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Renin-Aldosterone Axis in Ethanol Intoxication

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NIEMINEN, M. M., F. FYHRQUIST, J. LINKOLA, I. TIKKANEN AND K. TONTTI. *Renin-aldosterone axis in ethanol intoxication.* PHARMAC. BIOCHEM. BEHAV. 15(6) 879–882, 1981.—The effect of acute moderate ethanol intoxication on renin-aldosterone axis was studied in four healthy humans in normal sodium and water balance. The subjects drank ethanol 1.2 g/kg body weight during 90 minutes. A dissociation between plasma renin activity (PRA) and plasma aldosterone took place; PRA increased ($p<0.001$) and aldosterone showed a decreasing trend, which was not significant. Serum Na^+/K^+-ratio increased ($p<0.001$). We observed no significant change in serum osmolality, blood pressure nor heart rate. The increase in PRA was probably caused primarily by dehydration due to ethanol diuresis. The dissociation between plasma aldosterone and PRA may be associated with increasing serum Na^+/K^+-ratio or an inhibitory action of ethanol on aldosterone secretion.

Renin Aldosterone Ethanol Sodium balance

THERE are few reports on the effects of ethanol intoxication upon renin-aldosterone axis. They have focused primarily on long-term effects, or on changes during the hangover phase [5, 12, 13]. Thus, little is known of early changes in renin-aldosterone system during ethanol intoxication. This is true despite the known importance of this system in regulation of electrolyte and water balance. In the present study we have paid attention to the early phase of acute, moderate ethanol intoxication by monitoring plasma renin activity (PRA), plasma aldosterone, serum ethanol, electrolytes and osmolality, blood pressure and heart rate with short-interval measurements. PRA increased along with rising serum ethanol concentration, and the renin-aldosterone nexus was broken.

METHOD

Subjects

The experiments were performed in 4 male healthy subjects, aged 27–37 years. In addition there were two male control subjects, aged 27–30 years.

Study Design

Diet before the experiment was free, except for a 6 hour fast before the study, when only tap water was allowed. The experiment lasted 4 hours and was performed supine at 12–17 p.m. Ethanol, 1.2 g/kg body weight, diluted with lingonberry juice to 20 vol% solution was taken PO between 30 and 120 minutes at a steady rate. In the control experiments two subjects were studied according to the same schedule except ethanol solution, which was replaced by juice.

Blood samples were taken between 30 and 160 minutes at every 10–15 minutes, then at every 20–30 minutes. They were drawn into prechilled tubes using an intravenous cannula kept open by an infusion of isotonic NaCl, 40 ml per hour. For plasma, Na_2EDTA 6 g/liter was used and parallel serum tubes were collected, all stored at −20°C until assayed. Blood pressure and heart rate were checked at every 30 minutes. Urine was collected according to need.

Assays

PRA was measured by a radioimmunoassay method [7], and plasma aldosterone was determined with a radioimmunoassay kit (C.I.S.), using 1.2-H^3-labelled aldosterone (Amersham). Serum Na^+ and K^+ concentrations were determined by flame photometry (EEL), osmolality with vapour pressure osmometer (Wescor), and ethanol by gas chromatography (Perkin-Elmer).

Statistical Evaluation

For statistical evaluation the experimental PRA, plasma aldosterone, heart rate and blood pressure values were adjusted according to the control values in order to correct for the effect of supine position. One-way analyses of variance were performed using a PDP 11/34 computer and linear regression analyses with a SR-51A calculator (Texas Instruments).

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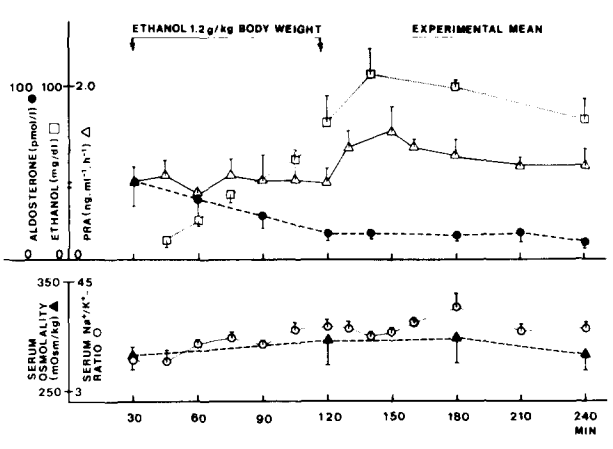

FIG. 1. Experimental means±S.E.M. of plasma renin activity (PRA) (△), plasma aldosterone (●), serum ethanol concentration (□), serum Na^+/K^+-ratio (○) and osmolality (▲).

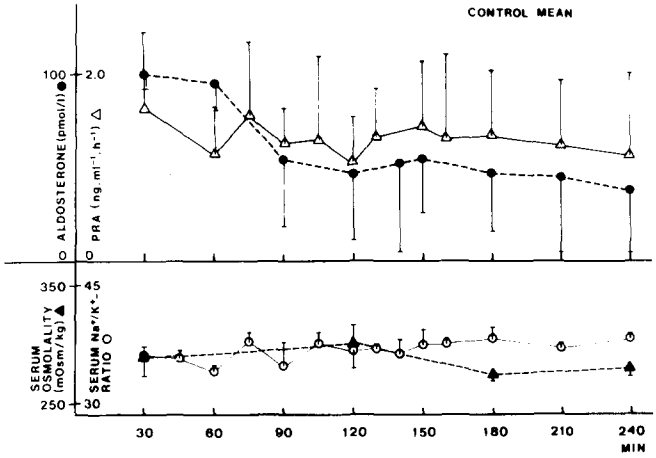

FIG. 2. Control means±S.E.M. of plasma renin activity (△), plasma aldosterone (●), serum Na^+/K^+-ratio (○) and osmolality (▲).

RESULTS

Renin

PRA did not change significantly during the first 120 minutes (Fig. 1). Thereafter there was an increase of PRA during the next 30 minutes, followed by a decreasing trend during the latter part of the experiment. PRA was significantly higher during the time period 120–240 minutes versus 30–120 minutes ($p<0.001$). The correlation of PRA to serum ethanol concentration was significant during 30–120 minutes ($r=0.52$, $p<0.01$) and during the whole experiment, 30–240 minutes ($r=0.72$, $p<0.001$). PRA and serum Na^+/K^+-ratio were significantly correlated during 30–240 minutes ($r=0.44$, $p<0.01$), but not during 30–120 minutes ($r=0.002$, n.s.). In two controls no significant changes in PRA were observed (Fig. 2).

Aldosterone

Aldosterone showed a decreasing trend, although not statistically significant, during the first 120 minutes and thereafter a further decline (Fig. 1). No correlation to PRA was observed. Thus, a marked dissociation between PRA and aldosterone occurred. Aldosterone was negatively correlated to serum Na^+/K^+-ratio during 30–120 minutes ($r=-0.67$, $p<0.01$) and during the whole experiment, 30–240 minutes ($r=0.62$, $p<0.001$).

In controls there was a declining trend of plasma aldosterone during the experiment, not however achieving significance (Fig. 2).

Serum Na^+/K^+-Ratio and Osmolality

Serum Na^+/K^+-ratio, with rising sodium and decreasing potassium concentrations, was higher during 120–240 minutes than 30–120 minutes ($p<0.001$) (Fig. 1). Serum ethanol concentration and Na^+/K^+-ratio were significantly correlated during the whole experiment, 30–240 minutes ($r=0.59$, $p<0.001$), but not during 30–120 minutes ($r=0.25$, n.s.). Serum osmolality showed an increasing trend, which was not statistically significant (Fig. 1).

In controls there were no changes in serum Na^+/K^+-ratio nor osmolality (Fig. 2).

Urine Output

Voiding of urine took place after 120 minutes and varied in amount from 17 to 29 ml/kg body weight (Table 1). In controls voiding was 11 ml/kg body weight (Table 2).

Blood Pressure and Heart Rate

Neither blood pressure nor heart rate showed significant changes in experimental subjects (Table 1) or controls (Table 2).

DISCUSSION

Diuresis, hydration electrolyte balance, hormone secretion, sympathetic nervous activity and cardiovascular functions are affected by ethanol [11,16]. These variables also affect renin-aldosterone axis [2,6]. In order to minimize postural effects on renin release, the present experiments were carried out while in a supine position. Diurnal variations were controlled by performing experiments at the same time of the day, at 12–17 p.m., when the activity of renin-aldosterone axis is known to slowly decrease [14]. This study focused on changes in PRA and plasma aldosterone with short time intervals during the phase of increasing blood ethanol concentration, which is considered crucial for ethanol diuresis [3], and the following 1.5–2.0 hours. Earlier studies have been concerned with long-term effects [12], longer time intervals [13], or renin-aldosterone axis during hangover [12,13].

We observed increasing PRA along with rising blood ethanol concentrations. When blood ethanol had achieved maximal levels, no further rise of PRA was seen. This is in disagreement with data of Farmer and Fabre [5]. These authors suggested that increased PRA was due to stress caused by withdrawal of alcohol, but our results do not support such a suggestion. Thus, neither heart rate nor blood pressure rose during our experiments, which is evidence against increased sympathetic tone. We would rather favour the idea that dehydration following rapid loss of water due to ethanol diuresis was the mean reason for increased PRA.

Plasma aldosterone concentration did not change significantly, but showed a decreasing trend. This implies dissoci-

TABLE 1

EXPERIMENTS

Time	30	60	90	120	140	150	160	180	210	240 min
RR systolic (mm Hg)										
A	90	90	95	90		85		85	90	
B	125	95	85	100		90		95	110	90
C	126	130	120	124		125		116	116	114
D	115	132	118	115		120		115	120	112
Mean ±	114.0	111.8	104.5	107.3		105.0		102.8	109.0	105.3
SD	±16.8	±22.3	±17.3	±15.2		±20.4		±15.3	±13.3	±13.3
Heart rate (beats/min)										
A	78	56	64	64		84		68	72	76
B	75	44	48	64		64		68	68	66
C	88	76	80	88		76		76	80	76
D	80	88	88	92		92		92	96	95
Mean ±	80.3	66.0	70.0	77.0		79.0		76.0	79.0	78.3
SD	±5.6	±19.7	±17.7	±15.1		±11.9		±11.3	±12.4	±12.1

TABLE 2

CONTROLS

Time	30	60	90	120	140	150	160	180	210	240 min	Total urine volume (ml)	(ml/kg b.wt)
Urine												
1				540						180	720	10.6
2					400					533	933	11.2
RR diastolic (mm Hg)												
1	75	70	68	64		68		64	60	65		
2	70	60	65	70		60		60	70	70		
RR systolic (mm Hg)												
1	115	110	112	115		110		110	110	115		
2	90	85	85	85		85		85	85	80		
Heart rate (beats/min)												
1	66	62	64	62		64		62	64	62		
2	48	48	48	54		54		54	54	48		

ation between PRA and plasma aldosterone during the early phase of ethanol intoxication. This agrees with an earlier report from this laboratory [12], showing reduction of plasma aldosterone in spite of increased PRA in ambulatory subjects 3 hours after starting ethanol ingestion (1.5–2.3 g ethanol per kg body weight). In prolonged studies, however, (14–24 hours), PRA was positively correlated to plasma aldosterone, both in ambulatory subjects [12], and in healthy volunteers studied in a metabolic ward [13]. Interestingly, in pentobarbital anaesthetized dogs [4], ethanol appeared to inhibit release of aldosterone in response to hemorrhage. During the early phase of ethanol intoxication, release of aldosterone may be inhibited, leading to the above mentioned lack of response to rising PRA. While the mechanism behind this remains unclear, hypothetical explanations may be offered.

First, ethanol may alter angiotensin I-converting enzyme activity, thereby decreasing the rate of angiotensin II formation. Lacking experimental evidence of such an effect of ethanol, this remains speculation. Secondly, ethanol may alter the response of adrenal cortical cells to angiotensin stimulus by inhibiting sodium-potassium ATP:ase [8, 9, 10]. Third, increasing serum concentrations of Na^+ and decreasing K^+, resulting in rising Na^+/K^+-ratio, may inhibit release of aldosterone [1,6]. Both phenomena occurred in this study, and in an earlier investigation concerning ambulatory subjects [12]. In addition to these postulated effects of ethanol on sodium, potassium and Na^+K^+-ATP:ase, still other ones cannot be excluded. Thus, while the reason for dissociation of PRA and plasma aldosterone concentration during early ethanol intoxication remained unclear in our study, the observation appears important, and calls for further investigation.

Serum osmolality showed a rising trend, which did not

achieve significance, however. This may be explained by the rather small number of subjects investigated. Rising serum osmolality along with increasing blood ethanol concentration has been reported earlier [15]. Neither blood pressure nor heart rate did change, which indicates that no major sympathetic discharge was likely to take place in the early phase of moderate ethanol intoxication in supine man. In upright position, however, a similar degree of ethanol intoxication may activate baro- and volume receptors, resulting in increased sympathetic nervous activity [11,16].

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