Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 3, 2015

Original Article

EFFECT OF TAMSULOSIN A SELECTIVE α_1-ANTAGONIST ON GLUCOSE HOMEOSTASIS IN RATS

GURUDATTA MOHARIR[1], SHIVAPRASAD[2], AMBADASU BHARATHA[3*], A. A. NAIKWADI[4], WALI R. S[5]

[1, 3]Lecturer, [2]Asst. Professor, [4]Professor, [5]Professor & Head, Department of Pharmacology, BLDE University's Shri B. M. Patil Medical College Hospital & Research Center, Bijapur 586103, Karnataka.
Email: ambu2mail@gmail.com

Received: 05 Dec 2014 Revised and Accepted: 25 Dec 2014

ABSTRACT

Objective: To assess the effect of tamsulosin (α_1-antagonist) on blood sugar and adrenaline levels in rats.

Methods: Wistar rats were divided in to four groups (n=6), Group-I (Normal control) administered normal saline, Group-II, Group-III &Group-IV induced diabetes by administering Streptozotocin IV 50 mg/kg. Group III and Group-IV were administered Tamsulosin 1mg/kg and Glimepiride 10µg/kg respectively for twenty one days. Serum insulin, adrenaline and blood glucose were estimated at before and after drug treatment.

Results: Adrenaline and insulin levels were increased significantly ($p<0.005$) in Diabetic control and Tamsulosin treated diabetic rats compared to Normal control rats. Blood glucose levelsincreased significantly ($p<0.005$) in Tamsulosin treated diabetic rats compared to Diabetic control rats. All the three parameters are compared at the end of drug treatment.

Conclusion: Several studies interpreted a potential role of the α-receptor in glucose metabolism. Inhibition of the α1-receptor pathway can lead to a decreased glucose uptake, and hence an increased plasma glucose concentration. Several studies in one or the other way indicating the correlation between diabetes and BPH and probably in such condition tamsulosin a α1 antagonist is the drug of choice along with oral hypoglycemic agents. Literature survey also shows that there is increase in the blood glucose levels during the use of tamsulosin which impacts blood sugar levels especially in diabetic state. T.h.is study shows increase in blood glucose levels with the use of tamsulosin is making further complications in diabetic patients. This adverse drug reaction and the proposed mechanism need to be proven further.

Keywords: α_1-antagonist, Wistar rats, Streptozotocin.

INTRODUCTION

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the Disease [1, 2]. According to Wild et al the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India [3]. Benign prostatic hyperplasia (BPH) is the most common benign tumor in men, and its incidence is age related. Many researchers published papers in scientific journals in view of an association between Type-II diabetes mellitus and BPH. In fact, both diabetes and BPH are very similar in men as they age and seem to be sharing common epidemiologic features. The etiology of BPH is still largely unresolved, but multiple partially overlapping and complementary systems (nerve, endocrine, immune, and vascular) as well as local factors are likely to be involved [4, 5]. Controversy surrounding BPH pathogenesis along with the fact that both BPH and diabetes mellitus type 2 (DM-2) are both highly prevalent diseases is posing doubts on the association between these two common diseases. Among available α_1-antagonist tamsulosin being safe with least side effects being preferred for the treatment of BPH. Thus, this study is carried out to assess the possible interaction of tamsulosin on glucose homeostasis in diabetic rats.

MATERIALS AND METHODS

Animals (Wistar rats) either sex weighing 150-250g was procured from the Central Animal House, BLDEU's Sri BM Patil Medical College Hospital & Research Center, Bijapur, India, were used in the study. They were housed in the quarantine room individually in polypropylene cages for one week of acclimatization before the experiment started. The study was approved by the Institutional Animal Ethics Committee (IAEC).

Tamsulosin was procured from Cipla Laboratories Ltd. Glimepiride was gift supplied by Unichem pharmaceuticals Ltd Mumbai and streptozotocin was purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Preparation of streptozotocin (STZ) and glimepiride solution

The STZ of required quantity (50 mg/kg body weight) was dissolved in distilled water. The animals were injected by streptozotocin at the dose of 60 mg/kg of the body weight intravenously. Glimepiride is administered in a dose of 4 micro gram/kg body weight dissolved in distilled water.

Group-I: Normal Control-Saline treated group

Group-II: Diabetic Control-Streptozotocin (60mg/kg) treated group.

Group-III: Diabetic rat treated with Tamsulosin (1mg/kg)

Group-IV: Diabetic rat treated with Glimepiride (4mg/kg)

Experimental induction of diabetes

Twenty four male albino rats of Wistar strain were weighed and randomly distributed into four groups of six rats each. Care was taken to maintain the weight between 200 to 250g. The animals were fasted for a night and diabetes was induced in groups II to IV by a single dose of intraperitoneal injection of a freshly prepared solution of streptozotocin (60 mg/kg body weight). Control animals received only physiological saline.

Confirmation of diabetes

The diabetic state was confirmed by estimating the blood glucose levels after 72 h of STZ injection. The animals with the blood glucose level above 200mg/dl were considered as diabetic. After confirmation of diabetic in all animals, the treatment was commenced.

Administration of drugs

Tamsulosin, glimepiride were administered daily morning at 10.00 AM for a period of twenty one days after induction of diabetes.

Estimation of biochemical parameters

To evaluate the biochemical parameters, blood was collected from the retro orbital plexus of the rats using heparinised capillary tubes under ketamine anesthesia at 0 day and 21st day of drug treatment.

The serum samples collected were subjected for biochemical estimation of serum glucose, insulin and adrenaline concentration.

Glucose values were estimated by using accuchek glucometer with standard accuchek strips, rat insulin was estimated by ELISA method by using ratUltra-sensitiveinsulin kit purchased from Genxbio Health Sciences Pvt. Ltd Delhi. Adrenaline was estimated at kanva diagnostic laboratory, Bangalore where adrenaline estimation was done by using ratultra-sensitive adrenaline kit.

Statistical analysis

Values are expressed as mean ± SEM. All the values were analyzed by one-way analysis of variance (ANOVA) followed by Games-Howell post hoc comparisons tests to study the differences between groups. The level of statistical significance was set at $p<0.05$.

RESULTS

The 0 day values of all the four groups were similar for all parameters and there is no significant difference. But 21st day values it is seen that there is the significant increase ($p<0.001$) in levels of adrenaline in Group-II and Group-III when compared to Group-I; normal control. The levels of insulin were decreased significantly ($p<0.001$) in Group-II and Group-III when compared to Group-I. It was found that glucose levels were found increased significantly in Group-III (Tamsulosin Group) compared to Group-II (table 1).

Table 1: Levels of adrenaline, insulin and blood glucose (mean±SEM)

Group	Adrenaline (pg/ml)		Insulin (ng/ml)		Glucose (mg/dl)	
	Day 0	Day 21	Day 0	Day 21	Day 0	Day 21
Group-I	111.83 ±1.97	110.83 ±1.89	3.76 ±0.18	3.10 ±.18	100.16 ±3.14	93.83 ±7.77
Group-II	109.66 ±1.20	141 ±3.89*	3.71±0.19	2.11 ±0.18*	266.33 ±9.70	297.5 ±12.84
Group-III	113.33 ±1.47	153.20 ±3.48*	3.54 ±0.19	1.31±0.15*	259.33 ±5.87	365.66 ±7.95#
Group-IV	104.83 ±1.99	147.16±16.76	3.79 ±0.18	1.96 ±0.33	253.16 ±4.84	196.33 ±22.25#

*p<0.001compared to control, #P<0.05 compared to diabetic control group.

DISCUSSION

Glucose is transported into the cell by the GLUT4 glucose transporter which is dependent on insulin. Glucose uptake is initiated after binding to the insulin receptor, diverse intracellular signaling pathways result in translocation of the GLUT4 glucose transporter [6]. However, in diabetic patients non-insulin dependent pathways may also contribute to glucose uptake. One of these is regulated by the α1-receptor [7-9]. Stimulation of the α1-receptor leads to phospholipase C activation initiating hydrolysis of phosphatidylinositol biphosphonate. This leads to activation of protein kinase C (PKC) by release of intracellular calcium and diacylglycerol [10]. Lipids in the phosphatidylinositol biphosphonate pathway can be substrates for phosphatidylinositol 3-kinase (PI3K), which is an important kinase for glucose uptake. The role of the α1-receptor in glucose uptake in humans was also shown. In two studies, stimulation with an α-agonist resulted in a decrease of interstitial glucose concentrations [11, 12]. The stimulatory effect of α1-antagonist on glucose uptake was inhibited by the α -receptor antagonist prazosin [7].

These studies elucidate a potential role of the α-receptor in glucose metabolism. Inhibition of the α1-receptor pathway can lead to a decreased glucose uptake, and hence an increased plasma glucose concentration. This adverse drug reaction and the proposed mechanism need to be proven further.

Several studies [13-16] in one or the other way indicating their correlation between diabetes and BPH and probably in such condition tamsulosin a α1 antagonist is the drug of choice along with oral hypoglycemic agents.

In this present study it was found that the use of tamsulosin is further increasing the blood sugar levels significantly. Increased plasma adrenaline levels in diabetic rats also suggest that diabetes is associated with increased sympathetic activity. Adeghate et al also observed a positive correlation between adrenalin level and diabetes [17].

CONCLUSION

Increase in blood glucose levels with the use of tamsulosin is making further complications in diabetic patients. Physicians should be aware of this hyperglycemia as a possible adverse drug reaction in diabetic patients with BPH using tamsulosin.

ACKNOWLEDGEMENT

My sincere thanks to BLDE University, Bijapur for funding & constant support. I thank Mr Gujarathi Bhairkadar animal house technician and staff, Dept. of Pharmacology for constant help throughout my work.

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Joshi SR, Parikh RM. India-diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India 2007;55:323-4.
2. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J 2013;6(10):524-31.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(5):1047-53.
4. Lee C, Kozlowski JM, Grayhack JT. Etiology of benign prostatic hyperplasia. Urologic Clin North Am 1995;22(2):237-46.
5. Partin W, Oesterling JE, Epstein JI, Horton R, Walsh PC. Influence of age and endocrine factors on the volume of benign prostatic hyperplasia. J Urol 1991;145(2):405-9.
6. Farese RV. Insulin-sensitive phospholipid signaling systems and glucose transport. Update II Exp Biol Med 2001;226(4):283-95.
7. Hutchinson DS, Bengtsson T. Alpha1A-adrenoceptors activate glucose uptake in L6 muscle cells through a phospholipase C, phosphati-dylinositol-3 kinase, and atypical protein kinase C-dependent pathway. Endocrinol 2005;146(2):901-2.
8. Cheng JT, Liu IM, Yen ST, Chen PC. Role of alpha1A-adrenoceptor in the regulation of glucose uptake into white adipocyte of rats in vitro. Auton Neurosci 2000;84(3):140-6.
9. Faintrenie G, Geloen A. Alpha-1 adrenergic stimulation of glucose uptake in rat white adipocytes. J Pharmacol Exp Ther 1998;286(2):607-10.
10. Zhong H, Minneman KP. Alpha1-adrenoceptor subtypes. Eur J Pharmacol 1999;375(1-3):261-76.
11. Boschmann M, Krupp G, Luft FC, Klaus S, Jordan J. *In vivo* response to alpha1-adrenoreceptor stimulation in human white adipose tissue. Obes Res 2002;10(6):555-8.
12. Flechtner-Mors M, Jenkinson CP, Alt A, Biesalski HK, Adler G, Ditschuneit HH. Sympathetic regulation of glucose uptake by the alpha1-adrenoceptor in human obesity. Obes Res 2004;12(4):612-20.
13. Bourke JB, Griffin JP. Hypertension, diabetes mellitus, and blood groups in benign prostatic hypertrophy. Br J Urol 1966;38(1):18-23.
14. Hammarsten J, Högstedt B, Holthuis N, Mellstrom D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1(3);157-62.

15. Safarinejad MR. Prevalence of benign prostatic hyperplasia in a population-based study in Iranian men 40 years old or older. Int Urol Nephrol 2008;40(4):921-31.
16. Sarma AV, Burke JP, Jacobson DJ, McGree ME, St Sauver J, Girman, *et al*. Associations between diabetes and clinical markers of benign prostatic hyperplasia among community-dwelling black and white men. Diabetes Care 2008;31(3):476–82.
17. Adeghate E, Ponery AS, Sheen R. Streptozotocin-Induced diabetes mellitus is associated with increased pancreatic tissue levels of noradrenaline and adrenaline in the rat. Pancreas 2001;22(3):311-6.