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Acute Effects of Ethanol and Acetaldehyde on Blood Pressure and Heart Rate in Disulfiram-treated and Control Rats[1]

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HELLSTRÖM, E. AND O. TOTTMAR. *Acute effects of ethanol and acetaldehyde on blood pressure and heart rate in disulfiram-treated and control rats.* PHARMAC. BIOCHEM. BEHAV. 17(6) 1103–1109, 1982.—The cardiovascular effects of ethanol and acetaldehyde were studied in control rats and rats pretreated with disulfiram. Ethanol administration to control rats decreased mean blood pressure and increased heart rate significantly. Injection of ethanol to disulfiram-treated rats decreased mean blood pressure, increased pulse pressure and increased heart rate and respiratory rate. The blood acetaldehyde levels were 10–15 times higher than those found in controls. The effects evoked by ethanol in disulfiram-treated rats were prevented or abolished in rats given 4-methylpyrazole before or after ethanol. Heart rate increased with increasing concentrations of acetaldehyde in control rats given acetaldehyde intravenously. Only a slight decrease in mean blood pressure was seen at high acetaldehyde levels (150–250 μM), whereas pulse pressure increased markedly as well as respiratory rate. At acetaldehyde levels lower than 50 μM, no effects on blood pressure were seen. The effects of acetaldehyde infusion in disulfiram-treated rats were similar to those observed in controls having comparable acetaldehyde levels. The results suggest that the disulfiram-ethanol reaction in rats is caused by the combined action of ethanol and acetaldehyde on the cardiovascular system.

Acetaldehyde Alcohol Ethanol Antabuse® Disulfiram Blood pressure

THE mechanism underlying the disulfiram-ethanol reaction (DER) is not fully understood. It is generally believed that the hypotension and vascular collapse observed after ethanol administration to subjects pretreated with disulfiram (Antabuse®) are produced by combined effects of an increased acetaldehyde level and a low neuronal content of norepinephrine caused by the inhibition of aldehyde dehydrogenase (ALDH) and dopamine-β-hydroxylase respectively [19, 27, 40]. However results from recent studies on disulfiram-treated patients and animals seem to indicate that the role of dopamine-β-hydroxylase in the DER has been overestimated in previous studies [22, 31, 39].

Acetaldehyde exerts in general hypotensive and chronotropic effects [1, 12, 21, 26]. It has been shown in more recent studies, however, that acetaldehyde is a rather potent vasodilator [2, 10, 12]. These effects of acetaldehyde are in most cases surmounted by its indirect sympathomimetic properties. The dual effect of acetaldehyde on the cardiovascular system probably explains some of the controversial opinions about the role of acetaldehyde in the DER.

Studies on humans pretreated with disulfiram indicate that the concentration of acetaldehyde is not solely decisive for the onset and intensity of the reaction [30, 33]. In the present authors' laboratory, it was observed that a hypotension was produced at lower acetaldehyde levels in disulfiram-treated rats than in rats pretreated with cynamide (the active component of Dipsan®) or coprine (the alcohol-sensitizing compound in the mushroom Coprinus atramentarius) [39]. Thus, it appears possible that also other factors, in addition to acetaldehyde, are involved in the reaction.

Compared to acetaldehyde, rather little attention has been focused on the role of ethanol in the DER, apart from its role as the precursor of acetaldehyde. It has been shown that ethanol can produce dose-dependent relaxant, vasodilator effects, as well as inhibitory actions of constrictor vasoactive agents on isolated rats arterial and venous smooth muscle both in situ and in vitro [3,9].

In the present study the acute effects of ethanol and acetaldehyde have been studied in control and disulfiram-treated rats in an attempt to find out their respective roles in the DER.

METHOD

Chemicals

Acetaldehyde was obtained from E. Merck AG, Darmstadt, Germany, and it was freshly distilled before use. Disulfiram was obtained from Fluka AG, Buchs, Switzerland, and it was recrystallized twice in 99.5% ethanol. 4-methylpyrazole was supplied by Lab Kemi, AB, Sweden.

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Animals

Female Sprague-Dawley rats (Anticimex, Sweden) weighing 200–250 g, were used in all experiments. The rats were fed on a standard diet and had free access to tap water.

Drug Administration

Ethanol was administered intraperitoneally to anesthetized rats (hexo-barbital sodium, Evipan®, 150 mg/kg, IP) as a 10% or 30% (v/v) solution in saline at doses of 1 and 3 g/kg, respectively. Disulfiram was suspended in 5% (w/w) gum arabicum (Acacia) by sonication and given intraperitoneally (100 mg/kg) 24 hr before the experiments. 4-Methylpyrazole (10 and 100 mg/kg) was injected intraperitoneally 15 min before or after ethanol administration. Acetaldehyde was diluted with saline to concentrations of 0.1–0.5 M and infused in v. saphenous at a speed of 0.02–0.04 ml/min (0.8–4 mg/min/kg) for 10–20 min by an infusion pump (B. Braun Melsungen AG). Adrenergic blockade was produced by administration of propranolol intravenously (1 mg/kg) 20 min before the injection or infusion of ethanol and acetaldehyde. Control rats received injections or infusions of saline at the corresponding volumes.

Determination of Ethanol and Acetaldehyde in Blood

Blood samples of 0.1 ml were taken from the tip of the tail. The ethanol concentration was determined enzymatically with yeast alcohol dehydrogenase [20]. Acetaldehyde was determined fluorimetrically with the use of a partially purified preparation of aldehyde dehydrogenase [38]. No corrections have been made for the non-enzymatic formation of acetaldehyde from ethanol in the blood extracts [11, 35, 38].

Determination of Aldehyde Dehydrogenase (ALDH)-Activity

The activity of the low-K_m ALDH in liver homogenates was assayed spectrophotometrically at 25°C by measuring the reduction of NAD^+ at 340 nm [37].

Recording of Blood Pressure, Heart Rate and Respiratory Rate

Blood pressure in the anesthetized rats was measured with a Statham P23 Db transducer connected to one of the carotid arteries via a polyethylene catheter (10 cm long, ID 0.6 mm) filled with heparinized saline. Heart rate was measured by the use of a tachograph connected to the blood pressure unit. The electronic equipment used was built in this laboratory. The system was statically tested and showed a good linearity in the range of 40–150 mm Hg. Dynamical tests were made by applying a stepforming pressure wave to the system. The resonance frequence for the total system was about 60 Hz. The respiratory rate was counted visually by following the ventilatory movements of the chest. Ethanol and acetaldehyde were administered when a stable base line had been obtained (after 20–30 min) and blood pressure was then recorded continuously during 30–60 min. Heart rate and respiratory rate were recorded every 10 min. The body temperature was kept at 37.0–37.5°C (rectal temperature) by placing the rats on an automatically regulated warming-pad. Mean blood pressure was calculated as the diastolic pressure + one-third of pulse pressure. Responses have been calculated from the changes in the initial resting

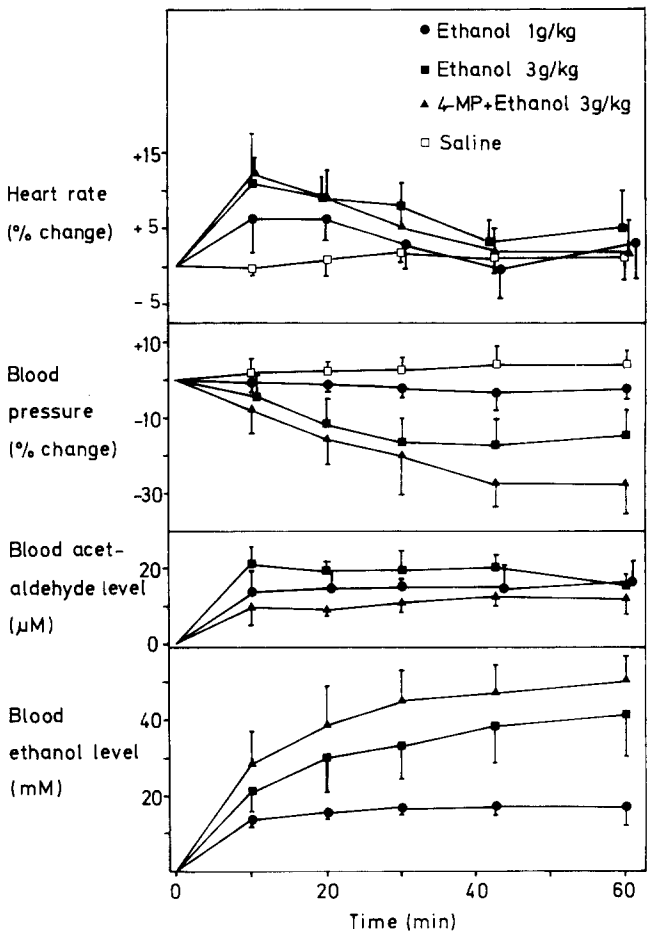

FIG. 1. Effects on heart rate and systemic arterial pressure in control rats and 4-methylpyrazole-treated rats after an intraperitoneal injection of ethanol. 4-Methylpyrazole (100 mg/kg, IP) was given 15 min before ethanol administration. The results are given as mean values ±S.D. from 4–8 experiments.

mean blood pressure, pulse pressure, heart rate and respiratory rate respectively. The initial values for control rats were as follows 83±11 mm Hg, 29±7 mm Hg, 396±21 beats/min (mean±S.D., n=70) 73±11 breaths/min (n=31). No significant changes were observed in the initial values after pretreatment with disulfiram or 4-methylpyrazole.

Statistics

An overall non-parametric test was performed by using the Kruskal-Wallis one-way analysis of variance [34]. This test was then followed up by the Mann-Whitney U-test for specific comparisons [34]. The Spearman's rank correlation coefficient was calculated according to Siegel [34].

RESULTS

Effects of Ethanol on Heart Rate, Blood Pressure and Respiratory Rate

Control rats. The effects of a single injection of ethanol, 1 and 3 g/kg, on heart rate and blood pressure were studied in anesthetized rats, and the results are shown in Fig. 1. Rats

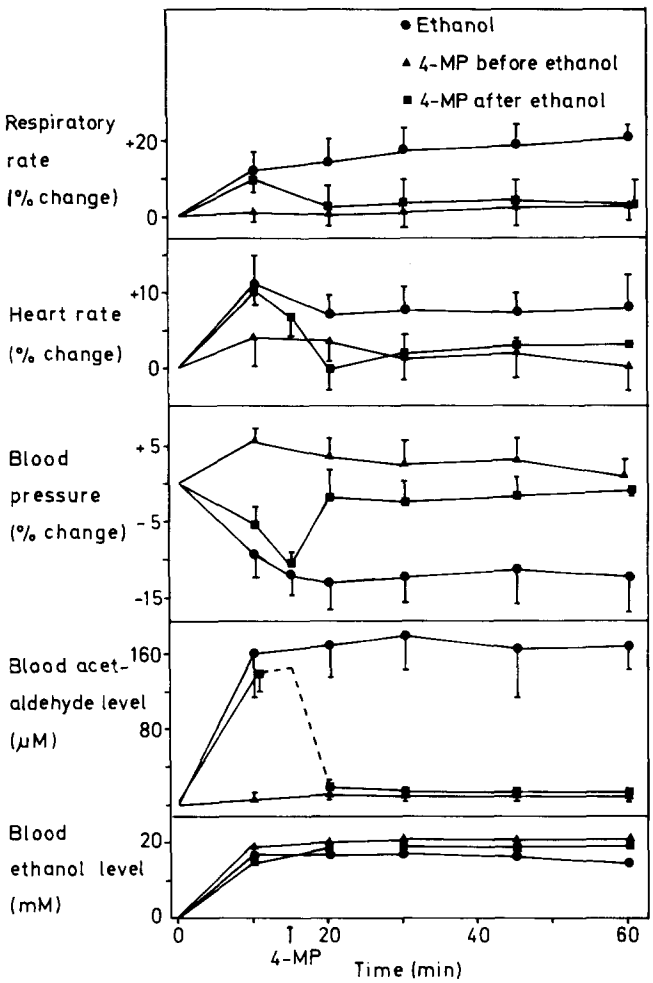

FIG. 2. Blood pressure response, heart rate and respiratory rate after ethanol administration to rats pretreated with disulfiram (100 mg/kg, IP). Ethanol (1 g/kg, IP) was injected 24 hr after administration of disulfiram. Two other groups of rats pretreated with disulfiram, were given 4-methylpyrazole (4-MP, 10 mg/kg, IP) 15 min before or after ethanol. The results are the mean values ±S.D. from 5 experiments. The S.D. for ethanol levels were less than 18% of the mean values and have for the clarity not been shown.

receiving ethanol at a dose of 3 g/kg had significantly higher blood levels compared to those who were given 1 g/kg of ethanol ($p<0.01$). The acetaldehyde levels in these two groups were not significantly different. At blood ethanol levels higher than 20mM, blood pressure decreased markedly ($p<0.01$) and progressively with increasing ethanol levels. Heart rate increased in both groups during the first 20 min after ethanol injection ($p<0.05$) and then returned almost to control values.

By use of the alcohol dehydrogenase inhibitor 4-methylpyrazole (4-MP) an attempt was made to separate the cardiovascular effects of ethanol from those of acetaldehyde. Pretreatment with 4-MP did not affect the initial blood pressure, heart rate or respiratory rate, and no effects were observed after injection of saline. Rats pretreated with 4-MP before administration of ethanol, 3 g/kg, had higher ethanol levels than those receiving ethanol only (Fig. 1). The depressant effect of ethanol on blood pressure was also more pronounced in these rats. Heart rate increased significantly ($p<0.01$) during the first 20 min and then returned towards the initial value at the end of the experiment. Blockade of beta adrenergic receptors with propranolol reduced or even reversed the chronotropic effect of ethanol, but did not prevent the hypotension (not shown). The change in heart rate 10 min after ethanol administration (3 g/kg) was $-1.3\pm6.3\%$ (n=3) in rats given propranolol before ethanol and $+12.3\pm2.4\%$ (n=7) in rats not treated with propranolol ($p<0.01$). As expected, very low levels of acetaldehyde were found in these rats pretreated with 4-MP ($<13\mu$M). Ethanol had no significant effects on respiratory rate in any of these groups.

Rats pretreated with disulfiram. In rats pretreated with disulfiram (100 mg/kg) for 24 hr, the low-K_m ALDH in the liver was inhibited by 65–75%. After administration of ethanol (1 g/kg), blood acetaldehyde levels increased rapidly during the first 10 min and then reached a plateau at a concentration of approximately 170 μM (Fig. 2). At the same time there was a significant and prolonged fall in mean blood pressure compared to the effects seen in control rats receiving the same dose of ethanol (Table 2). The increase in respiratory rate was higher in disulfiram-treated rats than in controls, whereas the increase in heart rate was similar.

After administration of 4-MP, 15 min after ethanol, the level of acetaldehyde in blood declined rapidly to concentrations below 15 μM within 10 min, and mean blood pressure, heart rate and respiratory rate gradually returned to initial values (Fig. 2).

When 4-MP was given before ethanol, no hypotension was observed and heart rate as well as respiratory rate were not significantly changed (Fig. 2). Very low levels of acetaldehyde were found in these rats (about 10 μM).

Effects of Acetaldehyde on Heart Rate, Blood Pressure and Respiratory Rate

Control rats. The cardiovascular effects of intravenous infusion of acetaldehyde given continuously for 20 min were studied in anesthetized rats. Heart rate increased as the blood level of acetaldehyde increased ($r_s=0.91$, $p<0.001$, n=31). No significant changes in heart rate and blood pressure were observed during infusion of saline at corresponding volumes. There was a significant increase in respiratory rate ($p<0.01$) during infusion of acetaldehyde as compared to controls receiving saline. In most experiments, blood pressure increased during the first minutes of infusion. Further infusion of acetaldehyde, resulting in blood levels of 50–100 μM, decreased mean blood pressure, whereas lower acetaldehyde levels (<50 μM) had no effect on blood pressure (Table 1). Acetaldehyde levels of 150–250 μM produced a significant increase in pulse pressure (42%), whereas only a slight decrease in the mean blood pressure was observed. A representative example of the results obtained at high acetaldehyde levels is shown in Fig. 3. After discontinuation of the infusion, acetaldehyde in blood disappeared within a few minutes and both heart rate and blood pressure returned to initial values within 10 min, whereas a delay in the normalization of the respiratory rate was seen Fig. 3).

Injection of ethanol (1 g/kg, IP) 10 min before infusion of acetaldehyde tended to potentiate the effects on mean blood pressure and pulse pressure (Tables 1 and 2).

Rats pretreated with disulfiram. The effects of intrave-

TABLE 1

COMPARISON OF THE EFFECTS OF ETHANOL AND ACETALDEHYDE ON MEAN BLOOD PRESSURE, PULSE PRESSURE AND HEART RATE IN CONTROL RATS AND RATS PRETREATED WITH DISULFIRAM*

	Pretreatment	Infusion or Injection		Acetaldehyde in blood (μM)	Decrease in mean blood pressure (%)	Increase in pulse pressure (mm Hg)	Heart rate (% change)
1.	Saline (10 min)	Saline, IV	(5)	0	0 ± 3	2 ± 2	↓ 1 ± 1
2A.	Saline (10 min)	Acetaldehyde, 0.8 mg/min/kg	(6)	32 ± 10	0 ± 3	2 ± 3	↑ 4 ± 3
2B.	Saline	Acetaldehyde, 2 mg/min/kg	(7)	75 ± 21	8 ± 4	5 ± 7	↑ 3 ± 2
2C.	Saline	Acetaldehyde, 4 mg/min/kg	(10)	189 ± 37	4 ± 4	14 ± 5	↑ 9 ± 4
3A.	Ethanol (10 min)	Acetaldehyde, 0.8 mg/min/kg	(9)	30 ± 12	6 ± 4	2 ± 4	↓ 1 ± 4
3B.	Ethanol	Acetaldehyde, 2 mg/min/kg	(6)	72 ± 8	8 ± 4	5 ± 2	0 ± 3
3C.	Ethanol	Acetaldehyde, 4 mg/min/kg	(6)	194 ± 38	14 ± 5	27 ± 10	↑ 7 ± 2
4.	Disulfiram (24 hr)	Acetaldehyde, 4 mg/min/kg	(6)	187 ± 63	0 ± 3	24 ± 5	↑12 ± 3
5.	Disulfiram (24 hr)	Ethanol, IP	(5)	173 ± 40	13 ± 3	20 ± 7	↑ 7 ± 3
6.	No treatment	Ethanol, IP	(4)	15 ± 5	1 ± 3	2 ± 1	↑ 6 ± 3

*Saline or acetaldehyde was infused in v. saphenous for 20 min. Ethanol was given intraperitoneally at a dose of 1 g/kg, 10 min before the infusion of acetaldehyde or 24 hr after administration of disulfiram (100 mg/kg). The results are expressed as the changes observed 20 min after the start of infusion (group no. 1–4), or 20 min after ethanol injection (group no. 5 and 6). An increase or decrease in the heart rate are indicated by arrows (↑) and ↓) respectively. The results are means±S.D. Numbers of experiments are shown in parentheses.

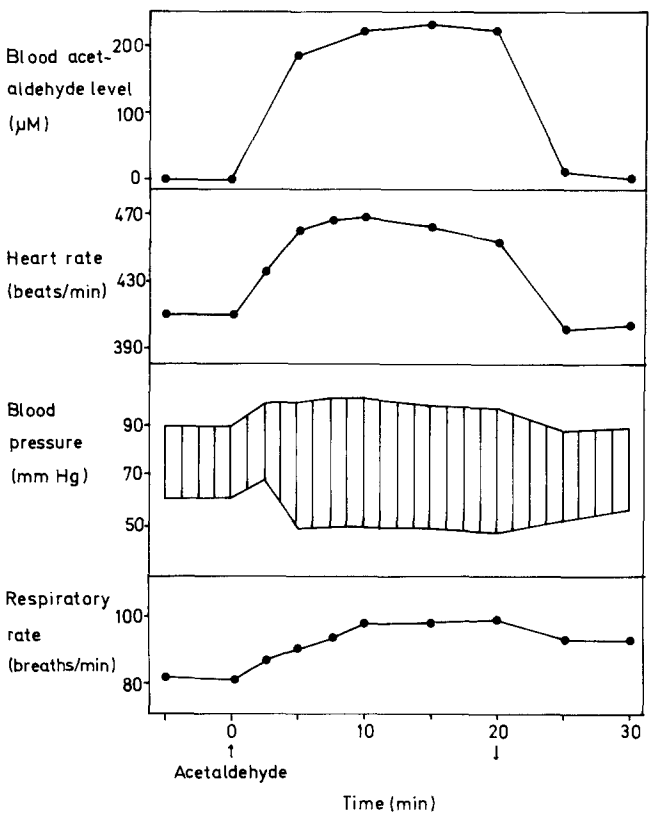

FIG. 3. Effects of intravenous infusion of acetaldehyde on respiratory rate, heart rate and systolic-diastolic blood pressure in a control rat. Acetaldehyde (0.5 M) was infused during 20 min (indicated by arrows) at a speed of 0.042 ml/min (4 mg/min/kg).

nous infusion of acetaldehyde on blood pressure was studied in 6 rats pretreated with disulfiram (Table 1). Acetaldehyde produced a much smaller hypotension in these rats as compared to the response observed at similar acetaldehyde levels in control rats given both ethanol and acetaldehyde or in disulfiram-treated rats given ethanol (Table 2). However, markedly increased pulse pressure was also observed in the disulfiram-treated rats as in all other groups having high acetaldehyde levels. Heart rate increased by 11% and respiratory rate by 15% at blood acetaldehyde levels of 150–250 μM. After infusion and when all acetaldehyde had been metabolized, blood pressure, heart rate and respiratory rate returned to initial values within 10–15 min in most experiments.

DISCUSSION

Studies of the acute effects of ethanol and acetaldehyde on the cardiovascular system in humans and animals have shown conflicting results. This may be attributed to differences in the dose of ethanol or acetaldehyde used, route of administration, timing of measurements, preparation methods and type of anesthesia.

In the present study on rats, heart rate increased after ethanol administration. Similar results have been obtained in studies on humans [18] and dogs [15]. This effect on heart rate has been considered to represent a compensatory autonomic mechanism in order to maintain normal cardiac output in the presence of an ethanol-induced depression of ventricular performance [15, 36]. This is supported by this study and by other studies [8, 42] showing that the use of autonomic blockade can abolish or even reverse the chronotropic effect of ethanol.

Ethanol caused an increased heart rate also in rats pretreated with 4-MP, indicating that the chronotropic effect in control rats was caused mainly by ethanol and not by acetaldehyde. The small amounts of acetaldehyde in blood from these rats (5–15 μM) can probably be explained by a nonenzymatic formation of acetaldehyde from ethanol, which occur during acid extraction of blood [11,35]. Tottmar *et al.* [38] obtained blood acetaldehyde concentrations of 5–12 μM after extraction of rat blood containing ethanol at concentrations of 20–50 mM.

A decreased systemic arterial pressure was observed at ethanol levels above 20 mM. This result is in agreement with previous observations made on other species [27]. Nakano and Prancan [26] found that the effect of intravenous infusion

TABLE 2

STATISTICAL COMPARISON OF THE RESULTS FROM THE DIFFERENT EXPERIMENTAL GROUPS SHOWN IN TABLE 1†

Group‡	2A			2B			2C			3A			3B			3C			4			5			6		
	BP	PP	HR	BP	PP	HR	BP	PP	HR	BP	PP	HR	BP	PP	HR	BP	PP	HR	BP	PP	HR	BP	PP	HR	BP	PP	HR
1	ns§	ns	**	**	ns	**	*	***	**	**	ns	ns	**	ns	ns	**	**	**	ns	**	**	**	**	**	ns	ns	**
2A				**	ns	ns	*	***	ns	**	ns	*	***	*	ns	***	**	ns	ns	**	***	**	**	ns	ns	ns	ns
2B							*	*	**	ns	ns	*	ns	ns	*	ns	**	**	**	**	***	ns	**	**	**	ns	ns
2C										ns	***	***	ns	***	**	**	*	ns	ns	**	ns	***	ns	ns	ns	***	ns
3A													ns	ns	ns	**	***	**	*	***	**	**	***	**	*	ns	**
3B																*	**	**	**	**	***	*	**	***	**	*	*
3C																			***	ns	**	ns	ns	ns	**	**	ns
4																						**	ns	*	ns	**	*
5																									**	**	ns

†Abbreviations are as follows: BP: blood pressure; PP: pulse pressure; and HR: heart rate.

‡See Table 1 for description of groups.

§ns: Not significant, the significance levels are $*p<0.05$; $**p<0.01$; $***p<0.001$ for a one-tailed test (Mann-Whitney U-test). The statistical comparison was preceded by the Kruskal-Wallis one-way analysis of variance ($p<0.001$ for all three parameters).

of ethanol was, at least in dogs, biphasic. Low blood ethanol levels increased systemic arterial pressure, heart rate and contractility. At higher concentrations of ethanol, they observed hypotension and negative inotropic effects.

The more pronounced vasodepressant effect of ethanol in rats pretreated with 4-MP might be explained by higher ethanol levels in these rats compared to control rats. However, a relatively large dose of 4-MP (100 mg/kg) was given, and it is possible that other factors are involved. It has been shown that 4-MP causes central depressant effects per se, and an enhancement and prolongation of ethanol-induced effects on coordination in the rat [32].

There is considerable support for the suggestion that the chronotropic effect of acetaldehyde are mediated by catecholamines [5, 16, 24, 26]. The positive chronotropic effect of acetaldehyde seen in the present study was in contrast to the study made by Egle *et al.* [10] on rats. They found that a single intravenous injection at doses of 5 and 20 mg/kg did not alter heart rate significantly, while a dose of 40 mg/kg produced a severe bradycardia. Since no information about blood acetaldehyde levels was given, these results are difficult to compare with the results obtained in our study. It is possible, however, that rapid injections of acetaldehyde at high concentrations into the circulation could result in a direct negative effect on the myocardium.

The increased respiratory rate during infusion of acetaldehyde is in agreement with earlier findings where acetaldehyde have been reported to stimulate the carotid chemoreceptors and to provoke hyperpnea both in man [4] and in animals [13,17].

Infusion of acetaldehyde to control rats and disulfiram-treated rats did not cause any marked effects on mean blood pressure. However, the pulse pressure increased markedly in most rats having acetaldehyde levels above 50 μM. An increased pulse pressure was also observed at high acetaldehyde levels in control rats given ethanol before infusion of acetaldehyde and in disulfiram-treated rats given ethanol. However, in these experiments a marked fall in mean blood pressure was also observed. Thus, in these rats, the increased pulse pressure was apparantly mainly due to a decreased diastolic blood pressure. It seems from the experiments that the diastolic pressure was more seriously affected by acetaldehyde in the presence than in the absence of ethanol both in controls and in disulfiram-treated rats. This suggests that the depressant effects of acetaldehyde is potentiated by ethanol, or vice versa, since the ethanol dose used produced only moderate effects in rats given ethanol alone. A reservation to this must be made since the hexobarbital anesthesia might have been differently influence by the different treatment.

The interpretation of the observed changes in blood pressure as actual changes in diastolic or systolic blood pressure might be erroneous, since measuring of blood pressure in rats can be very deceptive due to the very high heart rate. However, it seems that the increased pulse pressure can not be explained as an artefact due to increased heart rate, since it was found in separate experiments (not shown) that β-blockade (propranolol, 1 mg/kg, IP) reversed the chronotropic effect, but did not prevent the increase in pulse pressure. Furthermore, the results obtained in the present study are in a good agreement with those obtained in studies on humans pretreated with disulfiram or calcium carbimide. It was found in these studies that ethanol ingestion caused a markedly decreased diastolic blood pressure (up to 50%) whereas the systolic blood pressure was unchanged or slightly decreased [6, 7, 14, 25, 28]. In a study on the calcium carbimide-ethanol reaction Brien *et al.* [7] found a positive correlation between pulse pressure and the acetaldehyde level.

The effects on blood pressure, heart rate and respiratory rate evoked by ethanol in disulfiram-treated rats were prevented or abolished in rats given 4-MP before or after the ethanol injection, respectively. These results demonstrate that an increased acetaldehyde level is necessary not only to elicit but also to maintain these effects. Administration of 4-MP might prove to be an efficient and valuable antidote in the treatment of the disulfiram-ethanol reaction. In fact, a successful clinical trial with this drug has recently been reported [23].

It seems quite clear that acetaldehyde plays a dominant role in the DER. It is also conceivable that the intensity and the duration of the DER not only are related to the acetaldehyde level but also to the concentration of ethanol in blood. Both compounds produced vasodepressant effects in

rats. These effects are not observed at low blood concentrations of ethanol and acetaldehyde due to their sympathomimetic properties. At higher levels, the vasodepressant effect predominates and a hypotension is observed. The hypotension in disulfiram-treated subjects might be caused by a direct effect of acetaldehyde and ethanol on the vascular smooth muscles or through the release of vasoactive compound. Attempts to attribute the hypotension to a cholinergic vasodilation or to the release of histamine or plasma kinins have been unsuccessful [29,41]. Similarly, it has recently been shown that the inhibitory and depressant actions of ethanol and acetaldehyde on isolated vascular smooth muscles cannot be related to the release of histamine, acetylcholine, serotonin or prostaglandins [2, 3, 9]. Whether or not disulfiram causes some other effect which sensitizes the cardiovascular system to ethanol and acetaldehyde remains speculative at the present time.

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