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# New Approaches for the Therapy of Treatment Refractory Depression

Oguz Mutlu, Güner Ulak, Ipek Komsuoglu Celikyurt,  
Füruzan Yıldız Akar and Faruk Erden  
*Kocaeli University Medical Faculty, Pharmacology Department, Kocaeli  
Turkey*

## 1. Introduction

Depression is a common, chronic, recurrent and life debilitating illness with severe morbidity and increased suicide risk (Kiecolt-Glaser&Glaser, 2002). The mechanisms and brain areas underlying the pathophysiology of this disorder are not yet well understood. Treatment-resistant depression (TRD) or treatment-refractory depression is a term used in clinical psychiatry to describe cases of major depressive disorder that do not respond to adequate courses of at least two antidepressants. Clinical studies indicate elevated plasma nitrate levels and increased nitric oxide synthase (NOS) expression in the hippocampus of depressed patients (De Oliveira et al., 2008). The prevalence of depression during life is 17-19% and suicide during depression is 15% (Kessler et al., 1994). Conventional antidepressant treatment has many limitations such as some medicines are slow to take effect, side effect profile limits the success of therapy and there are also a large number of treatment resistant patients. Such a profile has necessitated new therapeutic strategies in offering faster onset of action and augmenting the therapeutic actions of currently existing antidepressants and thus getting a greater efficacy in a larger proportion of patients.

## 2. Pathways playing role in depression

### 2.1 5-hydroxytryptamine (5-HT), Noradrenaline (NA) and dopamine pathway

An important theory for the formation of depression is the monoamine hypothesis which suggests that there is a decreasing effect of biological amines like serotonin (5-HT), noradrenalin and dopamine in depression (Schildkraut, 1965). It is well known that the serotonin system plays an important role in the neural regulation of mood (Duman et al., 1997) and enhancement of 5-HT neurotransmission influences the therapeutic response to different classes of antidepressant treatment. In previous studies (Ulak et al., 2008; Yildiz et al., 2000) a SSRI fluoxetine shortened the immobility time in a forced swimming test (FST). In animal studies SSRI (selective serotonin reuptake inhibitor) drugs are believed to exert their clinical antidepressant effect by blocking the reuptake of serotonin at the synapse, resulting in an elevation of extracellular serotonin concentrations in the brain. In our previous study (Ulak et al., 2010), preadministration of parachlorophenylalanine (pCPA) to fluoxetine treated rats, significantly prolonged the immobilization time as in line with the

previous studies showing that the behavioural effects of the SSRI fluoxetine in FST could be blocked by serotonin depletion (Connor et al., 2001; Zomkowski et al., 2004).

Citalopram is established to be one of the most selective of the SSRIs (Goodnick & Goldstein, 1998) and it is postulated that citalopram administration do not alter hippocampal NOS activity under basal conditions (Wegener et al., 2004). Tianeptine is an atypical antidepressant which is reported to increase serotonin re-uptake and decrease extracellular 5-HT in the brain (in contrast with most antidepressant agents) (Datla & Curzon, 1993; Fattacini et al., 1990). How tianeptine exerts its effects is a question that remains. Although the neurochemical properties of tianeptine and of selective serotonin reuptake inhibitors differ, they demonstrate similar antidepressant efficacy (Wilde and Benfield, 1995). It is interesting how these two antidepressants with opposite molecular mechanisms act. The fact that both inhibitors and enhancers of the serotonin reuptake are potent antidepressants, challenges the hypothesis on the central mechanisms of actions of these drugs. Nowakowska et al. (2000) claimed that in reference spatial memory test (food finding time in a maze), tianeptine exerted no effect whereas fluoxetine caused a very marked improvement of spatial reference memory. So, besides the effects on serotonin re-uptake, other mechanisms must play an important role in the action of these drugs.

The classical antidepressant imipramine exerts its effects by inhibiting both 5-HT and noradrenalin reuptake (Carrodi & Fuxe, 1968). The novel antidepressant reboxetine is a selective noradrenalin reuptake inhibitor. It selectively inhibits the reuptake of synaptic norepinephrine with no marked affinity for other receptors or transporters (Wong et al., 2000). The antidepressant-like activity of reboxetine is described in animal models of depression like FST (Wong et al., 2000). There is a complex interaction between ventral and dorsal noradrenergic bundles projecting neurons in modulating the antidepressant-like effects of reboxetine in the forced swimming test (Cryan et al., 2002b). It is established that forced swimming test exposure increases serotonergic activity in the amygdala, frontal cortex and hippocampus and dopamine turnover in the striatum; and reboxetine attenuates forced swimming test-induced increases in amygdaloidal and cortical serotonin turnover and striatal dopamine turnover (Connor et al., 1999). The anti-immobility effects of reboxetine may be more closely related to its ability to antagonize the stressor-induced increase in dopaminergic turnover in the striatum since it is known that mesocorticolimbic dopaminergic activity may play a role in the behaviour of rats in the forced swimming test (Willner, 1995).

## 2.2 Role of 5-HT receptors

Studies using drugs affecting the serotonergic system do not only include the inhibition of serotonin reuptake in the synaptic terminal or inhibiting its metabolism (monoaminoxidase inhibitors); there are also antidepressants affecting 5-HT receptor subtypes and this class of antidepressants are also frequently used in the therapy of depression (Blier & Ward, 2003).

Recent studies have focused on the involvement of 5-HT<sub>1A</sub> receptors in the mechanism of action of antidepressant drugs (Blier & Ward, 2003). 5-HT<sub>1A</sub> receptor is the best known among 14 serotonergic receptor groups (Pucadyil et al., 2005) and it is important in psychiatric disorders like schizophrenia (Millan, 2000; Yasuno et al., 2004) and depression (Celada et al., 2004). The discovery of WAY 100635, the first highly selective, potent and

silent 5-HT<sub>1</sub> receptor antagonist (Forster et al., 1995), enabled further clarification on the role of 5-HT<sub>1A</sub> receptors in the antidepressant-like effects of drugs.

Inhibition of 5-HT<sub>2A</sub> receptor releases exerts antidepressant-like effects in FST (Sibille et al., 1997). Suicide attempt in severe depressive patients due to the polymorphism in the 5-HT<sub>2</sub> receptor gene is established (Du et al., 2000) and this supports the role of 5-HT<sub>2A</sub> receptors in depression. Inhibition of 5-HT<sub>2A/2C</sub> receptors play an important role in the antidepressant-like effects of conventional antidepressants in FST (Van Oekelen et al., 2003; Redrobe and Bourin, 1997).

It has been postulated that the inhibition of 5-HT<sub>1A</sub> receptors by WAY 100635 cause the synergic potentialization of increased extracellular 5-HT levels in serotonergic antidepressants (Romero et al., 1996). Besides, when WAY 100635 was given together with a subactive dose of fluoxetine in FST, it significantly decreased the immobility time in FST (Rocha et al., 1997).

### **2.3 Role of N-Methyl-D-Aspartate (NMDA) receptors**

NMDA receptor activity appears to play a role in some neurophysiological phenomena and administration of NMDA antagonists exerted antidepressant-like effects in the FST in animals, a pre-clinical behavioural method used for studying the antidepressant activity of drugs (Borsini, 1995; Cryan et al., 2002a; Trullas & Skolnick, 1990). Interestingly, competitive and non-competitive NMDA receptor antagonists induce

antidepressant-like effects in animal models (Eckeli et al., 2000) and combined therapy of NMDA receptor antagonists with subactive doses of antidepressants such as fluoxetine, venlafaxine and imipramine, resulted in an antidepressant response in the FST test (Rogoz et al., 2002).

Administration of NMDA antagonists has been shown to produce antidepressant-like effects in animal models (Trullas & Skolnick, 1990). NOS inhibition may exert similar effects to that NMDA receptor antagonists. Since it has been shown that NMDA receptor antagonists augment the activity of antidepressants such as fluoxetine, venlafaxine and imipramine when given in combination (Rogoz et al., 2002), it is a fact that interruption of the NMDA-NO synthase pathway may result in antidepressant-like and/or augmented antidepressant activity (Harkin et al., 2004).

### **2.4 Role of Nitric Oxide (NO) pathway**

NO plays an important role in the brain, and pharmacological manipulations of the NO pathway will constitute a novel approach for future therapeutic applications. In the brain, NO is synthesized from L-arginine by NOS, as a response to activation of NMDA receptors by excitatory amino acids (Garthwaite, 1991; Moncada et al., 1991). It plays an important role in regulating many behavioural, cognitive and emotional processes such as learning, aggression, locomotion, anxiety and depression (Dzolfic et al., 1997; Harkin et al., 1999; Holscher 1997; Nelson et al., 1995; Wiley et al., 1995). In recent studies, inhibition of NOS enzyme elicited antidepressant-like behavioural effects in several animal experiments (Harkin et al., 1999; Jefferys and Funder, 1996; Da Silva et al., 2000; Yildiz et al., 2000a,b) and this effect was reversed by NOS substrate L-arginine, suggesting that NO plays an

important role in these behavioural responses (Harkin et al., 1999; Jefferys and Funder, 1996; Yildiz et al., 2000a,b).

A number of studies have demonstrated that NOS could modulate the release of central noradrenalin (Sato et al., 1996), dopamine (Segieth et al., 2000; Wegener et al., 2000) and 5-HT (Smith&Whitton, 2000; Wegener et al., 2000). NOS activity is involved in the mechanism of action of several antidepressants. For example, the selective serotonin reuptake inhibitor paroxetine inhibits *in vitro* NOS activity and decreases plasma nitrite and nitrate levels significantly in depressed patients (Finkel et al., 1996). It is proposed that, NOS inhibitor 7-NI may increase serotonin (5-HT) levels in rat hippocampus after systemic therapy (Wegener et al., 2000), suggesting that antidepressant-like effects of NOS inhibitors can be related with the changes that occur in 5-HT levels in the brain. This is confirmed by the fact that NOS inhibition modulates central serotonin release (Kiss, 2000; Smith&Whitton, 2000; Wegener et al., 2000).

#### 2.4.1 Effects of NOS inhibitors in depression

Various inhibitors of nitric oxide synthase (NOS) have been shown to exert antidepressant-like behavioural effect in a variety of animal models (Harkin et al., 1999; Volke et al., 2003; Yildiz et al., 2000). In previous studies, a neuronal and inducible NOS inhibitor 1-[2-(trifluoromethyl) phenyl] imidazole (TRIM) exerted an antidepressant-like effect in the FST (Borsini, 1995; Cryan et al., 2002; Trullas & Skolnick, 1990; Ulak et al., 2008; Volke et al., 2003) and in the unpredictable chronic mild stress (UCMS) model (Mutlu et al., 2009) in animals. UCMS model is a promising and valuable animal model of depression which shows similar features to the depressive symptoms seen in human. This stress model consists from repeated mild physical and psychological stressors. Mice were subjected several times a day for 7 weeks to different kinds of stressors in a chronic, inevitable and unpredictable way.

In a previous study (Mutlu et al., 2009) we showed that UCMS regimen induced a coat state degradation and this effect was reversed by a selective neuronal and inducible nitric oxide synthase inhibitor TRIM as well as by fluoxetine. Interestingly, the onset of this action was faster after TRIM compared to fluoxetine (Fig. 1a). Indeed, coat state improvement occurred 3 weeks after TRIM treatment whereas 5 weeks therapy was necessary to observe fluoxetine's action. Similar effects were also observed in the splash test (Fig. 1b). Moreover, in the resident-intruder test, stressed mice demonstrated a larger degree of aggressivity, an effect abolished by both drugs (Fig. 1c). These results cannot be attributed to the effects of the drugs on activity since both TRIM and fluoxetine had no effect on locomotor activity.

It is proposed that, a NOS inhibitor 7-Nitroindazol (7-NI) may increase serotonin (5-HT) levels in rat hippocampus after systemic therapy (Wegener et al., 2000), suggesting that antidepressant-like effects of NOS inhibitor can be related to the changes that occur in 5-HT levels in the brain. This is confirmed by the fact that NOS inhibition modulates central serotonin release (Kiss, 2000; Smith&Whitton, 2000; Wegener et al., 2000). In rats exposed to chronic mild stress, 5-HT and 5-HIAA (5-hydroxy indol acetic acid) levels decreased significantly in many brain regions, compared to nonstressed animals (Li et al., 2003; Vancassel et al., 2008). Therefore, it can be the fact that effects of TRIM might be explained by its ability to reverse the UCMS-induced alteration of 5-HT.

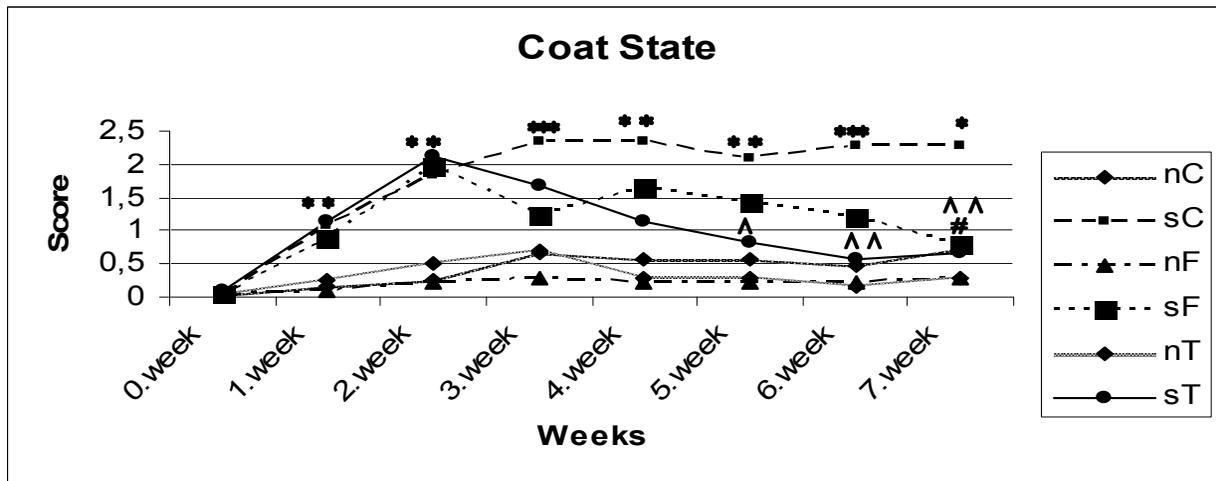


Fig. 1a. Effects of fluoxetine (15 mg/kg, i.p.) and TRIM (30 mg/kg, i.p.) given for 35 days on coat state in non-stressed and stressed groups during UCMS. All of the treatments begun after 2 weeks of stress regimen and were administered during 5 weeks. Data are means±SEM. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, difference between stressed and non stressed vehicle; ^p<0.05, ^^p<0.01 difference between stressed TRIM and stressed vehicle. # p<0.05, difference between stressed and non stressed fluoxetine group. nC = nonstressed control(vehicle) group, nF = nonstressed fluoxetine group, nT =nonstressed TRIM group, sC = stressed control (vehicle) group, sF = stressed fluoxetine group, and sT = stressed TRIM group.

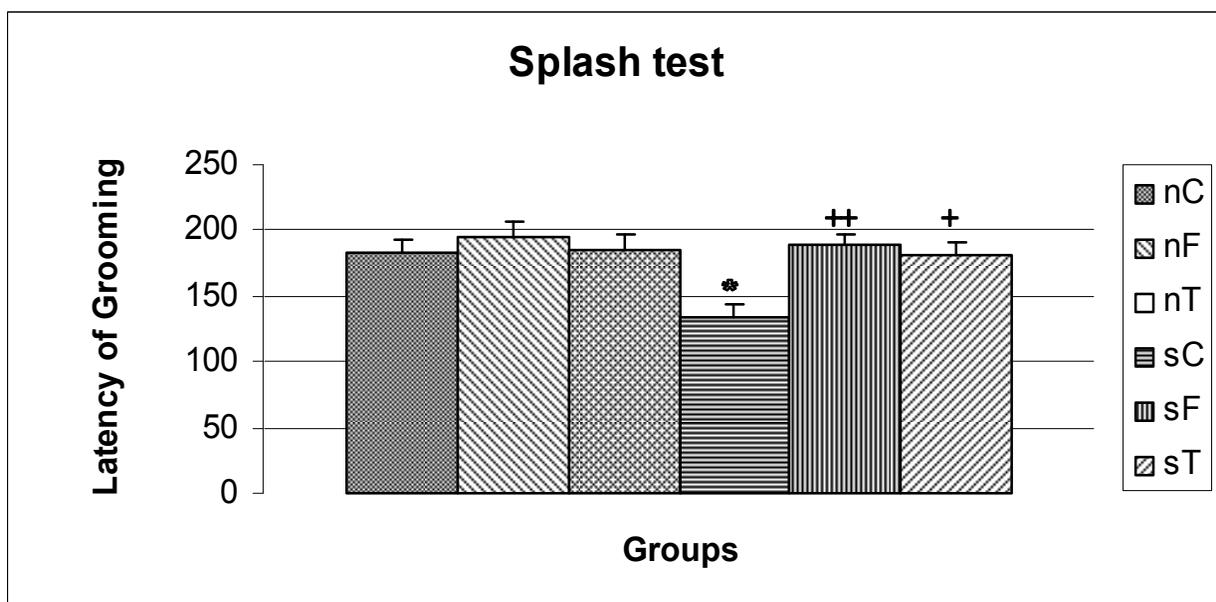


Fig. 1b. Effects of fluoxetine (15 mg/kg, i.p.) and TRIM (30 mg/kg, i.p.) given for 35 days on total time of grooming in the splash test in the end of the unpredictable chronic mild stress regimen. Data are means±SEM. \*p<0.01, compared to non-stressed vehicle group, +p<0.05, ++p<0.01, compared to the stressed vehicle group. nC = nonstressed control (vehicle) group, nF = nonstressed fluoxetine group, nT = nonstressed TRIM group, sC = stressed control (vehicle) group, sF = stressed fluoxetine group, and sT = stressed TRIM group.

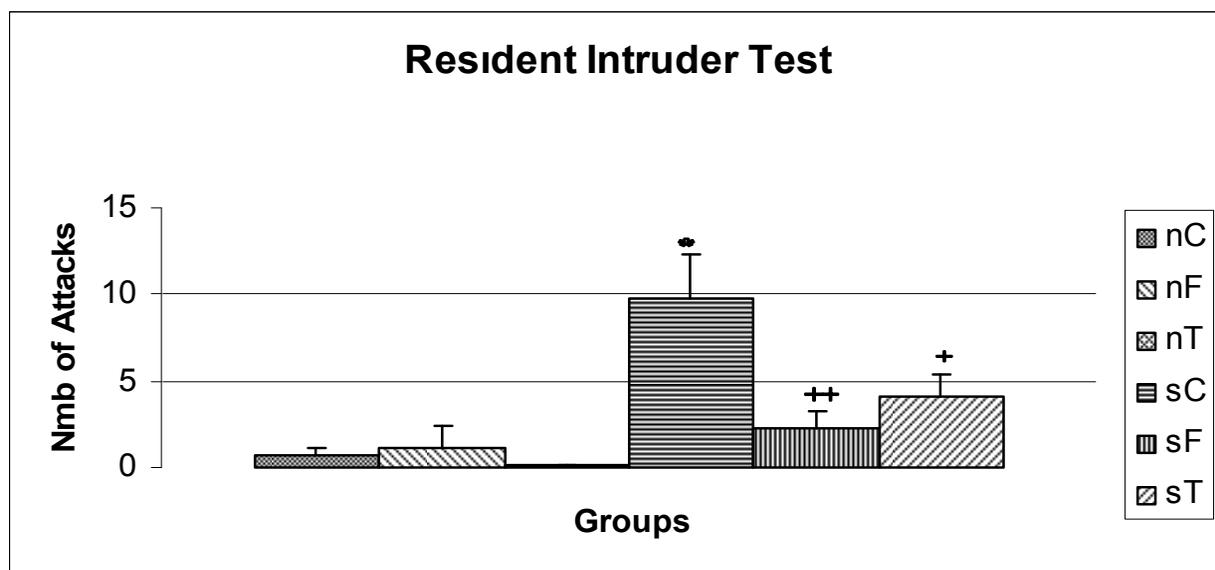


Fig. 1c. Effects of fluoxetine (15mg/kg, i.p./day, 35 days) and TRIM(30 mg/kg, i.p./day, 35 days) on attack frequency in the resident-intruder test after UCMS. Data are means±SEM. \* $p < 0.0001$ , compared to the non-stressed vehicle group, + $p < 0.05$ , ++ $p < 0.01$ , compared to the stressed vehicle group. nC = nonstressed control (vehicle) group, nF = nonstressed fluoxetine group, nT = nonstressed TRIM group, sC = stressed control (vehicle) group, sF = stressed fluoxetine group, and sT = stressed TRIM group.

Indeed inhibition of NO synthesis may exert similar effects to the NMDA receptor antagonists (Wiley et al., 1995) and it can be suggested that NOS inhibition can have antidepressant effects similar to NMDA receptor antagonists.

Recent studies postulated that various inhibitors of NOS such as competitive nonspecific NOS inhibitor NG-nitro-L-arginine methyl ester (L-NAME), NG-nitro-L-arginine (L-NA), selective neuronal NOS (nNOS) inhibitors 7-nitroindazole (7-NI) and NW-propyl-L-arginine (L-NPA) possess antidepressant-like properties in animal models (Ghasemi et al., 2008; Harkin et al., 2004; Volke et al., 2003; Yildiz et al., 2000a,b). It is suggested that nNOS plays a key role in the antidepressant-like effects of NOS inhibitors (Volke et al., 2003). This is in line with the observation that nNOS mRNA release increases after stress in several brain regions (De Oliveira et al., 2000) and that CMS exposure regulates nNOS expression selectively in hippocampus while it doesn't change inducible NOS (iNOS) and endothelial NOS (eNOS) expressions (Zhou et al., 2007). Furthermore, over-expression of nNOS suppresses hippocampal neurogenesis in the hippocampus of animals exposed to chronic stress while nNOS inhibition preserves and reverses CMS induced effects by promoting hippocampal neurogenesis (Zhou et al., 2007). Zhou et al. (2007) showed that CMS-induced behavioural despair and hippocampal neurogenesis impairment were prevented and reversed in mice receiving a nNOS inhibitor 7-NI. TRIM had different pharmacokinetic and pharmacodynamic features when compared with 7-NI and controversial results exist for the selectivity on nNOS inhibition of these two compounds (Fidecka, 2003; Handy et al., 1995; Volke et al., 2003). TRIM at 50 mg/kg doses inhibits nNOS and clearly exerts antidepressive and anxiolytic effects although it also inhibits locomotion and motor activity at this dose (Volke et al., 2003).

#### 2.4.2 Effects of the concurrent administration of NOS inhibitors and antidepressants on depression

Noradrenalin and serotonin are two neurotransmitters widely reported to be involved in the mechanism of action of antidepressants and the development of drugs selectively affecting these transmitters has provided the opportunity to determine the role of these transmitter systems, alone and in combination, in an antidepressant response. NOS activity is involved in the mechanism of action of several antidepressants. For example, the selective serotonin reuptake inhibitor paroxetine inhibits *in vitro* NOS activity and decreases plasma nitrite and nitrate levels significantly in depressed patients (Finkel et al., 1996), whereas chronic therapy with imipramine or citalopram did not change NOS activity in the examined brain regions (cortex, hippocampus or cerebellum) (Jopek et al., 1999). Furthermore, Wegener et al. (2003) showed that, serotonergic antidepressants paroxetine, citalopram and tianeptine and mixed serotonergic-noradrenergic antidepressant imipramine decreased hippocampal NOS activity *in vitro* in rats although they don't have direct effects on NOS under clinically relevant conditions. It seems that there are controversial results for the effects of different antidepressants on NOS activity but the actions on NOS are common to a variety of structurally dissimilar serotonergic antidepressants.

Ulak et al., (2008) examined the effects of a selective nNOS inhibitor TRIM, a 5-HT/NA reuptake inhibitor imipramine, SSRIs (selective serotonin reuptake inhibitors) citalopram and fluoxetine, serotonin reuptake enhancer tianeptine or selective NA reuptake inhibitor reboxetine alone or in combination in the FST in rats. TRIM decreased the immobility time at 50 mg/kg dose in the FST in rats. When given alone TRIM, imipramine, citalopram, fluoxetine, tianeptine and reboxetine did not shorten the immobility time of rats. The higher doses of these drugs, except citalopram produced a significant reduction in the immobility of rats. Coadministration subeffective doses of TRIM and reboxetine did not affect the behavior of rats in the FST whereas subeffective dose of TRIM given in combination with imipramine, citalopram, fluoxetine and tianeptine significantly reduced the immobility time of rats in the FST (Fig 2, 3, 4, 5, 6). Thus the pharmacological mechanism seems to be more due to serotonergic than adrenergic neurotransmission and co-administration of antidepressants acting via serotonergic system by TRIM may enhance beneficial effects in therapy-resistant depression and thus represent a potential source of novel drugs for antidepressant therapy.

Moreover the ability of TRIM to potentiate the behavioural activity of antidepressants acting via serotonergic system in the FST is not attributed to a nonspecific locomotor stimulant effect of these drugs.

Following reasons can be suggested to explain the augmentation of the effects of antidepressant drugs acting via the serotonergic system by nNOS inhibitor TRIM in the FST in rats: One is that activation of NMDA receptors result in the formation of NO and increases cyclic guanosine monophosphate (cGMP) levels (East and Garthwaite, 1991). Consistent with our findings, Harkin et al. (2004) showed that NO synthase inhibitor NGnitro- L-arginine (L-NA) augmented the effects of imipramine, fluoxetine, sertraline and citalopram but not reboxetine in the mouse FST; moreover this synergistic effect was also tested between 7-nitroindazole and imipramine or fluoxetine. Thus it was claimed that NOS inhibitors augment the effects of serotonin reuptake inhibitors in the FST. Moreover it has

been shown that L-NA and 7-NI exert similar antidepressant-like behavioural profiles as SSRI in FST in rats. Although it is not clear whether NMDA receptor antagonists exert antidepressant-like effects in the FST via the serotonergic mechanism, it has been postulated that this antidepressant-like behaviour of L-NA and 7-NI is endogenous serotonin dependent (Harkin et al., 2003). So it is postulated that the antidepressant augmenting effects of NOS inhibitors may be attributed to the modulation of serotonin release (Harkin et al., 2004). Since it has been demonstrated that inhibition of NOS can modulate the release of central serotonin (Kiss, 2000; Wegener et al., 2000), this may be the point of view.

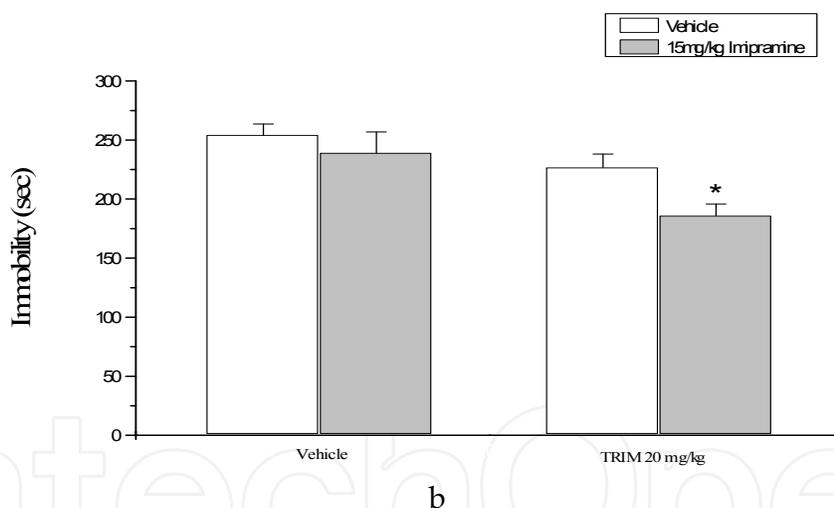
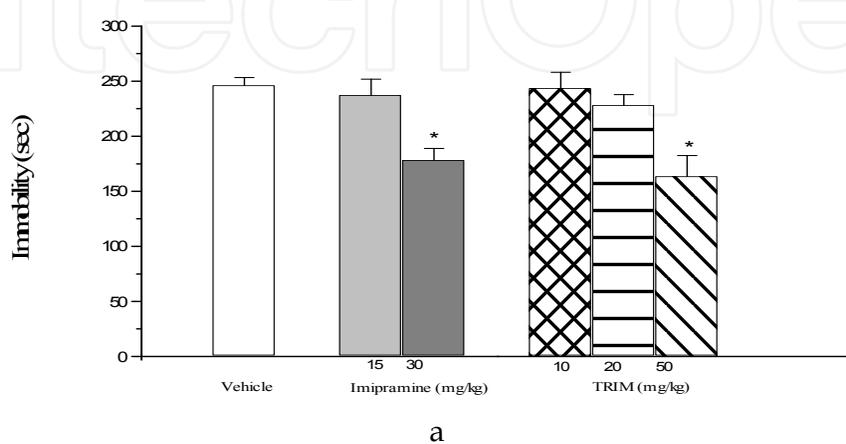
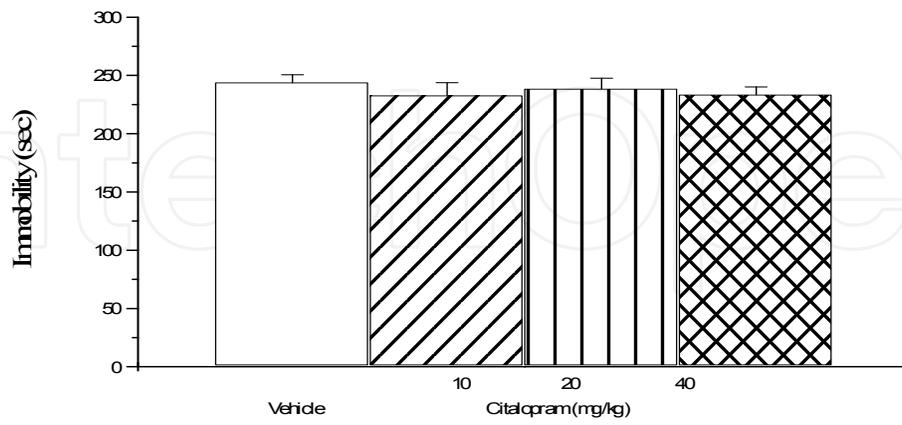


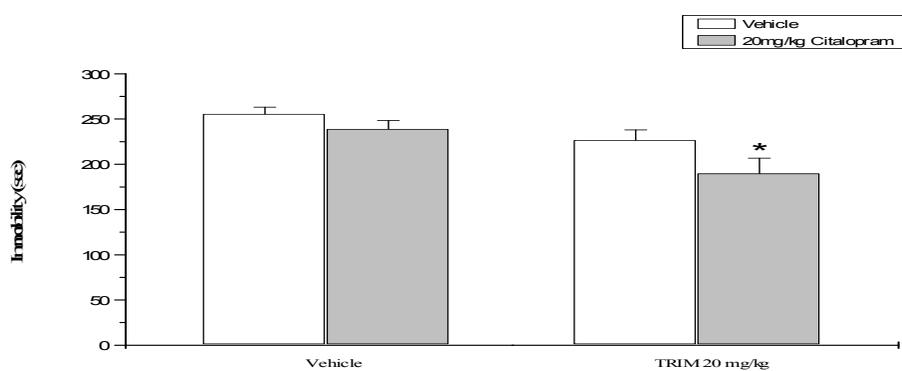
Fig. 2. (a). Effects of imipramine and TRIM on the immobility time in the rat FST. Each column represents the mean $\pm$ SEM of 7–14 animals. \* $p < 0.001$  compared to vehicle control (Tukey test). (b). TRIM potentiates the activity of imipramine in the rat FST. Each column represents the mean $\pm$ SEM of 7–10 animals. \* $p = 0.011$  compared to vehicle imipramine (15 mg/kg) (Dunnett test).

A second explanation for this result is that paroxetine, a selective serotonin reuptake inhibitor, is also a potent inhibitor of NOS enzyme activity (Finkel et al., 1996). Later, Wegener et al. (2003) showed that serotonergic antidepressants paroxetine, citalopram and tianeptine and the mixed serotonergic–noradrenergic antidepressant imipramine decrease NOS activity in vivo suggesting that actions on NOS are common to a variety of structurally dissimilar serotonergic antidepressants. From this point of view, it may be speculated that,

NOS inhibition in the brain plays some role in the antidepressant effect of drugs acting via serotonergic system. Since NMDA receptors play an important role in brain NOS activation, these effects may be due to secondary inhibitory effects on NMDA receptors.

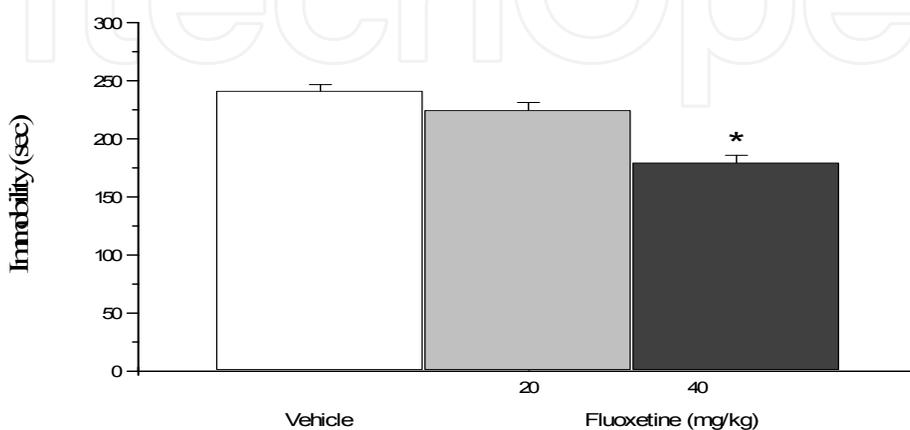


a



b

Fig. 3. (a). Effects of citalopram on the immobility time in the rat FST. Each column represents the mean±SEM of 7-9 animals. Citalopram failed to shorten the immobility time in the FST in rats. (b).TRIM (20 mg/kg) augments the activity of citalopram in the rat FST. Each column represents the mean±SEM of 7-9 animals.\*p=0.017 compared to vehicle citalopram (Dunnet test).



a

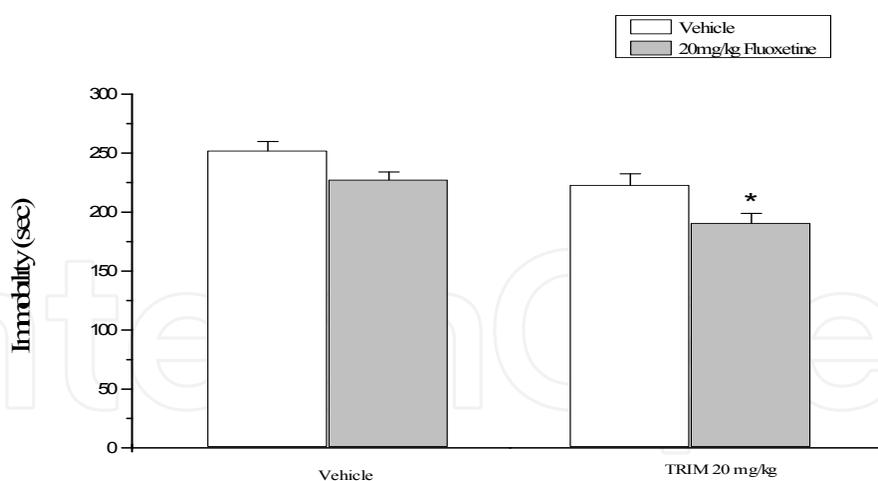
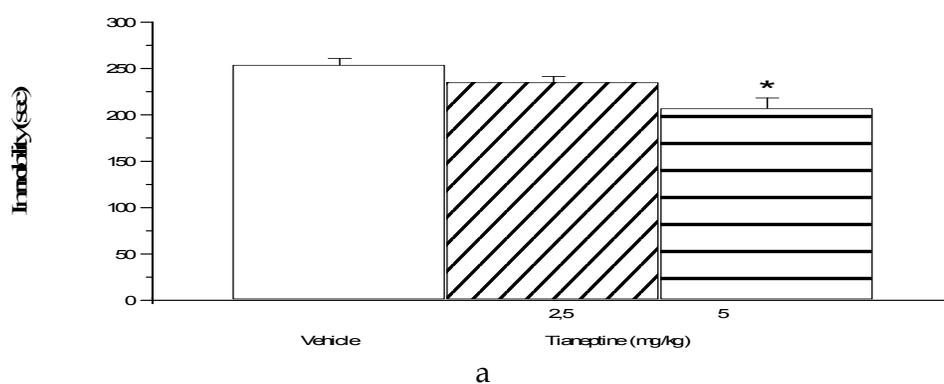
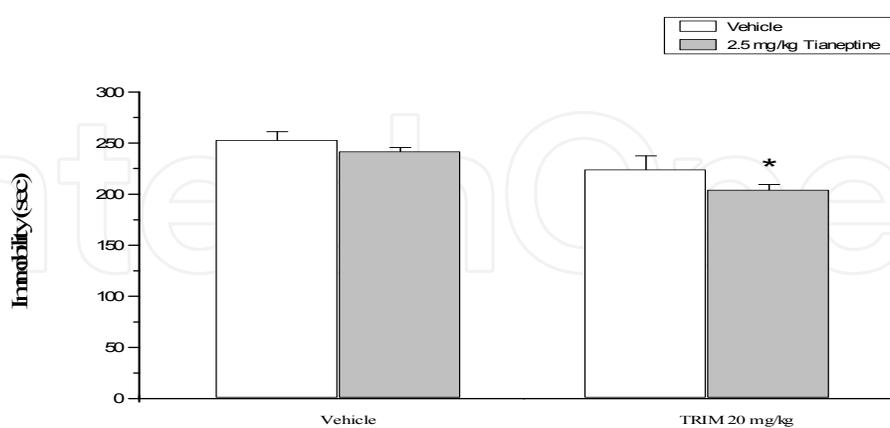


Fig. 4. (a). Effects of fluoxetine on the immobility time in the rat FST. Each column represents the mean $\pm$ SEM of 7 animals. \* $p < 0.001$  compared to vehicle control (Tukey test). (b). TRIM (20 mg/kg) augments the activity of fluoxetine in the rat FST. Each column represents the mean $\pm$ SEM of 6–10 animals. \* $p = 0.01$  compared to vehicle fluoxetine (Dunnet test).



a



b

Fig. 5. (a). Effects of tianeptine on the immobility time in the rat FST. Each column represents the mean $\pm$ SEM of 6–7 animals. \* $p < 0.01$  compared to vehicle control (Tukey test). (b). TRIM (20 mg/kg) augments the activity of tianeptine in the rat FST. Each column represents the mean $\pm$ SEM of 6–9 animals. \* $p = 0.015$  compared to vehicle tianeptine (Dunnet test).

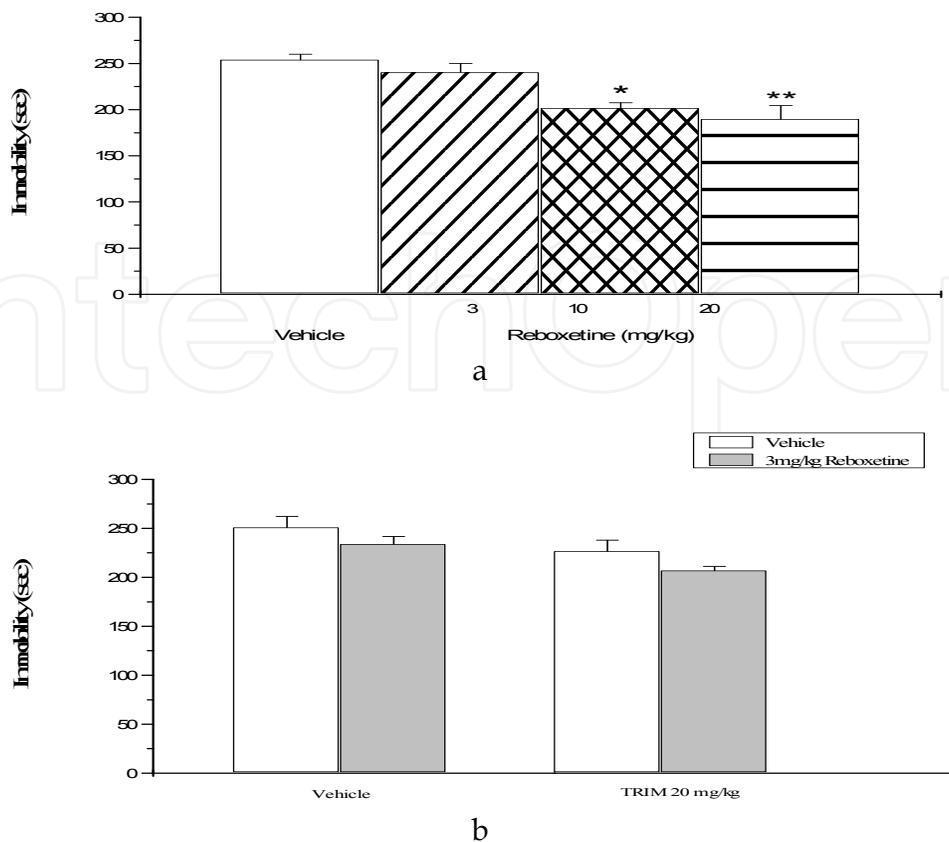


Fig. 6. (a). Effects of reboxetine on the immobility time in the rat FST. Each column represents the mean $\pm$ SEM of 7–9 animals. \* $p < 0.01$ , \*\* $p < 0.001$  compared to vehicle control (Tukey test). (b). TRIM (20 mg/kg) failed to augment the activity of reboxetine in the rat FST. Each column represents the mean $\pm$ SEM of 8–12 animals. Reboxetine+TRIM combined group compared to vehicle reboxetine group ( $p = 0.066$ , Dunnett test).

Thus the pharmacological mechanism seems to be more due to serotonergic than adrenergic neurotransmission and co-administration of antidepressants acting via the serotonergic system by TRIM, a selective nNOS inhibitor may enhance beneficial effects in therapy-resistant depression and thus represent a potential source of novel drugs for antidepressant therapy.

#### 2.4.3 Effects of the coadministration of NOS inhibitors and 5-HT receptor antagonists on depression

In a previous study in our laboratory (Ulak et al., 2010), the involvement of the serotonergic system in the antidepressant-like effect of TRIM in the FST in rats was studied by depleting endogenous 5-HT with the tryptophan hydroxylase inhibitor pCPA (Connor et al., 2001; Page et al., 1999) and by using 5-HT<sub>1</sub> and 5-HT<sub>2</sub> receptor antagonists to investigate the behavioural responses to TRIM in the FST since it is well known that these receptors play an important role in mood disorders (Clenet et al., 2001; Gardier et al., 1996; O'Neill and Conway, 2001; Redrobe et al., 1996; Redrobe and Bourin, 1998). This study extended the previous data of us, which had shown that TRIM augmented the effect of antidepressants acting via serotonergic system in the FST in rats (Ulak et al., 2008). In this study, TRIM exerted antidepressant-like activity comparable to that of the tricyclic antidepressant imipramine. Pretreatment of rats

with WAY 100635, a selective 5-HT<sub>1A</sub> receptor antagonist, or with GR127935, a selective 5-HT<sub>1B/1D</sub> receptor antagonist) slightly reversed the immobility-reducing effect of TRIM, but this failed to reach a statistically significant level; while alone they had no effect in the rat FST (Fig 8). Pretreatment with methiothepin (a non-selective 5-HT receptor antagonist), cyproheptadine (a 5-HT<sub>2</sub> receptor antagonist) or ketanserin (a 5HT<sub>2A/2C</sub> receptor antagonist) prevented the effect of TRIM in the FST (Fig 7, 9). So further experiments are needed to clarify the involvement of 5-HT<sub>1</sub> receptors in the antidepressant-like effect of TRIM.

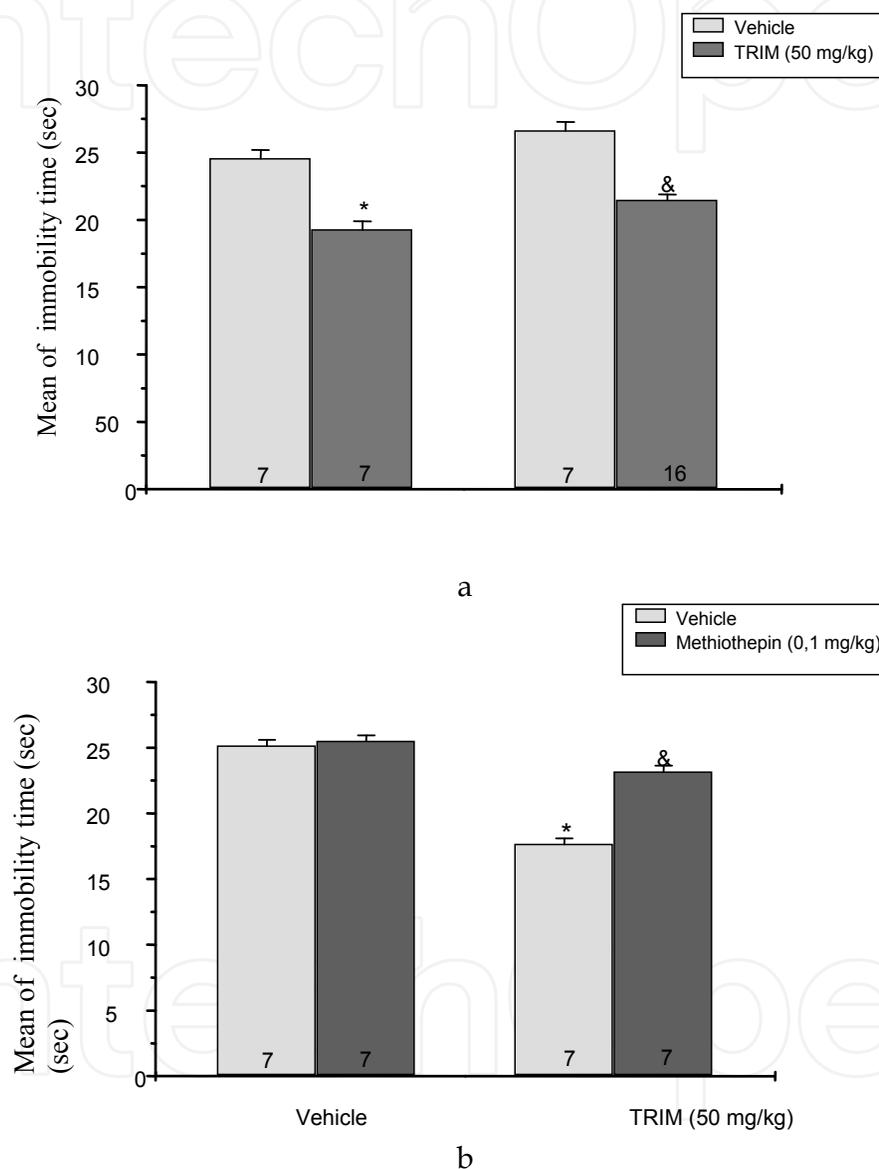


Fig. 7. a: Effects of the pretreatment of animals with pCPA on TRIM-induced reductions on immobility time in the rat FST. The number of animals per group is shown in the columns. Results are expressed as mean $\pm$ SEM \* $p$ <0.001 compared to control (Tukey's test), & $p$ <0.05 compared to pCPA untreated TRIM group (Tukey's test). b: Effects of pretreatment of animals with methiothepine on TRIM-induced reductions on immobility time in the rat FST. The number of animals per group is shown in the columns. Results are expressed as mean $\pm$ SEM \* $p$ <0.001 compared to control (Tukey's test), & $p$ <0.001 compared to methiothepine untreated TRIM group (Tukey's test).

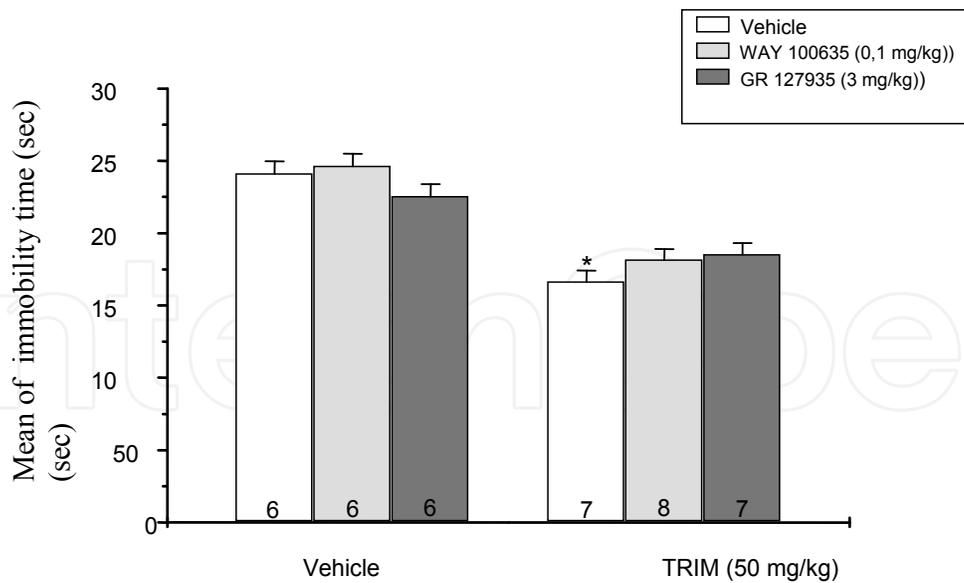


Fig. 8. Effects of pretreatment of animals with: WAY 100635, (b) GR 127935 on TRIM-induced reductions in immobility time in the rat FST. The number of animals per group is shown in the columns. Results are expressed as mean $\pm$ SEM. \* $p$ <0.001 compared to control (Tukey's test).

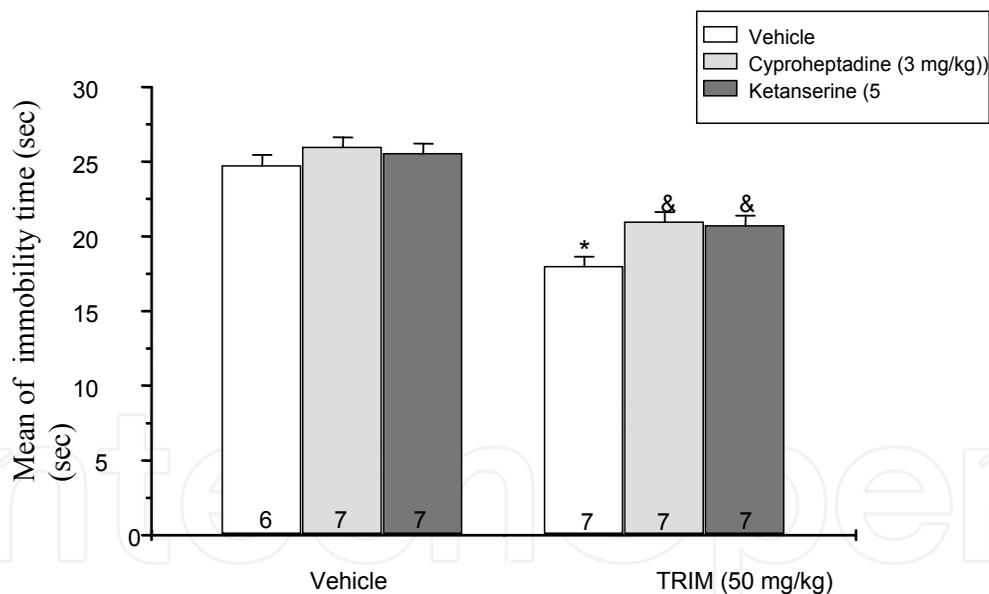


Fig. 9. The effect of pretreatment of animals with cyproheptadine or ketanserine on TRIM-induced reductions in immobility time in the rat FST. The number of animals per group is shown in the columns. Results are expressed as mean $\pm$ SEM. \* $p$ <0.001 compared to control (Tukey's test), & $p$ <0.05 compared to TRIM+vehicle administered group (Tukey's test).

The results of our previous study reveal that TRIM-induced reduction of immobility time in the FST was partially attenuated by pretreatment with the 5-HT depleting agent pCPA in rats. The treatment regimen of pCPA used in this study produced a greater than 90% depletion of cortical 5-HT concentration in the rat but had no effect on cortical dopamine and

noradrenalin concentrations (Connor et al., 2001; Harkin et al., 2003). Pretreatment with pCPA did not alter the immobility time of control animals but attenuated the anti-immobility effect of TRIM. Thus the results of our study suggested that endogenous 5-HT is involved in the antidepressant-like effect of TRIM. In line with our findings, serotonin depletion with pCPA prevented the antidepressant-like effect of the NOS inhibitors 7-NI and NG-nitro-L-arginine in FST (Harkin et al., 2003; Yildiz et al., 2000). The antidepressant-like effect of NOS inhibitors in the FST is dependent on NOS and NMDA receptor inhibition (Mutlu et al., 2009; Wiley et al., 1995). So reversal of the TRIM-induced antidepressant-like effect by pCPA treatment might be due to activation of 5-HT resulting from NOS inhibition and blockade of NMDA receptors (Zomkowski et al., 2002).

While methiothepin, a non-selective 5-HT receptor antagonist had no effect on immobility time in FST in our study and other studies (Buckley et al., 2004; Zomkowski et al., 2004), the reversal of antidepressant-like effect of TRIM by pretreatment of rats with methiothepin, reinforces the idea that 5-HT is involved in the action of TRIM in the FST. There are few studies investigating the interaction between the antidepressants and 5-HT receptor subtype affecting substances in animal depression models. Tatarczynska et al., (2004) suggested that pretreatment of rats with 5-HT1A receptor antagonist and with 5-HT1B/1D receptor antagonist reversed the immobility-reducing effect of TRIM, in the rat FST. 5-HT1B receptor antagonists were also reported to reverse the antidepressant-like effect of paroxetine and imipramine (Gardier et al., 2003; O'Neill and Conway, 2001). The results of our study revealed that pretreatment of rats with WAY 100635, a selective 5-HT1A receptor antagonist or with GR127935, a selective 5-HT1B/1D receptor antagonist) slightly reversed the immobility-reducing effect of TRIM, but this failed to reach a statistically significant level; while on its own, they had no effect in the rat FST.

Although the role of 5-HT2 receptors on the effect of antidepressants was investigated before (Middlemiss et al., 2002; Redrobe and Bourin, 1998), there is no study about the interaction of 5-HT2 receptor antagonists and nNOS inhibitors in animal models of depression. So another important finding of our study was that, the antidepressant-like effect of TRIM in the FST was prevented by pretreatment with cyproheptadine, a 5-HT2 receptor antagonist and with ketanserin, a 5HT2A/2C receptor antagonist having higher affinity for 5HT2A receptors than for 5HT2C receptors (Van Oekelen et al., 2003). TRIM may interact with both 5HT2A and 5HT2C receptors which are also reported to play role in the action of antidepressants (Clenet et al., 2001). Thus 5-HT2A receptors, at least partially, have a role on the antidepressant-like effect of TRIM. It is reported that NOS inhibitors increased the release of 5-HT in prefrontal cortex (Smith and Whitton, 2000). Therefore, it could be postulated that TRIM affects 5-HT2A receptors by increasing 5-HT level in the synaptic terminal.

### 3. Novel antidepressants

In current studies (unpublished data) in our laboratory we investigated the effect of tianeptine (5 mg/kg, 35 days) and olanzapine (2.5 mg/kg, 35 days), in (UCMS exposed mice when compared with the ones of the widely used selective serotonin reuptake antidepressant drug fluoxetine (15 mg/kg/day, 35 days). We revealed that olanzapine also has significant antidepressant like effects in the UCMS test which supports the efficacy of atypical antipsychotics as antidepressants in unipolar major depression and in treatment-

resistant unipolar depression. A significant difference between the coat state score of non-stressed and UCMS-exposed groups was observed (unpublished data). Both fluoxetine and olanzapine significantly reversed the UCMS-induced degradation in the coat state. Both olanzapine and fluoxetine blocked the stress-induced deficit in total latency of grooming in the splash test, decreased the attack frequency in the resident intruder test, decreased the immobility time in the tail suspension test. No significant effect was observed between stressed and nonstressed animals in the novelty suppressed feeding test. There was no significant difference between the body weight and locomotion of the animals at the end of UCMS regimen. Both olanzapine and fluoxetine decreased enhanced levels of plasma ACTH, cortisol and IL-6 while only fluoxetine reversed stress-induced increase of TNF- $\alpha$  levels in mice. Olanzapine had anxiolytic-like effects both in stressed and nonstressed mice in the open field test (unpublished data). Recent studies also showed that a new atypical antipsychotic asenapine reversed UCMS induced effects in rodents (Marston et al., 2010).

A large number of novel serotonin targets are in a testing phase. One particularly interesting novel serotonin target is the 5HT<sub>2C</sub> receptor. Blockade of 5HT<sub>2C</sub> receptors causes release of both norepinephrine and dopamine and these agents can be called norepinephrine dopamine disinhibitors or NDDIs. A novel antidepressant agomelatine combines this property of 5HT<sub>2C</sub> antagonism and thus NDDI actions with additional agonist actions at melatonin receptors (MT<sub>1</sub> and MT<sub>2</sub>). Agomelatine also has 5HT<sub>2B</sub> antagonist properties. This portfolio of pharmacological actions predicts not only antidepressant actions due to the NDDI mechanism of 5HT<sub>2C</sub> antagonism but also sleep-enhancing properties due to MT<sub>1</sub> and MT<sub>2</sub> agonist actions. Another NDDI with 5HT<sub>2C</sub> antagonist properties is flibanserin. This agent also has 5HT<sub>2A</sub> antagonist and 5HT<sub>1A</sub> agonist properties and, because of its robust NDDI properties, it is under investigation for sexual dysfunction linked to deficient dopamine activity, including conditions such as hypoactive sexual desire disorder (HSDD). Triple reuptake inhibitors (TRIs) or serotonin-norepinephrine-dopamine-reuptake inhibitors (SNDRIs), beta 3 receptor agonists, glucocorticoid antagonists, corticotrophin releasing factor 1 (CRF 1) antagonists, vasopressin 1B antagonists, and neurokinin antagonists are examined for depression. TRIs or SNDRIs combinations are applied in order to examine the idea that if one mechanism is good (i.e., SSRI) and two mechanisms are better (i.e., SNRI), then maybe targeting all three mechanisms of the monoamine neurotransmitter system would be the best in terms of efficacy. The question for TRIs is how much blockade of each monoamine transporter is desired, especially for the dopamine transporter or DAT. Too much dopamine activity can lead to drug abuse, not enough means that the agent is essentially an SNRI. Perhaps the desirable dose is robust inhibition of the serotonin transporter and substantial inhibition of the norepinephrine transporter, like the known SNRI, plus 10 to 25% inhibition of DAT. Some experiments suggest that TRI action also increases acetylcholine release, so TRIs may modulate a fourth neurotransmitter system and act as multitransmitter modulators (new study?). Further testing will determine whether the available TRIs will represent an advance over SSRIs or SNRIs in the treatment of depression. A very novel mechanism for an antidepressant is posed by amibegron, an agonist of beta 3 receptors. The role of beta 3 receptors in the brain is still being clarified, but it appears that they may be localized in high density in the amygdala, where they may regulate neuronal activity in ventromedial prefrontal cortex and thereby exert their antidepressant actions. Extensive testing reference? in animal models of depression demonstrates the

antidepressant actions of amibegron, and human testing is currently in progress. Glucocorticoid antagonists, corticotrophin releasing factor 1 (CRF 1) antagonists and vasopressin 1B antagonists will be further examined not only for depression but also for various stress-related conditions. Nemifitide is itself a novel pentapeptide modeled on the structure of melanocyte inhibitory factor (MIF-1), a tripeptide shown to be active in animal models of depression and in small clinical studies of depressed patients reference? MIF-1 (also known as L-prolyl-L-leucyl-L-glycinamide, or PLG) is also the tripeptide tail of oxytocin and its precursor neurophysin. Nemifitide is a pentapeptide analog not only of the tripeptide MIF-1 but also of the tripeptide tail of vasopressin. Nemifitide is administered by subcutaneous injection and has been shown to be active in animal models of depression; it is preliminary results of experiments with depressed patients, that early findings suggest possible efficacy with rapid onset, including effectiveness in treatment-resistant patientsreference?. Further testing in patients with major depressive episodes is ongoing (Stahl, 2010).

Another class of peptide antagonists is the neurokinin antagonists. Neurokinins belong to the family of peptides known as tachykinins. Tachykinins include not only neurokinins but also newly discovered endokinins and tachykinin gene-related peptides that act mostly outside the brain but at the same receptors where the tachykinins act (especially the NK1 receptor). Low-molecular-weight antagonists have been identified for each of the three known neurokinin receptors, NK1, NK2, and NK3. NK1 antagonists, also known as substance P antagonists, have been hotly pursued for many years as treatments not only for depression but also for pain, schizophrenia, and other psychiatric disorders. To date, the clinical results with substance P antagonists, from studies on major depression and in pain-related conditions, have been disappointing. However, recent evidencereference? suggests that saredutant, an NK2 antagonist, may be effective not only in animal models of depression but also in patients with major depressive episodes. Hypothetically, conditions associated with excessive release of endogenous NKA (or its extended or shortened versions), especially under conditions of stress or major depression, benefit from the blocking of NK2 receptors; that could explain why this mechanism may produce an antidepressant effect. NK3 antagonists are also tested for various psychiatric disorders (Stahl, 2010).

#### 4. Conclusion

In conclusion, NOS inhibitors can be a novel approach for antidepressant therapy, exerting their effect possibly on neuronal NOS and TRIM, by the selective inhibition of both nNOS and iNOS. The antidepressant-like effect of TRIM in the FST seems to be mediated, at least in part, by an interaction with 5-HT<sub>2</sub> receptors, while non-significant effects were obtained with 5-HT<sub>1</sub> receptors. Further studies are needed to enlighten whether the antidepressant-like effect of NOS inhibitors are dependent on endogene serotonin and to know how these serotonin receptors are playing a role in this effect. Besides, the potentiation of the antidepressant-like effect of fluoxetine by TRIM might have a therapeutic value for NOS inhibitors and form a new treatment strategy to increase the clinical effect of antidepressants. A large number of novel serotonin targets are in a testing phase for the treatment of depression. Norepinephrine dopamine disinhibitors or NDDIs, agomelatine, flibanserin, triple reuptake inhibitors (TRIs) or serotonin-norepinephrine-dopamine-

reuptake inhibitors (SNDRI), beta 3 receptor agonists, glucocorticoid antagonists, corticotrophin releasing factor 1 (CRF 1) antagonists, vasopressin 1B antagonists, and neurokinin antagonists are further examined for the treatment of depression.

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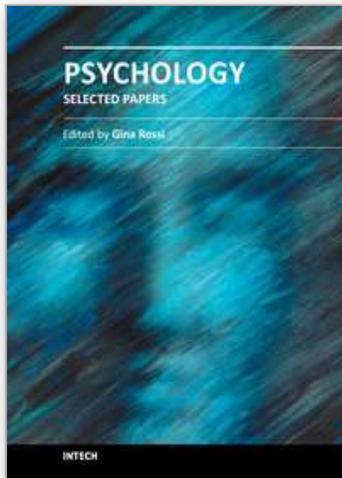
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