Pyrrolidine dithiocarbamate protects against scopolamine-induced cognitive impairment in rats

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ABSTRACT

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that leads to disturbances of cognitive functions. Although the primary cause of AD remains unclear, brain acetylcholine deficiency, oxidative stress and neuroinflammation may be considered the principal pathogenic factors. The present study was constructed to investigate the anti-amnestic effect of pyrrolidine dithiocarbamate (PDTC) on scopolamine-induced behavioral, neurochemical and biochemical changes in rats. PDTC (50 and 100 mg/kg) and donepezil (2.5 mg/kg) were orally administered for 14 successive days. Dementia was induced at the end of the treatment period by a single injection of scopolamine (20 mg/kg; i.p.), and Y-maze test was conducted 30 min thereafter. Rats were then sacrificed and homogenates of cortical and hippocampal tissues were used for the estimation of noradrenaline, dopamine, serotonin and heat shock protein 70 contents along with acetylcholinesterase activity. In addition, certain oxidative stress markers, pro-inflammatory and anti-inflammatory cytokines were assessed. Histological examination of cortical and hippocampal tissues was also performed. Scopolamine resulted in memory impairment that was coupled by alterations in the estimated neurotransmitters, heat shock protein 70, acetylcholinesterase activity, oxidative stress as well as inflammatory biomarkers. Histological analysis revealed serious damaging effects of scopolamine on the structure of cerebral cortex and hippocampus. Pretreatment of rats with PDTC in both doses mitigated scopolamine-induced behavioral, biochemical, neurochemical and histological changes in a manner comparable to donepezil. The observed anti-amnestic effect of PDTC makes it a promising candidate for clinical trials in patients with cognitive impairment.

1. Introduction

Incidence of dementia has alarmingly increased nowadays (McCarty, 2006). Alzheimer's disease (AD), the most common form of senile dementia, is characterized by memory loss accompanied by degeneration of basal forebrain cortical cholinergic neurons (Heo et al., 2004; Korczyn and Vakhapova, 2007). The pathogenesis of AD is largely unknown but a number of hypotheses have been proposed including abnormal phosphorylation of the protein tau, altered calcium homeostasis, oxidative stress, production of inflammatory cytokines, deficits in energy metabolism, and altered protein processing resulting in abnormal β-amyloid peptide (Aβ) accumulation (Butterfield et al., 2002; Hardy and Selkoe, 2002; Huang et al., 2003; Zhu et al., 2004; Ferreira et al., 2006).

The cholinergic system plays an important role in learning and memory (Ellis, 2005). Scopolamine, an anticholinergic drug causes amnesia in humans and animals (Ogura et al., 2000). Loss of cholinergic neurons and subsequent deficits in cholinergic neurotransmission in the hippocampus and cerebral cortex are strongly correlated with clinical signs of cognitive impairment and dementia in AD patients (Mesulam, 2004). Hence, scopolamine-induced amnesia is widely cited as a model simulating human dementia in general and AD in particular (Joshi and Parle, 2006).

Treatment of dementia of Alzheimer type is based upon the neurotransmitter replacement approach. Current medications approved by Food and Drug Administration include acetylcholinesterase (AchE) inhibitors as donepezil, for mild to moderate cases, and memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of moderate to severe Alzheimer dementia. All of these drugs seem to be able to produce modest symptomatic improvements in some of the patients (Scarpini et al., 2003; Cummings, 2004).

The dithiocarbamates are a class of metal chelating antioxidants reported to be potent inhibitors of nuclear factor kappa B (NF-κB), a transcription factor regulating expression of pro-
2.3. Experimental design

From Quimica Clinica Aplicada (S.A., Spain). The most potent member of this class is pyrrolidine dithiocarbamate (PDTC) which enhances cellular defense mechanisms via upregulation of cyto-protective genes, including heat shock protein 70 (HSP70) and endogenous antioxidants such as superoxide dismutase and reduced glutathione (GSH) (Borrello and Dempfle, 1997; Wild and Mulcahy, 1999; Kim et al., 2001). Moreover, PDTC possesses metal chelating activity (Seki et al., 2000) and reduces the transcription of numerous pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β) and inducible nitric oxide synthase (Ziegler-Heitbrock et al., 1993; Satriano and Schlondorff, 1994) via inhibition of NF-κB (Schreck et al., 1992; Li et al., 1999).

Although PDTC has been shown to improve learning and memory functions of the transgenic APP/PS1 mice model for AD (Malm et al., 2007), yet its effects on the role of oxidative stress and neuroinflammation in AD has not been fully elucidated. The present study was performed to investigate the possible modulatory effect of PDTC in scopolamine-induced dementia and to compare such effects with donepezil, a commonly used agent in dementia and AD. The study design included evaluated effects of PDTC on some of the underlying mechanisms involved in AD progression.

2. Material and methods

2.1. Animals

Adult male albino Wistar rats, weighing 150–200 g each, were used in the present study. Animals were allocated in groups and were allowed to accommodate for one week in the animal house at Faculty of Pharmacy, Cairo University, before subjecting them to experimentation. They were provided with a standard pellet diet and were given water ad libitum. The animals were kept at a temperature of 22 ± 3 °C and a 12 h light/dark cycle as well as a constant relative humidity throughout the experimental period. The study was approved by the Ethics Committee for Animal Experimentation at Faculty of Pharmacy, Cairo University, Egypt.

2.2. Drugs and chemicals

Scopolamine hydrobromide was purchased from Sigma-Aldrich (MO, USA). It was dissolved in saline and i.p. administered in a dose of 20 mg/kg (Casas et al., 1999). PDTC was purchased from Sigma-Aldrich (MO, USA). It was suspended in 1% tween 80 and administered p.o. in doses of 50 and 100 mg/kg (Pfeilschifter et al., 2010). Donepezil hydrochloride was purchased from Pfizer (Cairo, Egypt). It was dissolved in saline and administered p.o. in a dose of 2.5 mg/kg (Kosasa et al., 1999). Reagent kits for IL-1β, interleukin-10 (IL-10) and HSP70 were purchased from Invitrogen (California, USA), Bender MedSystems (Vienna, Austria), and R&D Systems Chemical (MN, USA), respectively. Kit for AchE was purchased from Quimica Clinica Aplicada (S.A., Spain).

2.3. Experimental design

Animals were classified into two sets, each of five groups (10 rats each). The treatment period for animals was 14 days, and at the end of the treatment period (1 h after the last dose of test agents), all animals were i.p. injected with scopolamine hydrobromide (20 mg/kg) except the first group of each set, which served as a normal group. Group II animals served as control dementia. Animals in groups I and II received 1% tween 80 (p.o.). Group III was daily treated with donepezil hydrochloride (2.5 mg/p.o.), while rats of groups IV and V were treated daily with PDTC ammonium salt at two dose levels (50 and 100 mg/kg, p.o.). The Y-maze spontaneous alternation test was conducted 30 min after scopolamine injection. Immediately after performing the behavioral test, rats were sacrificed by decapitation; thereafter, in the first set, both cortical and hippocampal tissues were homogenized in 75% (v/v) aqueous methanol (HPLC grade) for the evaluation of monoamines. In the second set of experimental animals, cortical and hippocampal tissues were homogenized in ice-cold 50 mM phosphate buffer (pH = 7.4) for the estimation of thiobarbituric acid reactive substances (TBARS), GSH, IL-1β, IL-10 and HSP70 contents as well as AchE activity. Finally, brains of 2–3 rats from each group were preserved in 10% formalin and kept for histopathologic examination.

2.4. Y-maze spontaneous alternation test

The Y-maze test was performed as described by Wall and Messier (2002). The maze was made of 3 identical arms, 40 cm long, 35 cm high and 12 cm wide, positioned at equal angles and labeled A, B, and C. Rats were placed at the end of one arm and allowed to move freely through the maze during a 5 min session. Spontaneous alternation was examined by visually recording the pattern of entrance into each arm in the maze for each rat. Arm entry was considered to be complete when the hind paws of the rat were completely placed in the arm. Alternation was defined as successive entries into the three arms on overlapping triplet set (i.e., ABC, BCA…). The spontaneous alternation performance score (SAP), spontaneous alternation percentage (SAP%) and total arm entries (TAE) were calculated.

2.5. Estimation of brain dopamine, noradrenaline and serotonin contents

Dopamine, noradrenaline and serotonin contents were estimated in cortex and hippocampus according to the method of Pagel et al. (2000) using a fully automated high pressure liquid chromatography system (HPLC; Perkin-Elmer, MA, USA). In brief, homogenates were spun at 4000 × g, for 20 min and supernatants were immediately extracted from trace elements and lipids by the use of solid phase extraction Chromabond column NH2 phase (Chromabond, USA). Monoamine standards or samples (20 μl) were injected directly into the AQUA column (150 × 4.6 mm 5 μ C18) from Phenomenex [CA, USA] and a mobile phase composed of 97:3 mixture (v/v) of methanol: acetonitrile was used. A constant flow rate of 1.5 ml/min was maintained throughout the experiment that lasted for 12 min and the absorbance of monoamines was measured at 270 nm.

2.6. Estimation of brain lipid peroxides content

The thiobarbituric acid reaction of Mihara and Uchiyama (1978) was adopted for estimation of lipid peroxides level. To cortical and hippocampal homogenates orthophosphoric acid (1%) and thiobarbituric acid (0.6%) were added, mixtures were boiled for 45 min at 100 °C, then cooled. The colored product was extracted by n-butanol, vortexed and centrifuged at 3000 × g for 15 min. The absorbance of the organic layer was read at 535 and 520 nm and the difference in absorbance was calculated as lipid peroxides level expressed as TBARS (nmol/g wet tissue).

2.7. Estimation of brain reduced glutathione content

The method for the assessment of GSH (mg/g wet tissue) in the cortex and hippocampus was based on that of Beutler et al. (1963). Homogenates were deproteinized with 5-sulfosalicylic acid (10%) for
30 min at 4 °C then centrifuged at 3000 × g for 15 min at 4 °C. An aliquot of the acid soluble supernatant was diluted with phosphate buffer (0.3 M, pH = 7.7) and 5,5′ -dithiobis-2-nitrobenzoic acid (1 mM) was added to the samples, where its optical density was determined at 412 nm.

2.8. Estimation of brain contents of interleukin-1beta, interleukin-10, and heat shock protein 70 as well as acetylcholinesterase activity

Cortical and hippocampal IL-1β, IL-10 and HSP 70 were assessed using ELISA kits and results were expressed as pg/g wet tissue. AChE activity (U/g wet tissue) was measured according to the method of den Blauwen et al. (1983) using a colorimetric reagent kit. All the procedures of the used kits were performed following the manufacturer’s instruction manual.

2.9. Histological examination of cortical and hippocampal tissues

Histological assessment was performed on the brains of 2–3 rats randomly selected from each group. Brains were immediately fixed in 10% phosphate buffered formaldehyde, subsequently embedded in paraffin, and 5 μm longitudinal sections were performed. The sections were stained with hematoxylin and eosin (H and E) and examined microscopically.

2.10. Statistical analysis

Data were expressed as means ± SEM. Comparisons between means were carried out using one way analysis of variance (ANOVA) followed by least significant difference (LSD) test. Results of behavioral experiments were analyzed using Kruskal–Wallis non-parametric one way ANOVA followed by Dunn’s multiple comparisons test. A probability level of less than 0.05 was accepted as being significant in all types of statistical tests.

3. Results

Administration of scopolamine (20 mg/kg) as a single i.p. injection resulted in a significant reduction in SAP% by 38.11% as compared to normal group. On the other hand, no significant changes were noted on TAE and SAP (%)(Fig. 1A and B); accordingly, scopolamine did not affect locomotor activity of rats. Pretreatments with donepezil and PDTC (50 and 100 mg/kg) increased SAP%, while no significant change was observed in any of the other tested parameters as compared to control dementia, except for PDTC (50 mg/kg) which resulted in a significant increase in TAE as compared to normal group (Fig. 1A–C).

Rats injected with scopolamine displayed a significant decrease in the cortical dopamine content by 53.64% as compared with the normal group (Table 1). Treatment with donepezil and PDTC (50 and 100 mg/kg) for 14 days significantly increased cortical dopamine content as compared with scopolamine-induced dementia group. On the other hand, no significant changes were elicited in both noradrenaline and serotonin cortical contents and in hippocampal catecholamine contents in all treated groups compared to normal group (Tables 1 and 2).

Administration of scopolamine significantly increased both cortical and hippocampal TBARS content by 86.39% and 19%, respectively as compared to that of the normal group. Administration of donepezil and PDTC (50 and 100 mg/kg) protected against scopolamine-induced increase in lipid peroxidation (Fig. 2A and B). Rats that received scopolamine showed significant increase in both

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**Fig. 1.** Effect of pyrrolidine dithiocarbamate (PDTC) on Y-maze behavioral test in scopolamine-induced demented rats. Each bar with vertical line represents the mean percentage of (A) spontaneous alternation percentage (SAP%), (B) total arm entries (TAE) and (C) spontaneous alteration performance (SAP) for each group (8 rats) ± SEM.

*P < 0.05 vs. normal, @P < 0.05 vs. scopolamine; using One-Way ANOVA followed by Dunn’s multiple comparisons test.
cortical and hippocampal GSH content by 35.6% and 23.1%, respectively as compared to that of the normal group. Pretreatment of rats with donepezil and PDTC in the dose of 50 mg/kg protected against scopolamine-induced elevation of GSH content. On the other hand, pretreatment with PDTC (100 mg/kg) resulted in a significant decrease in cortical GSH content, while failed to produce any significant change in hippocampal GSH content (Fig. 3A and B).

In the present experiment, scopolamine administration increased cortical and hippocampal cholinesterase enzyme activity by 48.39% and 70.73%, respectively as compared to normal group (Fig. 4A and B). Elevation of cortical and hippocampal cholinesterase activity was normalized by all of the used agents (Fig. 4A and B).

In the current investigation, administration of scopolamine resulted in 36.2% and 30.68% decrease in both cortical and hippocampal IL-10 content, respectively as compared to the normal group (Fig. 5A and B). Treatments with donepezil and PDTC (50 mg/kg) provided significant protection against scopolamine-induced IL-10 depletion. However, treatment with PDTC (100 mg/kg) increased cortical IL-10 as compared to control dementia and reduced hippocampal IL-10 content as compared with the normal group (Fig. 5A and B). Scopolamine resulted in a significant increase in both cortical and hippocampal IL-10 content by 98.72% and 54.83%, respectively as compared with the normal group. Treatments with donepezil and PDTC (50 and 100 mg/kg) prevented such increase in cortical and hippocampal IL-10 content (Fig. 6A and B).

Administration of scopolamine significantly increased both cortical and hippocampal HSP 70 content by 20.86% and 37%, respectively as compared with the normal group. Treatment of rats with donepezil significantly decreased scopolamine-induced elevation in cortical HSP 70 content as compared with control dementia. Treatment with PDTC (50 mg/kg) prevented scopolamine-induced increase in cortical and hippocampal HSP 70 content by 27.3% and 34.71%, respectively as compared to control dementia, while treatment with 100 mg/kg decreased cortical HSP 70 by 26.88% and did not significantly affect hippocampal HSP 70 content, when compared to control dementia (Fig. 7A and B).

Histological examination of stained brain sections revealed serious damaging effects of scopolamine on brain tissues (Figs. 8B and 9B) compared to normal brain sections (Figs. 8A and 9A). Scopolamine-induced brain damage consisted of focal gliosis in cerebral cortex; in addition, the hippocampus showed spongiosis associated with edema and congestion in the blood vessels at the brain fissure (Figs. 8B and 9B). Spongiosis was diagnosed based on the appearance of vacuoles in the brain matrix. Gliosis results from activation of glial cells following induction of dementia. The perivascular edema in scopolamine-induced dementia group appears to be associated with thickening in the endothelium resulting in increased fluid permeability (infiltration) outside the vascular wall. Administration of donepezil provided partial protection against scopolamine-induced brain injury by preventing blood vessels congestion, while showing only edema in the hippocampus and focal gliosis in cerebral cortex (Figs. 8C and 9C). Pretreatment with PDTC (50 mg/kg) showed edema and congestion in the blood vessels associated with focal spongiosis in the hippocampus, while restored the normal

### Table 1
Effect of pyrrolidine dithiocarbamate administration on cortical monoamines concentrations.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th>Dopamine (μg/g tissue)</th>
<th>Noradrenaline (μg/g tissue)</th>
<th>Serotonin (μg/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>0.466 ± 0.017</td>
<td>1.18 ± 0.02</td>
<td>0.094 ± 0.004</td>
</tr>
<tr>
<td>Scopolamine</td>
<td></td>
<td>0.216 ± 0.018</td>
<td>1.06 ± 0.03</td>
<td>0.085 ± 0.004</td>
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<tr>
<td>Donepezil</td>
<td></td>
<td>0.535 ± 0.045</td>
<td>1.8 ± 0.10</td>
<td>0.100 ± 0.012</td>
</tr>
<tr>
<td>PDTC 50</td>
<td></td>
<td>0.697 ± 0.038</td>
<td>1.09 ± 0.04</td>
<td>0.087 ± 0.004</td>
</tr>
<tr>
<td>PDTC 100</td>
<td></td>
<td>0.698 ± 0.055</td>
<td>1.01 ± 0.01</td>
<td>0.098 ± 0.003</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM of 8 animals.

* P < 0.05 vs. normal, using One-Way ANOVA followed by LSD multiple comparisons test.

### Table 2
Effect of pyrrolidine dithiocarbamate administration on hippocampal monoamines concentrations.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th>Dopamine (μg/g tissue)</th>
<th>Noradrenaline (μg/g tissue)</th>
<th>Serotonin (μg/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>0.333 ± 0.020</td>
<td>1.29 ± 0.08</td>
<td>0.085 ± 0.006</td>
</tr>
<tr>
<td>Scopolamine</td>
<td></td>
<td>0.333 ± 0.020</td>
<td>1.29 ± 0.08</td>
<td>0.085 ± 0.006</td>
</tr>
<tr>
<td>Donepezil</td>
<td></td>
<td>0.319 ± 0.017</td>
<td>1.16 ± 0.07</td>
<td>0.077 ± 0.007</td>
</tr>
<tr>
<td>PDTC 50</td>
<td></td>
<td>0.303 ± 0.041</td>
<td>1.11 ± 0.07</td>
<td>0.069 ± 0.005</td>
</tr>
<tr>
<td>PDTC 100</td>
<td></td>
<td>0.319 ± 0.011</td>
<td>1.22 ± 0.06</td>
<td>0.069 ± 0.005</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM of 8 animals. Statistical analysis were performed using One-Way ANOVA followed by LSD multiple comparisons test.

**Fig. 2.** Effect of PDTC on cortical (A) and hippocampal (B) thiobarbituric acid reactive substances (TBARS) content in scopolamine-induced demented rats. Each bar with vertical line represents the mean of 8 rats ± SEM. *P < 0.05 vs. normal, #P < 0.05 vs. scopolamine, *P < 0.05 vs. donepezil; using One-Way ANOVA followed by LSD multiple comparisons test.
structure of cerebral cortex tissues (Figs. 8D and 9D). On the other hand, pretreatment with PDTC (100 mg/kg) provided marked protection against scopolamine-induced brain injury revealed by near restoration of the normal structure of brain tissues and showing only edema in the hippocampus (Figs. 8E and 9E).

4. Discussion

Scopolamine-induced amnesia has been used extensively to evaluate potential therapeutic agents for treating AD (Blokland et al., 2006; Kwon et al., 2009). Scopolamine is a muscarinic receptor antagonist that inhibits central cholinergic neuronal activity and influences the expression of a broad spectrum of genes associated with muscarinic receptor signaling pathways, apoptosis, and cell differentiation in rat brain (Hsieh et al., 2003). Hence, it causes profound memory impairment in animals and humans as degeneration and dysfunction of cortical cholinergic neurons is closely associated with cognitive deficits in AD (Giacobini, 1998; Lieben and Blokland, 2005).

Indeed in the current study, single i.p. injection of scopolamine was coupled by significant decrease in spontaneous alternation percentage of rats in Y-maze test coupled with increased activity of AchE activity in cortex and hippocampus together with marked histopathologic changes in both regions. Scopolamine-induced changes were attenuated by pretreatment of rats with donepezil and PDTC in both doses used. Similar results regarding the effects of scopolamine (Jung et al., 2012; Kim et al., 2013; Oh et al., 2013) and donepezil (Hu et al., 2012; Jung et al., 2012; Kim et al., 2013) on the aforementioned parameters were reported.

Donepezil is a piperidine class AchE inhibitor, designed especially for AD (Sugimoto et al., 1995). It was proven to improve cognitive function of mild to moderate AD patients and showed excellent tolerability without hepatotoxicity (Mihara et al., 1993; Rogers et al., 1998).

PDTC was not previously investigated in scopolamine-induced amnesia model. However, in a study performed by Cheng et al. (2006), PDTC prevented Aβ-induced neuropathological and neuroinflammatory responses, as well as the learning and spatial memory deficits. Moreover, PDTC has been shown to improve learning and memory functions of the transgenic APP/PS1 mice model for AD (Malm et al., 2007). The reported protective effects of PDTC in models of cerebral ischemia (Nurmi et al., 2006; Pfeilschifter et al., 2010) were attributed to inhibition of NF-κB (Schneider et al., 1999; Zhao et al., 2012). Suppression of NF-κB pathway has been shown to attenuate cognitive deficits induced in rats by diabetes (Kuhad et al., 2009).

The observed neuroprotective effects of PDTC may also be related to its ability to inhibit expression of matrix metalloproteinase-9 (MMP-9) (Zhao et al., 2012); as increased expression of MMP-9 has been linked to cognitive impairment in elderly patients (Gaudet et al., 2010). Moreover, MMP-9 inhibition has also been reported to improve Aβ-mediated cognitive impairment and neurotoxicity (Mizoguchi et al., 2009).
In the current experiments, scopolamine-induced pathological and behavioral changes were coupled by decrease in cortical dopamine content that was prevented by pretreatment with donepezil or PDTC. Scopolamine-induced dementia was shown to be associated with reduced brain dopamine content (Zhou et al., 2009).

Neurotransmitters play a critical role in the brain circuits involved in various aspects of memory. The importance of acetylcholine is illustrated by the psychopathology of AD (Giacobini, 1998; Lieben and Blokland, 2005). Dopamine in the prefrontal cortex also contributes to information storage, particularly working memory (Iversen, 1998). In fact dopamine agonists improve scopolamine-induced deficits by increasing the release of acetylcholine (Steele et al., 1997).

Increased free radical activity appears to fuel Alzheimer’s pathology acting simultaneously as a mediator, product and trigger for this “clogging” process and its related neural damage (Jimenez-Jimenez et al., 1997; McIntosh et al., 1997). Lipid peroxidation produced by the attack of reactive oxygen metabolites (ROM) on cell membranes result in membrane fluidity and permeability, which eventually leads to oxidative destruction of cellular membranes and cell lysis (Halliwell and Gutteridge, 1990). Free radicals are thought to cause behavioral deficits in experimental animals.
Stadtman (1992) reported that balanced antioxidants are required to control the cognitive and motor functions of the cerebral cortex and the hippocampus. Indeed in the present study, scopolamine induced deficits was accompanied by increased cortical and hippocampal lipid peroxidation manifested by increased formation of TBARS in both regions. An

(Fukui et al., 2001, 2002). Stadtman (1992) reported that balanced antioxidants are required to control the cognitive and motor functions of the cerebral cortex and the hippocampus.
increase in cortical and hippocampal GSH contents by scopolamine was also observed.

GSH provides major protection in oxidative injury by participating in the cellular defense systems against oxidative damage (Jeffries et al., 2003). Decreased cellular GSH contents and capacity for GSH synthesis sensitize cells to certain drugs but GSH may be induced in cells exposed to oxidative stress as an adaptive process (Ilibey et al., 2009). This could probably explain the observed increase in cortical and hippocampal GSH content.

Treatment of rats with donepezil or PDTC reduced scopolamine-induced increase in brain TBARS. Regarding the present effect on changes induced in brain GSH content by PDTC, only the small dose level was effective.

PDTC functions as an antioxidant due to two structural features: direct scavenging of ROM by the dithiocarbony group and changes induced in brain GSH content by PDTC, only the small dose induced increase in brain TBARS. Regarding the present effect on the observed increase in cortical and hippocampal GSH content.

References

Increase of scopolamine dementia was coupled by increased cortical and hippocampal contents of HSP 70 that was prevented by pretreatment with PDTC. Although, HSP 70 mRNA is not detected in the brain under normal condition (Wagstaff et al., 1996), HSP 70 is expressed in the brain in response to any stressful condition and is therefore suggested as cytoprotective protein in ameliorating tissue damage (Kelly and Yenari, 2002; Yasuda et al., 2005).

In conclusion, the prevalence of AD and dementia has increased significantly nowadays. As none of the available medications appear to be able to stop the disease progression, there is enormous medical need for the development of novel therapeutic strategies that target the underlying pathogenic mechanisms in AD. Keeping in mind that PDTC has broad cytoprotective properties as observed in the current study; its use might slow progress of the multifactorial AD. Further studies may be needed, however, to examine the role of PDTC in scopolamine-induced dementia after development of symptoms to simulate what actually happens in patients with AD.

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References


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