# Mechanisms in the pressor effects of hepatic portal venous fatty acid infusion

ROGER J. GREKIN, CRAIG J. DUMONT, ALAN P. VOLLMER, STEPHANIE W. WATTS, AND R. CLINTON WEBB
*Endocrinology Section and Department of Physiology, Veterans Affairs Medical Center and the University of Michigan, Ann Arbor, Michigan 48105*

**Grekin, Roger J., Craig J. Dumont, Alan P. Vollmer, Stephanie W. Watts, and R. Clinton Webb.** Mechanisms in the pressor effects of hepatic portal venous fatty acid infusion. *Am. J. Physiol.* 273 (*Regulatory Integrative Comp. Physiol.* 42): R324–R330, 1997.—Portal venous infusion of oleate solution has pressor effects. We have examined efferent mechanisms, measured the response to sustained infusion, and determined the effect of linoleate. Eight conscious animals received concurrent infusions of prazosin or vehicle with portal venous infusion of oleate. Oleate alone increased mean arterial pressure from 109.0 ± 4.1 to 123.0 ± 5.8 mmHg ($P$ = 0.02), whereas no increase in blood pressure occurred when oleate was infused with prazosin. In 10 rats, concurrent infusion of losartan had no effect on the pressor activity of portal oleate infusion. Twenty-two animals received portal oleate or vehicle as a continuous infusion for 7 days. Mean arterial pressure (126.1 ± 2.0 vs. 107.8 ± 2.6 mmHg, $P <$ 0.001) and heart rate (383 ± 5 vs. 366 ± 5, $P$ = 0.0257) were increased in oleate-infused animals. No differences in plasma fatty acids, glucose, insulin, pressor hormones, liver enzymes, or in vitro arterial pressor responsiveness were observed. Portal venous infusion of linoleate increased arterial pressure by 12.2 ± 3.2 mmHg ($P$ = 0.033). These results indicate that α-adrenergic activity is necessary for the acute pressor effects of portal oleate, that sustained portal oleate infusion results in persistent blood pressure elevation, and that other long-chain fatty acids besides oleate have pressor effects.

hypertension; obesity; sympathetic activity; angiotensin

IN A PREVIOUS STUDY, we reported that short-term infusion of sodium oleate into the hepatic portal vein of conscious rats increased arterial blood pressure (5). Infusion of the same amount of oleate into a femoral vein also increased blood pressure, but to a lesser degree. The pressor response to portal oleate infusion was associated with tachycardia and an increase in plasma levels of corticosterone, epinephrine, and norepinephrine, suggesting that sympathetic activation played a role in the effect. In that report, we proposed that chronic increases in portal venous fatty acid levels contribute to the development of hypertension in individuals with visceral obesity.

In this study, we have examined the mechanisms involved in the pressor effects of portal venous fatty acid infusion. Studies have been performed to evaluate the roles of the sympathetic nervous system, the renin-angiotensin system, and the vasculature in the response. Sustained infusions of oleate have been carried out to determine whether a long-term effect is present. Infusions of sodium linoleate have been tested to assess the specificity of the pressor effect.

## METHODS

*Animals.* Male Sprague-Dawley rats (Charles River, Cambridge, MA) weighing 350–450 g were studied. Animals were prepared for study by placement of catheters in a jugular vein, a mesenteric vein, and a carotid artery using inhaled methoxyflurane anesthesia. The mesenteric vein catheter was advanced until its tip was positioned in the portal vein. The three catheters were tunneled subcutaneously to the top of the head, fixed to the skull, and brought to the top of the cage as previously described (5). Carotid catheters were filled with an 80% sucrose solution. Venous catheters were infused with heparinized saline at 2.7 μl/min.

*Effects of prazosin and losartan.* Eight rats were used to study the effect of the $\alpha_1$-adrenergic receptor antagonist prazosin on the pressor effect of portal oleate infusion. Rats were studied on three separate days. Each day began with a 30-min baseline period. This was followed by a 3-h jugular venous infusion, either prazosin at 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or its vehicle, 5% dextrose in water, at 5 μl/min. A concurrent portal infusion was administered at 26 μl/min during the second hour. This consisted of either 10 mM sodium oleate or 0.45% saline. The infusions were conducted in the following combinations: vehicle + oleate, prazosin + oleate, and prazosin + saline. The order of study was randomized among animals. Five additional animals were studied to determine the effectiveness of $\alpha_1$-adrenergic blockade with prazosin. These animals received an intravenous infusion of phenylephrine, 12.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min. After return of blood pressure to basal levels, prazosin was infused at 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 45 min. Phenylephrine was reinfused during the last 15 min of prazosin infusion.

To assess the role of the renin-angiotensin system, 10 additional rats underwent a similar protocol using the $AT_1$ receptor antagonist losartan in place of prazosin. Rats were studied on two occasions, once during a 3-h infusion of losartan at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and once during a 3-h infusion of 0.45% saline. During each study day, 10 mM sodium oleate was infused into the portal vein at 26 μl/min during the second hour. At the end of the protocol, four of these rats were studied on a third day to evaluate the effectiveness of the angiotensin II receptor blockade by losartan. After baseline readings, angiotensin II was infused at 16 $ng \cdot kg^{-1} \cdot min^{-1}$ into the jugular vein for 20 min. After a return to basal blood pressure levels, losartan, 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, was infused into the jugular vein. Angiotensin II was then infused a second time, commencing after 30 min of losartan infusion.

Throughout each study, mean arterial pressure and heart rate were monitored using a Grass polygraph and LabView diagnostic software. Blood pressure and heart rate were recorded at 1-min intervals. Mean levels for each 30-min period were calculated.

At the end of the study, each animal was examined to ensure that catheter placement was unaltered and that internal damage had not been sustained.

*Sustained oleate infusion.* Twenty-two rats were studied in this protocol. Initial preparation consisted of placement of a

portal venous catheter as described above. A second catheter was placed in the subcutaneous tissues of the neck. Both catheters were tunneled to the top of the head, fixed with dental acrylic, and brought to the top of the cage.

Three days after surgery, portal venous infusion was begun. Eleven animals received a continuous infusion of 10 mM sodium oleate in 0.45% saline (pH = 9.86), and 11 animals received 0.45% saline alone. The infusion rate of oleate was adjusted in each animal to find the highest rate that was not associated with neurological symptoms. As reported earlier, some animals develop stretched-out posture changes during portal oleate infusion (5). Discontinuation of the infusion results in rapid resolution of the posture change. Rates of infusion ranged from 3.5 to 26 $\mu$l/min. For each animal, the infusion rate administered was not associated with altered posture, change in food intake, or other evidence of adverse effects. Eleven rats received vehicle administration at a rate of 14 $\mu$l/min. All infusions were carried out for 7 days.

On the fifth day of infusion, animals were anesthetized with methoxyflurane, and the catheter in the neck was placed into the carotid artery. On the seventh day of infusion, blood pressure and heart rate were monitored over a 2-h period.

After completion of blood-pressure measurement, plasma was withdrawn through the carotid catheter for analysis of norepinephrine, epinephrine, renin activity, corticosterone, glucose, insulin, free fatty acids, aspartate amino transferase (AST), alanine amino transferase (ALT), and alkaline phosphatase. Animals were then killed with an arterial injection of pentobarbital sodium (60 mg/kg). All studies were approved by the Animal Care Committee of the Ann Arbor Veterans Affairs Medical Center.

*Isolated tissue preparation.* Superior mesenteric arteries were removed from four control and four oleate-treated animals for vascular reactivity studies. Arteries were placed in physiological salt solution (PSS), gently cleaned of extraneous tissue, and cut into intact helical strips (0.7 × 10 mm). Both ends of the helical strips were tied with surgical silk. Once the strip was placed in a 50-ml isolated organ bath, one end of the preparation was tied to a stationary stainless steel rod and the other to a transducer for measurement of isometric contractile force. Arteries from an oleate-infused rat and a control rat were placed in the same organ bath. At all times, tissues were bathed in PSS, kept at 37°C, and aerated with 95% $O_2$-5% $CO_2$. The composition of PSS was (in mM) 130 NaCl, 4.7 KCl, 1.18 $KH_2PO_4$, 1.17 $MgSO_4 \cdot 7H_2O$, 1.6 $CaCl_2 \cdot 2H_2O$, 14.9 $NaHCO_3$, 5.5 dextrose, and 0.03 $CaNa_2$-EDTA. Strips were allowed to equilibrate for 60–90 min at 600 mg of tension, and the presence of endothelium was confirmed by the ability of acetylcholine ($10^{-7}$ M) to relax phenylephrine ($10^{-6}$ M)-contracted tissues (percent relaxation with endothelium = 58 ± 11%). Tissues were challenged with KCl (100 mM) before initiation of the experiment. Cumulative concentration-response curves to phenylephrine ($10^{-9}$–$10^{-5}$ M) and 5-hydroxytryptamine ($10^{-9}$–$10^{-5}$ M) were generated. To test the G protein activator aluminum sulfate, 50 $\mu$M aluminum was incubated with mesenteric arteries for 10 min, followed by cumulative additions of sodium fluoride (0.25–8 mM). Each concentration of sodium fluoride was allowed to incubate 20 min before addition of the next concentration. When the relaxant effects of acetylcholine were investigated, the tissues were contracted with phenylephrine (half-maximal effective concentration), and acetylcholine ($10^{-9}$–$10^{-5}$ M) was added in a cumulative fashion.

*Portal linoleate infusion.* Six rats were studied to determine the effects of sodium linoleate. Animals were prepared surgically with placement of portal venous and carotid catheters as described above. After recovery from surgery, they were studied on 2 separate days. On 1 day, 10 mM sodium linoleate in 0.45% saline (pH = 9.87) was infused into the portal vein at a rate of 26 $\mu$l/min for 1 h. On a second day, 0.45% saline was infused. The order of infusion was randomized among animals. Blood pressure and heart rate were recorded during a 1-h basal period, 1 h of infusion, and a 1-h recovery period.

*Analytic methods.* Plasma levels of insulin, renin activity, aldosterone, and corticosterone were measured by radioimmunoassay. Insulin was measured with antibody purchased from Linco Research, renin activity with a kit purchased from DuPont, and aldosterone and corticosterone with kits from Diagnostic Products. Epinephrine and norepinephrine were measured using a radioenzymatic method. Free fatty acids were measured enzymatically with a kit purchased from Wako Chemicals, and glucose, triglycerides, AST, ALT, and alkaline phosphatase with Ektachem slides (Eastman Kodak).

*Statistical analysis.* All values are expressed as means ± SE. For prazosin, losartan, and linoleate experiments, mean blood pressures were calculated for each 30-min time period. Comparisons between groups and changes over time were made using analysis of variance for two repeated measures assessing the effects of both treatment and time. In addition, paired *t*-tests with Bonferroni protection were used to compare responses at 60 min of infusion. For studies on sustained oleate infusion, comparisons between groups were performed using unpaired *t*-tests.

## RESULTS

*Prazosin and losartan.* Figure 1 shows blood pressure responses to combined infusions using prazosin, oleate, and their vehicles. Blood pressure increased from 109.0 ± 4.1 to 123.0 ± 4.8 mmHg during oleate infusion when infused in conjunction with vehicle. When infused concurrently with prazosin, oleate failed to produce a significant rise in blood pressure. When considering the last five time points for the three data sets, there is a treatment effect ($P = 0.02$) but no time effect ($P = 0.06$). An increase in heart rate occurred during infusion of prazosin on both occasions. There

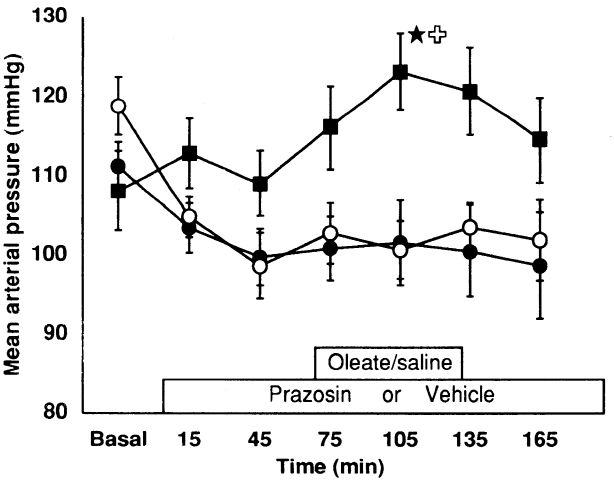


Fig. 1. Response of mean arterial pressure to portal venous infusion of oleate and saline during concurrent prazosin infusion. ●, Prazosin + oleate; ○, prazosin + saline; ■, vehicle + oleate. ★$P < 0.05$ compared with basal; cross, $P < 0.05$ compared with prazosin + saline and prazosin + oleate.

was no significant change in heart rate during oleate infusion.

Infusion of phenylephrine resulted in an increase in mean arterial pressure of 30.8 ± 2.0 mmHg. When phenylephrine infusion was repeated during concurrent infusion of prazosin, pressure rose by only 2.0 ± 1.4 mmHg ($P < 0.001$ compared with phenylephrine alone).

Figure 2 shows blood pressure responses for the losartan experiments. Oleate infusion was associated with a rise in blood pressure from 109.9 ± 3.8 to 121.0 ± 5.8 mmHg when infused with vehicle. A similar rise resulted during infusion of oleate when administered with losartan. In this case, blood pressure increased from 113.5 ± 3.8 to 125.7 ± 3.0 mmHg. There was no significant difference between the two interventions with regard to time or treatment. There were no significant changes in heart rate during either infusion.

Testing on the third day of study demonstrated that losartan was effective in blocking the pressor effect of angiotensin II. The rise in blood pressure was significantly greater after angiotensin II infusion alone (8.8 ± 1.4 mmHg) than after angiotensin II plus losartan (1.8 ± 1.2 mmHg, $P = 0.002$). During losartan infusion, the blood pressure after angiotensin II infusion was not significantly different from basal.

*Sustained infusion.* One animal that received oleate infusion had marked hypotension, with a mean arterial pressure of 76.9 mmHg. This animal was dropped from the analysis. In the remaining 21 animals, mean arterial pressure after 7 days of portal venous oleate infusion was elevated compared with that seen in rats receiving vehicle (126.1 ± 2.0 vs. 107.8 ± 2.6 mmHg, $P < 0.001$). These results are depicted in Fig. 3. The degree of blood pressure elevation did not vary with the rate of oleate infusion (Fig. 4). Heart rate was also increased in oleate-infused animals compared with controls (383 ± 5 vs. 366 ± 5 beats/min, $P = 0.0257$, Fig. 5). There was no difference between control and oleate-infused animals with regard to plasma levels of fatty acids, glucose, insulin, or pressor hormones or in liver function tests (Table 1). There was also no difference in vascular responsiveness in vitro between vessels from oleate-treated rats and controls for any of the substances tested (Fig. 6).

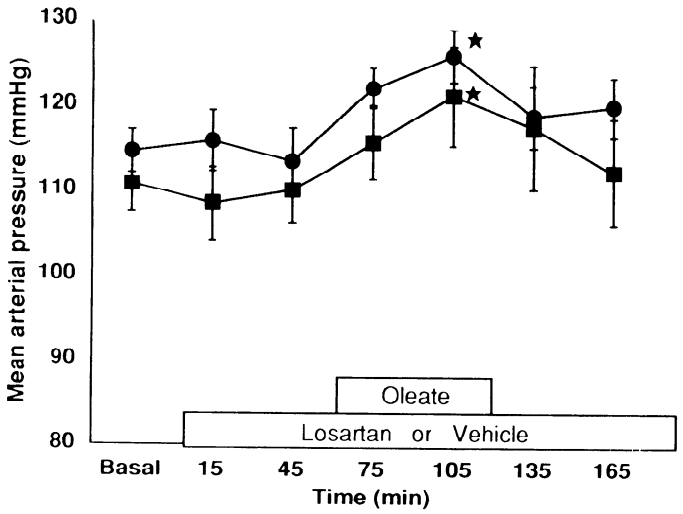


Fig. 2. Response of mean arterial pressure to portal venous infusion of sodium oleate during concurrent infusion of losartan (●) or saline (■). ★$P < 0.05$ compared with basal.

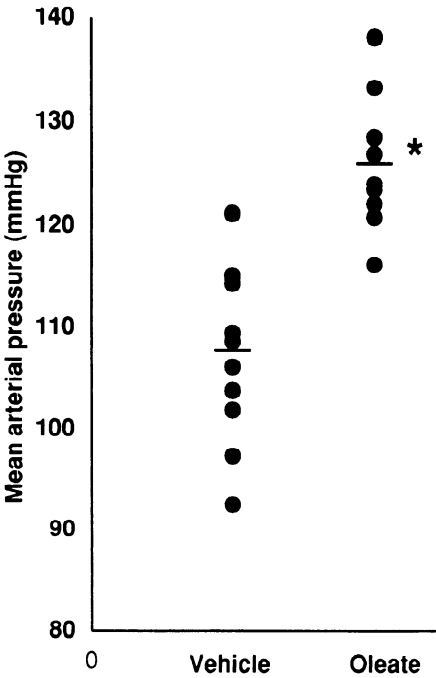


Fig. 3. Mean arterial pressure after portal venous infusion of sodium oleate or vehicle for 7 days (★$P < 0.001$).

*Linoleate.* During infusion of sodium linoleate into the portal vein, blood pressure was significantly increased after 60 min of infusion compared with basal ($P = 0.033$) and compared with levels during vehicle infusion ($P = 0.023$, Fig. 7). Heart rate did not change significantly during either infusion. None of the animals receiving linoleate infusion developed the stretched-out posture response that has been observed during oleate infusion.

## DISCUSSION

Obesity is an important risk factor for hypertension (8). More than one-half of hypertensive patients are

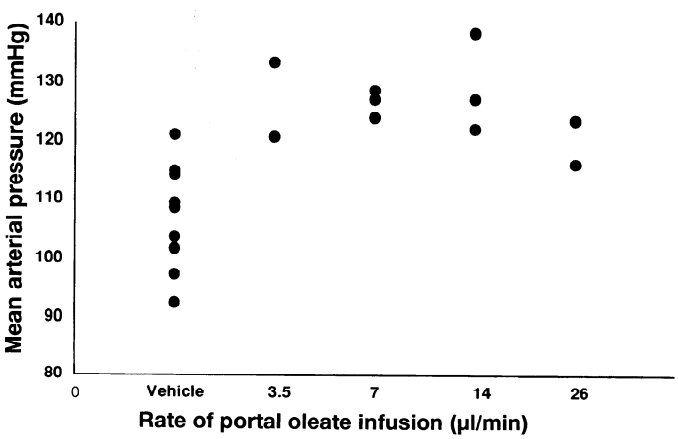


Fig. 4. Mean arterial pressure after portal venous infusion of sodium oleate or vehicle for 7 days.

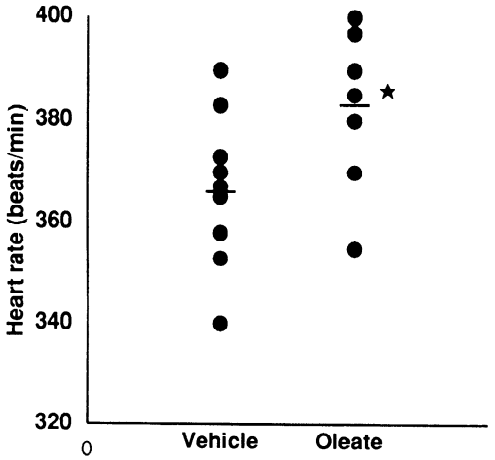


Fig. 5. Heart rate after portal venous infusion of sodium oleate or vehicle for 7 days ($\star P < 0.05$).

overweight (13), and hypertension is several times as common among overweight subjects as among normal-weight subjects (2). Blood pressure is directly correlated with body weight among both normotensive and hypertensive individuals (8, 13, 26). Experimental dietary obesity increases blood pressure in rats and dogs, and weight loss reduces blood pressure in obese individuals (18–20, 24). Among obese individuals, abdominal or upper body obesity is associated with a higher incidence of hypertension than is lower body obesity (6, 11). Studies using computed tomography indicate that these risks are primarily related to the amount of visceral fat rather than to abdominal subcutaneous fat (17). On the basis of our observations with portal oleate infusions, we have proposed that individuals with visceral obesity are likely to have increased portal fatty acid levels and that the pressor response to increased portal venous fatty acid levels plays a role in the relationship between visceral obesity and hypertension.

In our previous report (5), we proposed that an increase in portal venous fatty acid delivery to the liver is responsible for the hypertension that is associated with visceral obesity. This hypothesis argues that increases in visceral fat mass result in corresponding increases in the total amount of nonesterified fatty acids (NEFA) released into the portal venous drainage. Although no direct measurements of portal venous fatty acid levels are available in lean and obese humans, there is evidence supporting the suggestion that increased fat mass results in increased plasma NEFA levels (9, 22). This might be predicted, because a given plasma insulin level would be expected to suppress lipolysis equally in each fat cell. As the mass of fat cells increases, summation of the products of lipolysis from each fat cell would cause increased total NEFA release for the same level of circulating insulin. Because insulin resistance is commonly associated with visceral obesity, NEFA release is actually likely to be greater than would be predicted by fat mass alone (1). If this analysis is correct, individuals with visceral obesity would be expected to have increased portal venous NEFA levels. Evidence that increased NEFA concentration and turnover is present in obese hypertensives compared with obese normotensives further supports the conclusion that NEFA metabolism may be important in obesity hypertension (3).

Table 1. *Effect of chronic portal oleate infusion on plasma measurements*

| | Oleate | Vehicle |
|---|---|---|
| Free fatty acids, nmol/l | 183 ± 23 | 165 ± 19 |
| Glucose, mg/dl | 164 ± 6 | 171 ± 4 |
| Insulin, μU/ml | 33.1 ± 7.6 | 28.0 ± 2.7 |
| Renin activity, $ng \cdot ml^{-1} \cdot h^{-1}$ | 11.8 ± 1.5 | 15.6 ± 1.9 |
| Aldosterone, pg/ml | 377 ± 60 | 396 ± 47 |
| Corticosterone, ng/ml | 233 ± 34 | 295 ± 20 |
| AST, U/l | 120 ± 18 | 125 ± 23 |
| ALT, U/l | 47 ± 4 | 45 ± 2 |
| Alkaline phosphatase, U/l | 238 ± 27 | 303 ± 52 |
| Norepinephrine, pg/ml | 691 ± 104 | 760 ± 148 |
| Epinephrine, pg/ml | 158 ± 51 | 252 ± 123 |

Values are means ± SE. AST, aspartate amino transferase; ALT, alanine amino transferase.

Our initial observation that portal venous infusion of sodium oleate increases blood pressure is consistent with the argument that increases in portal NEFA could mediate the hypertension that occurs in visceral obesity. In that study, we observed prompt increases in blood pressure during both portal and femoral oleate infusion, but the magnitude of the pressure rise was significantly greater during portal infusion than during femoral infusion. The acute increases in blood pressure were associated with mild increases in heart rate and increases in plasma levels of epinephrine, norepinephrine, and corticosterone.

The mechanism by which portal venous infusion of oleate increases blood pressure has not been established. In the present study, we have explored the involvement of the adrenergic nervous system and the renin-angiotensin system as possible mediators of the pressor response. We have also performed in vitro studies using isolated vessels to explore the possibility that the increased blood pressure is associated with changes in vascular reactivity. Concomitant infusion of prazosin, an $\alpha_1$-adrenergic blocker, completely abolished the pressor response to portal venous oleate infusion in this study. This result suggests that efferent adrenergic activity plays a central role in the pressor response. Although it is possible that α-adrenergic activity is permissive rather than causal in this setting, it seems more likely that the pressor response is directly mediated by stimulation of adrenergic nerves.

Applying this result to our underlying hypothesis would suggest that the hypertension associated with visceral obesity is also mediated by increased adrenergic activity. Multiple studies of adrenergic activity in obesity have yielded conflicting results. Increased norepinephrine levels have been measured in obese rats and dogs (7, 14, 21, 27), and Kassab et al. (10) demonstrated that renal denervation prevented the development of obesity-induced hypertension in dogs, suggesting that efferent sympathetic nerve activity plays an important role in the development of hypertension.

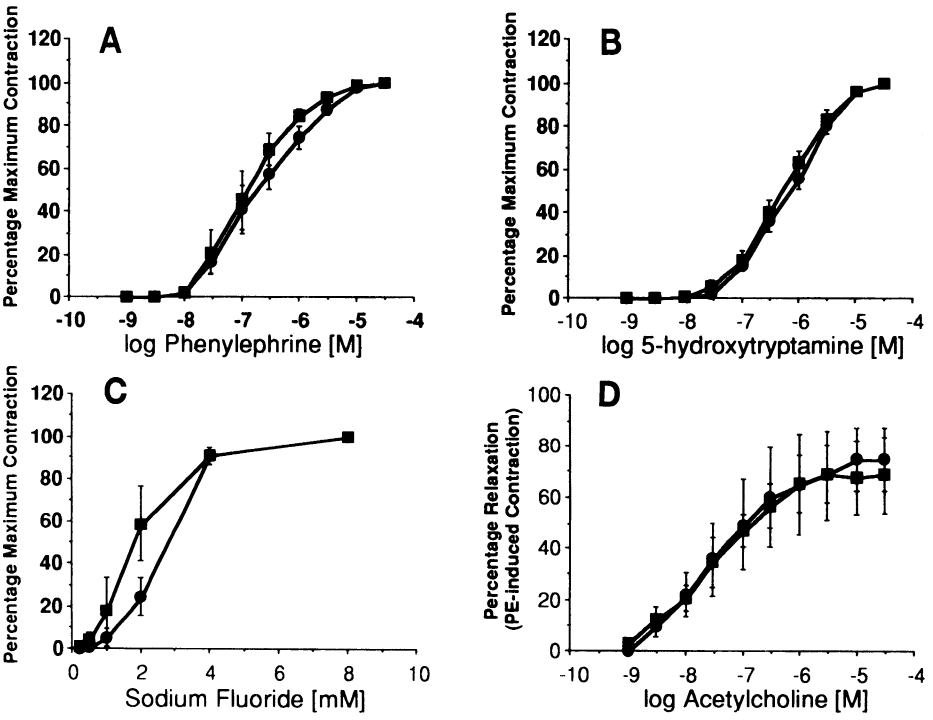


Fig. 6. Cumulative concentration-response curves of the $\alpha_1$-adrenergic agonist phenylephrine (*A*; normotensive, $n = 4$; oleate hypertensive, $n = 4$), 5-hydroxytryptamine (*B*; normotensive, $n = 4$; oleate hypertensive, $n = 5$), G protein agonist aluminum fluoride (*C*; normotensive, $n = 4$; oleate hypertensive, $n = 5$), and acetylcholine (*D*; normotensive, $n = 4$; oleate hypertensive, $n = 4$) in the superior mesenteric arteries from sham (●) and chronic oleate-hypertensive rats (■). PE, phenylephrine.

Measurements of norepinephrine in obese human subjects have been high, low, and normal (28), but recent studies using direct measurement of sympathetic nerve activity have found that body fat is a major determinant of muscle sympathetic nerve discharge in man (23). Spraul et al. (25) also found a direct correlation between percent body fat and muscle sympathetic nerve activity in Caucasians, but not in Pima Indians. These latter studies suggest that increased efferent adrenergic activity could be important in the genesis of obesity-related hypertension.

The failure of losartan to affect the pressor response to portal oleate appears to exclude a role for the renin-angiotensin system in the pressor response. Measurements of renin activity have been normal in obese individuals (21), but Licata et al. (12) reported that responsiveness to saline suppression was blunted.

The mechanism by which an increase in portal fatty acid levels might trigger an increase in efferent $\alpha$-adrenergic activity remains to be determined. Stimulation of afferent nerves from the liver would be an attractive explanation. Alterations in hepatic glucose and osmolality induce altered vagal afferent nerve traffic, indicating that metabolic receptors in the liver are capable of inducing neural reflexes (4, 15). A single study by Orbach and Andrews (16) reported that perfusion of the hepatic artery with long-chain fatty acids increased vagal activity. Interestingly, infusion of a short-chain fatty acid in that study did not trigger increased activity. A humoral afferent mechanism could also trigger efferent adrenergic activity. At this time, we have no evidence for such a humoral mechanism.

Sustained infusion of sodium oleate into the portal vein resulted in an increase in mean arterial pressure of 18 mmHg compared with vehicle control animals. This result indicates that the pressor effect of portal fatty acids is sustained and could play a role in long-term hypertensive states. Infusion was associated with a modest increase in heart rate, but, unlike the response to acute infusion, epinephrine, norepinephrine, and corticosterone were not elevated after a 1-wk infusion. There were also no changes in plasma levels of glucose, insulin, fatty acids, insulin, or aldosterone or in liver function tests. At this time, the mechanism of sustained blood-pressure increases is not clear. It is possible that modest increases in efferent adrenergic activity sustain the pressure rise but are not sufficient to affect plasma norepinephrine levels, although our failure to find altered vascular reactivity makes this possibility less likely. It is also possible that an unrelated mechanism mediates the chronic effect. Further

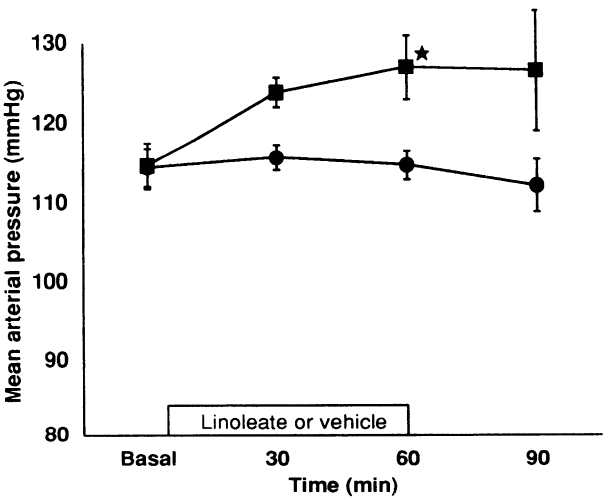


Fig. 7. Response of mean arterial pressure to portal venous infusion of linoleate (■) or vehicle (●). ★$P < 0.05$.

studies in chronically infused animals will be necessary to elucidate these mechanisms.

Several of the rats receiving sustained sodium oleate infusion developed a stretched-out posture response during infusion. This was also observed in a minority of animals studied during acute infusion. The response usually occurred during the first 2–3 h of infusion and is characterized by extension of the extremities and neck. Animals appear to lose equilibrium and have a tendency to roll onto one side. No evidence of labored breathing or discomfort has been observed during this response. In each instance when it has occurred, we have discontinued the infusion, and animals have appeared to recover fully within 5 min. After recovery, infusions were started at a lower dose, and successively lower rates of infusion were used until a rate was identified that was not associated with the postural response. The nature of the response suggests a neurally mediated reflex, perhaps also mediated through hepatic afferent nerves. Supporting this suggestion is the fact that we have never observed the stretched-out postural response in animals receiving femoral venous infusion of sodium oleate.

The blood pressure response did not differ in response to differing infusion rates of oleate. A possible explanation of this finding could be that the lowest rate of infusion represents a maximal effective dose. It seems more likely, however, that animals receiving the lowest infusion rates were those that were most sensitive to the effects of portal oleate, because infusion rates were determined by finding the highest rate that did not cause a stretched-out posture.

Failure of the oleate infusion to increase plasma fatty acid levels is not surprising, because the amounts of oleate infused ranged from 0.2 to 2% of endogenous portal oleate delivery (5). We presume that the observed effects on blood pressure are due to increases in unbound fatty acids.

The observation that portal infusion of sodium linoleate also raises blood pressure indicates that the pressor response is not specific for oleate and may occur with many or all long-chain fatty acids. Linoleate effects may also be mediated by conversion to eicosanoids, which could have important vascular effects. Studies with saturated fatty acids such as palmitate or stearate would be of interest, but we have been unable to prepare aqueous solutions of these substances.

The present studies lend support to the hypothesis that increased portal fatty acids mediate the hypertension associated with visceral obesity. They provide evidence that the α-adrenergic nervous system is involved in the response to acute infusions of oleate and indicate that chronic increases in portal fatty acids could cause sustained hypertension. They also demonstrate that portal linoleate infusion has pressor effects similar to those of portal oleate infusion. Further studies on the mechanisms of portal fatty acid-induced hypertension will be required to determine whether adrenergic mechanisms are involved in the pressor response to chronic infusion and to identify the afferent mediator of the effect.

*Perspectives*

These studies suggest the presence of hepatic fatty acid "receptors" that respond to an increased fatty acid load. These receptors might be located in hepatocytes or in hepatic afferent nerve terminals. The rapid response to fatty acid infusion would be most compatible with a membrane-bound receptor mechanism that initiates an afferent neural signal to increase efferent sympathetic activity.

It would be of interest to identify a physiological role for the observed responses. We speculate that increased sympathetic activity in response to fatty acid activation of hepatic receptors may be part of a homeostatic response directed toward preventing increased fat deposition during times of caloric excess. In this instance, organisms might respond to states of fat excess by increasing sympathetic activity, with a resultant increase in metabolic activity. If this were true, the observed reflex could serve to protect organisms from excessive weight gain during periods of excess fat intake. Obese individuals, in whom compensatory mechanisms had failed to prevent obesity, would have chronic sympathetic activation and an increased risk of hypertension.

Address for reprint requests: R. J. Grekin, 2215 Fuller Rd., Ann Arbor, MI 48105.

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