1 receptor stimulation. Eur. J. Pharmacol. 216, 157–166.

Baldessarini, R.J., 1996. Drugs and the treatment of psychiatric disorders — depression and mania. In: Limbird, L.E., Hardman, J.G. (Eds.), Goodman and Gilman's the Pharmacological Basis of Therapeutics. 9th edn. McGraw-Hill, New York, pp. 431–459.

Blackburn, J.R., Pfaus, J.G., Phillips, A.G., 1992. Dopamine functions in appetitive and defensive behaviors. Prog. Neurobiol. 39, 247–279.

Borsini, F., Nowakowska, E., Samanin, R., 1984. Effect of repeated treatment with desipramine in the behaviourai "despair" test in rats: antagonism by "atypical" but not "classical" neuroleptics or antiadrenergic drugs. Life Sci. 34, 1171–1176.

Borsini, F., Pulvirenti, L., Samanin, R., 1985. Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behaviourai "despair" test in the rat. Eur. J. Pharmacol. 110, 253–256.

Borsini, F., Lecci, A., Mancinelli, A., D'Aranno, V., Meli, A., 1988. Stimulation of dopamine D-2 but not D-1 receptors reduces immobility time of rats in the forced swimming test: implication for antidepressant activity. Eur. J. Pharmacol. 148, 301–307.

Brown, E.E., Nornikos, G.G., Wilson, C., Fibiger, H.C., 1991. Chronic desipramine enhances the effect of locally applied amphetamine on interstitial concentrations of dopamine in the nucleus accumbens. Eur. J. Pharrnacol. 202, 125–127.

Cabib, S., Zocchi, A., Puglisi-Allegra, S., 1995. A comparison of the behavioral effects of minaprine, amphetamine and stress. Psychopharmacology 121, 73–80.

Carlson, J.N., Visker, K.E., Nielsen, D.M., Keller, R.W. Jr., Glick, S.D., 1996. Chronic antidepressant drug treatment reduces turning behavior and increases dopamine levels in the medial prefrontal cortex. Brain Res. 707, 122–126.

Chagraoui, A., Vasse, M., Protais, P., 1990. Effects of chronic treatments with amineptine and desipramine on motor responses involving dopaminergic systems. Psychopharmacology 102, 201–206.

Cheetham, S.C., Kettle, C.J., Martin, K.F., Heal, D.J., 1995. D1 receptor binding in rat striatum: modification by various D1 and D2 antagonists, but not by sibutramine hydrochloride, antidepressants or treatments which enhance central dopaminergic function. J. Neural Transm.: Gen. Sect. 102, 35–46.

Chiodo, L.A., Antelman, S.M., 1980a. Electroconvulsive shock: progres-

sive dopamine autoreceptor subsensitivity independent of daily treatment. Science 210, 799–801.

Chiodo, L.A., Antelman, S.M., 1980b. Repeated tricyclics induce a progressive dopamine autoreceptors subsensitivity independent of daily drug treatment. Nature 287, 451–454.

Clark, D., White, F.J., 1987. D1 dopamine receptor — the search for a function: a critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. Synapse 1, 347–388.

Clark, R.N., Ashby, C.R. Jr., Dewey, S.L., Ramachandran, P.V., Strecker, R.E., 1996. Effect of acute and chronic fluoxetine on extracellular dopamine levels in the caudate-putamen and nucleus accumbens of rat. Synapse 23, 125–131.

Collu, M., Pani, L., Gessa, G.L., Serra, G., 1994. Chronic imipramine potentiates cocaine-induced CPP. Pol. J. Pharmacol. 46 (41), 315–316.

Collu, M., Poggiu, A.S., Serra, G., 1996. Antidepressants sensitize the dopamine mesolimbic system mediating reward. Behav. Pharmacol. 7 (Supplement 1), 18.

Collu, M., Poggiu, A.S., Devoto, P., Serra, G., 1997. Behavioural sensitization of D2 mesolimbic dopamine receptors in chronic fluoxetine-treated rats. Eur. J. Pharmacol. 322, 123–127.

Creese, I., Iversen, S.D., 1975. The pharmacological and anatomical substrates of the amphetamine response in the rat. Brain Res. 83, 419–436.

D'Aquila, P.S., Collu, M., Gessa, G.L., Serra, G., 1992a. Role of alpha1 receptor in the behavioural supersensitivity to D2 agonists induced by chronic treatment with imipramine. Pharmacol. Res. 25, 95–101.

D'Aquila, P.S., Sias, A., Gessa, G.L., Serra, G., 1992b. The NMDA receptor antagonist MK-801 prevents imipramine-induced supersensitivity to quinpirole. Eur. J. Pharmacol. 224, 199–202.

D'Aquila, P.S., Collu, M., Pani, L., Gessa, G.L., Serra, G., 1994. Antidepressant-like effect of selective D1 receptor agonists in the behavioural despair animal model of depression. Eur. J. Pharmacol. 262, 107–111.

D'Aquila, P.S., Collu, M., Gessa, G.L., Serra, G., 1997a. Dizocilpine prevents the enhanced locomotor response to quinpirole induced by repeated electroconvulsive shock. Eur. J. Pharmacol. 330, 11–14.

D'Aquila, P.S., Collu, M., Gessa, G.L., Serra, G., 1997b. Role of D_1 and $alpha_1$ receptor in the D_2 dopamine receptor sensitization induced by repeated electroconvulsive shock. J. Psycopharmacol. 11, 41–44.

D'Aquila, P., Monleon, S., Borsini, F., Brain, P., Willner, P., 1997c. Anti-anhedonic actions of the novel serotonergic agent flibanserin, a potential rapidly acting antidepressant. Eur. J. Pharmacol. 340, 121–132.

Delini-Stula, A., Radeke, E., Van Riezen, H., 1988. Enhanced functional responsiveness of the dopaminergic system — the mechanism of anti-immobility effects of antidepressants in the beahvioural despair test in the rat. Neuropharmacology 27, 943–947.

De Montis, M.G., Devoto, P., Gessa, G.L., Meloni, D., Porcella, A., Saba, P., Serra, G., Tagliamonte, A., 1989. Chronic imipramine reduces [3H]SCH 23390 binding and dopamine-sensitive adenylate cyclase in the limbic system. Eur. J. Pharmacol. 167, 299–303.

De Montis, G., Devoto, P., Gessa, G.L., Porcella, A., Serra, G., Tagliamonte, A., 1990. Selective adenyiate cyclase increase in the limbic area of long-term imipramine-treated rats. Eur. J. Pharmacol. 180, 169–174.

De Montis, M.G., Gambarana, C., Meloni, D., Taddei, I., Tagliamonte, A., 1993. Long-term imipramine effects are prevented by NMDA receptor blockade. Brain, 63–67.

Di Chiara, G., Corsini, G.U., Mereu, G.P., Tissari, A., Gessa, G.L., 1978. Self-inhibitory dopamine receptors: their role in the biochemical and behaviourai effects of low doses of apomorphine. In: Roberts, P.J. (Ed.), Advances in Biochemical Psychopharmacology. Raven Press, New York, pp. 275–284.

Diggory, G.L., Buckett, W.R. et al., 1984. Chronic antidepressant administration fails to attenuate apomorphine induced decreases in rats striatal dopamine metabolites. Eur. J. Pharmacol. 105, 257–263.

Durlach Misteli, C., Van Ree, J.M., 1992. Dopamine and melatonin in the nucleus accumbens may be implicated in the mode of action of antidepressant drugs. Eur. J. Pharmacol. 217, 15–21.

Dziedzicka Wasylewska, M., Rogoz, R., Klimek, V., Maj, J., 1997. Repeated administration of antidepressant drugs affects the levels of mRNA coding for D1 and D2 dopamine receptors in the rat brain. J. Neural Transm. 104, 515–524.

Fibiger, H.C., Phillips, A.G., 1981. lncreased intracranial self-stimulation in rats after long-term administration of desipramine. Science 214, 683–685.

Fibiger, H.C., Phillips, A.G., 1987. Role of catecholamine transmitters in reward systems: implications for the neurobiology of affect. In: Oreland, E. (Ed.), Brain Reward Systems and Abuse. New York Press, pp. 61–74.

Gambarana, C., Ghiglieri, O., De Montis, G.M., 1995a. Desensitization of the D1 dopamine receptors in rats reproduces a model of escape deficit reverted by imipramine, fluoxetine and clomipramine. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 19, 741–755.

Gambarana, C., Ghiglieri, O., Taddei, I., Tagliamonte, A., De Montis, M.G., 1995b. Imipramine and fluoxetine prevent the stress-induced escape deficits in rats through a distinct mechanism of action. Behav. Pharmacol. 6, 66–73.

Gambarana, C., Ghiglieri, O., Tagliamonte, A., Dalessandro, N., De Montis, M.G., 1995c. Crucial role of D1 dopamine receptors in mediating the antidepressant effect of imipramine. Pharmacol. Biochem. Behav. 2, 147–151.

Gessa, G.L., Canu, A., Dei Zompo, M., Burrai, C., Serra, G., 1991a. Lack of acute antipsychotic effect of SCH 23390, a selective dopamine D1 receptor antagonist. Lancet 337, 854–855.

Gessa, G.L., Canu, A., Dei Zompo, M., Burrai, C., Serra, G., 1991b. SCH 23390 and psychosis. Lancet 338, 185–186.

Gessa, G.L., Pani, L., Serra, G., Fratta, W., 1995. Animal models of Mania. In: Gessa, G.L., Fratta, W., Pani, L., Serra, G. (Eds.), Depression and Mania: From Neurobiology to Treatment. Raven Press, New York, pp. 43–66.

Golden, R.N., Dawkins, K., Nicholas, L., Bebchuk, J.M., 1998. Trazodone, nefazodone, bupropion and mirtazapine. In: Nemeroff, C. (Ed.), Textbook of Psychopharmacology. 2nd edn. The American Psychiatric Press, Washington, DC, pp. 251–269.

Jimerson, D.C., 1987. Role of dopamine mechanisms in affective disorders. In: Meltzer, H.Y. (Ed.), Psychopharmacology: The Third Generation of Progress. Raven Press, New York, pp. 505–511.

Hasan, F., Leonard, B.E., 1981. Changes in behaviour and neurotransmitter metabolism in the rat following acute and chronic sulpiride administration. In: Ackenheil, M., Matussek, N. (Eds.), Special Aspects of Psychopharmacology. Expansion Scientifique Francaise, Paris, pp. 67–82.

Holcombe, H.H., Bannon, M.J., Roth, M.H., 1982. Striatal dopamine autoreceptors uninfluenced by chronic administration of antidepressants. Eur. J. Pharmacol. 82, 173–178.

Hyman, S.E., Nestler, E.J., 1996. Initiation and adaptation: a paradign for understanding psychotropic drug action. Am. J. Psychiatry 153, 151–162.

Kelly, P.H., Seviour, P.W., Iversen, S.D., 1975. Amphetamine and Apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94, 507–522.

Klimek, V., Nielsen, M., 1987. Chronic treatment with antidepressants decreases the number of [3H]SCH 23390 binding sites in the rat striatum and limbic system. Eur. J. Pharmacol. 139, 163–169.

Ichikawa, J., Meltzer, H.Y., 1995. Effect of antidepressants on striatal and accumbens extracellular dopamine levels. Eur. J. Pharmacol. 3, 255–261.

Ichikawa, J., Kuroki, T., Meltzer, H.Y., 1998. Differential effects of chronic imipramine and fluoxetine on basal and amphetamine-induced extracellular dopamine levels in rat nucleus accumbens. Eur. J. Pharmacol. 350, 159–164.

Imperato, A., Obinu, M.C., Cabib, S., Cestari, V., Puglisi Allegra, S., 1994. Effects of subchronic minaprine on dopamine release in the

ventral striatum and on immobility in the forced swimming test. Neurosci. Lett. 166, 69–72.
Invernizzi, R., Pozzi, L., Garattini, S., Samanin, R., 1992. Tianeptine increases the extracellular concentrations of dopamine in the nucleus accumbens by a serotonin-independent mechanism. Neuropharmacology 31, 221–227.
MacNeil, D.A., Gower, M., 1982. Do antidepressants induce autoreceptor subsensitivity? Nature 298, 302–304.
Maj, J., Wedzony, K., 1985. Repeated treatment with imipramine or amitriptyline increases the locomotor response of rats to (+)-amphetamine given into the nucleus accumbens. J. Pharm. Pharmacol. 37, 362–364.
Maj, J., Papp, M., Skuza, G., Bigajska, K., Zazula, M., 1989. The influence of repeated treatment with imipramine, (+)- and (−)-oxaprotiline on behavioural effects of dopamine D-1 and D-2 agonists. J. Neural Transm. 76, 29–38.
Maj, J., Rogóz, Z., Skuza, G., 1992. The effects of combined treatment with MK-801 and antidepressant drugs in the forced swimming test in rats. Pol. J. Pharmacol. Pharm. 44, 217–226.
Maj, J., Dziedzicka Wasylewska, M., Rogoz, R., Rogoz, Z., Skuza, G., 1996. Antidepressant drugs given repeatedly change the binding of the dopamine D2 receptor agonist, [3H]N-0437, to dopamine D2 receptors in the rat brain. Eur. J. Pharmacol. 304, 49–54.
Maj, J., Dziedzicka Wasylewska, M., Rogoz, R., Rogóz, Z., 1998. Effect of antidepressant drugs administered repeatedly on the dopamine D3 receptors in the rat brain. Eur. J. Pharmacol. 351, 31–37.
Martin, K.F., Phillips, I., Cheetham, S.C., Heal, D.J., 1995. Dopamine D2 receptors: a potential pharmacological target for nomifensine and tranylcypromine but not other antidepressant treatments. Pharmacol. Biochem. Behav. 51, 565–569.
Martin-Iverson, M.T., Leclere, J.-F., Fibiger, H.C., 1983. Cholinergic–dopaminergic interactions and the mechanism of action of antidepressants. Eur. J. Pharmacol. 94, 193–201.
McDonald, J.W., Johnston, M.V., 1990. Physiological and pathophysiological roles of excitatory aminoacids during centrai nervous system development. Brain Res. Rev. 15, 41–70.
Meloni, D., Gambarana, C., De Montis, M.G., Dal Prá, P., Taddei, I., Tagliamonte, A., 1993. Dizocilpine antagonizes the effect of chronic imipramine on learned helplessness in rats. Pharmacol. Biochem. Behav. 46, 423–426.
Meltzer, T.L., Wiley, J.N., Williams, A.E., Heffner, T.G., 1988. Evidence for postsynaptic dopamine effects of B-HT 920 in the presence of the dopamine D1 agonist SKF 38393. Psychopharmacology 95, 329–332.
Morelli, M., Longoni, R., Spina, L., Di Chiara, G., 1986. Antagonism of apomorphine-induced yawning by SCH 23390: evidence against the dopamine autoreceptor hypothesis. Psychopharmacology 89, 259–260.
Muscat, R., Sampson, D., Willner, P., 1990. Dopaminergic mechanism of imipramine action in an animal model of depression. Biol. Psychiatry 28, 223–230.
Nielsen, J.A., 1985. Effects of chronic antidepressant treatment on nigrostriatal and mesolimbic dopamine autoreceptors in the rat. Neurochem. lnt. 9, 61–67.
Nomikos, G.G., Damsma, G., Wenkstern, D., Fibiger, H.C., 1991. Chronic desipramine enhances amphetamine-induced increases in interstitial concentrations of dopamine in the nucleus accumbens. Eur. J. Pharmacol. 195, 63–73.
Nomikos, G.G., Mathe, A.A., Mathe, J.M., Svensson, T.H., 1992. MK-801 prevents the enhanced behavioural response to apomorphine elicited by electroconvulsive treatment in mice. Psychopharmacology 108, 367–370.
Nowak, G., Skolnick, P., Paul, I.A., 1991. Down-regulation of dopamine1 (D1) receptors by chronic imipramine is species-specific. Pharmacol. Biochem. Behav. 39, 769–771.
Pallotta, M., Segieth, J., Whitton, P.S., 1999. Chronic but not acute clomipramine alters the effect of NMDA receptor regulation of dopamine release in rat frontal cortex. Neurosci. Lett. 262, 187–190.
Paetsch, P.R., Greenshaw, A.J., 1992. Effects of chronic antidepressant treatment on dopamine-related [3H]SCH 23390 and [3H]spiperone binding in the rat striatum. Cell. Mol. Neurobiol. 12, 597–606.
Papp, M., 1988. Different effects of short- and long-term treatment with imipramine on the apomorphine- and food-induced place preference conditioning in rats. Pharmacol. Biochem. Behav. 30, 889–893.
Papp, M., Moryl, E., 1994. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur. J. Pharmacol. 263, 1–7.
Post, R.M., 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am. J. Psychiatry 149, 999–1010.
Randrup, A., Munkvad, I., Fog, R., Geriach, J., Molander, R., Kjeiiberg, B., Scheel-Krüger, J., 1975. Mania, depression and brain dopamine. In: Essman, W.B., Valzelli, S. (Eds.), Currents Developments in Psychopharmacology vol. 2 Spectrum Publications, New York, USA, pp. 206–248.
Rogoz, R., Dziedzicka Wasylewska, M., 1999. Effects of antidepressant drugs on the dopamine D2/D3 receptors in the rat brain differentiated by agonist and antagonist binding — an autoradiographic analysis. Naunyn-Schmiedeberg's Arch. Pharmacol. 359, 178–186.
Rossetti, Z.L., D'Aquila, P.S., Hmaidan, Y., Gessa, G.L., Serra, G., 1991. Repeated treatment with imipramine potentiates cocaine-induced dopamine release and motor stimulation. Eur. J. Pharmacol. 201, 243–245.
Scheel-Krüger, J., 1986. The syndrome of sedation and yawning behaviour in the rat is dependent on postsynaptic dopamine D-2 receptors. Psychopharmacology 89, S32.
Schwaninger, M., Weisbrod, M., Knepel, W., 1997. Progress in defining the mechanism of action of antidepressants. CNS Drugs 8, 237–243.
Serra, G., Argiolas, A., Klimek, V., Fadda, F., Gessa, G.L., 1979. Chronic treatment with antidepressant prevents the inhibitory effect of small doses of apomorphine on dopamine synthesis and motor activity. Life Sci. 25, 415–424.
Serra, G., Collu, M., Gessa, G.L., 1986. Dopamine receptors mediating yawning: are they autoreceptors? Eur. J. Pharmacol. 120, 187–192.
Serra, G., Collu, M., D'Aquila, P., Pani, L., Gessa, G.L., 1988. Are D1 receptor agonists potential antidepressants? Pharmacol. Res. Commun. 20, 1121–1122.
Serra, G., Collu, M., D'Aquila, P.S., De Montis, M.G., Gessa, G.L., 1990a. On the mechanism involved in the behavioural supersensitivity to DA-agonists induced by chronic antidepressants. In: Gessa, G.L., Serra, G. (Eds.), Advances in the Biosciences: Dopamine and Mental Depression vol. 77 Pergamon, Oxford, pp. 121–138.
Serra, G., Collu, M., D'Aquila, P.S., De Montis, M.G., Gessa, G.L., 1990b. Possible role of dopamine D1 receptor in the behavioural supersensitivity to dopamine agonists induced by chronic treatment with antidepressants. Brain Res. 527, 234–243.
Serra, G., Collu, M., D'Aquila, P.S., De Montis, M.G., Gessa, G.L., 1991. Chronic imipramine "reverses" B-HT 920-induced hypomotility in rats. J. Neural Transm. 84, 237–240.
Serra, G., Collu, M., D'Aquila, P.S., Gessa, G.L., 1992. Role of the mesolimbic system in the mechanism of action of antidepressants. Pharmacol. Toxicol. 71 (Supplement 1), 72–85.
Spyraki, C., Fibiger, H.C., 1981. Behaviourai evidence of supersensitivity of postsynaptic dopamine receptors in the mesolimbic system after chronic administration of desipramine. Eur. J. Pharmacol. 74, 195–206.
Stahle, l., Ungerstedt, U., 1987. Reduction of extracellular dopamine levels can be dissociated from suppression of exploratory behaviour in rats. Acta Physiol. Scand. 130, 533–534.
Stahle, I., Ungerstedt, U., 1989. Yawning and suppression of exploration in amphetamine-treated rats, incompatibility with the autoreceptor hypothesis. Psychopharmacology 97, 553–560.
Suhara, T., Nakayama, K., Inoue, O., Fukuda, H., Shimizu, M., Mori, A., Tateno, Y., 1992. D1 dopamine receptor binding in mood disorders measured by positron emission tomography. Psychopharmacology 106, 14–18.
Stewart, J., Rajabi, H., 1996. Initial increases in extracellular dopamine in

the ventral tegmental area provide a mechanism for the development of desipramine-induced sensitization within the midbrain dopamine system. Synapse 23, 258–264.

Tanda, G., Carboni, E., Frau, R., Di Chiara, G., 1994. Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential? Psychopharmacology 115, 285–288.

Tanda, G., Frau, R., Di Chiara, G., 1995. Local 5HT3 receptors mediate fluoxetine but not desipramine-induced increase of extracellular dopamine in the prefrontal cortex. Psychopharmacology 119, 15–19.

Tanda, G., Bassareo, V., Di Chiara, G., 1996a. Mianserin markedly and selectively increases extracellular dopamine in the prefrontal cortex as compared to the nucleus accumbens of the rat. Psychopharmacology 123, 127–130.

Tanda, G., Frau, R., Di Chiara, G., 1996b. Chronic desipramine and fluoxetine differentially affect extracellular dopamine in the rat prefrontal cortex. Psychopharmacology 127, 83–87.

Trullas, R., Skolnick, P., 1990. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur. J. Pharmacol. 185, 1–10.

Vaccheri, A., Dall'Olio, R., Gaggi, R., Gandolfi, O., Montanaro, N., 1984. Antidepressant versus neuroleptic activities of sulpiride isomers on four animal models depression. Psychopharmacology 83, 28–33.

Walters, J.R., Bergstrom, D.A., Carlson, J.H., Chase, T.N., Braun, A.R., 1987. D1 dopamine receptor activation required for postsynaptic expression of D2 agonist effects. Science 236, 719–722.

Wedzony, K., Golembiowska, K., 1993. Concomitant administration of MK-801 and desipramine enhances extracellular concentration of dopamine in the rat prefrontal cortex. NeuroReport 5, 75–77.

Welch, J., Kim, H., Fallon, S., Liebman, J., 1982. Do antidepressants induce dopamine autoreceptors subsensitivity? Nature 298, 301–302.

Wise, R.A., 1989. The brain and reward. In: Liebman, J., Cooper, J. (Eds.), The Neuropharmacological Basis of Reward. Oxford Univ. Press, Oxford, pp. 55–78.

Willner, P., Muscat, R., Papp, M., 1992. Chronic mild stress-induced anhedonia: a realistic animals model of depression. Neurosci. Biobehav. Rev. 16, 525–534.