Effects of Oral Hypoglycemic Agent Methylpalmoxirate on Exercise Capacity of Streptozocin Diabetic Rats

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SUMMARY

The effect of the oral hypoglycemic agent methylpalmoxirate (methyl-2-tetradecylglycidate), a selective inhibitor of long-chain fatty acid oxidation, on the exercise capacity of diabetic rats was evaluated. Rats were made diabetic by injection of streptozocin (75 mg/kg i.p.), which was confirmed by 4+ glucosuria. Daily oral administration of 2.5 mg/kg for 5 days, or a single dose of 10 mg/kg, of methylpalmoxirate produced a slight, nonsignificant decrease in the ability of diabetic rats to perform strenuous exercise of an intensity that caused exhaustion in less than 30 min. The ability of diabetic rats to perform prolonged, moderately strenuous exercise of an intensity that could be maintained for more than 60 min was not affected by methylpalmoxirate treatment. Methylpalmoxirate normalized plasma glucose concentrations, with resting glucose levels reduced 71% compared with nontreated controls, and did not cause hypoglycemia during prolonged exercise to exhaustion. Hepatic glycogen content was significantly reduced in methylpalmoxirate-treated rats in the fed, resting state, and during exercise, suggesting that liver was forced to oxidize carbohydrate at the expense of carbohydrate storage. Blood ketone levels of methylpalmoxirate-treated rats were reduced by 82% at rest, and exercise-induced ketosis was prevented by drug treatment. Muscle glycogen concentration and the rate of muscle glycogen depletion during exercise were not altered by methylpalmoxirate. It appears that the liver is the major site of action of methylpalmoxirate in diabetic rats when given in low doses. DIABETES 1986; 35:744–48.

The effect of exercise on blood glucose homeostasis in healthy, normal individuals depends on the intensity and duration of the exercise, the preexercise diet, and the maximum oxygen uptake capacity.[1,2] In individuals with diabetes mellitus the state of metabolic control is also a consideration; i.e., glucose homeostasis depends on the interval after insulin administration and the blood glucose concentration before onset of exercise.[3,4] In moderate diabetics who are in control, exercise lowers blood glucose levels without producing any adverse metabolic effects.[3,4] Conversely, in severe insulin deficiency, exercise results in an increase in blood glucose and free fatty acid levels and an enhancement of ketone body production.[3,4]

The new oral hypoglycemic agent, methylpalmoxirate (methyl-2-tetradecylglycidate, McN-3716; McNeil Pharmaceutical, Spring House, PA), mediates its effect by inhibiting oxidation of long-chain fatty acids.[5,6] We have shown previously that treatment of normal rats with low doses of methylpalmoxirate results in a significant reduction in liver glycogen levels at rest and in a blunting of exercise-induced ketosis.[7] Consequently, methylpalmoxirate-treated rats become hypoglycemic during prolonged exercise, although they become exhausted only slightly earlier than control rats. Inhibition of fatty acid oxidation in muscle was minimal. Because the liver appears to be the major site of action of methylpalmoxirate when given in low doses, it seems possible that methylpalmoxirate could lower blood glucose levels without adversely affecting the exercise performance of diabetic rats. Our study was undertaken to determine the effects of low doses of methylpalmoxirate, such as might be used clinically, on the capacity of diabetic rats for strenuous and prolonged exercise.

MATERIALS AND METHODS

Animals and training program. Male specific-pathogen-free Sprague-Dawley rats (initial weight 75–100 g) were obtained from Charles River Breeding Laboratories (Wilmington, MA), housed individually, and fed a diet of Purina Rat Chow and water ad libitum.

Rats were taught to run on a treadmill. They were exercised

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5 days/wk, and running speed and duration were progressively increased until, after 4 wk, the rats were running at 24 m/min for 10 min/day and 16 m/min for 5 min/day. They were maintained at this exercise level for an additional 2 wk. After 3 wk of acclimation to treadmill running, rats were made diabetic. Rats were fasted overnight and diabetes was induced the next morning by a single injection, intraperitoneally, of 75 mg/kg body wt streptozocin (Sigma, St. Louis, MO) freshly prepared in 0.1 M citrate buffer, pH 4.5. On the following day, diabetes was confirmed by 4+ glucosuria. The injection procedure was repeated in any rats not made diabetic by the first injection. Rats were maintained on 1 U/kg i.p. of insulin (lente insulin, U-100; Squibb, Princeton, NJ), freshly diluted in 1% bovine serum albumin (BSA), every other day before use.

Before the exercise tests, the rats were randomly divided into four groups: *1*) a group given methylpalmoxirate, 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$ for 5 days; *2*) a placebo-treated control group off insulin for 5 days; *3*) a group given methylpalmoxirate, 10 mg/kg, 3 h before exercise; and *4*) a group given a placebo 3 h before exercise. The placebo consisted of the vehicle in which methylpalmoxirate was suspended. Methylpalmoxirate was suspended in 0.5% methylcellulose and administered by stomach tube. Methylpalmoxirate at a dose of 2.5 mg/kg did not affect food intake in this or previous studies.[5,7] Rats did not receive food during the 3-h period between drug administration and exercise. Insulin therapy was withdrawn 2 days before the initiation of any treatment.

Strenuous exercise test. The effect of methylpalmoxirate on the capacity for strenuous exercise was evaluated by exercising the rats to exhaustion at a running speed of 35 m/min. This exercise intensity requires close to the diabetic rats' maximal oxygen uptake capacity.[8,9] Exhaustion was defined as the point at which the rats were unable to maintain the pace and avoid the shock grid at the rear of the treadmill. Run time to exhaustion was the only measurement made, and insulin therapy was restarted the day after the test.

Moderate-intensity endurance exercise test. The effect of methylpalmoxirate on the capacity for prolonged, moderate-intensity exercise was evaluated by dividing each of the four treatment groups into three subgroups. One subgroup of each treatment group was not exercised. The animals in the exercising subgroups ran at a constant speed of 21 m/min. Subgroups of exercising animals were evaluated for biochemical parameters either after 20 min of running or after they had exercised to the point of exhaustion.

Tissue preparation and assay methods. Immediately after removal from the treadmill, the rats were anesthetized with pentobarbital sodium (6 mg/100 g body wt i.p.). As soon as the anesthetic took effect (~3 min), the plantaris muscles of both hindlimbs were rapidly exposed and clamp frozen in tongs cooled in liquid nitrogen. Next, one lobe of the liver was clamp frozen. Glycogen concentration was determined in these tissues.[10]

Blood was then drawn from the abdominal aorta. A 1.0-ml aliquot of blood was deproteinized by adding it to 2 ml of ice-cold 3 M perchloric acid. The acid extract was separated by centrifugation and the supernatant fraction neutralized with KOH and used for the measurement of lactate,[11] glycerol,[12] and β-hydroxybutyrate.[13] The remaining blood was anticoagulated with EDTA (24 mg/dl), centrifuged, and the plasma removed and used for the measurement of glucose (Glucose Analyzer, Model 23A, Yellow Springs Instruments, Yellow Springs, OH), and free fatty acids (FFAs).[14]

All plasma and tissue samples were stored frozen at −75°C until they were analyzed.

Statistical comparisons between and within groups were made with Student's *t* test or analysis of variance with Student-Newman-Keuls analysis. Data are presented as means ± SE.

TABLE 1
Strenuous exercise test, time to exhaustion

	Control	Methylpalmoxirate
Run time (min)	30.5 ± 4.4	23.8 ± 3.4
N	5	5

Values are means ± SE.

TABLE 2
Endurance exercise test, time to exhaustion

	Control	Methylpalmoxirate
Run time (min)	82 ± 20	76 ± 11
N	4	4

Values are means ± SE.

RESULTS

As expected from our previous study,[7] there were no significant differences in metabolic response between the rats given 2.5 mg/kg of methylpalmoxirate per day for 5 days and those given a single dose of 10 mg/kg. Therefore, the results obtained on these two groups have been combined for evaluation of the metabolic effects of treatment with methylpalmoxirate.

Strenuous exercise test. The ability to perform strenuous exercise of an intensity such that exhaustion occurs within 30 min was not significantly affected by the administration of methylpalmoxirate. As shown in Table 1, methylpalmoxirate-treated rats became exhausted ~20% sooner ($P > .2$) than nontreated diabetic control rats. This finding is not surprising because substrate depletion is not normally the cause of exhaustion in exercise of this severity.[15]

Moderately strenuous endurance exercise test. The ability of diabetic rats to perform moderately intense endurance exercise was not affected by treatment with methylpalmoxirate. As shown in Table 2, the methylpalmoxirate-treated rats were able to run as long as the controls before becoming exhausted.

As shown in Table 3, blood glucose concentration was normal at rest in methylpalmoxirate-treated rats (cf. ref. 7) and remained constant during exercise. In contrast, nontreated control rats were severely hyperglycemic at rest. Glucose concentration decreased significantly in the control rats during exercise ($P < .05$) but not to the point of normoglycemia.

Plasma FFAs were significantly increased at rest ($P < .01$) and during exercise ($P < .05$) in the methylpalmoxirate-treated rats compared with the controls (Table 3). This difference can be attributed to inhibition of fatty acid mobili-

TABLE 3
Plasma glucose, plasma free fatty acids, blood glycerol, β-hydroxybutyrate, and lactate concentrations

	Resting (6)	20 min exercise (6)	Exhaustion (4)
Glucose (mM)			
Control	32.4 ± 3.7	16.9 ± 3.8‡	15.0 ± 7.7
Methylpalmoxirate	9.5 ± 3.4†	9.9 ± 3.0*	7.9 ± 2.0*
Free fatty acids (mM)			
Control	0.55 ± 0.11	0.26 ± 0.07	0.49 ± 0.09
Methylpalmoxirate	1.38 ± 0.11†	0.90 ± 0.17*	1.66 ± 0.29*
Glycerol (mM)			
Control	0.56 ± 0.05	0.29 ± 0.04‡	0.38 ± 0.07
Methylpalmoxirate	0.23 ± 0.02†	0.32 ± 0.04	0.33 ± 0.02
β-Hydroxybutyrate (mM)			
Control	0.98 ± 0.20	0.35 ± 0.07‡	0.53 ± 0.11
Methylpalmoxirate	0.18 ± 0.04†	0.17 ± 0.02*	0.21 ± 0.03*
Lactate (mM)			
Control	9.4 ± 1.6	6.1 ± 1.6	1.8 ± 0.2‡
Methylpalmoxirate	2.0 ± 0.4†	4.7 ± 0.7‡	3.7 ± 2.0

Values are means ± SE for *N* given in parentheses.
*Methylpalmoxirate significantly different from control, $P < .05$, †$P < .01$; ‡significantly different from rest, $P < .05$.

zation by lactate in the control rats[16] and a decrease in fatty acid uptake and oxidation by liver in the methylpalmoxirate-treated rats.[17] Further evidence for the latter effect comes from the finding that β-hydroxybutyrate levels were significantly decreased at rest ($P < .01$) and during exercise ($P < .05$) in methylpalmoxirate-treated rats compared with controls. Levels of β-hydroxybutyrate were reduced by 80% in drug-treated rats at rest and did not rise above basal levels during exercise.

The resting blood glycerol concentration was 60% lower in drug-treated rats than in controls ($P < .01$; Table 3). Because hepatic glucose stores were severely diminished (Table 4) and fatty acid oxidation was blocked, glycerol uptake was enhanced to provide substrate for energy production in liver.[17]

Blood lactate levels were five times greater at rest in control rats than in drug-treated rats ($P < .01$). This may reflect the fact that with severe hyperglycemia, glucose can enter the muscle cell in the absence of insulin through a mass action effect.[18] However, when glycogen storage space is limited, i.e., glycogen stores are replete (Table 4), excess glucose taken up by the muscle is metabolized to lactate.[19]

Glycogen concentration in liver was reduced in both drug-treated and nontreated diabetic rats compared with normal controls (225 μmol/g; cf. refs. 7, 18). Hepatic glycogen was significantly reduced in methylpalmoxirate-treated rats relative to nontreated controls at rest and during exercise ($P < .05$; Table 4). As found previously in normal rats,[7] muscle glycogen concentration and the rate of muscle glycogen depletion during exercise were not significantly altered by methylpalmoxirate treatment in our study. This finding is consistent with the evidence that the rate of glycogen use during exercise is no different in insulin-deprived diabetic patients than in healthy subjects[20,21] and suggests that fatty acid oxidation was only minimally inhibited in muscles of methylpalmoxirate-treated diabetic rats.

DISCUSSION

Methylpalmoxirate, which has been shown to produce hypoglycemia in dogs, mice, and rats,[5] acts by inhibiting oxidation of long-chain fatty acids.[6] This effect is mediated by inhibition of palmitoyl-CoA:L-carnitine *O*-palmitoyltransferase.[22] We have found previously that the ability of rats to perform prolonged, moderately intense exercise was decreased slightly with methylpalmoxirate treatment.[7] This was attributed to the reduction in initial liver glycogen content, such that the rats became hypoglycemic during prolonged exercise. Because the effect of methylpalmoxirate in normal rats at the doses used was mediated primarily by an effect on the liver, with only a slight inhibition of fatty acid oxidation in muscle, we hypothesized that treatment with methylpalmoxirate would not limit the exercise capacity of diabetic rats.

The results of our study show that, as expected, treatment with methylpalmoxirate did not affect the ability of diabetic rats to perform strenuous exercise or their capacity for prolonged, moderately intense exercise. Methylpalmoxirate was effective in normalizing blood glucose levels at rest. During exercise, methylpalmoxirate appears to have effected an alteration in substrate use by muscle. Hypoglycemia did not occur in the drug-treated rats during prolonged exercise, despite normal blood glucose levels and a marked depletion of initial liver glycogen content. During exercise, glucose uptake by working muscle increases up to 20-fold and accounts for 25% of the total oxygen consumed by working muscle.[3]

TABLE 4
Liver and plantaris muscle glycogen concentrations

	Glycogen (μmol/g)		
	Resting (6)	20 min exercise (6)	Exhaustion (4)
Liver			
Control	46.3 ± 11.1	48.2 ± 9.8	30.0 ± 18.1
Methylpalmoxirate	8.7 ± 3.4*	10.8 ± 5.5*	10.4 ± 1.6
Plantaris			
Control	51.1 ± 9.4	28.4 ± 4.7	25.2 ± 4.4
Methylpalmoxirate	32.1 ± 2.0	28.2 ± 5.3	15.8 ± 4.9

Values are means ± SE for *N* given in parentheses.
*Methylpalmoxirate significantly different from control, $P < .05$.

Enhanced glucose uptake by contracting skeletal muscle is independent of insulin[23,24] and does not differ between ketotic and nonketotic diabetic patients or normal subjects.[25] This increased demand on the blood glucose pool is met primarily by increased hepatic glycogenolysis.[26] Because hepatic glycogen reserves were severely diminished in the palmoxirate-treated rats and gluconeogenesis, which is dependent on fatty acid oxidation in rat liver, is inhibited in the presence of methylpalmoxirate,[17] hypoglycemia should have occurred during prolonged exercise. The fact that rats treated with methylpalmoxirate did not become hypoglycemic during prolonged exercise can be attributed to the glucose-sparing effect of increased fatty acid oxidation in muscle.[27,28] The rate of carbohydrate use by muscle, judged from muscle glycogen values after 20 min of running, was not increased in the palmoxirate-treated rats, providing indirect evidence that fatty acid use was not significantly impaired. This is consistent with the finding that fatty acid oxidation was only minimally inhibited in isolated skeletal muscle from methylpalmoxirate-treated rats studied in vitro. Uptake of FFAs by working muscle rises in direct proportion to plasma concentration.[3] Plasma FFA concentration was significantly increased in the drug-treated rats, resulting in an increased uptake and a preferential oxidation of fatty acids by skeletal muscle at the expense of carbohydrate use.[29] In the nontreated diabetic rats, on the other hand, the results suggest that blood-borne glucose and β-hydroxybutyrate were also major substrates used by muscle during exercise. Glucose levels decreased significantly during exercise, whereas decreased levels of glycerol and lactate suggest that hepatic uptake of these precursors for gluconeogenesis was enhanced.[26] It has been reported that gluconeogenesis accounts for more than 60% of hepatic glucose output in diabetics during prolonged exercise.[25] The significant decrease in β-hydroxybutyrate concentration is consistent with the finding of a sevenfold increase in total ketone body use by exercising leg muscle in mildly ketotic diabetic patients.[25] The decrease in plasma FFA reflects an increased uptake by both muscle and splanchnic tissues[25,26] and an inhibition of FFA mobilization from adipocytes by lactate.[16]

The major effect of methylpalmoxirate, at the low doses used in our study, was exerted on the liver. Tutwiler and Dellevigne[17] reported that long-chain fatty acid oxidation to CO_2 and ketones is inhibited in isolated hepatocytes at very low concentrations of methylpalmoxirate. Whereas hepatic glycogen concentration was markedly decreased in both drug-treated and nontreated control diabetic rats compared with normal nondiabetic rats,[7,18] the initial liver glycogen concentration in methylpalmoxirate-treated rats was significantly lower than that of nontreated control diabetic rats. This finding supports the suggestion that liver normally derives much of its energy from fat oxidation and that with fatty acid oxidation blocked, the liver is forced to oxidize carbohydrate at the expense of carbohydrate storage.[7] Recent evidence suggests that in fasted rats the primary pathway for hepatic glycogen synthesis from glucose is through three-carbon metabolic intermediates,[30,31] whereas in fed rats a greater fraction of the glucose taken up by hepatocytes is directly incorporated into glycogen.[31] However, in the absence of the suppressive effects of insulin on glucagon secretion and counterregulatory hormone action, the liver is maintained in a catabolic state.[32] Thus, despite normal or even elevated blood glucose levels, the liver would tend to remain glycogen depleted. A further indication of this is the finding that glycerol concentration was significantly lower at rest in methylpalmoxirate-treated compared with control rats. Gluconeogenesis, which is dependent on fatty acid oxidation in rat liver, is inhibited in hepatocytes in the presence of methylpalmoxirate.[17] A decrease in the uptake of gluconeogenic precursors, especially glycerol, would be expected, as reflected in an increase in circulating plasma levels. However, the finding that glycerol levels were significantly lower in drug-treated rats is in agreement with the finding that, whereas gluconeogenesis is inhibited in the presence of palmoxirate, conversion of precursors such as glycerol, which enter the gluconeogenic pathway above the level of glyceraldehyde-3-phosphate dehydrogenase, to pyruvate is not.[17] Thus, with fatty acid oxidation blocked, glycerol uptake was enhanced to provide energy for the liver.

Evidence that hepatic fatty acid oxidation was inhibited in palmoxirate-treated rats comes from the finding that ketone body production was severely blunted at rest and during exercise. The plasma concentration of β-hydroxybutyrate in drug-treated rats was 20% of that found in the nontreated diabetic rats and was similar to the levels found in normal control rats.[7,27] This was true despite the fact that, based on the respective liver glycogen concentrations, the rate of ketogenesis in the methylpalmoxirate-treated rats should have far exceeded that of the untreated diabetic rats; i.e., an inverse relationship has been noted between hepatic glycogen concentration and ketone body production.[30] This relationship is curvilinear, so that at low glycogen concentrations, small decreases in glycogen levels are accompanied by large increases in ketogenesis.[30] In addition, plasma FFA levels were significantly elevated in the drug-treated rats, relative to the controls, so that substrate availability for ketogenesis was not a limiting factor. The enzymes necessary for activating acetoacetate to acetoacetyl-CoA are absent in the liver; hence there is a net production of ketone bodies by the liver with uptake and oxidation of these occurring in extrahepatic tissues. Whereas ketone bodies are readily oxidized in skeletal muscle, this effect is proportional to their concentration in the blood.[33] Thus, peripheral uptake of ketone bodies was enhanced during exercise in mildly ketotic diabetic patients but remained relatively unchanged in nonketotic diabetics.[34] Furthermore, peripheral use of ketones exceeded the rate of hepatic production, so that arterial levels decreased during exercise.[34] Our results in nontreated diabetic rats agree with these findings. On the other hand, in methylpalmoxirate-treated rats that were not ketotic, no decrease in arterial concentration of β-hydroxybutyrate was seen with exercise. Thus, the reduced arterial concentration of β-hydroxybutyrate in methylpalmoxirate-treated rats relative to nontreated control diabetic rats reflects a decreased rate of hepatic ketone body formation rather than an increased rate of peripheral use.

We conclude that orally administered methylpalmoxirate at the low doses used in this study was effective in lowering blood glucose without adversely affecting the exercise performance of diabetic rats. The hypoglycemic effect of methylpalmoxirate is mediated primarily by inhibiting fatty acid oxidation in the liver. Thus, despite a marked depletion of

liver glycogen and elevation of plasma FFA, ketone body production was inhibited at rest and during exercise. Hypoglycemia was prevented by the glucose-sparing effect of increased fatty acid oxidation by muscle. Whereas treatment with methylpalmoxirate did not directly enhance exercise performance, the normalization of blood glucose and the inhibition of ketogenesis suggest a beneficial effect of the drug on metabolic control both at rest and during exercise in the diabetic state.

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