Ethanol-induced increase in the penetration of exogenously administered L-dopa through the blood-brain barrier

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The flux of circulating substances through the blood-barrier occurs either through lipid barriers or via carrier-mediated mechanisms (Oldendorf 1975). Recently the existence of eight different and independent carrier systems have been demonstrated (Pardridge & Oldendorf 1977). One of these is a carrier system for neutral amino acids by which, among others, exogenously administered L-dopa may be assumed to pass into the brain (Oldendorf 1975).

Liljequist & Carlsson (1978) found that the dopa concentration in the mouse brain after exogenously administered L-dopa together with benserazid, α-methyltyrosine and pargyline, was higher in animals pretreated with ethanol.

The aim of the present study was to investigate whether the increased brain dopa concentration in the above mentioned study could be due to a change in the transport of L-dopa through the blood-brain barrier. It was felt that such an effect of low concentrations of ethanol on the penetration of an endogenously occurring compound through a biological membrane might help to throw some light upon the mode of action of ethanol.

Male rats (about 200 g) of the Sprague-Dawley strain (Anticimex, Sollentuna, Sweden) were used. Ethanol (20% w/v) 2 g kg^{-1} was injected intraperitoneally. Control rats received the equivalent volume of saline. Twenty min after the first injection all animals were injected with L-dopa 100 mg kg^{-1} intraperitoneally. At various times (10, 20, 40, 80 and 160 min after the L-dopa injection) the animals were decapitated and the brains immediately taken and frozen on dry ice and about 5 ml blood was collected in a tube containing EDTA. After homogenization of the brains and deproteinization (Atack & Magnusson 1978) the brains and the plasmas were purified on a strong action exchange column (Dowex 50 W × 4) (Atack & Magnusson 1970; Kehr et al 1972). Spectrophotofluorimetric analyses of dopa (Kehr et al 1972) and dopamine (Carlsson & Waldeck 1958; Atack 1973) were carried out.

Statistical significances were assessed by one-way analysis of variance followed by *t*-test, or by the Mann-Whitney U-test.

Tables 1 and 2 show that the concentrations of dopa and dopamine respectively, in whole brain were increased in animals pretreated with ethanol compared with the controls. This increase remained for at least 80 min.

The plasma concentration of dopa 10 min after the L-dopa injection was significantly increased in the ethanol group compared with controls but later there was no difference between alcohol-treated animals and controls (Table 3).

The ratio brain dopa/plasma dopa was calculated for each rat. This ratio was significantly increased in the ethanol-treated rats 20, 40 and 80 min after the L-dopa injection (Table 4).

The fact that both the brain dopa/plasma dopa ratio and the brain dopamine concentration were increased in the ethanol group compared with the controls for as long time as 80 min or more suggests that ethanol causes a change in the distribution of exogenously administered L-dopa between plasma and brain. The

Table 1. Effect of ethanol on rat brain concentrations of dopa after exogenously administered L-dopa. Ethanol 2 g kg^{-1} (20% w/v) or an equivalent volume of saline to the control rats was given followed 20 min later by L-dopa 100 mg kg^{-1} to all rats. At various intervals after the L-dopa injection the animals were killed. Dopa concentrations were measured in whole brain. Statistical significances were calculated by one-way analysis of variance followed by *t*-test.

	Time after L-dopa injection (min)				
	10	20	40	80	160
Controls μg g^{-1}					
Mean	1·69	2·01	2·56	0·88	0·12
± s.e.m.	±0·186	±0·083	±0·132	±0·126	±0·029
(n)	(6)	(6)	(17)	(6)	(6)
Ethanol-treated % of controls					
Mean	162	144	130	137	84
± s.e.m.	±12·8	±22·1	±5·6	±16·4	±19·2
(n)	(6)	(6)	(16)	(6)	(6)
P	<0·001	<0·001	<0·001	<0·01	N.S.

Table 2. Effect of ethanol on rat brain concentrations of dopamine after exogenously administered L-dopa The same experiment as in Table 1. Statistical significances were calculated by one-way analysis of variance followed by *t*-test.

	Time after L-dopa injection (min)				
	10	20	40	80	160
Controls μg g^{-1}					
Mean	1·00	1·16	1·65	0·88	0·61
± s.e.m.	±0·099	±0·079	±0·155	±0·068	±0·019
(n)	(6)	(6)	(11)	(6)	(6)
Ethanol-treated % of controls					
Mean	138	120	119	111	104
± s.e.m.	±9·1	±6·5	±7·7	±3·4	±3·2
(n)	(6)	(6)	(11)	(6)	(6)
P	<0·001	<0·005	<0·001	<0·1	N.S.

* Correspondence.

Table 3. Effect of ethanol on rat plasma concentrations of dopa after exogenously administered L-dopa. The same experiment as in Table 1. Statistical significances were calculated by one-way analysis of variance followed by *t*-test.

	Time after L-dopa injection (min)				
	10	20	40	80	160
Controls $\mu g\ g^{-1}$					
Mean	12·9	14·5	9·5	3·8	0·3
± s.e.m.	±1·64	±1·49	±0·39	±1·06	±0·06
(n)	(6)	(6)	(17)	(4)	(5)
Ethanol-treated % of controls					
Mean	148	104	86	117	119
± s.e.m.	±17·2	±9·5	±5·7	±7·1	±19·4
(n)	(6)	(4)	(16)	(4)	(5)
P	<0·001	N.S.	N.S.	N.S.	N.S.

through the blood-brain barrier into the brain. This could be a direct or indirect effect of ethanol on the blood-brain barrier due to a change in either the carrier mechanism or the barrier function. An alternative interpretation could be that ethanol causes a decrease in the plasma level of some other amino acids being transported into the brain by the same carrier as L-dopa leading to a higher carrier capacity available for the transport of L-dopa.

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Table 4. Effect of ethanol on the ratio brain dopa/plasma dopa after exogenously administered L-dopa. The same experiment as in Table 1. Statistical significances were calculated by the Mann-Whitney U-test.

	Time after L-dopa injection (min)				
	10	20	40	80	160
Median of controls	0·127	0·142	0·262	0·296	0·204
(Range)	(0·101–0·201)	(0·099–0·195)	(0·185–0·352)	(0·207–0·344)	(0·123–1·447)
(n)	(6)	(6)	(17)	(4)	(5)
Median of ethanol-treated	0·154	0·207	0·420	0·357	0·340
(Range)	(0·125–0·174)	(0·159–0·383)	(0·248–0·585)	(0·348–0·367)	(0·134–0·524)
(n)	(6)	(4)	(16)	(4)	(5)
P	N.S.	<0·025	<0·001	<0·025	N.S.

early and transient increase in the plasma concentration of dopa does not remain long enough to explain the increases in brain dopa. This peak of the plasma dopa indicates that ethanol influences the distribution of dopa in other locations as well. An ethanol-induced decrease in plasma volume (Pohorecky & Newman 1978) leading to a secondary increase in plasma dopa concentration may be considered in this context.

Subsequent work in this laboratory has shown that ethanol has a similar influence on the distribution of exogenously administered tyrosine, tryptophan and α-methyldopa as on dopa. We may thus be dealing with a general effect of ethanol on the distribution of amino acids.

These observations are in agreement with those of Picard & Morélis (1977) who found that the uptake of several large neutral amino acids over the blood-brain barrier of mice is increased by previously intraperitoneally administered ethanol.

These results favour the hypothesis that ethanol facilitates the penetration of dopa and other amino acids

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