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Pioglitazone, a PPARγ agonist rescues depression associated with obesity using chronic unpredictable mild stress model in experimental mice

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ABSTRACT

Pioglitazone, a peroxisome proliferator activated receptor gamma (PPARγ) agonist belonging to thiazolidinedione class, is mainly used in diabetes mellitus. Obese subjects are twice likely to become depressed than non-obese individuals. The biological mechanisms linking depression with obesity still remain poorly understood and there is immense need for better therapeutic intervention against such co-morbid disorders. The present study investigates the effect of pioglitazone on the chronic unpredictable mild stress (CUMS) induced depression in obese mice by using behavioral tests and biochemical estimations. Mice were fed with high fat diet (HFD) for 14 weeks and were further subjected to different stress procedures for 28 days to induce depressive behavior. Animals were administered orally with pioglitazone (30 mg/kg p.o.)/escitalopram (10 mg/kg p.o.)/vehicle (10 ml/kg p.o.) daily from day 15–28. Various behavioral paradigms such as sucrose preference test, forced swim test (FST), tail suspension test (TST) and elevated plus maze (EPM) were performed. Biochemical estimations including plasma glucose, total cholesterol, triglycerides, and total proteins were performed. The data obtained from behavioral assays and biochemical assessments indicated that obese animals exhibited severe depressive-like behavior compared to non-obese animals. Furthermore, obese animals subjected to CUMS worsen the depressive behavior compared to obese control animals. Repetitive treatment with pioglitazone reversed the CUMS induced behavioral and biochemical alterations in HFD fed obese mice which atleast in part may be mediated through improving altered plasma glucose. The study suggests that pioglitazone needs further attention with respect to molecular mechanisms that could provide a better therapeutic strategy against depression associated with obesity.

1. Introduction

National Comorbidity Survey reveals that major depressive disorder (MDD) is a debilitating disease with a prevalence rate of 16.2% (Kessler et al., 2003). In depression remission is achieved by only one third of the patients after treatment with antidepressant agents (Rush et al., 2006). Another major disease as a global burden is obesity as it is directly associated with increased morbidity from cardiovascular disease, type 2 diabetes and some cancers. Epidemiological data suggest that obesity is linked to an increased risk of depressive and mood disorders (Simon et al., 2006). The current antidepressants like citalopram and fluoxetine have been reported to show resistance in depression associated with obesity (Isingrini et al., 2010). Despite this information, there is presently little information on how the development of obesity heightens the risk for depression.

Chronic unpredictable mild stress (CUMS) is the most important pathogenic factor in several neuropsychiatric diseases such as depressive disorder, as stress exposure modifies the onset and evolution of some neurological diseases (Garcia-Bueno et al., 2008). In rodents, CUMS model is mostly used for assessing the pathophysiology of depression and to study the effect of various therapeutic interventions on CUMS induced depression (Willner, 2005). Furthermore, CUMS leads to various long term behavioral, neurochemical, neuroimmune and neuroendocrine alterations that resemble to those observed in patients with depression (Cryan and Holmes, 2005).

Clinical reports suggest that obesity and other metabolic disorders are frequently observed among the individuals seeking treatment for mood disorders (McElroy et al., 2004). Increased visceral

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fat mass heightens the risk for depression. The biological mechanisms associated with increased cardiometabolic risk may contribute to the development of mood disorders such as depression (Vogelzangs et al., 2010). The patients with metabolic syndrome or insulin resistance syndrome experience a significantly elevated risk of developing depression (Almeida et al., 2009).

Pioglitazone (PGZ),a well established drug known as peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist belonging to thiozolidinodienes (TZDs) class regulates lipid metabolism, exerts potent central and peripheral anti-neuroinflammatory action and possesses neuroprotective effect (Wozniak et al., 1993; Zhao et al., 2006; Garcia-Bueno et al., 2010; Heneka and Landreth, 2011). Several clinical and pre-clinical studies reported TZDs as superior treatments for neurological and psychiatric conditions including autism (Boris et al., 2007), Alzheimer's disease (Miller et al., 2011), multiple sclerosis (Kaiser et al., 2009) and MDD (Kemp et al., 2012). Insulin resistance and impaired glucose tolerance has been observed at higher frequency in depression (Almeida et al., 2009). A bidirectional relation between mood disorders and metabolic disturbances is well evident from the literature (Barry et al., 2009). Rosgan et al. (2002) documented that treatment of insulin resistance improves depressive symptoms.

Pioglitazone is well known drug in the treatment of insulin resistance or altered plasma glucose. Considering the "insulin resistance or altered plasma glucose" as important pathogenic link for depression associated with obesity, the present study was designed to investigate the effect of pioglitazone on CUMS induced depression in obese mice using behavioral tests and biochemical estimations.

2. Methods

2.1. Experimental animals

Behavioral experiments were conducted using male Swiss albino mice (20–25 g) that were procured from Hissar Agricultural University, Hissar, India (Reg. No. 417/01/a/CPCSEA). The animals were housed under standard laboratory conditions (temperature 22 ± 2 °C and room humidity 60 ± 10%) and maintained on 12:12 h light/dark cycle and had free access to food and water. In India, Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) is established under "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. Schedule for drug administration and behavioral tests

Animals were fed with high fat diet (HFD) for 14 weeks, prepared according to Srinivasan et al. (2005). Pioglitazone and escitalopram was obtained from Aarti Drugs Limited (Tarapur, India) and Ranbaxy Laboratories Limited (Gurgaon, India) respectively, as a generous gift sample. The diagnostic kits for estimation of plasma glucose, total cholesterol, triglycerides and total proteins were purchased from Spinreact, Girona, Spain. Pioglitazone was prepared as a suspension in 0.25% sodium carboxyl methyl cellulose (CMC) freshly every day. Pioglitazone was administered by oral gavage (p.o.) daily from day 14–28 of the CUMS procedure (Table 1). The dose of pioglitazone (30 mg/kg p.o.) was selected according to the earlier studies (Kashani et al., 2013; Sato et al., 2011; Kubota et al., 2006).

2.3. Experimental design

Sixty mice were randomized based on body weight and divided into ten different groups (n = 6/group). Group I consisted of Normal pellet diet (NPD) mice receiving vehicle by gavage (10 ml/kg p.o.), group II comprised of NPD + pioglitazone (30 mg/kg p.o.), group III comprised of NPD + CUMS control, group IV consisted of NPD + CUMS + pioglitazone (30 mg/kg p.o.), group V consisted of NPD + CUMS + escitalopram (10 mg/kg p.o.), group VI comprised of HFD control, group VII consisted of HFD + pioglitazone (30 mg/kg p.o.), group VIII comprised of HFD + CUMS control, group IX consisted of HFD + CUMS + pioglitazone (30 mg/kg p.o.) and group X comprised of HFD + CUMS + escitalopram (10 mg/kg p.o.). Initially, for one week period, animals were only subjected to different stress procedures. From day 8th to 28th along with stress, animals of group II, IV, VII and IX received pioglitazone (30 mg/kg p.o.), group V and X received escitalopram (10 mg/kg p.o.) using oral gavage daily once, whereas, group I, III, VI and VIII were administered with vehicle orally through oral gavage as a suspension of 0.25% sodium carboxyl methyl cellulose (CMC) (Table 1).

2.4. Chronic unpredictable mild stress procedure

The CUMS was performed as described earlier (Ducottet et al., 2003). Briefly, the CUMS protocol consisted of the sequential application of a variety of mild stressors. These stressors were randomly scheduled over one week period as shown in Table 2, and repeated throughout the 4 week experiment. Non-stressed animals were left undisturbed in their home cages except during housekeeping procedures such as cage cleaning.

2.5. Behavioral tests battery

2.5.1. Sucrose preference test

The test was performed as described earlier (Casarotto and Andreatini, 2007) with minor modifications. Briefly, before the test, mice were trained to adapt to sucrose solution (1%, w/v), two bottles of sucrose solution were placed in each cage for 24 h and then one bottle of sucrose solution was replaced with water for 24 h. After the adaptation, mice were deprived of water and food for 24 h. Sucrose preference test was conducted at 9:30 a.m. in which mice were housed in individual cages and were free to access to two bottles containing 100 ml of sucrose solution (1% w/v) and 100 ml of water, respectively. After 24 h, the volumes of consumed sucrose solution and water were recorded and the sucrose preference was

Table 1
Schematic representation of study protocol.

Days	0–14th day	15–28th day	29–37th day					39th day	40th day onwards
Study protocol	Chronic unpredictable mild stress (CUMS)	PGZ (30 mg/kg p.o.)/ESC (10 mg/kg p.o.)/vehicle (10 ml/kg p.o.)	Behavioral assays on day 29–33 Sucrose preference test	34 Locomotor score	35 FST	36 TST	37 EPM	Collection of blood Plasma glucose, plasma total cholesterol, plasma triglycerides, plasma total proteins	Biochemical assessment