Metabolic Brain Disease (2019) 34:941–950
https://doi.org/10.1007/s11011-019-00408-1

ORIGINAL ARTICLE

Resveratrol protects the brain against oxidative damage in a dopaminergic animal model of mania

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Received: 4 October 2018 / Accepted: 14 March 2019 / Published online: 27 March 2019

Abstract

The present study aimed to evaluate the effects of resveratrol on behavior and oxidative stress parameters in the brain of rats submitted to the animal model of mania induced by m-AMPH. In the first model (reversal treatment), rats received intraperitoneal (i.p.) injection of saline or m-AMPH (1 mg/kg body weight) once a day for 14 days, and from the 8th to the 14th day, they were orally treated with water or resveratrol (15 mg/kg), once a day. In the second model (maintenance treatment), rats were orally pretreated with water or resveratrol (15 mg/kg) once a day, and from the 8th to the 14th day, they received saline or m-AMPH i.p., once a day. Locomotor and exploratory activities were assessed in the open-field test. Oxidative and nitrosative damage parameters to lipid and proteins were evaluated by TBARS, 4-HNE, carbonyl, and 3-nitrotyrosine in the brain submitted to the experimental models. m-AMPH administration increased the locomotor and exploratory activities; resveratrol was not able to reverse or prevent these manic-like behaviors. Additionally, m-AMPH increased the lipid and protein oxidation and nitrosylation in the frontal cortex, hippocampus, and striatum of rats. However, resveratrol prevented and reversed the oxidative and nitrosative damage to proteins and lipids in all cerebral areas assessed. Since oxidative stress plays an important role in BD pathophysiology, supplementation of resveratrol in BD patients could be regarded as a possible adjunctive treatment with mood stabilizers.

Keywords Bipolar disorder · Resveratrol · Animal model of mania · m-amphetamine · Nutrition

Introduction

Bipolar disorder (BD) is a severe psychiatric condition associated to psychosocial, learn and memory dysfunctions (Mur et al. 2009; Jabben et al. 2010; Stringer et al. 2014). Although BD pathophysiology is not fully understood, it has been well established that oxidative stress is involved in the neurobiology of this disorder (Teixeira et al. 2016; Yui et al. 2016; Sigitova et al. 2017). In this context, the brain is prone to oxidative damage due to its high rate of oxygen consumption, abundant lipid content, and relatively small amount of antioxidant enzymes, as compared with other organs (Floyd and

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Carney 1992). Indeed, increased levels of oxidized nucleic acids, proteins, and lipids have been described in post mortem cerebral tissue of BD patients. In addition, decreased antioxidant capacity has been detected in blood samples obtained from these patients (Wang et al. 2009; Mustak et al. 2010; Andreazza et al. 2010, 2013).

Kim and colleagues (Kim et al. 2014) also found alterations in the levels of protein oxidation and nitration in dopamine-rich regions in prefrontal cortex from BD patients. It is well established in the literature that high levels of dopamine are associated with bipolar mania, and that dopamine produces reactive oxygen species (ROS) during its auto-oxidation (Berk et al. 2007). Indeed, the rats submitted to the model of mania induced by amphetamine present manic-like behaviors and oxidative damage to protein, lipids, and DNA in the brain. It is interesting that standard mood stabilizers, such as lithium (Li) and valproate (VPA), reverse manic-like behaviors and protect the brain against oxidative damage to biomolecules induced by amphetamines (Valvassori et al. 2011; da-Rosa et al. 2012a). Since BD is involved with oxidative stress (de Sousa et al. 2014), it is not surprising that many mood stabilizers play certain antioxidant roles as part of their therapeutic activity.

The animal model of mania induced by m-amphetamine (m-AMPH) is a suitable tool for the study of the bipolar mania, because it has the three validities recommended for an animal model: 1) face validity, which is the ability of the model to mimic the symptoms/behaviors of the disorder; 2) construct validity, which is the ability of the model to simulate the pathophysiology of the disorder; and 3) predictive validity, which is the ability of the model to mimic the pharmacological therapy for the disorder (Ellenbroek and Cools 1990). In agreement with the present study and reinforcing the face validity of the model, many papers demonstrated that m-AMPH administration in rats increased the locomotor and exploration activities, the risk behavior, and stereotypy in the animals (da-Rosa et al. 2012b; Feier et al. 2012; Feier et al. 2013). Moreover, treatment with Li and VPA, which are standard mood stabilizers, reversed and prevented these manic-like behaviors induced by m-AMPH (Feier et al. 2013). Therefore, administration of m-AMPH complies with the predictive validity of the model.

Resveratrol is a stilbene synthesized in many plants in response to several stressors (Siemann and Creasy 1992). A growing body of evidence has reported that this substance has therapeutic properties in the central nervous system disorders, such as Alzheimer's disease, ischemia, and stroke (Girbovan et al. 2012; Morris-Blanco et al. 2014; Ahmed et al. 2017). Resveratrol also induces several benefits that are modulated by multiple synergistic pathways, which control oxidative stress, inflammation, and cell death (Carrizzo et al. 2013; Cobb and Cole 2015). Additionally, a study carried out by Rege et al. (2013) showed that resveratrol decreases lipid oxidation and increases levels of antioxidant enzymes.

Since a number of studies has focused on the resveratrol effects on various diseases, including prevention of Alzheimer's disease (Sawda et al. 2017), Parkinson's disease (Gaballah et al. 2016), Huntington's disease and other neurological diseases (Tellone et al. 2015), it is tempting investigate the effect of this compound in the context of psychiatric disorders, such as BD. At present, it is not clear whether resveratrol could be effective to mitigate manic symptoms related to BD, and no clinical trials in this context were registered in Clinical Trials database (https://clinicaltrials.gov/ct2/home). Therefore, the present study aimed to evaluate the effects of resveratrol on behavior and oxidative stress parameters in the brain of rats submitted to the animal model of mania induced by m-AMPH.

Materials and methods

Animals

Adult male Wistar rats (*Rattus norvegicus*; body weight: 250–350 g) were obtained from the breeding colony at *Universidade do Extremo Sul Catarinense*. Animals were housed in five per cage, with food and water available ad libitum, and were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.) at a temperature of 22 ± 1 °C. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Brazilian Society for Neuroscience and Behavior. Experimental procedures were conducted after approval of the local ethics committee for animal use at *Universidade do Extremo Sul Catarinense* (protocol # 102/2016–2).

Drug administration

Rats were submitted to *reversal treatment* by intraperitoneal (i.p.) injection of either m-AMPH (1 mg/kg body weight) or saline solution (Sal, NaCl 0.09%) once a day, for 14 days. From the 8th to the 14th day, m-AMPH- or Sal-treated animals also received water (15 mL/kg, once a day) or *trans*-resveratrol (15 mg/kg, once a day) by gavage. Thus, in this experimental protocol, there are four experimental groups (10 animals per group): 1) Sal + Water; 2) Sal + Resveratrol; 3) m-AMPH + Water, 4) m-AMPH + Resveratrol.

In the *maintenance treatment*, rats received water or *trans*-resveratrol (15 mg/kg) once a day by gavage, for 14 days. From the 8th to the 14th day, trans-resveratrol-treated animals also received Sal or m-AMPH (1 mg/kg, i.p.) once a day. Therefore, the following experimental groups (10 animals per group) were included in this experimental protocol: 1) Water + Sal; 2) Resveratrol + Sal; 3) Water + m-AMPH; 4) Resveratrol + m-AMPH.

In both treatments (reversal and maintenance), no behavioral assessments were performed between days 1 and 14. On the 15th day of treatment, animals received a single i.p. injection of m-AMPH or Sal, and locomotor activity was assessed using the open-field test 2 h after the injection. All drugs, water or Sal were administrated in a volume of 1 mL/kg body weight. Dose of m-AMPH was based on da-Rosa and coworkers' study (da-Rosa et al. 2012b).

Open-field test

This behavioral test was performed in accordance with the Broadhurst's method (1960). Procedure was carried out in a 40 × 60 cm-open field surrounded by 50-cm-high walls made of brown plywood with a frontal glass wall. Floor of the open-field was divided into nine equal rectangles by black lines. Each animal was gently placed to explore the arena for 5 min. In the open field test, the locomotor (total number of square crossings during the entire test period) and exploratory (total number of erect postures during the entire test period) activities were evaluated.

Biochemical measures

Brain samples Following the behavioral test, animals were decapitated with guillotine and the brain was excised. Hippocampus, frontal cortex and, striatum were dissected on a cold surface, then immersed in liquid nitrogen and subsequently stored in a freezer at −80 °C for subsequent biochemical analysis.

Evaluation of oxidative damage parameters in the brain rat

Measurements of lipid peroxidation Thiobarbituric acid reactive species (TBARS) Assay Kit (Cayman; Ann Arbor, Michigan, USA; catalog no. 10009055) was used for the direct quantitative measurement of the malondialdehyde (MDA) level in the cerebral tissue samples. 4-Hydroxy-2-nonenal (HNE) content was measured using the assay kit provided by Cell Biolabs (Cell Biolabs, Inc.; San Diego, California, USA; catalog no. STA-338).

Measurements of protein oxidation and nitration Carbonyl group content was measured using a specific kit provided by Cell Biolabs (OxiSelect™ Protein Carbonyl ELISA Kit; catalog no. STA-310). 3-Nitrotyrosine quantification was performed using a kit from this same manufacturer (OxiSelect™ Nitrotyrosine ELISA Kit; catalog no. STA-305).

Protein quantification Total protein was measured by the Lowry and coworkers' method (1951), using bovine serum albumin as a standard.

Statistical analysis

Data are presented as mean ± standard error of mean (S.E.M.). Differences between groups were determined by two-way analysis of variance (ANOVA), followed by Tukey's *post-hoc* test. Software used in the analyses was Statistica 7 (StatSoft, Inc., Tulsa, Oklahoma, USA). Differences were rated as statistically significant when $p < 0.05$.

Results

In the present study, open field test was performed for the assessment of locomotor (crossings) and exploratory (rearings) activities in rats submitted to the animal model of mania receiving resveratrol (Fig. 1). Data from the reversal model are presented in the graphs a and b, and results from the maintenance model are presented in the graphs c and d. It can be observed that m-AMPH administration increased locomotor (crossings) and exploratory (rearings) activities in rats, in both experimental protocols. Administration of resveratrol did not reverse or prevent hyperlocomotion of the animals induced by m-AMPH. In addition, in the reversal model, it can be observed no significant differences between m-AMPH + Resveratrol and control groups (rearing and crossing). However, a trend to decrease of hyperactivity induced by m-AMPH was observed in the animals receiving resveratrol. Similarly, in the maintenance model, it was detected no significant differences in the number of rearings between the Resveratrol + m-AMPH and control groups, but a trend to decrease of hyperactivity induced by m-AMPH was also reported in the animals from the Resveratrol + m-AMPH group.

In this study, it was also evaluated the effect of resveratrol on the levels of TBARS in the frontal cortex, hippocampus and striatum of rats (Fig. 2) in the reversal (a, b, and c) and maintenance (d, e, and f) models of mania induced by m-AMPH. Administration of m-AMPH elicited increase in TBARS content in the brain of the animals, indicating lipid oxidative damage, whereas administration of resveratrol reversed and prevented the lipid peroxidation in all brain regions evaluated.

In addition, it was evaluated the levels of 4-hydroxynonenal (4-HNE) in the frontal cortex, hippocampus, and striatum of the rats submitted to the animal model of mania and treated with resveratrol (Fig. 3). Administration of m-AMPH induced increase in 4-HNE content in the brain of animals submitted to the reversal (a, b and c) and maintenance (d, e, and f) treatments. Treatment with resveratrol reverted and prevented this alteration elicited by m-AMPH in all brain tissues evaluated.

Figure 4 depicts the effect of resveratrol on the levels of carbonylated proteins in the frontal cortex, hippocampus, and striatum of rats submitted to the animal model of mania induced by m-AMPH, in the reversal (a, b, and c) and

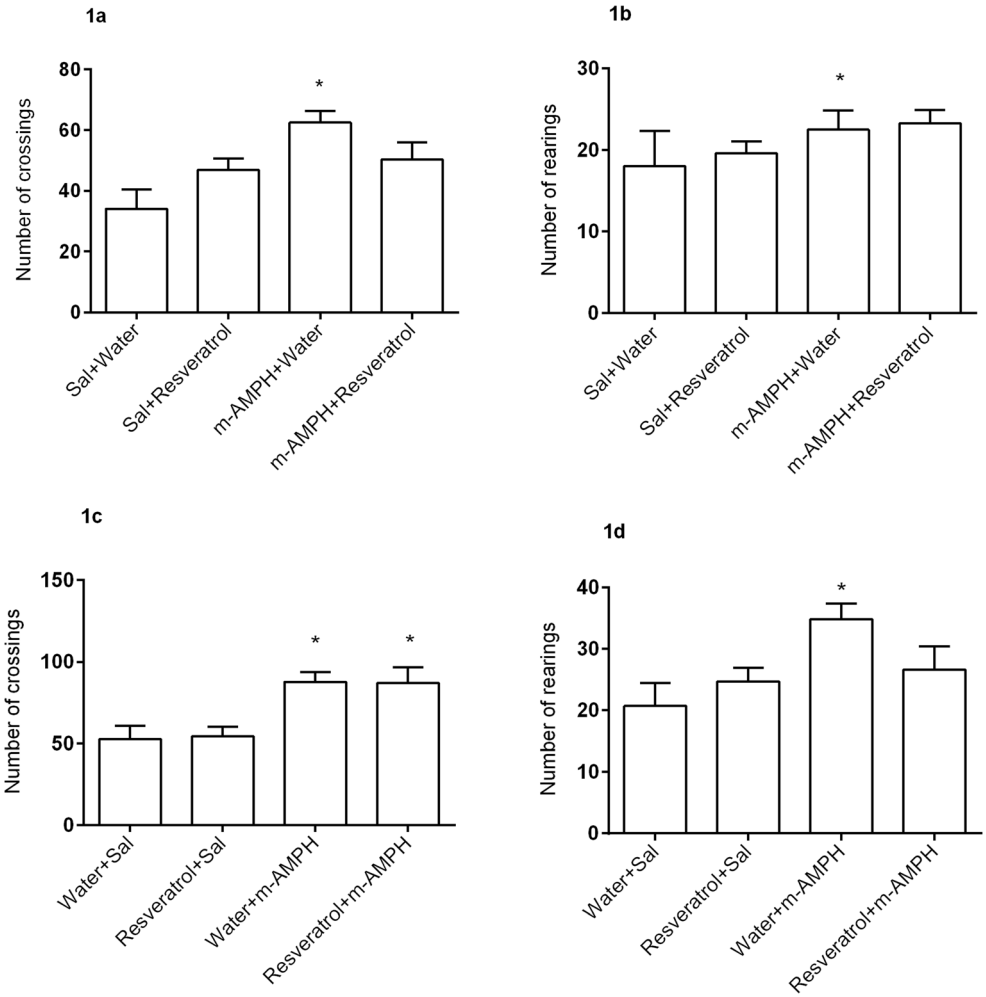

Fig. 1 Number of crossings (**a**) and rearings (**b**) in the reversal model ($n = 10$ for each group) and number of crossings (**c**) and rearings (**d**) in the maintenance model ($n = 10$ for each group). Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's test when p was significant. Values are expressed as mean ± S.E.M. $*p \leq 0.05$ as compared to Sal + Water group; $\#p \leq 0.05$ as compared to m-AMPH + Water group. Data were analyzed by two-way ANOVA followed by Tukey's test

maintenance (d, e, and f) models. Administration of m-AMPH increased the carbonylated protein levels in the brain of the animals, indicating protein oxidative damage. Nevertheless, administration of resveratrol reversed and prevented protein carbonylation in all brain regions assessed.

Levels of 3-nitrotyrosine in the frontal cortex, hippocampus and striatum are presented in Fig. 5, which shows the effects of resveratrol in rats submitted to the model of mania induced by m-AMPH, in the reversion (a, b, and c) and maintenance (d, e, and f) models. As can be observed, administration of m-AMPH increased the levels of 3-nitrotyrosine in all the brain tissues evaluated, indicating nitrosative damage to proteins. On the other hand, administration of resveratrol reversed and prevented the increase in 3-nitrotyrosine content in the brain regions evaluated.

Discussion

Administration of m-AMPH in the rats increases locomotion and exploration in the present paper, which are regarded manic-like behaviors. Indeed, many studies showed that administration of m-AMPH in rats increased the locomotor, exploratory and risk-taking behaviors, as well stereotypy (e.g. da-Rosa et al. 2012b; Feier et al. 2012, 2013). Moreover, treatment with Li, which is the standard mood stabilizer, reversed and prevented these manic-like behaviors induced by m-AMPH (Feier et al. 2013). Together, these studies suggest that the administration of Li in m-AMPH-administered rats mimics the pharmacological treatment of BD. Therefore, the animal model of mania induced by m-AMPH is a useful tool to the screening of drugs with possible mood stabilizer properties.

Administration of resveratrol did not reverse or prevent the increase in locomotor and exploratory activities induced by m-AMPH. Despite no significant differences in the crossing and rearing numbers between m-AMPH + Resveratrol and control groups in the reversal model, it was observed a trend to improvement in behavioral parameters in the group receiving resveratrol. According in part to our results, Miller and colleagues (Miller et al. 2013) showed that administration of resveratrol at doses of 1, 10 or 20 mg/kg body weight for 7 days attenuated, but not reversed, hyperactivity induced by m-AMPH in

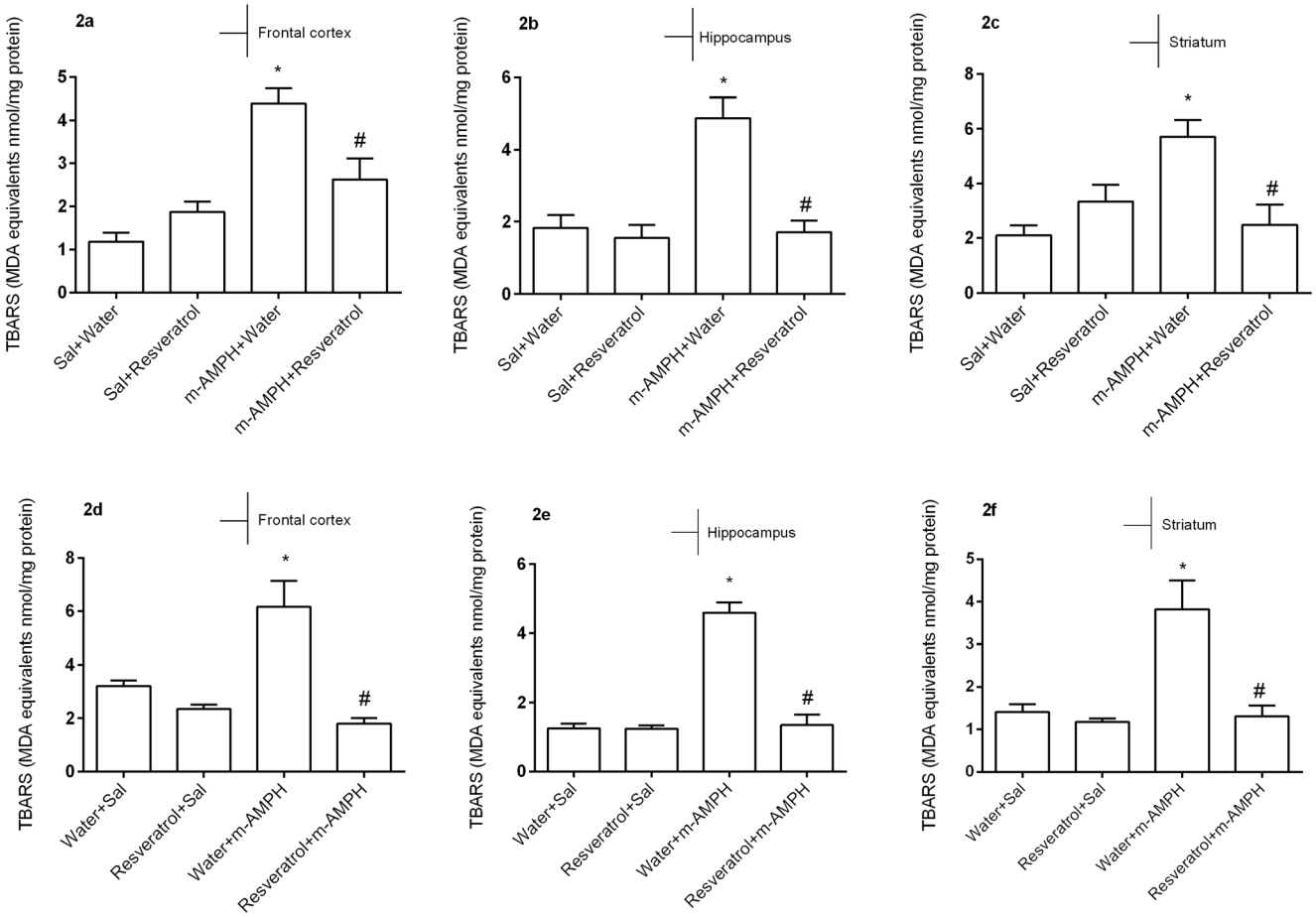

Fig. 2 TBARS levels in frontal cortex (**a**), hippocampus (**b**) and striatum (**c**) in the reversal model and in frontal cortex (**d**), hippocampus (**e**) and striatum (**f**) in the maintenance model. Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's test when p was significant. Values are expressed as mean ± S.E.M. $*p \leq 0.05$ as compared to Sal + Water group; $\#p \leq 0.05$ as compared to m-AMPH + Water group. Data were analyzed by two-way ANOVA followed by Tukey's test

rodents. However, the dose of m-AMPH used by these researchers (0.5 mg/kg) was half of that one in the present study. Additionally, treatment with resveratrol was not able to reverse cocaine-induced hyperactivity in the paper headed by Miller (2013). In an in vitro study, it was demonstrated that resveratrol prevented the m-AMPH-induced neurotoxicity in mesencephalic dopaminergic neurons (Sun et al. 2015). Sun and colleagues (Sun et al. 2015) showed that treatment with resveratrol increased cell viability and delayed m-AMPH-induced cellular apoptosis by decrease in the ROS content in dopaminergic neurons. Altogether, our findings and these studies suggest that treatment with resveratrol may protect the dopaminergic neurons against damage induced by m-AMPH and modulate, at least in part, the behavioral changes induced by this psychostimulant. Although resveratrol could not be effective to reverse locomotor and exploratory behaviors in all scenarios of present study, it could at least in part mitigate the oxidative disturbances elicited by m-AMPH. In this context, additional preclinical research is required to support use of resveratrol as a potential adjuvant therapy for manic symptoms in BD.

In the present study, it was demonstrated that m-AMPH induces oxidative damage to lipids and proteins in the brain of animals submitted to a model of mania. Administration of this compound induced increase in the TBARS, 4-HNE and protein carbonyl contents in frontal cortex, hippocampus and striatum, both in the reversal and maintenance protocols. It was also showed that m-AMPH induced increase in the levels of 3-nitrotyrosine, a marker of nitrosative damage to proteins. According to our data, studies also have reported that m-AMPH administration increases lipid and protein oxidation, expressed as increased TBARS and protein carbonyl contents (da-Rosa et al. 2012b; Feier et al. 2012, 2013). It is well described in the literature that amphetamine neurotoxicity is the result of ROS, which is generated from dopamine oxidation. Monoamine oxidase (EC 1.4.3.4)-catalyzed oxidation of others neurotransmitters, such as serotonin and norepinephrine, is the main mechanism of H_2O_2 generation in the brain (Halliwell 2001). Glutamate is also strongly involved in the effects of amphetamines (Tata and Yamamoto 2007). As the main excitatory neurotransmitter in the central nervous

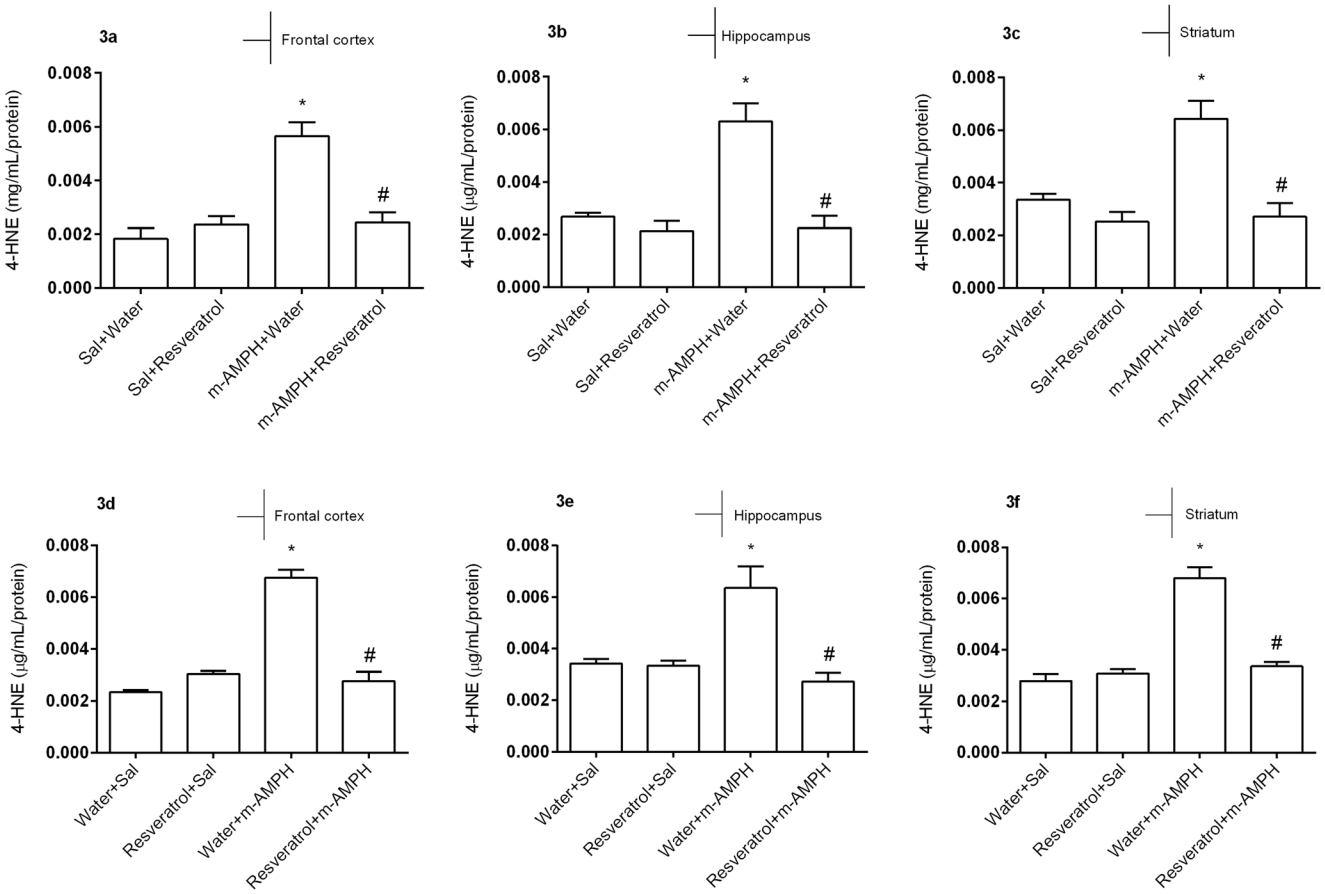

Fig. 3 4-HNE levels in frontal cortex (**a**), hippocampus (**b**) and striatum (**c**) in the reversal model and in frontal cortex (**d**), hippocampus (**e**) and striatum (**f**) in the maintenance model. Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's test when p was significant. Values are expressed as mean ± S.E.M. *$p \leq 0.05$ as compared to Sal + Water group; #$p \leq 0.05$ compared with m-AMPH + Water group. Data were analyzed by two-way ANOVA followed by the Tukey's test

system, prolonged increase in glutamate content induces increase in intracellular Ca^{2+} concentration and activation of nitric oxide synthase (NOS; EC 1.14.13.39) (Garthwaite 1991; Dawson and Dawson 1996). Nitric oxide (NO) biosynthesis is catalyzed by NOS; therefore, aberrant increase in NOS could induce nitrosative damage to proteins (Poon et al. 2004). Therefore, it can be suggested that m-AMPH induces protein and lipid damage through the production of ROS and reactive nitrogen species.

Oxidative damage to proteins has been reported in patients with BD and major depressive disorder, and high levels of protein carbonyl have been found in the serum of these patients (Magalhães et al. 2016). A clinical study demonstrated an increase in TBARS levels in the serum of BD patients during acute phases of mania, hypomania, and depression, as compared to healthy volunteers (Tsai and Huang 2015; Siwek et al. 2016). Post mortem studies have also showed increase in the protein carbonyl, 3-nitrotyrosine and 4-HNE contents in the frontal cortex of BD patients, as compared to healthy individuals (Kunz et al. 2008; Andreazza et al. 2010, 2013). Moreover, a study detected increase in the 3-nitrotyrosine levels in blood of BD patients (Andreazza et al. 2008). Since oxidative stress plays a pivotal role in BD physiopathology, it is of great interest that a compound with potential mood stabilizing activity present antioxidant effect, aiming the protection of the brain against oxidative damage.

Our data demonstrate that resveratrol administration prevented and reversed the oxidative and nitrosative damage to lipids and proteins induced by m-AMPH, in frontal cortex, hippocampus and striatum of the animals. Sun and colleagues (Sun et al. 2015) showed that treatment with resveratrol enhanced cell viability, delayed cell apoptosis and attenuated the ROS levels induced by m-AMPH in cultured dopaminergic neurons. In a study performed by Tadolini et al. (2000), resveratrol was showed inhibit lipid peroxidation, by removal of H_2O_2 from the cell membrane. These authors also demonstrated that resveratrol could easily enter in the lipid environment, which can substantiate, at least in part, its efficiency as an antioxidant (Tadolini et al. 2000). Corroborating with our results, a previous study showed that the chronic treatment with resveratrol (10 and 20 mg/kg body weight) during 25 days mitigated cognitive impairments induced by colchicine and

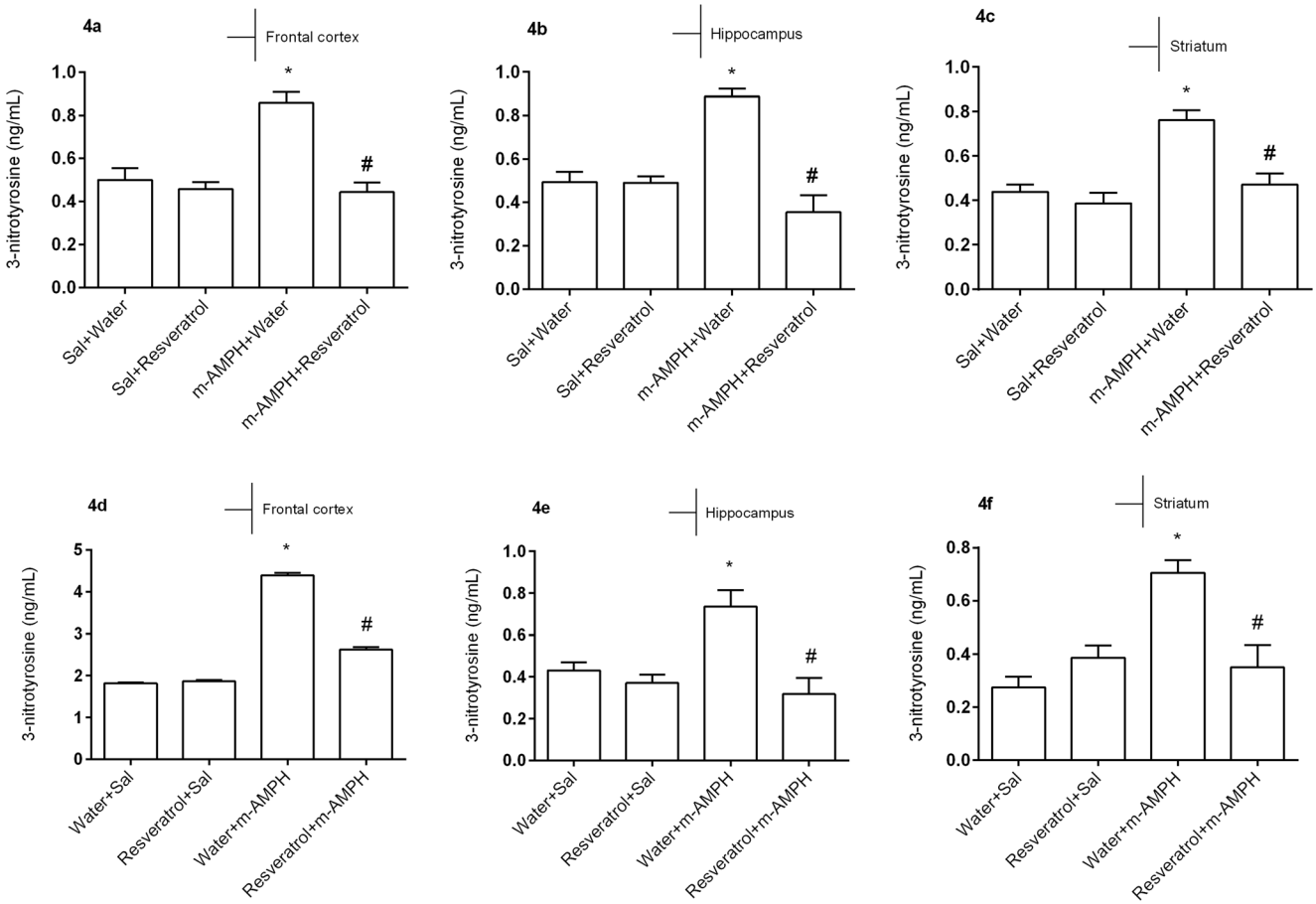

Fig. 4 3-Nitrotyrosine levels in frontal cortex (**a**), hippocampus (**b**) and striatum (**c**) in the reversal model and in frontal cortex (**d**), hippocampus (**e**) and striatum (**f**) in the maintenance model. Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's test when p was significant. Values are expressed as mean ± S.E.M. *$p \leq 0.05$ as compared to Sal + Water group; #$p \leq 0.05$ compared with m-AMPH + Water group. Data were analyzed by two-way ANOVA followed by the Tukey's test

decreased TBARS levels in rat brain (Kumar et al. 2007). These authors also showed that treatment with resveratrol restored glutathione levels, a radical scavenger, which is converted to oxidized glutathione through glutathione peroxidase (EC 1.11.1.9) and converted back to its reduced form by glutathione reductase (EC 1.8.1.7) (Kumar et al. 2007).

A previous study showed that the resveratrol i.p. administration in healthy rats decreased TBARS levels and increased catalase (EC 1.11.1.6) and superoxide dismutase (EC 1.15.1.1) activities in the brain, in a dose-dependent manner (Mokni et al. 2007). It is important to emphasize that in the present study resveratrol per se did not alter the levels of TBARS, 4-HNE, carbonyl and 3-nitrotyrosine. This discrepancy can be, in part, due to methodological differences. In the present study, administration of resveratrol was by gavage, while in the paper of Mokni and colleagues (Mokni et al. 2007) was i.p. In our study, resveratrol was diluted in water, while in the study headed by Mokni this substance was diluted in alcohol. It is well described in the literature that resveratrol has antioxidant properties and that its oral administration is promising in therapy of neurological diseases, mainly acting against oxidative stress (Singh et al. 2013). Additionally, resveratrol easily crosses the blood-brain barrier, which optimizes its effects in central nervous system (Baur et al. 2000; Tadolini et al. 2000).

Chemical structure of resveratrol enables the direct removal of free radicals by transference of hydrogen atoms and subsequent loss of protons in the transference of electrons, which can modulate the cell signaling and decrease the oxidative stress (Shang et al. 2009). Other action mechanism of this compound includes Nrf2 activation (Lee et al. 2003; Vargas and Johnson 2009; Singh et al. 2013). Nrf2 is a transcription factor expressed in all brain structures (Moi et al. 1994), and it plays an essential role in the cell defense against oxidative stress. Nrf2 also acts regulating inflammatory markers and increasing the expression of antioxidant enzymes (Shah et al. 2007; Innamorato et al. 2008). Therefore, it can be suggested two possible neuroprotector effects of resveratrol against brain lipid and protein oxidative damage: 1) resveratrol can act as radical scavenger, directly removing free radicals produced by dopamine oxidation induced by m-AMPH; 2) resveratrol can activate Nrf2, increasing the expression of antioxidant

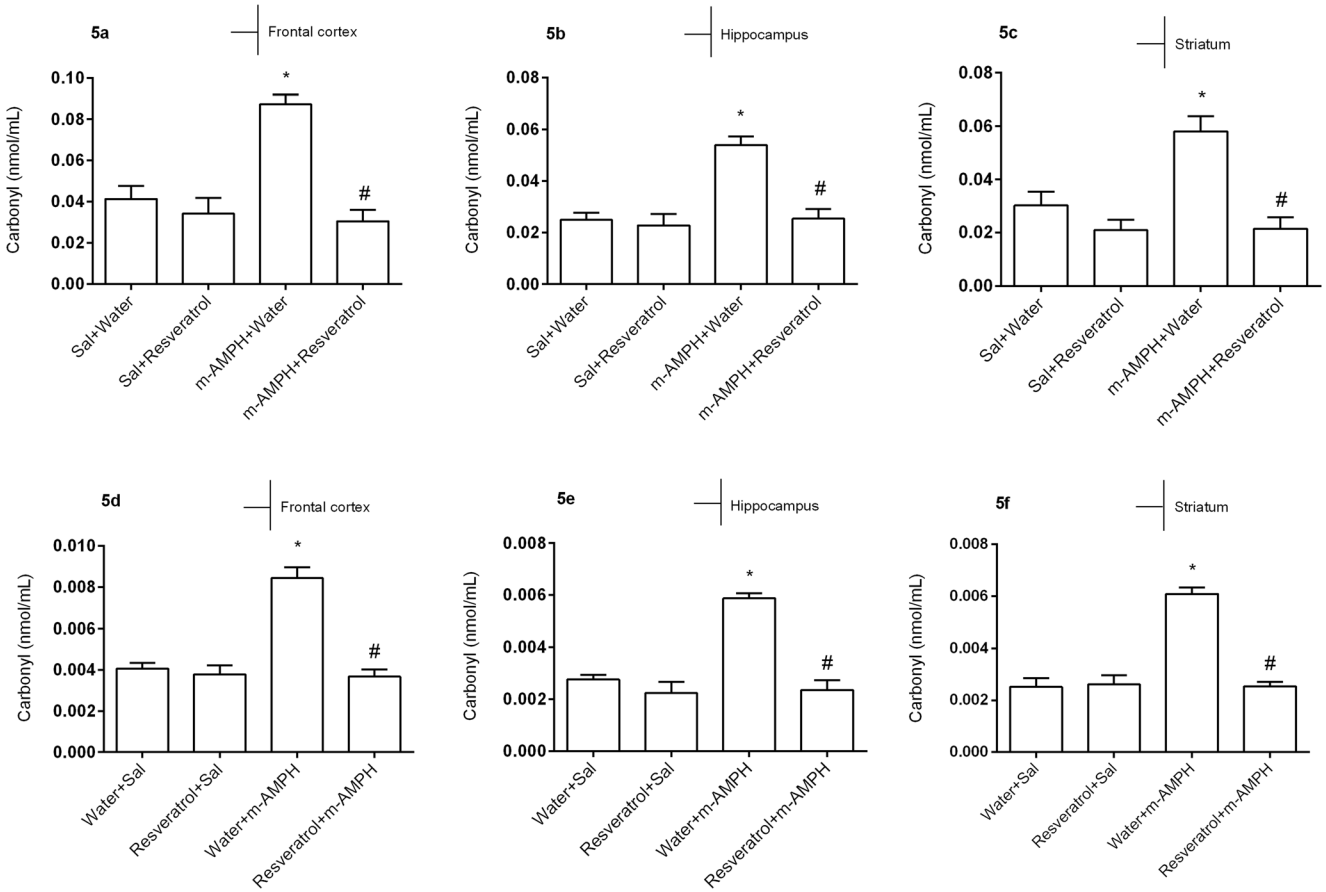

Fig. 5 Carbonyl levels in frontal cortex (**a**), hippocampus (**b**) and striatum (**c**) in the reversal model and in frontal cortex (**d**), hippocampus (**e**) and striatum (**f**) in the maintenance model. Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's test when p was significant. Values are expressed as mean ± S.E.M. *$p \leq 0.05$ as compared to Sal + Water group; #$p \leq 0.05$ compared with m-AMPH + Water group. Data were analyzed by two-way ANOVA followed by the Tukey's test

enzymes, preventing the brain from oxidative damage elicited by m-AMPH. One of the potential mechanisms involved in Nrf2 activation is the binding of resveratrol to estrogen receptors, whose activation triggers uncoupling of Nrf2 from Keap1 protein and renders Nrf2 prone to its activity as transcription factor (Lappano et al. 2009; Robb and Stuart 2011; Bastin and Djouadi 2016; Whitlock and Baek 2012; Xie et al. 2018). Thus, it cannot be ruled out that oxidative stress reported in the present study was balanced by an increase in the content of antioxidants in the brain triggered by resveratrol.

Indeed, 1 week acute dose of resveratrol could not be enough to detect any behavioral improvements in the present study. It is worthy to note that the dose of resveratrol could also have contributed in this context, but the dose included here was based in previous studies. On the other hand, oxidative stress was significantly decreased in the cerebral structures in this same concentration, indicating that the polyphenol could have mitigated the oxidative damage without significantly influence the dopaminergic pathway involved in the behavioral alterations.

In conclusion, data from the present study showed that resveratrol did not prevent or reversed utterly the manic-like behavior induced by m-AMPH. However, resveratrol administration in rats reversed and prevented the oxidative damage to proteins and lipids in the brain induced by m-AMPH. Regarding that oxidative stress plays important role in BD physiopathology, it would be of interest that new mood stabilizer candidates present antioxidant effects. Therefore, it can be suggested that an adequate resveratrol supplementation can be considered an adjunctive treatment for BD, in combination to the standard therapy of this condition.

Acknowledgements This study was in part funded by *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil* (CAPES - Finance Code 001), *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq), *Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina* (FAPESC), *Instituto Cérebro e Mente* and *Universidade do Extremo Sul Catarinense* (UNESC). JQ and SSV are CNPq Research Fellows. GCD, JHC and SM are holder of a FAPESC studentship and FFG is holder of a CNPq studentship.

Funding "This study was funded in part by the following brazillian institutions: *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) - Finance Code 001", *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq), *Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina* (FAPESC), *Instituto Cérebro e Mente* and *Universidade do Extremo Sul Catarinense* (UNESC), and *Associação Fundo de Incetivo à Pesquisa* (AFIP).

Compliance with ethical standards

Conflict of interest João Quevedo has the following conflicts of interest:
I. Clinical Research Support: Janssen Pharmaceutical (Clinical Trial), Allergan (Clinical Trial)
II. Advisory Boards, Speaker Bureaus, Expert Witness, or Consultant: Daiichi Sankyo (Speaker Bureau)
III. Patent, Equity, or Royalty: Instituto de Neurociencias Dr. Joao Quevedo (Stockholder)
IV. Other: Artmed Editora (Copyright), Artmed Panamericana (Copyright)

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