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Antidepressant drugs for beta amyloid-induced depression: A new standpoint?

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ABSTRACT

Mounting evidence suggests that depression represents a risk factor and an early manifestation of Alzheimer's disease (AD). Neuropsychiatric symptoms may derive from neurobiological changes in specific brain areas and may be considered prodromal of dementia. We have previously reported the depressive-like profile in rats receiving a single intracerebroventricular injection of soluble amyloid beta protein (ßA). Here, we verified the effect of different classes of antidepressants on the ßA-induced depressive behavior and on cortical monoamine levels. To these purposes, the forced swimming test was performed and cortical levels of serotonin (5-HT) and noradrenaline (NA) were quantified by high performance liquid chromatography (HPLC). We found that acute fluoxetine (20 mg/kg, s.c.), reboxetine (10 mg/kg, s.c.), and ketamine (15 mg/kg, i.p.) significantly reduced the immobility in ßA-treated rats compared to controls. Fluoxetine and reboxetine reversed 5-HT reduction, while βA-induced NA increase was further enhanced by all treatments. Treatments with fluoxetine, reboxetine and ketamine were able to revert soluble ßA-induced decrease of cortical BDNF levels, while only fluoxetine and ketamine, but not reboxetine, had the same effects on cortical NGF expression. Moreover, plasma soluble ßA-levels were lowered by fluoxetine, but not reboxetine and ketamine, treatments.

Our data suggest that different classes of antidepressants yield a short-acting effect on rat soluble ßA-induced depressive profile. Thus, we hypothesize a novel common mechanism of action of these drugs also based upon a "ßA lowering" effect. Although further investigations are still needed, our study might open a new scenario for unravelling the molecular antidepressant mechanisms of these drugs.

1. Introduction

Several epidemiological studies have confirmed the prevalence and the persistence of neuropsychiatric symptoms in Alzheimer's disease (AD) patients (Cherbuin et al., 2015; Mourao et al., 2016), represented by a heterogeneous group of non-cognitive symptoms and behaviors, such as delusions, depression and irritability. It has been estimated that the prevalence of these symptoms oscillates between 60% to 90% of cases, depending on either the selected population or the methodology of the studies (Cummings et al., 2016).

Among these symptoms, delusions and depression were the most persistent (Steinberg et al., 2004). These clinical manifestations can be the very first symptoms of a neurodegenerative process, thus being considered as prodromal of dementia (Andersen et al., 2005). It has been shown that a number of patients may develop depressive symptomatology in an early stage of neurological disorders, occurring before the appearance of cognitive impairments. Similarly, it has been reported that depressed individuals are nearly twice as likely to develop dementia, often in the form of AD, compared with non-depressed individuals (Jorm, 2001). Growing evidence has in most cases strengthened the notion that depression may represent a risk factor for AD development, even when it occurs earlier in life (Green et al., 2003; Sweet et al., 2004). Recently, it has been further confirmed that neurodegenerative disease may manifest as depressive traits in the early stages (Baquero and Martin, 2015).

As regard the association between depressive symptomatology and

Abbreviations: AD, Alzheimer's Disease; βA, amyloid beta protein; 5-HT, serotonin; NA, noradrenaline; HPLC, high performance liquid chromatography; DA, dopamine; Glu, glutamate; i.c.v., intracerebroventricular; FST, forced swimming test; SSRI, selective 5-HT reuptake inhibitors; NRI, NA reuptake inhibitors; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; ANOVA, analysis of variance; BDNF, brain derived neurotrophic factor; NGF, nerve growth factor; CSF, cerebrospinal fluid; APP, Amyloid Precursor Protein; IL, interleukin

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cognitive impairments, similar findings in terms of prevalence rate have been found across different cultures, as well as in developing countries (Shah et al., 2005) and industrialized societies (Pinto et al., 2011), thus suggesting that the underlying mechanisms of neuropsychiatric symptoms could be considered as neurobiologically determined. Indeed, neuropsychiatric symptomatology should not be regarded as an emotional reaction but as an emerging neurobiology (Cummings et al., 2016). Thus, neuropathological hallmarks found in cognitive impairment might also be present in depressive states. Neuropsychiatric behaviors result from anatomopathological and biochemical changes within several brain regions. This is supported by neuropathological evidences, associated with underlying neurotransmitter system imbalances including noradrenaline (NA), dopamine (DA), acetylcholine, serotonin (5-HT), glutamate (Glu), gamma-aminobutyric acid and nitric oxide (Panza et al., 2010; Sweet et al., 2004; Wegener et al., 2004). Nevertheless, neurotransmission and other biological pathways and mechanisms involved in the association of cognitive deficits and depression remain not clearly understood. More recently, depressive signs have been potentially linked, in part, to the presence of soluble beta amyloid (ßA) in the brain. ßA peptides are physiologically produced from the ßA protein precursor through ß and gamma secretase cleavage (Zetterberg et al., 2010). They possess different brain area-selective neuromodulatory actions (Morgese et al., 2014; Morgese et al., 2017; Mura et al., 2010; Trabace et al., 2007).

In the past, it has been widely accepted that progressive brain deposition of ßA proteins in neuritic plaques was a prominent feature of AD. Indeed, therapeutic strategies have been targeted against ßA depositions (see (Awasthi et al., 2016) for review) or acetylcholinesterase inhibition (Grutzendler and Morris, 2001; Trabace et al., 2000).

Recent studies suggest that early memory impairments might be explained by the presence of soluble forms of ßA peptides, rather than aggregated forms. Interestingly, several lines of evidence suggest that elevated levels of cerebral soluble ßA peptides, especially $ßA_{1–42}$, may also be associated with a high incidence of depression.

We have previously reported a depressive-like profile induced by a single intracerebroventricular (i.c.v.) injection of soluble ßA peptide in rats. Soluble ßA treated-rats exposed to the forced swimming test (FST) showed an increase in the immobility frequency, which has been shown to mimic a typical state of “behavioral despair”. This behavioral alteration was associated to significant reduction in cortical 5-HT and neurotrophin levels, suggesting that soluble ßA was able to induce a depressive-like state (Colaianna et al., 2010). In good agreement with our results, data from preclinical research have associated various risk factors for depression with increased soluble ßA production in the brain (Catania et al., 2009). Furthermore, plasma ßA disturbances in humans have been reported, although with conflicting results (Pomara et al., 2006; Qiu et al., 2007). Very recently, Yasuno and coworkers confirmed the presence of cortical amyloid burden in cognitively intact patients with depressive episodes, which were more likely to have underlying AD neuropathology (Yasuno et al., 2016). Thus, depressive symptoms may increase the predictive power for the identification of future AD cases.

Our aim was to investigate the effect of different classes of antidepressants on the depressive profile induced by exogenous soluble ßA in the brain, by using the FST paradigm. This test is useful to assess the capacity of antidepressant agents to switch passive behavior in active forms of coping (Cryan et al., 2002a).

To this end, we used acute fluoxetine (a selective 5-HT reuptake inhibitor, SSRI) and reboxetine (a NA reuptake inhibitor, NRI) to evaluate whether these drugs could alleviate or reverse soluble ßA-induced behavioral despair. Moreover, we also investigated the effects of ketamine [a *N*-methyl-D-aspartate receptor (NMDA) antagonist] administration on this animal model, as several clinical data reported rapid and powerful antidepressant effects of a single administration of a sub-psychomimetic dose of ketamine (Autry et al., 2011; Engin et al., 2009). Finally, as the alteration of serotonergic and noradrenergic systems may be primarily involved in the development of depressive symptomatology (Ressler and Nemeroff, 2000), we investigated whether serotonergic and noradrenergic neurotransmissions were affected by antidepressant treatments in the prefrontal cortex (PFC) of soluble ßA-treated rats.

2. Material and methods

2.1. Animals

All experiments were conducted on male Wistar rats (250–275 g, Harlan, S. Pietro al Natisone, Udine, Italy). Rats were group housed (three to four per cage) and maintained under controlled conditions of temperature (22 ± 1 °C), humidity (55 ± 5%) and lighting (12 h light/dark cycle; lights on from 7:00 AM to 7:00 PM). Food and water were available ad libitum. Procedures involving animals and their care were conducted in conformity with the institutional guidelines of the Italian Ministry of Health (D.L. 26/2014), the Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2004), the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. All procedures involving animals were conducted in accordance to ARRIVE guidelines. Animal welfare was daily monitored through the entire period of experimental procedures. No signs of distress were evidenced, anyway all efforts were made to minimize the number of animals used and their suffering.

2.2. Surgery and soluble ßA infusion

The soluble ßA peptide was purchased from Tocris (Bristol, UK) and was dissolved in sterile double-distilled water (vehicle) at a concentration of 4 μM. All solutions were freshly prepared. Surgery procedures were performed as previously described (Colaianna et al., 2010).

Briefly, rats were anesthetized and secured in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA). The skin was cut to expose the skull and a hole was drilled to insert the infusion needle (30-gauge stainless steel tubing; Cooper's Needles, Birmingham, UK). Coordinates for i.c.v. infusions were based on the atlas of Paxinos and Watson (1998): AP = − 0.5, ML = + 1.2 and DV = − 3.2 from bregma, with the incisor bar set at − 3.3 mm. Soluble ßA (5 μl) was delivered through a 25 μl Hamilton microsyringe at 2 μl/min infusion rate. Control rats were infused with vehicle only, because reverse soluble $ßA_{42–1}$, used in preliminary experiments, had no effect on the measured parameters and was indistinguishable from vehicle alone (unpublished observations). All experimental procedures were performed 7 days after i.c.v. administration (sham-operated or soluble ßA-treated groups).

2.3. Pharmacological treatments and experimental design

Fluoxetine hydrochloride and reboxetine mesylate were purchased from Sigma-Aldrich (Milan, Italy), dissolved in dH_2O (vehicle) and given subcutaneously (s.c.) 24, 5 and 1 h before the behavioral performance in the FST (test phase) at a dose of 20 mg/kg and 10 mg/kg, respectively. Ketamine hydrochloride was purchased from Sigma-Aldrich (Milan, Italy), dissolved in saline (vehicle) and administered intraperitoneally (i.p.) at a dose of 15 mg/kg. Animals received treatment with ketamine hydrochloride 1 h before FST (test phase).

Doses of fluoxetine and reboxetine used in this work were chosen according to (Cryan and Lucki, 2000; Cryan et al., 2002b, 2005b). The protocol we used was chosen as it results in prolonged brain penetration of the compounds, mimicking a state of subchronic drug exposure and, consequently, a continuously elevated drug concentration in the rat (Slattery and Cryan, 2012). Doses of ketamine used in the present work were chosen based on a previous study reporting that acute ketamine

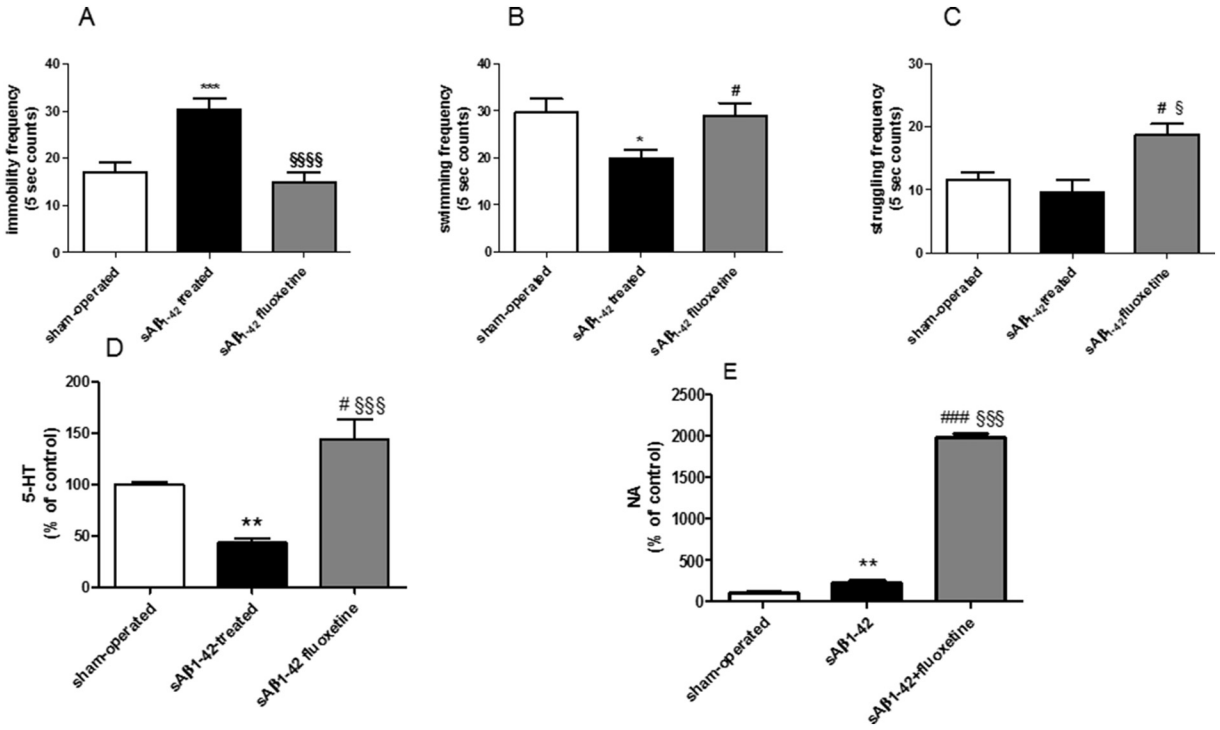

Fig. 1. Effect of fluoxetine on FST and cortical monoamine quantifications.
Effect of fluoxetine on immobility (A), swimming (B) and struggling (C) frequencies in the FST (n = 8–10 per group) and on cortical 5-HT (D) and NA (E) (n = 4–6 per group) in rats treated with vehicle (water icv, sham-operated), soluble beta amyloid (4 μM icv, βA-treated), and fluoxetine plus soluble beta amyloid (24, 5 and 1 h before the test phase at a dose of 20 mg/kg s.c., fluoxetine + βA-treated). *, **, *** $P < 0.05$, 0.01, 0.001, respectively, βA-treated versus sham-operated. #, ###, $P < 0.05$, 0.001, respectively, fluoxetine + βA-treated versus sham-operated. §, §§§, §§§§, $P < 0.05$, 0.001, 0.0001, respectively, fluoxetine + βA-treated versus βA-treated.

treatment in rats (15 mg/kg) induced a decrease in the immobility time in the FST, while the spontaneous locomotor activity, assessed by the open-field test, was not affected (Garcia et al., 2008).

2.4. Forced swimming test

As previously described by Cryan et al. (Cryan et al., 2005a), the apparatus consisted of two clear Perspex cylinders (70 cm height × 23 cm diameter). During the preconditioning period, animals were placed individually in the cylinders containing 30 cm of water maintained at a constant temperature of 25 °C and forced to swim for 15 min. Then, rats were removed from the apparatus, towel-dried in a clean plexiglas cage and then returned to their home cage. The cylinders were cleaned and the water was changed before each trial. Twenty-four hours later, each rat was tested for 5 min under identical conditions. This session (test phase) was recorded using a video camera placed above the cylinder for subsequent analysis. An observer blind to the treatment groups scored the frequency that rats spent performing the following behaviors: struggling (time spent in tentative of escaping), swimming (time spent moving around the cylinder) and immobility (time spent remaining afloat making only the necessary movements to keep its head above the water). Behavioral counts were taken at 5 s intervals during the 5 min test.

2.5. Post-mortem tissue analyses

Brains were placed dorsal side up in an ice chilled rat brain matrix (World Precision Instruments, Inc. FL, USA) PFC was carefully dissected out, weighed, freshly frozen in liquid nitrogen and stored at − 80 °C until neurotransmitter quantification was carried out. At the time of analysis, samples were homogenized in 10 volumes (w/V) of 0.1 N perchloric acid. The homogenates were stored on ice for 30 min and then centrifuged at 10.000 × g for 10 min at 4 °C, as previously described (Zotti et al., 2013). The supernatants were then filtered and diluted before HPLC analysis.

2.6. Chromatographic analysis

NA and 5-HT concentrations were determined by HPLC coupled with an electrochemical detector (Ultimate 3000RS -ECD, Dionex, ThermoScientific, UK), as previously described (Morgese et al., 2017).

2.7. Enzyme-Linked Immunosorbent Assay (ELISA)

Levels of plasma soluble ßA and of cortical NGF were quantified by using Cloud-Clone Corp. ELISA kits (Cloud-Clone Corp., Houston, TX, USA), according to manufacturer's instructions. Levels of cortical BDNF were quantified by using BDNF Simple Step ELISA Kit (Abcam, Cambridge, UK), according to manufacturer's instructions. BDNF and NGF data were normalized for tissue protein concentrations.

2.8. Statistical analysis

All statistical analyses were performed using Graph Pad® 6.0 for Windows. Behavioral and neurochemical data were analyzed by a One-way analysis of variance (One-way ANOVA) followed by Bonferroni's or Tukey's multiple comparison test. Differences were considered significant only when P-values were < 0.05.

All experimental procedures were also performed on sham-operated animals treated with antidepressant drugs and no statistical differences with respect to vehicle-treated sham operated animals were found (data not shown).

3. Results and discussion

3.1. Effects of fluoxetine on soluble ßA-induced depressive-like profile

From a behavioral point of view, as shown in Fig. 1A, results

indicated that immobility frequency was significantly increased in soluble ßA-injected animals compared to sham-operated rats (Fig. 1A, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.001$). Fluoxetine treatment (given 24, 5 and 1 h before the test phase at a dose of 20 mg/kg s.c.) induced a significant reduction of immobility in FST compared to rats receiving only soluble ßA, indicating that this drug is effective in producing an antidepressant-like effect in this behavioral test (Fig. 1A, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.0001$). Swimming frequency was decreased in soluble ßA-treated rats compared to controls (Fig. 1B, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.05$), and fluoxetine administration was able to revert this behavioral parameter to control levels (Fig. 1B, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.05$). A significant increase in struggling frequency was also observed in soluble ßA + fluoxetine group compared to soluble ßA-treated and sham-operated rats, while no difference in struggling activity was found between control and ßA-injected animals (Fig. 1C, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.05$). Although a decrease in motor strength or endurance may affect the FST, no apparent motor deficit was noticed during habituation, consisting of 15 min of swimming in the cylinder 24 h before the test session (data not shown). Treatments did not affect the locomotor behavior of animals in the open field test (data not shown).

We found that fluoxetine administration (24, 5 and 1 h before the test phase, 20 mg/kg s.c.) raised cortical content of 5-HT and NA in soluble ßA-injected rats, as shown in Fig. 1D and Fig. 1E, respectively (Fig. 1D, One-way ANOVA followed by Tukey's multiple comparison test, $P < 0.01$ soluble ßA versus sham-operated rats, $P < 0.05$ sham-operated versus soluble ßA + fluoxetine and $P < 0.001$ soluble ßA versus soluble ßA + fluoxetine, respectively; Fig. 1E, One-way ANOVA followed by Tukey's multiple comparison test, $P < 0.01$ soluble ßA versus sham-operated rats and $P < 0.001$ soluble ßA and sham-operated rats versus soluble ßA + fluoxetine).

3.2. Effects of reboxetine on soluble ßA-induced depressive-like profile

Statistical analysis demonstrated a significant increase of the immobility frequency in soluble ßA-treated animals compared to sham-operated rats (Fig.2A, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.001$). As shown in Fig. 2A, reboxetine treatment (given 24, 5 and 1 h before the behavioral performance in the FST (test phase) at a dose of 10 mg/kg s.c.) was able to reduce the soluble ßA-induced immobility to control levels (Fig.2A, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.001$ soluble ßA + reboxetine versus soluble ßA-treated rats). Swimming frequency was reduced in soluble ßA-treated animals and reboxetine treatment partially reverted this effect (Fig. 2B, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.01$ soluble ßA-treated animals compared to sham-operated rats, while ßA + reboxetine versus soluble ßA-treated and sham-operated n.s.). Moreover, a significant increase of struggling frequency was observed in soluble ßA + reboxetine treated animals compared to soluble ßA-treated and sham-operated rats (Fig. 2C, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.001$ and $P < 0.05$, respectively). Treatments did not affect the locomotor behavior of animals in the open field test (data not shown).

Cortical 5-HT content in soluble ßA-treated rats was significantly lower than sham-operated rats (Fig. 2D, One-way ANOVA followed by Tukey's multiple comparison, $P < 0.001$ soluble ßA-treated rats versus sham-operated) and reboxetine normalized such content in soluble ßA-injected rats (Fig. 2D, One-way ANOVA followed by Tukey's multiple comparison, $P < 0.01$ soluble ßA + reboxetine versus soluble ßA-treated rats). We found that soluble ßA injection increased cortical NA levels compared to sham-operated rats (Fig. 2E, One-way ANOVA followed by Tukey's multiple comparison, $P < 0.05$ soluble ßA-treated versus sham-operated rats), and reboxetine treatment further raised such levels (Fig. 2E, One-way ANOVA followed by Tukey's multiple comparison, $P < 0.01$ soluble ßA + reboxetine versus soluble ßA-treated and sham-operated rats).

3.3. Effects of ketamine on soluble ßA-induced depressive-like profile

As shown in Fig. 3A, in the FST, soluble ßA injection significantly increased immobility frequency with respect to control (Fig. 3 A, One-

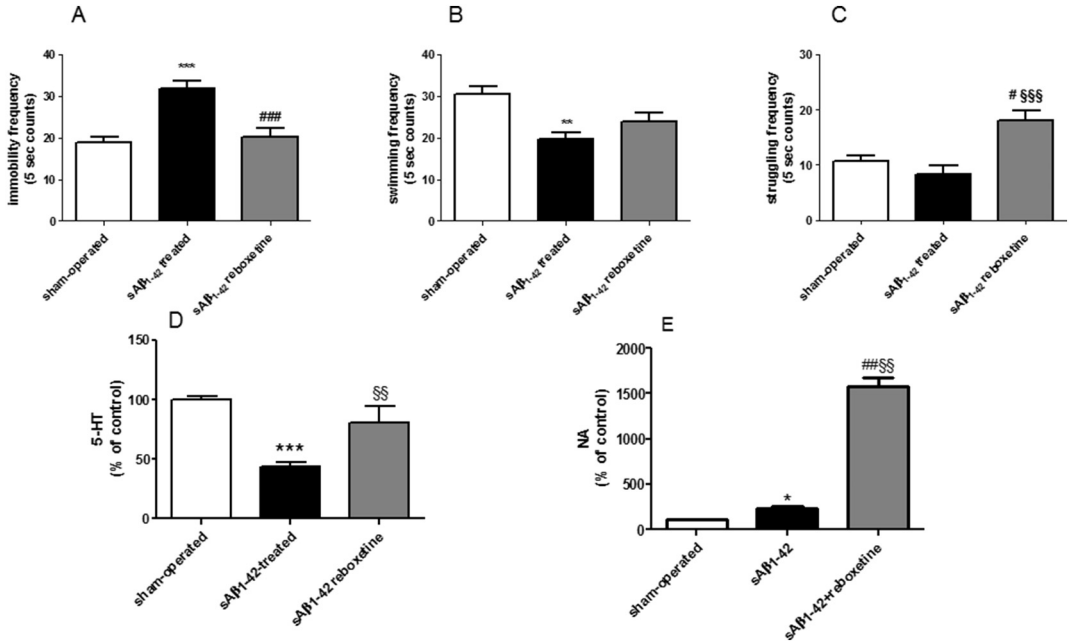

Fig. 2. Effect of reboxetine on FST and cortical monoamine quantifications.
Effect of reboxetine on immobility (A), swimming (B) and struggling (C) frequencies in the FST (n = 8–10 per group) and on cortical 5-HT (D) and NA (E) (n = 4–6 per group) in rats treated with vehicle (water icv, sham-operated), soluble beta amyloid (4 μM icv, βA-treated), and reboxetine plus soluble beta amyloid (24, 5 and 1 h before the test phase at a dose of 20 mg/kg s.c., reboxetine + βA-treated). *, **, *** $P < 0.05, 0.01, 0.001$, respectively, βA-treated versus sham-operated. #, ##, $P < 0.05, 0.01$, respectively, reboxetine + βA-treated versus sham-operated. §§, §§§, $P < 0.01, 0.001$, respectively, reboxetine + βA-treated versus βA-treated.

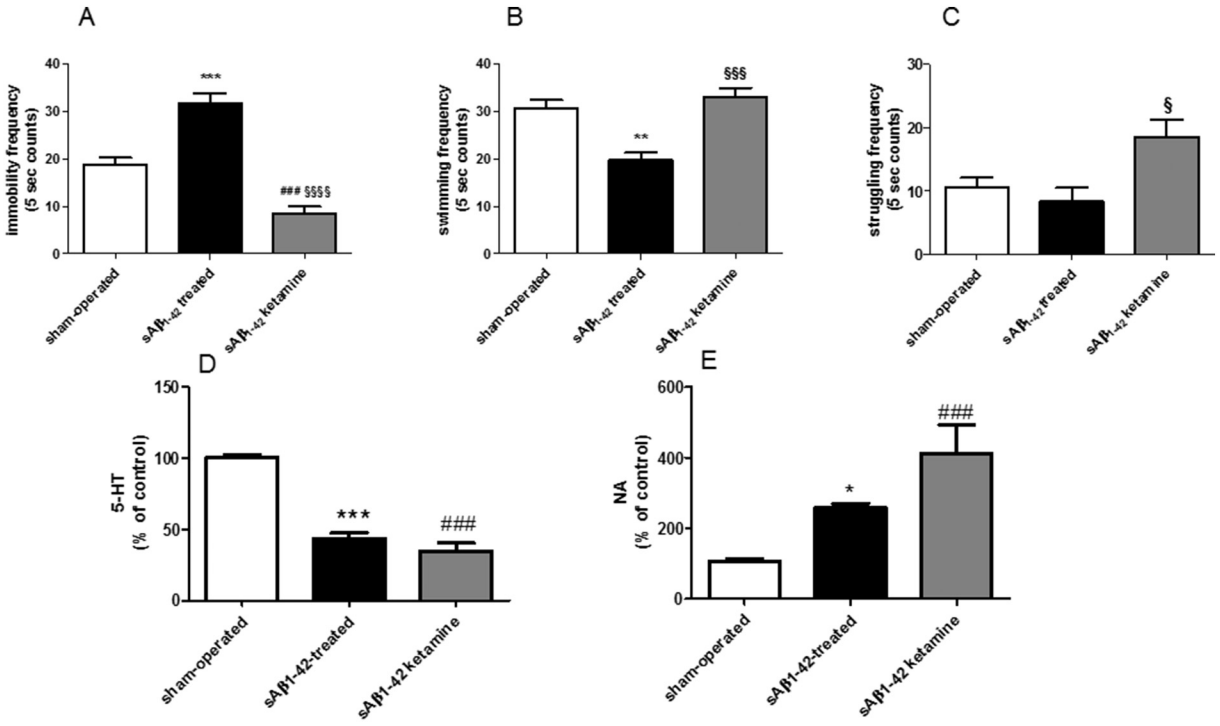

Fig. 3. Effect of ketamine on FST and cortical monoamine quantifications.
Effect of reboxetine on immobility (A), swimming (B) and struggling (C) frequencies in the FST (n = 8–10 per group) and on cortical 5-HT (D) and NA (E) (n = 4–6 per group) in rats treated with vehicle (water icv, sham-operated), soluble beta amyloid (4 μM icv, βA-treated), and ketamine plus soluble beta amyloid (1 h before the test phase at a dose of 15 mg/kg i.p., ketamine + βA-treated). *, **, *** $P < 0.05, 0.01, 0.001$, respectively, βA-treated versus sham-operated. ###, $P < 0.001$, respectively, ketamine + βA-treated versus sham-operated. §, §§§, §§§§, $P < 0.05, 0,001, 0.0001$, respectively, ketamine + βA-treated versus βA-treated.

way ANOVA followed by Bonferroni's post-hoc test, $P < 0.001$) and administration of an acute dose of ketamine (administered 1 h before the test phase at a dose of 15 mg/kg i.p.) significantly reduced immobility frequency compared to soluble ßA and control rats (Fig. 3 A, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.0001$ and $P < 0.001$, respectively). Moreover, ketamine reverted the soluble ßA-induced reduction of swimming frequency (Fig. 3B, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.01$ soluble ßA versus sham-operated rats and $P < 0.001$ soluble ßA + ketamine versus soluble ßA-treated rats). Statistical analysis also revealed a significant increase of struggling frequency in soluble ßA + ketamine-treated animals compared to soluble ßA-treated rats (Fig. 3C, One-way ANOVA followed by Bonferroni's post-hoc test, $P < 0.05$). The treatment did not affect the locomotor behavior of animals in the open field test (data not shown).

In the PFC tissue, we did not observe any effects of ketamine on soluble ßA-induced decrease of 5-HT levels (Fig. 3D, One-way ANOVA followed by Tukey's multiple comparison, $P < 0.001$ soluble ßA and soluble ßA + ketamine versus sham-operated rats). With respect to NA quantification, soluble ßA treatment significantly increased such monoamine levels (Fig. 3E, One-way ANOVA followed by Tukey's multiple comparison test, $P < 0.05$ soluble ßA versus sham). Treatment with ketamine further increased cortical NA levels in soluble ßA-treated rats (Fig. 3E, One-way ANOVA followed by Tukey's multiple comparison test, $P < 0.001$ soluble ßA + ketamine versus sham-operated rats).

3.4. Effects of fluoxetine, reboxetine and ketamine on cortical BDNF levels

As shown in Fig. 4, treatments with fluoxetine, reboxetine and ketamine were able to revert the decrease of BDNF expression observed in soluble ßA-treated animals. Interestingly, among antidepressants used, fluoxetine specifically induced an increase of BDNF expression in ßA-treated animals with respect to sham-operated (Fig. 4, One-Way ANOVA followed by Tukey's Post hoc test for fluoxetine = $P < 0.01$ sham-operated vs soluble ßA; $P < 0.001$ soluble ßA vs soluble ßA + fluoxetine; $P < 0.05$ sham-operated vs soluble ßA + fluoxetine; One-Way ANOVA followed by Tukey's Post hoc test for reboxetine = $P < 0.01$ sham-operated vs soluble ßA; $P < 0.01$ soluble ßA vs soluble ßA + reboxetine; One-Way ANOVA followed by Tukey's Post hoc test for ketamine = $P < 0.05$ sham-operated vs soluble ßA; $p < 0.01$ soluble ßA vs soluble ßA + ketamine).

3.5. Effects of fluoxetine, reboxetine and ketamine on cortical NGF levels

As shown in Fig. 5, treatments with fluoxetine and ketamine, but not reboxetine, were able to revert the soluble ßA-induced reduction of this neurotrophin. Furthermore, both fluoxetine and ketamine caused an increase in NGF levels in soluble ßA-treated animals with respect to sham-operated (One-Way ANOVA followed by Tukey's Post hoc test for fluoxetine = $P < 0.05$ sham-operated vs soluble ßA; $P < 0.01$ sham-operated vs soluble ßA + fluoxetine; $P < 0.001$ soluble ßA vs soluble ßA + fluoxetine; One-Way ANOVA followed by Tukey's Post hoc test for reboxetine = $P < 0.05$ sham-operated vs soluble ßA; One-Way ANOVA followed by Tukey's Post hoc test for ketamine = $P < 0.01$ sham-operated vs soluble ßA; $P < 0.01$ sham-operated vs soluble ßA + ketamine; $P < 0.001$ soluble ßA vs soluble ßA + ketamine).

3.6. Effects of fluoxetine, reboxetine and ketamine on plasma soluble ßA levels

Plasma soluble ßA levels were significantly increased after icv injection of the peptide (Fig. 6, One Way ANOVA followed by Tukey's Post hoc test = $P < 0.001$ sham-operated vs soluble ßA). Furthermore, we observed no differences in plasma soluble ßA levels between sham-operated and soluble ßA + fluoxetine-treated animals, while statistically significant differences in soluble ßA levels were detected between sham-operated and soluble ßA + reboxetine-treated rats, as well as sham-operated and soluble ßA + ketamine-treated animals

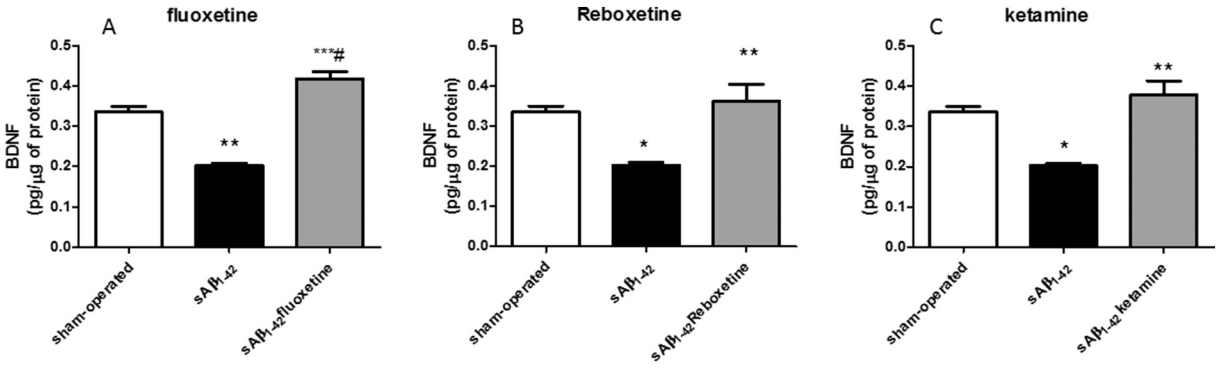

Fig. 4. Effects of fluoxetine, reboxetine and ketamine on BDNF.
Effects of fluoxetine (A), reboxetine (B) and ketamine (C) on BDNF expression in rats treated with vehicle (water icv, sham-operated), soluble beta amyloid (4 µM icv, βA-treated), and fluoxetine, reboxetine or ketamine plus soluble beta amyloid (fluoxetine, reboxetine or ketamine + βA-treated) (n = 3–6 per group). For fluoxetine: $^{**}P < 0.01$ βA-treated versus sham-operated; $^{***}P < 0.001$ fluoxetine + βA-treated versus βA-treated; $\#\ P < 0.05$ fluoxetine + βA-treated versus sham-operated; for reboxetine: $^{*}P < 0.05$ βA-treated versus sham-operated; $^{**}P < 0.01$ reboxetine + βA-treated versus βA-treated; for ketamine: $^{*}P < 0.05$ βA-treated versus sham-operated; $^{**}P < 0.01$ ketamine + βA-treated versus βA-treated.

(Fig. 6, One Way ANOVA followed by Tukey's Post hoc test = $P <$ 0.001 sham-operated vs soluble ßA + reboxetine; $P < 0.01$ sham-operated vs soluble ßA + ketamine).

4. Discussion

In our study, repeated administration of fluoxetine or reboxetine significantly improved behavioral performance in FST, when rats were tested 7 days after soluble ßA injection. Fluoxetine and reboxetine increased tissue content of 5-HT or NA in soluble ßA-injected rats PFC. Single injection of ketamine reverted increase of immobility and reduction of swimming frequency compared to soluble ßA-treated animals. Cortical 5-HT levels were not modified by ketamine administration, while NA concentrations were increased. Furthermore, antidepressants showed neuroprotective properties since neurotrophin levels were restored in soluble ßA-treated animals after fluoxetine or ketamine treatments.

Since behavioral and neurochemical alterations were observed at a time at which amyloid plaques were not visible in the rat brain (Trabace et al., 2007), we could hypothesize that cerebral injection of soluble ßA induced long-lasting neuronal circuits disruption responsible for depressive-like symptomatology. We previously showed that soluble ßA inhibits the expression of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and selectively reduces 5-HT content in the PFC, suggesting that soluble ßA may represent an important player in producing functional and biochemical deficits in rat depressive-like phenotype (Colaianna et al., 2010). Neurotrophic factors such as BDNF and NGF have been shown to be deficient in the AD brain and treatment

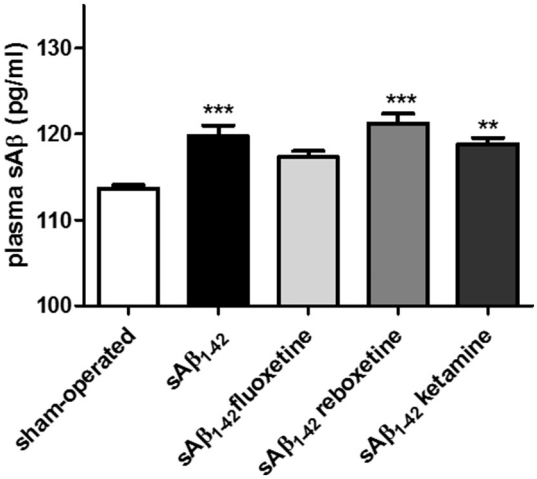

Fig. 6. Effects of fluoxetine, reboxetine and ketamine on plasma soluble ßA levels.
Effects of fluoxetine, reboxetine and ketamine on plasma soluble ßA levels of rats treated with vehicle (water icv, sham-operated), soluble beta amyloid (4 µM icv, βA-treated), and fluoxetine, reboxetine or ketamine plus soluble beta amyloid (fluoxetine, reboxetine or ketamine + βA-treated) (n = 4–7 per group). $^{***}P < 0.001$ βA-treated versus sham-operated and reboxetine + βA-treated versus sham-operated; $^{**}P < 0.01$ ketamine + βA-treated versus sham-operated.

able to restore their levels have been useful in limiting the neurotoxicity of Aß oligomers (Castren and Kojima, 2017; Iulita et al., 2016). In our experimental conditions, antidepressant compounds completely re-

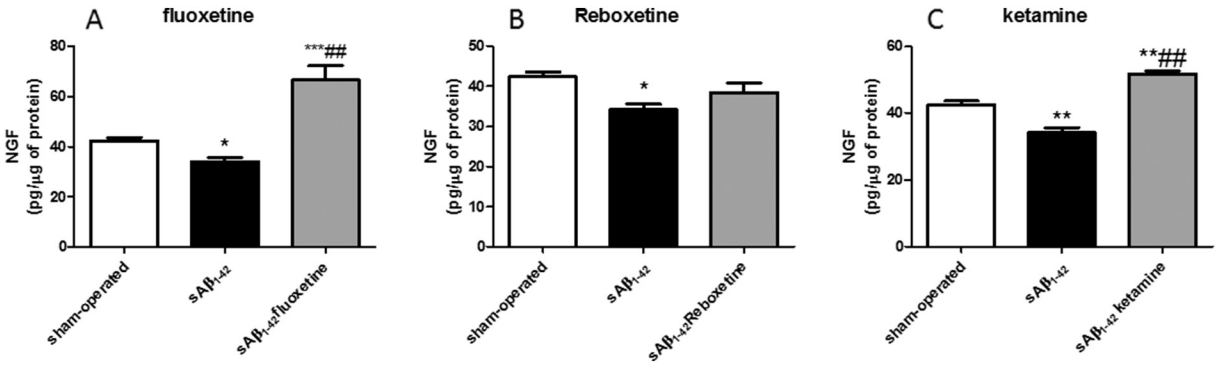

Fig. 5. Effects of fluoxetine, reboxetine and ketamine on NGF.
Effects of fluoxetine (A), reboxetine (B) and ketamine (C) on NGF expression in in rats treated with vehicle (water icv, sham-operated), soluble beta amyloid (4 µM icv, βA-treated), and fluoxetine, reboxetine or ketamine plus soluble beta amyloid (fluoxetine, reboxetine or ketamine + βA-treated) (n = 3–6 per group). For fluoxetine: $^{*}P < 0.05$ βA-treated versus sham-operated; $^{***}P < 0.001$ fluoxetine + βA-treated versus βA-treated; $\#\#P < 0.01$ fluoxetine + βA-treated versus sham-operated; for reboxetine: $^{*}P < 0.05$ βA-treated versus sham-operated; for ketamine: $^{**}P < 0.01$ βA-treated versus sham-operated and ketamine + βA-treated versus βA-treated; $\#\#\ P < 0.01$ ketamine + βA-treated versus sham-operated.

stored BDNF levels in soluble ßA-treated animals. This finding is in line with previous data indicating that these drugs significantly increase BDNF content in both visual cortex (Maya Vetencourt et al., 2008) and hippocampus (Duman and Monteggia, 2006), Moreover, these plastic effects have also been proposed for other antidepressant compounds (Castren and Rantamaki, 2010). Indeed, we observed the same neuroprotective property also following non-classical antidepressant, i.e. ketamine, administration. In this regard, synaptic plasticity has been associated with ketamine administration throughout BDNF mediated pathway (Autry et al., 2011; Liu et al., 2012). Noteworthy, fluoxetine was the only compound among antidepressants used in the present study able to induce a further increase in BDNF expression compared to sham-operated rats. Our observation is supported by previous evidence showing a specific fluoxetine-associated neuroprotective effects. Indeed, fluoxetine could prevent soluble Aß-induced neurotoxicity via paracrine signaling mediated by neurotrophins (Caraci et al., 2016; Jin et al., 2016). With the exception of reboxetine treatment, we observed the same pattern for NGF content, further endorsing the hypothesis that the antidepressant properties of these molecules in soluble Aß-treated rats may rely on their neuroprotective effects.

In our previous experience, treatment with soluble ßA did not modify level of anxiety and did not induce biochemical changes in the nucleus accumbens or striatum, suggesting a possible specific harmful effect of soluble ßA on defined brain networks related to depressive behavior (Colaianna et al., 2010; Morgese et al., 2014).

The relationship between depression and soluble ßA levels is still controversial. While some human studies evidenced that in elderly, depression was associated with lower plasma ßA concentrations than matched controls (Qiu et al., 2007), others reported an elevation in plasmatic ßA in geriatric depression (Pomara et al., 2006). Here we found that three doses of two different antidepressants, fluoxetine or reboxetine, administered in 24 h, reverted depressive soluble ßA-induced phenotype profile. Our results differ in some important aspects from previous data on the timing of the response to antidepressants treatment in human. This kind of therapy takes 2–3 weeks before improvements of symptomatology can be observed (Nierenberg et al., 2000; van Calker et al., 2009; Whyte et al., 2004).The explanation for these characteristic of SSRIs (fluoxetine) may be found in delayed neurochemical adaptations, in downregulation of 5-HT_{1A} auto-receptors and disinhibition of 5-HT release (Fabre et al., 2000), together with increased hippocampal neurogenesis (Possamai et al., 2015). As far as NRIs (reboxetine), chronic administration induces NA transporter down-regulation and this accounts for in vivo assessment of long-term effects of antidepressants on clinical improvements (Frazer and Benmansour, 2002).

In contrast, we found that fluoxetine and reboxetine exerted their effects much faster. We observed beneficial effects of fluoxetine and reboxetine after few hours. As its pharmacological classification implies, fluoxetine is thought to exert effect by blocking reuptake of 5-HT into presynaptic terminals. The mechanism by which fluoxetine reverted soluble ßA-induced depressive-like behavior in rats in a short period of time is not clear. Interestingly, present results raise the possibility that a novel mechanism might be proposed for this drug. Our data prompted us to hypothesize that enhancement of 5-HT neurotransmission in PFC through the acute blockade of the neuronal 5-HT reuptake mechanism, leads to a reduction of ßA levels. Accordingly, stimulation of 5-HT receptors reduces ßA production in vitro (Cho and Hu, 2007; Hashimoto et al., 2012). A recent report greatly strengthens our hypothesis. Authors demonstrated that reduction in brain interstitial fluid of soluble ßA is mediated by a select group of 5-HT receptors, and that 5-HT signaling acts within the cytoplasm to increase gamma secretase enzymatic activity in a matter of hours (Fisher et al., 2016). Also, it has been shown that a single injection of a 5-HT_{2C} agonist can stimulate cerebrospinal fluid (CSF) Amyloid Precursor Protein (APP) secretion and decrease ßA production in vivo (Arjona et al., 2002). To further support the hypothesis of potential role of old drugs as new “ßA-lowering” molecules for the treatment of this depression subtype, it is worth to note that an acute administration of fluoxetine rapidly reduced ßA production in brain interstitial fluid in few hours, as assessed by in vivo microdialysis (Cirrito et al., 2011). In good agreement, here we demonstrated that fluoxetine administration significantly reduced plasma soluble ßA levels.

Human studies strongly rely on the hypothesis that 5-HT reduces ßA levels. A neuroimaging study showed that antidepressant-treated individuals had less evidence of ßA plaque (Cirrito et al., 2011). Similarly, in healthy humans, an acute dose of citalopram was associated with a decreased CSF ßA concentrations (Sheline et al., 2014). These findings, taken together with our results on fluoxetine, endorse the hypothesis that SSRI share an antidepressant mechanism based on “ßA lowering” property.

Therefore, it is conceivable that, since we artificially raised the amount of ßA monomers in CSF of adult rats, our results can help to characterize a subgroup of depressed subjects, over and above the presence of plaques (Morgese et al., 2015).

These findings complement results from other experiments linking the effect of the 5-HT as an antidepressant molecule together with the ability of 5-HT to reduce ßA production and concentrations. In antidepressant therapy, about 20% of depressed patients do not respond to currently available molecules. Although underactivity of brain monoamines has been considered a leading hypothesis for the development of most therapies used for depression treatment, a large number of medicated depressed individuals find no benefit from conventional therapies. Residual symptoms, relapses and recurrences are frequently observed. Hence, data that could help to identify subgroups of patients in depression are certainly warranted and, for these patients, there is a pressing medical need to identify fast-acting molecules.

As far as reboxetine effects, we found, surprisingly, that reboxetine increased 5-HT levels in soluble ßA treated animals. Although in literature such effect has not been reported, it should be noted that it occurs in treated rats and this event could rely on the increased BDNF content in treated rats (Kraus et al., 2017).

Furthermore, as expected, three doses of reboxetine administered in 24 h increased NA levels in PFC. We have demonstrated an interesting interplay among ßA peptide and noradrenergic neurotransmission (Morgese et al., 2015; Morgese et al., 2014). Indeed, in our experience, increased NA levels occur very early after exogenous Aβ injection, as soon as 2 h after central administration, and is mediated through inducible nitric oxide synthase (iNOS) and central IL-1 receptors (Morgese et al., 2015). Astrocytic iNOS activation was shown to potentiate *N*-methyl D-aspartate (NMDA)-induced neurotoxicity (Hewett et al., 1994). We hypothesized that this increase in noradrenergic tone reflects a neuroprotective phenomenon. In this regard, it has been suggested that methods that increase NA levels or reduce damage to noradrenergic neurons might provide benefit in several neurological conditions having an inflammatory component (Braun et al., 2014). We also demonstrated that ßA stimulated interleukin (IL)-1β synthesis and release from primary microglia and microglia cell lines, and that ßA triggered IL-1β in vivo accumulation (Sanz et al., 2012; Sanz et al., 2009). NA, beyond its role as a classical neurotransmitter, suppresses ßA-induced activation of primary murine microglial cells. Indeed, reduced NA concentration in locus coeruleus projecting areas facilitates the inflammatory reaction of microglial cells after Aβ exposure, thus impairing microglial migration and phagocytosis, thereby decreasing Aβ clearance (Heneka et al., 2010a; Heneka et al., 2010b). Interestingly, it has been reported that NA inhibits iNOS induction after inflammatory stimuli in astrocytes (Feinstein et al., 1993) and microglia (Dello Russo et al., 2004). Given the fact that NA suppresses brain inflammation and enhances ßA phagocytosis at the same time, it is tempting to suppose that noradrenergic system seems to be activated possibly as a compensatory mechanism following soluble ßA increased levels (Morgese et al., 2015, 2014). To our knowledge, the present study is the first report on the beneficial effects of antidepres-

sant drugs on soluble ßA-induced depressive phenotype in rats. Intriguingly, fluoxetine further increased NA levels in PFC of soluble ßA-treated rats. This result, associated with the pronounced elevation in BDNF content, strongly points towards the hypothesis that such molecule displays neuroprotective properties. Furthermore, in vitro studies have evidenced a protective effect of NA towards Aβ-induced toxicity by increasing neurotrophic factor expression via activation of β-adrenergic receptor signaling cascade (Counts and Mufson, 2010; Liu et al., 2015).

We also found that a single dose of ketamine produces antidepressant-like effects in FST, and an increase in cortical NA levels. Unlike traditional antidepressants, the acute and fast-acting antidepressant properties of ketamine have been recently documented (Browne and Lucki, 2013; Diazgranados et al., 2010; Ibrahim et al., 2011; Li et al., 2011), and several mechanisms have been proposed, although not yet completely identified. Preclinical works have shown that a single treatment with ketamine increased number and function of spine synapses in the PFC (Li et al., 2010). A downregulation of neuregulin 1-ErbB4 signaling in parvalbumin interneurons in the rat brain has also been proposed as an antidepressant property of ketamine (Wang et al., 2014). Moreover, inhibition of the L-arginine-nitric oxide pathway seems to mediate the antidepressant effects of ketamine in rats (Zhang et al., 2013). The converging mechanisms by which ketamine induced antidepressant effect suggest that common pathways might be involved in the actions of this rapid-acting molecule. A crucial component that appears to start molecular signaling required for inducing a rapid antidepressant response is the “lowering ßA” effect. Although we did not detect a decrease in plasma soluble ßA levels, we cannot completely rule out a probable “lowering ßA” effect considering that this phenomenon can occur also at interstitial level.

Our hypothesis is further supported by Zhu et al. (2015). Authors suggested that ketamine exerted cognitive protective effects through its suppression of electroconvulsive shock-induced neuroinflammation and, interestingly, through the reduction of the levels of soluble ßA (Zhu et al., 2015). We have previously shown that blockade of NMDA receptors can restore memory impairment induced by soluble ßA central injection (Tucci et al., 2014).

5. Conclusions

Here we suggest a novel neurobiological mechanism, with treatment implications, that could account for a rapid onset of the antidepressant therapy. In conclusion, by revealing that molecules belonging to SSRI class, such as fluoxetine, produce short-acting antidepressive effects in rat soluble ßA-induced depressive profile. Our results suggest a new mechanism by which elevated brain levels of ßA may be counterbalanced by old molecules overhauled as new “ßA lowering” drugs. Furthermore, reboxetine and ketamine, although belonging to classical and non-classical antidepressants, respectively, share a common molecular mechanism related to neurotrophin level restoring. Our study might design a new scenario for unravelling the molecular mechanisms underlying the rapid onset of classical antidepressant molecules.

Conflicts of interest statement

The Authors declare no conflict of interest.

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References

Andersen, K., Lolk, A., Kragh-Sorensen, P., Petersen, N.E., Green, A., 2005. Depression and the risk of Alzheimer disease. Epidemiology 16 (2), 233–238.
Arjona, A.A., Pooler, A.M., Lee, R.K., Wurtman, R.J., 2002. Effect of a 5-HT(2C) serotonin agonist, dexnorfenfluramine, on amyloid precursor protein metabolism in guinea pigs. Brain Res. 951 (1), 135–140.
Autry, A.E., Adachi, M., Nosyreva, E., Na, E.S., Los, M.F., Cheng, P.F., et al., 2011. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475 (7354), 91–95.
Awasthi, M., Singh, S., Pandey, V.P., Dwivedi, U.N., 2016. Alzheimer's disease: An overview of amyloid beta dependent pathogenesis and its therapeutic implications along with in silico approaches emphasizing the role of natural products. J. Neurol. Sci. 361, 256–271.
Baquero, M., Martin, N., 2015. Depressive symptoms in neurodegenerative diseases. World J. Clin. Case. 3 (8), 682–693.
Braun, D., Madrigal, J.L., Feinstein, D.L., 2014. Noradrenergic regulation of glial activation: molecular mechanisms and therapeutic implications. Curr. Neuropharmacol. 12 (4), 342–352.
Browne, C.A., Lucki, I., 2013. Antidepressant effects of ketamine: mechanisms underlying fast-acting novel antidepressants. Front. Pharmacol. 4, 161.
van Calker, D., Zobel, I., Dykierek, P., Deimel, C.M., Kech, S., Lieb, K., et al., 2009. Time course of response to antidepressants: predictive value of early improvement and effect of additional psychotherapy. J. Affect. Disord. 114 (1–3), 243–253.
Caraci, F., Tascedda, F., Merlo, S., Benatti, C., Spampinato, S.F., Munafo, A., et al., 2016. Fluoxetine prevents Abeta1-42-induced toxicity via a paracrine signaling mediated by transforming-growth-factor-beta1. Front. Pharmacol. 7, 389.
Castren, E., Kojima, M., 2017. Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. Neurobiol. Dis. 97 (Pt B), 119–126.
Castren, E., Rantamaki, T., 2010. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev. Neurobiol. 70 (5), 289–297.
Catania, C., Sotiropoulos, I., Silva, R., Onofri, C., Breen, K.C., Sousa, N., et al., 2009. The amyloidogenic potential and behavioral correlates of stress. Mol. Psychiatry 14 (1), 95–105.
Cherbuin, N., Kim, S., Anstey, K.J., 2015. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open 5 (12), e008853.
Cho, S., Hu, Y., 2007. Activation of 5-HT4 receptors inhibits secretion of beta-amyloid peptides and increases neuronal survival. Exp. Neurol. 203 (1), 274–278.
Cirrito, J.R., Disabato, B.M., Restivo, J.L., Verges, D.K., Goebel, W.D., Sathyan, A., et al., 2011. Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans. Proc. Natl. Acad. Sci. U. S. A. 108 (36), 14968–14973.
Colaianna, M., Tucci, P., Zotti, M., Morgese, M.G., Schiavone, S., Govoni, S., et al., 2010. Soluble beta amyloid(1-42): a critical player in producing behavioural and biochemical changes evoking depressive-related state? Br. J. Pharmacol. 159 (8), 1704–1715.
Counts, S.E., Mufson, E.J., 2010. Noradrenaline activation of neurotrophic pathways protects against neuronal amyloid toxicity. J. Neurochem. 113 (3), 649–660.
Cryan, J.F., Lucki, I., 2000. Antidepressant-like behavioral effects mediated by 5-Hydroxytryptamine(2C) receptors. J. Pharmacol. Exp. Ther. 295 (3), 1120–1126.
Cryan, J.F., Markou, A., Lucki, I., 2002a. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol. Sci. 23 (5), 238–245.
Cryan, J.F., Page, M.E., Lucki, I., 2002b. Noradrenergic lesions differentially alter the antidepressant-like effects of reboxetine in a modified forced swim test. Eur. J. Pharmacol. 436 (3), 197–205.
Cryan, J.F., Page, M.E., Lucki, I., 2005a. Differential behavioral effects of the antidepressants reboxetine, fluoxetine, and moclobemide in a modified forced swim test following chronic treatment. Psychopharmacology 182 (3), 335–344.
Cryan, J.F., Valentino, R.J., Lucki, I., 2005b. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci. Biobehav. Rev. 29 (4–5), 547–569.
Cummings, J., Lai, T.J., Hemrungrojn, S., Mohandas, E., Yun Kim, S., Nair, G., et al., 2016. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies. CNS Neurosci. Therapeut. 22 (3), 159–166.
Dello Russo, C., Boullerne, A.I., Gavrilyuk, V., Feinstein, D.L., 2004. Inhibition of microglial inflammatory responses by norepinephrine: effects on nitric oxide and interleukin-1beta production. J. Neuroinflammation 1 (1), 9.
Diazgranados, N., Ibrahim, L., Brutsche, N.E., Newberg, A., Kronstein, P., Khalife, S., et al., 2010. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch. Gen. Psychiatry 67 (8), 793–802.
Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biol. Psychiatry 59 (12), 1116–1127.
Engin, E., Treit, D., Dickson, C.T., 2009. Anxiolytic- and antidepressant-like properties of ketamine in behavioral and neurophysiological animal models. Neuroscience 161 (2), 359–369.
Fabre, V., Beaufour, C., Evrard, A., Rioux, A., Hanoun, N., Lesch, K.P., et al., 2000. Altered expression and functions of serotonin 5-HT1A and 5-HT1B receptors in knock-out mice lacking the 5-HT transporter. Eur. J. Neurosci. 12 (7), 2299–2310.
Feinstein, D.L., Galea, E., Reis, D.J., 1993. Norepinephrine suppresses inducible nitric oxide synthase activity in rat astroglial cultures. J. Neurochem. 60 (5), 1945–1948.
Fisher, J.R., Wallace, C.E., Tripoli, D.L., Sheline, Y.I., Cirrito, J.R., 2016. Redundant Gs-coupled serotonin receptors regulate amyloid-beta metabolism in vivo. Mol. Neurodegener. 11 (1), 45.

Frazer, A., Benmansour, S., 2002. Delayed pharmacological effects of antidepressants. Mol. Psychiatry 7 (Suppl. 1), S23–S28.
Garcia, L.S., Comim, C.M., Valvassori, S.S., Reus, G.Z., Barbosa, L.M., Andreazza, A.C., et al., 2008. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 32 (1), 140–144.
Green, R.C., Cupples, L.A., Kurz, A., Auerbach, S., Go, R., Sadovnick, D., et al., 2003. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Arch. Neurol. 60 (5), 753–759.
Grutzendler, J., Morris, J.C., 2001. Cholinesterase inhibitors for Alzheimer's disease. Drugs 61 (1), 41–52.
Hashimoto, G., Sakurai, M., Teich, A.F., Saeed, F., Aziz, F., Arancio, O., 2012. 5-HT(4) receptor stimulation leads to soluble AbetaPPalpha production through MMP-9 upregulation. J. Alzheimers Dis. 32 (2), 437–445.
Heneka, M.T., Nadrigny, F., Regen, T., Martinez-Hernandez, A., Dumitrescu-Ozimek, L., Terwel, D., et al., 2010a. Locus ceruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. Proc. Natl. Acad. Sci. U. S. A. 107 (13), 6058–6063.
Heneka, M.T., O'Banion, M.K., Terwel, D., Kummer, M.P., 2010b. Neuroinflammatory processes in Alzheimer's disease. J. Neural Transm. 117 (8), 919–947.
Hewett, S.J., Csernansky, C.A., Choi, D.W., 1994. Selective potentiation of NMDA-induced neuronal injury following induction of astrocytic iNOS. Neuron 13 (2), 487–494.
Ibrahim, L., Diazgranados, N., Luckenbaugh, D.A., Machado-Vieira, R., Baumann, J., Mallinger, A.G., et al., 2011. Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (4), 1155–1159.
Iulita, M.F., Caraci, F., Cuello, A.C., 2016. A link between nerve growth factor metabolic deregulation and amyloid-beta-driven inflammation in down syndrome. CNS Neurol. Disord. Drug Targets 15 (4), 434–447.
Jin, L., Gao, L.F., Sun, D.S., Wu, H., Wang, Q., Ke, D., et al., 2016. Long-term ameliorative effects of the antidepressant fluoxetine exposure on cognitive deficits in 3 × TgAD Mice. Mol. Neurobiol.
Jorm, A.F., 2001. History of depression as a risk factor for dementia: an updated review. Australian New Zealand J. Psychiatry 35 (6), 776–781.
Kraus, C., Castren, E., Kasper, S., Lanzenberger, R., 2017. Serotonin and neuroplasticity - links between molecular, functional and structural pathophysiology in depression. Neurosci. Biobehav. Rev. 77, 317–326.
Li, N., Lee, B., Liu, R.J., Banasr, M., Dwyer, J.M., Iwata, M., et al., 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329 (5994), 959–964.
Li, N., Liu, R.J., Dwyer, J.M., Banasr, M., Lee, B., Son, H., et al., 2011. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol. Psychiatry 69 (8), 754–761.
Liu, R.J., Lee, F.S., Li, X.Y., Bambico, F., Duman, R.S., Aghajanian, G.K., 2012. Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. Biol. Psychiatry 71 (11), 996–1005.
Liu, X., Ye, K., Weinshenker, D., 2015. Norepinephrine protects against amyloid-beta toxicity via TrkB. J. Alzheimers Dis. 44 (1), 251–260.
Maya Vetencourt, J.F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary OF, et al., 2008. The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science 320 (5874), 385–388.
Morgese, M.G., Tucci, P., Colaianna, M., Zotti, M., Cuomo, V., Schiavone, S., et al., 2014. Modulatory activity of soluble beta amyloid on HPA axis function in rats. Curr. Pharm. Des. 20 (15), 2539–2546.
Morgese, M.G., Colaianna, M., Mhillaj, E., Zotti, M., Schiavone, S., D'Antonio, P., et al., 2015. Soluble beta amyloid evokes alteration in brain norepinephrine levels: role of nitric oxide and interleukin-1. Front. Neurosci. 9, 428.
Morgese, M.G., Tucci, P., Mhillaj, E., Bove, M., Schiavone, S., Trabace, L., et al., 2017. Lifelong nutritional omega-3 deficiency evokes depressive-like state through soluble beta amyloid. Mol. Neurobiol. 54 (3), 2079–2089 (April).
Mourao, R.J., Mansur, G., Malloy-Diniz, L.F., Castro Costa, E., Diniz, B.S., 2016. Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis. Int. J. Geriatr. Psychiatry 31 (8), 905–911 (Aug).
Mura, E., Preda, S., Govoni, S., Lanni, C., Trabace, L., Grilli, M., et al., 2010. Specific neuromodulatory actions of amyloid-beta on dopamine release in rat nucleus accumbens and caudate putamen. J. Alzheimers Dis. 19 (3), 1041–1053.
Nierenberg, A.A., Farabaugh, A.H., Alpert, J.E., Gordon, J., Worthington, J.J., Rosenbaum, J.F., et al., 2000. Timing of onset of antidepressant response with fluoxetine treatment. Am. J. Psychiatry 157 (9), 1423–1428.
Panza, F., Frisardi, V., Capurso, C., D'Introno, A., Colacicco, A.M., Imbimbo, B.P., et al., 2010. Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am. J. Geriatr. Psychiatry 18 (2), 98–116.
Paxinos, G., Watson, C., 1998. The Rat Brain in Stereotaxic Coordinates. Elsevier Academic Press.
Pinto, T., Lanctot, K.L., Herrmann, N., 2011. Revisiting the cholinergic hypothesis of behavioral and psychological symptoms in dementia of the Alzheimer's type. Ageing Res. Rev. 10 (4), 404–412.
Pomara, N., Doraiswamy, P.M., Willoughby, L.M., Roth, A.E., Mulsant, B.H., Sidtis, J.J., et al., 2006. Elevation in plasma Abeta42 in geriatric depression: a pilot study. Neurochem. Res. 31 (3), 341–349.
Possamai, F., dos Santos, J., Walber, T., Marcon, J.C., dos Santos, T.S., Lino de Oliveira, C., 2015. Influence of enrichment on behavioral and neurogenic effects of antidepressants in Wistar rats submitted to repeated forced swim test. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 58, 15–21.
Qiu, W.Q., Sun, X., Selkoe, D.J., Mwamburi, D.M., Huang, T., Bhadela, R., et al., 2007. Depression is associated with low plasma Abeta42 independently of cardiovascular disease in the homebound elderly. Int. J. Geriatr. Psychiatry 22 (6), 536–542.
Ressler, K.J., Nemeroff, C.B., 2000. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depression Anxiety 12 (Suppl. 1), 2–19.
Sanz, J.M., Chiozzi, P., Ferrari, D., Colaianna, M., Idzko, M., Falzoni, S., et al., 2009. Activation of microglia by amyloid beta requires P2X7 receptor expression. J. Immunol. 182 (7), 4378–4385.
Sanz, J.M., Chiozzi, P., Colaianna, M., Zotti, M., Ferrari, D., Trabace, L., et al., 2012. Nimodipine inhibits IL-1beta release stimulated by amyloid beta from microglia. Br. J. Pharmacol. 167 (8), 1702–1711.
Shah, A., Dalvi, M., Thompson, T., 2005. Behavioural and psychological signs and symptoms of dementia across cultures: current status and the future. Int. J. Geriatr. Psychiatry 20 (12), 1187–1195.
Sheline YI, West T, Yarasheski K, Swarm R, Jasielec MS, Fisher JR, *et al.* (2014). An antidepressant decreases CSF Abeta production in healthy individuals and in transgenic AD mice. Sci. Transl. Med. 6(236): 236re234.
Slattery, D.A., Cryan, J.F., 2012. Using the rat forced swim test to assess antidepressant-like activity in rodents. Nat. Protoc. 7 (6), 1009–1014.
Steinberg M, Munro CA, Samus Q, P VR, Brandt J, Lyketsos CG (2004). Patient predictors of response to treatment of depression in Alzheimer's disease: the DIADS study. Int. J. Geriatr. Psychiatry 19(2): 144–150.
Sweet, R.A., Hamilton, R.L., Butters, M.A., Mulsant, B.H., Pollock, B.G., Lewis, D.A., et al., 2004. Neuropathologic correlates of late-onset major depression. Neuropsychopharmacology 29 (12), 2242–2250.
Trabace, L., Cassano, T., Steardo, L., Pietra, C., Villetti, G., Kendrick, K.M., et al., 2000. Biochemical and neurobehavioral profile of CHF2819, a novel, orally active acetylcholinesterase inhibitor for Alzheimer's disease. J. Pharmacol. Exp. Ther. 294 (1), 187–194.
Trabace, L., Kendrick, K.M., Castrignano, S., Colaianna, M., De Giorgi, A., Schiavone, S., et al., 2007. Soluble amyloid beta1-42 reduces dopamine levels in rat prefrontal cortex: relationship to nitric oxide. Neuroscience 147 (3), 652–663.
Tucci, P., Mhillaj, E., Morgese, M.G., Colaianna, M., Zotti, M., Schiavone, S., et al., 2014. Memantine prevents memory consolidation failure induced by soluble beta amyloid in rats. Front. Behav. Neurosci. 8, 332.
Wang, N., Zhang, G.F., Liu, X.Y., Sun, H.L., Wang, X.M., Qiu, L.L., et al., 2014. Downregulation of neuregulin 1-ErbB4 signaling in parvalbumin interneurons in the rat brain may contribute to the antidepressant properties of ketamine. J. Mol. Neurosci. 54 (2), 211–218.
Wegener, G., Bandpey, Z., Heiberg, I.L., Volke, V., Trabace, L., Rosenberg, R., et al., 2004. Combined chronic treatment with citalopram and lithium does not modify the regional neurochemistry of nitric oxide in rat brain. J. Physiol. Pharmacol. 55 (3), 575–586.
Whyte, E.M., Dew, M.A., Gildengers, A., Lenze, E.J., Bharucha, A., Mulsant, B.H., et al., 2004. Time course of response to antidepressants in late-life major depression: therapeutic implications. Drugs Aging 21 (8), 531–554.
Yasuno, F., Kazui, H., Morita, N., Kajimoto, K., Ihara, M., Taguchi, A., et al., 2016. High amyloid-beta deposition related to depressive symptoms in older individuals with normal cognition: a pilot study. Int. J. Geriatr. Psychiatry 31 (8), 920–928 (Aug).
Zetterberg, H., Blennow, K., Hanse, E., 2010. Amyloid beta and APP as biomarkers for Alzheimer's disease. Exp. Gerontol. 45 (1), 23–29.
Zhang, G.F., Wang, N., Shi, J.Y., Xu, S.X., Li, X.M., Ji, M.H., et al., 2013. Inhibition of the L-arginine-nitric oxide pathway mediates the antidepressant effects of ketamine in rats in the forced swimming test. Pharmacol. Biochem. Behav. 110, 8–12.
Zhu, X., Li, P., Hao, X., Wei, K., Min, S., Luo, J., et al., 2015. Ketamine-mediated alleviation of electroconvulsive shock-induced memory impairment is associated with the regulation of neuroinflammation and soluble amyloid-beta peptide in depressive-like rats. Neurosci. Lett. 599, 32–37.
Zotti, M., Colaianna, M., Morgese, M.G., Tucci, P., Schiavone, S., Avato, P., et al., 2013. Carvacrol: from ancient flavoring to neuromodulatory agent. Molecules 18 (6), 6161–6172.