New Potent α-Glucohydrolase Inhibitor MDL 73945 With Long Duration of Action in Rats

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Inhibition of intestinal α-glucohydrolase activity is one approach for reducing the glycemic response from dietary carbohydrate and may prove useful for the treatment of diabetes mellitus. In this article, we describe the pharmacological properties of a time-dependent intestinal α-glucohydrolase inhibitor, MDL 73945. When preincubated 2 h with a rat intestinal mucosa preparation before substrate addition, MDL 73945 was a potent inhibitor of sucrase, maltase, glucoamylase, and isomaltase activities (MDL 73945 concentrations required to cause a 50% decrease in enzyme activity, 2×10^{-7}, 1×10^{-6}, 5×10^{-6}, and 8×10^{-6} M, respectively); without preincubation, it was 10- to 500-fold less potent. In rats, a single oral dose of MDL 73945 administered simultaneously with 2 g/kg body wt sucrose resulted in a dose-dependent reduction in the area under the 0- to 3-h glycemic response curve, which was significant at 1 (45% reduction) and 3 (65% reduction) mg/kg. When administered 1 h before sucrose, the compound was more potent, with 0.3 mg/kg MDL 73945 significantly reducing the glycemic response to sucrose by 62%. A reduction in the glycemic response to sucrose was accompanied by reduced insulin secretion. MDL 73945 was slightly less effective against a starch load, with 3 and 10 mg/kg MDL 73945 administered 0.5 h before starch reducing the glycemic response by 39 and 52%, respectively. MDL 73945 was more effective against a sucrose load in streptozocin-administered rats than in control rats and was as effective after 16 daily doses as after a single dose. Doses that reduced the glycemic response to carbohydrate did not inhibit liver lysosomal α-glucosidase activity or cause lysosomal glycogen accumulation. In cynomolgus monkeys, an oral dose of 1 mg/kg MDL 73945 reduced the glycemic and insulin responses to sucrose. Based on these findings, MDL 73945 may be useful for reducing postprandial hyperglycemia in subjects with diabetes mellitus. *Diabetes* 40:825–30, 1991

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Inhibitors of α-amylase and intestinal α-glucohydrolases represent a new class of potentially beneficial drugs for the treatment of diabetes (1–8). Puls and Keup (1) first showed that an α-amylase inhibitor could ameliorate the glycemic response to starch. More recently, inhibitors of intestinal α-glucohydrolases (sucrase, maltase, glucoamylase, and isomaltase) have shown similar application by reducing the glycemic response to starch and dietary disaccharides such as sucrose (2–8), and several are being clinically evaluated (2–4,6). Unlike the sulfonylureas, α-glucohydrolase inhibitors reduce insulin secretion (1,3,4) and therefore might preserve insulin secretory capability in non-insulin-dependent diabetic subjects. Additionally, α-glucohydrolase inhibitors should not cause hyperinsulinemia, which may contribute to atherosclerosis and hypertension in patients with diabetes (9,10).

With the exception of castanospermine and its derivatives (5,8,11,12), previously described α-glucohydrolase inhibitors appear to be readily reversible inhibitors (4,13,14) and should, as has been shown for several inhibitors (4,8), have short durations of action. 1,5-Dideoxy-1,5-[(6-deoxy-1-*O*-methyl-6-α,D-glucopyranosyl)imino]-D-glucitol (MDL 73945 [MDL]; Fig. 1) is a new molecule that shares structural features with some of the reversible short-acting α-glucohydrolase inhibitors. However, MDL is unique in that the amine is linked to the C-6 of a 6-deoxyglucoside, and it is a nearly irreversible inhibitor of the intestinal α-glucohydrolases (15). In this study, we found that MDL is a selective and potent intestinal α-glucohydrolase inhibitor that effectively reduces the glycemic and insulin responses to a carbohydrate load in rats and monkeys and has a long duration of action.

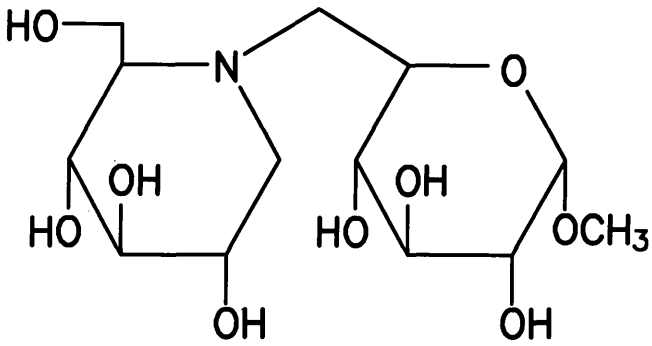

FIG. 1. Structure of MDL 73945.

RESEARCH DESIGN AND METHODS

MDL was synthesized at Merrell Dow (Strasbourg, France). Pork pancreatic α-amylase (type 1-A), heat-hydrolyzed wheat starch, and potato starch were obtained from Sigma (St. Louis, MO); amylase test kits were from Pharmacia (Piscataway, NJ); and insulin radioimmunoassay kits were from Ventrex (Portland, ME). Rat and human insulins were generous gifts from R. Chance (Lilly, Indianapolis, IN). Male 100- to 200-g Sprague-Dawley rats were obtained from Harlan (Indianapolis, IN).

In vitro studies. An intestinal glucohydrolase preparation was made from rat intestine as previously described (16) with minor modifications (4). This preparation, which could be stored at −20°C for at least 2 mo without loss of activity, contained 0.7 U/ml sucrase (sucrose α-glucosidase), 3 U/ml maltase (α-glucosidase), 0.8 U/ml isomaltase (oligo-1,6-glucosidase), 0.1 U/ml lactase (lactose galactohydrolase), 0.4 U/ml trehalase (α,α-trehalase), and 0.3 U/ml glucoamylase (1,4-α-glucosidase) activity (1 U is amount of enzyme that hydrolyzed 1 μmol of substrate/min under our experimental conditions). The MDL concentration required to cause a 50% decrease in enzyme activity (IC_{50}) was determined for each enzyme activity as previously described with 10 μl of the enzyme preparation, MDL, substrate, and buffer in a total volume of 0.1 ml (12).

In vivo rat studies. Overnight-fasted rats were orally dosed by gastrogavage to examine the effect of MDL on the glycemic response to carbohydrate. Sucrose and glucose (2 g/kg body wt) were dissolved in water (2 g/10 ml), and heat-hydrolyzed wheat starch (1.5 g/kg body wt) was suspended in water (1.5 g/20 ml). MDL was either added to the carbohydrate solution or, when given before the carbohydrate, was administered in water (10 ml/kg body wt water). Rats were briefly anesthetized with methoxyflurane before each dose was given to reduce stress and simplify dosing.

Rats were wrapped in towels for 1 h before the carbohydrate dose (17). This procedure facilitated blood sampling and appeared to calm the animals. The tip of the tail was cut once, and blood samples (70 μl) were collected into heparinized microhematocrit capillary tubes 0.5 h and immediately before unwrapping the rats to administer the carbohydrate. The rats were then rewrapped, and additional blood samples were collected at 0.5-h intervals to 3 h. In one experiment, in which MDL was administered 0.5 h before starch, the first two blood samples were collected 0.5 h and immediately before the MDL dose, and the rats were not rewrapped between doses. Plasma glucose was determined with glucose dehydrogenase (Seradyn, Indianapolis, IN).

In one experiment, overnight-fasted rats were anesthetized with methoxyflurane and injected in the tail vein with 35 or 65 mg/kg body wt streptozocin (STZ) in ice-cold 50 mM sodium citrate, pH 4.5. Approximately 1 wk later, the rats were fasted overnight and given an oral dose of 1 g/kg sucrose plus MDL. In the 65-mg/kg STZ-administered rats, the overnight-fasted glucose values were ranked to distribute the more and less severly hyperglycemic rats equally into treatment groups. Blood samples were collected and analyzed as described above.

To measure the insulin response to sucrose plus MDL, one carotid artery of the phenobarbital-anesthetized rat (35–40 mg/kg body wt i.p.) was cannulated for blood collection as previously described (4). Blood samples (0.3 ml) were collected into tubes containing heparin (9 U), aprotinin (270 KIU), and ethylenediaminetetraacetic acid tetrasodium salt (0.75 mg) at 0.5 h and immediately before and 0.5, 1, 2, and 3 h after dosage with 2 g sucrose plus 0 or 1 mg/kg body wt MDL. The plasma was quickly isolated and frozen at −20°C until radioimmunoassayed with rat insulin standard.

To determine whether MDL was effective after repeated administration, three groups of rats were given doses without anesthesia once per day for 15 days of 10 ml/kg body wt water containing 0, 0.3, or 1 mg/10 ml MDL, respectively. They were then fasted overnight and administered 2 g/kg body wt sucrose simultaneously with their respective dose of MDL. The glycemic response to sucrose was determined as described above.

The selectivity of MDL for intestinal α-glucohydrolases was evaluated by examining its effect on liver lysosomal α-glucosidase activity and glycogen accumulation. Rats were given oral doses of 1 or 10 mg/kg MDL, 1 mg/kg castanospermine in water (10 ml/kg), or water only. They were then fasted for 17 h to remove cytosolic glycogen and killed, and lysosomes were prepared and assayed for α-glucosidase (α-D-glucoside glucohydrolase) activity and glycogen content (18).

In vivo studies in monkeys. Experiments were performed on four adult male 5.6- to 8.3-kg cynomolgus monkeys (Charles River, Port Washington, NY). Monkeys were anesthetized with 10 mg/kg i.m. ketamine hydrochloride (Parke Davis, Morris Plains, NJ), and the saphenous vein was cannulated with sterile PE-50 tubing advanced into the inferior vena cava for blood collection. Antibiotic ointment was applied, and the leg and cannula were lightly wrapped with surgical tape. The monkeys were placed in primate restraint chairs (Charles River), and their legs were restrained with tape to prevent them from removing the cannulas. Heparinized (3 U/ml) lactated Ringer's solution was continuously infused through the cannula. Water was available ad libitum, and biscuits (monkey chow, Ralston-Purina, St. Louis, MO) were available between 1200 and 1630. The monkeys were given oral doses of water with or without MDL at 0800 via nasogastric tube for three consecutive days. On days 1 and 3, they received sucrose (2 g/kg body wt) in water (2.7 ml/kg body wt). On day 2, 1 mg/kg MDL was added to the sucrose solution. One monkey removed his cannula and could not be studied on day 3. Blood samples (1 ml) were collected 0.25 h and immediately before and 0.25, 0.5, 0.75,

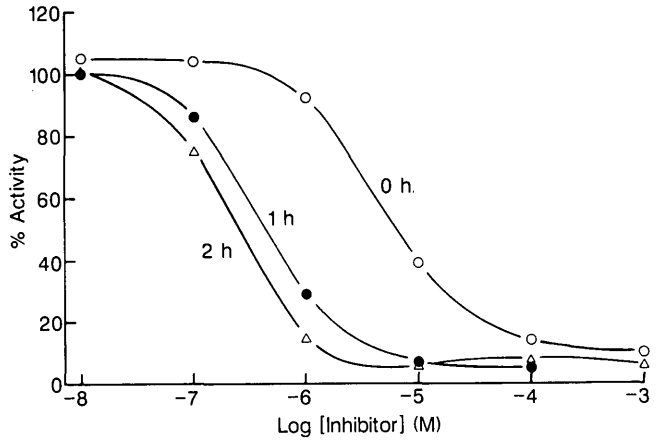

FIG. 2. MDL 73945 time-dependent sucrase inhibition. Enzyme preparation and MDL 73945 were preincubated for 0 (○), 1 (●), or 2 (△) h before addition of sucrose.

1, 1.5, and 2 h after doses were given for determination of plasma glucose and insulin levels and were processed as described above but with human insulin standard.

Statistical methods. To calculate the area under the glycemic response curve for each rat, the difference between the average of the two glucose values before the carbohydrate dose and each glucose value after the dose was obtained. Total area under the glycemic response curve was then obtained from these differences with trapezoidal rule (19). Values for areas under the curves represent the sum of the trapezoidal areas calculated for each 0.5-h interval and are expressed as millimolar times hour. One-sided Dunnett's *t* test (19) applied to areas under the curves was used to determine whether the glycemic response of a group of rats given carbohydrate plus MDL was smaller than the glycemic response of the group given sucrose only. Areas under the insulin response curves (nM · h) were determined and analyzed in a similar manner. To analyze the glycemic and insulin responses in the monkey study, the areas under the response curves after sucrose plus MDL were compared with the average of the areas under the response curves for the 2 days the monkeys received sucrose only by a one-sided paired *t* test. Two-sided *t* test was used to compare lysosomal α-glucosidase activity and glycogen content between groups. Statistical significance was achieved at $P < 0.05$.

RESULTS

Intestinal glucohydrolase inhibition. Preliminary experiments indicated that MDL produced greater sucrase inhibition if preincubated with the glucohydrolase preparation before addition of substrate (Fig. 2). A 1-h preincubation resulted in increased potency, and a 2-h preincubation appeared maximally effective. Therefore, 0- and 2-h preincubations were selected to evaluate MDL as a time-dependent inhibitor of other glucohydrolases. Preincubation resulted in increased potency of MDL for inhibiting rat sucrase, maltase, glucoamylase, and isomaltase activities but not for inhibiting lactase activity (Table 1). MDL (10^{-3} M) did not inhibit trehalase or pork pancreatic α-amylase activities. With or without preincubation, MDL was most potent against sucrase. The selectivity of MDL was determined by dividing the 2-h IC_{50} for each glucohydrolase by the 2-h IC_{50} for sucrase. MDL was slightly selective for sucrase and maltase relative to glucoamylase and isomaltase and very selective relative to lactase, trehalase, and α-amylase.

Glycemic response in rats. Our experience from these and other studies has been that a single oral dose of 2 g/kg sucrose given to overnight-fasted nondiabetic rats results in a plasma glucose elevation of 3.5–5 mM above baseline (5–7 mM) at 0.5–1 h that returns to near baseline by 2–3 h. MDL (0.1–3 mg/kg) administered simultaneously with 2 g/kg sucrose resulted in a dose-dependent reduction in the area under the 0- to 3-h glycemic response, which was significant at 1 and 3 mg/kg (Fig. 3; Table 2). From these data, the dose of MDL required to reduce the glycemic response to sucrose by 50% (ED_{50}) was 1.9 mg/kg. When administered 1 h before sucrose, MDL was more effective than when administered simultaneously with sucrose (Table 2). Three-tenths and 1 mg/kg MDL reduced the area under the 0- to 3-h glycemic response curve 15 and 45%, respectively, when administered with sucrose, and 62 and 87%, respectively, when administered 1 h before sucrose. When administered 4 h before sucrose, MDL was less effective. With starch as the carbohydrate source, 3 mg/kg MDL was in-

TABLE 1
Effect of MDL 73945 on rat intestinal mucosa glucohydrolases

Enzyme activity	MDL 73945 IC_{50} (M)		Fold increase	Relative selectivity
	No preincubation	2-h preincubation		
Sucrase	6×10^{-6}	2×10^{-7}	30	1
Maltase	5×10^{-4}	1×10^{-6}	500	5
Glucoamylase	5×10^{-5}	5×10^{-6}	10	25
Isomaltase	1×10^{-3}	8×10^{-6}	125	40
Lactase	8×10^{-4}	8×10^{-4}	0	4000
Trehalase	$>1 \times 10^{-3}$	$>1 \times 10^{-3}$		>5000
α-Amylase	$>1 \times 10^{-3}$			

IC_{50}, concentration of MDL 73945 required for 50% decrease in enzyme activity. Substrate concentration was 30 mM sucrase, maltase, isomaltase, lactase, and trehalase, and 0.5% starch for glucoamylase. α-Amylase activity declined when incubated at 37°C, and inhibition was not evaluated after 2 h of preincubation. Fold increase in potency of MDL 73945 with preincubation was calculated by dividing the IC_{50} obtained without preincubation by the IC_{50} obtained with a 2-h preincubation of MDL 73945 with enzyme before adding substrate. Relative selectivity was calculated by dividing the 2-h IC_{50} for each enzyme by the 2-h IC_{50} for sucrase.

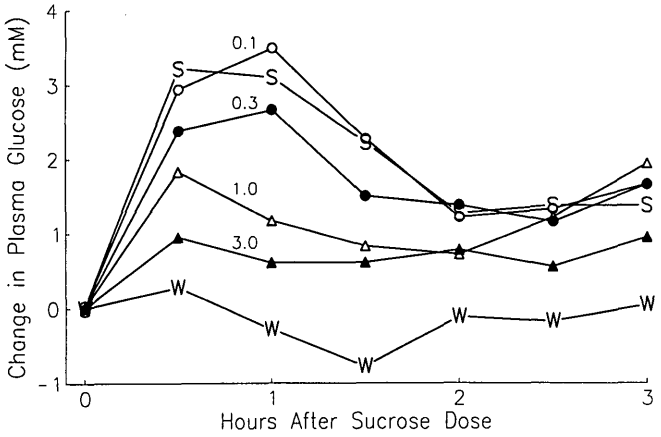

FIG. 3. Effect of MDL 73945 on glycemic response to sucrose in rats. Rats received single oral dose of 2 g sucrose plus 0 (S; *n* = 6), 0.1 (○; *n* = 5), 0.3 (●; *n* = 6), 1 (△; *n* = 6), or 3 (▲; *n* = 7) mg/kg body wt MDL 73945 or water only (W; *n* = 4). For clarity, data are presented without SE as change in plasma glucose from average of 2 baseline measurements. Baseline glucose concentrations, which ranged from 4.8 to 6 mM, were not different among groups as determined by Tukey's Studentized range test. SEs of mean glucose concentrations for all time points ranged from 0.07 to 0.48 mM.

effective when administered simultaneously with the starch. Administration of 1, 3, or 10 mg/kg of MDL 0.5 h before starch resulted in a dose-dependent reduction in the peak plasma glucose concentration from 13.4 mM without MDL to 10.6 mM with 1 mg/kg, 9 mM with 3 mg/kg, and 8.4 mM with 10 mg/kg. Three and 10 mg/kg significantly reduced the area under the 0- to 3-h glycemic response curve by 39 and 52%, respectively, with a calculated ED_{50} of 9.8 mg/kg. When administered 4 h before starch, 3 and 10 mg/kg MDL was ineffective. With glucose as the carbohydrate source, 3 mg/kg MDL had no effect on the 0- to 3-h glycemic response when administered with or 1 h before glucose. Also, MDL did not affect the plasma glucose concentration for 3 h when administered orally (3 mg/kg) with no carbohydrate (data not shown).

In STZ-administered rats, 1 g/kg sucrose resulted in a similar glycemic response to 2 g/kg sucrose in control rats. In 35-mg/kg STZ-administered rats, which did not have fasting hyperglycemia, 0.3 and 1 mg/kg MDL significantly reduced the glycemic response to sucrose by 45 and 105%, respectively (Table 2). In all 65-mg/kg STZ-administered rats, the nonfasting plasma glucose level was >27 mM (mean ± SE 30.7 ± 0.4, *n* = 26). Overnight fasting glucose varied greatly (8–29.5 mM). In these rats, 0.3 mg/kg MDL significantly reduced the peak glycemic response to sucrose and the area under the glycemic response curve (Fig. 4; Table 2). One milligram per kilogram MDL reduced the glycemic response to a level that was not significantly different from the group that received water. Administered simultaneously with sucrose, MDL was more effective in STZ-administered rats than in control rats.

Next, we determined if a reduction in the glycemic response was achieved in concert with a reduction in insulin secretion (Fig. 5). Areas under the glucose and insulin curves were calculated from 0 to 2 h rather than 0–3 h after sucrose because the insulin level had returned to baseline or below at 2 h. A 1-mg/kg dose of MDL, which reduced the area under the glycemic response curve to sucrose by 69% in this experiment, reduced the area under the insulin response curve to sucrose by 83%. The peak glucose response in this experiment was somewhat higher and returned toward baseline more rapidly than in most experiments. Possibly the mild stress of carotid cannulation caused this apparent alteration.

We examined the effectiveness of MDL after 16 days of 1 dose/day of 0.3 or 1 mg/kg (Table 2). Compared with rats that received water for 15 days and sucrose on day 16, 0.3 and 1 mg/kg significantly reduced the area under the 0- to 3-h glycemic response curve to sucrose by 43 and 73%, respectively, and reduced the peak plasma glucose con-

TABLE 2
Effect of MDL 73945 on glycemic response to an oral carbohydrate load in rats

Carbohydrate	Time (h)	Model	MDL 73945 (mg/kg body wt) 0	0.1	0.3	1	3	10	Water
Sucrose (2 g/kg)	0	Control	2.0 ± 0.1 (6)	2.0 ± 0.1 (5)	1.7 ± 0.2 (6)	1.1 ± 0.3 (6)*	0.7 ± 0.1 (7)*		
	1	Control	3.2 ± 0.4 (8)		1.2 ± 0.3 (8)*				
			2.4 ± 0.2 (10)			0.3 ± 0.2 (8)*			
	4	Control	2.7 ± 0.3 (9)			2.1 ± 0.3 (8)			
			1.9 ± 0.1 (10)				1.2 ± 0.2 (10)*		
	0	16 day	3.0 ± 0.3 (8)		1.7 ± 0.3 (9)*	0.8 ± 0.1 (10)*			
Starch (1.5 g/kg)	0	Control	2.9 ± 0.3 (7)				2.6 ± 0.2 (6)		
	0.5	Control	2.3 ± 0.2 (14)			2.4 ± 0.2 (8)	1.4 ± 0.2 (9)*	1.1 ± 0.3 (7)*	
	4	Control	3.6 ± 0.2 (11)				3.5 ± 0.1 (11)	3.3 ± 0.3 (7)	
Glucose (2 g/kg)	0	Control	2.8 ± 0.4 (8)				3.0 ± 0.3 (9)		
	1	Control	4.9 ± 0.2 (6)				5.2 ± 0.2 (7)		
Sucrose (1 g/kg)	0	35 mg/kg STZ	2.2 ± 0.1 (8)		1.2 ± 0.3 (8)*	−0.1 ± 0.4 (8)*			
	0	65 mg/kg STZ	3.8 ± 0.6 (7)		1.6 ± 0.8 (6)*	−2.0 ± 0.6 (7)*			−3.2 ± 0.6 (6)*

Values represent the areas under the glycemic response curves in millimolar · hour and are presented as mean ± SE of *n* animals/group (in parentheses). See METHODS for calculation of area under the curve. Time is time at which the MDL 73945 dose preceded the carbohydrate dose. For 0 h, the drug and carbohydrate were mixed in the same solution. The rat models used are as follows. STZ, rats injected with 35 or 65 mg/kg body wt streptozocin 1 wk before the experiment; 16 day, rats orally given MDL 73945 once per day for 15 days before being given sucrose plus MDL 73945.
*$P < 0.05$ vs. 0 mg/kg body wt MDL 73945 as determined by 1-sided Dunnett's *t* test.

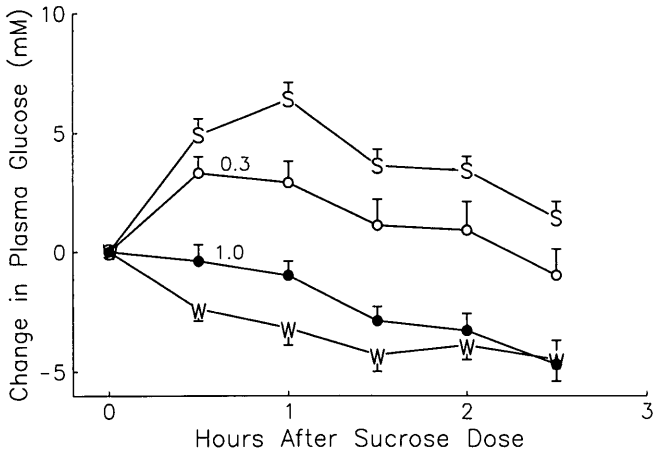

FIG. 4. Effect of MDL 73945 on glycemic response to sucrose in diabetic rats. Rats received single oral dose of 1 g sucrose plus 0 (S, *n* = 7), 0.3 (○; *n* = 6), or 1 (●; *n* = 7) mg/kg body wt MDL 73945 or water only (W; *n* = 6). Values are means ± SE and represent changes in plasma glucose from baseline measurement, which were 16.1 ± 2.6, 16.9 ± 2.7, 16.8 ± 2.4, and 17.1 ± 3.4 mM in sucrose plus 0, 0.3, or 1 mg/kg MDL 73945, and water groups, respectively.

centration from 12.6 to 11.7 and 9.8 mM. Compared with a single dose administered simultaneously with sucrose, MDL appeared to be slightly more effective after 16 doses.

To evaluate the in vivo selectivity of MDL for the intestinal α-glucohydrolases, we examined liver lysosomal α-glucosidase activity and glycogen accumulation. Castanospermine, a nonselective α-glucohydrolase inhibitor, was used for comparison (5,18,20). Neither 1 nor 10 mg/kg MDL affected lysosomal α-glucosidase activity or glycogen concentration, whereas castanospermine reduced α-glucosidase activity by 46% and increased lysosomal glycogen concentration five- to sixfold (Table 3).

TABLE 3
α-Glucosidase activity and glycogen concentration in liver lysosomes from MDL 73945–treated or castanospermine-treated rats

Treatment	*n*	α-Glucosidase (mU/mg protein)	Glycogen (μg/mg protein)
Control	6	1.2 ± 0.1	11 ± 2
MDL 73945			
1 mg/kg	4	1.5 ± 0.1	10 ± 1
10 mg/kg	4	0.93 ± 0.1	10 ± 1
Castanospermine	4	0.65 ± 0.04*	70 ± 8*

Values are means ± SE and represent α-glucosidase activity or glycogen concentration in the lysosomal faction. Rats were orally given 1 or 10 mg/kg MDL 73945, 1 mg/kg of castanospermine, or water and then fasted 17 h and killed.
*$P < 0.05$ vs. control.

Glycemic response in monkeys. MDL significantly reduced the glycemic and insulin responses to sucrose in monkeys, as determined by area under the curve (Fig. 6). The glycemic and insulin responses to sucrose (2 g/kg) on experimental

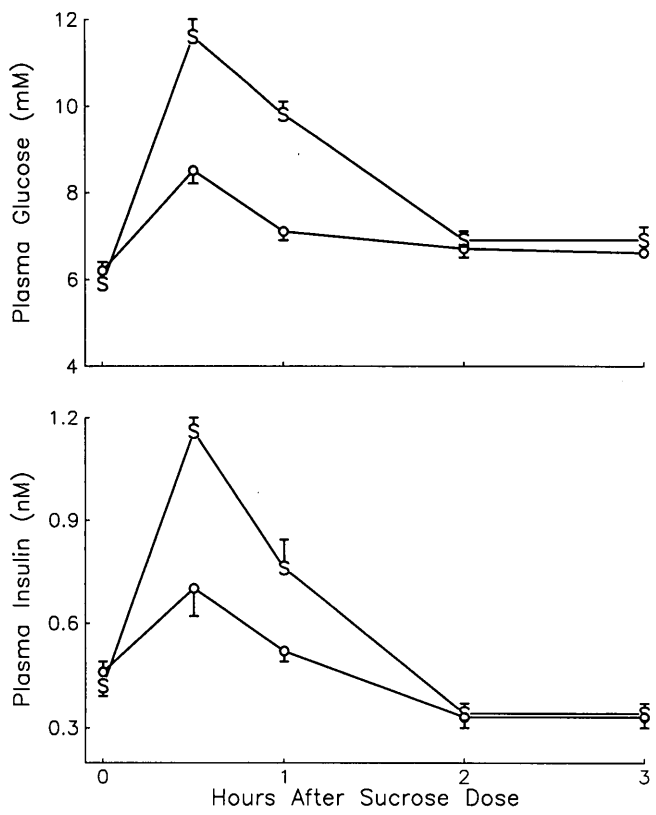

FIG. 5. Rat plasma glucose and insulin response to 2 g sucrose plus 0 (S) or 1 (○) mg/kg body wt MDL 73945. Values are means ± SE (*n* = 8/group).

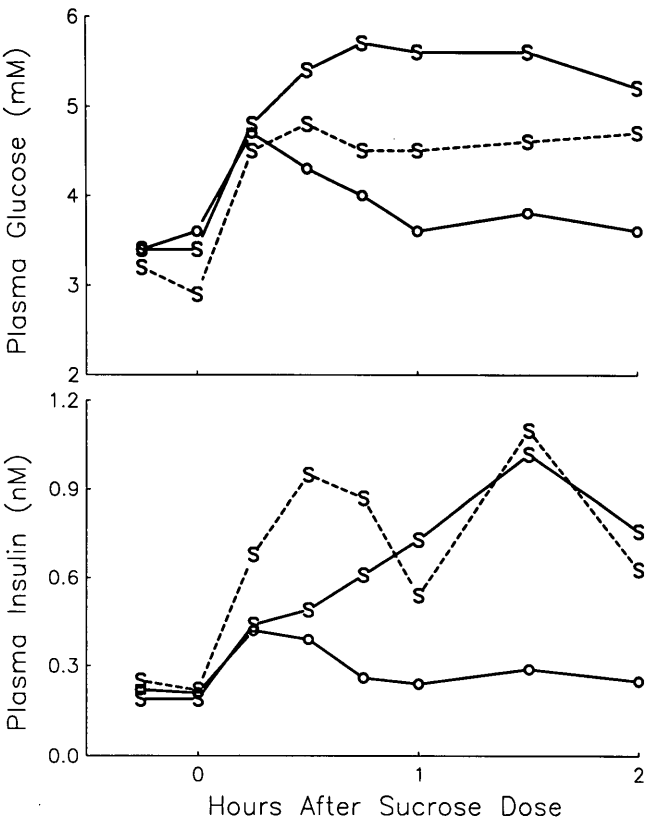

FIG. 6. Monkey plasma glucose and insulin response to 2 g/kg body wt sucrose on day 1 (S, *solid line*; *n* = 4) or day 3 (S, *dashed line*; *n* = 3) or to sucrose plus 1 mg/kg body wt MDL 73945 on day 2 (○; *n* = 4). Values are means of 3–4 rats/group. SEs, omitted for clarity, ranged from 0.14 to 0.83 mM for glucose and from 0.02 to 0.48 nM for insulin.

days 1 and 3 were not significantly different and were averaged for comparison to sucrose plus MDL (1 mg/kg). Mean ± SE areas under the 0- to 2-h glycemic response curves after sucrose or sucrose plus MDL were 1.7 ± 1.0 and 0.42 ± 0.40 mM · h, respectively, which is a 75% reduction with MDL. Mean ± SE areas under the 0- to 2-h insulin response curves after sucrose or sucrose plus MDL were 0.52 ± 0.13 and 0.08 ± 0.06 mM · h, respectively, which is an 85% reduction with MDL.

DISCUSSION

MDL reduced the glycemic response to an oral dose of sucrose or starch by inhibition of the intestinal α-glucohydrolases. It was effective at doses of 0.3–3 mg/kg in control and STZ-administered rats, was effective when administered up to 4 h before sucrose, and showed no indication of tachyphylaxis. Although the experimental design permutations of drug dose, timing, and carbohydrate source that were evaluated in rats could not readily be duplicated in monkeys, 1 mg/kg clearly reduced the glycemic and insulin responses to oral sucrose in both rats and monkeys.

Inhibition of the intestinal α-glucohydrolases was probably the only mechanism through which MDL reduced the glycemic response to sucrose or starch. Although it was ineffective against pancreatic α-amylase, starch must also be hydrolyzed by the disaccharidases and/or glucoamylase before being absorbed as glucose. The ineffectiveness of MDL against a glucose load indicated that inhibition of gastric emptying, gastrointestinal motility, and glucose transport did not contribute to its effectiveness. Also, MDL did not affect fasting glucose concentration, suggesting that it did not affect endogenous glucose metabolism. Reduction in the insulin response to sucrose very likely resulted from the action of MDL on sucrose digestion. If MDL reduced insulin secretion directly, the glycemic response to oral glucose should have been elevated.

The pharmacological activity of MDL is unique compared with structurally similar compounds (deoxynojirimycin, *N*-hydroxyethyl deoxynojirimycin, and *O*-glucosyl-α-homonojirimycin) in that it has a long duration of action in vivo (4,8). The basis of its prolonged activity is probably tight binding inhibition of sucrase (15) and possibly other intestinal α-glucohydrolases, a profile that has previously been demonstrated only with castanospermine and its glucoside derivatives (5,8). However, castanospermine is not selective for the intestinal α-glucohydrolases. As shown here and elsewhere (5,18,20), it inhibits lysosomal α-glucosidase, resulting in the accumulation of lysosomal glycogen, which can be demonstrated with the minimum effective dose to reduce the glycemic response to sucrose (1 mg/kg). *O*-glucosylation of castanospermine improves selectivity for the intestinal α-glucohydrolases (8); however, these compounds may be susceptible to in vivo hydrolysis generating castanospermine. In contrast to castanospermine, a dose of MDL 10-fold higher than required to reduce the glycemic response to sucrose did not affect liver lysosomal α-glucosidase activity or glycogen accumulation.

In summary, MDL is a new α-glucohydrolase inhibitor that, in rats, is more potent and has a longer duration of action than structurally similar molecules and appears to be selective for the intestinal α-glucohydrolases. Because of its uniqueness among the known intestinal α-glucohydrolase inhibitors, this new compound warrants further evaluation as a drug for reducing postprandial hyperglycemia in both insulin-dependent and non-insulin-dependent diabetes mellitus. Additionally, the insulin-reducing activity of MDL or other intestinal α-glucohydrolase inhibitors may prove useful in treating or preventing atherosclerosis and hypertension and preserving insulin secretory capability in non-insulin-dependent diabetic subjects.

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