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Central actions of ibotenic acid and muscimol

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THE BIOLOGICAL activity of ibotenic acid and muscimol,[1] two isoxazoles found in mushrooms of the genus *Amanita*, and the structural similarities with glutamic acid and γ-aminobutyric acid (GABA), prompted an investigation of their possible action on central neurones. Experiments were carried out on spinal interneurones and Renshaw cells in cats (decerebrate or sodium pentobarbitone anaesthetized) using multibarrelled micropipettes for drug administration and recording.[2]

Ibotenic acid, administered electrophoretically as an anion from 0·2M pH 7 solutions (NaOH), was a more powerful excitant of spinal interneurones and Renshaw cells than L-glutamic acid (2M, pH 7). The excitant action, which was comparable to that of DL-homocysteic acid (0·2M, pH 7), was of slower onset and more prolonged duration than that of L-glutamic acid. If the taste enhancing properties of monosodium glutamate stem from a depolarization of taste receptors, a similar effect by ibotenic acid presumably accounts for the observation that the taste of this substance is apparently more intense than that of the glutamic acid salt.[1]

Muscimol, administered as a cation from 0·5M, pH 3 solutions (HCl), was a strong depressant of the spontaneous or chemically evoked firing of spinal interneurones and Renshaw cells. The activity of muscimol as a depressant was similar to that of GABA (0·5M, pH 3) and glycine (0·5M, pH 3)

administered with equal ejecting currents. The effect of this substance was not antagonized by strychnine administered electrophoretically in concentrations which blocked the depressant action of glycine.[3] Thus, with respect to its central action, muscimol is apparently a "GABA-like" amino acid,[3] as anticipated on structural grounds.[4]

It remains to be established whether ibotenic acid or muscimol pass through the blood–brain barrier after ingestion, so contributing to the neurological manifestations of *Amanita* poisoning. The excitant action of ibotenic acid and the depressant action of muscimol is in accordance with previously established structure–activity relationships for amino acids,[4] α-decarboxylation of an excitant leading to an amino acid with depressant activity. However, these isoxazoles are the first heterocyclic amino acids exhibiting such activity, and their relatively strong effects on central neurones indicates that further examination of analogues of glutamic acid and GABA which are of similarly restricted conformation might be rewarding in understanding the interaction between amino acids and membrane receptors.

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Intracellular distribution of pyridine nucleotides in the liver of rats after long-term exposure to carbon disulphide*

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PROLONGED exposure to carbon disulphide leads to disturbances in the urinary excretion of nicotinamide metabolites both in animals[1–3] and in human beings.[4] It seemed interesting to investigate whether the above phenomena are accompanied by changes in the levels of the individual pyridine nucleotides in some of subcellular fractions of liver cells.

The levels of the individual pyridine nucleotides were recently investigated in connection with exposure to other chemicals and some changes were found after administration of substances showing hepatotoxic and carcinogenic properties.[6–10]

METHODS

Female albino rats of the Wistar strain were exposed in a toxicological chamber to CS_2 vapours at concentration of approximately 2 mg/l. of air, for 5 hr daily, 6 days in the week for the total of 9

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