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ORIGINAL ARTICLE

Rutin alleviates cadmium-induced neurotoxicity in Wistar rats: involvement of modulation of nucleotide-degrading enzymes and monoamine oxidase

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Abstract

Rutin is a flavonoid commonly found in many vegetables, fruits and other plant species. Thus, this study investigated the protective role of rutin on cognitive function and impairment of ectonucleotidase, monoamine oxidase (MAO) and antioxidant enzymes activities in the cortex and hippocampus of cadmium-induced rats. Cognitive impairment was induced by an oral administration of 5 mg/kg Cadmium chloride for 14 consecutive days. Rutin was dissolved in 2% dimethyl sulfoxide (DMSO) and administered orally at the doses of 25 and 50 mg/kg for 14 days. Thereafter, animals were divided into six groups ($n = 6$) as follows: control, rutin 25 mg/kg, rutin 50 mg/kg, cadmium, cadmium plus rutin 25 mg/kg, cadmium plus rutin 50 mg/kg. After treatment period of 14 days, animals were sacrificed and the brain was dissected into cortex and hippocampus. Results showed that cadmium caused a significant increase in ectonucleotidases, adenosine deaminase (ADA) and MAO activities, with a concomitant decrease in thiol levels and antioxidant enzymes activities. However, treatment with rutin decreased ectonucleotidase, ADA and MAO activities in cadmium-induced rats. In addition, rutin reduced residual level of cadmium ion in the brain of cadmium-induced rats. Conclusively, present findings revealed that rutin could prevent/restored the impairment of the enzymes that regulate the purinergic and monoaminergic extracellular signaling and restore antioxidant status in cognitive impairment caused by prolonged cadmium exposure.

Keywords Rutin · Ectonucleotidases · Cognitive function · Monoamine oxidase · Cadmium chloride

Introduction

Normal cognitive function involves the ability to retain information for a certain period of time and still remember when needed (Devi et al. 2011). Cognitive dysfunction is associated with impairment of normal cognitive function and poor memory retention (Scullin and Bliwise 2015). Several factors such as age, emotions, and stress have been reported to lead to memory loss, and if not well managed, to more ominous threats like Parkinson's and Alzheimer's diseases (Foyet et al. 2015). Signaling events originated from extracellular nucleotides are directly related to ectonucleotidases activity such as ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase) and ecto-5′-nucleotidase (Robson et al. 2006; Yegutkin 2008; Bagatini et al. 2018). Adenosine triphosphate and its nucleoside derivative adenosine are signaling molecules necessary for a number of physiological and pathological events (Kepp et al. 2017; Safarzadeh et al. 2016). The level of these important signaling molecules is curtailed by a cascade of surface-bound enzymes called ectonucleotidases. NTPDase catalyzes the hydrolysis of ATP and ADP into AMP, which is subsequently converted by 5′-nucleotidase into adenosine (Robson et al. 2006; Sperlágh et al. 2006). Adenosine is further cleaved into inosine by adenosine deaminase at the synaptic cleft. In view of aforementioned, ectonucleotidases form an organized network for the regulation of nucleotide-mediated signaling, controlling rate, hydrolysis, and nucleoside formation (Bagatini et al. 2018;

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Zimmermann 2006). Furthermore, their involvement in learning, memory process and cognitive functions has been reported (Akinyemi et al. 2016). Another important signaling pathway responsible for modulation of mood, motor control and cognitive functions is monoaminergic signaling. Monoamine oxidease (MAO) is an enzyme that catalyzes the oxidative deamination of some important biogenic amines and amine neurotransmitters. The reactions catalyzed by MAO convert amines into their corresponding aldehydes, with byproducts such as H_2O_2 and NH_3. Of these byproducts, H_2O_2 is capable of initiating reactive oxygen species production and may induce neuronal apoptosis (Youdim et al. 2006).

Cadmium (Cd), one of the trace elements commonly found in nature, is presently among the top 20 hazardous substances known (He et al. 2005). Cd has been implicated in several diseases such as Wilson's disease and Menkes syndrome (Poujois et al. 2016). In addition, its accumulation in organs like liver, testis, pancreas, kidney and brain has been validated (Kumar et al. 2018; Renugadevi and Prabu 2010). Cd accumulates in the brain where it causes cognitive dysfunctions/disorders because of its ability to cross blood brain barrier (Yokel 2006; Karri et al. 2016). In most of the organs, Cd elicits its toxicity through oxidative stress, by increasing the production of free radicals through upregulation of NADPH oxidase and its associated proteins (Renugadevi and Prabu 2010; Ognjanović et al. 2008). Furthermore, there are growing evidences supported the fact that Cd induces oxidative stress via antioxidant enzymes inhibition, oxidation of membrane lipid and reduction in thiol (-SH) level (Renugadevi and Prabu 2010; Ognjanović et al. 2008).

Rutin (also known as quercetin-3-O-rutinoside) is a glycoside consists of flavonol (quercetin) and disaccharide (rutinose). It is commonly found in some fruits and vegetables such as apple, buckwheat, green tea and most citrus species (Ignat et al. 2011; Kesavan et al. 2018). The antioxidant and anti-inflammatory properties of rutin have been validated (Panchal et al. 2011). Moreover, the protective role of rutin in toxicant-induced toxicities in several organs has been reported; cisplatin and potassium bromate-induced nephrotoxicity (Kamel et al. 2014), high fructose-induced kidney damage (Hu et al. 2009), oxaliplatin-induced painful peripheral neuropathy (Azevedo et al. 2013) and STZ-induced oxidative damage to β pancreatic cells (Kamalakkannan and Prince 2006).

Although, there are reports on the neuroprotective properties of rutin, but much is still desirable especially its potential role on purinergic and monoaminergic systems in cadmium-induced rats. Therefore, this study aimed at evaluating the activity of monoamine oxidase and nucleotide-degrading enzymes in cortex and hippocampus of cadmium-induced rats treated with rutin, so as to validate the therapeutic potential of rutin in cognitive dysfunction associated with exposure to heavy metal.

Materials and methods

Rutin hydrate, Adenosine triphosphate, Adenosine monophosphate, Adenosine, 5,5′ dithio-bis-2-nitrobenzoic acid, semicarbazide, benzylamine and Coomassie Brilliant Blue G were obtained from Sigma Chemical Company, St. Louis, MO, USA. Cadmium chloride was procured from Oxford Laboratory, Mumbai, India. Other chemicals used were analytical grade and distilled water was used throughout.

Animal care and experimental design

Thirty-six (36) male Wistar albino rats weighing 150–180 g were procured from the Animal House, Department of Biochemistry, Federal University of Technology, Akure, Nigeria. The animals were acclimatized for two weeks and allowed to ad libitum access to water and commercial diet. The animals were housed in stainless steel cages and kept in a room where 12 h light/12 h dark cycle was maintained throughout the period of the experiment. All animal experiments were performed according to the protocols and recommendation of the Ethical committee of the School of Sciences, Federal University of Technology, Akure, Nigeria.. After two weeks of acclimatization, the animals were divided into six (6) groups ($n = 6$). Rutin was dissolved in 2% dimethyl sulfoxide (DMSO) (Ujah et al. 2018), and a dose of 25 mg/kg and 50 mg/kg (Tian et al. 2016) was administered orally for 14 days. Cadmium-induced group were rats orally administered with 5 mg/kg cadmium (Nna et al. 2017) for 14 consecutive days, rats in control group received 1 mL/kg of vehicle, cadmium +25 mg/kg and cadmium +50 mg/kg were cadmium-induced rats treated with 25 mg/kg and 50 mg/kg orally for 14 days respectively (Fig. 1). Rats were anesthetized under mild diethylether and sacrificed 24 h after last treatment. The brain tissue was quickly excised and rinsed in cold saline solution, blotted on filter paper to remove adhering blood, and dissected into cortex and hippocampus. The tissues were homogenized in 100 mM sodium phosphate, pH 7.4. The homogenates were centrifuged at 10,000 g for 10 min at 4 °C, and the supernatant was used for subsequent assays.

Monoamine oxidase activity

Monoamine oxidase (MAO) activity was determined using the standard method of Green and Haughton (1961) with slight modifications (Nwanna et al. 2019). In brief, the reaction mixture contained 0.025 mol/L phosphate buffer (pH 7.0), 0.0125 mol/L semicarbazide, 10 mmol/L benzylamine, and tissue homogenate. After 30 min incubation, acetic acid was added and incubated for 3 min in boiling water bath followed by centrifugation. Then, 1 ml of resulting supernatant was mixed with equal volume of 2, 4-dinitrophenylhydrazine, and 1.25 ml of benzene was added

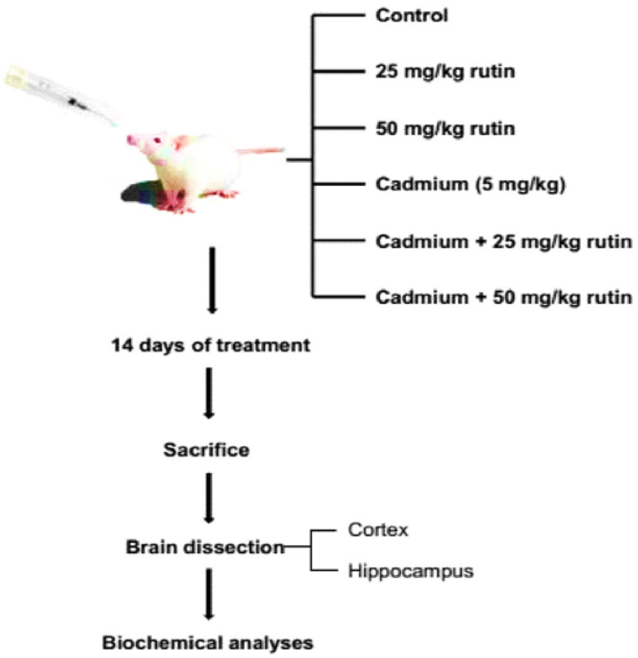


Fig. 1 Experimental design

after 10-min incubation at room temperature. Thereafter, the Benzene layer was separated and mixed with equal volume of 0.1 N NaOH. The alkaline layer was decanted and incubated at 80 °C for 10 min. The absorbance of orange–yellow color developed was measured at 450 nm in a UV/visible spectrophotometer.

Ectonucleotidase activity assay

The NTPDase enzymatic assay of the cortex and hippocampal homogenates was carried out in a reaction medium containing 5 mM KCl, 1.5 mM $CaCl_2$, 0.1 mM EDTA, 10 mM glucose, 225 mM sucrose and 45 mM Tris– HCl buffer, pH 8.0, in a final volume of 200 mL as previously described method (Schetinger et al. 2000). The 5′-nucleotidase activity was determined (Heymann et al. 1984) in a reaction medium containing 10 mM $MgSO_4$ and 100 mM Tris–HCl buffer, pH 7.5, in a final volume of 200 mL. In cortex (or hippocampus) homogenate, 20 mL of enzyme preparation was added to the reaction mixture and pre-incubated at 37 °C for 10 min. The reaction was initiated by the addition of ATP to obtain a final concentration of 1.0 mM and incubation proceeded for 20 min. For AMP hydrolysis, the 5′-nucleotidase activity was carried out as previously described (Heymann et al. 1984) and the final concentration of the nucleotide AMP added was 2 mM. The reactions were stopped by the addition of 200 mL of 10% trichloroacetic acid (TCA) to provide a final concentration of 5%. Subsequently, the tubes were chilled on ice for 10 min. The inorganic phosphate (Pi) produced was assayed using malachite green as the colorimetric reagent and KH_2PO_4 as standard (Chan et al. 1986). Enzyme specific activities were reported as ηmol Pi/min/mg of protein.

Adenosine deaminase assay

Adenosine deaminase (ADA) activity was determined in cortex and hippocampal homogenates as previously described (Guisti and Galanti 1984) with minor modifications. The assay measure amount of ammonia produced when ADA acts on adenosine. The cortex (or hippocampus) homogenate was added to the reaction mixture containing 21 mM of adenosine, pH 6.5, and were incubated at 37 °C for 60 min. The reaction was stopped by adding phenol–nitroprusside solution. The reaction mixture was immediately mixed with 125/11 mM alkaline-hypochlorite (sodium hypochlorite). 75 mM ammonium sulfate was used as ammonium standard. The protein content used for this experiment was between 0.4 to 0.6 mg/mL. Results were expressed as unit of specific enzyme activity/mg protein.

Antioxidant enzymes activity

Superoxide dismutase (SOD) activity was evaluated using the previously described method of Alia et al. (2003). 0.05 mL of cortex (or hippocampal) homogenate was treated with 1.0 mL carbonate buffer (5 mM, pH 10.2) and 0.017 mL of adrenaline. Change in absorbance was measured at 480 nm for 2 min at 15 s interval. Thereafter, SOD activity was calculated and expressed as Unit/mg protein. Catalase (CAT) activity was estimated using hydrogen peroxide as substrate according to the method of Claiborne (1985). In brief, 0.1 mL of each tissue homogenate was treated with 0.4 mL H_2O_2 (2 M) in the presence of 1.0 mL phosphate buffer (0.01 M, pH 7.0). The reaction was stopped by the addition of 2.0 mL dichromate acetic acid. The absorbance of the reaction mixture was read at 620 nm using spectrophotometer.

Total thiol and non-protein thiol determination

Total thiol content was determined in a reaction mixture contained cortex (or hippocampal) homogenate and Ellman reagent (10 mM 5,5′-dithiobis-2-nitrobenzoic acid in 0.1 M phosphate buffer, pH 7.5). The mixture was incubated at 37 °C for 10 min, and the absorbance was read at 412 nm (Ellman 1959). The same procedure was used for non-protein thiol determination except that cortex (or hippocampal) homogenate was first precipitated using 10% trichloroacetic acid. A standard curve was plotted using cysteine as standard. Both total thiol and non-protein thiol content of the tissue were calculated and expressed as mmol/mg protein.

Total protein determination

Total protein in cortex and hippocampal homogenates was determined according to the standard method of Bradford (1976), using serum albumin as standard.

Determination of cadmium residues

Whole brain tissue was digested according to the method of Babalola et al. (2009). Thereafter, the cadmium ion concentration of the digested tissue was measured using atomic absorption spectrophotometer. Analytical blank was run the same way as the samples and standard solution for the calibration curve was prepared in the same matrix. Cadmium concentration in brain tissue was expressed as ng/g dry weight.

Data analysis

Graphs were constructed using GraphPad Prism version 5.00 for Windows (GraphPad Prism Software, Inc., San Diego, California). The results were analyzed using One-way analysis of variance (ANOVA) followed by the Bonferroni multiple range test post-hoc and data were expressed as mean ± standard error of the mean (SEM). Significant was accepted at *p* values less than 0.05.

Results

Effect of rutin on MAO activity in cadmium-induced rats

Figure 2 showed the MAO activity in the cortex and hippocampal homogenates of cadmium-induced rats. From the results, cadmium significantly increased MAO activity in both cortex and hippocampal homogenates. However, rutin reversed the effect of cadmium on MAO activity by causing a significant reduction in MAO activity.

Effect of rutin on ectonucleotidase activities in cadmium-induced rats

Effect of cadmium and rutin on ectonucleotidases activities in cortex and hippocampus of cadmium-induced rats was presented in Fig. 3. Cadmium elevated NTPDase activity using ATP as substrate. Rutin restored the effect of cadmium on both cortex and hippocampus (Fig. 3a and b). Conversely, cadmium reduced 5′-nucleotidase activity in both cortex and hippocampus (Fig. 3c and d). However, treatment with rutin significantly increased 5′-nucleotidase activity ($p < 0.05$).

Effect of rutin on adenosine deaminase activity in cadmium-induced rats

As revealed in Fig. 4, cadmium enhanced hydrolysis of adenosine to inosine through elevated adenosine deaminase activity. However, rutin (25 and 50 mg/kg) reversed this effect in cadmium-induced rats treated with rutin.

Effect of rutin on antioxidant enzymes activities in cadmium-induced rats

The results of the effect of rutin and cadmium on the antioxidant enzymes activities were presented in Fig. 5. Cadmium caused a significant reduction in the activities of catalase (Fig. 5a and b) and superoxide dismutase (Fig. 5c and d). However, rutin significantly ($p < 0.05$) increased the activities of these antioxidant enzymes in both cortex and hippocampus of cadmium-induced rats treated with rutin.

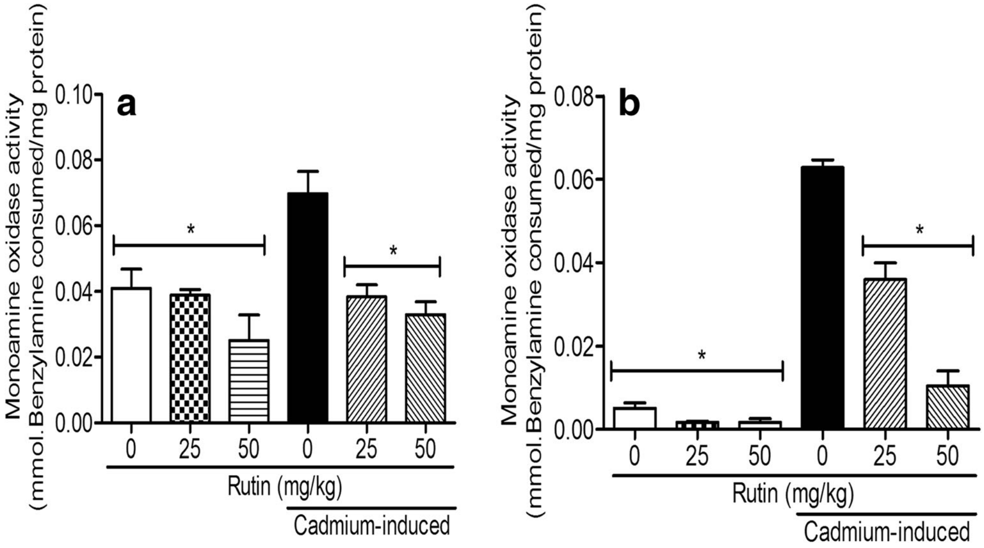


Fig. 2 Effect of rutin on (**a**) hippocampal and (**b**) cortex monoamine oxidase (MAO) activity in cadmium-induced rats. Bar represent mean ± standard error of mean (SEM) ($n = 6$). *$p < 0.05$ compared with cadmium-induced rats

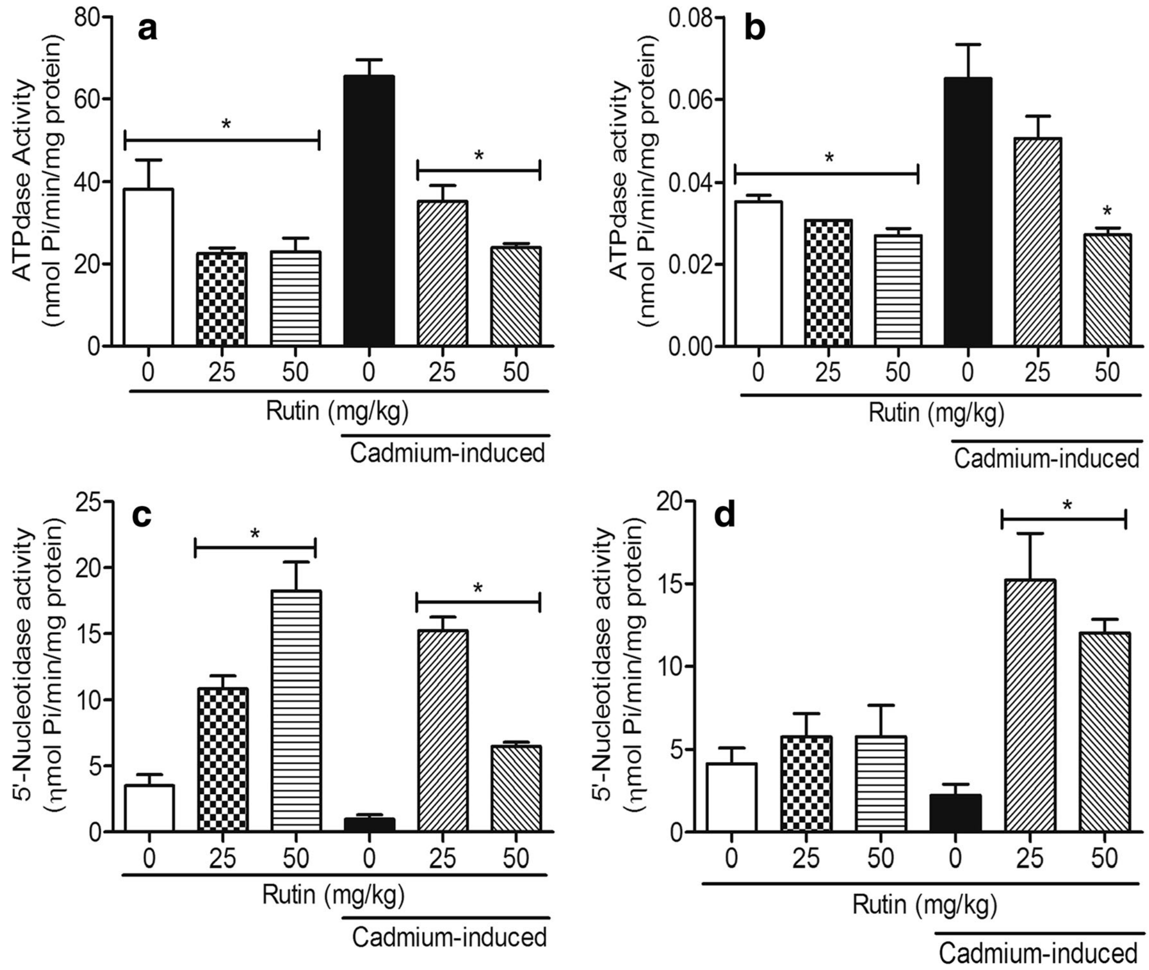
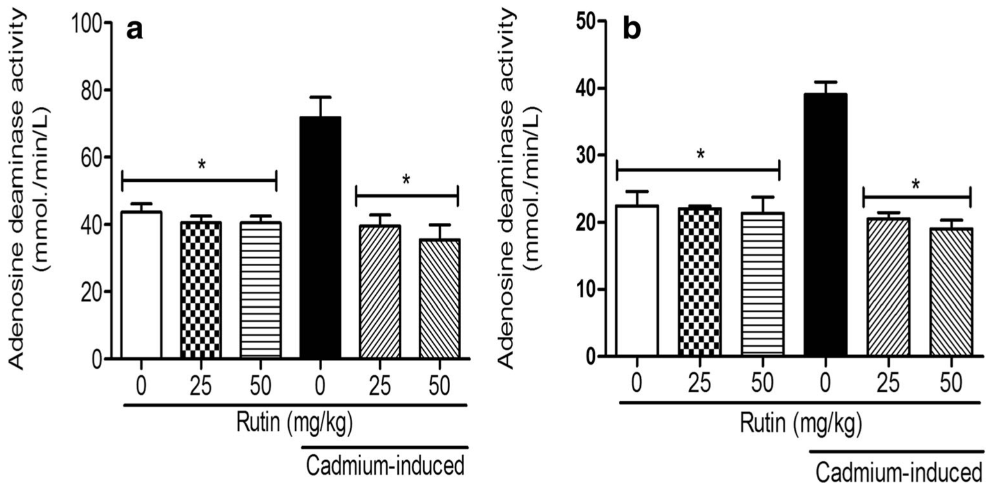


Fig. 3 Effect of rutin on (**a**) hippocampal and (**b**) cortex ectonucleotidase (ATPDase) and (**c**) hippocampal and (**d**) cortex 5′-nucleotidase activities in cadmium-induced rats. Bar represent mean ± standard error of mean (SEM) ($n = 6$). $^*p < 0.05$ compared with cadmium-induced rats

Effect of rutin on total thiol and non-protein thiol levels in cadmium-induced rats

Figure 6 showed the total thiol and non-protein thiol levels in the cortex and hippocampus of cadmium-induced rats. Cadmium-induced rats showed a reduced level of total thiol in both cortex and hippocampal homogenates (Fig. 6a and b). However, rutin (25 and 50 mg/kg) enhanced the reduction in total thiol level induced by cadmium administration. Similarly, cadmium

Fig. 4 Effect of rutin on (**a**) hippocampal and (**b**) cortex adenosine deaminase activity in cadmium-induced rats. Bar represent mean ± standard error of mean (SEM) ($n = 6$). $^*p < 0.05$ compared with cadmium-induced rats



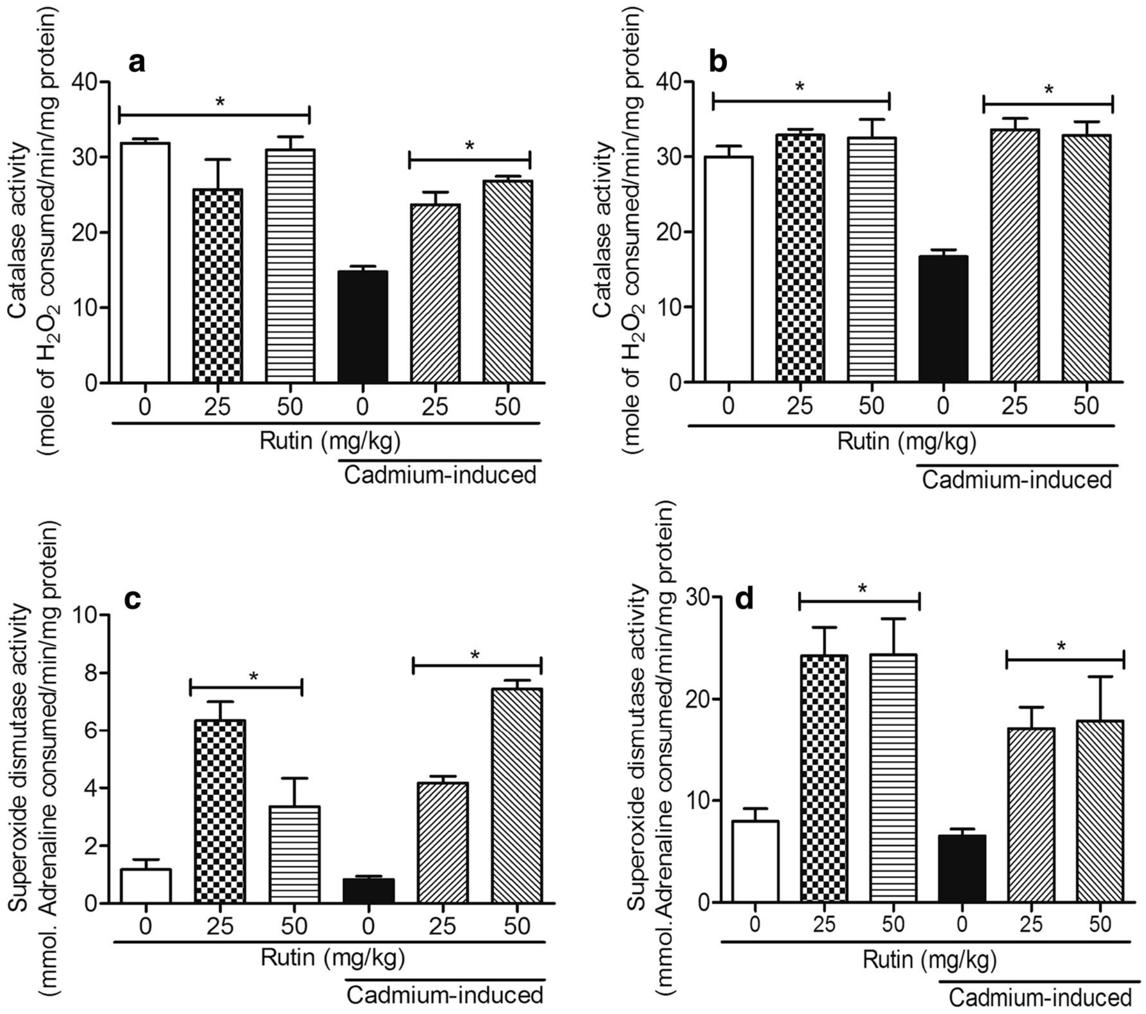


Fig. 5 Effect of rutin on (**a**) hippocampal and (**b**) cortex catalase and (**c**) hippocampal and (**d**) cortex superoxide dismutase activities in cadmium-induced rats. Bar represent mean ± standard error of mean (SEM) ($n = 6$). $^*p < 0.05$ compared with cadmium-induced rats

caused a significant decrease in non-protein thiol level in both cortex and hippocampus. However, rutin reversed the effect of cadmium in both cortex and hippocampus of cadmium-induced rats (Fig. 6c and d).

Effect of rutin on the level of cadmium ion in the brain of cadmium-induced rats

Result presented in Table 1 revealed accumulation of cadmium in the brain of cadmium-induced rats when compared with rats in the control group. Oral administration of cadmium (5 mg/kg) for 14 days significantly increased accumulation of cadmium in the brain of cadmium-induced rats. In contrast, treatment with rutin reduced the residual level of cadmium in the brain of cadmium-induced rats.

Discussion

Cadmium is neurotoxic and is implicated in the etiology of several neurological disorders (Jomova et al. 2010). Polyphenolic compounds, especially flavonoids have recently received unimaginable attention because of their neuroprotective properties (Solanki et al. 2015; Ablat et al. 2016). However, the effects of rutin on nucleotide- and monoamine-degrading enzymes in animal model of cadmium-induced neurotoxicity remain unclear. Thus, we investigated the effects of rutin on ectonucleotidase, 5′-nucleotidase, monoamine oxidase and antioxidant enzymes activities in cortex and hippocampal homogenates of cadmium-induced rats. Several studies have shown that ectonucleotidase and monoamine oxidase play an important role in neurotransmission and their alterations represent the underlying factor in the

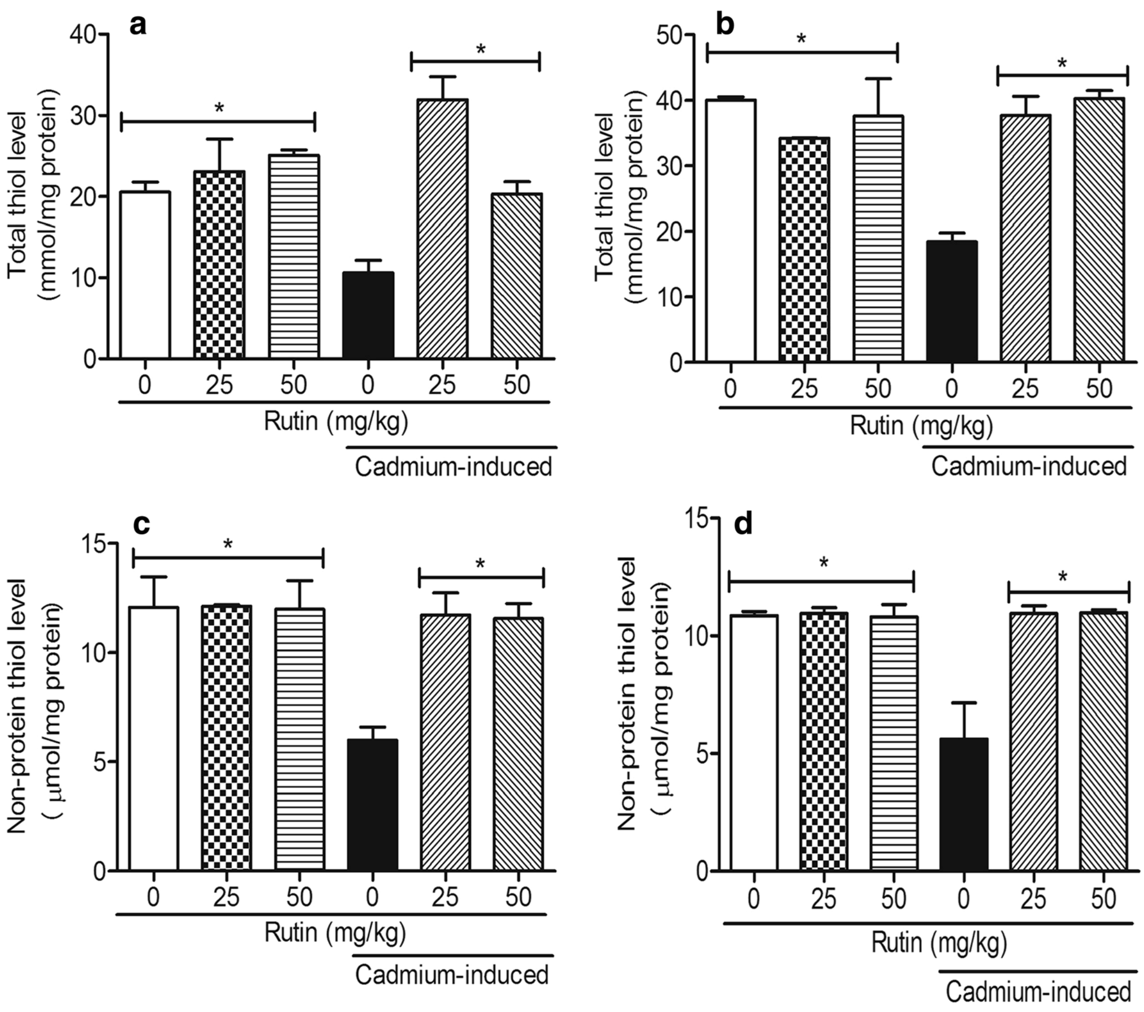


Fig. 6 Effect of rutin on (**a**) hippocampal and (**b**) cortex total thiol and (**c**) hippocampal and (**d**) cortex non-protein thiol levels in cadmium-induced rats. Bar represent mean ± standard error of mean (SEM) (*n* = 6). *$p < 0.05$ compared with cadmium-induced rats

manifestation of various pathological conditions (Burnstock 2009).

Monoamine oxidase (MAO) inhibition has been proposed as another way of managing cognitive dysfunction. In addition, studies have revealed increase in MAO activities in the brain of Alzheimer's disease patient compared with control (Borroni et al. 2017). Overexpression of MAO results in rapid hydrolysis of some important amine neurotransmitters that are crucial to memory function (Thomas 2000). Increased MAO activity give rise to elevated hydroxyl radical in the brain (Lee et al. 2001). In this study, we observed elevated MAO activity in cadmium-induced rats compared with control. However, treatment with rutin reversed the elevated MAO activity. There is notion that heavy metals induce neurotoxicity through oxidative stress. Therefore, it would be reasonable at this point to assume that increased MAO activity could be one of possible mechanisms underlying neurotoxic effect of cadmium, since increased MAO activity increases free radical production. Studies have shown that phenolic compounds are potent inhibitors of MAO (Sloley et al. 2000; Bandaruk et al. 2012; Saaby et al. 2009; Hou et al. 2005). Therefore, the tendency of rutin to reverse the elevated

Table 1 Effect of rutin on brain cadmium level in cadmium-induced rats

Groups	Cd concentration (ng/g)
Control	0.80 ± 0.14*
Rutin (25 mg/kg)	0.06 ± 0.005*
Rutin (50 mg/kg)	ND
Cadmium (5 mg/kg)	19.50 ± 6.36
Cadmium + Rutin (25 mg/kg)	9.50 ± 0.70*
Cadmium + Rutin (50 mg/kg)	7.49 ± 0.68*

Values represent mean ± standard error of mean (SEM) (n = 6). *ND* Not detected. *$p < 0.05$ compared with cadmium-induced rats

MAO activity in cadmium-induced rats could make food substances rich in rutin a functional food with potential to inhibit MAO activity.

The role of ATP in the peripheral and central nervous system (CNS) has been reported (Burnstock 2007; North and Verkhratsky 2006). Conversely, findings in this study revealed elevated NTPDase activities following cadmium administration in both cortex and hippocampus region of the brain. However, treatment with rutin (25 and 50 mg/kg) reversed the process. The increased NTPDase activity is tantamount to reduced level of ATP, an important neuromodulatory molecule. ATP is an excitatory molecule involved in several events in both peripheral and CNS (Burnstock 2007). In addition, there are existing evidences that ATP acts as neurotransmitter, co-transmitter in autonomic nerves and as a presynaptic modulator (Burnstock 2006; Cunha and Ribeiro 2000). Furthermore, elevated NTPDase activities could affect learning, memory and cognitive functions adversely since ATP has considerable influence on synaptic plasticity, learning and memory function (Wieraszko 1996).

In addition, our findings showed that cadmium caused a significant increase in adenosine deaminase activity, with concomitant decrease in 5′-nucleotidase activity in cortex and hippocampus of cadmium-induced rats. The activity of these enzymes is crucial as it determines the concentration and bioavailability of adenosine in the synaptic cleft (Burnstock 2006). A decrease in 5′-nucleotidase reduces adenosine formation, whereas, increased adenosine deaminase activity promotes its hydrolysis to form inosine. Thus, cadmium could alter adenosinergic neurotransmission through increased adenosine deaminase activity and/or decreased 5′-nucleotidase activity. Interestingly, treatment with rutin restored the alteration, thus, improving extracellular levels of adenosine in the brain. Majorly, two physiological activities of adenosine have been reported: (1) modulation of neuronal and synaptic activity; and (2) regulation of cerebral blood flow (Dunwiddie and Masino 2001; Brundege and Dunwiddie 1997). There are growing evidences support the modulatory activity of adenosine in learning and memory, which include fundamental cellular mechanisms involved in memory formation, for example the hippocampus long-term potentiation (LTP) and long-term depression (LTD) (De Mendonca et al. 1997).

Oxidative stress is one of mechanisms through which heavy metals elicit their toxic effect. In this study, cadmium altered antioxidant defense systems, emphasizing oxidative stress as a possible underlying mechanism for cadmium-induced damage. Thiol/sulfhydryl group is believed to be the first line of defense against toxicity induced by heavy metals (Flora et al. 2008). Most thiol containing compounds such as GSH act as non-enzymatic antioxidant through direct interaction of their –SH group with reactive oxygen species (ROS), or through enzymatic detoxification of ROS (Limón-Pacheco and Gonsebatt 2009). In this study, we observed a significant decrease in the levels of both total thiols and non-protein thiols, corroborating the general believe that cadmium bind exclusively to the –SH group (Khan and Parvez 2015). There are several reports on the alteration of sulfhydryl group upon cadmium administration. Reports have shown decrease in GSH level in various organs including brain of heavy metal induced animals (Khan and Parvez 2015; Hernández et al. 2015). The rationale behind this is not farfetched and could be attributed to the fact that cadmium exposure generates ROS that outweigh GSH production; thus, GSH depletion occurs. In addition, some antioxidant enzymes have –SH group in their catalytic site. Therefore, binding of cadmium to such –SH group may render the antioxidant enzyme inactive. Furthermore, we observed a significant decrease in antioxidant enzymes (superoxide dismutase (SOD) and catalase) activities following cadmium administration. Catalase, an antioxidant enzyme with heme prosthetic group, converts hydrogen peroxide to oxygen and water. The observed decrease in catalase activity finds agreement with earlier report that heavy metals (cadmium, lead) inhibit heme biosynthesis (Chen et al. 2015). Interestingly, the ability of rutin to enhance catalase and SOD activities and improve total and non-protein thiol levels in cadmium-induced rats could represent one the mechanisms by which rutin could help overcome neurotoxicity arise as a result of cadmium exposure.

The brain is one of the major organs affected by cadmium toxicity (Nemmiche et al. 2007). Cadmium can cross the blood-brain barrier, accumulate in the brain and cause toxicity to the neurons (da Costa et al. 2017). Several studies have unveiled the neurotoxic effect of cadmium and possible mechanisms of its toxicity (Flora et al. 2008; Méndez-Armenta and Ríos 2007; Nemmiche et al. 2007). It is important to note that residual cadmium level in the brain of rats administered cadmium was significantly increased. However, treatment with rutin significantly reduced cadmium level in the brain of cadmium-induced rats. The reduced cadmium level in rats induced with cadmium could be as a result of a metal-ligand relationship between cadmium and rutin, thereby lowering the heavy metal load in the brain. Blood-brain barrier is important for CNS to function properly. It forms an organized network of endothelial cells with low permeability. Oxidative stress has been reported to interrupt the physiological integrity of blood-brain barrier (Lochhead et al. 2010; Obermeier et al. 2013). This disruption gives room for toxic substances to gain access into the brain, thereby leading to pathogenesis and progression of different neurologic diseases. Accumulation of cadmium in the brain of cadmium-induced rats observed in this study agrees with previous report that cadmium is associated with leakage of blood-brain barrier in vivo (Shukla et al. 1996).

Conclusion

Findings in this study revealed that rutin alleviated cadmium-induced neurotoxicity by modulating activity of monoamine oxidase and nucleotide-degrading enzymes in cadmium-induced rats. In addition, it could be inferred that rutin is not only a strong antioxidant but also compound with modulatory effect on monoamine oxidase and ectonucleotidase activities, and this could be part of biochemical mechanisms underlying the neuroprotective properties of rutin. Thus, foods rich in rutin could protect against cognitive deficits in prolonged cadmium exposure.

Compliance with ethical standards

Conflict of interest None to declare.

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