Comparison of Verapamil and Felodipine Treatment on Lipid and Glucose Metabolism in Obese Female SHHF/Mcc-*fa*^{cp} Rats (44408)

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Abstract. **Calcium channel blockers, verapamil or felodipine, were given to genetically obese 6 and 11-month-old female SHHF/Mcc-*fa*^{cp} (SHHF: Spontaneous Hypertension Heart Failure) rats for 8 weeks to investigate their effects on glucose and lipid metabolism and obesity. Both antihypertensive agents significantly decreased systolic blood pressure. In 11-month-old rats, verapamil treatment significantly decreased body weight after 4 weeks whereas with felodipine it was only significantly reduced after 8 weeks. In 6-month-old rats, verapamil significantly curtailed body weight gain. Subcutaneous fat depots were smaller, and abdominal fat depots were larger in verapamil rats compared to felodipine or control rats. Oral glucose tolerance tests in the 6-month-old verapamil and the 11-month-old felodipine groups showed improved glucose tolerance compared to their respective control groups. After 8 weeks of treatment, fasting plasma glucose levels were lower in 6-month-old verapamil rats compared to felodipine and control rats and were decreased by both verapamil and felodipine treatments as compared to control in 11-month-old rats. During the oral glucose tolerance test in 6-month-old rats, both fasting plasma insulin and the area under the insulin curve were increased in verapamil compared to both control and felodipine groups. When compared to controls, plasma cholesterol was increased by verapamil in both age groups, but was significantly decreased by felodipine after 8 weeks of treatment in the 11-month-old group. Plasma triglycerides increased in all control rats compared to initial levels; however, verapamil and felodipine groups showed lower triglycerides in both age groups. In 6-month-old rats, the percentages of plasma HDL significantly increased in both treatment groups as compared to control. This study shows that verapamil and felodipine depressed body weight gain in the young rats, reduced body weight in the old rats, improved lipid parameters and glucose tolerance, but had the opposite effects on body fat distribution and insulin levels in obese female SHHF rats.** [P.S.E.B.M. 1999, Vol 221]

In a previous study in our laboratory, we found that a 3-month treatment of 9-month-old obese female SHHF/Mcc-*fa*^{cp} (SHHF: Spontaneous Hypertension Heart Failure) rats with 0.25% nifedipine, a calcium channel blocker (CCB), not only lowered blood pressure as expected, but also reduced body weight, total fat mass, and plasma triglyceride levels as well as improved glucose tolerance (1). Body weight reduction is one of the most important issues in treatment of obese hypertensive and/or diabetic patients (2–6). If body weight reduction *via* improvement of carbohydrate and lipid metabolism is achieved in addition to blood pressure control by this class of antihypertensive agents, it would be very beneficial for obese and diabetic patients with hypertension.

There have been many reports suggesting paradoxical influences of CCB on glucose and lipid metabolism in humans and animals (1, 7–11). Enyeart *et al.* (11) reported that a verapamil overdose caused hyperglycemia in a woman. Verapamil has been shown to increase while dihydopyri-

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dines decrease insulin secretion by pancreatic islets in rats (12–15). Russell *et al.* (9) observed that nifedipine treatment increased plasma insulin levels in obese male JCR:LA-cp rats. Likewise, effects on lipid metabolism may be impacted by class of CCB. In rabbits fed a cholesterol-rich diet, verapamil injection increased serum cholesterol levels (16). In contrast, felodipine treatment did not change plasma lipid levels or lipoprotein concentrations (17, 18).

Although there have been many studies done with animals using CCB, the effect of CCB on weight reduction may have been overlooked since most studies have been performed on normal-weight males. Experiments with females or animals that naturally develop obesity, hypertension, and noninsulin-dependent diabetes mellitus (NIDDM) have been rare. In a recent study, Yoshida *et al.* (19) observed a reduction in body weight and the amount of retroperitoneal white adipose tissue by benidipine hydrochloride (a dihydropyridine CCB) treatment in mice made obese with monosodium-L-glutamate (MSG) pretreatment. Therefore, it is important to explore the effect of CCB on lipid and glucose metabolism as well as body weight change in obese animals.

The present study was performed to compare the effects of another dihydropyridine CCB, felodipine with verapamil, a phenylalkylamine CCB on obesity, lipid metabolism, and glycemic control in obese female SHHF rats. The SHHF rat model is unique in that all SHHF rats spontaneously develop hypertension, show cardiac hypertrophy, and eventually die from congestive heart failure (CHF) (20, 21). Obese SHHF rats, homozygous for the corpulent gene (fa^{cp}/fa^{cp}), are diabetic or glucose intolerant with hyperinsulinemia, hyperlipidemia, and hyperlipoproteinemia. Because metabolic abnormalities progress with age in this model, the impact of the two classes of CCB was compared in two different age groups of obese female SHHF rats.

Materials and Methods

Animals and Drug Treatments. Obese (fa^{cp}/fa^{cp}) female SHHF rats were from S.A. McCune's colony at The Ohio State University. To minimize the effect of body weight differences among the groups, the obese rats in each study were matched by initial body weight and randomly divided into three groups. The facilities were AAALAC approved, and all procedures were approved by the Institutional Laboratory Animal Care and Use Committee. Rats were housed in a temperature (23°C)- and light-controlled room (6 AM–6 PM light and 6 PM–6 AM dark cycle). Except for 24-hr fasting periods for metabolic studies, food and water were available *ad libitum.*

Experiment 1. Eleven-month-old obese female SHHF rats were fed either 0.25% (w/w) verapamil (n = 4, verapamil HCl, Sigma, St. Louis, MO), 0.1% (w/w) felodipine (n = 5, Astra Pharmaceuticals, Hassle, Sweden) or no drug (n = 4, controls) in powdered rat chow (RMH 3200 Rodent Meal, Agway, Syracuse, NY) for 8 weeks.

Experiment 2. After the observation of the metabolic changes by both CCB treatments and the earlier onset of CHF in verapamil-treated 11-month-old rats, the study was repeated with 6-month-old obese SHHF female rats to determine if age at the time of drug treatment was important for maximizing blood pressure and metabolic control. Details on the effect of verapamil on the development of CHF are discussed in Park *et al.* (22). In the 6-month age group, rats were fed 0.25% verapamil (n = 5), 0.1% felodipine (n = 5), or control chow (n = 4) for 8 weeks.

Procedures and Assays. The following measurements were made at 0, 4, and 8 weeks of treatment in all the rats in both experiments: systolic blood pressure, fasted body weights, food intake, and fasted plasma glucose, cholesterol, triglycerides, and insulin. An oral glucose tolerance test (OGTT) was done only at the 8-week time point. For better understanding of the drug effects on metabolism in 6-month-old rats, we added measuring plasma insulin levels during OGTT and lipoprotein patterns.

Systolic blood pressure was determined by the tail cuff method (Gilson Medical Electronics, Middleton, WI). Rats were then placed in metabolic cages and fasted for a 24-hr period. At the end of the 24-hr fasting period, body weights were measured in the morning between 8 and 9 AM. Additionally, blood samples were collected from the tail vein into tubes containing heparin (1000 U/ml) and aprotinin (250 KIU/ml).

Plasma glucose was determined by the hexokinase method (23). Plasma cholesterol and plasma triglyceride concentrations were determined by enzymatic methods using commercially available kits (Stanbio Lab., San Antonio, TX). Insulin concentrations were measured by a radioimmunoassay kit (Binax, South Portland, ME). After 8 weeks of treatment, OGTTs were performed. Following a 24-hr fast, initial blood samples were collected. The rats were then given a 75% glucose solution at a dose of 0.3 ml/100 g body weight, and additional blood samples were taken at 0.5, 1, and 2 hr following the oral glucose load. The total area under the curves of glucose and insulin in OGTT were calculated using the following equation: total area under curve = 0.25 (a + 2b + 3c + 2d), where a, b, c, and d correspond to the concentrations of glucose or insulin at 0, 0.5, 1, and 2 hr after glucose load, respectively (24). Plasma lipoproteins were separated into HDL (high-density lipoprotein), LDL (low-density lipoprotein) and VLDL (very low-density lipoprotein) using agarose gel electrophoresis. Gels were stained with Fat Red 7B and Sudan Black, destained with 75% methanol, and analyzed with an LKB densitometer (Bromma, Sweden, AB) (25).

One week after the last metabolic cage study, all rats in a fed state were sacrificed between 8 and 11 AM by intraperitoneal injection of sodium pentobarbital. Mesenteric, gonadal, retroperitoneal, and subcutaneous fat masses were dissected out and weighed. Total abdominal fat was obtained by summing the weights of mesenteric, gonadal, and retroperitoneal fat pads. Total fat mass was considered the

sum of all four fat pads. Several rats in the 11-month-old verapamil group died or developed CHF and had to be euthanized before the end of the treatment period. Samples were collected and weighed to determine fat masses on these rats.

Statistical Analysis. One way analysis of variance (ANOVA) followed by least-significant difference (LSD) mean separation tests was performed when a significant difference among the groups at the level of $P < 0.05$ was detected using SPSS (Chicago, IL). Since there was only one rat left in the 11-month-old verapamil group, that group was excluded from analysis. Paired Student's t tests were performed to compare the difference between 0 and 4- or 8-week results within the same group (26).

Results

Experiment 1: 11-Month-Old Female Rats. In this section the reason for the lack of data for the verapamil group at the 8-week time point is that there was only one surviving rat. Most of the findings on this rat (data not shown) were similar to the group mean at 4 weeks. The other rats of this group developed CHF before the end of the treatment period (22).

Systolic blood pressure. Felodipine significantly lowered blood pressure after 4 and 8 weeks of treatment. Verapamil also significantly lowered blood pressure after 4 weeks (Fig. 1).

Food intake. Food intake was significantly lower after 4 weeks in the verapamil-treated group (Fig. 2A). In the felodipine group, food intake tended to be lower at 4 and 8 weeks of treatment but did not achieve significance. (Fig. 2A).

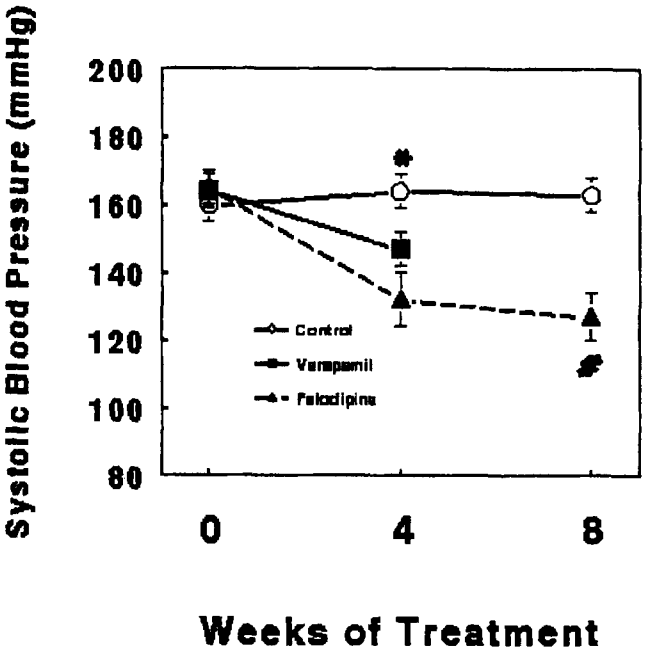

Figure 1. Systolic blood pressure (mmHg) in 11-month-old obese female SHHF rats treated with verapamil and felodipine. Data are mean ± SE. * $P < 0.05$ for control compared to both verapamil and felodipine. # $P < 0.05$ for felodipine compared to control.

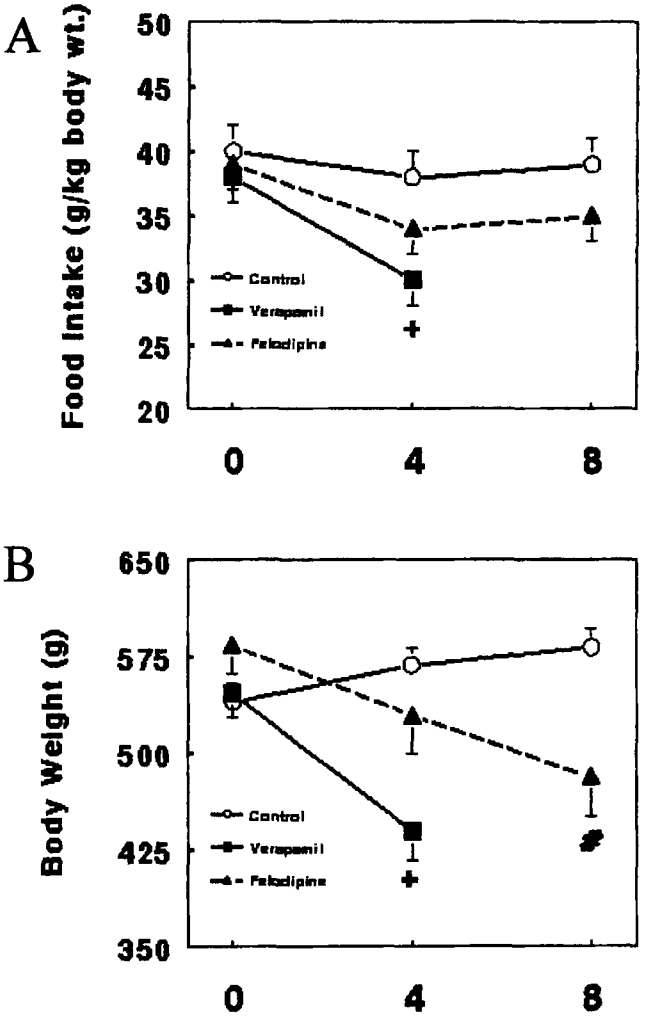

Figure 2. (A) Food intake (g/kg body weight/day) and (B) body weight (g) in 11-month-old obese female SHHF rats treated with verapamil and felodipine. Data are mean ± SE. * $P < 0.05$ for verapamil compared to control. # $P < 0.05$ for felodipine compared to control.

Body weight. After 4 weeks of treatment, body weight of the verapamil group was significantly lower compared to control rats. The felodipine-treated rats averaged a 9% decrease in body weight whereas controls increased 5% compared to initial body weights (Fig. 2B). Body weights of felodipine-treated rats reached a significant reduction compared to those of the controls after 8 weeks of treatment (Fig. 2B).

Fat pad weight and fat distribution. Total, abdominal, and subcutaneous fat masses were significantly lower in both verapamil- and felodipine-treated rats compared to controls (Fig. 3A). Subcutaneous fat as a percentage of total fat was significantly lower, and abdominal fat as a percentage of total fat was significantly higher in the verapamil group than in the control group (Fig. 3B). Therefore, verapamil treatment changed fat distribution toward relatively

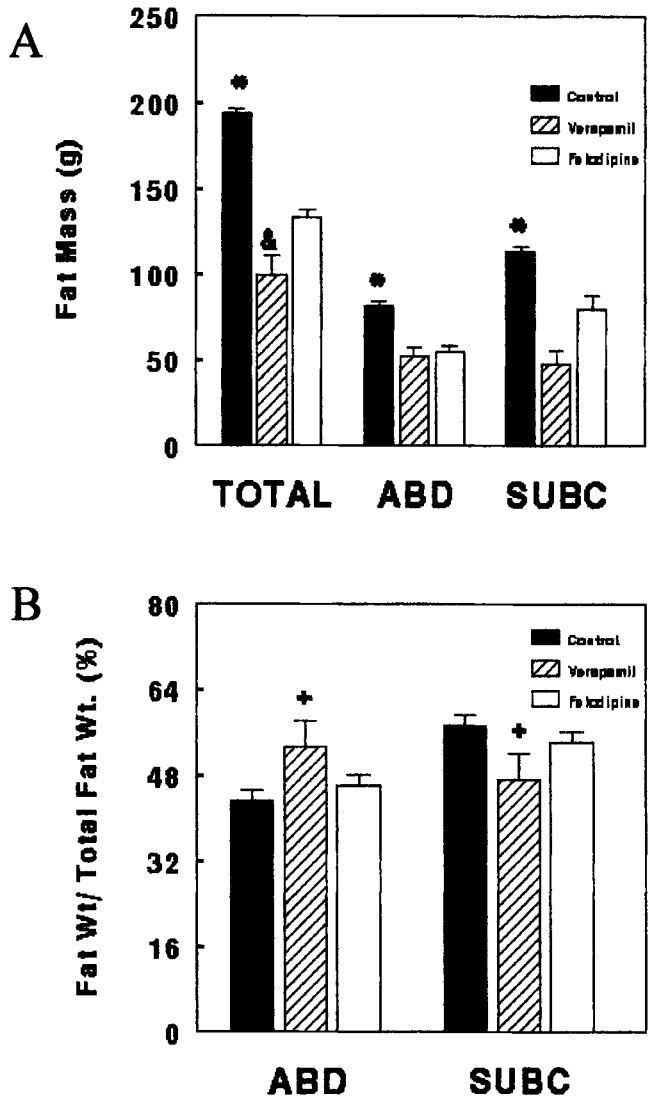

Figure 3. Fat depots in 11-month-old obese female SHHF rats treated with verapamil and felodipine: each fat pad expressed as (A) fat mass (g) and as (B) percentage total fat mass. Data are mean ± SE. * $P < 0.05$ for control compared to both verapamil and felodipine. + $P < 0.05$ for verapamil compared to control. & $P < 0.05$ for verapamil compared to felodipine. Total: Total fat mass; ABD: Abdominal fat including mesenteric, gonadal and retroperitoneal fat; SUBC: Subcutaneous fat.

less subcutaneous and more abdominal fat compared to controls. Although it did not reach significance, felodipine treatment tended to have the opposite effect as verapamil on the fat distribution.

Plasma glucose. Verapamil treatment caused significantly lower fasting plasma glucose levels compared to the controls after 4 weeks, and glucose was significantly lower compared to the initial levels within the verapamil group (Table I). There were no significant effects of felodipine treatment on fasting glucose levels.

Oral glucose tolerance tests. Felodipine treatment improved glucose tolerance as evidenced by lower plasma glucose concentrations at time points 0.5, 1, and 2 hr after glucose (Fig. 4). The area under the glucose tolerance curve was also significantly lower with felodipine (226 ± 14 mg/dl/hr* (* $P < 0.05$) vs. control 321 ± 20 mg/dl/hr). In this experiment, there was only one verapamil rat alive at the time the OGGT tests were performed, and that rat had an area under the curve of 150 g/dl/hr.

Plasma cholesterol and triglycerides. Fasting plasma cholesterol was significantly lowered after 8 weeks of felodipine treatment compared to the control group whereas verapamil had no effect (Table I). The felodipine group had significantly lower plasma triglycerides at both 4 and 8 weeks compared to age-matched controls. Verapamil-treated rats also showed significantly lower triglycerides at 4 weeks. When plasma triglyceride levels were compared to initial values within each group, controls showed no change at 4 weeks and increased 26% by 8 weeks whereas the verapamil group significantly decreased 79% at 4 weeks, and the felodipine group significantly decreased 69% at 4 weeks and 71% at 8 weeks (Table I).

Experiment 2: 6-Month-Old Female Rats. *Systolic blood pressure.* Systolic blood pressure was significantly decreased by both verapamil and felodipine as compared to the control after 4 and 8 weeks of treatment (Fig. 5).

Food intake. The average food intake of controls was significantly higher than in the verapamil or felodipine groups, but there was no difference in food intake between verapamil- and felodipine- treated rats (Fig. 6A). At 4 and 8 weeks, control rats showed significantly higher food intake compared to 0 weeks (Fig. 6A).

Body weight. Body weight of the verapamil group was significantly lower than that of controls after 4 and 8

Table I. Effect of Verapamil and Felodipine on Plasma Glucose, Cholesterol, and Triglycerides in 11-month-old Obese Female SHHF rats

Weeks of treatment	Plasma glucose (mg/dl)			Plasma cholesterol (mg/dl)			Plasma triglycerides (mg/dl)		
	Control ($n = 4$)	Verapamil ($n = 4$)	Felodipine ($n = 5$)	Control ($n = 4$)	Verapamil ($n = 4$)	Felodipine ($n = 5$)	Control ($n = 4$)	Verapamil ($n = 4$)	Felodipine ($n = 5$)
0	115 ± 7	124 ± 8	102 ± 5	145 ± 12	160 ± 10	165 ± 12	1107 ± 65	1643 ± 261	1781 ± 328
4	127 ± 7[a]	73 ± 5*[b]	95 ± 5[a,b]	138 ± 15	178 ± 19	128 ± 19	1109 ± 53[a]	348 ± 100*[b]	555 ± 122*[b]
8	113 ± 11		98 ± 8	148 ± 8[a]		109 ± 8*[b]	1394 ± 258[a]		513 ± 161*[b]

Note. Data are mean ± SE. Different letters in the same row mean that values are significantly different among groups at $p < 0.05$. *, Significantly different from 0 week value at $p < 0.05$ paired Student's t test.

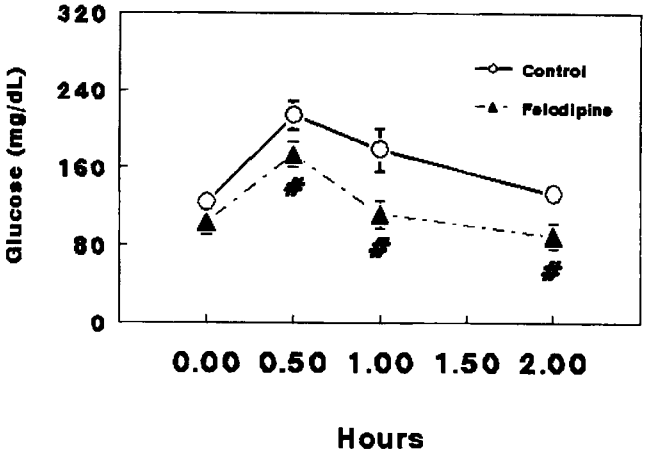

Figure 4. Plasma glucose level (mg/dl) during oral glucose tolerance test in 11-month-old obese female SHHF rats treated with verapamil and felodipine. Data are mean ± SE. # $P < 0.05$ for felodipine compared to control.

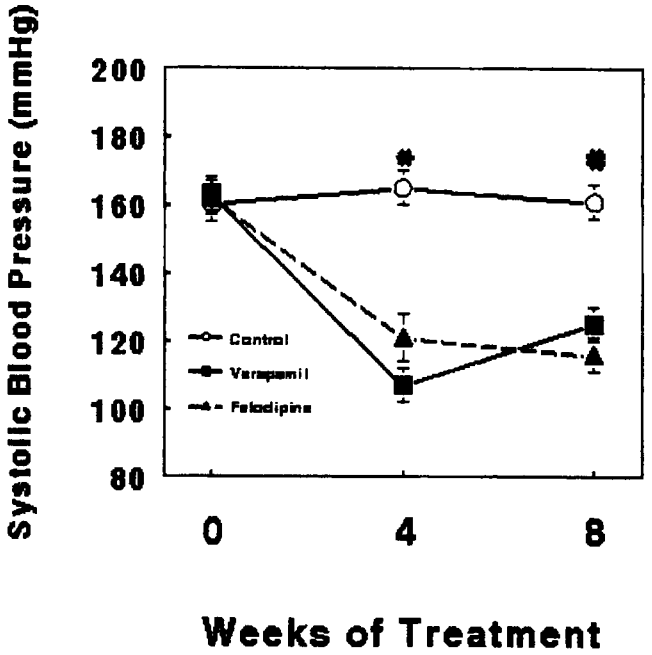

Figure 5. Systolic blood pressure (mmHg) in 6-month-old obese female SHHF rats treated with verapamil and felodipine. Data are mean ± SE. * $P < 0.05$ for control compared to both verapamil and felodipine.

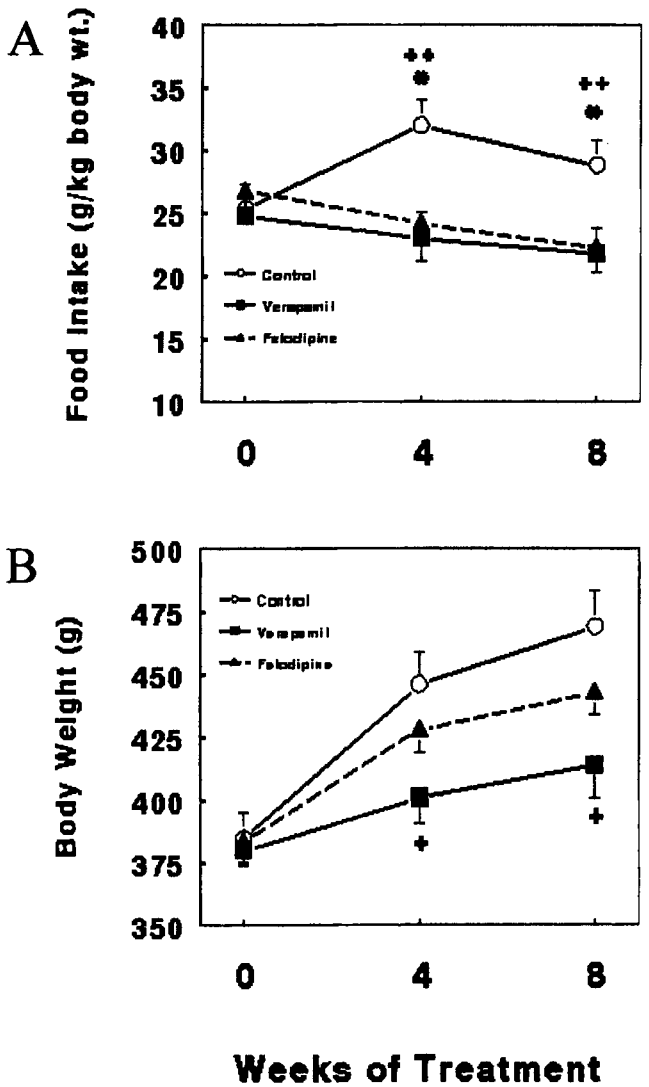

Figure 6. (A) Feed intake (g/kg body weight/day) and (B) body weight (g) in 6-month-old obese female SHHF rats treated with verapamil and felodipine. Data are mean ± SE.* $P < 0.05$ for control compared to both verapamil and felodipine. ++ $P < 0.05$ for 4 weeks and 8 weeks compared to 0 weeks in the control group. + $P < 0.05$ for verapamil compared to control.

weeks of treatment (Fig. 6B). Felodipine-treated rats also showed lower body weight and were intermediate between control and verapamil groups (Fig. 6B).Fat pad weight and fat distribution.Although there were no statistically significant differences, total fat mass of the four depots was 15% lower in verapamil and 4.5% lower in felodipine groups compared to controls (Fig. 7A). Mesenteric fat as a percentage of total fat was significantly higher in the verapamil group than in controls or felodipine groups. Subcutaneous fat as a percentage of total fat was significantly lower, and gonadal plus retroperitoneal as a percentage of total fat was significantly higher in the verapamil group compared to the felodipine group (Fig. 7B). Therefore, verapamil-treated rats had relatively more abdominal and less subcutaneous fat in comparison to the felodipine treated rats.

Plasma glucose. Fasted plasma glucose was significantly lower in the verapamil group compared to controls at 4 weeks and to felodipine at 8 weeks (Table II). When compared to initial values, plasma glucose levels were significantly lower in the verapamil group at 4 and 8 weeks.

Oral glucose tolerance tests. Glucose concentrations during OGGTs were significantly lower at the 0.5- and 1-hr time points in the verapamil group compared to the other groups (Fig. 8A). The area under the glucose tolerance curve was also significantly lower in verapamil than in other groups (Table III).

Insulin levels during the OGGTs were found to be significantly higher in the verapamil group at 0-, 0.5-, and 1-hr time points compared to the control or felodipine group

(Fig. 8B). The area under the insulin curve was also significantly greater in the verapamil group than in the other groups (Table III).

Plasma cholesterol and triglycerides. In all groups plasma cholesterol concentration tended to increase over time (Table II). At 4 and 8 weeks, cholesterol was significantly higher with verapamil when compared to the initial values for that group.

Verapamil and felodipine treatments tended to blunt the rise in plasma triglycerides compared to controls (Table II). By the end of the study, triglycerides were 36% lower in verapamil and 33% lower in felodipine vs. controls (Table II); however, because of the wide variation in triglyceride levels in the obese rats, no significant differences were found among the groups. By 8 weeks, control and felodipine rats had significantly increased plasma triglycerides compared to their initial levels in their respective groups.

Plasma lipoproteins. At 8 weeks, both felodipine and verapamil treatments significantly increased the percentage of the HDL fraction as compared to control (Table IV). Felodipine-treated rats showed a significantly lower LDL fraction compared to control. Felodipine treatment also significantly decreased the LDL percentage at 8 weeks when compared to that group's initial levels.

Discussion

The present study demonstrated that verapamil and felodipine had similar effects on blood pressure and body weight whereas different effects were observed on glucose and lipid metabolism. These effects seemed to vary not only with the type of CCB but also with the age of the obese female SHHF rats used for the study.

Antihypertensive Effect. Both verapamil and felodipine were quite effective in lowering systolic blood pressure; however, there was a greater reduction in the 6-month-old rats than in the 11-month-old group. This is in contrast to the finding that obese female SHHF rats are relatively unresponsive to another major category of antihypertensive therapy, angiotensin converting enzyme inhibitors (1).

Body Weight and Fat Distribution. In the 11-month-old groups body weight was reduced, whereas in the 6-month-old groups weight gain was attenuated by both CCB treatments. Suppression of body weight gain in the younger rats could partially be explained by the lack of increase in food intake that was observed in the control rats. However, this is probably not the only reason because the younger verapamil-treated rats had lower body weights than felodipine rats without any difference in food intake between these groups. Likewise, the decline of body weight in the older rats might be explained partially by reduced food intake since rats on both drug treatments decreased food intake. Development of CHF with concurrent wasting (20, 21), also may have contributed to the greater loss in the older verapamil-treated rats. In the older felodipine group, there tended to be a slight and similar degree of decrease in food intake at both 4 and 8 weeks of treatment but no

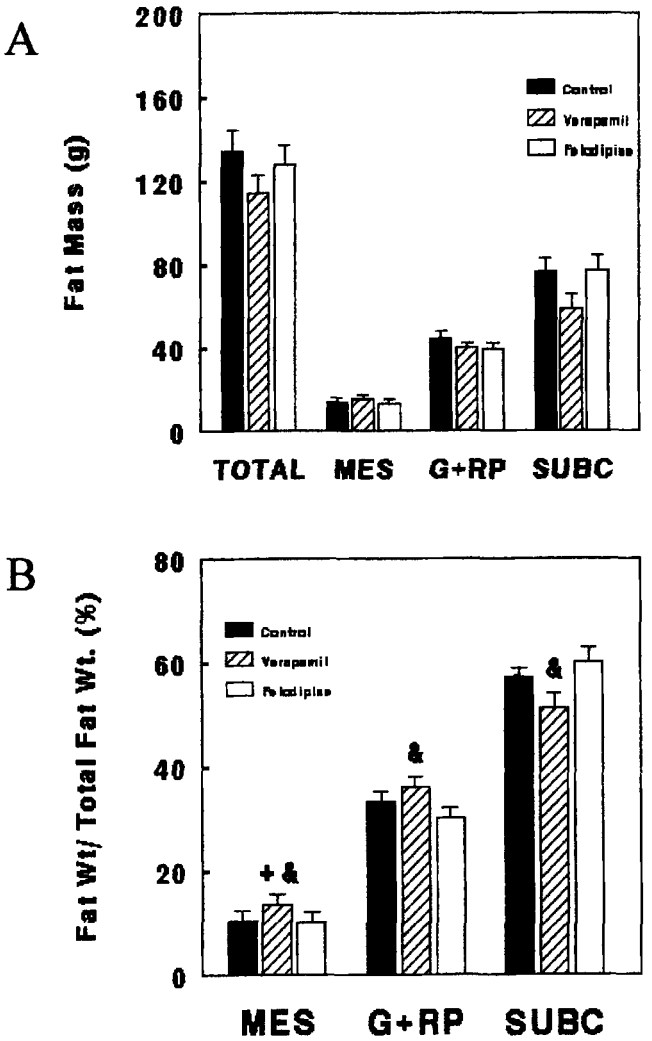

Figure 7. Fat depots in 6-month-old obese female SHHF rats treated with verapamil and felodipine: each fat pad is expressed as (A) fat mass (g) and as (B) percentage total fat mass. Data are mean ± SE. $^{+}$ $P < 0.05$ for verapamil compared to control. $^{\&}$ $P < 0.05$ for verapamil compared to felodipine. TOTAL: total fat mass; MES: mesenteric fat; G + RP: Gonadal and retroperitoneal fat; SUBC: Subcutaneous fat.

significant differences observed compared to the control group; however, there was a significant decline in body weight after 8 weeks of treatment. While verapamil treatment in humans may result in diminished food intake due to constipation (27), there was no evidence of this in our study. It is more likely that the rats did not like the taste of the drug since they decreased intake on the first day drug was given in the food, prior to when this effect would have been present.

Body weight loss during treatment with CCB has been reported in both animal and human studies and has not always been related to a decline in food intake. A significant decrease in body weight with nifedipine treatment has been demonstrated in overweight to obese patients, but not in normal-weight humans (10). Likewise, nifedipine treatment was associated with weight loss without an effect on food intake in obese female SHHF (1) and obese male JCR:LA-

Table II. Effect of Verapamil and Felodipine on Plasma Glucose, Cholesterol, and Triglycerides in 6-month-old Obese SHHF Females

Weeks of treatment	Plasma glucose (mg/dl)			Plasma cholesterol (mg/dl)			Plasma triglycerides (mg/dl)		
	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)
0	118 ± 4	135 ± 18	123 ± 16	69 ± 9	65 ± 11	70 ± 9	544 ± 33	656 ± 122	517 ± 64
4	112 ± 6[a]	94 ± 3*[b]	101 ± 6[a,b]	76 ± 16	117 ± 13*	91 ± 13	966 ± 195	793 ± 45	782 ± 94*
8	124 ± 7[a,b]	102 ± 5*[b]	139 ± 10[a]	99 ± 13	129 ± 23*	92 ± 11	1292 ± 116*	823 ± 200	865 ± 152*

Note. Data are mean ± SE. Different letters in the same row mean that values are significantly different among groups at $p < 0.05$. *, Significantly different from 0 week value at $p < 0.05$ by paired Student's t test.

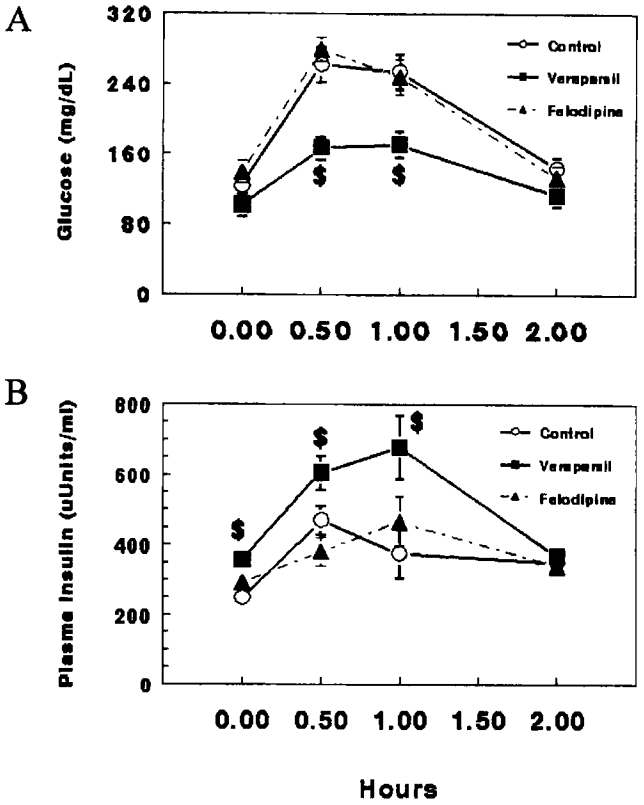

Figure 8. (A) Plasma glucose level (mg/dl) and (B) plasma insulin level during oral glucose tolerance test in 6-month-old obese female SHHF rats treated with verapamil and felodipine. Data are mean ± SE. $ $P < 0.05$ for verapamil compared to both control and felodipine.

cp rats (a normotensive obese strain related to the SHHF rat) (9). Glass *et al.* (28) observed significant body weight loss following nifedipine and verapamil treatments in cardiomyopathic turkeys. In male SHR rats, verapamil induced a 5% weight reduction despite a significantly higher food intake (29).

There are several possible mechanisms that may explain weight loss independent of a decline in food intake during CCB treatment. When hepatocytes and adipocytes were isolated from obese female SHHF rats given nifedipine, it was found that hepatic lipogenesis was decreased and lipolysis in subcutaneous adipocytes was increased (30). Alternatively, a possible increase in thermogenesis by brown adipose tissue might contribute to the weight loss. This theory might have some support in that benidipine has been shown to augment regional blood flow and decrease vascular resistance in brown adipose tissue (31).

Table III. Effect of Verapamil and Felodipine on Areas under Glucose and Insulin Curves in Glucose Tolerance Test in 6-month-old Obese SHHF Female Rats

Groups	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)
Area under glucose curve¶ (mg · dl^{-1} · h^{-1})	425 ± 25[a]	294 ± 10[b]	427 ± 24[a]
Area under insulin curve (mU · ml^{-1} · h^{-1})	756 ± 64[b]	1087 ± 130[a]	781 ± 70[b]

Data are mean ± SE. Values within a row followed by different letters are significantly different at $p < 0.05$. ¶, Area under the curve = 0.25 (a + 2b + 3c + 2d), where a, b, c, and d correspond to the concentrations of glucose or insulin at 0, 0.5, 1, and 2 hr after glucose load, respectively.

Verapamil and felodipine had differential effects on fat mass distribution that may relate to the differences observed in glucose and insulin metabolism and progression of cardiovascular disease in this study. Interestingly, verapamil treatment resulted in a decrease in subcutaneous and an increase in abdominal fat as a percentage of total fat content in both age groups studied. Despite a decrease in obesity, verapamil treatment increased insulin resistance. These results suggest that verapamil treatment may induce a more android (male) type of fat topography in obese female SHHF rats. Abdominal obesity (android type) has been shown to confer greater risk for development of diabetes and cardiovascular disease compared to lower body obesity (gynoid distribution) (32–35). The loss of more subcutaneous fat compared to abdominal fat may be associated with the progression of cardiovascular disease in the verapamil rats (22). In contrast, felodipine-treated rats had relatively less abdominal fat and improved glucose metabolism, which may have contributed to the slower progression of cardiovascular disease in this group (22).

Glucose Metabolism. In both age groups, verapamil treatment significantly decreased fasting plasma glucose. However, they had elevated insulin levels at baseline and a greater rise in insulin during the OGGT, indicating an increased insulin resistance and/or decreased hepatic insulin clearance. With felodipine there was little change in fasting

Table IV. Effect of Verapamil and Felodipine on Plasma Lipoproteins: VLDL, LDL, and HDL in 6-month-old Obese SHHF Female Rats

Weeks of treatment	VLDL (%)			LDL (%)			HDL (%)		
	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)	Control ($n = 4$)	Verapamil ($n = 5$)	Felodipine ($n = 5$)
0	81 ± 3	77 ± 3	81 ± 2	11 ± 3	13 ± 1	10 ± 1	9 ± 1	10 ± 3	9 ± 2
8	79 ± 3	70 ± 5	76 ± 2	13 ± 3[a]	11 ± 2[a,b]	7 ± 1*[b]	9 ± 2[b]	19 ± 3*[a]	17 ± 2*[a]

Note. Data are mean ± SE. Different letters in the same row mean that values are significantly different among groups at $p < 0.05$. *, Significantly different from 0 week value at $p < 0.05$ by paired Student's t test.

glucose levels in either age group compared to controls. During the OGGT in the felodipine groups, there was no difference from controls in the younger rats; however, in the older rats, there was some improvement in glucose tolerance.

There is controversy in the literature on actions of CCB on glucose and insulin metabolism. Results may vary according to conditions of subjects, experimental protocol, as well as class of CCB. Treatment with the dihydropyridine class of CCB seems to either improve or have no effect on glycemic control. No effect of felodipine or isradinpine on response during OGGT was observed in patients with NIDDM (17, 36, 37). In obese and nonobese hypertensive patients, nitrendipine therapy did not change serum insulin levels or glucose removal rate after intravenous glucose load (38, 39). In contrast, nifedipine improved the glycemic control by lowering fasting glucose levels as well as improving both glucose and insulin responses to OGGT in obese female SHHF rats (1). In the current study, improved glucose tolerance by felodipine was dependant on the age of the obese female SHHF rat.

From our observations and those of others, it appears that verapamil may cause a decrease in blood glucose levels; however, this may be accompanied by some form of insulin resistance. Verapamil treatment of obese Zucker rats for 4 weeks increased hyperinsulinemia without altering the glucose level (40). However, verapamil plus trandropril treatment significantly improved glucose tolerance and insulin levels in response to a glucose load in these studies (40). This improvement was associated with increased skeletal muscle glucose transport activity, GLUT-4 glucose transporter protein, hexokinase activity, and citrate synthase activity.

Lipid Metabolism. The effect on lipid metabolism depends on the CCB used. Plasma triglycerides and cholesterol progressively increase with age in obese female SHHF rats. Both verapamil and felodipine treatment decreased plasma triglycerides in older rats but had less effect on the young group. In contrast, verapamil and felodipine had opposite effects on plasma cholesterol. Verapamil increased cholesterol in the 6-month-old rats but had less effect on the older female SHHF group. A similar effect on cholesterol has been observed previously (16). Felodipine treatment had no effect on cholesterol in 6-month-old rats, but significantly lowered it in older rats. In a previous study, nifedipine also lowered triglycerides but had no effect on cholesterol in 9-month-old obese female SHHF rats (1).

Felodipine- and verapamil-treated SHHF rats had higher HDL, and felodipine had lower LDL lipoprotein percentages as compared to control rats. These effects may be mediated by CCB-induced alterations of lipoprotein metabolism (41–44). Isradipine, a dihydropyridine CCB, increased HDL cholesterol and decreased LDL and total cholesterol in elderly hypertensive patients (45). In contrast, no change in triglycerides or total and HDL cholesterol in the blood was induced by nitredipine therapy in hypertensive patients with or without obesity (38, 39). These changes in lipoprotien fractions may be mediated, in part, by enhanced uptake of LDL (42, 44, 46) and increased receptor-mediated endocytosis of LDL by an increase in the number of LDL receptors (43).

Conclusion

This study with obese female SHHF rats, demonstrates that two different classes of CCB, verapamil and felodipine, produce quite different responses and that some of these responses are age dependent. From our results, and in agreement with other investigators, it would appear that felodipine and other dihydropyridine CCB produce a more favorable outcome when compared to verapamil. Felodipine decreased body weight and fat mass while improving insulin resistance. Verapamil also caused weight loss in this study and under most circumstances, the loss of body weight in obesity would be considered a beneficial effect. However, since weight loss with verapamil was also associated with an impairment of glycemic control and with earlier development of CHF (22), this would negate any potential positive effect of weight loss on metabolism. Our study would seem to indicate that obese patients with a positive family history of CHF could exhibit similar problems with verapamil.

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