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BLOOD ACETALDEHYDE AND THE ETHANOL-INDUCED INCREASE IN SPLANCHNIC CIRCULATION

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Abstract—Acute oral administration of ethanol significantly increases (50–60%) portal blood flow to the liver. As earlier studies have indicated that this effect is maximal at concentrations of ethanol that saturate the alcohol dehydrogenase (ADH) system and is blocked by the ADH inhibitor 4-methylpyrazol, we investigated the possible role of acetaldehyde, a product in the ADH reaction, as a mediator of this effect. In the first series of experiments it was shown that, contrary to expectations, cyanamide administration prior to alcohol suppressed fully the effect of ethanol on portal blood flow without altering it in the absence of ethanol [ethanol = 69.5 ± 5.6; ethanol + cyanamide 42.9 ± 2.4; control = 43.0 ± 3.0; cyanamide = 55.1 ± 3.7 $ml \cdot min^{-1} \cdot (kg\ body\ wt)^{-1}$]. Arterial blood concentrations of acetaldehyde were elevated from 3.6 ± 0.3 μM in the presence of ethanol to 293 ± 48 μM in the presence of ethanol + cyanamide. Infusion of acetaldehyde either into the left ventricle, resulting in aterial blood acetaldehyde levels of 227 ± 77 μM, or into the portal circulation, resulting in arterial blood levels of 198 ± 40 μM, did not modify portal blood flow or splanchnic hemodynamics, nor the effect of ethanol *per se*. The combination of cyanamide + ethanol significantly reduced total peripheral resistance (from 28 ± 3 to 19 ± 2 $dyne \cdot cm \cdot sec^{-5}$), while neither ethanol or cyanamide *per se*, nor acetaldehyde affected total peripheral resistance. Data suggest that acetaldehyde is not involved in the ethanol-mediated increase in portal vein flow. Further studies indicate that the effects of cyanamide in suppressing the ethanol-induced increase in portal blood flow and in increasing total peripheral resistance appear to be related to an ethanol–cyanamide interaction which is independent of the acetaldehyde levels in the circulation.

Acute administration of ethanol is known to result in an increase in liver blood flow in several species of animals including humans [1–5]. This enhanced blood flow is due to an increase in portal vein blood flow [5]. It is suppressed by 4-methylpyrazole, a powerful inhibitor of alcohol dehydrogenase [6], and this suggests that ethanol metabolism mediates the augmentation in flow following ethanol administration [5]. The possibility arises that acetaldehyde, a product in the metabolism of ethanol, is involved in that hemodynamic response to alcohol.

While the reports on the direct effects of acetaldehyde on the splanchnic circulation have been contradictory, showing both vasodilatation and vasoconstriction [7–11], the administration of ethanol to animals pretreated with drugs that inhibit acetaldehyde dehydrogenase (disulfiram and cyanamide) leads to systemic vasodilatation [12, 13], suggesting a vasodilator role for acetaldehyde.

In this study, we investigated the role of acetaldehyde in the increased blood flow to the liver following ethanol administration. First, we conducted studies to determine whether the administration of an inhibitor of acetaldehyde dehydrogenase, cyanamide, would potentiate the effects of ethanol on liver blood flow. Second, we investigated the direct actions of infused acetaldehyde on the splanchnic circulation. The results provide no support for a role of acetaldehyde in the increase in hepatic blood flow induced by ethanol.

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METHODS

Male Sprague–Dawley rats (Charles River Breeding Laboratories, St. Constant, Quebec, Canada) weighing 250 ± 36 g (SEM) were used. The rats were housed in a temperature and humidity controlled environment and were fasted overnight with water *ad lib*. Ethanol (1 g/kg) was administered orally 1 hr before blood flow determinations in a volume of 1 ml/100 g body weight. Controls were given an equal volume of water by gavage.

Hemodynamic studies

Blood flow and cardiac output were measured by the microsphere method as we reported previously [5]. In brief, under ether anesthesia (the complete operation lasting 17–22 min), the left femoral artery was cannulated with polyethylene tubing. The right carotid artery was then cannulated, and the catheter was advanced into the left ventricle while the pressure was monitored. The cannulae were capped with rubber injection ports and tunnelled subcutaneously to the midback where they were brought out into the skin surface. The rats were allowed to wake up and recover for 2–3 hr prior to blood flow studies. During the experiments, rectal temperatures were maintained at 37 ± 0.6° with heating lamps.

In two groups of rats, following the insertion of femoral artery and left ventricular cannulae, a small laparotomy was performed. In the sham group, the liver was elevated and the omentum and small intestine were manipulated to expose the portal vein (no catheter inserted), after which the incision was closed and the rat allowed to wake up. In the portal vein group, the portal vein was exposed as above and a bevelled silastic catheter was inserted into the portal vein. The catheter was sutured into place, without occlusion of the portal vein, and was capped and tunnelled under the skin to the midback and brought out onto the surface. The rats were then allowed to wake up.

Liver blood flow experiments

Microspheres ($15 \pm 3\ \mu m$ diameter) labeled with either ^{46}Sc or ^{57}Co (New England Nuclear, Boston, MA) were used for blood flow determinations. The microspheres were mixed and diluted as described elsewhere [14] and were drawn up into polyethylene tubing for counting prior to injection. Initial counts were determined in a gamma counter (Nuclear Chicago, model 1185, Chicago, IL). The microspheres were injected into the left ventricle over a period of 20 sec using an infusion pump. Starting 10 sec before the infusion of microspheres, a reference blood sample of 1.5 ml was taken from the femoral artery over a period of 90 sec using a withdrawal pump. Ficoll (13%, 0.6 ml) was given for volume replacement after injection of the isotope as has been described [14], which prevented a fall in blood pressure due to blood withdrawal.

The rats were then killed and the heart, lungs, liver, kidneys, spleen, stomach, small intestine and large intestine were removed for counting.

Calculations

Cardiac output (CO) in ml per min per kg body weight was determined as follows:

$$CO = \frac{\text{net counts injected} \times \text{reference sample withdrawal rate}}{\text{netcounts in reference sample} \times \text{body weight}}$$

Organ blood flow rates (OBF) in ml per kg body weight were determined as follows:

$$OBF = \frac{\text{net counts in organ} \times CO}{\text{net counts injected}}$$

All flow rate calculations were based upon body weight and were expressed as ml per min per kg body weight. Early studies showed no difference in the conclusions derived when results were calculated in this form as opposed to blood flows expressed per gram organ.

Portal blood flow was determined indirectly using the sum of blood flow to the spleen, stomach, and small and large intestines. The pancreas and omentum, which cannot be readily isolated in the rat, were included with the stomach and intestinal flows. Hepatic artery flow was calculated from counts in the liver. Total liver blood flow was taken as the sum of the portal vein blood flow and hepatic artery blood flow.

Total peripheral resistance was calculated as: mean arterial pressure (mm Hg) $\times$ 80 $\div$ cardiac output and expressed as dyne · cm · sec^{-5}.

Experimental design

Effect of cyanamide on the ethanol-induced increase in liver blood flow. Thirty rats were divided into four groups of seven or eight animals each. In two of the groups, cyanamide (10 mg/kg) was infused intra-arterially in 1 ml of saline, while the other two groups were infused with an equal volume of saline. Ethanol (1 g/kg) was then administered to rats in One of the cyanamide and one of the saline groups. one hour later, cardiac output and organ blood flows were determined. Immediately following blood flow determinations, blood from the femoral artery was withdrawn for acetaldehyde and ethanol determination.

Effect of acetaldehyde on splanchnic hemodynamics. Forty-four rats were divided into four groups. Two groups received ethanol (1 g/kg) while the other groups received water. In one of the ethanol and one of the water groups, acetaldehyde, 240 mM in 5% dextrose, was infused into the left ventricle at a rate of 0.1 ml/min for 60 min. The other groups received 5% dextrose by the same method. Cardiac output and organ blood flow were determined at 60 min immediately after which blood samples were taken for acetaldehyde determina tions.

Effect of acetaldehyde infusion into the portal vein on splanchnic hemodynamics. Twenty-six rats with portal vein catheters were divided into four groups. Two groups received ethanol (1 g/kg) and two groups received water by gavage. Acetaldehyde, 240 mM, was infused into the portal vein at a rate of 0.1 ml/min for 60 min in one of the ethanol and one of the water groups. The remaining two groups were infused with 5% dextrose. Cardiac output and organ blood flow were determined at 60 min, and immediately afterwards blood samples were taken for acetaldehyde determinations.

To control for the effect of laparotomy, twenty-eight sham-operated rats received ethanol or water by gavage and acetaldehyde or dextrose by infusion into the left ventricle as described above. Cardiac output and organ blood flow were determined at 60 min.

Determination of blood ethanol and acetaldehyde levels

Blood samples were analyzed for ethanol and acetaldehyde by headspace gas chromatography. A 100-μl aliquot of blood was added to an Eppendorf tube (2 ml) containing 50 μl thiourea (12.5 mg/ml) and 850 μl perchloric acid (34 mg/ml). The tube which had been kept at 0° was vortexed and centrifuged. A 750-μl aliquot of the supernatant fraction was placed in a 20-ml vial, sealed before heating for 30 min at 65°, and then analyzed as described previously [15].

Table 1. Effect of cyanamide on ethanol-induced increase in liver blood flow

	Blood flow ($ml \cdot min^{-1} \cdot kg^{-1}$)			
	Control (7)	Cyanamide (7)	Ethanol (8)	Ethanol + Cyanamide (8)
Portal vein	43.0 ± 3.0	55.1 ± 3.7	69.5 ± 5.6*	42.9 ± 2.4†
Hepatic artery	11.0 ± 2.5	5.7 ± 1.4*	5.7 ± 0.7*	8.5 ± 1.7
Total liver	55.0 ± 5.1	60.0 ± 4.5	75.2 ± 5.5*	51.2 ± 2.9
Stomach	4.3 ± 0.4	4.2 ± 0.5	5.0 ± 0.8	3.6 ± 0.3
Spleen	4.4 ± 0.5	4.4 ± 0.7	6.5 ± 0.9	3.8 ± 0.4
Small bowel	27.1 ± 2.4	35.7 ± 2.3	43.1 ± 4.5*	24.2 ± 1.5
Large bowel	8.1 ± 1.0	10.0 ± 0.4	14.9 ± 1.3*	11.3 ± 1.2
Kidney	28.5 ± 1.4	25.6 ± 1.7	32.1 ± 3.4	27.6 ± 2.5
	Portal vein data as % of cardiac output			
	16.8 ± 2.2	19.1 ± 1.1	26.6 ± 1.4*	13.5 ± 1.2†

Analyses of variance and least significant difference were used to compare all groups. Data are mean ± SEM; the numbers in parentheses equal the number of animals.
* $P < 0.05$, compared to control animals.
† $P < 0.01$, compared to ethanol animals.

Determination of ethanol metabolic rate

The rate of ethanol metabolism was determined in a separate group of twelve rats receiving an intraperitoneal injection of 2.5 g/kg ethanol, given as a 12.5% (w/v) solution in 0.9% NaCl. Samples (100 μl) of capillary blood were taken from the cut tails of the animals, using glass microsampling pipettes at 2, 3, 4, 5, and 6 hr after the administration of ethanol. Six animals received ethanol alone and six received ethanol plus 10 mg/kg of cyanamide as described above. The linear portion of the ethanol concentration versus time profile of each rat was extrapolated to the abscissa. This value, in hours, was divided into the dose of ethanol administered to give the metabolic rate of ethanol in mg per kg body weight per hr.

Data analysis

Data are presented as means ± SEM. Values in percentage were subjected to arcsin transformation. Significance was considered to be $P < 0.05$. All data were subjected to analysis of variance with intergroup differences being determined by the least significant method [16].

RESULTS

Effect of cyanamide on the ethanol-induced increase in liver blood flow

Ethanol increased portal vein blood flow and total liver blood flow by 58 and 36%, respectively, as a result of an increase in intestinal blood flow (Table 1). There was a decrease in hepatic artery blood flow of 48%. In combination with ethanol, cyanamide completely inhibited, rather than enhanced, the ethanol-induced increase in blood flow. Portal vein blood flow, total liver blood flow, hepatic artery blood flow and renal blood flow in the ethanol plus cyanamide group were not different than control values (Tables 1 and 2). The cardiac output, mean arterial pressure and total peripheral resistance were not altered significantly in the alcohol group compared to controls (Table 2).

Cyanamide by itself did not alter portal vein blood flow, or the percentage of the cardiac output delivered to the portal circulation, but was accompanied by a decrease in hepatic arterial blood flow (Table 1). The cardiac output, mean arterial pressure, and total peripheral resistance were unaffected by cyanamide (Table 2). However, in the alcohol-plus-cyana-

Table 2. Cardiovascular effects of cyanamide and ethanol

	Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	Mean arterial pressure (mm Hg)	Total peripheral resistance ($dyne \cdot cm \cdot sec^{-5}$)
Control (7)	253 ± 26	90 ± 5	28 ± 3
Cyanamide (7)	268 ± 21	90 ± 3	26 ± 2
Ethanol (8)	263 ± 21	92 ± 6	31 ± 3
Ethanol + cyanamide (8)	332 ± 30	81 ± 7	19 ± 2*

Analyses of variance and least significant difference were used to compare all groups. Data are mean ± SEM; the numbers in parentheses equal the number of animals.
*$P < 0.05$, compared to controls.

Table 3. Effects of acetaldehyde infusion into the left ventricle on blood flow and cardiac output

Blood flow ($ml \cdot min^{-1} \cdot kg^{-1}$)	Control (11)	Acetaldehyde (17)	Ethanol (5)	Ethanol + Acetaldehyde (11)
Portal vein (PVF)	47.8 ± 4.2	44.6 ± 4.3	59.9 ± 4.8*	67.3 ± 4.6†
Hepatic artery	10.9 ± 2.0	11.5 ± 1.7	8.2 ± 2.8	9.7 ± 2.0
Total liver	58.6 ± 5.0	56.1 ± 3.7	68.1 ± 4.6*	77.1 ± 5.4†
PVF as % of cardiac output	19.8 ± 3	19.5 ± 2	30.4 ± 4†	25.7 ± 3*
Stomach	3.3 ± 0.2	2.6 ± 0.4	4.1 ± 1.1	4.0 ± 0.5
Spleen	8.4 ± 1.4	8.4 ± 1.1	7.9 ± 0.6	9.7 ± 1.0
Small bowel	26.5 ± 2.8	25.4 ± 2.5	34.8 ± 2.7†	36.6 ± 2.2†
Large bowel	9.5 ± 0.8	8.3 ± 0.8	13.1 ± 1.8*	17.0 ± 2.1*
Kidney	26.8 ± 2.4	29.8 ± 2.2	29.3 ± 2.1	36.0 ± 2.6*
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	241 ± 12	299 ± 14	197 ± 13	261 ± 17
Mean arterial pressure (mm Hg)	104 ± 10	111 ± 11	92 ± 6	91 ± 7
Total peripheral resistance ($dyne \cdot cm \cdot sec^{-5}$)	35 ± 9	42 ± 8	31 ± 3	32 ± 7

Data are mean ± SEM; numbers in parentheses equal the number of animals.
* $P < 0.05$, compared to controls.
† $P < 0.01$, compared to controls.

mide group, a significant decrease in total peripheral resistance was observed. Mean arterial pressure and cardiac output were not altered significantly in this group (Table 2). The percentage of cardiac output delivered to the splanchnic circulation was increased significantly by ethanol but was reduced markedly below control values in the ethanol-plus-cyanamide group (Table 1).

Cyanamide in the presence of ethanol increased arterial acetaldehyde levels from 3.6 ± 0.3 to 293 ± 48 μM. Acetaldehyde levels were not detectable in the absence of ethanol. Cynamide decreased the rate of ethanol metabolism by 22% (rate of ethanol metabolism in controls: 291 ± 3.4 $mg \cdot kg^{-1} \cdot hr^{-1}$; in cyanamide-treated animals: 227 ± 6.4 $mg \cdot kg^{-1} \cdot hr^{-1}$; $P < 0.001$).

Effect of acetaldehyde injection into the left ventricle on organ blood flow

The infusion of 240 mM acetaldehyde into the left ventricle at a rate of 0.1 ml/min resulted in blood acetaldehyde levels of 227 ± 77 μM in the arterial circulation and 94 ± 92 μM in the portal circulation. No effect of acetaldehyde was seen on the cardiovascular system, cardiac output, total peripheral resistance or mean arterial pressure even at arterial levels of more than 290 μM, the highest previously obtained with the combination of cyanamide plus ethanol. Likewise, acetaldehyde did not influence splanchnic hemodynamics; the blood flows were not different from controls (Table 3).

Experiments performed concomitantly showed

Table 4. Effect of acetaldehyde infusion into the portal vein (A) or left ventricle (B)

	Blood flow ($ml \cdot min^{-1} \cdot kg^{-1}$)			
	Control	Acetaldehyde	Ethanol	Ethanol + Acetaldehyde
(A)	(5)	(6)	(5)	(10)
Portal vein	37.1 ± 3.9	38.9 ± 1.9	51.4 ± 3.4*†	50.8 ± 2.0*†
Hepatic artery	12.2 ± 1.7	17.3 ± 2.1†	12.5 ± 2.9	17.4 ± 2.0†
Cardiac output	188 ± 13	217 ± 17	266 ± 27*	233 ± 6.0
Kidney	18.8 ± 2.7	23.7 ± 1.9	27.0 ± 1.6*	33.3 ± 3.4*
(B) Sham operated (acetaldehyde infused) into left ventricle	(7)	(6)	(5)	(10)
Portal vein	35.4 ± 2.5	44.9 ± 6.1	69.0 ± 7.1‡	61.2 ± 7.1‡
Hepatic artery	9.6 ± 2.3	6.0 ± 0.5	7.8 ± 2.6	8.7 ± 3.3
Cardiac output	185 ± 11	224 ± 31	263 ± 28*	251 ± 22*
Kidney	19.9 ± 1.0	25.2 ± 2.5	30.3 ± 1.9	34.1 ± 1.7

Data are mean ± SEM; The numbers in parentheses equal to the number of animals.
* $P < 0.05$, compared to controls.
† $P < 0.05$, compared to respective group sham-operated.
‡ $P < 0.01$, compared to controls.

that the infusion of acetaldehyde did not modify the ethanol-induced increase in portal and liver blood flows (Table 3).

Effect of acetaldehyde infusion into the portal vein on organ blood flow

The infusion of 240 mM acetaldehyde into the portal vein at a rate of 0.1 ml/min resulted in arterial levels of acetaldehyde of 198 ± 40 μM. Acetaldehyde had no effect on the cardiovascular parameters studied, the splanchnic circulation, or the renal hemodynamics (Table 4). Ethanol increased portal vein blood flow and total liver blood flow and also increased renal blood flow with no effect on hepatic artery flow. Acetaldehyde did not modify the effects of ethanol.

In a comparison of sham-operated rats with portal-vein-infused rats (Table 4), the presence of a catheter in the portal vein had effects on the hemodynamic response to both acetaldehyde and ethanol. In the acetaldehyde groups there was a significant increase in hepatic artery blood flow in the presence of the portal vein catheters compared to the sham-operated controls. In the groups receiving ethanol there was an attenuation of the portal vein blood flow response to ethanol. However, ethanol administration still resulted in a significant increase in portal vein blood flow (Table 4). The prior laparotomy and catheterization had no effect on basal hemodynamics and flows.

DISCUSSION

Earlier studies have indicated that the increase in portal blood flow induced by ethanol administration is independent of the blood ethanol levels at concentrations that "saturate" alcohol dehydrogenase [5] and is fully blocked by 4-methylpyrazole, an inhibitor of this enzyme [6]. The increase in liver blood flow induced by ethanol may, at least in part, compensate for the increased oxygen requirements of the liver following acute [4] or chronic [17] ethanol ingestion (for a review, see Ref. 18).

In the present study we have analyzed the possible role of acetaldehyde, the first product in the metabolism of alcohol, on the splanchnic hemodynamic effects of ethanol. The literature on the effects of acetaldehyde on liver blood flow is contradictory [7–11]. It has been claimed that acetaldehyde has a vasodilator action [7, 8] and that at high concentrations, such as those associated with the ethanol–cyanamide reaction, acetaldehyde relaxes both inervated and non-inervated blood vessels, inhibiting all neurohormonal agents from maintaining their constrictor responses [19]. The latter effect, however, has not been subsequently confirmed [10, 11]. The dose of cyanamide used in the present study (10 mg/kg) increased the arterial levels of acetaldehyde following ethanol administration from 3.6 ± 0.3 to 293 ± 48 μM. Contrary to what was expected, cyanamide administration resulted in a complete inhibition of the ethanol-induced increase in portal vein blood flow. Furthermore, acetaldehyde administration *per se* did not result in hemodynamic changes, independently of the route of administration, nor did it block the effects of ethanol on portal blood flow. These data indicate that blood acetaldehyde is unlikely to mediate the increase in liver blood flow induced by ethanol. In addition, they point to an effect of cyanamide in inhibiting the latter effect by a mechanism unrelated to the increase in blood acetaldehyde levels.

Our studies also suggest that the reduction in peripheral resistance obtained by the cyanamide–ethanol combination is not related to blood acetaldehyde levels, since they could not be reproduced by the administration of acetaldehyde alone at arterial concentrations similar to those obtained by administration of ethanol plus cyanamide. It should be noted that in our studies a reduction in peripheral resistance induced by ethanol plus cyanamide was not accompanied by a significant reduction in mean arterial pressure. A small increase in cardiac output was observed but this was not statistically significant.

If the effect of cyanamide on the ethanol-induced increase in portal blood flow is not the result of an increase in circulating acetaldehyde, it must result from another presently undetermined effect of cyanamide on splanchnic hemodynamics. Treatment with cyanamide resulted in a 22% decrease in the rate of ethanol metabolism. While this effect is much smaller than the inhibition induced by 4-methylpyrazole which at the doses used inhibits ethanol metabolism by 60–90% [20, 21], it still could theoretically have been sufficient to suppress the portal vein blood flow response to ethanol. Nevertheless, this mechanism is unlikely to be operative since the effect of cyanamide on the rate of ethanol metabolism has been attributed to the high concentrations of acetaldehyde that result from the inhibition of acetaldehyde dehydrogenase [22, 23]. If this mechanism were correct, a similar inhibition should also have been observed after the infusion of acetaldehyde into the circulation at rates that yielded arterial concentrations similar to those observed with cyanamide.

Cyanamide *per se* is clearly not the cause of this effect since, by itself, cyanamide had no effect on portal blood flow and did not alter the splanchnic vascular resistance as evidenced by the same percentage of the cardiac output as in the control rats being delivered to the splanchnic territory. Thus, it appears more likely that the effect on the splanchnic circulation resulted from the combination of cyanamide with ethanol. When combined, these two drugs resulted in hypothermia and hypotension [12, 13] that have been shown to be independent of blood acetaldehyde concentrations [24].

In the present study, the probable increase in splanchnic vascular resistance suggests that a catecholamine response via the sympathetic nervous system or perhaps the adrenal gland may have been involved. This possibility should be explored in the future.

Also of interest in the present study is the observation that prior laparotomy did not affect basal blood flows or the hemodynamic responses to ethanol, as seen in the sham-operated rats. This is similar to the findings of Bond *et al.* [25], who found that laparotomy is without effect on splanchnic blood flow in the dog. Also, the presence of a catheter in the portal vein was without hemodynamic effects

under basal conditions. However, the presence of the portal vein catheter attenuated the ethanol-induced increase in portal vein blood flow. This may simply be due to partial obstruction of flow when the portal vein was required to carry increased amounts of blood in the presence of ethanol. Alternatively, the presence of the catheter may have altered autonomic or humoral responses which modified the portal vein blood flow response to ethanol.

We have shown that acetaldehyde is not involved in the ethanol-mediated increase in portal vein blood flow. In addition, we have shown that the effect of cyanamide resulting in a suppression of the ethanol-induced increase in portal blood flow is probably part of an ethanol–cyanamide interaction which is independent of acetaldehyde levels in the circulation.

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