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Effects of royal jelly on genotoxicity and nephrotoxicity induced by valproic acid in albino mice

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ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form
13 January 2014
Accepted 16 January 2014
Available online 21 March 2014

Keywords:
Valporic acid
Royal jelly
Kidney
Ultrastructural
Chromosomal aberrations
Mice

ABSTRACT

Epilepsy is one of the most common neurological diseases affecting at least 50 million people worldwide. Valproic acid (VPA) is a widely used antiepileptic medication for both generalized and partial seizures of epilepsy. The objective of the study was to investigate the anti-mutagenic and anti-histopathologic effects of royal jelly (RJ) on VPA-induced genotoxicity and nephrotoxicity in male albino mice (*Mus musculus*). 80 Mice were used for 21 days; they were divided into eight groups, (G1) served as normal control group, G2 received VPA (100 mg/kg) and (G3–G5) received RJ at doses 50, 100 and 200 mg/kg respectively. While (G6–G8) were administrated RJ simultaneously with VPA. In RJ treated mice at doses of 50 and 100 mg/kg, the kidney sections showed normal histological structure with non significant changes in chromosomal aberrations (CA) and mitotic index (MI), while RJ at dose of 200 mg/kg showed mild inflammatory cells infiltration and hyperemic glomeruli but not highly significant changes in CA and MI. The cortex of VPA treated mice revealed congested glomeruli with inflammatory cells infiltration, and marked degeneration of almost structures of the glomeruli including some vacuoles in mesangial cells with dark mesangial substances on the ultrastructure level. Some proximal tubules showed degeneration of microvilli on the apical parts of some cells. Cells of the distal tubules attained obliterated lumen and vacuolated lining epithelium. The results also revealed that valproic acid induced a high frequency of CA in bone marrow cells of mice and MI was significantly decreased indicating bone marrow cytotoxicity. The treatment of mice with RJ at doses 50, 100 and 200 mg/kg for 21 days simultaneously with VPA resulted in abating the histological alterations in renal tissues with significant reduction in chromosomal aberrations, for doses of 50 and 100 mg/kg, and elevation in mitotic index ($P < 0.05$). RJ at doses 50 and 100 mg/kg appeared more potent in exerting the ameliorative effect.

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Peer review under the responsibility of Beni-Suef University

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.bjbas.2014.02.001

1. Introduction

Valproic acid (VPA), the common name of 2-propylpentanoic acid or dipropylacetic acid (Aktaş et al., 2010), is commonly prescribed worldwide as a broad spectrum antiepileptic drug with specific indications for many forms of epilepsy and many types of seizures affecting both children and adults (Silva et al., 2008). VPA is usually well tolerated. Nevertheless, along with the desired effects, VPA therapy can induce side effects such as dyspepsia, obesity, hematological toxicity, teratogenicity, idiosyncratic hepatotoxicity and important endocrine dysfunctions (Dutheil et al., 2008; Verrotti et al., 2005; Zhang and Wang, 2009).

Verrotti et al. (2000) indicated that patients treated with VPA had an impairment of renal tubular functions. As well, Altunbaşak et al. (2001) reported that epileptic children who were ambulatory and depend on VPA monotherapy developed clinically insignificant proximal renal tubular dysfunction. Recently, the experiment of Mazaheri et al. (2011) concerning children on anti-epileptic treatment with valproic acid recorded signs of renal tubular dysfunction, reflected by N-acetyl beta glucosaminidase/creatinine (NAG/Cr) activity index.

Kortenhorst et al. (2009) reported that VPA treatment caused significant nuclear alterations in normal drug-filtering organs (liver and kidney tissues). VPA further induced a depletion of several members of the structural maintenance of chromatin (SMC) proteins, SMC-associated proteins, DNA methyltransferase and heterochromatin proteins (Marchion et al., 2005).

Long-term mono-therapy or poly-therapy with anti-epileptic drugs leads to the formation of toxic metabolites of these drugs, reactive oxygen species and free radicals (Witczak et al., 2008). In particular, reactive oxygen species and free radicals show genotoxic activity (Mitchell et al., 2004). In order to overcome the potential harmful effect of free radicals and to reduce the damage by oxidants, many natural substances have been tried as antioxidants.

Royal jelly (RJ) is a honeybee product secreted from the hypopharyngeal and mandibular glands of the worker honeybees (Silici et al., 2009). It is a mixture that contains protein, glucose, lipid, vitamins, minerals (Nakajima et al., 2009), aspartic acid, gelatin, sterols, phosphorous compounds, acetylcholine, nucleic acids, and numerous trace ingredients, which are all important in RJ's documented therapeutic and nutritional properties (Çavuşoğlu et al., 2009). These ingredients are in the form of 65% water, 12% crude protein and 10% monosaccharides. The remainder of the royal jelly is composed of an ether-soluble fraction of fatty acids (Spannhoff et al., 2011).

Previous studies have shown that RJ has number of physiological effects, such as anti-inflammatory, anti-tumor, antimetastatic effect (Kimura et al., 2003) anti-allergic, antioxidant activities (Guo et al., 2008), antibacterial, vasodilative and hypotensive activities, disinfectant action and anti-hypercholesterolemic activity (Ramadan and Al-Ghamdi, 2012).

RJ has received particular attention because of studies that have reported that it is a highly efficient antioxidant and has free radical scavenging capacity (Cemek et al., 2010) and used for decreasing the toxic effects of chemical agents (El-Nekeety et al., 2007). Several studies revealed biological evidence supports the use of RJ in the treatment of chemical induced genotoxicity (Türkmen et al., 2009). It has a DNA-protective effect (Inoue et al., 2003) and also stimulates bone marrow formation (Narita et al., 2006). Abd El-Monem (2011) revealed that RJ caused a significant recovery in antioxidant status of reduced glutathione (GSH) and a significant inhibition of malondialdehyde (MDA) production and ameliorated DNA damage and genotoxicity induced by malathion in rat cells.

Therefore, the present study was undertaken to evaluate the possible protective effects of royal jelly against valproic acid induced chromosomal abnormalities in bone marrow cells and histological alterations in kidney tissue of male mice (*Mus musculus*).

2. Materials and methods

2.1. Chemicals

Sodium valproate (salt of Valproic acid) was purchased from pharmacy in the form of tablets with trade name Depakine (Sanofi Synthelabo, France), each containing 200 mg of sodium valproate dissolved in distilled water according to the used dose. Royal Jelly was purchased from pharmacy in the form of capsules (Techno Pharma Egypt for Pharco Pharmaceuticals, Alexandria, Egypt) each containing 340 mg of natural royal jelly dissolved in distilled water according to the used dose. All other chemicals were obtained from Sigma (St. Louis, MO, USA).

2.2. Experimental animals

The experimental animals used in this work were 80 random bred adult males of laboratory mice *M. musculus* (20–30 g in weight). All animals were housed in plastic cages with wired covers and kept under normal laboratory conditions. Experiments were performed as per internationally followed ethical standards and according to the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (Institute of Laboratory Animal Resources, 1996). The animals were not treated with antibiotics or insecticides and fed a standard commercial diet (ATMID Company, Egypt) and tap water *ad libitum*.

2.3. Experimental design

A single dose (100 mg/kg) of VPA was selected with reference to the dose range of the cytotoxicity and genotoxicity of VPA (Lee et al., 2007). However, RJ concentrations used in the study were 50, 100 and 200 mg/kg. These concentrations were selected according to (Cemek et al., 2010).

Experimental groups were organized into eight groups including 10 animals per each. Because colchicine is toxic, five animals were used for cytogenetic analysis while the other five animals were used for histopathological studies. The animals of group one (G1) served as normal control receiving 0.9% of NaCl solution by intraperitoneal injection (i.p.) daily