Brain Research Bulletin 124 (2016) 116–122

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Blood glucose regulation mechanism in depressive disorder animal model during hyperglycemic states

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ARTICLE INFO

Article history:
Received 1 December 2015
Received in revised form 29 February 2016
Accepted 22 March 2016
Available online 23 March 2016

Keywords:
Depression animal model
D-glucose-fed
Immobilization stress
Clonidine
Blood glucose
Glucocorticoid

ABSTRACT

Depression is more common among diabetes people than in the general population. In the present study, blood glucose change in depression animal model was characterized by various types of hyperglycemia models such as D-glucose-fed-, immobilization stress-, and drug-induced hyperglycemia models. First, the ICR mice were enforced into chronic restraint stress for 2 h daily for 2 weeks to produce depression animal model. The animals were fed with D-glucose (2 g/kg), forced into restraint stress for 30 min, or administered with clonidine (5 μg/5 μl) supraspinally or spinally to produce hyperglycemia. The blood glucose level in depression group was down-regulated compared to that observed in the normal group in D-glucose-fed-, restraint stress-, and clonidine-induced hyperglycemia models. The up-regulated corticosterone level induced by D-glucose feeding or restraint stress was reduced in the depression group while the up-regulation of plasma corticosterone level is further elevated after i.t. or i.c.v. clonidine administration in the depression group. The up-regulated insulin level induced by D-glucose feeding or restraint stress was reduced in the depression group. On the other hand, blood corticosterone level in depression group was up-regulated compared to the normal group after i.t. or i.c.v. clonidine administration. Whereas the insulin level in depression group was not altered when mice were administered clonidine i.t. or i.c.v. Our results suggest that the blood glucose level in depression group is down-regulated compared to the normal group during D-glucose-fed-, immobilization stress-, and clonidine-induced hyperglycemia in mice. The down-regulation of the blood glucose level might be one of the important pathophysiologic changes in depression.

1. Introduction

Depression not only affects brain and behavior but also affects the entire body. Depression has been associated with other health problems, including diabetes. Medically ill commonly shows depressive symptoms, although they are frequently unrecognized and untreated (Rodin and Voshart, 1986). A chronic medical condition such as diabetes mellitus could be associated with depressive syndromes (Pompili et al., 2009). Similarly, the presence of depressive symptoms makes the influenced individual more susceptible to become diabetic (Brownlee, 2008).

Stress is like the most significant health problem in modern life (Kudielka and Wust, 2010). Stress is an imbalance condition of homeostasis and results in various physiological and behavioral changes in the human body. Chronic stress may lead to depressive disorder (Raison et al., 2006). Repeated chronic stress, in general, promotes structural and functional alterations within the stress neurocircuitry system, and harmful effects on the regulation of a variety of brain functions (Gunn et al., 2011). Furthermore, stress stimulates the release of various stress-related hormones, and these effects can only endanger the brain. Stress hormones such as glucocorticoid and norepinephrine increase the blood glucose level (Surwit et al., 1992). Excessive exposure to stress-related hormones such as glucocorticoid can damage the brain and make the brain more vulnerable to normal neural damage (Sapolsky, 2000).

In general, during the stressful situations, the sympathetic nervous system (SNS) is activated, leading to a release of catecholamine from the adrenal medulla (Jansen et al., 1995). Catecholamines result in an increase of the blood glucose level by inhibiting insulin release and also stimulate the glycogenolysis (Ullrich and Wollheim, 1984). In addition, the hypothalamic-pituitary-adrenal (HPA) axis plays a major role in stress systems. The principal regu-

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http://dx.doi.org/10.1016/j.brainresbull.2016.03.014
0361-9230/

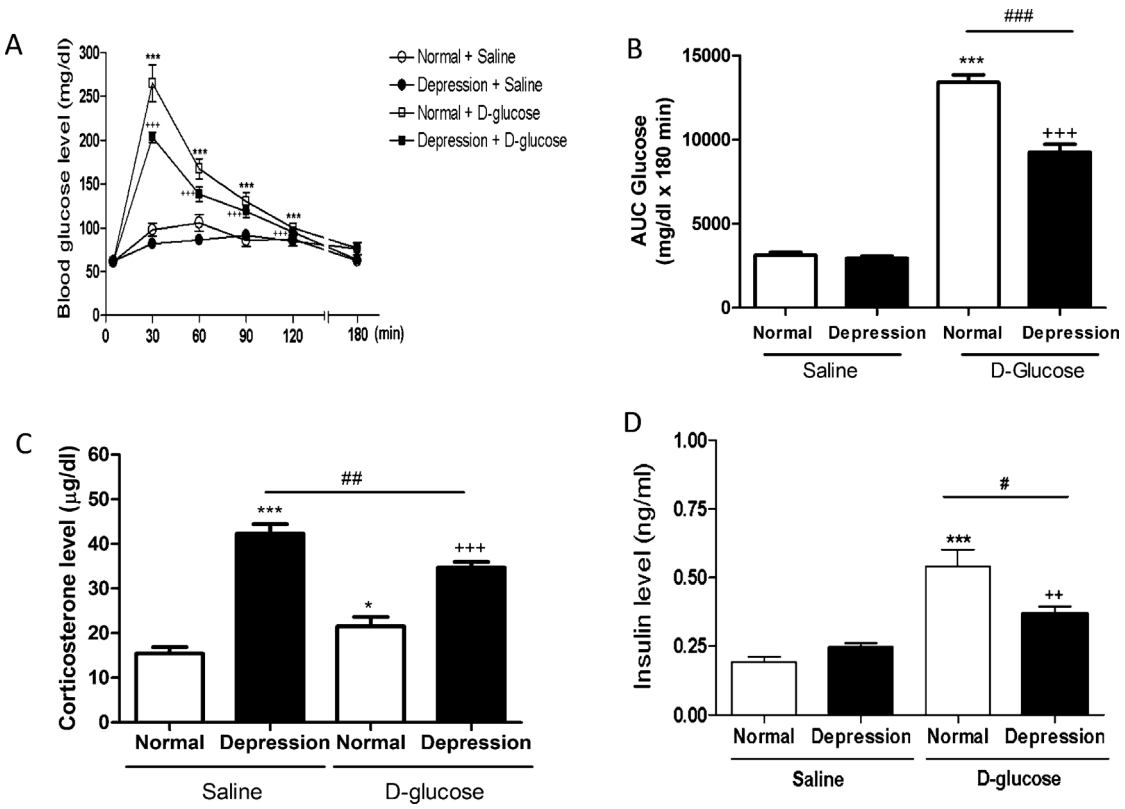

Fig. 1. Alteration of the blood glucose, corticosterone, and insulin level by OGTT in depression group.
Mice were enforced into chronic restraint stress for 2 h daily for 2 weeks to produce a depression animal model. Each mice group was fed saline (as vehicle) or D-glucose (2 g/kg) by oral administration. (A) The blood glucose level was measured at 30, 60, 90, 120 and 180 min after the D-glucose feeding. The blood was collected from tail vein. ($^{***,+++}P < 0.001$; compared with control group). (B) Area Under the Curve (AUC) of blood glucose level (F value of 214.9, $^{\#\#\#}P < 0.0001$, analysis of variance, Normal + D-glucose vs. Depression + D-glucose). The blood corticosterone (C) and insulin (D) levels were measured at 30 min after the D-glucose feeding. For plasma corticosterone and insulin level measurement, a whole mouse blood sample was collected by puncturing the retro-orbital venous plexus. The number of animals used for each group was 5. The vertical bars indicate the standard error of the mean. ($^{\#}P < 0.05$; Normal + D-glucose vs. Depression + D-glucose, $^{++}P < 0.01$; compared with Depression + Saline group, $^{***}P < 0.001$; compared with Normal + Saline group, $^{+++}P < 0.001$; compared with Normal + D-glucose group, $^{\#\#}P < 0.001$; Depression + Saline vs. Depression + D-glucose;).

lator of the HPA axis is a corticotrophin-releasing hormone (CRH). CRH is synthesized in the hypothalamus (Ito et al., 2005), and CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) and subsequently, promotes glucocorticoid secretion from the adrenal cortex (Kalantaridou et al., 2010). It has been well demonstrated that glucocorticoid, in general, causes the hyperglycemia by activating a gluconeogenesis pathway (Fagerholm et al., 2011).

The stress-induced hyperglycemia effect has been well known for a long time (Mazzon and Cuzzocrea, 2008). Several lines of evidence have demonstrated that the chronic stress is closely associated with the pathogenesis of depression (Raison et al., 2006). Although the relationship between depression and the diabetes mellitus has been well known in some previous studies, the exact relationship of blood glucose regulation is chronic stress-induced depression has not been well characterized yet. Thus, the present study was designed to characterize the relationship between chronic stress-induced depression and blood glucose level in three hyperglycemic animal models in mice. First, we forced mice into chronic restraint stress for 2 h daily for two weeks to produce depression animal model. Then, we have characterized the possible role of the depression in the regulation of the blood glucose level in D-glucose-fed-, immobilization stress-, and clonidine-induced hyperglycemia animal model.

2. Materials and methods

All the experiments with animals were approved by the University of Hallym Animal Care and Use Committee (Registration Number: Hallym 2013-72). All procedures were conducted in accordance with the 'Guide for Care and Use of Laboratory Animals' published by the National Institutes of Health.

2.1. Experimental animals

Male ICR mice (Koatech, Seoul, Korea) were used weighing 20–25 g for all the experiments. Animals were housed 5 per cage in a room maintained at 22 ± 0.5 °C with an alternating 12 h light-dark cycle. Food and water were available *ad libitum*. The animals were allowed to adapt to the laboratory for at least 2 h before testing and were only used once. Experiments were performed during the light phase of the cycle (10:00–17:00).

2.2. Depression animal model

Restraint stress was applied for 2 h per day and was repeated for 14 consecutive days. After each session of restraint, the animals were returned to their normal plastic cages (Park et al., 2014; Seo et al., 2012). Depression behavior was assessed by force swimming and tail suspension tests (Baek et al., 2015).

2.3. Immobilization stress procedure

The mice were subjected to restraint stress as described in a previous study (Suh et al., 2000). In brief, single exposure of restraint was carried out by placing the mouse in a 50 ml Corning tube, and adjusting it with an iron nail on the outside, which crossed in the