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ORIGINAL ARTICLE

Alleviation of haloperidol induced oxidative stress in rats: Effects of sucrose vs grape seed extract

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KEYWORDS

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Abstract Haloperidol (HP) is a classic antipsychotic drug known for its propensity to cause extrapyramidal side effects. HP is known to induce oxidative stress due to increased turnover of dopamine. The aim of the present study was to investigate the effect of sucrose (1 and 5 mg/kg; p.o.) and grape seed extract (GSE; 100, 200 and 400 mg/kg; p.o.) on the oxidative stress induced in rats by HP (1 mg/kg; p.o.) in the liver and the brain tissues. Oxidative stress was induced by injection of HP for 14 consecutive days which was concurrently administered with sucrose and GSE. Liver and brain levels of malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide (nitrite) levels were determined in the brain and liver. Results of the present study revealed that HP-treated rats showed elevated levels of NO in the brain and MDA in the brain and liver. HP-treated rats showed also decreased levels of NO levels in the liver and GSH in the brain and liver. Treatment of HP-treated rats with GSE reversed all the oxidative stress markers in both the brain and liver due to its potent antioxidant property. On the other hand, sucrose attenuates the levels of NO in the brain and liver and the brain levels of MDA and GSH. It can be concluded that both GSE (a potent anti-oxidant) and sucrose (as a source of energy) have beneficial impacts on the brains of HP-treated rats. However, GSE is more potent in alleviating the oxidative stress associated with HP in the liver.
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1. Introduction

Haloperidol (HP), a butyrophenone, has been used as an antipsychotic drug in human. Unfortunately, the therapeutic effects of HP are accompanied by severe extrapyramidal side effects, resulting in movement disorders in patients. HP has been used clinically in the treatment of psychiatry, obstetrics, and anesthesiology, and its pharmacology has been widely reported.[1,2]

There has been increasing indication, implicating oxidative stress as a causative factor in neuropsychotic disorders including schizophrenia.[3,4] Free radicals have been implicated in the pathogenesis and clinical course of neuropsychiatric disorders such as schizophrenia and in the development of tardive dyskinesia. Increased superoxide dismutase (SOD) activity has been reported in the red blood cells of schizophrenic patients by some groups.[5–7] Abnormal activity of catalase (CAT) has also been reported.[8] Some studies have shown decreased CAT and increased SOD in schizophrenic patients.[6] Increased blood levels of malondialdehyde MDA have been

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found in schizophrenic patients relative to normal controls.[9] The brain is deficient in oxidative defense mechanisms and hence is at a greater risk of damage mediated by reactive oxygen species (ROS), resulting in molecular and cellular dysfunctions.[10] ROS can damage virtually any biological molecule in its vicinity, including DNA, essential proteins and membrane lipids.[11] There have been reports of membrane pathologies and alterations in membrane phospholipids, essential fatty acids and signal transduction,[12] which are believed to be ROS mediated.

Chronic treatment of HP is known to induce oxidative stress due to increased turnover of dopamine.[13] HP is cytotoxic to primary hippocampal neurons.[14] It was demonstrated that it causes necrotic death rather than apoptotic. Some studies reported the cytotoxic nature of HP but have not specified the type of cell death.[15] Others in their investigations, have demonstrated that amyloid beta resistant cells were opposed to HP toxicity, implying the role of free radicals in HP-induced cell death.[16] Typical neuroleptics such as HP and chlorpromazine are known to cause oxidative stress,[16] which is thought to be responsible for its extrapyramidal side effects.[16,17] It has also been shown that increasing doses of HP in rats[17] attenuate the extrapyramidal side effects caused by the same drug. Previous research has also shown that coadministration of haloperidol and antioxidants such as vitamin E resulted in a beneficial effect in patients with tardive dyskinesia.[18]

The aim of the present study was to investigate the effect of sucrose (as a source of energy) and grape seed extract (as a potent antioxidant) on the oxidative stress induced in rats by HP in both the liver and the brain. Oxidative stress was induced by injection of HP for 14 consecutive days which was concurrently administered with sucrose and GSE. Liver and brain levels of some relevant biomarkers for oxidative stress and nitric oxide (NO) were determined. Lipid peroxide levels (measured as malondialdehyde; MDA) were taken as *in vivo* reliable indices for the contribution of free radical generation in oxidative stress. Nitrate/nitrite levels were used as a convenient marker for NO formation.

2. Materials and methods

2.1. Animals

Rats with 120–150 g of body weight were used. Rats were obtained from animal house colony of the National Research Centre (Cairo, Egypt). Rats were housed under standardized conditions with free access to standard laboratory food and water. Animal procedures were performed in accordance with the Ethics Committee of the National Research Centre and followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). Equal groups of 6 rats each were used in all experiments.

2.2. Drugs and chemicals

Grape seed extract (Mepaco, Egypt), haloperidol (ChemiPharm, Egypt), sucrose were used in the present investigation. They were freshly prepared in distilled water and given orally. Thiobarbituric acid (TBA) was purchased from Merck (Germany). All other chemicals were of the highest commercially available grade.

2.3. Experimental design

Rats were randomly allocated into seven groups (8–10 rats each) and the following groups were studied: Group I: containing rats receiving saline. Group II: containing rats receiving HP (1 mg/kg). Group III: containing rats receiving HP (1 mg/kg) and sucrose (1 mg/kg; p.o.). Group IV: containing rats receiving HP (1 mg/kg) and sucrose (5 mg/kg; p.o.). Group V: containing rats receiving HP (1 mg/kg) and GSE (100 mg/kg; p.o.). Group VI: containing rats receiving HP 1 mg/kg and GSE (200 mg/kg; p.o.). Group VII: containing rats receiving HP (1 mg/kg) and GSE (400 mg/kg; p.o.).

Twenty-four hours after the last dose, the rats were sacrificed by cervical dislocation, the liver and brain were isolated and homogenized in phosphate buffer.

2.3.1. Biochemical analysis

Rats were euthanized by decapitation under ether anesthesia, brains and livers were excised, washed with ice-cold saline solution (0.9% NaCl), weighed and stored at −80 °C for biochemical analyses. The liver was homogenized with 0.1 M phosphate buffer saline at pH 7.4, to give a final concentration of 10% w/v for biochemical assays.

2.3.2. Determination of nitric oxide

Nitric oxide measured as nitrite was determined by using Griess reagent, according to the method of Moshage et al. (1995) where nitrite, stable end product of NO radical, is mostly used as an indicator for the production of NO.[19]

2.3.3. Determination of lipid peroxidation

Lipid peroxidation was assayed by measuring levels of malondialdehyde (MDA) in the brain and liver tissues. Malondialdehyde was determined by measuring thiobarbituric reactive species using the method of Ruiz-Larrea et al. (1994), in which the thiobarbituric acid reactive substances react with thiobarbituric acid to produce a red colored complex having peak absorbance at 532 nm.[20]

2.3.4. Determination of reduced glutathione

Reduced glutathione (GSH) was determined by Ellman's method (1959). The procedure is based on the reduction of Ellman's reagent by –SH groups of GSH to form 2-nitro-s-mercaptobenzoic acid, the nitromercaptobenzoic acid anion has an in-tense yellow color which can be determined spectrophotometrically.[21]

2.4. Statistical analysis

Drug effects on HP-induced biochemical changes were expressed as the mean ± SEM. Data were analyzed with a one-way ANOVA followed by post hoc comparisons using Tukey's multiple comparisons test.

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