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Depression mediates impaired glucose tolerance and cognitive dysfunction: A neuromodulatory role of rosiglitazone

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ABSTRACT

Comorbidity of depression and diabetes is a serious risk factor worsening the complications such as cognitive function and locomotion. Treatment under this condition becomes extremely complicated. Insulin signaling and autophagy pathways are involved in modulation of learning and memory. Rosiglitazone (ROSI) ameliorate cognitive deficit associated with depression and insulin resistance. In the present study, we investigated the effect of ROSI against chronic unpredictable stress (CUS) induced depression as a risk factor for diabetes and behavioral dysfunctions. Adult male Swiss albino mice were exposed to CUS alongside ROSI (5 mg/kg/day) treatment for 21 days. Thereafter, animals were subjected to different behavioral studies to assess depressive like behavior, cognition and locomotion. The effect of ROSI on insulin signaling, autophagy and apoptosis were evaluated in the hippocampus. CUS resulted in depressive like behavior, cognitive impairment and hypolocomotion associated with oxidative stress, impaired glucose tolerance and hypercorticosteronemia. CUS significantly impaired hippocampal insulin signaling, membrane translocation of glucose transporter type 4 (GLUT4) as well as decreased the expression of autophagy5, autophagy7, B-cell lymphoma 2 and apoptosis inhibitory protein 2. ROSI significantly reduced depressive like behavior, postprandial blood glucose, hypercorticosteronemia, oxidative and inflammatory stress, and apoptosis in stressed mice. Moreover, ROSI treatment effectively improved hippocampal insulin signaling, GLUT4 membrane translocation and cognitive performance in depressed mice. ROSI administration might prove to be effective for neurological disorders associated with depressive like behavior and impaired glucose tolerance.

Introduction

The chronic unpredictable stress (CUS) model is widely used for the induction of depressive like behavior in rodents, which consists of repeated exposure to an array of unpredictable stressors over a sustained period of time (Katz, 1982; Kessler et al., 1985). Repeated stressors are associated with hyperactivation of hypothalamic–pituitary–adrenal axis (HPA axis) which is known to induce neurodegeneration, depression and cognitive dysfunction (Rossetti et al., 2014; Sousa et al., 2008). Chronic activation of HPA axis mediates hypercorticosteronemia, inhibits insulin secretion from pancreatic β-cells, reduces glucose uptake and utilization, stimulates glucagon secretion and induces type 2 diabetes like state (Ghaisas et al., 2009; Jatwa et al., 2007) as well as impairs neuronal plasticity in hippocampus (Grillo et al., 2009; Piroli et al., 2007). Depressed diabetics show impaired cognitive performance in attention and information processing (Watari et al., 2006).

Hypercorticosteronemia induces neuronal oxidative stress and inflammation resulting in cognitive impairment (Pariante and Miller, 2001; Peng et al., 2012; Suwanjang et al., 2013). Reactive nitrogen species such as nitric oxide (NO) has been implicated in stress mediated inflammation and cognitive deficit (Peng et al., 2012). In addition, NO impairs autophagy in rat cortical neurons, which is known to modulate neuronal health (Sarkar et al., 2011). Dysfunctioning of neuronal peroxisome proliferator-activated receptor-γ (PPARγ), insulin receptor (IR), brain derived neurotrophic factor and mitogen activated protein kinase (MAPK) have been observed in brain regions during depressive like behavior and cognitive impairment (Gottschalk et al., 1999;

Abbreviations: AIP2, apoptosis inhibitory protein 2; BCL2, B-cell lymphoma 2; CUS, chronic unpredictable stress; FST, forced swim test; GLP1, glucagon like peptide 1; GLUT4, glucose transporter type 4; HPA axis, hypothalamic–pituitary–adrenal axis; INSG1, insulin induced gene 1; ILGF 1r, insulin like growth factor 1 receptor; IR, insulin receptor; IRS1, insulin receptor substrate 1; IRS2, insulin receptor substrate 2; MAPK1, mitogen activated protein kinase 1; MWM, Morris water maze; NO, nitric oxide; OGTT, oral glucose tolerance test; PA task, passive avoidance step-through task; PPARγ, peroxisome proliferator activated receptor gamma; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; ROSI, rosiglitazone; STL, step through latency; TST, tail suspension test; TBARS, thiobarbituric acid reactive substances.

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Greene-Schloesser et al., 2014; Grillo et al., 2011; Sadaghiani et al., 2011; Zhang et al., 2012).

Rosiglitazone (ROSI) is a selective agonist for nuclear PPARγ receptor, known to increase glucose influx in adipose tissue and muscle by enhancing synthesis and translocation of glucose transporters (Hardman and Limberd, 2001; Tripathi, 2013). ROSI improves cognitive performance, β-cell functions, attenuates insulin resistance and inflammation in diabetics (Abbatecola et al., 2010; Awara et al., 2005; Hanley et al., 2010; Hsu et al., 2005). ROSI attenuates depression associated insulin resistance (Rasgon et al., 2010) and impaired hippocampal neurogenesis (Cheng et al., 2015).

The present study was designed to investigate the effect of CUS induced depression as a risk factor for diabetes and associated behavioral dysfunction. We investigated the involvement of insulin signaling and autophagy in the hippocampus region of brain during chronic stress. Further, we studied the neuromodulatory role of ROSI, an antidiabetic drug, against CUS induced depression.

Materials and methods

Animals

Male Swiss albino mice weighing 25–30 g were housed under a 12 h light/dark cycle at 26 ± 2 °C. The animals had access to food and water *ad libitum*. All animal experiments were carried out in accordance with CPCSEA guidelines and Institutional Animal Ethical Committee. All efforts were made to minimise pain or discomfort.

Experimental design

Animals were divided into four groups: group I received 0.3% carboxymethyl-cellulose (0.3% CMC, p.o.) and served as control; group II was exposed to CUS and received vehicle (0.3% CMC, p.o.); group III was subjected to CUS and received ROSI (5 mg/kg, p.o.) and group IV received ROSI (5 mg/kg, p.o.). Dose of ROSI was selected from previous study (Lee et al., 2006) and administered once daily for 21 days.

The animals were subjected to CUS paradigm as described previously (Bhutani et al., 2009; Katz, 1981) with modifications. Animals underwent stress paradigm once a day over a period of 21 days (Fig. 1). After 3 weeks of CUS and drug treatment, animals were subjected to different behavioral studies to assess depressive like behavior, cognition and locomotion. On day 25, immediately after behavioral studies (3–5 pm) blood was collected via retro-orbital puncture. Serum and plasma were separated for biochemical estimation. Animals were sacrificed by cervical dislocation and the hippocampus was dissected for further studies.

Behavioral assessment

Forced swim test (FST)

The animals were individually forced to swim in a cylinder with radius 24 cm and height 25 cm filled with water (26 ± 2 °C) up to a height of 18 cm. An animal was considered immobile whenever it remained floating passively in the water in a slightly hunched but upright position and its nose just above the water surface. The total immobility period of each animal during the 6 min test was recorded (Kulkarni and Mehta, 1985).

Tail suspension test (TST)

The animals were individually suspended on the edge of a shelf by adhesive tape placed approximately 1 cm from the tip of the tail. Animals were considered immobile when they hang passively and motionless. The duration of immobility was recorded for the periods of 6 min during the test (Steru et al., 1985).

Morris water maze task (MWM)

Spatial memory was assessed using MWM, which consisted of a white circular pool of 1 m diameter, filled with water at room temperature and had a submerged transparent escape platform kept 1 cm below the water surface. The pool was made opaque with addition of nontoxic water-soluble white paint, which makes the submerged platform invisible to the mice. The pool was divided into four hypothetical quadrants. Each mouse was individually allowed to swim freely (habituation trial) in the maze for 5 min (without platform) on day 21. During training trial (days 22–25) the platform was positioned in the centre of a quadrant and each mouse was released facing toward the wall of the pool in the randomly selected quadrant. The mice were allowed to search the platform spontaneously within 60 s. Mice that failed to find the submerged platform within 60 s were placed onto the platform by the experimenter and allowed to remain on the platform for 5 s (learning trial). Each

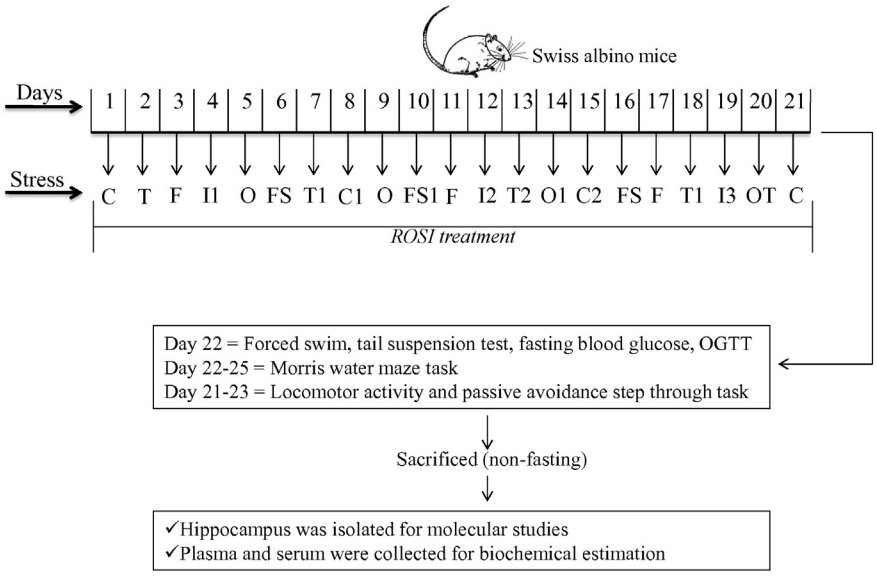

Fig. 1. CUS procedure and experimental design: C — cold swim (8 °C, 3 min); T — tail pinch (1 min); F — food and water deprivation (24 h); I1 — immobilization (3 h); O — overnight illumination; FS — foot shock (20 trials, 0.5 mA, 5.0 s maximum duration, 1 min intervals); T1 — tail pinch (2 min); C1 — cold swim (10 °C, 5 min); FS1 — foot shock (20 trials, 0.5 mA, 5.0 s maximum duration, 30 s intervals); I2 — immobilization (4 h); T2 — tail pinch (3 min); O1 — overnight illumination with wet cage; C2 — cold swim (6 °C, 3 min); I3 — immobilization (5 h); OT — overnight illumination with tilted cage.