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EFFECT OF ACUTE ETHANOL ADMINISTRATION ON RAT PLASMA PROTEIN SYNTHESIS

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Abstract—Plasma albumin synthesis was inhibited within 1·5 hr of oral administration of ethanol (4 ml/kg) to adult rats. The inhibition was temporary however, as albumin synthesis returned to normal at 3·0 hr and rose significantly thereafter. In contrast, the same dose of ethanol, administered intraperitoneally, did not inhibit albumin synthesis. Fibrinogen synthesis was stimulated by ethanol administration, the effect being observed after 3 hr. The effect of ethanol on total plasma proteins was similar to that on albumin.

It is concluded that the effect of ethanol on plasma protein synthesis is dependent on the level of ethanol attained in the blood, which is influenced by the route of administration. The reversal of the initial inhibition and subsequent elevation of synthesis by ethanol may be mediated by the pituitary–adrenal and pituitary–thyroid axis.

IT IS well known that ethanol is metabolized in the liver in mammals.[1] Liver is also the major site for the synthesis of plasma proteins, except gamma globulins.[2] A relationship may exist therefore between the metabolism of ethanol and plasma proteins. The acute effect of a massive dose of ethanol on *in vivo* plasma protein synthesis is not very well understood. The precise time interval between the administration of ethanol and its effects on plasma protein synthesis is also not clear. Recently Jeejeebhoy *et al.*[3] have studied the acute effect of ethanol on albumin, fibrinogen and transferrin synthesis 2 hr after the administration of ethanol. However, the effects may be apparent and differ in magnitude earlier or later than 2 hr. The relationship between blood ethanol levels and plasma protein synthesis has not been elucidated. It is probable that there are independent control mechanisms for the synthesis of different plasma proteins.[4] In this study the incorporation of [1 – ^{14}C]-glycine into albumin, fibrinogen and total plasma proteins was estimated at four time intervals, (1·5, 3·0, 4·5 and 6·0 hr), after intraperitoneal or oral administration of ethanol, in order to determine plasma protein synthesis at different blood ethanol levels. Blood ethanol levels were also estimated at various time intervals.

MATERIALS AND METHODS

Male, Wistar rats, weighing between 200–250 g were maintained on a synthetic diet providing 24 per cent protein (Hindustan Lever Ltd.); food and water were available *ad lib* until sacrifice. Ethanol at a dose of 4 ml/kg body wt was injected intraperitoneally as a 20 per cent solution in saline, administered orally as a 50 per cent solution. [1 – ^{14}C]-Glycine, 6 μCi/100 g body wt, (19 mCi/mM from Isotope Division, Bhabha Atomic Research Centre, Trombay) was injected intraperitoneally 1·5, 3·0, 4·5 and 6·0 hr after the ethanol administration. Blood was collected in heparinized

TABLE 1. EFFECT OF ACUTE ORAL ADMINISTRATION OF ETHANOL ON PLASMA PROTEIN METABOLISM

Time after ethanol adm. (hr)	Albumin			Fibrinogen			Total plasma proteins		
	Concn (g%)	Sp. act. (cpm/mg)	RSR	Concn (mg%)	Sp. act.	RSR	Concn (g%)	Sp. act.	RSR
Control (0)	2·728 (±0·103)	700 (±30)	100 (±4·3)	258 (±21)	1503 (±183)	100 (±12·2)	6·285 (±0·303)	1142 (±126)	100 (±11·0)
1·5	2·420[f] (±0·192)	547[a] (±21)	78·1[a] (±3·0)	231 (±15)	1411 (±304)	93·8 (±20·2)	5·371[b] (±0·074)	848[b] (±39)	74·2[b] (±3·4)
3·0	2·764 (±0·125)	708 (±73)	101·1 (±10·4)	279 (±6)	1678 (±176)	111·6 (±11·7)	6·051 (±0·213)	1130 (±62)	98·9 (±5·4)
4·5	2·519[f] (±0·123)	80·7[e] (±63)	115·2[e] (±9·0)	273 (±49)	2090[d] (±353)	139·0[d] (±23·5)	5·708[f] (±0·258)	1373[d] (±45)	120·1[d] (±3·9)
6·0	2·425[d] (±0·127)	890[a] (±47)	127·1[a] (±6·7)	215[d] (±15)	3175[b] (±886)	211·1[b] (±58·9)	5·321[a] (±0·093)	1519[b] (±65)	132·9[b] (±5·7)

$P \geqslant 0{\cdot}05$ not significant; a, $P < 0{\cdot}001$; b, $0{\cdot}005 > P > 0{\cdot}001$; d, $0{\cdot}02 > P > 0{\cdot}01$; e, $0{\cdot}025 > P > 0{\cdot}02$; f, $0{\cdot}05 > P > 0{\cdot}025$.

TABLE 2. EFFECT OF INTRAPERITONEAL ADMINISTRATION OF ETHANOL ON PLASMA PROTEIN METABOLISM

Time after ethanol adm. (hr)	Albumin			Fibrinogen			Total plasma proteins		
	Concn (g%)	Sp. act. (cpm/mg)	RSR	Concn (mg%)	Sp. act.	RSR	Concn (g%)	Sp. act.	RSR
Control (0)	2·697 (±0·171)	709 (±62)	100 (±8·7)	189 (±39)	1290 (±88)	100 (±6·8)	6·004 (±0·458)	1108 (±78)	100 (±7·0)
1·5	2·425[d] (±0·030)	784 (±5)	110·5 (±0·7)	214 (±27)	2087[b] (±311)	161·7[b] (±24·1)	4·922[b] (±0·173)	1244[f] (±23)	112·2[f] (±2·0)
3·0	2·591 (±0·239)	1141[a] (±136)	160·9[a] (±19·2)	162 (±19)	3300[a] (±320)	255·7[a] (±24·8)	5·746 (±0·334)	1754[a] (±80)	158·2[a] (±7·2)
4·5	2·348[d] (±0·115)	1244[a] (±167)	175·4[a] (±23·5)	185 (±67)	6909[a] (±720)	535·4[a] (±55·8)	5·196[c] (±0·194)	2626[a] (±389)	236·9[a] (±35·1)
6·0	2·719 (±0·155)	1000[a] (±24)	141·0[a] (±3·4)	168 (±60)	6719[a] (±10 4)	520·7[a] (±80·9)	5·981 (±0·215)	1966[a] (±56)	177·3[a] (±5·0)

$P \geq 0{\cdot}05$ not significant; a, $P < 0{\cdot}001$; b, $0{\cdot}005 > P > 0{\cdot}001$; c, $0{\cdot}01 > P > 0{\cdot}005$; d, $0{\cdot}02 > P > 0{\cdot}01$; f, $0{\cdot}05 > P > 0{\cdot}025$.

syringes by cardiac puncture 2 hr after the administration of the isotope. A group of six to eight animals was used at each time point. The fractionation, counting and calculation of relative synthesis rate (RSR) of albumin and fibrinogen have been described in detail elsewhere.[5] In brief, albumin was fractionated and quantitated by the method of Fernandez *et al.*;[6] fibrinogen was separated by the method used by Goodwin.[7] An aliquot of the separated proteins in 3 per cent (w/v) NaOH was counted in a liquid scintillation spectrometer at constant efficiency (65 per cent). [1 – ^{14}C]-Glycine incorporation into the proteins was expressed as specific activity (cpm/mg). The relative synthesis rate was calculated as

$$\text{RSR} = \frac{\text{Sp. act. in treated animal}}{\text{Sp. act. in control animal}} \times 100.$$

Specific activities were not corrected for normal protein concentration because plasma volume is altered by ethanol administration,[3] perhaps due to diuresis.[8] Plasma ethanol levels were determined by a modification of the method used by Williams *et al.*[9]

RESULTS

The results are summarized in Tables 1–3. Sleep was induced in all the animals within 5–10 min after the intraperitoneal administration of ethanol and intoxication persisted for about 5–6 hr. This was corroborated by the blood ethanol levels. However, following oral administration of the same dose of ethanol rats remained alert and showed no visible sign of intoxication. In orally-treated rats ethanol was detected in the blood only up to 3·5 hr.

Intraperitoneally-treated rats. At 1·5 hr the RSR of fibrinogen was increased by ethanol and continued to rise, showing more than five-fold increase at 4·5 and 6·0 hr. The response of albumin was delayed and at 1·5 hr there was no significant change in its RSR. The maximum increase was observed at 4·5 hr but even at 6·0 hr the RSR was significantly increased. The changes in total protein synthesis were similar to those of albumin, except that the rise at 1·5 hr was significant.

Orally-treated rats. Albumin synthesis was inhibited 1·5 hr after oral administration of ethanol but returned to normal at 3·0 hr and thereafter was significantly elevated. There was no effect on fibrinogen synthesis until 4·5 hr. Again the changes in total protein synthesis paralleled those of albumin.

TABLE 3. BLOOD ETHANOL LEVELS AFTER INTRAPERITONEAL AND ORAL ADMINISTRATION OF ETHANOL

Time after ethanol administration (hr)	Intraperitoneal (mg/ml)	Oral (mg/ml)
0 (control)	N.D.	N.D.
0·5	>4·08	1·77 ± 0·36
1·5	>4·08	0·293 ± 0·097
3·5	2·366 ± 0·375	0·122 ± 0·048
5·0	1·38 ± 0·39	N.D.
6·5	0·995 ± 0·228	N.D.
8·0	0·603 ± 0·195	N.D.
24·0	N.D.	N.D.

N.D. = Not detectable.

DISCUSSION

There was a significant inhibition of albumin synthesis 1·5 hr after oral administration of ethanol to rats. This confirms the findings of Jeejeebhoy *et al.*[3] However, this inhibition appears to be temporary, since at 3·0 hr the RSR rose to normal, when ethanol was still detectable in the blood. Surprisingly in i.p. treated rats no inhibition of synthesis was observed, even though blood ethanol levels were very high.

Thus a large amount of ethanol circulating in the body appears to overcome the inhibition. At longer times after administration, ethanol has an anabolic effect on plasma proteins in well-nourished rats. This effect may be mediated by hormones.

Ethanol is known to be a powerful activator of the pituitary-adrenal system.[10–12] According to Ellis,[10] the adrenocortical response corresponds to the period of detectable blood ethanol. Ethanol also seems to enhance thyroid function[13] and the release of thyroid hormones.[14] Jeejeebhoy *et al.*[3] have postulated that ethanol may interfere with the hepatic plasma protein synthesis through a disturbance of amino acid availability and utilization. In orally-treated animals the amino acid availability might have been affected because of the presence of ethanol in the small intestine. In everted sacs of rat small intestine alcohol exposure alters amino acid transport and is easily reversed.[15] Since adrenal corticosteroids and thyroid hormones are known to increase liver amino acids[16,17] the disturbance in amino acid availability may have been overcome in intraperitoneally treated rats due to very high blood ethanol levels and subsequent stimulation of pituitary-adrenal and pituitary-thyroid axis. Thus the acute effect of ethanol seems to be dependent on the ethanol level in the blood, which is dependent on the route of administration of ethanol.

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