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Original Article

Evaluation of Glutamate Dehydrogenase Activity and Insulin Secretion in Mice Exposed to Dexamethasone

Hamid Reza Jamshidi* Ph.D., Elham Ebrahimi Pharm.D.

Department of Toxicology, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

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Background and Aims: Diabetes is one of the most important endocrine disrupters and is associated with various hormones, including those that can lead to diabetes. Glucocorticoid use may lead to insulin resistance. Dexamethasone is one of these glucocorticoid compounds. Glutamate dehydrogenase plays a key role in the production of glutamate in the secretion of insulin. Based on these hormonal interactions, the aim of this study was to determine the activity of glutamate dehydrogenase and insulin secretion in dexamethasone-exposed mice.

Materials and Methods: Twenty eight mice were divided into 4 experimental groups. Group 1 received standard normal saline as a control. Group 2 received standard food and received 1 mg / kg dexamethasone per day. Group 3 received standard diet and dexamethasone 3 mg / kg / day and group 4 with standard diet 5 mg / kg dexamethasone per day. After 21 days, the animals were killed, the pancreas and glutamate dehydrogenase, insulin, and serum glucose levels were determined.

Results: Dexamethasone increased serum glucose levels significantly ($P < 0.05$). Dexamethasone increased the glutamate dehydrogenase activity and insulin levels in dexamethasone treated mice ($p<0.05$)

Conclusions: These results suggestd that dexamethasone increases glucose which leads to elevating glutamate dehydrogenase activity, and then increasing insulin. However, insulin was not enough to normalize glucose levels and led to hyperglycemia. Therefore, it is suggested to reduce dexamethasone administration.

***Corresponding Author:** Department of Toxicology, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. **Tel:** +989126014975, **Email:** hrz.jamshidi@gmail.com

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Introduction

Excess secretion or administration of glucocorticoids leads to hyperglycemia, hyperinsulinemia and insulin resistance [1]. Glucocorticoids decrease the rate of basal and insulin-stimulated glucose uptake in skeletal muscle [2]. Glucocorticoid-induced insulin resistance is related to deficiency in post-receptor insulin activity [3]. Deleterious effect and cellular mechanisms of the glucocorticoid therapy are well-known [4]. Glucocorticoid therapy leads to cell apoptosis, inhibits osteoblast genesis and bone formation which can lead to low bone turnover state [5, 6]. Glutamate dehydrogenase (GDH) is a mitochondrial enzyme enzyme controlling the oxidation of glutamate [6]. The GDH serves as a link among anabolic and catabolic pathways which catalyzes the reversible oxidative deamination of glutamate to α-ketoglutarate [7].

The GDH has a key role in insulin secretion from pancreatic beta cells in response to glutamine [8]. Overexpression of the GDH increases insulin secretion through glutamine stimulation [9]. Based on the animal studies, insulin secretion at low glucose is not mediated by GDH overexpression whereas high glucose-stimulated insulin secretion is influenced by GDH overexpression [10]. Also, Rehman et al. identified that dexamethasone treatment alters insulin, leptin, and adiponectin levels in male mice [11]. Overexpression of the GDH modifies insulin secretion in pancreatic islets [12]. Additionally, diabetes is one of the main endocrine diseases and interacts with several hormones such as glucocorticoids which presumably lead to insulin resistance [10]. The GDH controls the insulin secretion in the pancreatic beta cells and inhibition of the GDH activity decreases insulin release and glutamate concentrations [9] while activation of the GDH is associated with hyperinsulinemia [10]. Therefore, the aim of the current study was to determine the GDH activity in mice exposed to dexamethasone.

Materials and Methods

Animals

A total 28 Wistar rats (weight 250-300 g) were purchased from the Pasteur Institute. Animals were kept under constant room temperature of 20±1°C, relative humidity of 42±1% on a 12-hour light/ dark cycle and were allocated into 4 experimental groups (n=7). All animals had *ad libitum* access to chow pellets and fresh water. Animals were acclimatized to laboratory conditions for one week prior to experiments; each animal was used only once and killed immediately after the experiment. All experimental procedures were carried out in accordance with the Guide for Care and Use of Laboratory Animals to Investigate Experimental Pain in Animals [12]. Animal handling and experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and the current laws of the Iranian government. All protocols for animal experiments were approved by the institutional animal Ethical Committee,

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Faculty of Pharmacy, Shahid Sadughi University of Medical Sciences, Yazd, Iran.

Experimental protocol

Group 1 was kept as control (received normal saline and standard pellet). Group 2 was fed with standard chew pellet and 1mg/kg per day of dexamethasone. Group 3 received standard diet and was injected with dexamethasone (3 mg/kg per day). Group 4 was fed with standard diet + 5 mg/kg dexamethasone per day. After 21 days, rats were euthanized with an overdose injection of pentobarbital (300 mg/kg, i.p.), pancreas was obtained and GDH, insulin and serum glucose levels were determined [13].

Biochemical activity

The GDH activity was determined using experimental kit (Sigma-Aldrich Co. LLC; Catalog Number MAK099).

$$\text{GDH activity} = \frac{\text{B}\times\text{sample dilution factor}}{(\text{Reaction time})\times\text{V}}$$

B = Amount (nmole) of NADH generated between Tinitial and Tfinal and V= sample volume (mL) added to well.

GDH activity is determined by a coupled enzyme assay in which glutamate is consumed by GDH generating NADH, which reacts with a probe generating a colorimetric (450 nm) product proportional to the GDH activity. One unit of GDH is the amount of enzyme that will generate 1.0 µmole of NADH per minute at pH 7.6 at 37 °C. The insulin level was determined by mouse insulin enzyme-linked immunosorbent assay (Mercodia AB, Sweden; atalog Number 10-1247-10) and insulin level was determined using spectrophotometer at absorbance of the 450 nm. The blood glucose level was determined before euthanizing them from the tail.

Statistical analysis

Data were prepared in excel; the parametric data were analyzed by repeated measure two-way analysis of variance (ANOVA) using SPSS 24.0 for Windows (SPSS, Inc., Chicago, IL, USA). Data were expressed as mean values ± standard error of mean (SEM). For treatments found to have an effect according to ANOVA, mean values were compared with Bonferroni test. $P < 0.05$ was considered to denote significant differences between groups.

Results

The results of the dexamethasone on serum insulin, glucose and GDH activity in mice is presented in figures 1-3. As seen in figure 1, dexamethasone significantly increased serum glucose levels compared to the begining of the study ($p<0.05$). Based on figure 2, serum insulin levels in a dose dependent manner increased in dexamethasone treated mice. Also, this drug dose dependently increased GDH activity in dexamethasone treated mice (Fig. 3).

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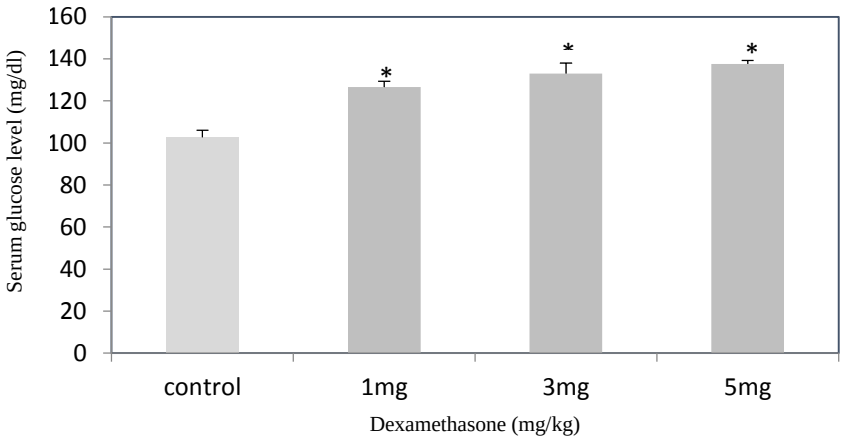

Fig. 1. The effect of the Dexamethasone (1, 3 and 5mg/kg) on serum glucose level in mice. *p<0.05

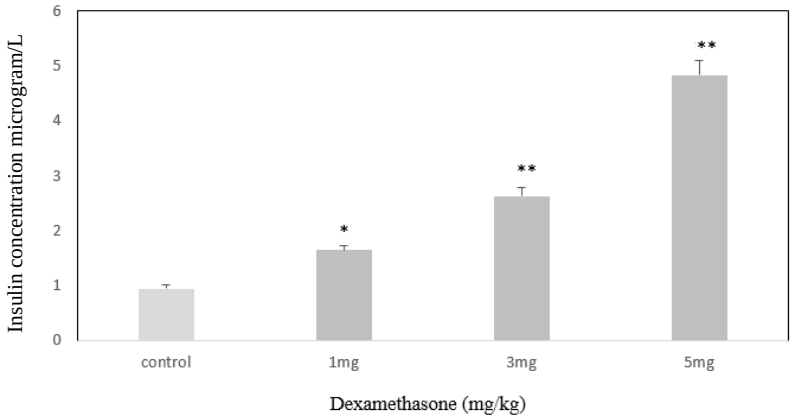

Fig. 2. The effect of the Dexamethasone (1, 3 and 5mg/kg) on insulin concentration in mice. *p<0.05, **p<0.001

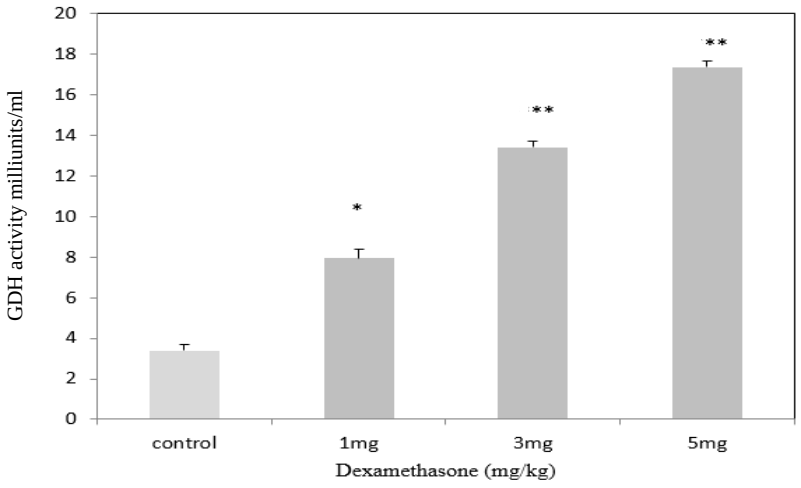

Fig. 3. The effect of the Dexamethasone (1, 3 and 5mg/kg) on serum GDH activity in mice. GDH= glutamate dehydrogenase. *p<0.05, **p<0.001

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Discussion

Diabetes is one of the prominent endocrine disorders in the world with deranged metabolism and energy expenditure [13]. Insulin resistance is the conditions such as diabetes, obesity and dyslipidemia [14]. Excess administration of glucocorticoids causes hyperglycemia and hyperinsulinemia with insulin resistance [15]. Glutamate is the main product of glutamate dehydrogenase activity that can help insulin secretion. Despite previous studies conducted on the role of glutamate on dexamethasone-induced diabetes, there is scarce information regarding role of the dexamethasone on pancreatic GDH, insulin and serum glucose in the mice exposed to dexamethasone. So, the novelty of the current study was to determine GDH activity in mice exposed to dexamethasone. Based on the findings of the current study, dexamethasone significantly increased serum glucose levels compared to the begining of the study. Also, dexamethasone dose dependently increased glutamate dehydrogenase activity and insulin levels in dexamethasone treated rat.

The dexamethasone-induced increase in the serum insulin and glucose indicates that insulin resistance is observed by rosiglitazone administration [16]. Glucocorticoids admin-istration inhibits pancreatic insulin secretion, reduces glucose utilization and increases glucagon secretion [13]. Glucose stimulation of insulin release was associated with suppression of flux through the GDH in normal and transgenic mouse pancreatic islets. Glucose stimulation of the insulin release was related to GDH, consistent with the well-known allosteric inhibitory effect of the GTP and ATP on activity of the enzyme [17]. Glucocorticoids decrease glucose utilization in muscles by modulating the insulin receptor [13, 18].

Dexamethasone has diabetogenic effects by dysregulation of glucose expenditure in liver, muscles and adipose tissue [19]. Reduction in peripheral insulin sensitivity may be compensated by the intensified pancreatic β-cells function, but, as the latter is also directly affected by glucocorticoids, over time decompensation arises. Administration of glutamine partially prevents glucocorticoids-induced muscle atrophy. Glutamine blocks glucocorticoids induction of myostatin mRNA and protein expression [20]. Despite direct mechanism(s) for how the GDH and dexamethasone impress cellular mechanism on insulin release is not fully elicited, but the oxidative deamination of glutamate by GDH stimulates insulin release in the beta cell mitochondria [21]. Oxidative deamination of glutamate increase the mitochondrial α-ketoglutarate, raises the NADH/NAD and NADPH/NADP ratios [22].

The GDH regulates insulin secretion by its role on generation of the α-ketoglutarate to inhibit isocitrate dehydrogenases, NADPH to inhibit NADP-isocitrate dehydrogenases and NADH to inhibit NAD-isocitrate dehydrogenase [23]. Glutamine was not able to stimulate insulin release while following conversion to glutamate, it can increase α-ketoglutarate production by GDH and subsequent insulin

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release [21]. Glutamate decreases the oxaloacetate and pyruvate level by reversing the mitochondrial aspartate and alanine aminotransferase reactions. The formation of the trienzyme complex is favored through activation of the GDH by Mg^{2+} and ATP, which increases binding of the GDH to mitochondrial aspartate aminotransferase [24].

Despite the studies conducted on the role of the glucocorticoid-induced diabetes mellitus, glucocorticoid can impress its effect by increased hepatic gluconeogenesis, inhibition of glucose uptake and metabolism in peripheral tissues and altered insulin receptor and functions. Risk factors such as age, glucocorticoid therapy, family history of diabetes, obesity, genetics and race are the main factors for glucocorticoid-induced diabetes [17].

Conclusion

These results suggest that dexamethasone increases glucose which leads to elevating GDH activity and then then increasing insulin. However, insulin was not enough to normalize glucose levels and led to hyperglycemia. Therefore, it is suggested to reduce dexamethasone administration.

However there was no similar study to compare the results. Further research is needed to determine the accuracy of the results. Also, cellular and molecular studies are required to determine cellular mechanism(s) for the obtained results.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

The authors declare no acknowledgment.

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