

The results show that some putative neurotransmitter substances can influence the concentration of cerebral cyclic AMP *in vivo*, and indicate that there may be a metabolic role for cyclic AMP in the C.N.S.

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## Evidence of a role for brain monoamines in ethanol dependence

P. J. GRIFFITHS, J. M. LITTLETON and A. ORTIZ\* (introduced by G. BROWNLEE)

*Department of Pharmacology, University of London King's College*

Brain monoamines have often been implicated in the neurochemical changes leading to ethanol dependence, although few attempts have been made to relate tolerance to, and dependence on ethanol with direct measurements of central monoamine metabolism.

We have measured changes in mouse brain monoamine concentrations during the chronic administration of ethanol by inhalation. Withdrawal of ethanol after ten days is followed by a marked withdrawal syndrome which lasts for some 12 h (Griffiths, Littleton & Ortiz, 1973).

In our experiments mice were killed by immersing them in liquid nitrogen after varying periods of ethanol administration and withdrawal. Brains were dissected out and taken for fluorimetric estimation of monoamines. Noradrenaline and dopamine were estimated by the method of Brownlee & Spriggs (1965). 5-Hydroxytryptamine was estimated by the method of Curzon & Green (1970).

There was an initial significant reduction in brain monoamine concentrations during ethanol administration, but this was short-lived. Otherwise chronic administration of ethanol was associated with a slow rise in catecholamines so that after ten days they were some 50% higher than controls. Withdrawal of ethanol at this time was associated with a further transient rise in catecholamine concentrations, followed by a fall back to control levels over the next 10 h. These changes were also shown to a smaller extent by brain 5-hydroxytryptamine.

Arresting the withdrawal syndrome by the intraperitoneal injection of ethanol (2 g/kg) also arrested the changes in brain monoamine concentrations associated with withdrawal.

The administration of the tyrosine hydroxylase inhibitor,  $\alpha$ -methyltyrosine methylester, and and dopamine  $\beta$ -hydroxylase inhibitor FLA-63 before ethanol withdrawal modified the withdrawal syndrome.

These experiments are thought to provide evidence for the involvement of noradrenaline, dopamine and perhaps 5-hydroxytryptamine in ethanol dependence and withdrawal.

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