Chronic administration of acetaldehyde to mice: behavioural and biochemical similarities with chronic ethanol administration

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

Department of Pharmacology, King's College, London

Acetaldehyde has been implicated by many workers in some of the pharmacological effects of ethanol, and recent theories ascribe an important role to acetaldehyde in ethanol dependence (Truitt & Walsh, 1971). If acetaldehyde formed from ethanol is responsible for the development of dependence on ethanol, then chronic administration of acetaldehyde alone should produce dependence of an ethanol type. Also, biochemical changes similar to those associated with ethanol dependence should be produced by acetaldehyde administration if they play some part in the production of dependence.

Griffiths, Littleton & Ortiz (1973a, b) reported that chronic administration of ethanol to mice by inhalation produces ethanol dependence, as shown by tolerance and a recognizable withdrawal syndrome, and also changes in brain catecholamine concentrations. We now report that chronic administration and withdrawal of acetaldehyde by inhalation will produce similar behavioural and biochemical changes. The methods were those described by Griffiths, Littleton & Ortiz (1973a, b).

Groups of male white mice were exposed to ethanol or acetaldehyde vapour for 10 days. Ethanol concentrations were increased from about 10 mg/l on the first day to about 25 mg/l on the last day. Acetaldehyde concentrations were increased from about 1 mg/l on the first day to about 4 mg/l on the last day of acetaldehyde administration. After 10 days' ethanol or acetaldehyde was withdrawn and behavioural changes assessed. At intervals mice were killed and blood and brain ethanol, and acetaldehyde concentrations, or brain catecholamine concentrations, were measured.

Concentrations of acetaldehyde in blood were similar in ethanol treated and acetaldehyde treated mice. Brain acetaldehyde concentrations were apparently higher in the ethanol treated group. Mice showed no increase in the rate of elimination of acetaldehyde from blood during chronic acetaldehyde administration. After withdrawal of acetaldehyde, blood and brain acetaldehyde concentrations fell to control levels within about 20 min, whereas the corresponding period for ethanol withdrawn mice was about 3 hours. The withdrawal syndromes for ethanol and acetaldehyde were similar, except that the syndrome of acetaldehyde withdrawal was shorter and more intense; and there was some degree of cross dependence. The changes in brain catecholamine concentrations, reported previously during chronic ethanol administration and withdrawal, were also shown by mice receiving acetaldehyde, although the time course of these changes during withdrawal was much shorter.

It is thought that these results suggest that acetaldehyde may play some part in the behavioural and biochemical changes associated with ethanol dependence.

This work was supported in part by a grant from the Benescience Foundation. Dr Ortiz received maintenance grants from the British Council and the Medical Council on Alcoholism.

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Hypothermia produced by inhibitors of catecholamine biosynthesis

J.M. LITTLETON* & SUSAN M. RYAN
(introduced by G. BROWNLEE)

Department of Pharmacology, King's College, London

Although there is little doubt that peripheral noradrenaline (NA) turnover is increased by cold stress, there is disagreement on the extent to which central NA turnover is altered. It has been reported that brain NA depletion is more rapid after inhibition of catecholamine biosynthesis in the rat when the animals are kept in a cold environment (Gordon, Spector, Sjoerdsma & Udenfriend, 1966) and this has been adduced as evidence for an increased central NA turnover. Others (e.g., Simmonds & Iversen, 1969) have found no increase in [^{3}H]-NA elimination from

brain under cold conditions, or an increase only in the hypothalamus (Simmonds, 1969).

The difference in results obtained may be related to the use of an inhibitor of catecholamine synthesis in Gordon's experiments, since it has been reported that α-methyl tyrosine can produce hypothermia (Papeschi & Randrup, 1973) and this may be the effect which is associated with the increased noradrenaline turnover, rather than the cold stress alone. To investigate this possibility we have attempted to relate hypothermia to brain catecholamine depletion in the rat after the administration of inhibitors of catecholamine biosynthesis (α-methyl tyrosine methylester, 400 mg/kg i.p.; 3-iodo-tyrosine, 200 mg/kg i.p.; and sodium diethyldithiocarbamate, 500 mg/kg i.p.). In addition, we have attempted to modify the effects of these drugs either by stimulating heat production after administration of thyroxine, or by inhibiting heat production with very large doses of methimazole, an inhibitor of thyroid hormone synthesis. We have found a relationship between hypothermia and dog brain catecholamine depletion, which is altered by exposing the animals to cold stress (4-5°) for 2 hours. This relationship is largely independent of drug treatment, except that α-methyl tyrosine produced a more marked hypothermia than was anticipated from the associated depletion of brain catecholamines.

It is thought that this relationship between hypothermia and central catecholamine depletion may explain some differences between interpretation of experimental results obtained by others. Also, it is suggested that this work may have implications for the feedback control of core temperature, and that it throws some doubt on the validity of using inhibition of brain catecholamine biosynthesis as a means of assessing central catecholamine turnover.

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The role of brain dopamine in the hyperactivity syndrome produced in rats after administration of L-tryptophan and a monoamine oxidase inhibitor

D.G. GRAHAME-SMITH & A.R. GREEN*

M.R.C. Unit and Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE

Administration to rats of tranylcypromine (20 mg/kg) followed 30 min later by L-tryptophan (100 mg/kg) results in a characteristic syndrome of hyperactivity and hyperpyrexia, which appears to be due to the central action of the increased rate of brain 5-hydroxytryptamine (5-HT) synthesis produced by this treatment (Grahame-Smith, 1971a). The role of brain catecholamines in the production of this syndrome has now been studied.

Injection of 2 x 200 mg/kg α-methyl p-tyrosine (α-MPT) i.p., a tyrosine hydroxylase inhibitor, at 18 and 16 h before administration of the tranylcypromine (20 mg/kg) followed 30 min later by L-tryptophan (100 mg/kg) completely abolished the hyperactivity and hyperpyrexia. At this time brain noradrenaline (NA) and dopamine (DA) concentrations were both decreased about 75%, while brain tryptophan and 5-hydroxytryptamine (5-HT) rose to the concentrations observed in rats not pretreated with αMPT. The αMPT analogue α-methyl m-tyrosine which does not inhibit brain catecholamine synthesis did not inhibit hyperactivity. Administration of L-dopa (150 mg/kg) i.p., 1 h after the second injection of α-MPT restored brain DA concentrations to 75% of control values, did not restore brain NA concentrations but did bring back the hyperactivity response to tranylcypromine and tryptophan. Brain tryptophan and 5-HT concentrations rose as before. The dopamine-β-hydroxylase inhibitor, disulfiram (400 mg/kg) i.p., given 6 h before the tranylcypromine and L-tryptophan did not inhibit hyperactivity. Disulfiram caused a 75% depletion of brain NA concentrations but had no effect on brain DA levels. These findings suggested that dopamine might be involved in the post-synaptic responses to increased 5-HT release produced by tranylcypromine and tryptophan treatment.