EFFECT OF BUSPIRONE : AN ANXIOLYTIC DRUG ON BLOOD GLUCOSE IN HUMANS

S. K. Ojha, M. Nandave and C. Sharma*

Department of Pharmacology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi –110 029 and
*Clinical Research and Medical Services, Dabur Research Foundation (DRF),
22, Site IV, Sahibabad, Ghaziabad-201 010, India

ABSTRACT

The present study investigated the effect of an antianxiety drug, buspirone on blood glucose and plasma insulin level concerning the role of 5-HT_{1A} receptors in blood glucose regulation in healthy humans. Twelve healthy male volunteers were administered single oral doses of buspirone (10 mg) or placebo, in a randomized, crossover way, followed by oral glucose load (75 gm in 200 ml) at reported T_{max} i.e. the time of peak plasma concentration of the respective administered drug. The blood samples were collected as predose, postdose and post oral glucose load at 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 hr to investigate the effect of buspirone or placebo at basal blood glucose and plasma insulin level and after oral glucose load induced (postprandial) blood glucose and plasma insulin level. Blood glucose and plasma insulin concentrations were estimated by glucose hexokinase method and enzyme linked immunosorbent assay (ELISA) method respectively. The concentration of blood glucose was significantly ($p < 0.05$) decreased after oral glucose load following administration of buspirone in comparison with placebo however no significant change was observed in the fasting blood glucose and plasma insulin (fasting and oral glucose load induced) level. In conclusions, the present study findings show that buspirone produced a significant alteration in blood glucose level in healthy humans. In addition, study results also indicate that the involvement of serotonergic (5-HT₁ receptors) mechanism of blood glucose regulation in humans is different from animals.

KEY WORDS

Antianxiety drug, Oral glucose load, healthy volunteers.

INTRODUCTION

Anxiety disorders and diabetes mellitus are one of the most common psychiatric and endocrine disorders in general populations, respectively (1, 2). The incidence and prevalence of anxiety disorders are very common in diabetic patients than in the general population (3, 4). In diabetic patients, recognition and control of anxiety symptoms are of utmost importance to increase compliance with treatment and to improve quality of life. Several anxiolytics are available for clinical use including benzodiazepines and the newer anxiolytic agent's azaspirodecanedione derivatives such as buspirone, gepirone and ipsapirone (5). Buspirone is a prototype in family and it

possesses comparable anxiolytic activity without sedative, hypnotic, anticonvulsant and muscle relaxant property and structurally unrelated to the benzodiazepines (5). However the main concern about drug treatment for disorders other than diabetes is that several non-diabetic drugs may also interfere with plasma glucose and insulin level in healthy as well as diabetics. It has been shown that complex mechanism of blood glucose homeostasis involves several hormonal and non-hormonal components such as serotonin, dopamine and nor-adrenaline, which affect blood glucose level (6). In recent years, serotonin (5-hydroxytryptamine, 5-HT), serotonin receptor agonists, antagonists and selective serotonin reuptake inhibitors have been demonstrated to produce alteration in blood glucose level (7-10). Buspirone has been demonstrated to possess its anxiolytic property because of its action on 5-HT_{1A} receptors (5, 11). Anxiolytics used in diabetes are reported to produce alteration in blood glucose and insulin level (12). In pre-clinical studies, anxiolytics such as buspirone acting through serotonin receptors demonstrated to alter the plasma glucose and insulin levels (13-15). Despite

Address for Correspondence:

Dr. S. K. Ojha
Department of Pharmacology
All India Institute of Medical Sciences
Ansari Nagar, New Delhi –110 029
E-mail : shreeshojha@yahoo.co.in

of its wide use in general population, glucose intolerant as well as diabetic patients, no study is available in literature regarding the effect of buspirone on fasting and oral glucose load induced (postprandial) blood glucose and plasma insulin levels in healthy human volunteers.

MATERIALS AND METHODS

Study subjects:

The study protocol and informed consent form was approved by Institutional Review Board (IRB) and signed informed consent was obtained from each participant. The study was conducted at Ranbaxy Clinical Pharmacology Unit (RCPU), Majeedia Hospital, New Delhi. Twelve healthy adult male volunteers [age [mean $\pm$ SD] 24.8 $\pm$ 2.8 years; range 20 to 30 years, body weight [mean $\pm$ SD] 64.25 $\pm$ 6.42 Kg; range 58 to 72 Kg, height [mean $\pm$ SD] 168.75 $\pm$ 6.64; range 160 to 181 cms] participated in the study. The subjects were deemed healthy according to medical history, physical examination, laboratory test and electrocardiogram. The subjects were selected on the basis of exclusion and inclusion criteria. The inclusion criteria were of normal health as determined by medical history, physical and clinical examination of the subjects. The exclusion criteria were history of any allergy to buspirone and related compounds or any physical or clinical abnormality.

Study procedure:

Each volunteer was randomized to either receive a single 10 mg oral dose of buspirone (Buspin®, Intas Pharmaceuticals, Ahmedabad) or identical placebo containing lactose (10 mg) at 09.15 am after an overnight fast of 12 hours (phase I) and vice versa (phase II) with a one week wash out period in between. The common therapeutic dose of buspirone was used in the study. A standardized oral glucose load containing 75 gm glucose in 200 ml water (16) was given to all the subjects after buspirone or placebo administration on previously reported scheduled T_{max} , i.e. the time when respective drug or placebo achieved the peak plasma concentration; 45 min (17). The blood samples (2 ml each) were collected as predose (before drug or placebo administration), post dose (after drug or placebo administration, at T_{max} of the respective administered drug or placebo) and post oral glucose load (after oral glucose load administration followed by drug or placebo administration) at 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 hr. Blood samples were collected through an indwelling canula placed in a forearm vein during each period. After collection, the blood samples were immediately centrifuged to separate the

plasma. All plasma samples were analyzed immediately for plasma glucose and insulin level. None of the subjects received any medication during the two weeks prior to the start of the study and during study periods. At the time of screening they were instructed not to take any prescription and over the counter (OTC) medications subsequently until the completion of the study. All the subjects were required to abstain from any xanthine derivative food or beverages or alcoholic products for 48 hours prior to dosing and throughout the study periods. Subject safety was monitored for oral temperature, radial pulse, sitting blood pressure at the time of admission, prior to dose administration and before discharge in each period.

Sample analysis:

Both, blood glucose and insulin levels were estimated in plasma samples. Blood glucose concentrations (3 μ l samples) were estimated by glucose hexokinase method (18) using Dade Behring® Glucose Flex™ kit. The concentration of glucose was analyzed on Dimension®, clinical chemistry system at RCPU, New Delhi. The unit of glucose concentration was mg/dl with the normal range of 70-100 mg/dl. Plasma insulin levels (10 μ l samples) were estimated quantitatively by enzyme linked immunosorbent assay (ELISA) using ORGENTEC®, a commercially available active ELISA KIT (19). The concentration of insulin was analyzed on a microplate reader with a 450 nm filter at RCPU, New Delhi. The concentration of insulin was expressed in U/ml. The sensitivity of insulin assay was 0.5 mg/l.

Statistical analysis:

The results are presented as mean $\pm$ SD. The data were analyzed statistically using student 't' test. The null hypotheses was rejected at $P < 0.05$.

RESULTS AND DISCUSSION

No adverse effect has been observed in the present study. Figure 1 and 2 show the effects of buspirone and placebo on blood glucose and insulin level predose, post dose and at different time points during oral glucose load. Administration of buspirone (10 mg) produced a significant fall in postprandial blood glucose level (at 0.5 hr after oral glucose load in comparison with placebo) without alteration in the plasma insulin level. Buspirone has no significant effect on fasting blood glucose and plasma level and oral glucose load induced plasma insulin level (Fig. 1, $p < 0.05$). Although a modest but insignificant decrease in plasma insulin level was observed

at all time intervals during oral glucose tolerance test as compared to placebo (Fig. 2).

Any abnormality in regulation of blood glucose level has importance in healthy volunteers and diabetic patients, both. A large number of drugs such as ethanol, β adrenergic receptor antagonism and salicylates etc. can cause hypoglycemia or may alter the response of diabetic patients to their existing therapeutic regimen (13, 20). Concerning the effect of certain anxiolytic agents such as chlordiazepoxide could increase the insulin requirement in diabetics indirectly indicating that it may dysregulate normal blood glucose control mechanism (12). As described earlier, serotonin, found to be co-stored

and co-released with insulin from pancreas participates in blood glucose homeostasis (21). The functional diversity of serotonin stems from the ability of this neurotransmitter to interact with multiple 5-HT receptors (currently classified as 5-HT₁ through to 5-HT₇ with further subtypes within receptor class) that can trigger and activate distinct intracellular signaling system (22). In general, 5-HT is reported to be an endogenous inhibitor of insulin and believed to alter the blood glucose and insulin level. There is a prevailing view that blood glucose is lowered by 5-HT and this response can be suppressed by 5-HT receptor antagonists (7, 23-25). 5-HT, 5-HT agonists and its precursors are reported to produce fall in blood glucose level in preclinical studies and few human studies (7-10, 23-25). As buspirone has been shown to produce hyperglycemia in animals, its necessary to assess its effect on blood glucose and insulin level in humans. In the present study, we observed the effect of buspirone, a HT_{1A} receptor partial agonist on basal (fasting) and oral glucose tolerance test (postprandial) induced blood glucose and insulin levels in healthy humans.

In rats, buspirone administration has been reported to alter the hypoglycemic effect of tolbutamide and produce hyperglycemia probably through 5-HT₁ receptor agonist activity (13-15). In another study in rabbits, buspirone in doses of 0.5 mg/kg/per orally has no effect on blood glucose level (26). In the present study buspirone administration produced a significant decrease in the postprandial blood glucose level following an oral glucose load without altering fasting and oral glucose load induced postprandial plasma insulin level. However, we could not find significant alteration in fasting plasma insulin level as well as postprandial plasma insulin level.

Our results are consistent with previous reports suggesting that buspirone has no significant effect on plasma insulin level in rats (13, 15). However in rats, the hyperglycemia was suggested to be mediated by the activation of 5-HT_{1A} receptors without significant alteration in insulin level, similar to the present study in which no significant effect on insulin was observed. The exact mechanism underlying such bioactivities results in fall in plasma glucose level with buspirone administration to humans are obscure. However, in animals the ability of 5-HT₁ receptor agonist to facilitate adrenaline release is suggested to produce increases in plasma glucose and glucagon levels (14). The hyperglucagonemic effects of buspirone without any significant alteration in plasma insulin level are suggested probable mechanism of hyperglycemia. Concerning plasma insulin level, the results of our study are in agreement with

*P<0.05; Placebo vs. buspirone

Fig. 1 Mean plot of blood glucose level vs. time profile before and after administration of buspirone and placebo at predose, postdose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 hrs following oral glucose load (n=12).

Fig. 2 Mean plot of blood insulin level vs. time profile before and after administration of buspirone and placebo at predose, postdose and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 hrs following oral glucose load (n=12).

these animal studies as buspirone did not produced significant change in plasma insulin level in humans.

However, contrary to our study results i.e. a significant fall in postprandial blood glucose level, buspirone in rabbits did not show any effect on blood glucose level (26). The precise role of serotonergic mechanism in blood glucose control mechanism in animals and humans appears different. Although in response to 5-HT receptor activation both decreased and increased insulin levels respectively with hyperglycemia and hypoglycemia have been reported in animals (8, 24, 27). Regarding effect of 5-HT on blood glucose and plasma insulin level, 5-HT and precursor has been shown to produce fall in blood glucose level without affecting insulin release (7, 23). Therefore, present study observations suggest that the effect of buspirone on blood glucose level is independent of insulin components of blood glucose regulation. The possible mechanism may be due to an increase in glucose uptake across the cell membrane in skeletal muscle through non-insulin dependent pathways of blood glucose regulation.

From the present study findings it can be inferred that serotonergic receptors (5-HT_{1A} receptors) participate in blood glucose regulation. On the basis of present observations it is concluded that buspirone produced a significant alteration in blood glucose level in healthy human volunteers. Furthermore, the present results, also suggest that those who are on glucose lowering therapy need lesser doses of buspirone and may improve compliance with treatment with oral hypoglycemic agents. However, it could be possible that its beneficial effects in reducing the doses of hypoglycemic agents may be due to an increase in glycogen synthetase activity or increased sensitivity of hepatic and peripheral insulin receptors without no change in insulinemia as observed in a previous study (28). Furthermore, earlier fall in 5-HT levels in diabetes, a condition during which utilization of glucose is significantly modulated in skeletal muscle has been demonstrated and postulated that 5-HT could modulate glucose transport (29). Similarly, in the present investigation the participation of 5-HT receptor in blood glucose control mechanisms has been demonstrated. Though these results are encouraging, planned clinical studies using buspirone in individuals with diabetes and anxiety are worthwhile. The 5-HT₁ receptor is functionally significant in blood glucose regulation and it is likely that further research into the role and function of this receptor will yield important new insights into the regulation of blood glucose homeostasis which may have potential to provide safe and effective therapeutic strategies for patients with decreased insulin secretion.

ACKNOWLEDGEMENTS

The authors would like to gratefully acknowledge Ranbaxy Research Laboratories, Gurgaon for providing clinical & analytical services and University Grants Commission for providing research fellowship.

REFERENCES

1. Lustman, P.J., Griffith, L.S., Clouse, R.E. and Cryer, P.E. (1986) Psychiatric illness in diabetes mellitus, relationship to symptoms and glucose control. *J. Nerve Ment. Dis.* 174, 736-742.
2. Popkin, M.K., Callies, A.L., Lentz, R.D., Colon, E.A. and Sutherland, D.E. (1988) Prevalence of major depression, simple phobia and other psychiatric disorders in patients with longstanding type 1 diabetes mellitus. *Arch. Gen. Psychiatry* 45, 64-68.
3. Simon, N.M. and Pollack, M.H. (1999) Anxiety disorders, in *Conn's current therapy*, edited by Rakel, R.E. (W. B. Saunders, Philadelphia), 1126.
4. Foster, D.W. (1998) Diabetes mellitus, in *Harrison's Principles of Internal Medicine*, edited by Fauci, A.S., Martin, J.B., Braunwald, E., Kasper, D.L., Isselbacher, K.J., Hauser, S.L., Wilson, J.D. and Longo, D.L. McGraw Hill USA 2060.
5. Collin Dollery. (1999) Buspirone, In *therapeutic Drugs* 2nd Edn., Churchill Livingstone, New York, pp B114-B117.
6. Nonogaki, K. and Iguchi, A. (1997) Role of central neural mechanisms in the regulation of hepatic glucose metabolism. *Life Sci.* 60, 797-807.
7. Smith, S.A., Pogson, C.I. Smith S.A., Pogson C.L. (1977) Tryptophan and the control of plasma glucose concentrations in the rat. *Biochem. J.* 168, 495-506.
8. Chaoulloff, F. and Jeanrenacid, B. (1987) 5-HT-1A and adrenergic receptors mediate the hyperglycemic and hypoinsulinemic effect of 8-hydroxy -2-(di-n-propylamino) tetraline in the conscious rat. *J. Pharmacol. Exp. Ther.* 243, 1159-1166.
9. Yamada, J., Sugimoto, Y. and Yoshikawa, T. (1998) p-Chloroamphetamine a serotonin releasing drug, elicited in rats a hyperglycemia initiated by 5-HT_{1A} and 5-HT_{2B/2C} receptors. *Eur. J. Pharmacol.* 359, 185-190.
10. Wozanik, K.M. and Linnoila, M. (1991) Hyperglycemic properties of serotonin receptor antagonists. *Life Sci.* 49, 101-109.

11. Bridge, M.W., Marvin, G., Thompson, C.E., Sharma, A., Jones, D.A. and Kendall, M.J. (2001) Quantifying the 5-HT_{1A} agonist action of buspirone in man. *Psychopharmacol.* 158, 224-227.
12. Martindale the complete drug reference (1999) 32nd edition edited by Parfitt, K. Pharmaceutical Press, 326.
13. Yamada, J., Sugimoto, Y., Kimura, I., Wantanabe, Y. and Horisaka, K. (1992) The effect of the serotonin-1A receptors agonist buspirone on the blood glucose and pancreatic hormones in the rats. *Jpn. J. Pharmacol.* 60, 145-148.
14. Chaouloff, F., Baudrie, V. and Laude, D. (1990) Evidences that the 5-HT 1A receptor agonist buspirone and iprapirone activates adrenaline release in the conscious rat. *Eur. J. Pharmacol.* 177, 107-110.
15. Sugimoto, Y., Yamada, J., Kimura, I. and Horisaka, K. (1995) The effects of the serotonin 1A agonist buspirone on tolbutamide-induced hypoglycemia in rats. *Biol. Pharm. Bull.* 18, 1296-1298.
16. Massari, V., Eschwege, E., Valleron, A.J., Massari, V., Eschwege, E. and Valleron, A.J. (1983) Imprecision of new criteria for the oral glucose tolerance test. *Diabetologia* 24, 100-106.
17. Gammans, R.E., Mayol, R.F. and Labudde, J.A. (1986) Metabolism and disposition of buspirone. *Am. J. Med.* 80, 41-51.
18. Kunst, A., Drager, B. and Ziagenhorn, J. (1983) UV methods with hexokinase and glucose 6-phosphate dehydrogenase, In *Methods of Enzymatic Analysis*. 163-172.
19. Willein, T., Nicholsan, S. and Casey, C. (1985) A micro enzyme-linked immunosorbent assay for insulin antibodies in serum. *J. Immunol. Methods* 76, 185-194.
20. Furman, B.L., (1980) Impairment of glucose tolerance produced by diuretics and other drugs. *Pharmacol. Ther.* 12, 613-640.
21. Lundquist, I., Ahren, B. and Hankson, R. (1989) Monoamines in pancreatic islets of guinea pig, hamster, rat and mouse determined by high performance liquid chromatography. *Pancreas* 4, 662-667.
22. Hoyer, D., Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mytecharane, E.J., Saxena, P.R. and Humphrey, P.R. (1994) International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol. Rev.* 46, 157-203.
23. Furman, B.L. and Wilson, G.A. (1980) Further studies on the effects of 5- hydroxytryptophan on plasma glucose and insulin in the mouse. *Diabetologia* 19, 386-390.
24. Yamada, J., Sugimoto, Y., Kimura, I., Tekeuchi, N. and Horisaka, K. (1989) Serotonin induced hypoglycemia and increased plasma insulin levels in mice. *Life Sci.* 45, 1931-1936.
25. Uvnas-moberg, K., Ahlenius, S., Alstel, P. and Hillegart, V. (1996) Effects of selective serotonin and dopamine agonists on plasma levels of glucose, insulin and glucagon in the rat. *Neuroendocrinol.* 63, 269-274.
26. Dixit, R.K., Puri, J.N., Sharma, M.K., Jain, I.P., Singh, S., Ansari, N.A. and Singh, S.P. (2001) Effect of anxiolytics on blood sugar level in rabbits. *Indian J. Exp. Biol.* 39, 378-380.
27. Bjorkstrand, E., Ahlenius, U., Smedh, U. and Uvans-Moberg. (1996) The oxytocin receptor antagonist 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin inhibits effects of the 5-HT_{1A} receptor agonist 8-OH-DPAT on plasma levels of insulin, cholecystokinin and somatostatin. *Regul. Pept.* 63, 47-52.
28. Breum, L., Bjerre, U., Bak, J.F., Jacobson, S. and Astrup, A. (1995) Long term effects of fluoxetine on glycemic control in obese patients with non-insulin-dependent diabetes mellitus or glucose intolerance: influence on muscle glycogen synthase and insulin receptor kinase activity. *Metabolism* 44, 1570-1576.
29. Martin, F.J., Miguez, J.M., Aldegunde, M. and Atienza, G. (1995) Effect of streptozotocin-induced diabetes mellitus on serotonin measured of peripheral tissues in rats. *Life Sci.* 56, 51-59.