Effect of Alprazolam on Serum Insulin Levels in Non-Diabetic Rats

Alireza Vahidi[1,2], Mohammad Afkhami-Ardekani[3*], Mohammad Yahya Vahidi[4], Maryam Rashidi[3], Ahmad Shojaoddiny-Ardekani[3]

1. Department of Pharmacology, School of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2. Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
4. Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

***Correspondence:**
Mohammad Afkhami-Ardekani, Diabetes Research Center, Jomhoori Blvd., Yazd, Iran.
Fax: (+98-351) 5258354
Tel: (+98-351) 5223999
Email: afkhamiam@yahoo.com

Received: 5 August 2012
Accepted: 25 September 2012

Abstract

Objective: Stress and cortisol increase blood glucose. Considering the role of central catecholaminergic pathways on hypothalamic-pituitary adrenocortical axis, and results of some studies that alprazolam (a benzodiazepine) has inhibitory effect on catecholamines, it seems that alprazolam may reduce blood glucose. The aim of this study was to evaluate the effect of alprazolam on serum insulin level in non-diabetic rats.

Materials and Methods: This was an experimental study done on 20 male adult rats weighing 180-200g which were selected randomly and divided into three treatment and one control groups. Animals in test groups were administrated different alprazolam doses (0.5, 1 and 2 mg/kg) intraperitoneally and blood insulin and glucose levels were assessed 0, 2, 4 and 6 hours following the treatment. General Linear Model was used to compare the alterations in serum insulin and glucose levels between four groups in different times. For comparison of mean serum glucose levels between two different times paired t-test and for insulin, Wilcoxon test was used.

Results: The serum insulin level alternations were significant in 2 mg/kg group (P=0.0001), with a peak at 4 hour. These alternations were not significant in 0.5 and 1 mg/kg groups, as well as controls.

Conclusion: Our findings show thatblood insulin increases in response to alprazolam injection and this effect is dose-dependent. Maximum increase is induced by the dose of 2 mg/kg.

Keywords: Insulin, Alprazolam, Non-diabetic rat

Introduction

It has been shown that stress can induce hyperglycemia in several animal models of type II diabetes (1). Cori theorized a link between the physiologic stress response and development of hyperglycemia. In his experiments with rabbits, Cori demonstrated that continuous infusion of epinephrine exacerbated hyperglycemia (2).

Van Loon continued these researches by infusing beta endorphins intracisternally in

conscious, unrestrained, adult male rats. He showed an increase in plasma glucose exacerbated by infusion. Also, he could abolish this effect via adrenal denervation. Disabling neural control of the adrenal gland disrupted the production of cortisol, eliminating the stimulus for the development of hyperglycemia (3).

Some studies have indicated that benzodiazepines regulate central and peripheral catecholaminergic activities. Alprazolam, a benzodiazepine -activating GABAergic receptors, has been shown, in fact, to lower both basal and stimulated noradrenaline and adrenaline levels in animals and humans probably through α2-adrenergic regulation (4-6). As central catecholaminergic pathways play a relevant role in the control of hypothalamic-pituitary-adrenocortical axis (7), it has been hypothesized that alprazolam-induced reduction in catecholaminergic activity could contribute to their inhibitory effect on corticotrophin secretion.

Based on these data, the aim of this study was to evaluate the effect of alprazolam on serum insulin and glucose level in non-diabetic rats.

Materials and Methods

For this study, male Wistar rats weighing 180-200g were housed at 22-23°C and humidity-controlled rooms. The animals were fed rat chow (Parse Co. Tehran, Iran) and water ad libitum and were acclimatized to a 12-hour light-dark cycle for a period of 1 week before experimental manipulation. Principles of laboratory animal care were followed, and experimental protocols were approved by medicalethics committee of ShahidSadoughi University of Medical Sciences.

A blood sample was collected for insulin measurement before the trial. Twenty rats were randomly and equally divided into four groups: control rats administered artificial extracellular fluid;other rats were given intraperitoneal injection of alprazolam (Abidi Co. Tehran, Iran) 0.5, 1 (n=5) and 2mg/kg (n=5 for all groups).

Blood collections were performed at 0, 2, 4 and 6 hours of injection by retro-orbital sinus puncture. Serum was analyzed for glucose and insulin. The glucose was analyzed by Dunken testAuto-Analyzer (Echo-plus, Italy) with Vis chini kit. Insulin was determined by radioimmunoassay with ELIZA-2943 kit using star fax 3200.

Data were analyzed using SPSS version 17 (SPSS Inc., Chicago, US). For comparison of alternation in serum insulin and glucose levels between four groups in different times, General Linear Model (Repeated Measures Factor) was used. To compare the mean serum glucose levels between four groups in different times, General Linear Model (Repeated Measures Factor) was used. For comparison of means of serum glucose between two different times paired t-test and for insulin which had not normal distribution, Wilcoxon Signed Ranks Test was used.

Results

The serum insulin level alternations were statistically significant in baseline and after 2, 4 and 6 hours in 2 mg/kg trial group (P=0.0001), with a peak at 4 hour; but this alternations were not significant for0.5 and 1 mg/kg groups, as well as for controls (P=0.53, 0.64 and 0.48 respectively) (Figure 1).

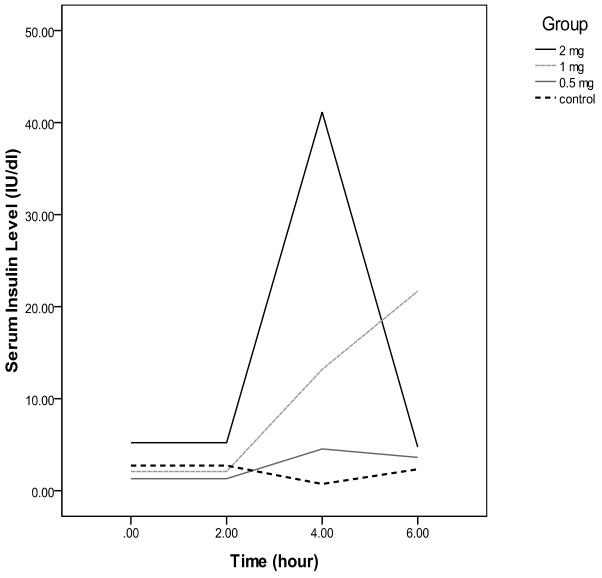

Figure 1: Serum insulin levels at baseline and after 2, 4 and 6 hours in four trial (n=5).

No significant alternations were seen in serum glucose level at baseline and after 2, 4 and 6 hours in 0.5, 1 and 2 mg/kg trial groups (P=0.32, 0.12 and 0.39 respectively), but this alternation was significant in control group (P=0.04) (Figure 2).

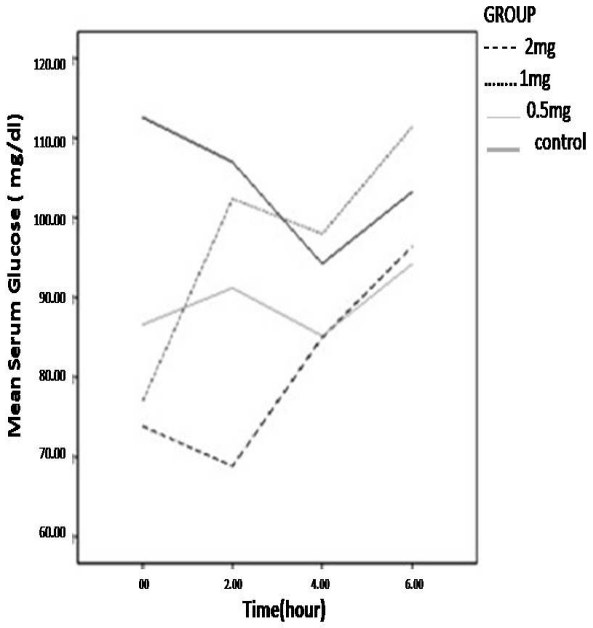

Figure 2: The serum glucose levels at baseline and after 2, 4 and 6 hours in four trial groups.

When the differences of serum glucose and insulin levels at baseline and after 6 hours were compared in four trial groups, no significant differences were seen (P=0.08 and 0.8 respectively).

Discussion

Results of present study showed that the serum insulin level increased significantly after four hours of receiving 2 mg/kg alprazolam, but no significant changes was seen in blood glucose level.

Hyperglycemia increased by physical or psychological stress is a known complicating factor in the treatment of diabetes mellitus (8). However, little is known about efficient treatment for stress hyperglycemia. Some studies reported that alprazolam reduces stress-induced hyperglycemia in animal model of type 2 diabetes (9). Surwit et al. showed that alprazolam significantly lowered plasma corticosterone in obese mice at rest and following stress (9). In their study, although alprazolam increased plasma insulin in all mice at rest and following stress, plasma glucose level only reduced in obese animal during stress. Thus the results of present study are in agreement with the findings of Surwit et al.

Some human studies haveshown that alprazolam could have beneficial effects on glycemic control. In Lustman study (10), fifty-eight patients with poor glycemic control were entered into a randomized, double-blind, placebo-controlled, 8-week trial using alprazolam (up to 2 mg/day) as the active agent. A statistically significant reduction in glycated hemoglobin level was observed in patients treated with alprazolam compared with those receiving placebo. In another parallel clinical trial, administration of 5.0 mg alprazolam for 6 weeks led to a significant decrease in fasting blood sugar and glycated hemoglobin levels (11).

Reduction of hyperglycemia may be due to the effect of alprazolam on hypothalamic-pituitary-adrenocortical axis or catecholaminergic response to stress (9). It has been shown that alprazolam decreases both basal and stimulated noradrenaline and adrenaline levels in animals and human probably through α2-adrenergic modulation (4-6). Since central catecholaminergic pathways play an important role in the control of hypothalamic-pituitary-adrenocortical axis (7), it has been hypothesized that alprazolam-induced reduction in catecholaminergic activity could contribute to its inhibitory effect on corticotrophin secretion (12).

It has been hypothesized that alprazolam increases insulin secretion by reduction of glucocorticoids. Deuster et al. showed that acute administration of alprazolam restrains stress-induced hypothalamic-pituitary-adrenocortical axis activation, as indicated by reduced exercise-induced secretion of ACTH, AVP, cortisol, and DHEA (13). Additionally, glucocorticoids have direct effects on

pancreatic beta cells, which result in a generalized inhibition of insulin secretion (14-16). This inhibition is caused by a reduction in the effectiveness of cytoplasmic Ca21 on the secretory process (17).

Nevertheless, the results of some studies suggest that alprazolam may have a direct effect on insulin secretion by stimulating insulin release from beta cells or some unknown mechanisms (9) and the recognition of benzodiazepine receptors in the periphery strengthened this hypothesis (18).

Conclusion

Our findings show that blood insulin is increased due to the alprazolam injection in a dose-dependent mannerand maximum increase is obtained by 2 mg/kg.The mechanisms contribute to this phenomenon should be evaluated in further studies.

References

1. Surwit RS, Schneider MS, Feinglos MN. Stress and diabetes mellitus. Diabetes Care 1992;15(10):1413.
2. Cori GT, Cori CF, Buchwald KW. The mechanism of epinephrine action. V. Changes in liver glycogen and blood lactic acid after injection of epinephrine and insulin. Journal of Biological Chemistry 1930;86(1):375-88.
3. Van Loon GH, Appel NM. Beta-Endorphin-induced hyperglycemia is mediated by increased central sympathetic outflow to adrenal medulla. Brain research 1981;204(1):236.
4. Charney DS, Breier A, Jatlow PI, Heninger GR. Behavioral, biochemical, and blood pressure responses to alprazolam in healthy subjects: interactions with yohimbine. Psychopharmacology 1986;88(2):133-40.
5. Risby ED, Hsiao JK, Golden RN, Potter WZ. Intravenous alprazolam challenge in normal subjects. Psychopharmacology 1989;99(4):508-14.
6. Zemishlany Z, McQueeney R, Gabriel SM, Davidson M. Neuroendocrine and monoaminergic responses to acute administration of alprazolam in normal subjects. Neuropsychobiology 1990;23(3):124-8.
7. Plotsky PM, Bruhn TO, Vale W. Hypophysiotropic regulation of adrenocorticotropin secretion in response to insulin-induced hypoglycemia. Endocrinology 1985;117(1):323.
8. Surwit RS, Feinglos MN, Scovern AW. Diabetes and behavior. American Psychologist 1983;38(3):255-62.
9. Surwit RS, McCubbin JA, Kuhn CM, McGee D, Gerstenfeld D, Feinglos MN. Alprazolam reduces stress hyperglycemia in ob/ob mice. Psychosomatic medicine 1986;48(3):278.
10. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, et al. Effects of alprazolam on glucose regulation in diabetes. Results of double-blind, placebo-controlled trial. Diabetes Care 1995;18(8):1133.
11. Afkhami-Ardekani M, Shojaoddiny-Ardakani A, Soltani V, Molanoori E. Comparing the Effects of Fluoxetine and Alprazolam on Blood Glucose in Patients with Type 2 Diabetes. Journal of Qazvin University of Medical Sciences 2008; 12(1):21-25.
12. Giordano R, Grottoli S, Brossa PC, Pellegrino M, Destefanis S, Lanfranco F, et al. Alprazolam (a benzodiazepine activating GABA receptor) reduces the neuroendocrine responses to insulin-induced hypoglycaemia in humans. Clinical Endocrinology 2003;59(3):314-20.
13. Deuster PA, Faraday MM, Chrousos GP, Poth MA. Effects of dehydroepiandrosterone and alprazolam on hypothalamic-pituitary responses to exercise. Journal of Clinical Endocrinology & Metabolism 2005;90(8):4777.
14. Billaudel B, Sutter BC. Direct effect of corticosterone upon insulin secretion studied by three different techniques. HormMetab Res 1979;11(10):555-60.
15. Barseghian G, Levine R. Effect of corticosterone on insulin and glucagon secretion by the isolated perfused rat pancreas. Endocrinology 1980;106(2):547.
16. Barseghian G, Levine R, Epps P. Direct effect of cortisol and cortisone on insulin and glucagon secretion. Endocrinology 1982;111(5):1648.
17. Lambillotte C, Gilon P, Henquin JC. Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. Journal of Clinical Investigation 1997;99(3):414.
18. Johnson RW TJSRYH. Benzodiazepine receptor heterogeneity and regulation. In: Malick JB ESaYHe, editor. Anxiolytics. Raven. New York; 1983;93-112.