Eur J Clin Pharmacol (1989) 36: 351–355

European Journal of Clinical Pharmacology

Modulation of catecholamine effects during hypoglycaemia in man by urapidil and propranolol

K.-G. Petersen, P. Katschker, and L. Kerp

Department of Endocrinology, Albert-Ludwigs-Universität, Freiburg, Federal Republic of Germany

Summary. The hypothesis that in hypoglycaemia adrenoceptor-blocking drugs may enhance those metabolic effects of the catecholamines that remain unblocked has been investigated in 12 volunteers.

α-Adrenoceptor blockade with urapidil increased the heart rate and the plasma noradrenaline level, and increased the β-adrenoceptor mediated cellular uptake of potassium and phosphate, and the production of lactate. Posthypoglycaemic glucose intolerance and the counterregulatory responses of hGH and cortisol remained unchanged. Plasma adrenaline, the α-adrenoceptor mediated responses of cortisol and hGH, and the diastolic blood pressure were increased by propranolol.

Adrenoceptor blocking drugs produce an indirect stimulatory effect by eliciting a reflex increase in sympathetic tone, which is manifested as stimulation of receptors of the type that has not been blocked.

Key words: urapidil, propranolol, hypoglycaemia; alpha-/beta-adrenergic blockade, catecholamine/metabolic effects, cortisol, growth hormone

The metabolic effects of adrenaline and noradrenaline are less strictly defined than those of other hormones, since both of them bind to α- and β-adrenoceptors. Animal studies have shown that specific adrenoceptor blockade can increase the effects of stimulation of those adrenoreceptors that remain unblocked as well as augment the corresponding metabolic responses [1, 2]. Adrenoceptor blockade should, therefore, alter the metabolic patterns produced by endogenous catecholamines during hypoglycaemia by the inhibitory effect of the blockade itself, and by increasing the effects of stimulation of the unblocked adrenoceptors.

Accordingly, a study has been made of the metabolic activity of endogenous catecholamines in the presence of α- and β-blockade by urapidil and propranolol, respectively.

Materials and methods

Twelve healthy male volunteers gave their informed consent to the study; age 27.1 (1.5) years, body weight 81.3 (1.5) kg; height 184.4 (2.5) cm. Physical examination, ECG, clinical chemistry tests, and response to an oral glucose load were normal.

In a randomized double-blind cross-over study at intervals of one week, oral doses of 160 mg propranolol, 90 mg urapidil or placebo were given at 06.00 h after an overnight fast (10 h). An indwelling catheter was inserted into an antecubital vein at 08.00 h. Hypoglycaemia was induced at 08.30 h by an i.v. bolus injection (0.1 U/kg body wt) of semisynthetic human insulin. An oral test load of glucose (100 g) was given at 10.30 h.

Urapidil was chosen as the α-blocker, because it is well tolerated. Three-times the therapeutic dose of urapidil was used to overcome its preference for α_1-adrenoceptors [3]. Propranolol is a non-specific β_1-β_2-blocker.

Plasma glucose was analyzed with a Beckman Glucose Analyzer (glucose oxidase method). Lactate was measured as described [4]. Potassium, sodium, phosphate and chloride were measured with an Auto-Analyzer. Adrenaline and noradrenaline were measured by HPLC using electrochemical detection (Waters, Eschborn, FRG). The other hormone measurements employed commercial radioimmunoassays: hGH (MCA Wellcome, Burgwedel, FRG), cortisol (MAJA, Serono, Freiburg, FRG); Insulin (Riagnost, Behringwerke AG, Marburg, FRG).

Results are expressed as mean (SEM). Interassay variation was 5% using individual assays for each volunteer. Areas under the curves were calculated as described [5]. Wilcoxon's test for paired differences was used and the level of significance was corrected to allow for the multiple tests carried out [SPSS software].

Results

Hypoglycaemia was induced by insulin in volunteers 2.5 h after an oral dose of propranolol 160 mg, urapidil 90 mg or placebo, and 2 h later an oral load

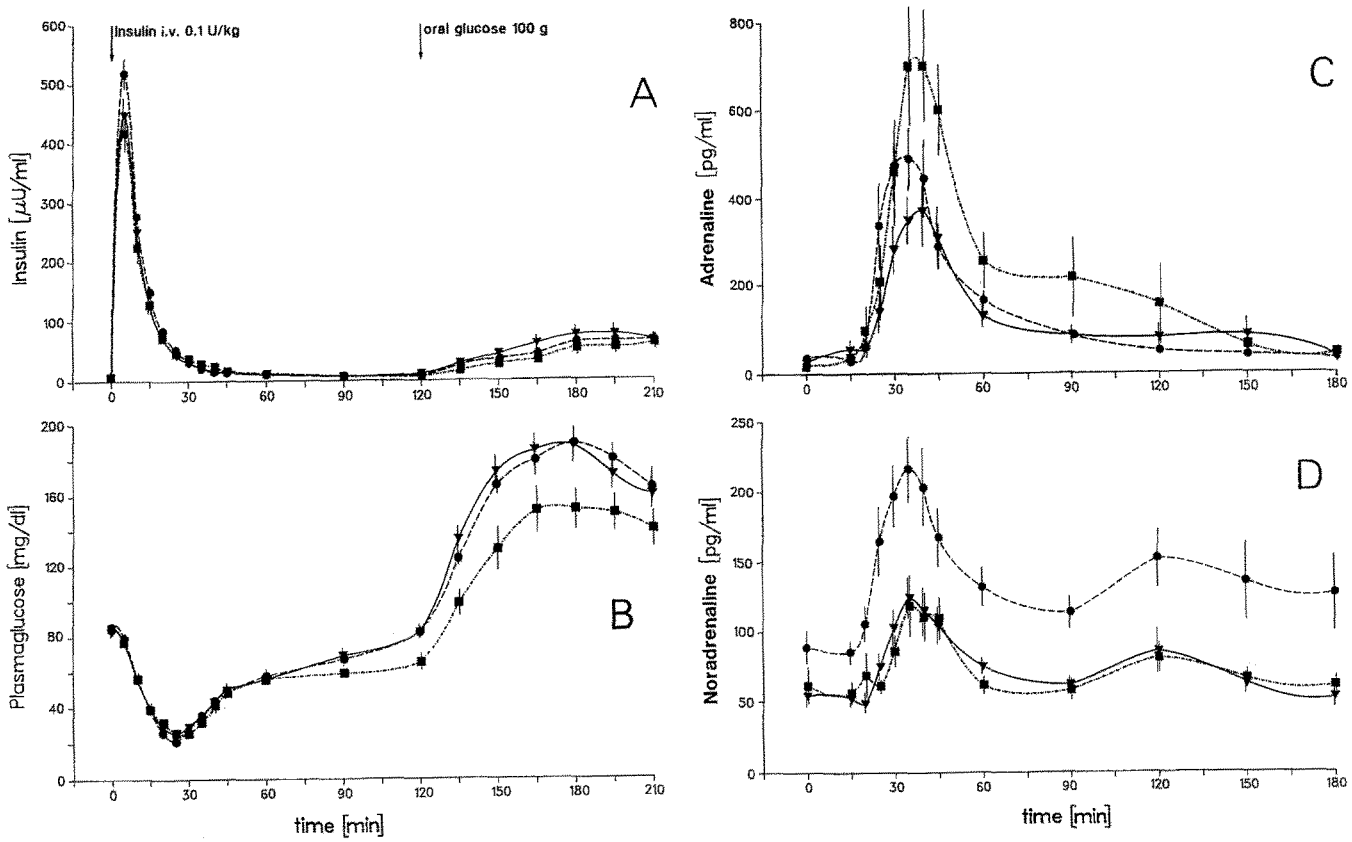

Fig. 1 A–D. Insulin-induced hypoglycaemia and posthypoglycaemic oral glucose load as indicated (**A**). Effects of α-adrenoceptor blockade with urapidil 90 mg (●----●) or β-adrenoceptor blockade with propranolol 160 mg (■----■), in comparison to control values (▼—▼) on serum insulin (**A**), and plasma glucose (**B**), adrenaline (**C**) and noradrenaline (**D**); (mean (SEM), $n = 12$)

of 100 g glucose was given. The concentrations of serum insulin in response to oral glucose (Fig. 1A) did not differ after urapidil and placebo but were significantly lower in the propranolol group (area 120–210 min, $2p < 0.02$). The plasma glucose concentration (Fig. 1B) fell to a comparable nadir after placebo 25.3 (1.7) $mg \cdot dl^{-1}$, propranolol 25.3 (1.4) $mg \cdot dl^{-1}$, and urapidil 21.3 (0.9) $mg \cdot dl^{-1}$; propranolol versus urapidil $2p < 0.05$) with a delay after propranolol. The medications did not significantly inhibit the recovery from hypoglycaemia, but the plasma glucose was lower at the beginning of the oral glucose load in the propranolol group ($2p < 0.01$). Posthypoglycaemic glucose intolerance was observed after placebo and urapidil but not after propranolol (area 120–210 min, $2p < 0.01$).

The adrenaline concentrations (Fig. 1C) were augmented by propranolol (area 20–120 min, $2p < 0.05$) and its clearance was delayed. Following urapidil, elevated concentrations of noradrenaline (Fig. 1D) were observed before the insulin injection, during the response to hypoglycaemia (area 20–120 min, $2p < 0.0002$), and during the oral glucose load.

The increase in heart rate during hypoglycaemia was augmented by urapidil (area 20–60 min, $2p < 0.05$), and prevented by propranolol (area 20–60 min, $2p < 0.001$). Systolic pressure rose from 104 (4) to 116 (5) mm Hg (area 20–60 min, $2p < 0.05$) and the diastolic was unchanged. An increase in the diastolic pressure from 68 (3) to 83 (3) mm Hg occurred after propranolol (area 20–60 min, $2p < 0.01$).

The fall in serum potassium during hypoglycaemia (Fig. 2A) was increased by urapidil ($2p < 0.05$) and diminished by propranolol ($2p < 0.005$). The fall in serum phosphate (Fig. 2B) was accentuated by α- (area 25–45 min, $2p < 0.05$) and prevented by β-blockade (area 25–45 min, $2p < 0.05$). The production of lactate (Fig. 2C) was increased in the placebo group and this effect was augmented by urapidil (area 25–60 min, $2p < 0.05$) and prevented by propranolol (area 25–60 min, $2p < 0.02$).

Propranolol (Fig. 3A) increased the growth hormone response to hypoglycaemia (area 45–210 min, $2p < 0.01$), while the responses following urapidil and placebo were comparable. The change in cortisol (Fig. 3B) was augmented by propranolol (area 45–210 min, $2p < 0.05$), and remained unchanged after urapidil.

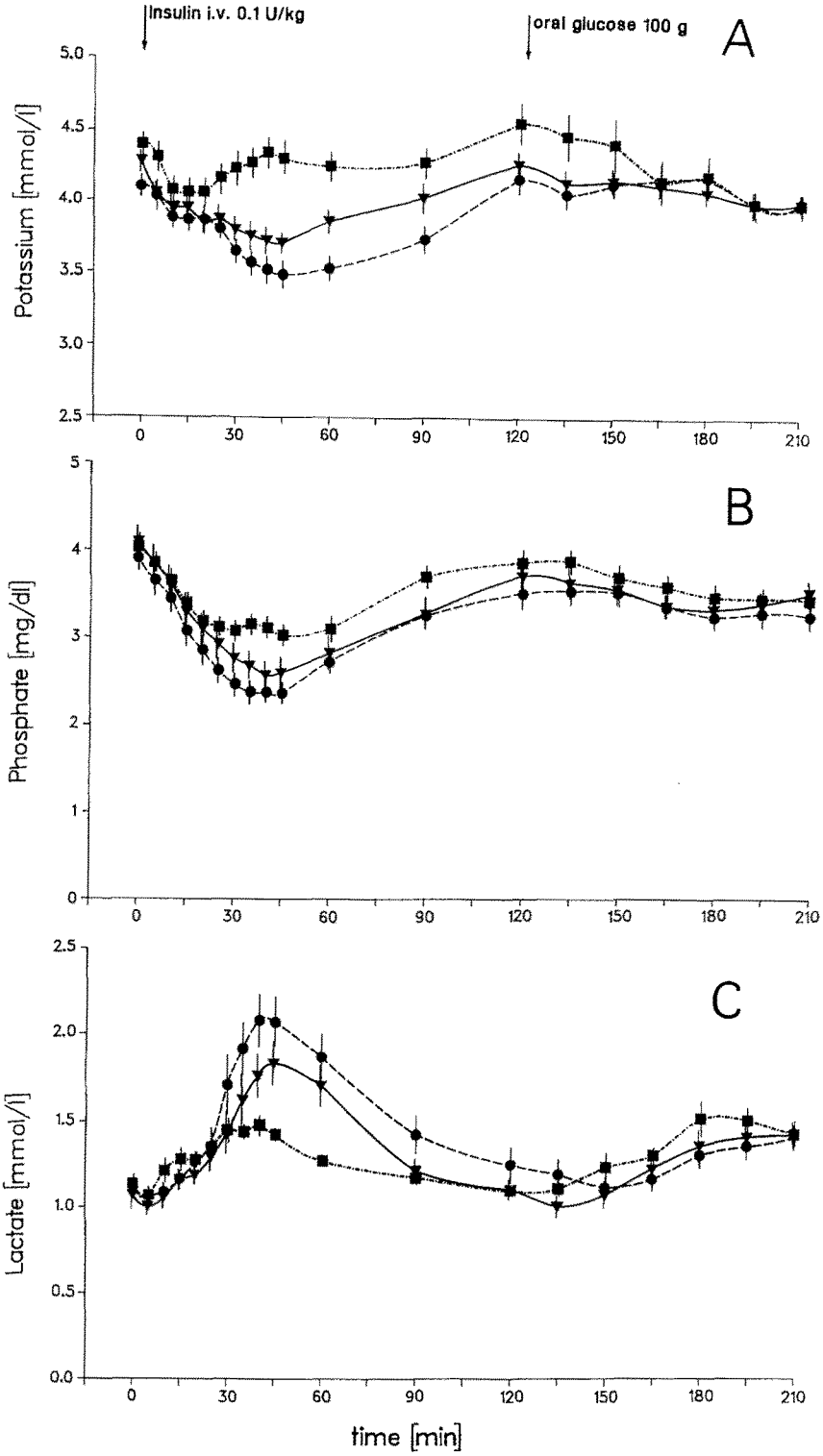

Fig. 2 A–C. Effects of α- or β-adrenoceptor blockade on serum potassium (**A**), phosphate (**B**) and lactate (**C**) during insulin-induced hypoglycaemia followed by an oral glucose load (**A**); for symbols see legend to Fig. 1, (mean (SEM), $n = 12$)

Discussion

The present study describes indirect stimulatory effects of adrenoceptor blocking drugs shown by enhancement of the effects of endogenous catecholamines on unblocked receptors during hypoglycaemia in man.

Alpha-blockade with urapidil produced elevated circulating levels of noradrenaline, which were persistent, indicating that they were mainly the result of

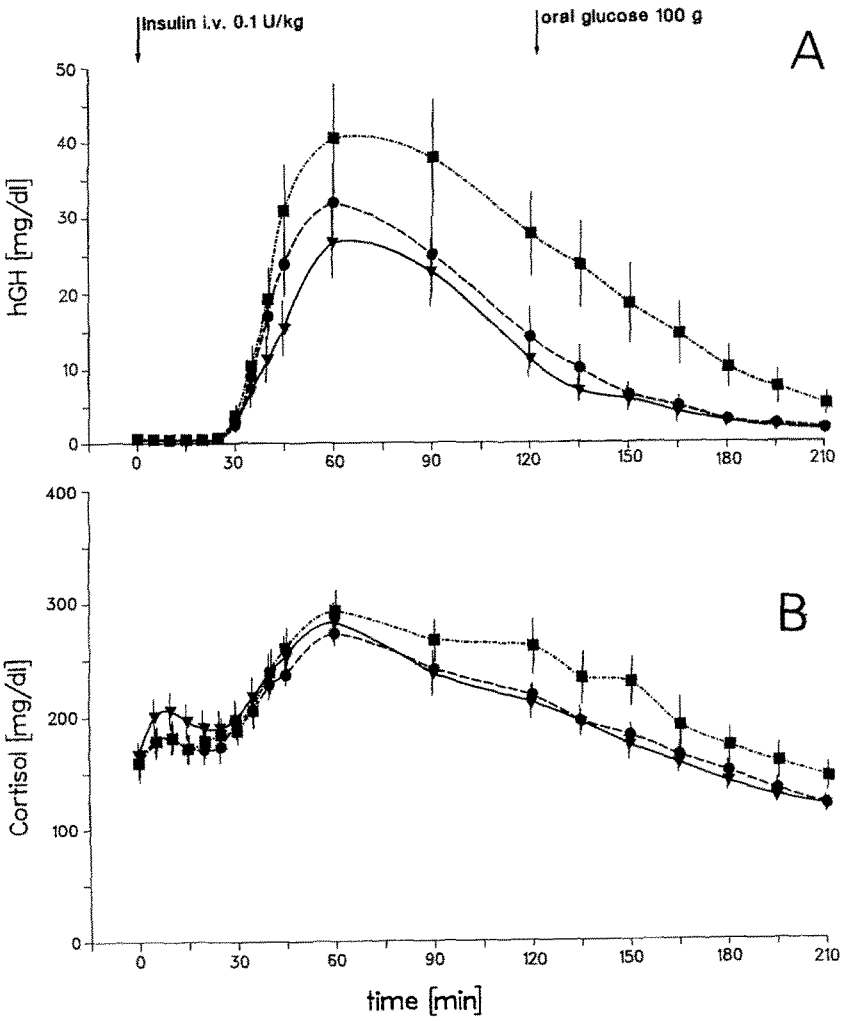

Fig. 3 A, B. Effects of α- and β-adrenoceptor blockade on hGH (**A**) and cortisol (**B**) in experiment as shown in (**A**); symbols see legend Fig. 1, (mean (SEM), $n = 12$)

reduced clearance by α-adrenoceptors [6]. The increase in plasma noradrenaline at rest, prior to the induction of hypoglycaemia, was attributed to release of the catecholamine from adrenergic axon terminals [2]. Beta-blockade inhibits the clearance of adrenaline [7, 8].

The metabolic effects of circulating catecholamines include β-adrenoceptor-specific actions such as increased cellular uptake of potassium [5] and phosphate [9], and the production of lactate from skeletal muscle [9]. These effects were suppressed during hypoglycaemia by prior medication with propranolol. α-Blockade with urapidil, on the other hand, led to greater falls in potassium and phosphate, and a larger increase in serum lactate. This indicates that α-adrenoceptor blockade elicits an increase in sympathetic tone, which becomes manifest as β-adrenoceptor stimulation, because α-adrenoceptors are blocked. The increase in the heart rate after α-blockade is compatible with this view, and is not reflex in origin, compensating for a fall in blood pressure.

Posthypoglycaemic hyperglycaemia is also mediated by β_2-adrenoceptors [10], and propranolol is a potent suppressor of this effect [8, 11]. Urapidil did not further impair glucose tolerance, possibly because the effect was already maximal.

The responses of growth hormone [12, 13] and ACTH [14] to hypoglycaemia were augmented by an α-adrenergic mechanism. Inhibition was attributed to β-stimulation, since propranolol increased the responses of ACTH and hGH during hypoglycaemia. Beta-stimulation with isoproterenol did not, however, decrease the concentrations of serum hGH [13]. It is proposed that the elevated levels of adrenaline after propranolol cause the augmented responses of hGH and ACTH to hypoglycaemia by α-stimulation, due to enhancement of the effects of unblocked receptors. The increase in the diastolic blood pressure during hypoglycaemia after propranolol indicates increased levels of adrenaline, the α-stimulating effect of which is more pronounced as β-adrenoceptors are blocked.

Alpha- or Beta-adrenoceptor blockade alters the sympathomimetic metabolic effects related to hypoglycaemia in addition to the effects of blockade. β-Blockade results in α-adrenergic stimulation, while α-blockade enhances the β-stimulatory effects of the endogenous catecholamines. The significance of these effects in man depends on the concentrations present and the relative affinities of the agonist, antagonist and spare receptors in the tissues.

Acknowledgements. The study was supported by the Deutsche Forschungsgemeinschaft.

We thank Mr. A. Rynk for his excellent technical assistance, and Mr. P. Jägle for helpful discussion of mathematical problems.

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Received: August 22, 1988
accepted in revised form: November 9, 1988

Prof. Karl-Georg Petersen
Hugstetter Straße 55
D-7800 Freiburg
Federal Republic of Germany