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β-adrenoceptor blockade and hypoglycaemia. A randomised, double-blind, placebo controlled comparison of metoprolol CR, atenolol and propranolol LA in normal subjects

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1 The effect of 1 week of treatment with propranolol LA (160 mg), atenolol (100 mg) and metoprolol CR (100 mg) on awareness of and the physiological responses to moderate hypoglycaemia were compared with placebo using a randomised, cross-over design in 12 healthy volunteers.

2 All three β-adrenoceptor antagonists reduced resting heart rate, systolic blood pressure and heart rate responses to submaximal exercise compared with placebo.

3 Under hyperinsulinaemic (60 mu m^{-2} min^{-1}) clamp conditions, at a blood glucose of 2.5 mmol l^{-1}, atenolol prevented the rise in systolic and atenolol and metoprolol CR prevented the fall in diastolic blood pressure usually associated with hypoglycaemia. At this level of hypoglycaemia, the expected increase in heart rate was inhibited by atenolol but not metoprolol CR. Pre-treatment with propranolol LA resulted in a significant pressor response and a bradycardia during hypoglycaemia. In addition the normal increase in finger tremor was abolished by propranolol LA.

4 During hypoglycaemia all three β-adrenoceptor blockers augmented sweating compared with placebo but hypoglycaemic symptoms, awareness and slowing of reaction time were the same with drugs and placebo.

5 The rise in plasma adrenaline and other counter-regulatory hormones during hypoglycaemia was enhanced by β-adrenoceptor blockade.

6 We conclude that β-adrenoceptor antagonists modify the physiological and hormonal responses to, but do not adversely affect awareness of, moderate hypoglycaemia in healthy volunteers.

Keywords β-adrenoceptor blockade hypoglycaemia counter-regulation hypoglycaemic awareness

Introduction

Patients with diabetes are at an increased risk of ischaemic heart disease and hypertension (Colwell, 1988) and are therefore prime candidates for treatment with β-adrenoceptor antagonists. However, for patients on insulin it has been suggested that non-selective β-adrenoceptor blockers should be avoided as they may: (a) delay blood glucose recovery, (b) alter the physiological responses and thereby mask warning symptoms of low blood glucose and (c) cause clinically important hypertension during hypoglycaemia (Waal-Manning, 1979). There are

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conflicting reports on the effects of selective β-adrenoceptor blockers during hypoglycaemia (Lager *et al.*, 1979; Popp *et al.*, 1984) but general agreement that selective agents are preferable in insulin treated patients (Clausen-Sjobrom *et al.*, 1987; Smith *et al.*, 1980).

Metoprolol CR is a new controlled-release formulation of metoprolol intended for once daily administration (Ragnarsson *et al.*, 1987). It has a more even plasma concentration profile over 24 h compared with atenolol, and may confer improved β_1 selectivity in the first few hours after dosing (Blomquist *et al.*, 1988).

Mild to moderate hypoglycaemia impairs reaction time, even in subjects who are unaware of being hypoglycaemic (Heller *et al.*, 1987). It is recognised that β-adrenoceptor antagonists impair psychomotor function, and we were interested to determine whether this might be additive with the effect of hypoglycaemia.

Thus, we have compared the effects of metoprolol CR with a non-selective (propranolol LA) and selective (atenolol) β_1-adrenoceptor blocker on awareness of hypoglycaemia and the hormonal response to it, and cognitive function as assessed by reaction time.

Methods

Twelve healthy nurses or medical students (eight female) were recruited (median age 23, range 22–34 years). None was taking any medication apart from the oral contraceptive pill. Written consent was obtained for the study which was approved by the Medical School Ethics Committee.

The study had a double-blind, cross-over design. Subjects were randomised to placebo, metoprolol CR (100 mg), atenolol (100 mg) and propranolol LA (160 mg) once daily for 7 days, with at least 7 days in between. Before treatment, each subject performed a submaximal exercise test on a bicycle ergometer for 5 min at a work load sufficient to raise heart rate to 145 ± 5 beats min^{-1}. This work load was used 24 h after the final dose of each drug to assess the degree of residual β-adrenoceptor blockade. With each treatment, on the day before the exercise within 2–4 h of the last dose, physiological responses to hypoglycaemia were assessed using a hyperinsulinaemic glucose clamp.

Glucose clamp

On the final day of each treatment, subjects had a light breakfast and fasted until 13.00 h. The last dose of the drug was taken at 11.30 h on the morning of the experiment. Under local anaesthetic a cannula was placed in the non-dominant arm for infusion of human Actrapid insulin (Novo Laboratories, Copenhagen, Denmark) at a fixed rate of 60 mu m^{-2} min^{-1} and a variable infusion of 20% dextrose. A modified hyperinsulinaemic glucose clamp (De Fronzo *et al.*, 1979) was used to maintain blood glucose at predetermined levels. Arterialised venous samples were obtained from a cannula in a dorsal hand vein of the same arm; the hand was placed in a heated box (55–60° C) and the cannula kept patent by a saline infusion. Glucose was administered by an IVAC 560 pump (IVAC, San Diego, CA, USA) adjusted every 2.5 min according to blood glucose measured at the bedside with a glucose oxidase method (Yellow Springs Instruments, Yellow Springs, Ohio, USA).

Subjects had their blood glucose clamped at 4.5 mmol l^{-1} for 30 min and then lowered, by varying the glucose infusion rate, to 2.5 mmol l^{-1} for a further 40 min. The insulin pump was then stopped, the glucose infusion rate maintained and blood glucose allowed to rise over the next 30 min. All subjects were told of the likely symptoms of hypoglycaemia before each experiment. They knew that blood glucose would be lowered but did not know the level at any stage.

Physiological measurements

Heart rate and blood pressure were measured by an automated method (Accutor 1A monitor, Datascope Corp, New Jersey, USA). Rates of sweating were measured over the lower sternum with a ventilated capsule using dew-point sensors (Michell Instruments, Cambridge, UK) to estimate the water content of inflowing and outflowing air (Wilcox *et al.*, 1984). Finger tremor was measured by an accelerometer (Bruel & Kjaer, 4367) attached by a 'Perspex' ring to the terminal phalanx of the middle finger of the dominant hand. Measurements were made for periods of 1 min, with the forearm supported and hand outstretched as previously described (Birmingham *et al.*, 1985).

Awareness of hypoglycaemia was assessed by asking 'do you feel as if your blood glucose is low?' In addition a 'hypoglycaemic symptom score' was obtained by asking subjects to rate seven symptoms as absent, mild or moderate or severe (scored 0, 1, 2 or 4 respectively). The symptoms were facial flushing, tingling of the fingers or around the mouth, trembling, palpitations, sweating, blurred vision and sleepiness. Dummy questions (not scored) were included to detect individuals who were answering auto-

matically because of neuroglycopaenia. Physiological measurements were made once at a blood glucose of 4.5 mmol l^{-1}, after 10 min and 40 min at 2.5 mmol l^{-1}, and 30 min after stopping the insulin infusion during blood glucose recovery.

Reaction time was used as an index of cognitive function and was measured with a four choice reaction timer (Wilkinson & Houghton, 1975) over 5 min at baseline (blood glucose 4.5 mmol l^{-1}), and once during hypoglycaemia. Subjects depress a microswitch corresponding to one of four flashing lights illuminated automatically in a random order. The latency period and number of errors (incorrect button pressed) are recorded on cassette tape for subsequent computer analysis.

Counter-regulatory hormone analysis

Blood was taken from the heated hand vein at the end of the baseline period of euglycaemia, after 40 min of hypoglycaemia, and 15 and 30 min after stopping the insulin infusion. It was immediately centrifuged at 4° C and 3500 rev min^{-1} for 10 min and the plasma added to tubes containing 75 μl of EGTA-glutathione for measurement of catecholamines, 75 μl of Trasylol (Bayer UK Ltd, Newbury, Berks, UK) for glucagon and pancreatic polypeptide, and into plain tubes for insulin, growth hormone and cortisol. Plasma β-adrenoceptor blocker concentrations were measured (Blomquist *et al.*, 1988) on the first and fourth samples, thus providing levels approximately 2 and 4 h after the final dose of each drug. All samples were stored at −80° C. Adrenaline was measured by h.p.l.c. with electrochemical detection (Macdonald & Lake, 1985). Cortisol and growth hormone were measured by an in-house direct radioimmunoassay. Insulin (Hales & Randle, 1963), glucagon (Stout *et al.*, 1976) and pancreatic polypeptide (O'Hare *et al.*, 1983) were measured by radioimmunoassay. All samples for each subject were analysed in one run with intra-assay coefficients of variations of: glucagon 11.1%, adrenaline 6%, growth hormone 6.8%, insulin 9% and cortisol 6%.

Statistical analysis

Results are expressed as mean and s.e. mean. Where appropriate, data were logarithmically transformed before two-way and one-way analysis of variance with Duncan's range test were performed. When two-way analysis of variance indicated significant treatment by time interactions, the nature of these differences was determined by paired *t*-tests on the contrasts in group means. All active treatments were compared with placebo using two-way ANOVA.

Results

Measurement of β-adrenoceptor blockade (Table 1)

All three β-adrenoceptor blockers reduced ($P < 0.01$) resting seated heart rate 24 h after the final dose. The maximum increase in heart rate during sub-maximal exercise was also reduced compared with placebo ($P < 0.01$). The increase in heart rate during exercise was less after pretreatment with propranolol LA than atenolol and metoprolol CR ($P < 0.05$). Resting systolic blood pressure was reduced more by propranolol LA and atenolol than metoprolol CR ($P < 0.05$). All three drugs reduced the maximum increase in systolic blood pressure during submaximal exercise compared to placebo ($P < 0.05$). Over the 2 h of the glucose clamp, there was a rise in mean plasma levels of propranolol (from 137.4 [23.6] to 154.9 [27.0] nmol l^{-1}) and metoprolol (from 111.4 [19.0] to 137.5 [10.1] nmol l^{-1}), whereas the concentration of atenolol fell (from 3388.4 [802.0] to 3029.0 [555.0] nmol l^{-1}).

Heart rate, systolic and diastolic blood pressure during hypoglycaemia (Figure 1)

All three agents significantly reduced ($P < 0.01$) mean resting heart rate and systolic and diastolic blood pressures. Thus the responses to hypoglycaemia have been considered as the maximum change [s.e. mean] from baseline. During

Table 1 Assessment of β-adrenoceptor blockade: exercise responses 24 h after the final dose (mean ± s.e. mean)

	Heart rate (beats min^{-1})			*Systolic blood pressure (mm Hg)*		
	Resting	*Peak*	*Maximum increase*	*Resting*	*Peak*	*Maximum increase*
Placebo	79 [2.2]	149 [2.8]	+69.4 [2.6]	119.4 [3.2]	164.1 [4.7]	+44.7 [5.0]
Propranolol LA	69 [2.9]	119 [2.1]	+49.6 [2.1]	112.6 [2.8]	149.9 [5.9]	+37.3 [5.7]
Atenolol	67 [2.2]	126 [2.3]	+59.2 [2.1]	111.8 [2.0]	149.5 [5.1]	+37.8 [4.1]
Metoprolol CR	67 [2.8]	126 [2.9]	+57.6 [3.6]	118.2 [2.7]	150.7 [4.3]	+32.5 [4.0]

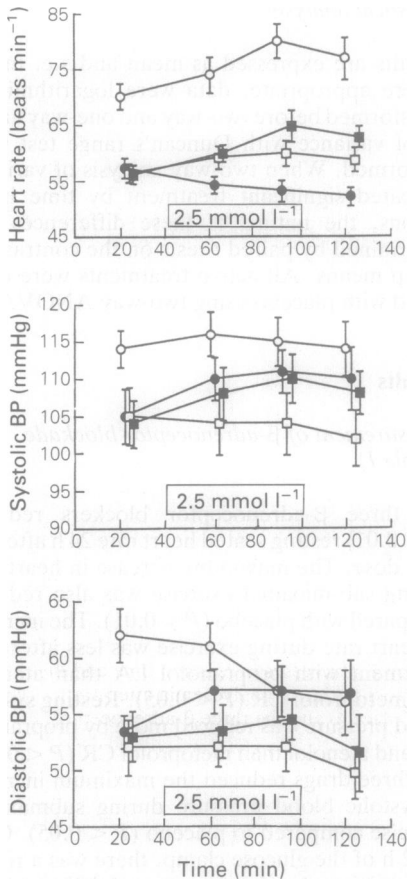

Figure 1 Mean (s.e. mean) heart rate, systolic and diastolic blood pressure at baseline, during hypoglycaemia (2.5 mmol l^{-1}) and recovery after pre-treatment with placebo (○) and the three β-adrenoceptor antagonists. (● propranolol LA, □ atenolol and ■ metoprolol CR).

hypoglycaemia heart rate increased on treatment with placebo (+10.4 [1.6] $P < 0.001$) and metoprolol CR (+11.3 [2.4] $P < 0.01$), was unchanged during treatment with atenolol but fell (−8.7 [1.8] $P < 0.01$) after pre-treatment with propranolol LA. Systolic blood pressure increased during hypoglycaemia after pre-treatment with propranolol LA (+9.5 [1.1] mm Hg $P < 0.05$) and metoprolol CR (+8.6 [1.6] mm Hg $P < 0.05$) but was unchanged after placebo or atenolol. On placebo diastolic blood pressure fell (−7.2 [2.4] mm Hg, $P < 0.05$) during hypoglycaemia but was unchanged after pre-treatment with atenolol or metoprolol CR. In contrast to placebo, diastolic pressure increased (+7.9 [1.1] mm Hg $P < 0.05$) during hypoglycaemia after pre-treatment with propranolol LA.

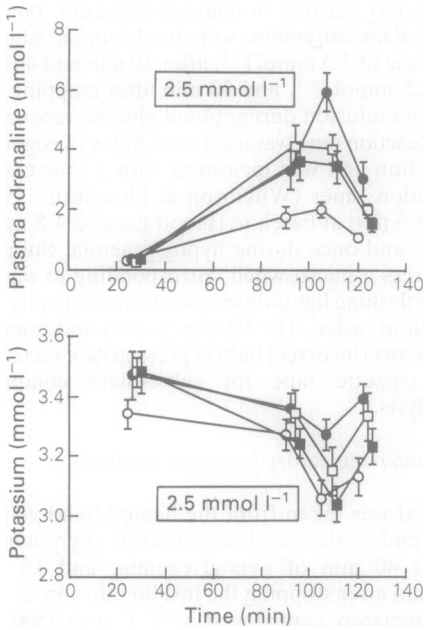

Figure 2 Mean (s.e. mean) plasma levels of adrenaline and potassium at baseline, during hypoglycaemia (2.5 mmol l^{-1}) and recovery after pre-treatment with placebo (○) and the three β-adrenoceptor antagonists (○ propranolol LA, □ atenolol, ■ metoprolol CR).

Finger tremor and sweating

Resting finger tremor was not altered by pre-treatment with any of the three β-adrenoceptor blockers and increased significantly during hypoglycaemia on placebo (from 0.198 [0.03] to 0.356 [0.05] m s^{-2}, $P < 0.01$), atenolol (from 0.170 [0.02] to 0.315 [0.03] m s^{-2}, $P < 0.01$) and metoprolol CR (from 0.184 [0.04] to 0.273 [0.03] m s^{-2}, $P < 0.01$). However the expected rise in tremor during hypoglycaemia was abolished by pre-treatment with propranolol LA. Sweat production did not increase above baseline during hypoglycaemia on placebo but was enhanced by all three β-adrenoceptor blockers (from 5.9 [0.7] to 26.5 [6.4] g m^{-2} h^{-1} after propranolol LA, from 7.6 [1.5] to 28.6 [9.2] g m^{-2} h^{-1} after atenolol and from 8.3 [1.1] to 31.1 [8.7] g m^{-2} h^{-1} after metoprolol CR, all $P < 0.05$). The sweat response did not differ between drugs.

Counter-regulatory hormone, plasma insulin, potassium and pancreatic polypeptide levels (Figures 2 and 3)

Baseline plasma adrenaline levels were not altered by pre-treatment with any of the β-

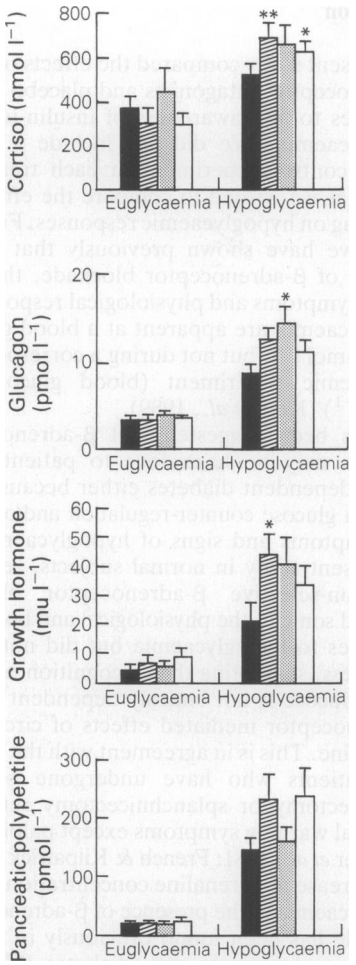

Figure 3 Mean (s.e. mean) baseline and peak levels of counter-regulatory hormones and pancreatic polypeptide during hypoglycaemia after pre-treatment with placebo (■) and the three β-adrenoceptor antagonists (▨ propranolol LA, ▩ atenolol, □ metoprolol CR). Significant increases compared with placebo are denoted by * $P < 0.05$, ** $P < 0.01$.

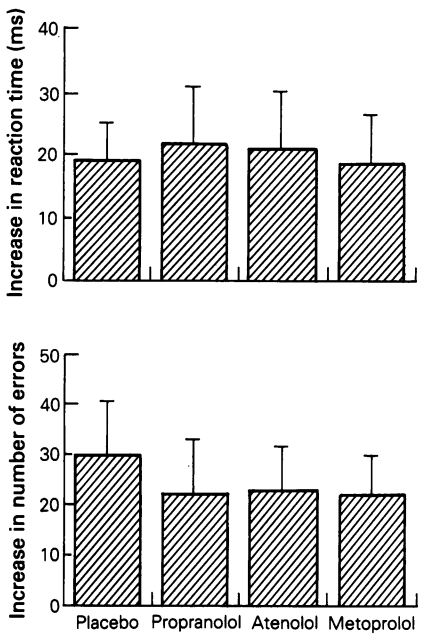

Figure 4 Increases in reaction time and the number of errors during hypoglycaemia after pre-treatment with placebo and the three β-adrenoceptor antagonists. Values are mean and s.e. mean.

adrenoceptor blockers. During hypoglycaemia plasma adrenaline increased in all four experiments but the response was significantly ($P < 0.01$) greater with propranolol LA (+5.68 [0.68] nmol l^{-1}), atenolol (+4.40 [0.64] nmol l^{-1}), and metoprolol CR (+3.49 [0.59] nmol l^{-1}), compared with placebo (+1.87 [0.26] nmol l^{-1}). The response with propranolol LA was also significantly greater compared with metoprolol CR and atenolol ($P < 0.05$). Cortisol, growth hormone, glucagon and pancreatic polypeptide increased significantly above baseline in all four experiments ($P < 0.01$). The peak increase in cortisol after treatment with propranolol LA (+388.4 [28.4] nmol l^{-1}) and metoprolol CR (+340.0 [52.5] nmol l^{-1}) was significantly greater than after placebo (+186.2 [35.1]) (both $P < 0.01$). Likewise the peak increase in growth hormone was greater after propranolol LA (+35.5 [5.5] mu l^{-1}) than placebo (+16.7 [7.5] mu l^{-1}) ($P < 0.05$). Increases in pancreatic polypeptide were not significantly different between treatments. However the rise in plasma glucagon during hypoglycaemia was greater after pre-treatment with atenolol (+10.5 [1.7] pmol l^{-1}) than after placebo (+5.7 [1.2] pmol l^{-1}) ($P < 0.05$).

After pre-treatment with propranolol LA, plasma insulin levels were higher at each stage of sampling during and after the insulin infusion compared to placebo (99.6 [5.6] with placebo *vs* 108.4 [6.4] mu l^{-1} with propranolol LA during euglycaemia, 96.8 [6.0] *vs* 114.9 [7.1] mu l^{-1} during hypoglycaemia, 10.9 [0.9] *vs* 18.0 [1.7] mu l^{-1} 15 min after stopping the insulin infusion and 5.6 [0.6] *vs* 7.6 [0.8] mu l^{-1} at the end of the experiment, $P < 0.05$). Potassium levels were only measured under hyperinsulinaemic conditions when they fell ($P < 0.01$) during hypoglycaemia after all four treatments but more markedly after placebo (from 3.34 [0.05] to 3.06

[0.06] mmol l^{-1}) and metoprolol CR (from 3.48 [0.07] to 3.04 [0.06] mmol l^{-1}) than after propranolol LA (from 3.47 [0.8] to 3.27 [0.05] mmol l^{-1}). On atenolol, plasma potassium fell from 3.48 [0.05] to 3.15 [0.08] mmol l^{-1}.

Serial reaction time, number of errors, symptom score and awareness of hypoglycaemia

During euglycaemia no subject reported any symptoms of hypoglycaemia. At a blood glucose of 2.5 mmol l^{-1}, four subjects 'felt hypoglycaemic' on placebo, seven on propranolol LA, four on atenolol and seven on metoprolol CR. It is interesting that four subjects did not 'feel hypoglycaemic' at any time on treatment with placebo or any of the active drugs. The cumulative symptom scores for the 'classical' symptoms of hypoglycaemia are shown in Table 2. The symptom of 'sweating' was significantly enhanced by propranolol LA and 'trembling' by metoprolol CR. The increase above baseline (euglycaemia) in total symptom score during hypoglycaemia was significant ($P < 0.05$) for placebo and the three drugs, and although the increases were greater after the drugs than after placebo, the differences were not significant.

Euglycaemic serial reaction times were similar (placebo 541 [21] ms, propranolol LA 552 [19] ms, atenolol 550 [21] ms and metoprolol CR 546 [20] ms). Reaction time slowed during hypoglycaemia after pre-treatment with all three β-adrenoceptor blockers (+22 [10] ms on propranolol LA, +21 [9] m s on atenolol and +21 [9] ms on metoprolol CR) and placebo (+19 [6] ms) (all $P < 0.05$). Similarly the number of errors during reaction time testing increased to the same extent under all four conditions (+30 [11] on placebo, +22 [9] on propranolol LA, +23 [9] on atenolol and +22 [8] on metoprolol CR – all $P < 0.05$).

Discussion

The present study compared the effects of three β-adrenoceptor antagonists and placebo on the responses to and awareness of insulin-induced hypoglycaemia. We did not include a euglycaemic control experiment in each treatment period, as we wished to compare the effects of each drug on hypoglycaemic responses. Furthermore, we have shown previously that in the absence of β-adrenoceptor blockade, the subjective symptoms and physiological responses to hypoglycaemia are apparent at a blood glucose of 2.8 mmol l^{-1}, but not during a corresponding euglycaemic experiment (blood glucose 4.5 mmol l^{-1}) (Kerr *et al.*, 1989).

It has been suggested that β-adrenoceptor blockers may be hazardous to patients with insulin-dependent diabetes either because they diminish glucose counter-regulation and/or mask the symptoms and signs of hypoglycaemia. In the present study in normal subjects, selective and non-selective β-adrenoceptor blockers modified some of the physiological and hormonal responses to hypoglycaemia but did not affect awareness, suggesting that recognition of a low blood glucose is not entirely dependent on the β-adrenoceptor mediated effects of circulating adrenaline. This is in agreement with the finding that patients who have undergone bilateral adrenalectomy or splanchnicectomy retain all the usual warning symptoms except palpitations (Altorfer *et al.*, 1981; French & Kilpatrick, 1955). The increase in adrenaline concentration during hypoglycaemia in the presence of β-adrenoceptor blockade has been found previously in normal subjects and patients with diabetes (Clausen-Sjobrom *et al.*, 1987; Lager *et al.*, 1980; Schluter *et al.*, 1982) and is probably a result of decreased clearance (Cryer, 1980). Similarly the increase in both growth hormone and cortisol may have

Table 2 Cumulative symptom scores during hypoglycaemia

	Placebo	*Propranolol*	*Atenolol*	*Metoprolol*
Flushing	5	9	6	2
Sweating	5	23**	13	11
Sleepiness	5	8	5	9
Trembling	5	3	2	12**
Palpitations	1	0	0	2
Tingling	5	1	4	3
Blurred vision	2	3	4	3

** $P < 0.01$ *vs* placebo.

been due to the effect of increased levels of circulating catecholamines on secretion of these hormones (Blackard & Hubbel, 1970; Taylor & Fishman, 1988). Direct adrenergic stimulation of glucagon secretion has been reported by some (Gerich *et al.*, 1976), but not all groups (Clutter *et al.*, 1980), and one might have expected β-adrenoceptor blockers to reduce glucagon release although this would be offset to some extent by the greater plasma adrenaline concentration.

In our study sweating, a sympathetic cholinergic response to hypoglycaemia (Corrall *et al.*, 1983), was enhanced by pre-treatment with all three β-adrenoceptor blockers probably as a result of increased α-adrenoceptor stimulation (Foster *et al.*, 1971) from higher plasma levels of adrenaline. Both subjective and objective enhancement of sweating during hypoglycaemia have been reported previously in normal subjects and diabetic patients using propranolol (Abramson *et al.*, 1966; Deacon & Barnett, 1976; Schluter *et al.*, 1982) and metoprolol (Schluter *et al.*, 1982; Viberti *et al.*, 1980).

In contrast to sweating, finger tremor is thought to be mediated through peripheral β-adrenoceptors (Marsden *et al.*, 1967). This is supported by our observation that tremor did not increase during hypoglycaemia after pre-treatment with propranolol LA. The increase in tremor during treatment with atenolol and metoprolol CR was similar to that after placebo which suggests that tremor is at least partly mediated by β_2-adrenoceptors. However, there were significantly higher levels of plasma adrenaline during hypoglycaemia with atenolol and metoprolol CR, which would be expected to augment tremor if it was entirely β_2-mediated. Thus it is likely that some component of tremor is mediated via β_1-adrenoceptors.

There is growing concern about impairment of cognitive function during hypoglycaemia, as this phenomenon can be demonstrated at blood glucose levels at or above 3.0 mmol l^{-1} (Heller *et al.*, 1987; Pramming *et al.*, 1986). Our concern in the present study was whether β-adrenoceptor blockers, which are known to affect mental processes (Garvey *et al.*, 1984), might have an additive effect with hypoglycaemia. Our findings are reassuring in this respect and in agreement with others (Ogle *et al.*, 1976; Van Rooy *et al.*, 1985); β-adrenoceptor blockers did not prolong reaction time during euglycaemia, and at a blood glucose of 2.5 mmol l^{-1} had no additive effect over and above that of hypoglycaemia. However, four-choice reaction time is a psychomotor test and it is possible that tests measuring different aspects of cognition (Stevens *et al.*, 1989) might have shown an adverse effect of β-adrenoceptor blockers.

The absences of an increase in heart rate and awareness of palpitations during hypoglycaemia after pre-treatment with propranolol has been known for many years (Abramson *et al.*, 1966). Both selective and non-selective β-adrenoceptor blockers have been reported to abolish the tachycardia in response to a low blood glucose in healthy volunteers (Deacon *et al.*, 1977; Newman, 1976; Saunders *et al.*, 1981) and patients with diabetes (Ostman *et al.*, 1982). We found that after pre-treatment with propranolol LA, heart rate slowed during hypoglycaemia, probably due to reflex vagal activation in response to the rise in systolic and diastolic pressure. The pressor response, as a consequence of the elevated plasma catecholamine levels producing unopposed α-adrenoceptor stimulation, may be exaggerated in hypertensive diabetic patients (Ostman *et al.*, 1982). Indeed, profound bradycardia and convulsions have been reported with propranolol during hypoglycaemia (Lager *et al.*, 1979). In contrast to previous observations, we found that metoprolol CR did not abolish the heart rate response to hypoglycaemia. This may have been because it produced slightly less β-adrenoceptor antagonism than atenolol under the present conditions, although it cannot be determined whether this was due to differences in β_1- or β_2-adrenoceptor blockade.

We found that after the insulin infusion was stopped, plasma insulin levels were elevated after propranolol compared with placebo. Clausen-Sjobrom *et al.* (1987) also found that free insulin levels after a prolonged infusion (2.4 u h^{-1} for 3 h) were elevated by 20% after metoprolol compared to placebo. The effect of the raised plasma insulin levels on the secretion of other counter-regulatory hormones and blood glucose recovery remains speculative. The study design did not allow formal evaluation of the effect of β-adrenoceptor blockade on blood glucose recovery, but such elevated insulin concentrations may delay blood glucose recovery.

In conclusion, we found that despite modifying some of the physiological responses to hypoglycaemia, none of the drugs examined in the present study adversely affected awareness of hypoglycaemia in normal subjects.

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