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Effect of Ethanol on Cardiac Function in Rats Genetically Selected for their Ethanol Preference

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HILLBOM, M. E. AND K. VON BOGUSLAWSKY. *Effect of ethanol on cardiac function in rats genetically selected for their ethanol preference.* PHARMAC. BIOCHEM. BEHAV. 8(5) 609–614, 1978. – The heart rate of male ANA (Alko, Non-alcohol) and AA (Alko, Alcohol) rats was significantly increased after peroral administration of 2.7 g ethanol/kg, but the tachycardia was of shorter duration in ANA rats, which avoid the drinking of ethanol solution. The PR intervals in the electrocardiograms of ANA rats became significantly longer than those of AA rats when 13.5 g ethanol/kg was given. The QT intervals were likewise longer in the electrocardiograms of ANA rats, but before as well as after the administration of ethanol. The results suggest that intracardiac conduction is more depressed by acute ethanol in the ANA than the AA strain of rats.

Ethanol Rat strain differences Cardiac function

SELF-SELECTION experiments have suggested that the degree of voluntary consumption of ethanol by experimental animals is genetically determined and that differences exist not only among various species [3] but among various strains of the same species [5, 22, 23]. Recent investigations in several centers of biological alcohol research have proved that both metabolic and pharmacological actions of ethanol may vary in different mouse and rat strains [8, 9, 10, 11, 16, 17, 19, 25, 26, 27, 28, 29, 30].

Since 1963 two rat strains, one which avoids ethanol and the other which prefers it to water, have been developed and raised in our laboratory [7]. The strains are designated AA (Alko, Alcohol) and ANA (Alko, Non-Alcohol). Glucose tolerance and ethanol elimination tests reveal no differences between these strains [10] but the blood level of acetaldehyde during ethanol oxidation seems to be significantly higher in ANA rats [9]. Behavioral differences exist too [8], and, for example, the ethanol-induced sleeping time is longer in ANA than in AA rats [27].

In general, rat and mouse strains that avoid drinking of ethanol appear to be more sensitive to the depressant effect of ethanol on the central nervous system [8, 17, 19, 25, 26, 27, 28, 29] and to have slightly higher blood levels of acetaldehyde [9,30]. Thus far, strain differences in cardiac sensitivity to ethanol or acetaldehyde have not been reported, although ethanol seems to have a direct depressant effect on intracardiac conduction [12]. Accordingly it can be hypothesized that strain differences also exist in this parameter. The present study was designed to examine this possibility and the cardiac function of AA and ANA rats was carefully followed after peroral administration of small and large doses of ethanol.

MATERIALS AND METHOD

Animals

Two strains of rats genetically selected for their voluntary ethanol consumption [5,7] and designated AA (Alko, Alcohol: a strain that prefers ethanol solution to water) and ANA (Alko, Non-Alcohol: a strain that avoids ethanol solution) were tested for their cardiac sensitivity to ethanol. All the animals were males belonging to the two generations F_{22} and F_{25} and were given ordinary laboratory food ad lib. Before testing, seven ANA and eight AA rats of the F_{22} generation were kept for two months on a free choice between tap water and 10% (v/v) ethanol [6]. The animals were 2 months old at the beginning of the free choice period and 5 months old when tested for cardiac function. During the free choice period the mean consumption of ethanol ± SD of the ANA rats was 0.19 ± 0.08 g/kg/day and that of the AA rats 5.22 ± 1.19 g/kg/day. To see if previous consumption of ethanol influenced the results, a group of eight ANA and eight AA rats belonging to the F_{25} generation and never kept on a free choice between tap water and ethanol was subsequently tested. These tests were made when the rats were 6–7 months old. All the rats were fasted for 6 hr and those (F_{22}) kept on a free choice between ethanol and water were withdrawn from ethanol one month before the tests.

Procedure

Electrocardiograms were registered with a polygraph (Devices M 19). Each rat in turn was placed in a cage, 60 × 80 × 180 mm, the inner dimensions of which could be

TABLE 1

DIFFERENCES BETWEEN AA AND ANA RATS IN HEART RATE AND THE DURATIONS OF P WAVE, PR INTERVAL, QRS COMPLEX AND QT INTERVAL AS MEASURED FROM ELECTROCARDIOGRAMS AFTER PERORAL ADMINISTRATION OF 2.7 g/kg OF ETHANOL AS A 3.3 M SOLUTION

Time (min)	Strain	Heart Rate (beats/min)	Duration of P Wave	PR Interval	QRS Complex	QT Interval
				(msec)		
–	AA	388 ± 33	23 ± 2	53 ± 5	15 ± 1	77 ± 5
	ANA	360 ± 29	24 ± 3	56 ± 4	16 ± 2	95 ± 11†
10	AA	459 ± 21	21 ± 4	52 ± 5	15 ± 1	70 ± 5
	ANA	442 ± 44	24 ± 5	53 ± 4	15 ± 2	79 ± 13
20	AA	453 ± 29	23 ± 3	52 ± 4	15 ± 1	71 ± 6
	ANA	428 ± 50	21 ± 2	54 ± 5	15 ± 2	83 ± 14*
30	AA	455 ± 18	21 ± 2	51 ± 4	14 ± 2	71 ± 3
	ANA	425 ± 46	24 ± 4	55 ± 4	15 ± 2	83 ± 14*
40	AA	452 ± 17	22 ± 2	51 ± 5	15 ± 1	72 ± 3
	ANA	403 ± 38†	24 ± 4	56 ± 4	16 ± 2	88 ± 15*
50	AA	438 ± 27	21 ± 2	52 ± 4	15 ± 2	73 ± 4
	ANA	387 ± 42*	24 ± 4	58 ± 4†	16 ± 2	91 ± 15‡
60	AA	446 ± 14	21 ± 3	50 ± 4	14 ± 1	72 ± 4
	ANA	383 ± 40†	24 ± 4	57 ± 5*	15 ± 2	92 ± 13‡
70	AA	440 ± 25	21 ± 2	51 ± 4	14 ± 1	72 ± 5
	ANA	359 ± 48†	25 ± 4*	58 ± 6*	16 ± 3	96 ± 13‡

Figures represent the mean ± SD for eight AA or seven ANA rats (F_{22} generation).
*$p<0.05$, †$p<0.01$, ‡$p<0.001$, for differences from AA rats.

changed according to the size of the animal. The rats were left to calm down for a period of 30 min in the cage after placement of the needle electrodes and before the control curves were recorded. During the test the animals were momentarily removed from the cage to receive ethanol via a stomach tube.

When F_{22} rats were tested only 2.7 g/kg of ethanol as a 3.3 M solution in tap water was given, and seven electrocardiograms of a period of 1 min each recorded at a paper speed of 100 mm/sec were taken every 10 min thereafter. Accordingly we obtained one control curve and seven others representing the intoxication period for further analysis. We measured the duration of P wave, PR interval, QRS complex and QT interval only from lead 2 since in rat electrocardiograms the individual waves are best seen there [13].

In testing F_{25} animals, we first gave, via stomach tube, a single dose of either 2.7 g/kg of ethanol as a 2 M solution or 5.4 g/kg as a 4 M solution in tap water. Two weeks thereafter the same animals were tested with 13.5 g/kg of ethanol as a 4 M solution in tap water. Electrocardiograms were taken before and 1/2, 1 and 2 hr after ethanol administration, and cardiac function (lead 2) was monitored for a period of several hours. Three ANA rats survived the 13.5 g ethanol/kg dose; the other 13 rats died within 4 hr of its administration. There was no significant difference of mortality between the strains.

Analytical Methods

For determination of blood glucose and ethanol concentrations samples were drawn from the tip of the tail into tubes containing ice-cold perchloric acid and the protein precipitates were centrifuged down. The details of the methods are described elsewhere [14,32]. Glucose was determined only when 2.7 g/kg of ethanol was given.

Statistical Evaluation

Statistical comparisons were made using Student's *t* test if not otherwise stated. Data were considered significant if the P value was less than 0.05.

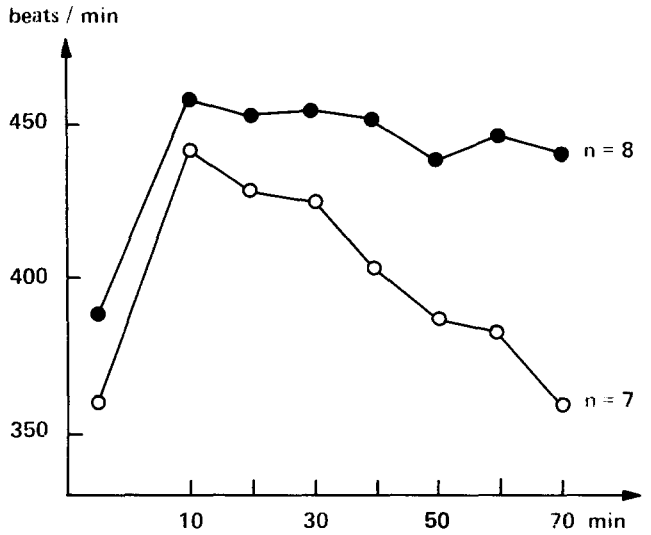

FIG. 1. Effect of ethanol on heart rate of AA (●———●) and ANA (○———○) rats. 2.7 g/kg of ethanol as a 3.3 M solution was given perorally to 5 months old F_{22} animals (see also Table 1).

RESULTS

Peroral administration of 2.7 g/kg of ethanol as a 3.3 M solution increased the mean heart rate of the eight AA rats of the F_{22} generation. Tachycardia was also observed in the seven ANA rats but in these animals it rapidly disappeared (Fig. 1). A two-way analysis of variance with repeated measures of one factor proved that the heart rate curves (Fig. 1) had significantly ($F = 3.62$, $p<0.01$) different directions and the AA rats had significantly ($F = 10.67$, $p<0.01$) higher heart rates than the ANA ones. Hence the ethanol-induced tachycardia was greater and lasted for a longer period in the AA rats than in the ANA ones. This strain difference in cardiac function provoked by acute ethanol was not due to different blood ethanol levels (24 mmol/l in both groups 75 min after administration). Neither was it due to previous ethanol consumption of the AA rats, as was later observed when rats of the F_{25} generation that were never given a free choice between ethanol and water were tested.

Since intubation is considered a stressful event for rats [4] we gave corresponding volumes of pure tap water via stomach tube to the same animals to determine the effect of the procedure itself. The increase in heart rate proved to be slight and insignificant and did not last for more than 10 min. No significant difference could be observed between the rats of the two strains.

In the present study ethanol produced cardiac arrhythmias only twice. In one ANA rat a few ectopic systoles were observed about 30 min after administration of 2.7 g/kg of ethanol. One AA rat developed ventricular tachycardia shortly after receiving the large dose of ethanol (13.5 g/kg), but the condition lasted only a few seconds and was followed by ectopic systoles for half an hour.

The data from the successive electrocardiograms are collected in Table 1. Changes in the durations of the P wave (activation of artrial muscle fibers) and the QRS complex (activation of ventricular muscle fibers) after acute ethanol were insignificant in both groups of rats. Before receiving ethanol, rats of the ANA strain had significantly longer QT intervals than rats of the AA strain, suggesting a slower repolarization of ventricular fibers. In both strains administration of ethanol significantly ($p<0.05$) shortened the duration of the QT interval within 10 min. The effect was due to the ethanol-induced tachycardia. When the tachycardia disappeared in rats of the ANA strain their QT intervals increased back to the initial level. A statistically significant difference between the two strains in the duration of the QT interval could be observed during the whole follow-up, except at 10 min when the difference was only nearly significant.

The duration of the PR interval, which reflects conduction from sinoatrial node to ventricular muscle, was slightly but insignificantly shortened by the ethanol-induced tachycardia in animals of both strains. This effect was to be expected since it is generally known that the durations of the PR interval and the QRS complex tend to decrease with rapid heart rate. At 50, 60 and 70 min after 2.7 g/kg of 3.3 M ethanol the duration of the PR interval became significantly longer in the ANA rats than in the AA ones. At first we believed that this difference only reflected that of heart rate, but further experiments suggested that there exists a strain difference in intracardiac conduction as well.

The rats were tested with a 2 M ethanol solution (2.7 g/kg) because it is known to lead to higher blood ethanol levels [31]. When given to the ANA rats of the F_{25} generation it produced a slight but insignificant increase in the duration of the PR interval (Table 2). Blood glucose and ethanol concentrations were not significantly different in the two strains of rats but a difference in the degree of ethanol-induced tachycardia was again present.

The experiments continued with rats belonging to the same generation but this time the dose of ethanol and the concentration of the solution were doubled (Table 3). The initial ethanol-induced increase in heart rate lasted for a shorter period in this experiment, as was also seen when 13.5 g/kg of ethanol was given. However, the PR interval again tended to be longer in the electrocardiograms of ANA than of AA rats.

From Table 4 we can see that the heart rate of ANA rats decreased significantly ($p<0.05$) within 1 hr as the level of blood ethanol increased after administration of the large dose (13.5 g/kg). A similar effect was not found in AA rats. The duration of the PR interval was already significantly ($p<0.05$) prolonged within half an hour in both group of rats but the effect was greater in ANA ones. No correlation was found between the heart rate and the PR interval in rats of the AA strain. On the other hand, the longer the PR interval the slower was the heart rate ($r = -0.63$, $p<0.01$) in rats of the ANA strain.

DISCUSSION

The normal basal heart rate of the adult albino rat has been reported to be just over 300 beats/min [2]. The values obtained in the present study were substantially higher. The variation in heart rates in rats belonging to the two generations was probably due to the age difference since slower rates were registered for older rats.

Nakano and Prancan [24] have proved with anesthetized dogs that intravenous infusion of ethanol increases the heart rate. The tachycardia, which most likely is due to the increased release of catecholamines from the sympathetic nerve endings and adrenal medullas, is dose-dependent

TABLE 2

CHANGES IN BLOOD ETHANOL AND GLUCOSE CONCENTRATIONS, HEART RATE AND PR INTERVAL IN AA AND ANA RATS AFTER PERORAL ADMINISTRATION OF 2.7 g/kg OF ETHANOL AS A 2 M SOLUTION

		Time in Hours after Ethanol			
	Strain	0	1/2	1	2
Blood ethanol	AA	–	42 ± 2	49 ± 5	47 ± 7
(mmol/l)	ANA	–	45 ± 7	51 ± 5	49 ± 5
Blood glucose	AA	6.1 ± 1.0	7.6 ± 1.0	8.5 ± 0.9	7.7 ± 1.1
(mmol/l)	ANA	6.4 ± 0.2	8.3 ± 1.0	8.3 ± 1.0	8.3 ± 1.5
Heart rate	AA	337 ± 26	478 ± 18	428 ± 23	448 ± 30
(beats/min)	ANA	333 ± 13	428 ± 12†	397 ± 32	395 ± 7*
PR interval	AA	50 ± 2	51 ± 3	51 ± 3	51 ± 3
(msec)	ANA	51 ± 9	58 ± 7	58 ± 7	55 ± 8

Figures represent the mean ± SD of four animals (F_{25} generation). *$p<0.05$, †$p<0.01$, for differences from AA rats.

TABLE 3

CHANGES IN HEART RATE AND PR INTERVAL IN AA AND ANA RATS AFTER PERORAL ADMINISTRATION OF 5.4 g/kg OF ETHANOL AS A 4 M SOLUTION

		Time in Hours after Ethanol			
	Strain	0	1/2	1	2
Heart rate	AA	328 ± 11	440 ± 24	410 ± 47	381 ± 42
(beats/min)	ANA	352 ± 23	374 ± 37*	376 ± 23	369 ± 13
PR interval	AA	50 ± 4	50 ± 4	51 ± 3	53 ± 5
(msec)	ANA	56 ± 5	60 ± 4*	61 ± 3†	64 ± 5*

Figures represent the mean ± SD of four animals (F_{25} generation). *$p<0.05$, †$p<0.01$, for differences from AA rats.

however. It is elicitable with small doses of ethanol, but disappears when the blood ethanol level reaches about 65 mmol/1. Our peroral administration of various doses of ethanol to rats gave similar results. However, the duration of the tachycardia was longer in AA rats, probably indicating that the ethanol-induced sympathetic stimulation was somewhat higher or lasted for a longer period than in ANA rats.

Previous reports have indicated that acetaldehyde induces heart palpitation, probably via release of catecholamines [15,24], but if very large amounts (0.1 g/1) are given, unconsciousness accompanied by very marked slowing of the heart rate may follow [21]. Although a higher concentration of acetaldehyde is found in the peripheral blood of ANA rats after a moderate dose of ethanol (1.5 g/kg), no real accumulation of this metabolite has been observed and the rate of oxidation of ethanol to acetaldehyde is not different in AA and ANA rats [10]. Since we did not determine blood acetaldehyde concentration in the present experiment the relationship between acetaldehyde and the observed strain difference in heart rate remains unsettled.

Minor arrhythmias have been observed in dogs given sublethal doses of ethanol [20]. However, acute intravenous administration of ethanol is considered to reduce the incidence of cardiac arrhythmias in rats [33] and to elevate the ventricular fibrillation threshold in dogs [18]. In the present study cardiac arrhythmias were rare and neither of the rat strains seemed more susceptible than the other to them.

The most conspicuous effect of acute ethanol on cardiac function proved to be the prolongation of the PR interval

TABLE 4

CHANGES IN BLOOD ETHANOL CONCENTRATION, HEART RATE AND PR INTERVAL IN AA AND ANA RATS AFTER PERORAL ADMINISTRATION OF 13.5 g/kg OF ETHANOL AS A 4 M SOLUTION

	Strain	Time in Hours after Ethanol 0	1/2	1	2
Blood ethanol	AA	–	71 ± 20 (5)	86 ± 9 (3)	125 ± 2 (2)
(mmol/l)	ANA	–	57 ± 18 (5)	86 ± 10 (5)	118 ± 18 (5)
Heart rate	AA	333 ± 19 (8)	342 ± 45 (5)	356 ± 42 (3)	315 ± 17 (2)
(beats/min)	ANA	343 ± 20 (8)	328 ± 17 (5)	313 ± 24 (5)	298 ± 15 (5)
PR interval	AA	50 ± 6 (8)	60 ± 4 (8)	58 ± 6 (3)	55 ± 7 (2)
(msec)	ANA	55 ± 5 (8)	75 ± 6*(5)	78 ± 8*(5)	82 ± 8*(5)

Figures represent the mean ± SD of as many animals (F_{25} generation) as indicated within parentheses.
*$p<0.01$, for differences from AA rats.

in ANA rats. This result indicates that intracardiac conduction is more depressed by ethanol in the ethanol-avoiding than in the ethanol-preferring strain of rats. The present experiment does not explain whether this is due to a direct effect of ethanol on the cardiac conduction system or to some indirect action of ethanol or acetaldehyde.

The mechanism that could explain the observed strain difference in intracardiac conduction during ethanol intoxication can only be speculated upon. Even in the absence of ethanol a difference in the duration of repolarization of ventricular fibers could be observed. This suggests that the hearts of the two rat strains differed from each other also in other respects. Most probably the prolongation of intracardiac conduction in ANA rats by ethanol was due to its direct effect on the heart, but the sedative effect of ethanol on the central nervous system must also be taken into consideration since the nervous system and the heart are functionally interdependent. This and previous experiments [24] indicate that ethanol at low doses is a cardiac stimulant and at high doses a depressant. The effect of ethanol on the central nervous system corresponds exactly.

Alexander [1] has stressed the connection between genetic constitution and cardiac reactions to ethanol. The present results support the existence of such a connection but should not be interpreted to mean that a causal relationship exists between the cardiac depressant effect and the voluntary consumption of ethanol.

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