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Involvement of PKA, CaMKII, PKC, MAPK/ERK and PI3K in the acute antidepressant-like effect of ferulic acid in the tail suspension test

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ABSTRACT

Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is a phytochemical compound naturally present in several plants and foods that is approved as an antioxidant additive and food preservative. It exerts a beneficial action in chronic mild stress-induced depressive-like behavior and produces an acute antidepressant-like effect in the tail suspension test (TST) through the activation of the serotonergic system. This study was aimed at investigating the possible involvement of signaling pathways in the antidepressant-like effect of acute and oral administration of FA, in the TST in mice. The anti-immobility effect of orally administered FA (0.01 mg/kg, p.o.) was prevented by pretreatment of mice with H-89 (1 μg/site, i.c.v., an inhibitor of PKA), KN-62 (1 μg/site, i.c.v., an inhibitor of CaMKII), GF109203X (5 ng/site, i.c.v., an inhibitor of PKC), U0126 (5 μg/site, i.c.v., an inhibitor of MAPK/ERK) or LY294002 (10 nmol/site, i.c.v., an inhibitor of PI3K), all involved with neurotrophic signaling pathways. The results demonstrated that FA exerts antidepressant-like effect in the TST in mice, through the activation of signaling pathways related to neuroplasticity, neurogenesis and cell survival.

1. Introduction

Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid, Fig. 1A) is a phenolic compound present in several plants and in natural extracts of medicinal plants, spices, chocolate and coffee (Graf, 1992; Virgili et al., 2000). In Japan FA has been approved as an antioxidant additive and food preservative (Graf, 1992; JFCRF, 1996). Moreover, FA, as sodium ferulate, has been popularly used for the treatment of cardiovascular and cerebrovascular diseases also approved by the State Drugs Administration of China (Wang and Ou-Yang, 2005).

Interestingly, FA is a phytochemical, which exhibits antioxidant and anti-inflammatory properties that may be used in the therapy for neurodegenerative diseases. In addition, FA produced a potent protection against excitotoxic effects of glutamate monosodium, a result that may indicate that FA is an *N*-methyl-D-aspartate (NMDA) receptor antagonist (Yu et al., 2006). FA has also shown to affect cell cycle, by increasing proliferation of neural stem/progenitor cells *in vitro* and *in vivo*. It has also been reported to ameliorate the stress-induced depression-like behavior in mice (Yabe et al., 2010) and exerted antidepressant-like behavior in mice through the involvement of the serotonergic system (Zeni et al., 2012). Previously, Zhang et al. (2011a) showed FA-induced anti-immobility effect in rats in the forced swimming test (FST) and Zhang et al. (2011b) demonstrated that sodium ferulate (sodium salt of FA) also exerts antidepressant-like effect, in mice or rats using TST and FST tests or chronic mild stress (CMS) model, respectively.

Depression treatment with the available medications provides a complete remission just for 50–60% of the patients (Nestler et al., 2002). Additionally, they are hindered by adverse side effects and are slow to produce beneficial effects (Rush et al., 2006). Therefore, it is necessary to continue the search for novel molecules that have a potential antidepressant effect. FA has been reported to have many pharmacological effects such as, antioxidant, neuroprotective and anti-inflammatory (Graf, 1992; Zhang et al., 2011b; Murakami et al., 2002). Moreover positive pre-clinical effects have been found in FA in diseases that have a link between neurodegeneration and excitotoxicity (Perluigi et al., 2006). Considering the lack of studies dealing with the signaling pathways implicated in the antidepressant-like effect of FA, this study sought to investigate the hypothesis that its effect in the TST would be mediated through the modulation of protein kinase A (PKA), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) or phosphatidylinositol-3-kinase (PI3K) pathways.

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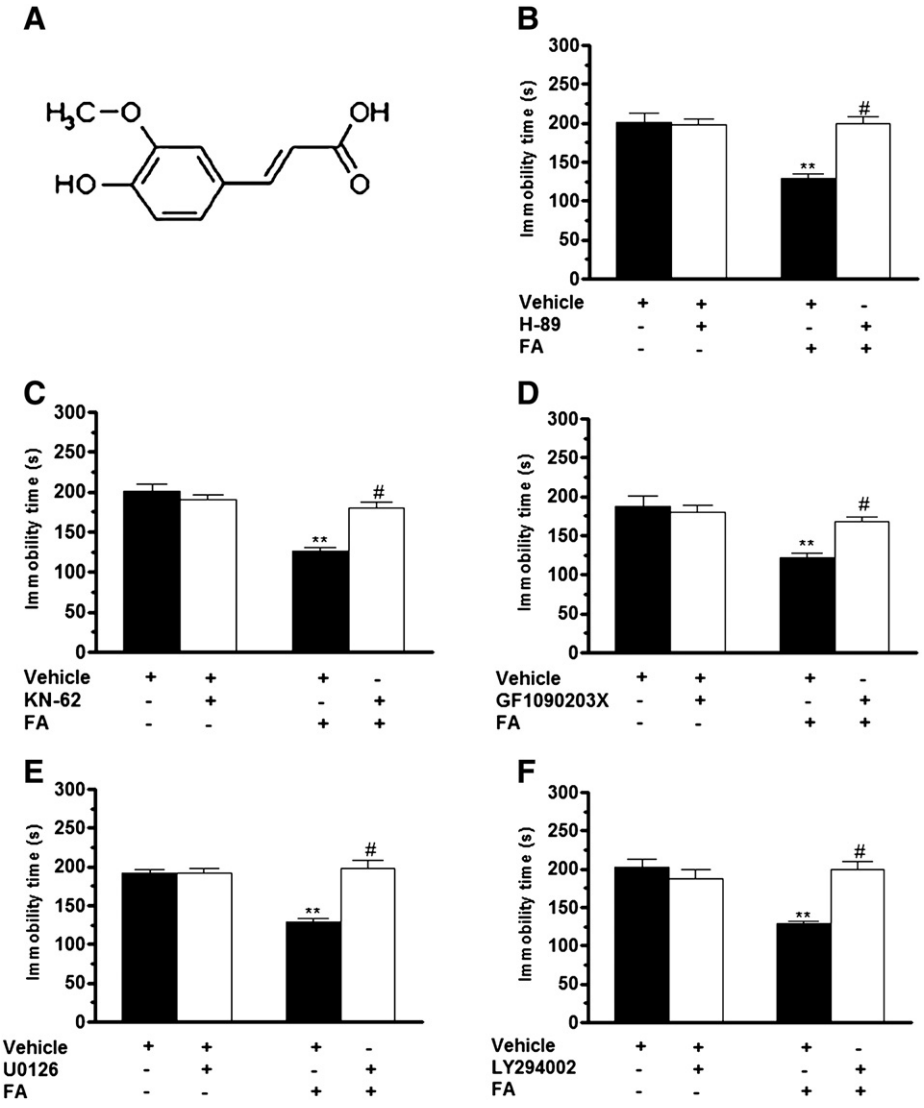

Fig. 1. Evaluation of the involvement of signaling pathways in the antidepressant-like effect of ferulic acid (FA) in the tail suspension test (TST) in mice. Chemical structure of FA (A). Effect of the pretreatment of mice with H-89 (a PKA inhbibitor, 1 μg/site, i.c.v.) (B), KN-62 (a CaMKII inhibitor, 1 μg/site, i.c.v.) (C), GF1090203X (a PKC inhibitor, 5 ng/site, i.c.v.) (D), U0126 (a MAPK/ERK inhibitor, 5 μg/site, i.c.v.) (E) or LY294002 (a PI3K inhibitor, 10 nmol/site, i.c.v.) (F) on the anti-immobility action of FA (0.01 mg/kg, p.o.) in the TST. Values are expressed as mean ± S.E.M. ($n = 6$–7). $^{**}P \leq 0.01$ compared with the vehicle-treated control group; $^{\#}P < 0.01$ compared with the same group pre-treated with vehicle (two-way ANOVA followed by Tukey's HSD test).

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 the approval of the protocol by the Institutional Ethics Committee (CEUA/UFSC-23080.004955/2009-35) 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 (FA), N-[2-(p-bromocinnamylamino) ethyl]-5-isoquinolinesulfonamide (H-89),4-[2-[(5-isoquinolinyl-sulfonyl) methyl-amino]-3-oxo-3-(4-phenyl-1-piperazinyl) propyl] phenyl ester (KN-62), bisindoylmaleimide I (GF109203X), 1,4-diamino-2,3-dicyano-1,4-bis [2-aminophenylthio] butadiene (U0126) and 2-(4-morpholino)-8-phenyl-4H-1-benzopyran-4-one (LY294002—all from Sigma Chemical Company, St. Louis, MO, U.S.A.) were used. Drugs were dissolved in saline except ferulic acid that was diluted in saline with 1% Tween 80. Control animals received appropriate vehicle.

The signaling pathway inhibitors were administered by intracerebroventricular (i.c.v.) route. I.c.v. administration was performed under light ether anesthesia as previously described (Brocardo et al., 2008). A 0.4 mm external diameter hypodermic needle was briefly attached to a cannula, which was linked to a 25 μl Hamilton syringe, inserted perpendicularly through the skull no more than 2 mm into the brain of the mouse. A volume of 5 μl was then administered in the left lateral ventricle. The injection was given over 30 s, and the needle remained in place for another 30 s in order to avoid the reflux of the substances injected. The injection site was 1 mm to the right or left from the mid-point on a line drawn through to the anterior base of the ears.

To investigate the hypothesis that the antidepressant-like effect of FA in the TST is mediated through the activation of PKA, CaMKII, PKC, MAPK/ERK or PI3K, mice were pre-treated by i.c.v. route, with vehicle or H-89 (1 μg/site), KN-62 (1 μg/site), GF109203X (5 ng/site), U0126 (5 μg/site) or LY294002 (10 nmol/site), respectively. Fifteen minutes after pre-treatment vehicle or FA (0.01 mg/kg, p.o.) was orally administered, and within 30 min later the TST was carried out.

The doses of the drugs used were selected on the basis of literature data and from previous results from our laboratory and are reported not to increase locomotor activity (Stemmelin et al., 1999; Vianna et al., 2000; Narita et al., 2002; Sato et al., 2004; Almeida et al., 2006; Ueno et al., 2006).

2.3. 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 (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.

2.4. Open-field test

The ambulatory behavior was assessed in an open-field test as described by Zomkowski et al. (2010). The open field arena used was a wooden box (40×60×50 cm) 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.

2.5. Data analysis

Comparisons between treatment groups and control were performed by one-way or two-way analyses of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) test when appropriate. Data are expressed as mean as S.E.M. and the value of $P<0.05$ was considered to be significant.

3. Results

3.1. Effect of the pretreatment with signaling pathways inhibitors on the FA antidepressant-like effect in the TST

We have previously shown that FA (0.01 mg/kg, p.o.) induced a reduction in the immobility time in the TST in mice, thus showing an antidepressant-like effect of FA (Zeni et al., 2012). In this study, we have evaluated the putative signaling pathways involved in the antidepressant-like effect of FA.

Fig. 1B shows that the pretreatment with H-89 (1 μg/site, i.c.v., an inhibitor of PKA), significantly ($P<0.01$) inhibited the decrease in the immobility time caused by FA in the TST. A two-way ANOVA revealed a main effect of pretreatment [F (1,24) = 15.01, $P<0.01$], treatment [F (1,24) = 17.29, $P<0.01$] and of treatment × pretreatment interaction [F (1,24) = 18.27, $P<0.01$]. Fig. 1C shows the effect of pretreatment with KN-62 (1 μg/site, i.c.v., an inhibitor of CaMKII) on the reduction of immobility time elicited by FA. A two-way ANOVA revealed significant differences of pretreatment [F (1,24) = 9.86, $P<0.01$], treatment [F (1,24) = 36.65, $P<0.01$], and of treatment × pretreatment interaction [F (1,24) = 21.23, $P<0.01$].

The results depicted in Fig. 1D shows the influence of pretreatment GF109203X (5 ng/site, i.c.v., an inhibitor of PKC) on the reduced anti-immobility effect of FA in the TST. A two-way ANOVA showed a significant effect of pretreatment [F (1,20) = 4.57, $P<0.01$], treatment [F (1,20) = 19.42, $P<0.01$], and of treatment × pretreatment interaction [F (1,20) = 8.81, $P<0.01$]. Fig. 1E shows the effect of pretreatment with U0126 (5 μg/site, i.c.v., an inhibitor of MAPK/ERK specifically, MEK1/2) on the reduction in immobility time elicited by FA in the TST. A two-way ANOVA showed a significant effect of pretreatment [F (1,20) = 25.44, $P<0.01$], treatment [F (1,20) = 16.16, $P<0.01$, and of treatment × pretreatment interaction [F (1,20) = 25.20, $P<0.01$]. Fig. 1F shows the effect of pretreatment with LY294002 (10 nmol/site, i.c.v., an inhibitor of PI3K) in the anti-immobility effect exerted by FA in the TST. A two-way ANOVA showed a significant effect of pretreatment [F (1,24) = 8.36, $P<0.01$], treatment [F (1,24) = 10.06, $P<0.01$], and of treatment × pretreatment interaction [F (1,24) = 19.17, $P<0.01$].

3.2. Effects of FA and inhibitors of signaling pathways on the locomotor activity in the open-field test

The results illustrated in Table 1 show the analysis of the locomotor activity observed in the open-field test after i.c.v. administration of H-89 (1 μg/site), KN-62 (1 μg/site), GF109203X (5 ng/site), U0126 (5 μg/site) or LY294002 (10 nmol/site) alone or in combination with FA. This administration of inhibitors alone or in combination with FA did not affect the ambulation in the open-field test. A two-way ANOVA did not reveal significant differences for the pretreatment, treatment and interaction (data not shown).

4. Discussion

The research and development of more effective and faster response to antidepressant therapies is necessary since antidepressants remain inadequate for several individuals and a delay of several weeks in order to achieve its clinical efficacy are the main points in quitting the treatments by patients.

FA has low toxicity and the acute oral DL_{50} in male F344 rats was 2.4 g/kg as determined by Tada et al. (1999). Chang et al. (1993) have previously reported that free FA was recovered in several organs, including brain, at approximately 30 min after oral administration of FA in rats. Such observations were recently confirmed by Zhang et al. (2011a), showing that FA reached the hippocampus 30 min after oral administration in rats.

FA has been previously shown to exert an antidepressant-like effect, in CMS-induced depressive-like behavior in mice (Yabe et al.,

Table 1
Effect of ferulic acid and signaling pathways inhibitors on the number of crossings in the open-field test in mice.

Experimental groups	Number of crossings
Vehicle	80.5 ± 3.9
Ferulic acid	76.2 ± 3.6
H-89	71.3 ± 3.3
Ferulic acid × H-89	74.7 ± 3.1
KN-62	70.2 ± 3.8
Ferulic acid × KN-62	71.0 ± 3.4
GF1090203X	78.0 ± 7.9
Ferulic acid × GF1090203X	77.0 ± 6.8
U0126	76.7 ± 2.7
Ferulic acid × U0126	75.8 ± 2.7
LY294002	76.7 ± 2.8
Ferulic acid × LY294002	72.8 ± 2.4

Effect of the pretreatment of mice with H-89 (1 μg/site), KN-62 1 μg/site), GF1090203X (5 ng/site), U0126 (5 μg/site) or LY294002 (10 nmol/site) followed by ferulic acid (0.01 mg/kg, p.o.) or vehicle on the number of crossings in the open-field test. Values are expressed as mean ± S.E.M. (n = 6).

2010), in FST in rats and TST in mice through the involvement of serotonergic system (Zhang et al., 2011a; Zeni et al., 2012). Zhang et al. (2011b) also observed the antidepressant-like effect with sodium ferulate in mice and rats. However, the role of signaling pathways in anti-immobility effect of FA has not yet been investigated. In the present study, the involvement of signaling cascades implicated in the pathophysiology of depressive disorders, namely PKA, CaMKII, PKC, MAPK/ERK and PI3K, in the antidepressant-like effect of FA in the TST in mice was investigated.

A wide variety of standard antidepressant treatments (e.g. noradrenaline-reuptake inhibitors, selective serotonin-reuptake inhibitors and electroconvulsive seizures) increase the cAMP response element binding protein (CREB) activity (Nibuya et al., 1996; Song et al., 1997). Furthermore, accumulating evidence suggests that roles for CREB-regulated expression of neural growth factors, as for instance, the increased expression of brain-derived neurotrophic factor (BDNF) in humans treated with antidepressants (Hashimoto, 2010). Accordingly, Okamoto et al. (2003) reported that administration of amitriptyline increased BDNF protein levels and Yu et al. (2011) showed that sodium ferulate also up-regulated the expression of BDNF inducing cell proliferation in the rat hippocampus.

Modulation of diverse protein kinases directly or indirectly converges to the activation of CREB, mainly through PKA, CaMKII and MAPK as well as PI3K and PKC activation (Mathew et al., 2008; Pittenger and Duman, 2008). These studies have suggested that the ability to control a signaling process eventually yields therapeutic approaches to treat mood disorders, perhaps with the decrease on the onset treatment of depression.

In this work the reduction of immobility time in TST elicited by FA was fully abolished by the pretreatment of mice with H-89, a compound which acts as a competitive inhibitor at the ATP binding site in the catalytic subunit of PKA. It has been reported that PKA is involved in several functions in the brain, including synthesis and release of neurotransmitters, gene expression, memory and, cell growth, differentiation and survival (Gould and Manji, 2002). The major mechanism of PKA-mediated function is through the phosphorylation of substrates as CREB that modulates the activation of proteins such as BDNF, implicated in cell survival and neuronal plasticity (D'as and Duman, 2002).

In addition, we showed that the acute antidepressant-like effect of FA was significantly reversed by the pretreatment of mice with KN-62, a selective inhibitor of CaMKII that did not cause an effect in the TST *per se*. This result indicates that the antidepressant-like effect of FA is associated with the activation of CaMKII. Our results are in agreement with the fact that CaMKII may play an important role in the pathophysiology and treatment of many stress-related disorders (Du et al., 2004).

Suggesting an important role in the pathophysiology of depression, it was observed that protein kinase C (PKC) activity is significantly decreased in the prefrontal cortex and hippocampus of teenage suicide victims (Pandey et al., 2004). Our data demonstrated that antidepressant-like effect of FA was also prevented by the pretreatment with GF109203X, a selective agent that is competitive to the ATP binding site on the catalytic domain of PKC, suggesting that this signaling pathway is involved in antidepressant-like action of FA in the TST.

According to Adayev et al. (2005), it is expected that 5-HT receptors (e.g., 5-HT_1 and 5-HT_2 receptors), which mediate the activation of ERK1/2 could play an important role in proliferation, differentiation and protection of brain cells. The present study demonstrated the involvement of the MAPK/ERK pathway in the acute antidepressant-like effect of FA in the TST. The results showed that the pretreatment of mice with a selective extracellular permeable inhibitor of MAPK/ERK, U0126, at a dose that did not produce any effect in the TST, significantly inhibited the anti-immobility effect of FA. This result may indicate that the antidepressant-like effect of FA is possibly due to the activation of the MAPK/ERK pathway. In addition, U0126 has been shown to inhibit ERK-inducing depressive-like behavior (Qi et al., 2009) and also has blocked the antidepressant effects of BDNF (Shirayama et al., 2002), suggesting that this signaling pathway plays a role in the therapeutic action of antidepressants.

PI3K/Akt signaling has also been shown to be implicated in the mechanism of action of antidepressant drugs (Beaulieu et al., 2009). Previous observations have suggested a close association between hippocampal neurogenesis and the pathology of depression, since hippocampal neurogenesis seems to be required for the behavioral recovery effects of antidepressant treatments (Czeh et al., 2001; Santarelli et al., 2003).

Not surprisingly, when we used LY294002 (an inhibitor of PI3K pathway), it prevented the reduction of immobility time exerted by FA. Accordingly, GSK-3β phosphorylation, a target for Akt activity, is reduced by the PI3K inhibitor (Shapira et al., 2007), and treatment with selective GSK-3β inhibitors produced antidepressant-like effect in the FST in mice (Gould et al., 2004; Rosa et al., 2008).

The reversal of the antidepressant-like effect of FA in the TST observed here in the presence of signaling pathway inhibitors is not due to any alteration in the locomotor activity, since the administration of H-89, KN-62, GF109203X, U0126 and LY294002 alone or in combination with FA did not significantly alter the locomotor activity of mice.

Long-term administration of sodium ferulate was capable of preventing amyloid β-induced neurotoxicity through activation and up-regulation of ERK and Akt in the rats' hippocampus (Jin et al., 2005). In the aged rats' hippocampus, sodium ferulate was able to exert neuroprotection through suppression of IL-1β and IL-1β-induced JNK signaling and also via up-regulation of ERK and Akt survival pathways (Jin et al., 2008). These studies point towards a close correlation between neuroprotective and antidepressants-like actions of FA.

The influence of FA exerts on the serotonergic neurotransmission was highlighted in a recent publication of Zhang et al. (2011a) who demonstrated that FA exerted antidepressant-like effect and significantly increased 5-HT in hippocampus, confirming simultaneously antidepressant and prokinectic effects of FA in the FST in rats. Furthermore we have recently shown that pretreatment with WAY100635 or ketanserin was able to reverse the antidepressant-like effect of FA in the TST in mice. Moreover, a synergistic antidepressant-like effect of FA with selective serotonin reuptake inhibitor (SSRI) antidepressants was shown (Zeni et al., 2012). Furthermore, Yu et al. (2006) suggested that FA is a novel competitive antagonist of NMDA receptors, and antagonists of these receptors have been reported to increase serotonin release in the brain (Callado et al., 2000; Tso et al., 2004; Gaikwad et al., 2005). Accordingly, the administration of antidepressants that increases levels of serotonin at the synapse activates CREB by triggering different signaling transduction pathways, i.e., PKA, MAPK and CaMKII pathways (D'as and Duman, 2002). In fact, oral administration of FA was capable to increase CREB phosphorylation and BDNF mRNA expression in mice (Yabe et al., 2010 — Fig. 2).

In conclusion, our study provides evidence of the involvement of known signaling pathways in the acute antidepressant-like effect of FA in the TST. Moreover, the effect of FA is prevented by selective inhibitors of several signaling cascades, involving modulation of synaptic plasticity, neurogenesis and cell survival (D'as and Duman, 2002; Hashimoto, 2010) that might culminate in the antidepressant-like effect of FA. Diverse findings support the hypothesis that neuronal loss as well as oxidative stress and inflammation contribute significantly to the pathophysiology of mood disorders (Maes et al., 2011). Therefore, the results showed here suggest that FA could be further investigated as a potential antidepressant or an additive polypharmacological therapeutic strategy.

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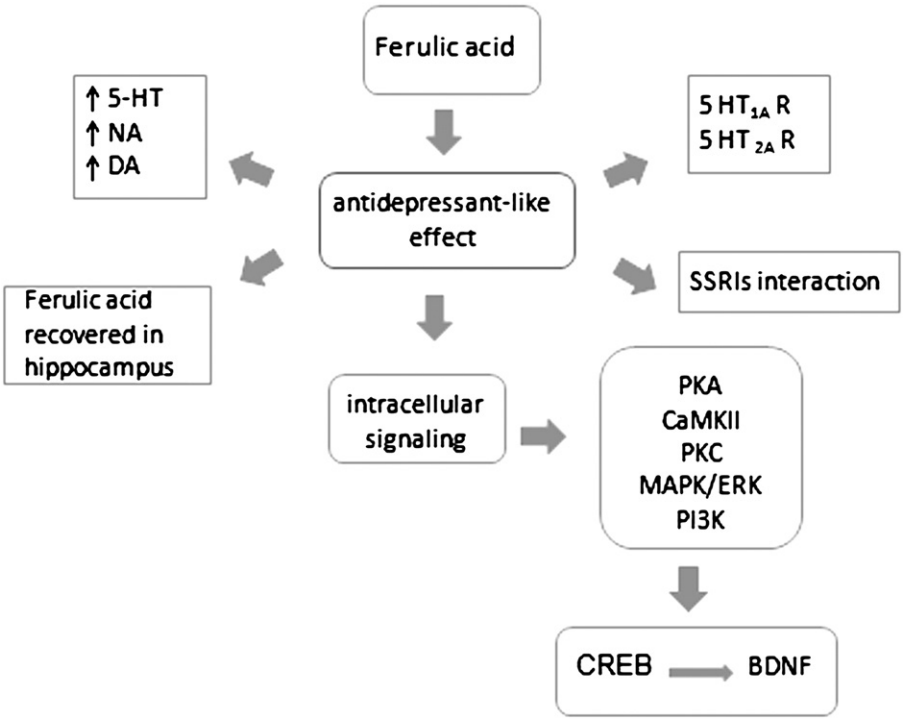

Fig. 2. Schematic showing of intracellular pathways underlying the antidepressant-like effect of ferulic acid. Administration of ferulic acid increases levels of 5-hydroxytryptamina (5-HT), norepinephrine (NE) and dopamine (DA) and activates 5-HT_{1A} and 5-HT_{2A} receptors (Zhang et al., 2011a; Zeni et al., 2012). Administration of ferulic acid can also interact with SSRI antidepressants evidencing an activation of the serotonergic system elicited by ferulic acid (Zeni et al., 2012). In addition, the ferulic acid was capable to increase cAMP response element binding protein (CREB) phosphorylation and brain-derived neurotrophic factor (BDNF) mRNA expression (Yabe et al., 2010) and was recovered into mice hippocampus (Zhang et al., 2011a). In the present study the antidepressant-like effect of ferulic acid was prevented by pretreatment of mice with inhibitors of PKA, CaMKII, PKC, MAPK/ERK or PI3K, demonstrating that these signaling pathways are involved in the mechanism of antidepressant-like effect of ferulic acid. Therefore, these pathways ultimately activate CREB converging in modulation of proteins such as BDNF (Hashimoto, 2010), that activate signaling pathways.

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