Cyclic nucleotides and ethanol withdrawal head-twitches in mice

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In a previous communication it was reported that head-twitches are a consistent response to ethanol withdrawal in mice and this response was interpreted as hallucinatory (Hammond & Schneider, 1973). The relationship of ethanol withdrawal head-twitches to 5-hydroxytryptamine and noradrenaline and to drugs that inhibit the biosynthesis of or antagonize these amines has also been discussed (Collier, Hammond & Schneider, 1974).

We have explored the relationship of guanosine 3',5'-cyclic monophosphate (cyclic GMP) and adenosine 3',5'-cyclic monophosphate (cyclic AMP) to head-twitches induced by ethanol withdrawal, 5-hydroxytryptophan (5-HTP) or α-methyl-p-tyrosine (α-MPT).

Physical dependence on ethanol was induced in mice (T/O) strain; 23-25 g) with a once daily dose over a period of 4 days of 4, 5, 6 and 7 g/kg of ethanol as a 40% w/v solution in distilled water. Twenty-four hours after the last dose, head-twitches were counted for a period of 4 minutes. Fifteen minutes after injection of 5-HTP (400 mg/kg i.p.), or 6 h after α-MPT (200 mg/kg orally), head-twitches were also counted for 4 minutes. Drugs to modify the incidence of head-twitches were administered intracerebroventricularly (i.c.v.) under light ether anaesthesia or orally. Administration of modifying drugs was timed so that, after i.c.v. administration, the observation period fell 35-39 min later and after oral administration this period fell 60-64 min later.

Table 1 summarizes our findings on the modification by cyclic nucleotides, or some drugs interacting with them, of the incidence of head-twitches. Dibutyryl cyclic GMP increased and dibutyryl cyclic AMP lessened the incidence of head-twitches induced in all three ways. Theophylline also increased this incidence, whereas imidazole decreased only the response to 5-HTP. These results indicate a close involvement of cyclic nucleotides with the head-twitch response, including that to ethanol withdrawal. The effects of the amines may arise from interaction with cyclic nucleotides.

Table 1 Effects of drugs on incidence of head-twitches induced by ethanol withdrawal, 5-hydroxytryptophan (5-HTP; 400 mg/kg i.p.) or α-methyl-p-tyrosine (α-MPT; 200 mg/kg orally) in mice

			Mean head-twitch score, as percentage of control, induced by:		
Drug	*Dose*	*Route*	*Ethanol withdrawal*	*5-HTP*	*α-MPT*
Ethanol†	4 g/kg	oral	30**	30**	25**
Methergoline†	4 mg/kg	oral	10***	15***	0**
Noradrenaline†	5 μg	i.c.v.	25**	40***	25***
Theophylline	100 mg/kg	oral	260**	260***	185**
Imidazole	100 mg/kg	oral	115	20***	110
Dibutyryl cyclic GMP	50 μg	i.c.v.	228**	320**	175*
Dibutyryl cyclic AMP	100 μg	i.c.v.	10**	35**	5**

† Collier, Hammond & Schneider (1974).
i.c.v., intracerebroventricular.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (Mann-Whitney U test).

References

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