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Antidepressant-like activity of beta-carotene in unstressed and chronic unpredictable mild stressed mice

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ABSTRACT

The antidepressant-like activity of beta-carotene in Swiss young male albino mice subjected to chronic unpredictable mild stress was evaluated. Beta-carotene (50 and 100 mg/kg, p.o.) and imipramine (15 mg/kg, p.o.) per se were administered for 21 successive days to separate groups of unstressed and stressed mice. Higher dose (100 mg/kg) of beta-carotene and imipramine significantly decreased immobility period of mice in tail suspension test. These compounds significantly restored the reduced sucrose preference in stressed mice. There was no significant effect on locomotor activity of mice by the drugs. Beta-carotene significantly reversed stress-induced increase in brain catalase, monoamine oxidase (MAO-A), thiobarbituric acid-reactive substances (TBARS); and plasma nitrite and corticosterone levels; and increased stress-induced decrease in reduced glutathione levels. Thus, beta-carotene showed significant antidepressant-like activity in unstressed and stressed mice probably through inhibition of MAO-A and oxidative stress. Its antidepressant-like activity in stressed mice might also be due to decrease in plasma corticosterone levels.

1. Introduction

Depression is an incapacitating psychiatric ailment which is characterized by a pervasive low mood, loss of interest in usual activities, diminished ability to experience pleasure (anhedonia), withdrawal of interest, feelings of worthlessness, and suicidal tendencies (Schechter et al., 2005; Strauman et al., 2006). The report on Global Burden of Disease estimates the point prevalence of depressive episodes to be 1.9% for men and 3.2% for women, and the 1-year prevalence has been estimated to be 5.8% for men and 9.5% for women. It is estimated that by the year 2020 if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years (Grover, Dutt, & Avasthi, 2010). According to the World Health Organization, more than 121 million people worldwide suffer from depression, making depression the fourth leading cause of disability (Gorwood, 2010). Research over the second half of the 20th century provided extensive evidence that abnormal monoamine neuronal function is an important underlying pathology in depression. The monoamine hypothesis explains that depletion of monoamines like serotonin, norepinephrine and dopamine in the hippocampus, limbic system and frontal cortex are responsible for the depressive symptoms (Delgado & Moreno, 1999; Tanabe & Nomura, 2007). Thus, drugs reported to possess antidepressant activity increase brain levels of norepinephrine, dopamine and serotonin (Hao, Lai, Ho, & Sheen, 2013). Monoamine oxidase (MAO) is a key enzyme that is associated with the metabolism of these neurotransmitters. Medications such as tricyclic antidepressants, selective serotonin reuptake

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inhibitors), MAO inhibitors and specific serotonin-norepinephrine reuptake inhibitors are clinically employed for drug therapy (Anthony, Bertram, & Susan, 2010). However, these drugs can impose a variety of side effects including sedation, apathy, fatigue, sleep disturbance, extrapyramidal side effects, akathisia, cognitive impairment, and sexual dysfunction (Lane, 1998; Mayers & Baldwin, 2005; Segraves, 1998; Vandel, Bonin, Leveque, Sechter, & Bizouard, 1997). Approximately two-thirds of the depressed patients respond to the currently available treatments but the magnitude of improvement is still disappointing (Mora et al., 2006).

The hypothalamic–pituitary–adrenal (HPA) axis is an important node in the brain's stress circuit and suggested to play a role in several subtypes of depression (Schutter, 2012). Chronic hyperactivity of the HPA axis and resultant excessive glucocorticoid (hypercortisolism) may be causal to depression (Kunugi, Hori, Numakawa, & Ota, 2012). Stress is an everyday burden, endured by most living creatures. The failure of successful adaptation during stressful situations will result in stress-related diseases including depression (Maes et al., 2000; Michel et al., 2007). The chronic unpredictable mild stress (CUMS) model has been claimed to be one of the more relevant animal models of depression (Willner, Towell, Sampson, Sophokleous, & Muscat, 1987). CUMS model is an important behavioural model that resembles human depression (Willner, 1997). It is proposed that chronic stress causes behavioural changes such as reduced locomotor activity, reduced food and water intake, decreased responding to reward stimuli (Griffiths, Shanks, & Anisman, 1992) which are reflective of clinical depression.

Initially, CUMS functions as a stimulant, increasing metabolic rates and increasing the production of reactive oxygen species (ROS). The generation of appropriate ROS would be an effective way to induce organism's adaptability (Parsons, 1996). However, if the concentration of the ROS exceeds the body's capacity to neutralize them, the superfluous ROS begin to harm cells, tissues and organs, and result in oxidative stress. Oxidative stress has been proposed to impair the antioxidant defence system, leading to oxidative damage by changing the balance between oxidant and antioxidant factors (Fontella et al., 2005; Yu & Chung, 2006). CUMS-induced oxidative damage has been involved in the etiopathogenesis of psychiatric disorders such as depression and anxiety (Bhattacharya & Muruganandam, 2003). There is a correlation of depressive disorders in humans with oxidative stress either in the brain and blood (Bilici et al., 2001). Imipramine and melatonin attenuated stress-induced increase in oxidative parameters (Detanico et al., 2009). NO (nitric oxide) is an important modulator of depression (Wang, An, & Zhang, 2008; Yildiz, Erden, Utkan, & Gacar, 2000) because NO production is increased in depression (Suzuki, Yagi, Nakaki, Kanba, & Asai, 2001). Nitric oxide is an important neurotransmitter in the nervous system (Barañano, Ferris, & Snyder, 2001) and regulates many behavioural, cognitive, and emotional processes, including depression. Stressful conditions in rats have also been reported to significantly increase plasma nitrite levels, an index of nitric oxide production (Lee, Cheng, & Sim, 2007).

There is co-existence of increased oxidative stress with depressive symptoms in patients, as evidenced by defective plasma antioxidant defences in association with enhanced susceptibility to lipid peroxidation (Maes et al., 2000). Moreover, preclinical studies have suggested that antioxidants in the form of free radical scavengers may have antidepressant properties (Zafir, Ara, & Banu, 2009). Therefore, it appears reasonable to propose that exogenous antioxidants may be effective in treating depression. Thus, drugs with potential antioxidant action could be for the treatment of depressive disorders.

β-Carotene is a strongly coloured red–orange pigment present abundantly in many plants. It is a known source of vitamin A and has exceptional antioxidant and free radical scavenging potential (Krinsky, 1989). Beta-carotene has been reported to possess hepatoprotective, photoprotective, anti-inflammatory and anti-tumour activities (Bai et al., 2005; Chew, Park, Wong, & Wong, 1999; Hadad & Levy, 2012; Katsumura et al., 1996; Manda & Bhatia, 2003; Stahl & Sies, 2012). Due to its antioxidant property, beta-carotene has been reported to possess antiepileptic (Sayyah, Yousefi-Pour, & Narenjkar, 2005), memory enhancing (Grodstein, Kang, Glynn, Cook, & Gaziano, 2007) and anti-Alzheimer (Ono & Yamada, 2012) activities. But beta-carotene has not been studied for its potential in the management of depression. Therefore, the present study was designed to explore the antidepressant-like effect of beta-carotene in mice subjected to chronic unpredictable mild stress.

2. Materials and methods

2.1. Experimental animals

Swiss male albino mice (3 months old, weighing around 25–30 g) were purchased from Disease Free Small Animal House, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (Haryana, India). Since estrogens (female sex hormones) have been found to have antidepressant effect, so we excluded female mice and used only male mice for the study (Kandi & Hayslett, 2011) Animals were housed separately in groups of 10 per cage (Polycarbonate cage size: $29 \times 22 \times 14$ cm) under laboratory conditions with alternating light and dark cycle of 12 h each. The animals had free access to food and water. The animals were kept fasted 2 h before and 2 h after drug administration. The animals were acclimatized for at least five days before behavioural experiments which were carried out between 09:00 and 17:00 h. The experimental protocol was approved by Institutional Animals Ethics Committee (IAEC) vide letter number IAEC/136-144 of dated 10th January, 2013. Animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Registration No. 0436).

2.2. Drugs and chemicals

Imipramine hydrochloride (Sigma–Aldrich, St. Louis, MO, USA), beta-carotene, sulphanilamide, N-(1-Naphthyl) ethylenediamine dihydrochloride, meta-phosphoric acid (HiMedia Laboratories Pvt. Ltd., Mumbai, India); were used in

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