The Effect of a New Calcium Channel Blocker (TA-3090) on Lipoprotein Profile and Intestinal Lipid Handling in Rodents (43340)

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Abstract. **Recent interest has focused on findings that drugs used to lower blood pressure may adversely modify plasma lipids and lipoprotein metabolism. This observation may explain why pharmacologic control of hypertension has failed to reduce the incidence of morbidity and mortality from coronary artery disease. The present study aims to evaluate the effect of TA-3090, a new calcium channel blocker, on fasting plasma lipids and lipoproteins, as well as on processes of intestinal fat absorption. Rats were treated by gavage with TA-3090 (10 mg/kg twice daily) for 4 days and compared with controls ($n = 6$ per group). Plasma cholesterol was increased in the treated group to (mean ± SE) 74 ± 2 vs 60 ± 4 mg/dl ($P < 0.01$), due mainly to an increased high density lipoprotein-cholesterol level (50 ± 2 vs 37 ± 3 mg/dl, $P < 0.005$). Notably plasma triglycerides (TG) and low density lipoprotein-cholesterol were not significantly affected. Another group of TA-3090-treated animals was given an intraduodenal fat meal, and the rise in plasma TG and chylomicrons followed over 4 hr. Postprandial hypertriglyceridemia and chylomicronemia were significantly lower at 2 hr ($P < 0.05$) and 3 hr ($P < 0.01$) compared with controls. In a separate group of animals, the addition of TA-3090 to a 2% Intralipid infusion intraduodenally was associated with significantly reduced TG and chylomicron-TG transport into lymph ($P < 0.05$). Furthermore, experiments in rats pretreated with TA-3090 intraperitoneally and then given 2% Intralipid intraduodenally were shown to have a significant decrease in mean flow rate (27%), TG transport (31%) and chylomicron-TG output (37%), when compared with controls. *In vitro* studies using jejunal organ culture to examine the effect of TA-3090 on intracellular lipid synthesis and secretion revealed that the addition of the drug to the medium resulted in significantly decreased TG synthesis and secretion. These data suggest that TA-3090 could be effective in increasing HDL-cholesterol and reducing postprandial chylomicronemia. Our findings support a role for TA-3090 directly on enterocyte absorption and/or intracellular lipid transport, and thus indicate the importance of intracellular calcium on these processes.** [P.S.E.B.M. 1992, Vol 199]

Calcium antagonists comprise a heterogenous group of therapeutic agents which, in addition to their antihypertensive effects, have been found beneficial in the treatment of a number of cardiovascular and circulatory disorders (1). A putative antiatherosclerotic role is also thought to take place given that calcium is implicated in the pathogenesis plaque formation (2), including an increased endothelial permeability (3), migration into the intima and proliferation of smooth muscle cells (4), secretion of extracellular matrix proteins (5), as well as degeneration and necrosis (6). Alterations in plasma lipoproteins and stimulation of the high affinity binding of low density lipoprotein mediated by specific receptors are among the reported antiatherogenic properties of calcium channel blockers (7). In spite of these observations, data from other studies do not support the effectiveness of calcium antagonists in suppressing or preventing atherosclerosis (8, 9).

TA-3090 is a new benzothiazepine calcium antagonist ((+)-cis-(2S,3S)-3-(acetoxy)-8-chloro-5-2-(dimeth-

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ylamino)ethyl-2,3-dihydro-2-(4-methozyphenyl)-1,5-benzothiazepin-4(5H)one maleate) that blocks voltage-sensitive channels and thus produces a sustained decrease in blood pressure (10). In addition to its effects on calcium flux into cells, TA-3090 may possess other cellular actions, i.e., reduction of calcium uptake by the sarcoplasmic reticulum and inhibition of sodium-induced release by mitochondria (11). At this time, the influence of this calcium channel blocker on plasma lipids and lipoproteins is not known. Furthermore, no information is available on the effects of calcium antagonists on lipid synthesis and chylomicron secretion by the intestine. This is particularly important, since the intestine has long been recognized as an organ active in lipoprotein formation, and a modification of gut lipoproteins synthesis might alter their plasma concentration. Moreover, data originating from TA-3090 administration will emphasize the requirement of Ca^{2+} for chylomicron processing by enterocytes.

Materials and Methods

Animals. Nine-week-old male Sprague-Dawley rats (Charles River Breeding Laboratories, Montreal, Quebec) weighing 250–300 g were used for experiments. The animals were housed in cages located in a room kept at 24 ± 1°C and were maintained on a 12:12-hr light:dark cycle. Animals were fed a stock diet (Rodent Laboratory Chow No. 4020) *ad libitum*.

Effect of TA-3090 on Lipid Absorption. Fat absorption was determined after a 12-hr fast without restriction of water in rats chronically pretreated with TA-3090 (Nordic Laboratories, Montreal, Quebec), 10 mg/kg twice a day intragastrically, for 4 days. Control rats were gavaged with 0.9% NaCl, the TA-3090 solvent. On Day 5, 4 ml of 10% Intralipid solution containing TA-3090 (10 mg/kg) were delivered into the duodenum by tube feeding. Blood was drawn from the jugular vein before the fat loading and hourly at 4 hr postprandially for lipid and lipoprotein determinations. A similar fat meal test without TA-3090 was performed for control rats that had not been pretreated with TA-3090.

Effect of Acute TA-3090 Administration on Lymph Flow and Intestinal Lipid Absorption. In order to determine the effect of acute TA-3090 administration on lymphatic flow and lipid absorption directly into lymph, a second group of six rats were studied. Mesenteric lymph duct cannulation was performed by a modified technique of Bollman *et al.* (12), as described previously (13), using a duodenal fistula for infusion of fluids through silastic tubing (Dow Corning, Midland, MI). After the closure of the abdominal incision and the exteriorization of the cannulae and tubings, animals were transferred into restraining cages kept at 30°C. The rats were infused intraduodenally with 150 m*M* NaCl, 4 m*M* KCl, and 10 m*M* glucose at 3 ml/hr and allowed to recover for 48 hr before being given a lipid containing infusate at the same rate. Basal lymph was then collected, weighed, and placed on ice for 8 hr during continuous infusion of 2% Intralipid solution, as described above. Subsequently, the effect of acute intraluminal TA-3090 administration was examined by collecting lymph samples at 2-hr intervals for 8 hr during continuous 2% Intralipid infusion containing TA-3090 (10 mg/kg/day), which was delivered intraduodenally at the same rate as the basal infusion (3 ml/hr). In order to test the effect of systemic administration of TA-3090 on lymphatic flow and lipid absorption, another group of six animals were studied in which basal Intralipid infusion (8 hr) was followed by an intraperitoneal injection of TA-3090 (10 mg/kg). A second 8-hr period of lymph collection was then obtained during infusion of 2% Intralipid without added TA-3090. Aliquots of lymph were allowed to clot at room temperature and the fibrin was removed by filtration through glass wool. For these experiments, animals served as their own controls, allowing for comparison of lymph flow and lipid transport during identical periods of fat infusion with and without the test drug, which was administered intraluminally or intraperitoneally.

Chylomicron isolation. Chylomicrons were separated from lymph by ultracentrifugation at 25,000 rpm × 30 min at 4°C. Lymph and lymphatic chylomicrons were dialyzed exhaustively against 0.15 *M* NaCl 0.04% disodium EDTA (pH 7.4) before chemical analyses were performed.

Jejunal organ culture. Since organ culture of adult rat intestine does not allow a sufficiently good preservation of the ultrastructure of the absorptive cells, mouse jejunal explants were used in this study (14). Male Swiss IRC mice (28–30 g) were fasted overnight with free access to water, and were sacrificed by rapid cervical dislocation. A jejunal segment (3 cm) was excised 11 cm proximal to the pylorus, washed, and cut into small explants (2 mm). These specimens were immediately placed in RPMI 1640 culture medium (Gibco, Grand Island, NY) containing 10% inactivated fetal calf serum. The medium was saturated with 95% O_2 and 5% CO_2 and cultures were set up by methods described previously (15, 16). Small, well-laid-out pieces of intestinal tissue, mucosal side up, were placed on a stainless steel wire screen over the middle well in sterile plastic culture dishes (Falcon Plastics, Los Angeles, CA). Filter paper soaked in sterile distilled water was placed around the well to keep the environment saturated with moisture. The tissue culture medium (0.8 ml) consisted of RPMI 1640 with fetal calf serum, soybean trypsin inhibitor (60 μg/ml), and gentamycin (100 μg/ml). The medium was also supplemented with 8 m*M* sodium taurocholate, 20 m*M* oleic acid, and 10 m*M* monooleylglycerol to stimulate intracellular lipid

esterification. Lipid synthesis and secretion by explants were studied by adding 1 μCi of [^{14}C]oleic acid (sp act 40–60 mCi/mmol; New England Nuclear, Montreal, Quebec). The petri dishes were thereafter placed in anaerobic jars, sealed, gassed with 5% CO_2 and 95% O_2, and incubated for 5 hr at 37°C. Explants were then sonicated (Kontes Microultrasonic Cell Disruptor; Ultrasonics, Vineland, NJ) at a setting of 4 for 3- to 10-sec bursts. The biopsy homogenates and their respective incubation medium were lipid-extracted with chloroform-methanol (2:1, v/v) (17). Small amounts of lipid standards were added to the samples before separation of individual lipid classes by one-dimensional, thin-layer chromatography (Silica gel; Eastman Kodak, Rochester, NY), as described previously (18). The developing solvent system was heptane-diethyl ether-glacial acetic acid (80:20:3, v/v/v). The radioactivity of the separated fractions was measured in a Beckman liquid scintillation spectrometer. Quenching was corrected using computerized curves generated with external standards. An aliquot of the tissue was used for protein determination (19). Optimal morphologic preservation was confirmed by light and electron microscopy. The villi were covered with well-differentiated enterocytes, and well-formed crypts were apparent. No modification of intracellular organelles was noted. The viability of the explants was reflected by the sustained and linear incorporation of [^{3}H]leucine and of [^{14}C] oleic acid (data not shown).

Analyses. Triglycerides were quantitated by enzymatic methods and total cholesterol was quantitated by the oxidase-esterase method (20) using the Boehringer-Mannheim kit (Montreal, Quebec). High density lipoprotein (HDL)-cholesterol was measured after precipitation of very low density lipoproteins with phosphotungstic acid (21). Low density lipoprotein-cholesterol was directly determined using polyvinylsulphate (Boehringer-Mannheim) (22). Lipoprotein electrophoresis on agarose was performed as described previously (23). The lipoprotein bands were stained and the relative composition of the different lipoproteins was determined by integration with a Canalco densitometer. Only the chylomicron data, expressed as percentages of total lipoprotein, were reported.

Statistics. Data are reported as mean ± SE. The Student's t test was employed to evaluate the significance between plasma lipid parameters. Statistical comparisons between basal and test values of mesenteric lymph were performed using the paired t test.

Results

Effects on Plasma Lipids and Lipoproteins. TA-3090 treatment (10 mg/kg twice a day) for 4 days did not affect fasting plasma triglycerides (Table I). However, plasma total cholesterol increased by 23% when compared with the control group ($P < 0.01$). Most of the elevation was accounted for by a 35% increase in the HDL-cholesterol fraction ($P < 0.005$). The other lipoprotein fractions did not display changes in their cholesterol moiety.

Effect of TA-3090 on Lipid Absorption. In order to examine the effect of TA-3090 on lipid absorption, plasma triglyceride concentrations were measured at hourly intervals for 4 hr after an oral fat load. In control rats, fat absorption peaked at 3 hr and subsequently dropped toward baseline values at 4 hr (Fig. 1). Postprandial hypertriglyceridemia was lower in the TA-3090-treated group, with significantly decreased triglyceride concentrations at 2 hr ($P < 0.05$) and 3 hr ($P < 0.01$). In order to counterbalance the effect of fasting plasma triglyceride (TG) variability on postprandial lipemia, the percentage of increase of triglycerides over fasting values after the ingestion of the fat meal was also calculated. A similar impairment of lipid absorption was noted in TA-3090-treated rats. Despite the fact that both groups' fat absorption peaked at 3 hr, the percentage of increase in TG levels over baseline was significantly lower in TA-3090-treated animals (251 ± 36% vs 348 ± 31%, $P < 0.01$). Furthermore, a nearly identical pattern of decreased percentage output ($P < 0.05$) was also found for chylomicrons, indicating reduced intestinal fat absorption in TA-3090-treated rats (Fig. 2). However, since triglyceridemia is influenced by various other circulating factors, such as lipoprotein lipase, we performed additional studies using lymphatic cannulation.

Effect of Acute TA-3090 Administration on Lymph Flow and TG Transport. The volume of lymph flow and TG output were measured before and after intraluminal administration of TA-3090 in a group of rats receiving 2% Intralipid intraduodenally. Figure 3 shows the lymph flow rate, TG output, and chylomicron-TG (CM-TG) transport for animals that received an infusion of Intralipid before and after the addition of TA-3090. While only a trend toward a decrease was observed for lymph flow rate, a marked fall in TG secretion was noted in treated rats ($P < 0.05$). Similarly, a reduction in CM-TG output was measured in the lymph of treated rats ($P < 0.05$). Subsequently, in another group of rats, the effects of intraperitoneal administration of TA-3090 on lymph flow rate and lipid transport were investigated. As shown in Table II, when a dose of 10 mg/kg was injected intraperitoneally, a significant decrease in lymph flow rate was observed for up to 8 hr, compared with baseline. A significant decrease was also seen in the rate of TG transport following the addition of TA-3090, noted 2 hr after the start of lymph collection ($P < 0.01$), and which persisted for the duration of the experiment (8 hr). The overall lymph flow and TG transport rate at 8 hr amounted to 1.82 ± 0.04 vs. 1.33 ± 0.09 ml/hr and 51.2 ± 1.8 vs 32.7 ± 2.4 mg/hr, before and after intraperitoneal

Table I. Plasma Lipid and Lipoprotein-Cholesterol Concentrations[a]

Rats	Triglycerides	Cholesterol (mg/dl)	VLDL-C	LDL-C	HDL-C
Controls (n = 18)	51 ± 5	60 ± 4	19 ± 2	3.4 ± 0.2	37 ± 3
Treated (n = 18)	48 ± 3	74 ± 2	20 ± 1	3.5 ± 1.0	50 ± 2
P	NS	<0.01	NS	NS	<0.005

[a] Abbreviations used in this table: VLDL-C, very low density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol. Results are expressed as means ± SE.

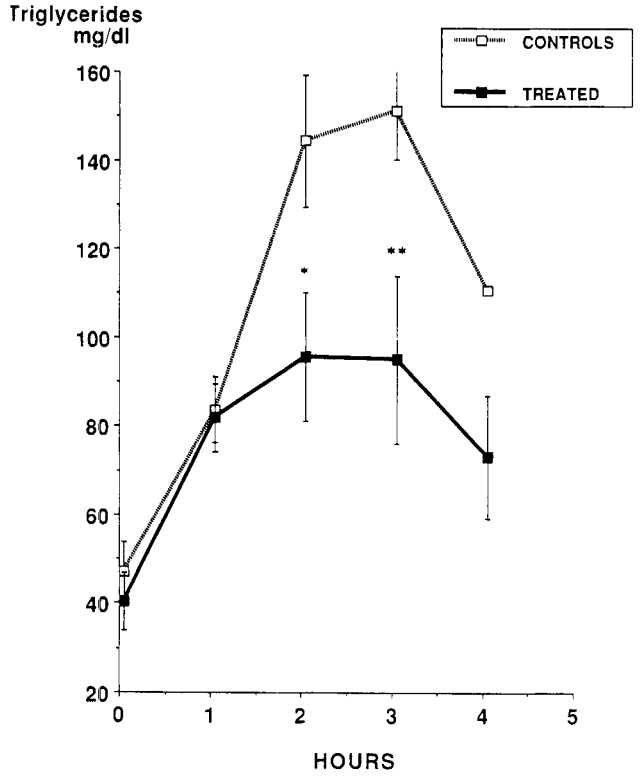


Figure 1. Effect of TA-3090 administration (10 mg/kg twice daily intragastrically) for 4 days (treated group) on rat postprandial plasma triglyceride levels. Following a fat meal test (2% Intralipid infusion intraduodenally), plasma triglyceride levels in TA-3090-treated rats were significantly lower than those in controls during peak absorption times. Results are expressed as means ± SE of six rats in each group (*$P < 0.05$; **$P < 0.01$).

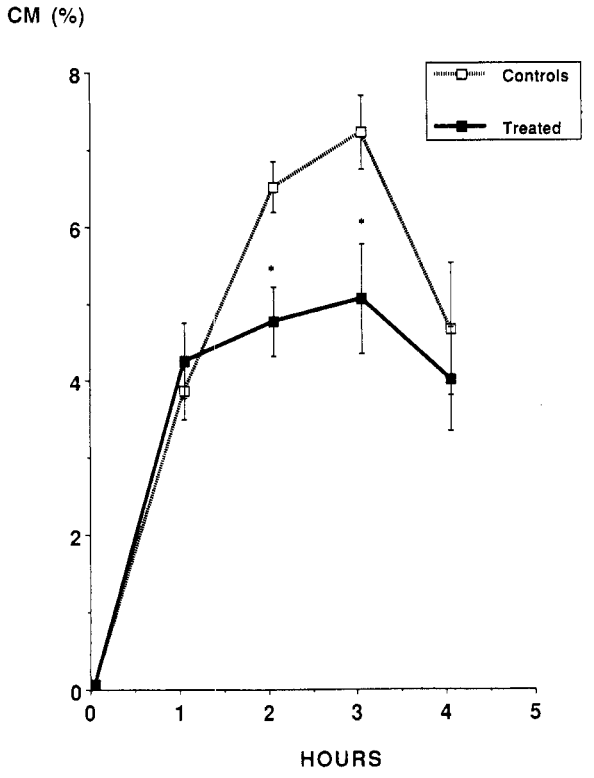


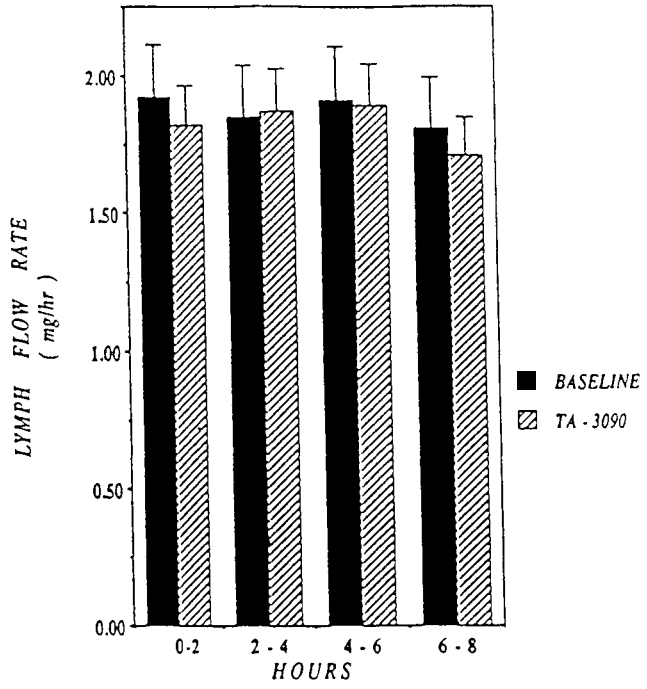
Figure 2. Percentage of increase of plasma chylomicron-triglycerides over fasting values in TA-3090-treated (10 mg/kg twice daily intragastrically for 4 days) and control rats following a fat load (2% Intralipid intraduodenally). Results are means ± SE, $n = 6$ per group, and were obtained following lipoprotein electrophoresis on agarose. To determine the chylomicron percentage, lipoprotein bands were stained and integrated (*$P < 0.05$).

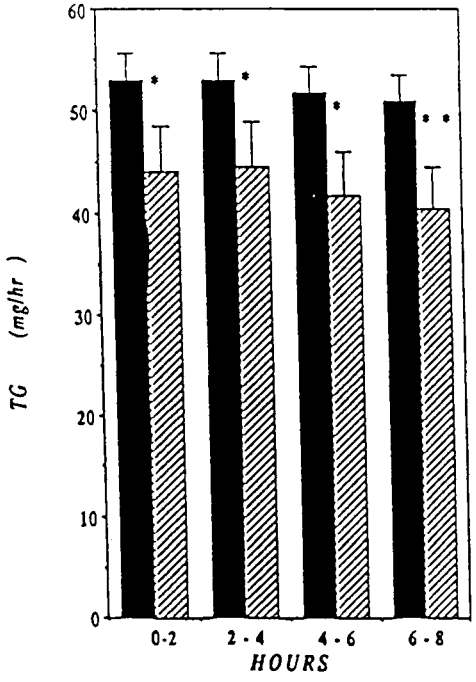
administration of TA-3090, respectively. Concordant with these changes, the measurement of lymph CM-TG (mg/hr) revealed a persistent low output (37%) in treated rats throughout the infusion of triacylglycerol. The mean CM-TG output was 41.41 ± 6.75 vs 25.02 ± 3.61 mg/hr ($P < 0.05$) before and after intraperitoneal administration of TA-3090, respectively.

Plasma Lipoprotein Lipase Activity. In order to determine whether impaired TG hydrolysis could account for the relative plasma TG decrease following TA-3090 administration lipoprotein lipase was measured. Total heparin plasma lipoprotein lipase activity (μmol free fatty acid/ml/hr) in the TA-3090-treated group (21.9 ± 0.5) was not different from that in controls (22.5 ± 0.7).

Synthesis of Labeled Triacylglycerols by Jejunal Explants. To determine whether TA-3090 had a direct effect on TG biosynthesis, we studied these processes *in vitro* using cultured jejunal explants. As noted in Figure 4, the incorporation of [^{14}C]oleic acid into TG was diminished by the addition of the drug to the medium. The reduction of TG synthesis amounted to about 20% of the basal values with low concentrations of TA-3090 (10–100 μg/ml), and to 80% with higher concentrations (1000–2000 μg/ml). Similarly, the drug markedly impaired TG secretion into the medium to less than 50% of release, even in the presence of low TA-3090 concentrations.

TA-3090 did not affect free fatty acid incorporation into tissue. However, the esterification activity was





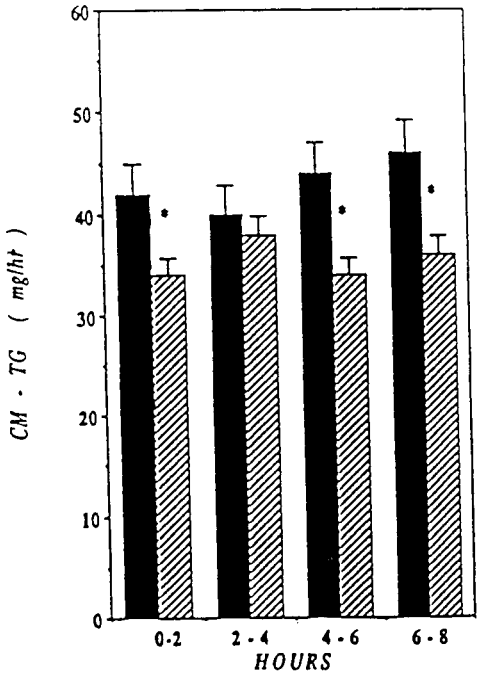


Figure 3. Effect of TA-3090 on rates of lymph flow, triglyceride output, and (CM-TG) transport. Studies were performed after 48 hr of stabilization following lymphatic cannulation using intraduodenal infusion of 2% Intralipid (baseline) or Intralipid containing TA-3090 (10 mg/kg/24 hr). Results are the means ± SE of six rats.

markedly inhibited by the addition of TA-3090 to the organ culture medium.

Discussion

Various α_1-inhibitors and β-blockers have been shown to affect plasma lipid levels differentially in a number of animal models (24). While correcting hypertension, these antihypertensive agents often induce hyperlipoproteinemia, a well-known risk factor for atherosclerosis (25, 26). Calcium antagonists also used for the treatment of hypertension have been found to be beneficial for a number of other cardiovascular and

Table II. Effect of Intraperitoneal Administration of TA-3090 on Lymph Flow Rate and Triglyceride Transport[a]

	Collection time (hr)			
	2	4	6	8
Flow rate (ml/hr^{-1})				
Baseline	1.82 ± 0.22	1.81 ± 0.21	1.88 ± 0.21	1.77 ± 0.17
TA-3090	1.23 ± 0.21	1.32 ± 0.19	1.32 ± 0.26	1.45 ± 0.35
P	<0.005	<0.005	<0.01	<0.05
TG transport (mg/hr^{-1})				
Baseline	48.5 ± 2.9	52.2 ± 4.2	52.5 ± 1.6	51.5 ± 2.6
TA-3090	29.2 ± 4.2	37.7 ± 5.7	33.8 ± 7.0	34.2 ± 9.5
P	<0.01	<0.025	<0.025	<0.05
CM-TG transport (mg/hr^{-1})				
Baseline	33.7 ± 1.7	38.7 ± 3.1	49.4 ± 7.5	43.9 ± 4.6
TA-3090	28.9 ± 4.9	26.9 ± 3.0	23.5 ± 4.6	20.8 ± 5.4
P	NS	<0.025	<0.05	<0.025

[a] Lymph flow, triglyceride transport, and mesenteric chylomicron output were determined in rats pre- and postinjected intraperitoneally with TA-3090 (10 mg/kg). Values are means ± SE for the time course of lymph collection (n = 6 per group).

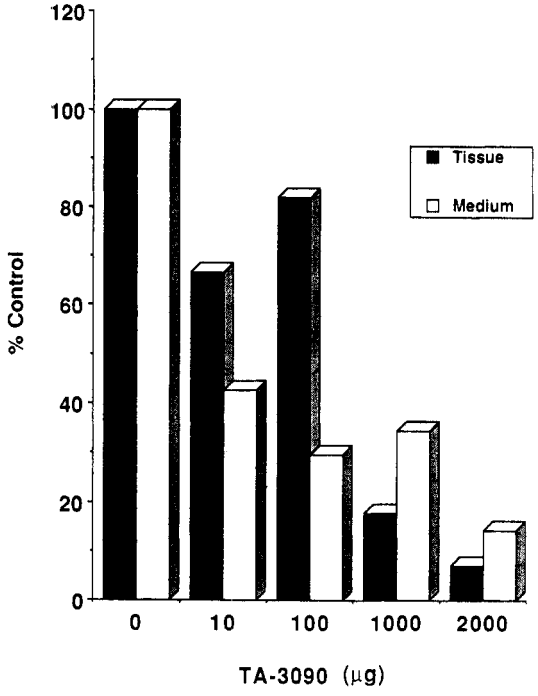


Figure 4. Effect of addition of various concentrations of TA-3090 on the *in vitro* lipid synthesis and secretion by mouse jejunal explants. Organ cultures were incubated for 5 hr in medium supplemented with 1 μCi of [^{14}C]oleic acid. Results are expressed in percentage of [^{14}C] oleic acid incorporation into triglycerides in tissue (■) and release into the medium (□) in explants exposed to different concentrations of TA-3090. Results are means of two experiments, three dishes in each experiment.

circulatory disorders (1). The role of organic calcium antagonists in the prevention of cardiovascular diseases is as yet undefined. In the present study, we explored the effect of a new calcium antagonist on lipid absorption and lipoprotein profile in the rat.

Three experimental strategies were used to investigate the effect of TA-3090 on intestinal fat absorption. First, using a standardized fatty meal, the normal postprandial biphasic pattern, consistent with concomitant absorption of exogenous fat from the gut and its subsequent clearing from the circulation, was examined. In TA-3090-treated animals, the postprandial level of triglycerides, as well as of chylomicrons, was significantly lower, suggesting the defective delivery of intestinal TG. However, plasma TG concentration results not only from gut release, but is also influenced by various other factors, including the rate of TG secretion by the liver, the activity of lipoprotein lipase that catalyzes the TG hydrolysis in the circulation, and the rate of uptake of TG-containing lipoproteins by receptor- and nonreceptor-mediated processes. Therefore, we performed mesenteric lymphatic cannulation in order to determine the intestinal TG delivery and thereby define the effect of TA-3090 on lipid absorption. Using the rat mesenteric lymph duct fistula model, we have shown that intraduodenal infusion of TA-3090 in combination with Intralipid results in a markedly depressed intestinal flow rate and transport of absorbed lipid into lymph. These data, therefore, suggest that TA-3090 directly impairs fat absorption.

Fat absorption by the gut is a complex process influenced by a number of intraluminal and intracellular factors (27). Thus, in a third set of experiments, we aimed to define the direct effect of TA-3090 on intracellular processes, including lipid synthesis and secretion. For these studies, jejunal organ culture was employed, a technique which we have shown to be useful for investigating abnormalities in intestinal function related to different disorders of lipid metabolism (15, 16). Unequivocally, the TA-3090 drug was shown to decrease the ability of the jejunal explants to elaborate and release TG. On the basis of these combined data, we were able to conclude that this calcium antagonist impairs fat absorption at the cellular level. Furthermore, these findings suggest that intracellular calcium is necessary for normal intestinal lipid processing.

Our studies do not exclude a possible effect of TA-3090 on intraluminal factors, including pancreatic lipase, bile salts, formation of micelles, and adequate intraluminal pH.

The mechanism by which TA-3090 reduces intestinal chylomicron synthesis or secretion remains to be elucidated. Previous studies with another calcium antagonist, verapamil, which binds to the voltage-dependent channel and thereby inhibits passage of calcium through the plasma membrane, have shown that it inhibits secretion from different types of cells (28–31). In particular, Nossen *et al.* (32) demonstrated that verapamil had a marked inhibitory effect on triglyceride secretion by cultured rat hepatocytes that could not be explained by decreased synthesis of TG or of apolipoproteins (32). Thus, it is possible that TA-3090 may influence the continuous exocytosis of chylomicron, particularly because calcium is important in functions involving microtubules, microfilaments, and fusion of transport vesicles with different cell membranes (30). This is supported by the observation of Strauss and Jacob (33), showing that Ca^{2+} stimulated the secretion of TG in hamster everted jejunum.

Maximum inhibition of lymph flow and TB transport has been observed with intraperitoneal injection of TA-3090 compared with intraduodenal infusion. Previous studies by Lee (34) have shown that lymph pressure waves indicate the occurrence of rythmical contractions of the lymphatic duct or its surrounding tissues, which may play a role in the propulsion of lymph (34). Furthermore, Tso *et al.* (35) have shown that lymph flow has a profound effect on intestinal chylomicron transport. Our observations showing a profound decrease of lymphatic flow subsequent to intraperitoneal TA-3090 administration may reflect an effect of TA-3090 on the above processes.

It has become increasingly evident that drugs used routinely for the management of hypertension, such as diuretics and β-blockers, have an adverse effect on blood lipids, reducing HDL-cholesterol and increasing TG levels (36, 37). These observations may explain the failure of such treatments to prevent myocardial infarction in hypertensive patients, as well as to produce the anticipated reductions in morbidity and mortality (25, 38). In the present study, we have demonstrated the ability of the antihypertensive drug TA-3090 to increase HDL-cholesterol, without unfavorable effects on TG levels. Taken together, these observations suggest the existence of separate mechanisms of lipid absorption and lipoprotein synthesis and secretion associated with β-blocker and calcium antagonist treatment. By its combined effect on lipoproteins and hypertension, TA-3090 offers potential advantages over other antihypertensive drugs, and may lead to the realization of a decrease in risk factors for ischemic heart disease. These preliminary observations warrant more extensive studies on the mechanisms of these responses using hypercholesterolemic models, such as nonhuman primates. Moreover, to what extent the same mechanisms are operative in humans remains to be determined.

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