ENHANCEMENT OF INSULIN HYPOGLYCAEMIA BY BETA ADRENOCEPTOR ANTAGONISTS

R.C. SINGH, V.K. SRIVASTAVA*, G. TAYAL**, R.K. SRIVASTAVA*** AND D.N. PRASAD

Department of Pharmacology,
L.L.R.M. Medical College, Meerut (U.P.)

Summary : Interaction of insulin with β-adrenoceptor antagonists was studied in conscious rabbits. Propranolol and metoprolol did not modify the peak of insulin hypoglycaemia but delayed its recovery. Practolol, sotalol and 1-INPEA enhanced the peak effect and delayed the recovery of insulin-induced hypoglycaemia. H 35/25 and d-INPEA did not modify insulin hypoglycaemia. The β-blockers did not produce significant hypoglycaemia *per se*. Since sotalol, 1-INPEA (specific β-adrenoceptor antagonists devoid of local anaesthetic activity); practolol and metoprolol (selective cardiac β-1 adrenoceptor antagonists) enhanced hypoglycaemic action of insulin and H 35/25 (a selective β-2 adrenoceptor antagonist) failed to affect it, it seems that selective β-adrenoceptor blockade (similar to cardiac β-1 adrenoceptors) mediates enhancement of insulin hypoglycaemia. Caution should, therefore, be exercised in administering β-adrenoceptor antagonists and insulin together. A reduction in the dose of insulin may be necessary.

Key words: β-blockers insulin hypoglycaemia drug interaction

INTRODUCTION

Beta-adrenoceptor blocking agents are finding increasing use in the treatment of cardiovascular disorders, viz. angina pectoris, cardiac arrhythmias and hypertension (11). The association of diabetes with such cardiovascular diseases is frequently encountered. β-blockers have also been shown to be of value in diabetic children maintained on insulin for preventing attacks of ketoacidosis (6). Hence concomitant use of β-blockers with antidiabetic therapy is of common occurrence. Propranolol is well-known to enhance hypoglycaemic action of insulin (3, 4, 11). Insulin-induced hypoglycaemia is associated with signs of sympathetic stimulation such as tachycardia and sweating (8). The possibility that β-blockers may mask the development of signs of hypoglycaemia (11) increases the importance of studying interaction of insulin with β-blockers.

It was, therefore, planned to study the effect of β-blockers on insulin hypoglycaemia with a view to investigate the role of β-adrenoceptors in mediating such interactions. The role of β-adrenoceptors was studied by observing the effect of specific and selective β-blockers on insulin hypoglycaemia, adrenaline hyperglycaemia and on fasting blood sugar levels in rabbits.

MATERIALS AND METHODS

The study was conducted on conscious rabbits of either sex weighing between 1 to 2 *kg*. Animals were fasted for 18 hr before the experiment. Blood samples (0.1 *ml* each time) were collected from ear vein before and ½, 1, 2 and 4 hr following insulin (2 *U/kg*, sc) in saline treated and β-blocker treated rabbits and blood sugar was estimated by the micro method as described by Sharma *et al.* (14). Propranolol, metoprolol and H 35/25 (each 2 *mg/kg*, ip); practolol, sotalol,

Present address : * Department of Pharmacology, B.R.D. Medical College, Gorakhpur (U.P.).
** Department of Pharmacology, Maulana Azad Medical College, New Delhi-110002.
*** Department of Pharmacology, M.L.B. Medical College, Jhansi (U.P.)

l-INPEA and d-INPEA (each 5 *mg/kg*, ip) were given half hr before insulin injection. The saline treated group served as control. β-blockers which significantly altered the hypoglycaemic action of insulin, were also studied for their effect on normal blood sugar *per se* and on adrenaline (100 *μg/kg*, sc) hyperglycaemia. Blood sugar was represented as per cent of control blood sugar of the same animal (before drug administration) which was taken as 100%. Student's 't' test was applied to determine the level of significance of results.

RESULTS

Effect of β-blockers on insulin hypoglycaemia : In control rabbits insulin (2 *U/kg*, sc, n=10) produced a hypoglycaemic response. Maximum hypoglycaemia was observed at 1 hr which tended to recover at 4 hr. The hypoglycaemic effect of insulin in β-blocker treated rabbits is summarized in Fig. 1. Propranolol and metoprolol pretreatment (n=6 each) did not affect the peak hypoglycaemic action of insulin but only delayed its recovery as blood sugar in these treated animals at 4 hr was significantly lower in comparison to control group. The peak effect of insulin and its effect at 4 hr in the case of practolol, sotalol and l-INPEA treated rabbits (n=6 each) was significantly more in comparison to control. Pretreatment with H 35/25 and d-INPEA (n=6 each), however, did not significantly modify insulin hypoglycaemia

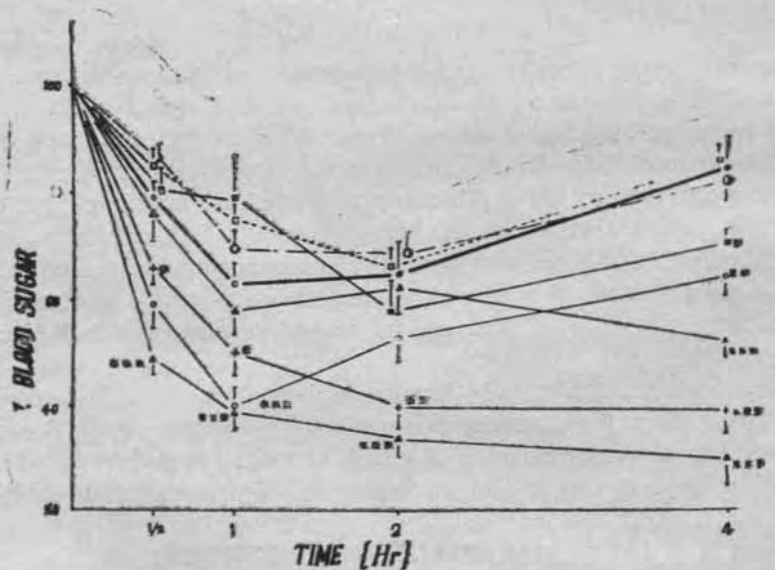

Fig. 1 : Effect of insulin on blood sugar (expressed as % of control) in saline (●), propranolol (△), sotalol (▲), practolol (○), metoprolol (■), H 35/25 (□), d-INPEA (◑) and l-INPEA (+) treated rabbits. * P=<0.05, ** P=<0.01, *** P=<0.001.

Effect of β-blockers on normal blood sugar : Propranolol, metoprolol (each 2 *mg/kg*, ip, n=4 each) and sotalol, practolol and l-INPEA (each 5 *mg/kg*, ip, n=4 each) had no effect on resting blood sugar *per se* in fasted rabbits (Fig. 2).

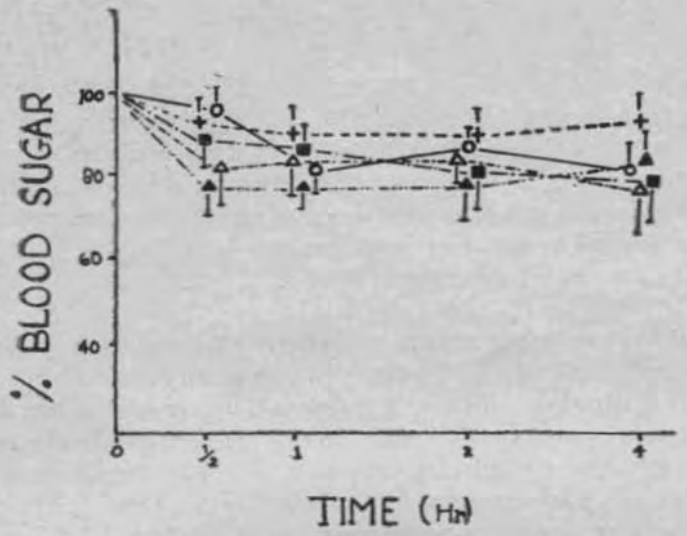

Fig. 2 : Effect of propranolol (△), metoprolol (■), sotalol (▲), practolol (○) and 1-INPEA (+) on blood sugar levels in rabbits.

Effect of β-blockers on adrenaline hyperglycaemia : Adrenaline (100 *μg/kg*, sc) produced the usual hyperglycaemic response (peak at 2 hr). Four groups of rabbits (n=4 each) were pretreated with propranolol, metoprolol (each 2 *mg/kg*), sotalol and practolol (each 5 *mg/kg*, ip) ½ hr before adrenaline injection to study the effect of β-blockers on adrenaline hyperglycaemia. Adrenaline in these treated animals induced hyperglycaemia which was much more marked in comparison to untreated group. The maximum hyperglycaemic effect of adrenaline obtained with each β-blocker treated group is presented in Fig. 3.

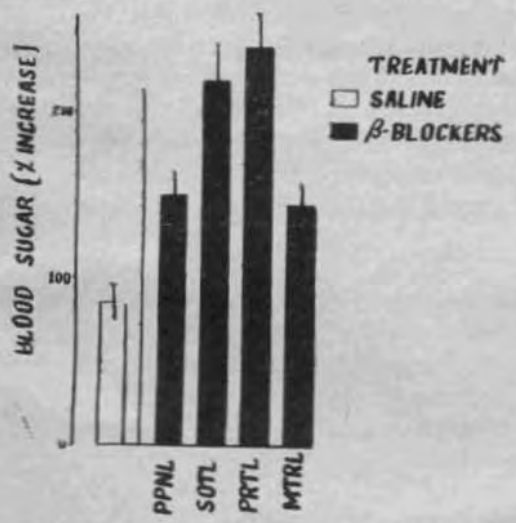

Fig. 3 : Effect of adrenaline on blood sugar level in saline, propranolol (PPNL), sotalol (SOTL), practolol (PRTL) and metoprolol (MTRL) treated rabbits.

DISCUSSION

In the present study propranolol and metoprolol prolonged while practolol, sotalol and l-INPEA not only prolonged but also enhanced the peak hypoglycaemic effect of insulin. Potentiation (peak or/and duration) of insulin hypoglycaemia by β-blockers appears to be due to blockade of specific β-adrenoceptors as sotalol and INPEA which are devoid of local anaesthetic activity (15, 16) also potentiated the hypoglycaemic action of insulin. Involvement of specific β-adrenoceptors is further confirmed by the observation that only l-INPEA which is the specific β-blocker (and not d-INPEA) potentiated the effect of insulin.

Propranolol has been reported to precipitate hypoglycaemia only in susceptible patients (7, 10). Its interaction with insulin could, therefore, be thought to be a result of simple summation of hypoglycaemic action. However, this does not appear to be the case in our studies as β-blockers were found to be devoid of any hypoglycaemic effect *per se*. Adrenaline and isoprenaline are known to cause insulin resistance by inducing inhibition of insulin stimulated glucose uptake. The resistance is prevented by β-adrenoceptor blockade *in vitro* (2). This might at least in part account for the enhancement of insulin hypoglycaemia by β-blockers.

Insulin hypoglycaemia is known to be associated with signs of adrenergic stimulation and release of catecholamines resulting in rebound hyperglycaemia (8, 11). It has also been proposed that propranolol inhibits this adrenergically mediated rebound hyperglycaemia and thereby augments the action of insulin (11). However, in the present study β-blockers failed to inhibit adrenaline-induced hyperglycaemia. As adrenaline induced release of insulin from the pancreas is mediated through β-adrenoceptors (12), blockade of adrenaline-induced release of insulin by β-blockers may account for enhancement of adrenaline hyperglycaemia in our studies.

Another factor responsible for the enhancement of insulin hypoglycaemia by β-blockers may be the interference with the release/hyperglycaemic action of glucagon released as a result of insulin hypoglycaemia. Insulin hypoglycaemia induces massive sympatho-adrenal discharge which results in the release of glucagon (8). β-blockers may interfere with this sympathetic induced release of glucagon to bring about enhancement of insulin hypoglycaemia. Furthermore, the action of glucagon to induce hyperglycaemia is brought about through the stimulation of adenyl cyclase (8), which has been hypothesized to be identical with β-adrenoceptors (13). β-blockers may therefore be thought to block this stimulation of adenyl cyclase thereby preventing the glucagon to exert its hyperglycaemic effect.

On further analysis into the subtypes of β-adrenoceptors involved in the interaction of β-blockers with insulin it was found that only practolol and metoprolol, cardioselective (β-1) adrenoceptor antagonists (1, 5) enhanced insulin hypoglycaemia while H 35/25, a selective adrenoceptor antagonist of β-2 type (9) failed to do so. The results indicate involvement (blockade) of specific and selective β-1 adrenoceptors (similar to cardiac β-adrenoceptors) mediating β-adrenoceptor antagonist-induced enhancement of insulin hypoglycaemia.

Caution should therefore be exercised in administering β-blockers to patients receiving

insulin or vice versa. A reduction in the dose of insulin may be necessary. Further work in other species and diabetic animals is, however, required before such interaction studies are taken up in diabetic patients.

ACKNOWLEDGEMENTS

The authors are grateful to Selvi & Co., Italy for the supply of INPEA; Bristol Myers, U.S.A. for sotalol; I.C.I., U.K. for propranolol and practolol and Ciba Geigy, Basle for metoprolol.

REFERENCES

1. Ablad, B.E., E. Carlsson and E.K. Lars. Pharmacological studies of the two new cardioselective adrenergic beta receptor antagonists. *Life Sci.*, **12** : 107-119, 1973.
2. Abramson, E.A. and R.A. Arky. Role of β-adrenergic receptors in counter regulation to insulin-induced hypoglycaemia. *Diabetes*, **17** : 141, 1968.
3. Abramson, E.A., R.A. Arky and K.A. Woeber. Effects of propranolol on the hormonal and metabolic responses to insulin induced hypoglycaemia. *Lancet*, **2** : 1386-1388, 1966.
4. Brown, J.H. and D.A. Riggilo. Effect of sotalol (MJ 1999) and propranolol on insulin induced hypoglycaemia in rats. *Proc. Soc. Exp. Biol. Med.*, **127** : 1158-1160, 1968.
5. Dunlop, D. and R.C. Shanks. Selective blockade of adrenergic beta-receptors in heart. *Br. J. Pharmac.*, **32** : 201-218, 1968.
6. Hanstein, P.D. Drug Interactions, Lea & Febiger, Philadelphia, II Ed., p. 11-12, 1973.
7. Kotler, M.N., L. Berman and A.H. Rubenstein. Hypoglycaemia precipitated by propranolol. *Lancet*, **2** : 1389-1390, 1966.
8. Larner, J. and C. Haynes Jr. Insulin and oral hypoglycaemic durgs. In : The Pharmacological Basis of Therapeutics by L.S. Goodman and A. Gilman, V Ed., MacMillan Publishing Co., New York, p. 533-564, 1975.
9. Levy, B. and B. Wilkenfield. Analysis of selective beta receptor blockade. *European J. Pharmac.*, **5** : 227-234, 1969.
10. Mackintosh, T.F. Propranolol and hypoglycaemia. *Lancet*, **1** : 104-105, 1967.
11. Nickerson, M. and B. Collier. Drugs inhibiting nerves and structures innervated by them. In : The Pharmacological Basis of Therapeutics by L.S. Goodman and A. Gilman, V Ed., MacMillan Publishing Co., New York, pp. 1507-1533, 1975.
12. Porte, D. Jr. and R.P. Robertson. Control of insulin secretion by catecholamines, stress and the sympathetic nervous system. *Fed. Proc.*, **32** : 1792-1796, 1973.
13. Robinson, G.A., R.W. Butcher and E.W. Sutherland. Adenyl cyclase as an adrenergic receptor. *Ann. N.Y. Acad. Sci.*, **139** : 703-723, 1967.
14. Sharma, N.C., B.K. Sur and R.K. Shukla. A simplified technique for estimation of blood sugar. *Ind. J. Physiol. Pharmac.*, **16** : 349-353, 1972.
15. Somani, P. and K.B. Lum. The antiarrhythmic actions of beta-adrenergic blocking agents. *J. Pharmac. Exp,. Ther.*, **147** : 194-204, 1965.
16. Stanton, H.C., T. Kirchgessner and K. Parmenter. Cardiovascular pharmacology of two beta-adrenergic receptor antagonists. *J. Pharmac. Exp. Ther.*, **140** : 174-183, 1965.