Effects of Ingestion of Long-chain and Medium-chain Triglycerides on Glucose Tolerance in Man

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SUMMARY

A mild hyperketonemia was induced in seven normal subjects by oral administration of a medium-chain triglyceride (MCT) composed of C8 and C10 fatty acids. One hour following MCT administration and during the period of hyperketonemia, an intravenous glucose tolerance test was performed on each subject. On other occasions, similar glucose tolerance tests were performed on the same subjects one hour following the ingestion of either water or corn oil. K values for the slopes of the disappearance curves following glucose administration were derived, and mean K values and their standard errors following water, corn oil, and MCT, respectively, were 1.80 ± 0.38; 2.64 ± 0.41; and 2.99 ± 0.89. Thus MCT-induced hyperketonemia did not inhibit the rate of disappearance of the intravenously given glucose.

The apparent enhancement of glucose tolerance after ingestion of the MCT and corn oil meals is not readily explained. It is possible that the presence of these fats in the gastrointestinal tract promoted the secretion of certain beta-cytotropic enteric hormones. In addition, the mild hyperketonemia induced by the MCT may, of itself, have accelerated the rate of glucose disappearance by stimulating insulin production. Finally, the medium-chain fatty acids derived from MCT may have enhanced glucose tolerance by virtue of an inhibitory effect on hepatic-glucose output. DIABETES *16*:796-99, November, 1967.

Previous experiments have shown that medium-chain fatty acids administered intravenously can induce hyperketonemia. Sixty years ago, Embden[1] perfused the dog liver with octanoate and observed a rapid rise in hepatic output of acetoacetate. A decade ago, Werk et al.[2] infused sodium octanoate into a group of healthy volunteer subjects and measured a fivefold increase in "splanchnic" production of ketones. Bergen et al.[3,4] have shown that ingestion of 100 gm. of medium-chain triglyceride (MCT), taken in a liquid formula, can induce a predictable hyperketonemia in healthy adult subjects that is sustained for at least two and one-half hours. Freund and Weinsier[5] have called attention to the reproducibility with which hyperketonemia can be induced by MCT in individual subjects. These results confirmed and extended similar observations reported by Schön, Lippach and Gelpke.[6]

Recent studies, both in vitro and in vivo, have shown that ketones can influence glucose metabolism. Williamson and Krebs[7] found that acetoacetate is oxidized in preference to glucose by the perfused rat heart. Ottaway[8] reported that addition of acetoacetate to the medium reduces the uptake of glucose by normal rat diaphragm up to 20 per cent. Newsholm et al.[9] showed that the phosphofructokinase system in rat heart is inhibited by the presence in the medium of acetoacetate and β-hydroxybutyrate.

The purpose of the present study was to determine whether the hyperketonemia associated with MCT administration might influence glucose tolerance in man. MCT was used to induce hyperketonemia because the elevated blood ketone levels occur predictably and can be made to take place in the nonfasted state. Thus the complicating effects of fasting, which by itself affects glucose tolerance, can be avoided.

MATERIAL AND METHODS

Seven healthy young adults, five male and two female, aged twenty to thirty-one years, served as volunteers. Each subject acted as his own control. On three separate days, while in the postabsorptive state, each subject ingested, in sequence, 1.0 gm. per kilogram of body weight of MCT or corn oil emulsified by ultrasonication in 2 volumes of water containing 0.3 per cent oxyethyleneoxypropylene polymer (Pluronic F68), or simply water of equal volume. The MCT prepara-

Presented in part at the Twenty-fifth Annual Meeting of the American Diabetes Association in New York City on June 20, 1965.

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tion* was 80 per cent caprylic acid and 20 per cent capric acid. The fatty acids in the MCT were obtained by molecular distillation of hydrolyzed coconut oil. They were collected as a fraction and then converted back to triglycerides by esterification of glycerol.

The experiments lasted three hours. Following a baseline period of one hour, each subject was given the MCT, corn oil or water. One hour later, a rapid intravenous glucose tolerance test was performed. Twenty-five grams of glucose were given as a 50 per cent solution in one minute in one arm. Blood was drawn from the other arm at ten-minute intervals up to sixty minutes. Throughout the experiment, determinations were made of serum glucose, total blood ketones and serum free fatty acids. Serum glucose was measured by an automated procedure (Technicon). Total blood ketones were determined by a modification of the Greenberg and Lester[10] method, similar to that described by Boshell et al.[11] However, instead of screw cap tubes, ampules were employed in the procedure. The ampules were sealed prior to the step involving heating to prevent any possible loss of ketones. Serum free fatty acids (FFA) were determined by a single-phase system[12] of titration with an organic base, following extraction of the fatty acids by Dole's[13] method.

Glucose uptake was compared in terms of the K value, signifying the rate of disappearance from the blood of the intravenously administered glucose.[14,15] Following induced hyperglycemia, glucose levels decreased exponentially with time. Thus, when the blood glucose concentration was plotted on a semilogarithmic graph against time in minutes, it was transformed into a straight line by the method of least squares, and the rate of glucose uptake (K†) was the slope of this line.

RESULTS

In the experiments involving ingestion of either water or MCT, the serum obtained from all the samples was clear. However, turbid serum was observed in all subjects following the ingestion of corn oil. Serum lactescence was mild to moderate throughout the corn oil period.

The mean blood ketone levels prior to and following the administration of the three test meals are shown in figure 1. Ketone concentrations rose significantly after the ingestion of MCT, but not after corn oil or water. The mean peak ketone level induced by MCT was 5.3 mg. per 100 ml. of whole blood. When the mean maximal ketone levels that followed MCT were compared with those that followed corn oil or water, the differences were statistically significant ($p < .01$). In contrast, no statistically significant difference was discernible when the mean ketone levels that followed the ingestion of corn oil and water were compared. It is of interest that 25 gm. of glucose given intravenously sixty minutes after MCT ingestion did not abolish the hyperketonemia. Serum glucose values up to sixty minutes following MCT, corn oil or water did not change significantly from their respective pre-meal controls. Mean serum glucose levels (milligrams per 100 ml. ± standard error) at minus sixty, minus thirty minutes, and immediately prior to MCT, corn oil and water were, respectively, 70 ± 1.8, 72 ± 2.6, 74 ± 2.6; 76 ± 2.4, 76 ± 2.2, 78 ± 2.2; and 77 ± 2.0, 74 ± 1.2, 80 ± 2.2. Mean glucose levels at thirty and sixty minutes after ingestion of MCT, corn oil and water were, respectively, 71 ± 1.7, 73 ± 1.9; 78 ± 1.9, 73 ± 1.6; and 75 ± 3.2, 81 ± 2.1.

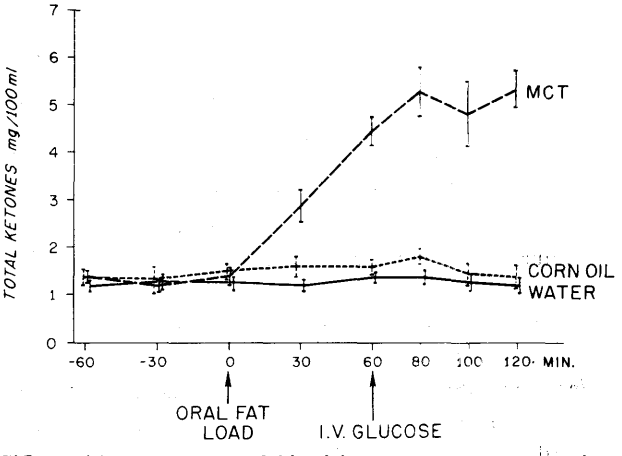

FIG. 1. Mean responses of blood ketones to water, corn oil or MCT test meals and intravenous glucose administered on separate occasions to each of the subjects. (Vertical bars represent standard errors.)

The changes in serum FFA in all subjects are shown in figure 2. The mean (± standard error) serum FFA levels at sixty minutes prior to ingestion of MCT, corn oil, or water were, respectively, 868 ± 137, 1,057 ± 188, and 949 ± 123 μEq. per liter. Free fatty acid levels did not change significantly during the baseline

*Kindly supplied by Mr. Alec Robertson, Drew Chemical Company, Boonton, N.J.

†If G_1 and G_2 are the levels of blood glucose at times t_1 and t_2, respectively, on the derived line, then $G_2 = G_1e^{-Kt}$, the equation becomes $\ln G_2 = \ln G_1 - Kt \ln e$, where $t = t_2 - t_1$ and $\ln e = 1$. Therefore, the K value can be determined from the levels G_1 and G_2 and times t_1 and t_2:

$$K = \frac{\ln G_1 - \ln G_2}{t_2 - t_1}.$$

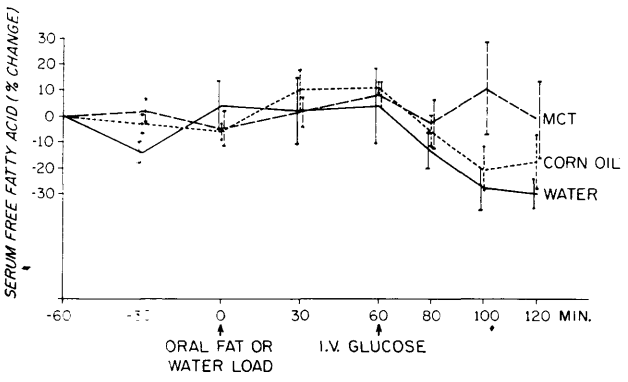

FIG. 2. Mean changes in serum FFA in response to water, corn oil or MCT test meals and intravenous glucose in seven normal subjects. (Vertical bars represent standard errors.)

periods nor during the subsequent experimental periods prior to glucose administration, regardless of the test meal. Thus, neither MCT nor corn oil increased the FFA concentration. In the MCT experiment FFA levels did not change during the period immediately following glucose administration; however, in the corn oil and water experiments, a decrease in FFA levels was observed at twenty minutes after glucose administration ($p < .7$ for MCT, $p < .02$ for corn oil, $p < .05$ for water).

The rates of disappearance from blood of intravenously administered glucose during MCT-induced hyperketonemia and after corn oil and water administration were compared. Mean K values (with their standard errors) following MCT, corn oil and water were, respectively, 2.99 ± 0.34; 2.64 ± 0.41; and 1.80 ± 0.38. Differences in K values between water and corn oil experiments and between water and MCT experiments were statistically significant in both instances ($p < .01$), while the difference between the K's associated with the corn oil and MCT test meals was of borderline significance ($p < .02$). In every subject the rate of disappearance of glucose was consistently slower after water ingestion than after the corn oil or MCT loads. Thus, compared to the results following water ingestion, administration of corn oil or MCT appears to have been associated with an increased rate of disappearance of intravenously given glucose.

DISCUSSION

The data clearly confirm previous studies[3,4,6] indicating that orally administered MCT induces a mild but consistent hyperketonemia. The possible mechanism of MCT-induced hyperketonemia has been discussed in an earlier publication.[4] The hyperketonemia appears to result from the rapid transport and delivery to the liver via the portal vein of medium-chain FFA derived from MCT following digestion and absorption.[16] In the liver, the medium-chain FFA are rapidly degraded to two-carbon fragments. Moreover, octanoate appears to depress glycolysis in the liver, resulting in a diminished rate of fatty acid biosynthesis[17] which may further enhance ketogenesis.[18]

The present study indicates that during the height of MCT-induced hyperketonemia glucose tolerance is not impaired. The mean K value of 1.80 in the control experiment in which water was administered is consistent with results of other reported studies. Conard[19] found a mean K value of 1.74 with a range of 1.07 to 2.79 in a group of seventy-five healthy subjects, and a mean K of 0.54 with a range of 0.15 to 0.99 in a group of ninety diabetic patients. Silverstone et al.[20] observed a mean K of 1.67 in a group of thirty healthy, nonpregnant women. Schalch and Kipnis[21] found a mean K of 2.74 ± 0.14 in twelve normal subjects. Thus, the K values of the present study all fell within the generally accepted "normal range." However, in the present series both MCT and corn oil ingestion were associated with relative enhancement in rate of glucose disappearance.

The improvement in glucose tolerance following MCT ingestion may be explained in part by the MCT-induced hyperketonemia. Mebane and Madison[22] found that hyperketonemia in dogs, induced by ketone infusion, stimulated an increased rate of endogenous insulin secretion resulting in diminished glucose output by the liver. It was their belief that the hypoglycemic response to hyperketonemia was entirely an hepatic effect and occurred in the face of a reduced rate of peripheral glucose uptake. In another study by the same group,[23] involving the use of suitably cannulated dogs, a striking increase in pancreatic venous plasma insulin concentration was observed after infusion of ketones into the pancreatic artery. Sunbar et al.[24] and Campbell et al.[25] found in dogs perfused peripherally with octanoate that a significant decrease in blood sugar occurred without apparent enhancement of peripheral glucose utilization. The hypoglycemia was attributed to a diminished hepatic glucose output. Thus, during MCT ingestion, the liver may reduce its output of glucose. In addition, glycolysis may be inhibited while the production of ketones increases. The resulting hyperketonemia may promote insulin secretion. Under these conditions, the disposal of an administered glu-

cose load might well be enhanced.

The mechanism by which corn oil ingestion could have increased the rate of glucose disappearance is not clear. The presence of corn oil in the intestinal tract may have stimulated increased production of insulin by promoting secretion of certain enteric hormones that have been reported to have a "β-cytotropic effect."[26] However, in preliminary experiments in normal adult subjects, Pi-Sunyer[27] has been unable to demonstrate a rise in immunoreactive insulin measured in peripheral venous plasma after corn oil ingestion.

In the water and corn oil experiments, there was a prompt decrease in the serum level of free fatty acids after glucose was given intravenously. In contrast, in the MCT studies, the change in serum FFA levels after intravenous glucose was not significant. The explanation for the lack of fall in serum FFA after glucose administration in the subjects receiving MCT as the test meal is not certain. It is possible that, after MCT ingestion, small amounts of medium-chain fatty acids escaped metabolism in the liver, enlarging the circulating FFA pool, and thereby offsetting the FFA-lowering effect of glucose.

ACKNOWLEDGMENT

This study was supported by grants from the National Institutes of Health (Grant No. AM-08107), the Special Dairy Industry Board, and the Irwin M. Strasburger Memorial Medical Foundation.

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