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Ondansetron attenuates co-morbid depression and anxiety associated with obesity by inhibiting the biochemical alterations and improving serotonergic neurotransmission

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ABSTRACT

In our earlier study we reported the antidepressant activity of ondansetron in obese mice. The present study investigates the effect of ondansetron on depression and anxiety associated with obesity in experimental mice with biochemical evidences. Male Swiss albino mice were fed with high fat diet (HFD) for 14 weeks to induce obesity. Then the subsequent treatment with ondansetron (0.5 and 1 mg/kg, p.o.), classical antidepressant escitalopram (ESC) (10 mg/kg, p.o.) and vehicle (distilled water 10 ml/kg, p.o.) was given once daily for 28 days. Behavioral assay for depression including sucrose preference test, forced swim test (FST) and anxiety such as light dark test (LDT) and hole board test (HBT) were performed in obese mice. Furthermore, in biochemical estimations oral glucose tolerance test (OGTT), plasma leptin, insulin, corticosterone, brain oxidative stress marker malonaldehyde (MDA), antioxidant reduced glutathione (GSH) and serotonin assays were performed. Results indicated that HFD fed obese mice showed severe depressive and anxiety-like behaviors. Chronic treatment with ondansetron inhibited the co-morbid depression and anxiety in obese mice by increasing sucrose consumption in sucrose preference test and reducing the immobility time in FST, increasing time and transitions of light chamber in LDT, improving head dip and crossing scores in HBT compared to HFD control mice. Ondansetron in obese mice inhibited glucose sensitivity in OGTT, improved plasma leptin and insulin sensitivity, reversed hypothalamic pituitary adrenal (HPA) axis hyperactivity by reducing the corticosterone concentration, restored brain prooxidant/anti-oxidant balance by inhibiting MDA and elevating GSH concentrations and facilitated serotonergic neurotransmission. In conclusion, ondansetron reversed the co-morbid depression and anxiety associated with obesity in experimental mice by attenuating the behavioral and biochemical abnormalities.

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1. Introduction

Major depressive disorder (MDD) is a serious public health issue concerned with psychiatric disorders that affects the quality of life, leads to disability and increases tendency of suicide (Levinstein and Samuels, 2014). Around 16% of the population is expected to undergo MDD one or more times during their entire life span. Current antidepressants suffer from severe drawbacks because of limited, effectiveness in less than 50% of depressed population (Fournier et al., 2010). Moreover, with antidepressants chronic treatment is required for the desired effect and there exist few undesired unwanted side effects (Undurraga and Baldessarini, 2012). Another psychiatric disorder anxiety, which is a known trait in personality disorders, globally imposes heavy burden on socio-economic status of the affected individuals (Baxter et al., 2013). The co-morbid association of depression and anxiety is evidenced in several clinical reports (de Ornelas Maia et al., 2013; Watkins et al., 2013). Obesity is another major health issue that has great impact on the quality of life, mainly due to several genetic and behavioral factors (Griffiths et al., 2014; Gao et al., 2015). Interestingly, literature reported obesity as a major risk factor for depression and anxiety (Abildgaard et al., 2011; Pearson et al., 2010; Mizunoya et al., 2013). The high prevalence of such co-morbidities demands timely needed research in the concerned area (Vogelzangs et al., 2010; Mizunoya et al., 2013). 50% of obese individuals are twice likely to develop depression than non-obese individuals (Fabricatore and Wadden, 2004; Luppino et al., 2010). Clinically relevant meta-analysis studies have mentioned the association of various types of anxiety disorders in obese population (Gariepy et al., 2010; Gadalla, 2009; Lykouras and Michopoulos, 2011). Despite the advances in the neuropsychopharmacological research no clear biological mechanism has been drawn suggesting the pathogenic links between co-morbid depression and anxiety with obesity (Sharma and Fulton, 2012; Jorm et al., 2003).

Leptin is an anti-obesity hormone secreted in the adipose tissues in response to dietary fats. Animal models of depression displayed low leptin concentration in earlier reports (Guo and Lu, 2014; Willlner, 2005). Clinical observation finds that dysregulation of leptin results in depression and anxiety like disorders (Lawson et al., 2012). Leptin resistance

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and leptin deficiency observed respectively in obesity and psychiatric disorders, such as depression and anxiety, suggest an important pathogenic link for such co-morbidities (Kloiber et al., 2013; Lu et al., 2006; Simon et al., 2006).

Insulin regulates many key processes of life such as energy homeostasis, reproduction, food intake, body weight, cognitive functions and depression (Vogt and Brüning, 2013). Reduced insulin sensitivity or insulin resistance is commonly associated with the pathogenesis of depression, anxiety and obesity (Adriaanse et al., 2006; Pan et al., 2008; Weber-Hamann et al., 2006; 2008; Salim et al., 2010). Clinical data supports the proportional relationship between insulin level and the severity of depression. Additionally, insulin resistance in obesity is due to the failure of excess insulin to normalize the raised plasma glucose (Qatanani and Lazar, 2007). Treatment with antidepressants improves insulin resistance along with the severity of depressive symptoms (Weber-Hamann et al., 2006, 2008).

Corticotropin-releasing hormone (CRH) is involved in the regulation of hypothalamic pituitary adrenal (HPA) axis function (Holsboer and Ising, 2010). HPA axis hyperactivity leads to excess corticosteroids in the circulation that result in co-morbid disorders such as depression and anxiety (Vreeburg et al., 2009, 2010). The exogenous administration of glucocorticoids results in metabolic changes which are typical of obesity such as beta-cell hyperplasia, hyperinsulinemia and poor insulin sensitivity (McMahon et al., 1988). Earlier relevant clinical and pre-clinical reports suggested that excess corticosteroids result in insulin resistance and altered glucose level (Aguilera, 1994; Dinnee et al., 1993). Additionally, abnormally raised corticosteroids cause the alterations in glucose and insulin concentrations in response to intake of dietary nutrients. Cortisol has been found to play a crucial role in visceral fat deposition that inhibits the insulin receptors (Weber et al., 2000). Obesity is a pro-inflammatory state that leads to increased oxidative stress markers, such as lipid peroxidation or malondialdehyde (MDA) and diminished antioxidant enzymes like reduced glutathione (GSH) in the brain (Esposito et al., 2006). The role of oxidative stress induced damage in the pathogenesis of depression, anxiety and other psychiatric disorders is reported earlier (Schiepers et al., 2005; Liu et al., 1994).

Serotonin is an important neurotransmitter that is involved in depression. Reduced level of serotonin is majorly associated with depression (Owens and Nemeroff, 1994). Serotonin also plays a crucial role in obesity as it controls appetite (Lam et al., 2010; Sargent and Henderson, 2011). An important finding of serotonin remains the regulation of insulin secretion by beta-pancreatic cells (Paulmann et al., 2009). The mood regulator serotonin has been effective in improving the severity of several types of anxiety symptoms. Selective serotonin reuptake inhibitors (SSRIs) which act by improving serotonin transport are prescribed for the treatment of various anxiety disorders (Kodish et al., 2011; Schirman et al., 2010). By regulating mood and appetite, serotonin plays a significant role in co-morbid depression, anxiety and obesity. 5-HT_3 receptors are highly expressed in several areas of the brain such as the area postrema, hippocampus and amygdala (Tecott et al., 1993). Eisensamer et al. (2003) documented the functional antagonist property of the SSRI class of antidepressants on 5-HT_3 receptors. Ondansetron, a 5-HT_3 receptor antagonist is currently being used for the treatment of post-operative nausea and vomiting (PONV) and chemotherapy induced nausea and vomiting (CINV) (Tramer et al., 1997; Parker et al., 2001; Cohen, 2007). Several preclinical studies have demonstrated the antidepressant and anxiolytic effects of serotonergic type 3 (5-HT_3) receptor antagonists, such as ondansetron (Ramamoorthy et al., 2008; Rajkumar and Mahesh, 2010; Roychoudhury and Kulkarni, 1997), 3-methoxy-*N*-*p*-tolylquinoxalin-2-carboxamide (QCM-4) (Kurhe et al., 2014a) and (4-phenylpiperazin-1-yl) (quinoxalin-2-yl) methanone (4a) (Kurhe et al., 2015). Earlier we reported the antidepressant activity of ondansetron based on the behavioral tests in obese mice subjected to chronic stress (Kurhe et al., 2014b).

The present study investigates the effect of ondansetron in co-morbid depression and anxiety associated with obesity in experimental mice by performing behavioral assay including sucrose preference test forced swim test (FST), light dark test (LDT), hole board test (HBT) and biochemical assessments such as oral glucose tolerance test (OGTT), plasma leptin, insulin, corticosterone, brain lipid peroxidation marker malonaldehyde (MDA), antioxidant enzyme reduced glutathione (GSH) and serotonin concentrations.

2. Materials and methods

2.1. Experimental animals

Male Swiss albino mice (20–25 g) were obtained from Hissar Agricultural University, Hissar, India (reg. no. 417/01/a/CPCSEA). The mice were housed under standard laboratory conditions (temperature 22 ± 2 °C and room humidity 60 ± 10%) and maintained on a 12:12 h of light/dark cycle and had free access to food and water. In India, the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) is established under the "Prevention of Cruelty to Animals Act 1960". CPCSEA has a representative body at institute level named as Institutional Animal Ethics Committee (IAEC). The experimental procedures performed on animals were in compliance with the protocol approved by IAEC of Birla Institute of Technology & Science, Pilani, India (protocol no. IAEC/RES/18/09).

2.2. Experimental high fat diet (HFD)

Animals were fed with high fat diet (HFD) for 14 weeks, prepared according to Srinivasan et al. (2005) for induction of obesity. Lard was purchased from a local vendor and the remaining contents of HFD were procured from Hi-Media. The composition of HFD includes powdered normal chow 365 g, lard 310 g, casein 250 g, cholesterol 10 g, vitamin and mineral mix 60 g, dl-methionine 03 g, yeast powder 01 g and NaCl 01 g for 1.0 kg of diet. Moreover, feeding with HFD was continued throughout the study protocol.

2.3. Drugs and chemicals

Ondansetron (OND) and escitalopram (ESC) were procured from Akums Drugs and Pharmaceuticals Limited (India) and Ranbaxy Research Laboratory (Gurgaon, India) respectively, as generous gift samples. ELISA kit for leptin was purchased from Aviscera Bioscience Inc., USA. Elisa kit insulin was purchased from Crystal Chem Inc., USA.

2.4. Experimental design

Forty eight mice were randomly divided into 8 different groups (n = 6/group): group I normal pellet diet (NPD) control mice receiving vehicle (distilled water 10 ml/kg, p.o.), group II NPD + OND (0.5 mg/kg, p.o.), group III NPD + OND (1 mg/kg, p.o.), group IV NPD + ESC (10 mg/kg, p.o.), group V HFD control receiving vehicle (10 ml/kg, p.o.), group VI HFD + OND (0.5 mg/kg, p.o.), group VII HFD + OND (1 mg/kg, p.o.) and group VIII HFD + ESC (10 mg/kg, p.o.). Ondansetron and standard escitalopram were administered by oral gavage (p.o.) once daily for 28 days as shown in Table 1. Dose selection of ondansetron was in compliance with our earlier studies (Ramamoorthy et al., 2008; Kurhe et al., 2014b).

2.5. Behavioral assays

2.5.1. Sucrose preference test

The method was adopted as described earlier (Strekalova et al., 2004). Animals were allowed free access to 1% sucrose solution and water in two individual bottles for 24 h. In order to avoid side preference the bottles were switched after 12 h. The amount of sucrose and water

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