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Ferulic acid exerts antidepressant-like effect in the tail suspension test in mice: Evidence for the involvement of the serotonergic system

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ABSTRACT

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phenolic compound present in several plants with claimed beneficial effects in prevention and treatment of disorders linked to oxidative stress and inflammation. In this study, we aimed to verify the possible antidepressant-like effect of acute oral administration of ferulic acid in the forced swimming test (FST) and tail suspension test (TST) in mice. Additionally, the mechanisms involved in the antidepressant-like action and the effects of the association of ferulic acid with the antidepressants fluoxetine, paroxetine, and sertraline in the TST were investigated. Ferulic acid produced an antidepressant-like effect in the FST and TST (0.01–10 mg/kg, p.o.), without accompanying changes in ambulation. The pretreatment of mice with WAY100635 (0.1 mg/kg, s.c., a selective 5-HT_{1A} receptor antagonist) or ketanserin (5 mg/kg, i.p., a 5-HT_{2A} receptor antagonist) was able to reverse the anti-immobility effect of ferulic acid (0.01 mg/kg, p.o.) in the TST. The combination of fluoxetine (5 mg/kg, p.o.), paroxetine (0.1 mg/kg, p.o.) or sertraline (1 mg/kg, p.o.) with a sub-effective dose of ferulic acid (0.001 mg/kg, p.o.) produced a synergistic antidepressant-like effect in the TST, without causing hyperlocomotion in the open-field test. Taken together, these results demonstrate that ferulic acid exerts antidepressant-like effect in the FST and TST in mice through modulation of the serotonergic system.

1. Introduction

Depression is a disorder that has high incidence in the world population (Berton and Nestler, 2006) with impact in the life quality of patients (Nemeroff, 2007). The treatment of depression with conventional antidepressants provides a complete remission just for 50% of the individuals (Rush et al., 2003), produces side effects (Brunello et al., 2002) that may reduce the adhesion of patients to the treatment (MacGillivray et al., 2003), and the majority of patients takes more than 5–8 weeks to respond to the treatment. Thus, novel or additional treatments with low side effects and costs are of particular interest (Laakmann et al., 1998).

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phenolic compound present in several plants and in natural extracts of herbs, spices, and coffee (Graf, 1992; Virgili et al., 2000). Ferulic acid has been approved as an antioxidant additive and food preservative in Japan (Graf, 1992; JFCRF, 1996) and sodium ferulate, a salt of ferulic acid, has been used in traditional medicine and is approved by State Drugs Administration of China for the treatment of cardiovascular and cerebrovascular diseases (Wang and Ou-Yang, 2005).

Ferulic acid has been shown to exert a potent antioxidant activity (Anselmi et al., 2004; Bourne and Rice-Evans, 1998; Graf, 1992; Itagaki et al., 2009; Ogiwara et al., 2002; Srinivasan et al., 2007). The connection between inflammation and oxidative stress has suggested that ferulic acid may also be an effective agent against inflammatory diseases as previously reported (Chawla et al., 1987; Fernandez et al., 1998; Murakami et al., 2002). Ferulic acid has been shown to be beneficial in prevention and/or treatment of disorders linked to oxidative stress and inflammation (Jin et al., 2005; Kim et al., 2004; Perluigi et al., 2006; Yan et al., 2001; Zhang et al., 2003). In addition, Yu et al. (2006) reported that ferulic acid produced a potent protection against excitotoxic effects of monosodium glutamate, since maternal administration of ferulic acid reduced glutamate-induced toxicity in their filial mice.

Several studies have shown that the glutamatergic system plays an important role in the neurobiology and treatment of depression, probably through the N-methyl-D-aspartate (NMDA) receptor. Indeed, NMDA receptor antagonists possess antidepressant activities and conventional antidepressants are reported to decrease the binding, expression and function of NMDA receptors (Sanacora et al., 2008).

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Considering that excitotoxicity is an event directly associated with neural cell death and the direct relationship between hippoccampal and cortical damage and depressive disorders (Sapolsky, 2000), in this study we have hypothesized that ferulic acid could display an antidepressant property in the widely-accepted predictive models of depression in mice, which are used to screen new antidepressant drugs. For that we performed an investigation to verify the antidepressant-like effect of ferulic acid by using the forced swimming test (FST) and the tail suspension test (TST).

This study also aimed to investigate the participation of the serotonergic system in the antidepressant-like effect of an acute administration of ferulic acid in the TST and a possible interaction of ferulic acid with conventional antidepressants.

2. Material and methods

2.1. Animals

Male Swiss mice (30–40 g) were maintained at 21–23 °C with free access to water and food, under a 12:12 h light/dark cycle (lights on at 07:00 h). All manipulations were carried out between, 9:00 and 16:00 h, with each animal used only once. All procedures in this study were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. The experiments were performed after approval of the protocol by the Institutional Ethics Committee (CEUA/UFSC) and all efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

2.2. Drugs and administration

Ferulic acid, N-{2-[4-(2-methoxy-phenyl)-1-piperazinyl]ethyl}-N-(2-pyridynyl)cyclohexanecarboxamide (WAY100635), ketanserin tartarate, fluoxetine, paroxetine, and sertraline (all from Sigma Chemical Company, St. Louis, MO, U.S.A.) were used. The drugs were dissolved in saline and ferulic acid was diluted in saline containing 1% (v/v) Tween 80. The control animals received appropriate vehicle.

In order to investigate the antidepressant-like effect of ferulic acid, it was administered at a dose range of 0.001–10 mg/kg, by oral route (p.o.) 60 min before the FST, TST or open-field test. To address some of the mechanisms by which ferulic acid exerts antidepressant-like action in the TST, animals were pre-treated with different pharmacological agents.

To investigate a possible contribution of the serotonergic system (5-HT receptor subtypes) in the antidepressant-like effect of ferulic acid, animals were pretreated with WAY100635 (0.1 mg/kg, a selective 5-HT_{1A} receptor antagonist) by subcutaneous route (s.c.), ketanserin (5 mg/kg, a preferential 5-HT_{2A} receptor antagonist) by intraperitoneal route (i.p.), or vehicle and after 30 min, received ferulic acid (0.01 mg/kg, p.o.) or vehicle before being tested in the TST 60 min later. The drugs were administered in a volume of 10 mL/kg body weight.

We also assessed the ability of ferulic acid to potentiate the antidepressant-like effect of selective serotonin reuptake inhibitors (SSRIs). To this end, mice received by p.o. route sub-effective dose of fluoxetine (5 mg/kg), paroxetine (0.1 mg/kg) or sertraline (1 mg/kg) and immediately after a sub-effective dose of ferulic acid (0.001 mg/kg, p.o.) or vehicle. Sixty minutes later, the TST or the open-field test was carried out.

The doses of the drugs used were selected on the basis of literature data and of previous results from our laboratory which reported that those drugs do not increase locomotor activity (Capra et al., 2010; Cunha et al., 2008; Doyle and Shaw, 1998; Genedani et al., 1984; Kaster et al., 2005; Mikolajczak et al., 2002).

2.3. Forced swimming test (FST)

The FST was carried out in mice individually which were forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 ± 1 °C; the total duration of immobility during the 6-min test was scored as described previously (Kaster et al., 2005; Zomkowski et al., 2010). Each mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water.

2.4. Tail suspension test (TST)

The total duration of immobility induced by tail suspension was measured according to the method of Steru et al. (1985). Mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6-min test (Cunha et al., 2008; Machado et al., 2007; Rodrigues et al., 2002). Mice were considered immobile only when they hung passively and completely motionless. The immobility time was recorded by an observer blind to the drug treatment.

2.5. Open-field behaviour

The ambulatory behaviour was assessed in an open-field test as described previously (Zomkowski et al., 2010). The open field arena used was a wooden box measuring 40 × 60 cm and 50 cm height with the floor divided into 12 equal squares. At the start of each trial a mouse was placed in the left corner of the field and was allowed to freely explore the arena. The number of squares crossed with all paws (crossing) was counted in a 6 min session. The arena floor was cleaned between the trials with a 10% ethanol solution and the test was carried out in a temperature, noise, and light controlled room.

2.6. Data analysis

Comparisons between treatment groups and control were performed by one-way or two-way analyses of variance (ANOVA) followed by Tukey's HSD test, when appropriate. A value of $P<0.05$ was considered to be significant.

3. Results

3.1. Effect of ferulic acid on the immobility time in the FST and TST and locomotor activity in the open-field test

The results illustrated in Fig. 1A and B show that ferulic acid (0.01, 0.1, 1 or 10 mg/kg) given by oral route decreased significantly the immobility time in the FST and in the TST. Fig. 1C shows that the administration of ferulic acid (dose range of 0.001–10 mg/kg, p.o.) produced no effect in the open-field test, indicating that a confounding locomotor impairment can be discarded in the antidepressant-like effect observed, in both FST and TST.

3.2. Investigation of the mechanisms underlying the antidepressant-like effect of ferulic acid in the TST

3.2.1. Involvement of the serotonergic system

Fig. 2A shows the effect of the pretreatment of mice with WAY100635 (0.1 mg/kg, s.c., a 5-HT_{1A} receptor antagonist) and ferulic acid (0.01 mg/kg, p.o.) in the TST. The pretreatment with WAY100635 was able to prevent the anti-immobility effect of ferulic acid. The administration of WAY100635 alone or in combination with ferulic acid did not affect the ambulation in the open-field (Fig. 2B).

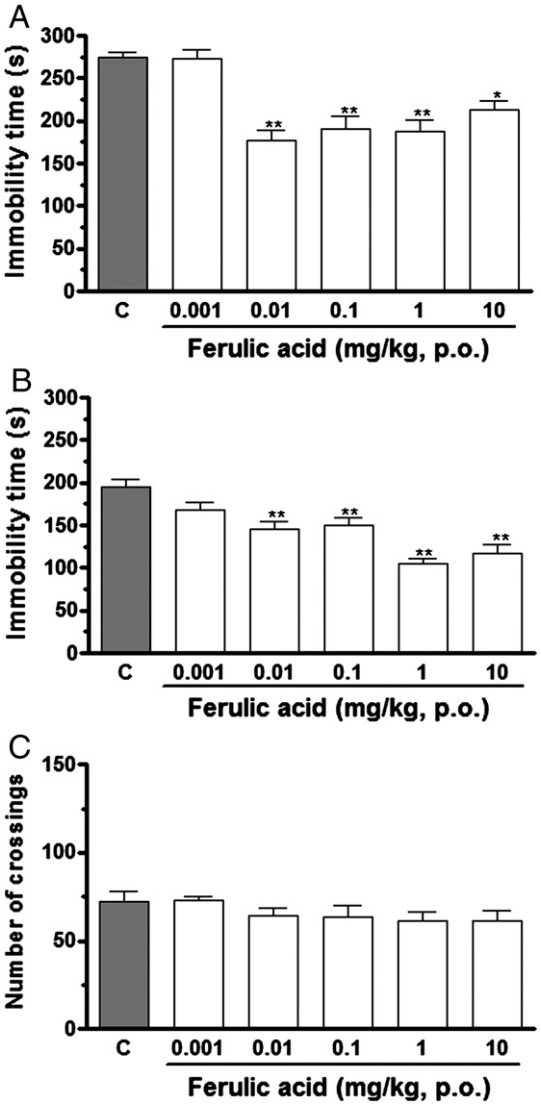

Fig. 1. Effect of the administration of ferulic acid (dose range 0.001–10 mg/kg, p.o.) in the FST (panel A), in the TST (panel B), and in the open-field test (panel C). Values are expressed as mean ± S.E.M. ($n = 6–9$). *$P<0.05$ and **$P<0.01$ as compared with the vehicle-treated group. A) $F(5,31) = 15.05$, $P<0.01$. B) $F(5,38) = 15.40$, $P<0.01$. C) $F(5,31) = 1.01$, $P = 0.43$.

Fig. 2C shows the effect of the pretreatment of mice with ketanserin (5 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist) on the anti-immobility effect of ferulic acid (0.01 mg/kg, p.o.). The pretreatment with ketanserin blocked the decrease in immobility time produced by ferulic acid in the TST. The administration of ketanserin alone or in combination with ferulic acid did not affect the ambulation in the open-field (Fig. 2D).

3.2.2. Interaction of ferulic acid with conventional antidepressants in the TST

In this study the potential synergistic effect of the administration of sub-effective doses of antidepressants and ferulic acid was also investigated. Fig. 3A shows that the administration of ferulic acid (0.001 mg/kg, p.o.) boosted the antidepressant-like effect of fluoxetine (5 mg/kg, p.o.) in the TST. Previous studies from our group (Cunha et al., 2008; Freitas et al., 2010; Machado et al., 2009) reported that fluoxetine (10 mg/kg, p.o.), paroxetine (1 mg/kg, p.o.) or sertraline (10 mg/kg, p.o., unpublished result), caused a reduction in the immobility time in the TST. The results depicted in Fig. 3C shows that the combined administration of ferulic acid (0.001 mg/kg, p.o.) and paroxetine (0.1 mg/kg, p.o.) reduced the immobility time of mice submitted to the TST. Fig. 3E shows that the administration of sertraline (1 mg/kg, p.o.) exhibited a potent antidepressant-like effect when combined with ferulic acid (0.001 mg/kg, p.o.). The results obtained here revealed a synergistic antidepressant-like effect induced by fluoxetine, paroxetine or sertraline when co-administered with ferulic acid in the TST.

Moreover, the effect of the treatment with antidepressants fluoxetine (5 mg/kg), paroxetine (0.1 mg/kg) or sertraline (1 mg/kg) and ferulic acid alone or in combination was verified in the open-field test. The results depicted in Fig. 3B, D and F show that the administration of the antidepressants in combination with ferulic acid did not alter the locomotor activity of mice in the open-field test.

4. Discussion

There is a large number of current pharmacological treatments for depression, but the success rate of medication is not more than 50–60% (Kiss, 2008) and most of them are poorly tolerated because of adverse side effects (Guadarrama-Cruz et al., 2008). Therefore, there is a need for research and development of more effective antidepressant therapies without any or with less adverse effects. In this study, we have shown that the ferulic acid administered by oral route produced a significant antidepressant-like response in the FST and TST. Noteworthy, ferulic acid was able to produce a synergistic action with the conventional antidepressants, fluoxetine, paroxetine or sertraline, in the TST.

The FST and TST are widely used as behavioural tools for screening antidepressant activity of several classes of drugs (Cryan et al., 2005). In this study, the antidepressant-like effect of the ferulic acid was observed at the same doses in both TST and FST (0.01–10 mg/kg, p.o.). A previous study developed by Yabe et al. (2010) has reported that ferulic acid (250 mg/kg) ameliorated the chronic mild stress-induced depressive-like behaviour observed in the FST in mice. However, it should be considered that the above mentioned study has a protocol of stress-induced depressive-like behaviour, different from our experimental approach. In the present study, ferulic acid (0.01–10 mg/kg) was effective in both FST and TST predictive tests of antidepressant agents. Additionally, ferulic acid induces no dose–response-related effect, as both low and high doses of that compound decreased the immobility period. Therefore, it is possible that such findings result from a saturation of ferulic acid sites of interaction, since maximum effect was achieved at lower doses. Similar results were found in a previous study performed with *Aloysia gratissima* aqueous extract (10 mg/kg, p.o.) species having ferulic acid as the major polyphenolic compound (Zeni et al., 2011), and with curcumin (2.5–10 mg/kg, p.o.), a polyphenol isolated from *Curcuma longa* with chemical similarity to ferulic acid (Xu et al., 2005).

The major neurochemical process known in depression is the impairment of monoaminergic neurotransmission and the concomitant decrease of extracellular concentration of noradrenaline and/or serotonin (Schildkraut, 1965). Moreover, the serotonergic system in the pathogenesis of depression is an important target for the conventional pharmacotherapy (Duman et al., 1997; Wong and Licinio, 2001). The antidepressants commonly affect serotonin balance, inhibiting serotonin reuptake and also exerting modulation of 5-HT_{1A} and 5-HT_2 receptors (Cryan et al., 2005). In the present study, the administration of WAY100635 (a competitive antagonist at the 5-HT_{1A} receptors) prevented the anti-immobility effect of ferulic acid in the TST, an indicative that this 5-HT_{1A} receptor subtype is involved in the antidepressant-like effect of ferulic acid. According to results of our research group (Machado et al., 2009) and Wang et al. (2008), it has been demonstrated that the antidepressant-like effect of *Rosmarinus officinalis* and *C. longa*, which contain ferulic acid, was prevented by 5-HT_{1A} antagonists in the TST and FST, respectively. Studies have

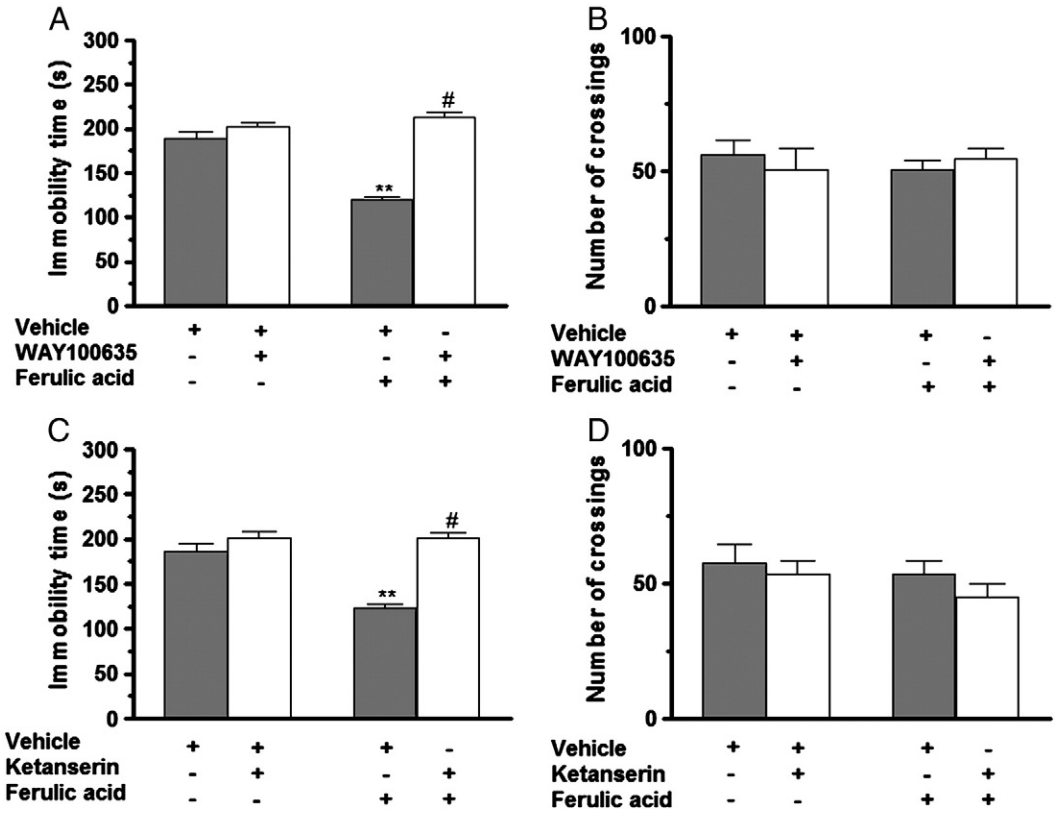

Fig. 2. Effect of the pretreatment of mice with WAY100635 (0.1 mg/kg, s.c., panel A) or ketanserin (5 mg/kg, i.p., panel C) on the anti-immobility effect of ferulic acid (0.01 mg/kg, p.o.) in the TST and on the number of crossings in the open-field tests (panels B and D, respectively). Values are expressed as mean ± S.E.M. ($n = 6$). $^{**}P < 0.01$ compared with the vehicle-treated control. $\#P < 0.01$ as compared with the ferulic acid alone. A) Ferulic acid treatment [$F(1,20) = 96.01$, $P < 0.01$]; WAY100635 pretreatment [$F(1,20) = 29.41$, $P < 0.01$]; WAY100635 × ferulic acid interaction [$F(1,20) = 53.84$, $P < 0.01$]. B) WAY100635 pretreatment [$F(1,20) = 0.02$, $P = 0.88$]; ferulic acid treatment [$F(1,20) = 0.02$, $P = 0.88$]; WAY100635 × ferulic acid interaction [$F(1,20) = 0.81$, $P = 0.38$]. C) Ketanserin pretreatment [$F(1,20) = 45.74$, $P < 0.01$]; ferulic acid treatment [$F(1,20) = 20.37$, $P < 0.01$]; ketanserin × ferulic acid interaction [$F(1,20) = 21.02$, $P < 0.01$]. D) Ketanserin pretreatment [$F(1,20) = 1.26$, $P = 0.27$]; ferulic acid treatment [$F(1,20) = 1.26$, $P = 0.27$]; ketanserin × ferulic acid interaction [$F(1,20) = 0.12$, $P = 0.73$].

demonstrated the involvement of 5-HT_{1A} receptors in the mechanism of action of antidepressant drugs and compounds that could block these receptors might be effective in producing antidepressant responses (Blier and Ward, 2003).

It was previously suggested that also an activation of the 5-HT_2 receptors is implicated in the modulation of mood (Hoyer et al., 1986) and these receptors have also been related to the aetiology of depression (Nestler et al., 2002). In addition, preclinical reports showed that the preferential 5-HT_{2A} receptor agonist R(−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl (DOI) enhances the antidepressant-like effect of some compounds in the FST (Khisti and Chopde, 2000; Zomkowski et al., 2004). Since the antidepressant-like effect elicited by ferulic acid in the TST was prevented by the pretreatment of mice with ketanserin (a preferential 5-HT_{2A} serotonin receptor antagonist), it is also feasible to suggest the possible involvement of the 5-HT_{2A} in the antidepressant-like effect of ferulic acid. Our results are in accordance with data from the literature showing that the reduction in the immobility time elicited by scopoletin, a coumarin isolated from *Polygala sabulosa* (Capra et al., 2010), and *R. officinalis* (Machado et al., 2009) was also prevented by the pretreatment with ketanserin, in the TST.

This study showed that the ferulic acid was able to produce a synergistic antidepressant-like effect with some conventional antidepressants, all SSRIs, fluoxetine, paroxetine, and sertraline in the TST. This effect was not accompanied by hyperlocomotion that could produce a false positive antidepressant-like effect. Therefore, the present study suggests that the combination of the ferulic acid with conventional antidepressants might be an alternative approach to treat depression. Interestingly, Warner-Schmidt et al. (2011) suggested that anti-inflammatory drugs decrease the antidepressant effects of SSRIs in mice and humans. Although ferulic acid was reported to have anti-inflammatory properties (Jin et al., 2005; Kim et al., 2004; Perluigi et al., 2006), it remains to be established if this effect would be produced by very low doses of ferulic acid, such as the sub-effective dose employed in the present study. However, given the potential role of inflammatory factors in depression, it might be expected that antagonists of this system would have beneficial effects with respect to mood, or could serve as an adjunct to more typical antidepressant medications. Indeed, it was reported that cyclooxygenase-2 inhibitors may have positive effects in reducing depression in preclinical trials, and when coupled to fluoxetine the production of proinflammatory cytokines was reduced and the antidepressant effects observed were more pronounced comparatively to the elicitation with fluoxetine alone (Anisman, 2011). Besides, SSRIs such as fluoxetine and paroxetine also have anti-inflammatory effects (Maes et al., 2011).

The exact mechanism by which ferulic acid modulates 5-HT receptors activity in order to produce an antidepressant-like effect is not clear. It should be taken into account that ferulic acid has been reported to act as a putative competitive antagonist of NMDA receptors (Yu et al., 2006). The involvement of glutamate in the pathophysiology of depression has been suggested in several studies (for review, see Sanacora et al., 2008). Increased levels of glutamate in the frontal cortex in postmortem samples (Hashimoto et al., 2007) and in the plasma of patients with depression (Mauri et al., 1998) have been reported. Additionally, NMDA receptor antagonists possess antidepressant properties and antidepressants have been reported to reduce the binding, expression, and function of NMDA receptors (Sanacora et al., 2008; Skolnick, 1999). Noteworthy, NMDA receptor antagonists have been reported to increase serotonin release in the

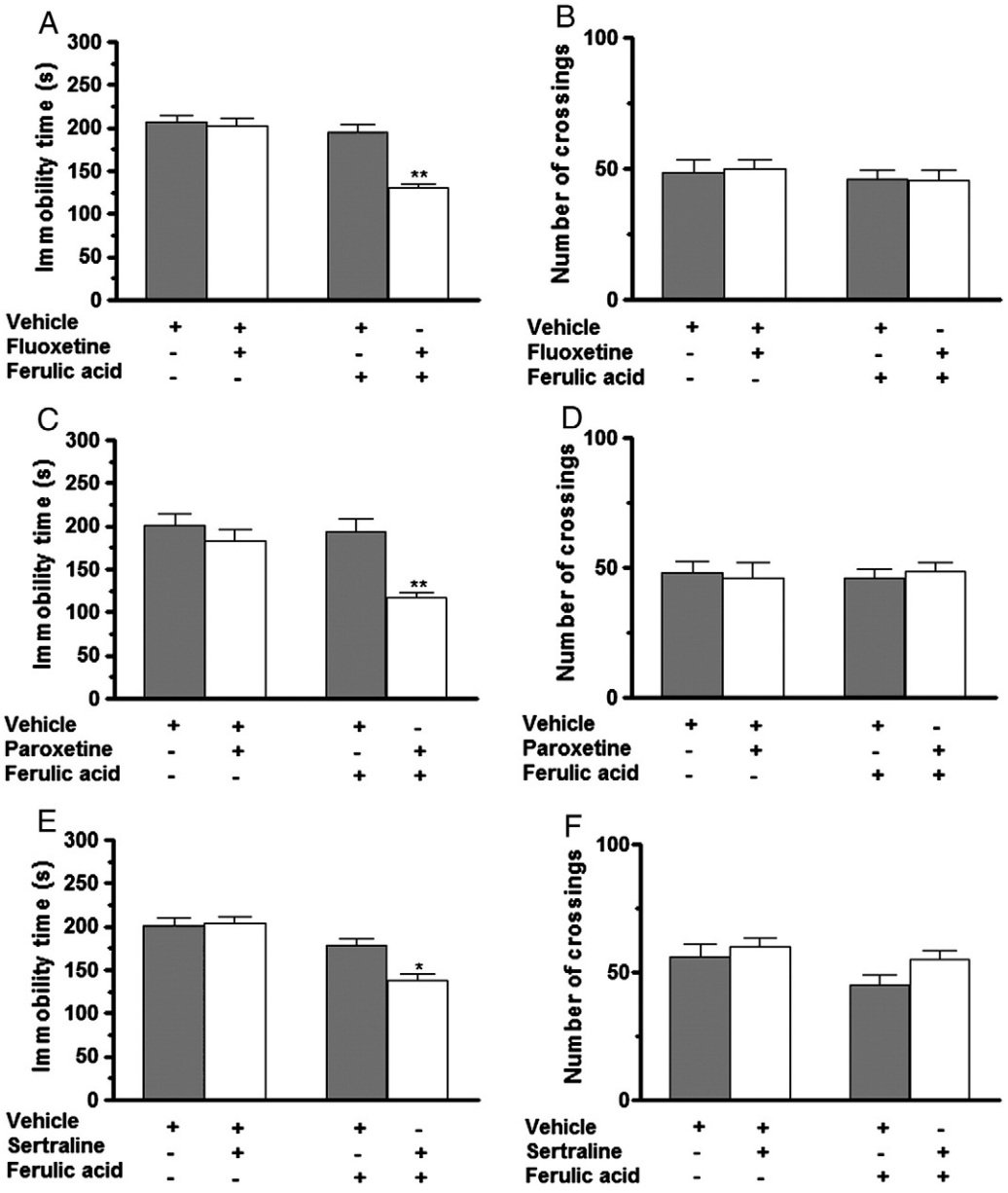

Fig. 3. Effect of the administration of a sub-effective dose of ferulic acid (0.001 mg/kg, p.o.) in association with sub-effective doses of fluoxetine (5 mg/kg, p.o.), paroxetine (0.1 mg/kg, p.o) or sertraline (1 mg/kg, p.o.) in the TST (panels A, C and E, respectively) and in the open-field test (panels B, D and F, respectively). Values are expressed as mean ± S.E.M. (n = 6–8). *P<0.05 and **P<0.01 as compared with the vehicle-treated group. A) Fluoxetine pretreatment [$F(1,24) = 18.05$, P<0.01]; ferulic acid treatment [$F(1,24) = 26.29$, P<0.01]; fluoxetine × ferulic acid interaction [$F(1,24) = 13.65$, P<0.01]. B) Fluoxetine pretreatment [$F(1,20) = 0.02$, $P = 0.89$]; ferulic acid treatment [$F(1,20) = 0.69$, $P = 0.41$]; fluoxetine × ferulic acid interaction [$F(1,20) = 0.03$, $P = 0.86$]. C) Paroxetine pretreatment [$F(1,28) = 15.10$, P<0.01]; ferulic acid treatment [$F(1,28) = 8.91$, P<0.01]; paroxetine × ferulic acid interaction [$F(1,28) = 5.70$, P<0.05]. D) Paroxetine pretreatment [$F(1,20) = 0.01$, $P = 0.93$]; ferulic acid treatment [$F(1,20) = 0.01$, $P = 0.93$]; paroxetine × ferulic acid interaction [$F(1,20) = 0.28$, $P = 0.60$]. E) Sertraline pretreatment [$F(1,28) = 5.08$, P<0.05]; ferulic acid treatment [$F(1,28) = 29.36$, P<0.01]; sertraline × ferulic acid interaction [$F(1,28) = 6.53$, P<0.05]. F) Sertraline pretreatment [$F(1,20) = 2.97$, $P = 1.00$]; ferulic acid treatment [$F(1,20) = 3.56$, $P = 0.07$]; sertraline × ferulic acid interaction [$F(1,20) = 0.54$, $P = 0.47$].

brain (Callado et al., 2000; Gaikwad et al., 2005; Tso et al., 2004). Therefore, one possibility to account for this antidepressant-like effect of ferulic acid might be its action as a NMDA receptor antagonist, thus affecting serotonin neurotransmission. In line with this, the administration of antidepressants that increases the levels of serotonin at the synapse modulates mood *via* different signalling transduction pathways (D'Sa and Duman, 2002; Hashimoto, 2010). Therefore, the possibility that ferulic acid exerts its action in the TST through an interaction with NMDA receptors, thus, affecting serotonergic neurotransmission is feasible and deserves further studies.

In conclusion, in relation to the mechanism, our study provides evidence for the involvement of serotonergic system in the antidepressant-like effect of ferulic acid in the TST. The effect of ferulic acid is prevented by 5-HT_{1A} and 5-HT_2 receptor, which are both serotonergic antagonists, and is enhanced by antidepressants that act as SSRIs. Further research will be necessary to clarify in more details the exact mechanism by which ferulic acid induces antidepressant-like effect.

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