J. Pharm. Pharmacol. 1992, 44: 851–855
Received August 1, 1991

The Calcium Channel Blocker LAS 30538, Unlike Nifedipine, Verapamil, Diltiazem or Flunarizine, Potently Inhibits Insulin Secretion In-vivo in Rats and Dogs

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Abstract—The effects of a novel calcium channel blocker, LAS 30538 (1-[2-(2,6-dimethylphenoxy)ethyl]-α,α-bis-(*p*-fluorophenyl)-4-piperidine methanol), were studied on glucose tolerance and insulin secretion in rats and dogs in-vitro and in-vivo. Some comparisons were made with nifedipine, verapamil, diltiazem, flunarizine, diazoxide, cromakalim and minoxidil. LAS 30538, like a number of calcium channel blockers, was found to inhibit insulin secretion in-vitro, but was 1000-fold more potent than verapamil or diltiazem in this respect. LAS 30538 differed from the other calcium channel blockers studied in that it also potently inhibited insulin secretion and impaired glucose tolerance in-vivo. The evidence that LAS 30538 is more potent than diazoxide as a hyperglycaemic agent in-vivo suggests that this could be a useful drug for the treatment of hyperinsulinaemia in man.

The release of insulin from pancreatic β-cells is believed to be initiated by Ca^{2+} influx, at least in part, through voltage-operated Ca^{2+} channels (Malaisse 1973; Lebrun et al 1982). Evidence for this has come from studies with a number of Ca^{2+}-channel blocking drugs some of which are used clinically. For example nicardipine, verapamil and diltiazem have been found to potently inhibit the in-vitro secretion of insulin from the pancreas (Malaisse et al 1976; Semple et al 1988), and there appears to be a correlation between this effect and the in-vitro potency of compounds in blocking Ca^{2+} channels in certain vascular beds, and in cardiac tissue (Semple et al 1988).

There has been some debate as to whether the clinical use of calcium channel blocking drugs is associated with the suppression of insulin secretion in man (Semple et al 1988). However, the balance of published work suggests that at haemodynamically active doses, they do not normally interfere with insulin release nor impair glucose tolerance in man (Collins et al 1987; Semple et al 1988; Tahara et al 1988).

This conclusion is supported by studies in animals in which a number of calcium antagonists have been shown to inhibit insulin secretion in-vitro but do not do so in-vivo (Semple et al 1988).

We now report results obtained with a novel calcium channel blocking drug, 1-[2-(2,6-dimethylphenoxy)ethyl]-α,α-bis-(*p*-fluorphenyl)-4-piperidine methanol, LAS 30538 (Bou et al 1991; Cardelús et al 1992), on glucose tolerance and insulin secretion in animals, which indicate that this compound, unlike the Ca^{2+}-channel blocking agents mentioned above, potently inhibits insulin secretion not only in-vitro but also in-vivo.

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Materials and Methods

Effect on plasma glucose concentrations in conscious rats

In one series of experiments, the effects of LAS 30538 given orally or intravenously were studied on plasma glucose concentrations in rats. Female Sprague-Dawley rats (CERJ-France, 190–220 g) were used and the animals had free access to food and water up to the time of dosing with LAS 30538 or vehicle.

One hour after dosing, all animals were administered 3 g kg^{-1} glucose in aqueous solution (30% w/v) orally. Blood samples were obtained from the retro-orbital sinus, under light ether anaesthesia at times of 30, 60 , 120 and 240 min after glucose administration. The blood was treated with fluorurea heparin to prevent coagulation, and glucose concentrations were determined using a Kem-O-mat automatic analyser.

In another series of experiments the effects of LAS 30538 were compared with those of the Ca^{2+}-channel blocking agents nifedipine, verapamil, diltiazem, flunarizine and also with the K^+-channel activators, cromakalim, diazoxide and minoxidil (Quast & Cook 1989; Dunne & Petersen 1991). In these experiments male Wistar rats, 180–200 g, were used. The experimental methods were the same as described above except that animals received the oral glucose load 30 (instead of 60) min after dosing orally with the test drug. This was carried out in order to maximize the chances of seeing a drug effect on glucose tolerance.

Glucose tolerance and insulin secretion in anaesthetized rats

Male, Sprague-Dawley rats, 250–300 g, were fasted for 18 h and then treated with either LAS 30538 (5 mg kg^{-1}, i.p.) or an equivalent volume of vehicle (2 mL kg^{-1}). Thirty min later the animals were anaesthetized with pentobarbitone (60 mg kg^{-1}, i.p.) and the left femoral vein and carotid artery were cannulated. Arterial blood samples were removed before and

at 5 and 15 min after a 0·25 g kg^{-1} i.v. glucose load. Plasma was separated immediately and a sample frozen for later assay of immunoreactive insulin (IRI).

In these experiments glucose was determined using a Beckman glucose analyser and IRI was determined using the method of Hales & Randle (1963) using materials obtained from Amersham International.

Insulin secretion by rat islets in-vitro

Rats were allowed free access to food until the experiment. The animals were then anaesthetized with pentobarbitone and the pancreas removed following distension with cold Krebs solution injected via the common bile duct. The tissue was chopped and digested at 37°C using collagenase (Lacy & Kostianovsky 1967). After two transfers in isolation medium the islets were transferred to the preincubation Krebs solution (containing glucose 3 mmol L^{-1} and bovine serum albumin 3 mg mL^{-1}).

Batches of 5 islets were placed in vials and preincubated for 30 min in a shaking incubator (60 oscillations min^{-1}) with continuous gassing (95% O_2–5% CO_2 at 37°C). The preincubation medium was removed and replaced by incubation Krebs solution containing drug or vehicle and either 27·8 or 8·3 mmol L^{-1} glucose.

The islets were then incubated for 60 min and a sample of the medium stored deep frozen for later assay of insulin. Insulin secretion was expressed in (ng islet)$^{-1}$ h^{-1}. The n values (8–10) represent 3–4 batches of islets from 3 different isolates.

Glucose tolerance and insulin secretion in conscious dogs

For this experiment 6 beagle dogs of either sex (weight range 9–13 kg) were used. Food was withheld from the animals 17 h before the experiment. At time 0, blood samples (8 mL) were taken from the jugular vein and then drug vehicle was administered orally (1 mL kg^{-1} aqueous methylcellulose at 1%, 0·1% Tween 80). One h later the animals received glucose given either i.v. (600 mg kg^{-1} in solution at 30%) or orally (3 g kg^{-1} in solution at 30%). Further blood samples were taken at times of 5, 10, 15, 20, 25 and 30 min (for i.v.) or at 30, 60, 90 and 120 min (for oral) after glucose administration. One week later the experiment was repeated administering LAS 30538 orally at 10 mg kg^{-1} (given in 1% aqueous methylcellulose) 1 h before the glucose challenge. A 2 mL sample of blood was used to determine the glucose concentration and 5 mL samples were chilled immediately and allowed to clot in the cold (2–4°C) for 3–4 h. The samples were then centrifuged at 1500 *g* for 15 min in the cold and the serum separated and stored at −20°C for the subsequent analysis of insulin. Insulin was determined as described previously. In the i.v. glucose tolerance study, glucose disappearance constants (k_g) were calculated (eqn 1) by plotting log glucose excess against time and calculating half-life ($t_{\frac{1}{2}}$) by regression analysis.

$$k_g = \frac{0{\cdot}693}{t_{\frac{1}{2}}} \times 100\% \text{ min}^{-1} \quad (1)$$

Drugs

LAS 30538 and cromakalim were synthesized by the Chemistry Department of Laboratorios Almirall. Verapamil, diltiazem, flunarizine and minoxidil were obtained from Impex Química (Mollet del Vallés, Spain) and diazoxide from Disproquima (Barcelona, Spain).

For administration in-vitro or in-vivo by the i.v. or i.p. routes, LAS 30538, was dissolved in PEG 400 and the volume made up with distilled water. For oral administration all drugs were administered in a 1% methylcellulose, 0·1% Tween 80 and water suspension.

Statistics

Statistical comparisons were carried out using Student's *t*-test for non-paired data.

Results

Effects of LAS 30538 on plasma glucose concentrations in conscious rats

Mean plasma glucose concentrations in control rats before glucose administration were 7·0 mmol L^{-1}. Following glucose administration (3 g kg^{-1}, p.o.) there were only slight increases in plasma glucose levels as shown in Fig. 1.

The plasma glucose in animals administered LAS 30538 orally (10 mg kg^{-1}) or i.v. (5 mg kg^{-1}) were markedly higher than controls both before and following administration of the glucose load. The mean peak plasma glucose concentrations observed in treated animals (1 h after glucose administration), approached 38 mmol L^{-1}, and concentrations were still markedly elevated 5 h after drug administration (4 h after glucose administration) as shown in Fig. 1.

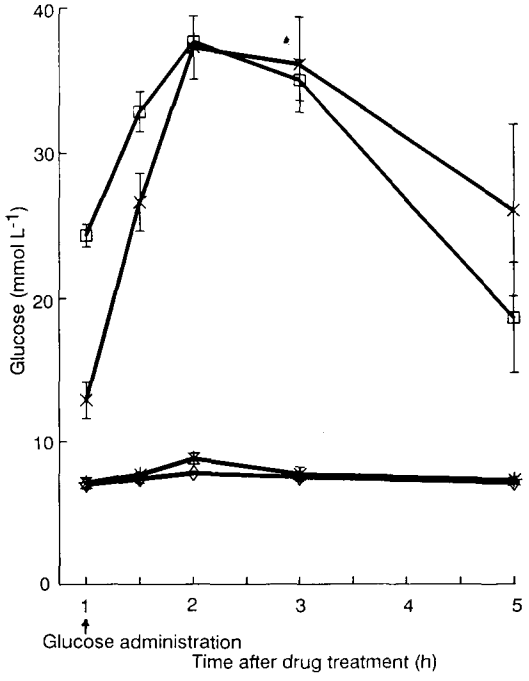

FIG. 1. Plasma glucose concentrations in control and LAS 30538-treated rats. Glucose (3 g kg^{-1}) was given orally 1 h after oral or intravenous administration of LAS 30538 and plasma insulin concentrations measured for up to 5 h after drug administration. Values are means ± s.e.m., n = 5. LAS 30538 10 mg kg^{-1} p.o., □; LAS 30538 5 mg kg^{-1} i.v., ×; control p.o., *; control i.v., ◇.

Table 1. Effects of LAS 30538 on insulin secretion from rat islets in-vitro.

Glucose concn (mmol L^{-1})	Insulin secretion (ng/islet h^{-1}) concn of LAS 30538 (M) 0	10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}
27·8	16·6±3·8 (10)	11·8±3·6 (8)	6·7±1·0* (8)	6·7±1·4** (10)	4·6±0·7** (10)	3·2±0·7** (10)
8·3	3·1±0·6 (8)	1·8±0·4 (8)	2·8±0·9 (7)	1·9±0·2 (11)	2·5±0·7 (7)	1·7±0·4 (10)

Values significantly different from controls are indicated. *$P<0.05$; **$P<0.01$. Numbers are means±s.e.m., with n values shown in parentheses.

Effects of LAS 30538 on glucose tolerance and insulin secretion in anaesthetized rats

Mean resting plasma glucose concentrations in control anaesthetized animals were 5·2±0·8 mmol L^{-1}. Administration of glucose (0·25 g kg^{-1}, i.v.) resulted in a significant increase in plasma glucose concentration that had largely returned to base level after 15 min. At the same time the plasma concentrations of IRI were elevated (Fig. 2).

LAS 30538 given at 5 mg kg^{-1} i.p. produced slight fasting and marked post-glucose hyperglycaemia as shown in Fig. 2. The compound also caused a marked decrease of fasting plasma IRI concentrations and virtually abolished the insulin response to the administered glucose (see Fig. 2).

Insulin secretion by rat islets in-vitro

LAS 30538 inhibited glucose-induced (27·8 mM) insulin secretion in a concentration dependent manner as shown in Table 1. The effect was evident although not statistically significant at 1×10^{-9} M and was most marked at 1×10^{-5} M. Complete inhibition of insulin secretion (to the basal value of 1·5±0·6 ng/islet h^{-1}) did not appear to occur even with the highest concentration of LAS 30538 used.

The insulin response to glucose 8·3 mmol L^{-1} was smaller than that caused by glucose 27·8 mmol L^{-1}. LAS 30538 appeared to inhibit insulin secretion at this glucose concentration but the effects were not statistically significant and no clear concentration-response relationship was seen (Table 1).

Glucose tolerance and insulin secretion in conscious dogs

Administration of LAS 30538 (10 mg kg^{-1}, p.o.) to dogs had no significant effect on fasting plasma glucose or plasma IRI concentrations measured 1 h later (Table 2). When glucose was given intravenously there were increases in plasma glucose concentrations and IRI in vehicle control animals. There was clear evidence of an inhibition of the serum insulin response to glucose in LAS 30538 treated dogs. However,

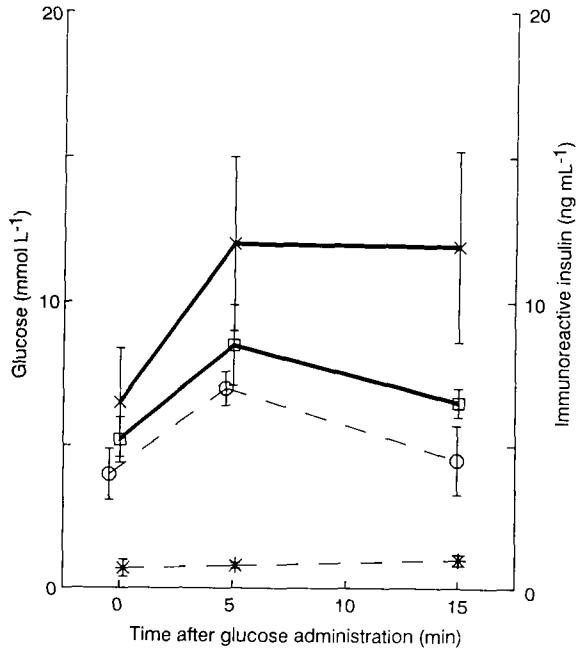

FIG. 2. Effects of LAS 30538 on plasma glucose (solid line) and immunoreactive insulin (IRI, broken line) concentrations in anaesthetized rats. LAS 30538 at 5 mg kg^{-1} i.p. was given 30 min before administration of anaesthetic and the subsequent administration of a 0·25 g kg^{-1} i.v. glucose load. Values are means±s.e.m., and numbers in brackets are the number of animals. Plasma glucose: LAS 30538 5 mg kg^{-1} i.p. (6), *; control (4) □. Immunoreactive insulin: LAS 30538 5 mg kg^{-1} i.p. (4), *; control (3), ○.

Table 2. Effects of LAS 30538 (10 mg kg^{-1}, p.o.) on plasma glucose concentration and insulin concentrations in conscious dogs.

Time after glucose administration (min)	Treatment	Plasma glucose (mmol L^{-1})	Plasma insulin (μ units mL^{-1})
a. Intravenous			
0†	Control	5·1±0·4	16±4
	Treated	5·8±0·2	15±3
5	Control	15·1±1·2	94±32
	Treated	17·6±0·6	45±18
10	Control	13·4±0·9	71±13
	Treated	15·5±0·9	38±20
20	Control	10·4±6·3	80±22
	Treated	11·7±0·9	33±24
30	Control	7·7±0·25	37±6
	Treated	10·2±1·0	29±17
b. Oral			
0†	Control	5·4±1·0	15·4±5·7
	Treated	5·5±0·3	17·8±5·5
30	Control	11·1±1·5	54·7±2·0
	Treated	17·7±1·4	33·3±13·5
60	Control	11·5±1·1	54·6±11·2
	Treated	23·2±1·2*	36·0±14
90	Control	10·5±3·0	47·7±9·4
	Treated	19·8±6·6	51·9±25
120	Control	7·9±6·4	31·0±22
	Treated	13·7±8·0	31·7±25·8

†=1 h after treatment. For each time point data are paired. Values are means±s.e.m., n=3. *$P<0.05$.

Table 3. Effects of pretreatment with calcium antagonists on plasma glucose concentrations in conscious rats following an oral 3 g kg^{-1} glucose load.

Treatment dose (mg kg^{-1}, p.o.)	Plasma glucose concn (mmol L^{-1}) (at time after glucose administration) (min) 30	60	120
Control	8·7±0·2	8·9±0·4	8·9±0·3
LAS 30538			
1	10·7±0·9	8·7±0·6	10·2±0·5
3	11·1±0·4	9·2±0·4	9·0±0·4
10	19·4±2·1***	24·1±2·7***	30·2±2·3***
Nifedipine			
1	9·3±1·0	7·9±0·2	8·8±0·4
3	9·3±0·3	9·4±0·8	10·7±1·3
10	11·7±0·4**	12·5±1·8*	11·3±1·2*
Verapamil			
10	9·0±0·2	8·5±0·4	8·0±0·2
30	9·0±0·4	9·6±0·5	8·5±0·3
100	9·4±0·5	9·2±0·3	9·2±0·2
Diltiazem			
100	8·4±0·2	8·4±0·3	8·3±0·1
Flunarizine			
100	11·1±0·9*	13·1±0·9**	10·2±0·6

*$P<0·05$, **$P<0·01$, ***$P<0·001$ compared with controls. Values are means±s.e.m. n=6.

Table 4. Effects of potassium channel activators on plasma glucose concentrations in conscious rats following an oral 3 g kg^{-1} glucose load.

Treatment dose (mg kg^{-1})	Plasma glucose concn (mmol L^{-1}) (at time after glucose administration) (min) 30	60	120
Control	7·4±0·3	8·4±0·2	8·5±0·1
Diazoxide			
10	8·2±0·6	8·6±0·4	8·5±0·3
100	10·7±1·0*	17·2±1·6**	17·2±2·3*
Minoxidil			
100	8·4±0·5	10·9±0·6*	11·8±0·5**
Cromakalim			
10	9·0±0·2*	10·6±0·3**	9·8±0·2**

*$P<0·05$, **$P<0·01$ compared with controls. Values are means±s.e.m. n=5.

neither the initial hyperglycaemia following glucose nor the rate of disappearance of glucose were modified (control k_g, % $min^{-1}=4·85±0·9$; in animals receiving LAS 30538 $k_g=4·15±0·6$, difference not significant).

Glucose given orally similarly resulted in increased plasma glucose and IRI concentrations (Table 2b). LAS 30538 inhibited the early phase of this insulin response and resulted in a post-glucose hyperglycaemia, as shown in Table 2b.

Comparison of the effects of LAS 30538 with other Ca^{2+}-channel blockers and K^+-channel activators on plasma glucose concentrations in conscious rats

When given orally 30 min before administration of the glucose load (3 g kg^{-1}, p.o.) LAS 30538 at 1, 3 and 10 mg kg^{-1} produced increases in subsequent plasma glucose concentrations compared with control values (Table 3). The effect was particularly marked and sustained at 10 mg kg^{-1}.

In contrast to the effects of LAS 30538, neither verapamil orally at doses up to 100 mg kg^{-1} nor diltiazem orally at 100 mg kg^{-1} significantly affected the plasma glucose concentrations (Table 3). Administration of nifedipine at 3 and 10 mg kg^{-1} and flunarizine at 100 mg kg^{-1} produced small elevations in plasma glucose concentrations; however, these effects were not as marked as the effects of LAS 30538, given at 10 mg kg^{-1}.

The effects of the three K^+-channel activators, diazoxide, minoxidil and cromakalim, on plasma glucose concentrations are shown in Table 4. Diazoxide at 100 mg kg^{-1}, orally, clearly produced a post-glucose hyperglycaemia, whereas both minoxidil (100 mg kg^{-1}) and cromakalim (10 mg kg^{-1}) had little effect on glucose tolerance. The effects of diazoxide were not as marked as those seen with LAS 30538 at 10 mg kg^{-1}.

Discussion

The present work has shown that LAS 30538, characterized as a Ca^{2+}-channel blocking agent (Cardelús et al 1992), has a marked effect on glucose tolerance in rats and dogs in-vivo. Comparative studies carried out in rats showed that in this respect LAS 30538 is unlike nifedipine and flunarizine, which had minor effects on glucose tolerance, and verapamil and diltiazem, which had no effect. Studies on insulin secretion both in-vitro and in-vivo have indicated that the most likely cause of the decrease in glucose tolerance observed in rats and dogs was due to the ability of LAS 30538 to inhibit insulin secretion. An interesting but unexplained observation was the failure of LAS 30538 to modify intravenous glucose tolerance in dogs, although clearly reducing glucose-induced increases in serum insulin concentrations.

The link between Ca^{2+}-channel blocking drugs and inhibition of insulin secretion is not new. Indeed, a range of these agents has been shown to inhibit insulin secretion in-vitro, including verapamil (Malaisse et al 1976; Semple et al 1988), gallopamil (Malaisse et al 1976), nifedipine (Malaisse & Sener 1981), diltiazem, nicardipine, darodipine (Semple et al 1988) and flunarizine (Clarke et al 1988).

Semple et al (1988) commented on the close similarity of the rank order of potency of the compounds they studied in-vitro, with their known potencies in blocking voltage-sensitive Ca^{2+} channels in vascular and cardiac muscles in-vitro. However, despite the high sensitivity of pancreatic β cells to these agents in-vitro they were unable to demonstrate inhibition of glucose-induced hyperinsulinaemia in-vivo.

It is in its in-vivo activity that LAS 30538 appears to differ from the above Ca^{2+}-channel blockers. The reasons for this difference are not clear from our studies. It does not appear to be a simple question of in-vivo potency. Thus, the oral vasodilator potency of LAS 30538 in rats is about 3 times that of verapamil (Cardelús et al 1992) and yet verapamil at 10 times the oral dose of LAS 30538 which produced marked glucose intolerance was without effect on this parameter.

The in-vitro inhibitory potency of LAS 30538 against insulin secretion in rats (IC50 = approx. 3×10^{-9} M) is about 1000-fold that reported (Semple et al 1988) for diltiazem (IC50 = $2·04\times10^{-6}$ M) or verapamil (IC50 = $3·1\times10^{-6}$ M).

Considering these data and the relative potencies of these 3 compounds as haemodynamic agents (Cardelús et al 1992) it would appear that LAS 30538 has a marked selectivity for the pancreatic β cell.

Another mechanism by which insulin secretion is modulated, is by manipulation of the K^+ channels of the pancreatic β cells. This is the proposed mechanism of action of the insulin secretion-stimulating compound, glibenclamide, which blocks specific K^+ channels (Schmid-Antomarchi et al 1987). Conversely the ability of diazoxide to inhibit insulin secretion is thought to be at least partly due to its K^+ channel activating properties (e.g. Bergsten & Hellman 1987; Dunne & Petersen 1991) resulting in hyperpolarization of the cell membrane.

Since diazoxide is used clinically in the treatment of hyperinsulinaemia associated with β-cell tumours (Seltzer & Allen 1965; Henquin et al 1982) we thought that it would be interesting to examine and compare the effects of diazoxide and two other K^+-channel activators, cromakalim and minoxidil, with LAS 30538 in our glucose tolerance test. Of the three K^+-channel activators tested, only diazoxide at a very high dose (100 mg kg^{-1}) had appreciable effects, although the magnitude of the impairment of glucose tolerance was not as great as that seen with LAS 30538 10 mg kg^{-1}. The lack of a major effect of high doses of minoxidil and cromakalim on glucose tolerance is interesting and suggests that these agents are affecting different K^+ channels to those blocked by diazoxide.

In conclusion, our studies have shown that LAS 30538 is a much more potent hyperglycaemic agent, than diazoxide and has a sustained duration of activity. These findings suggest that LAS 30538 could be a useful drug for the treatment of hyperinsulinaemia in man.

Acknowledgements

We would like to thank Sr. Pedro Servera for his expert technical assistance in these studies.

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