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Effect of valproic acid on 5-hydroxytryptamine turnover in mouse brain

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The effect of the antiepileptic drug valproic acid (di-n-propylacetic acid, 200 mg kg^{-1}) on brain 5-hydroxytryptamine (5-HT) synthesis during monoamine oxidase inhibition by pargyline hydrochloride (120 mg kg^{-1}) was studied in mice. Valproic acid increased 5-HT synthesis and elevated 5-hydroxyindoleacetic acid level in brain indicating that turnover of 5-HT is increased. The possible significance of this effect in relation to anticonvulsant action of valproic acid is discussed.

The anticonvulsant drug valproic acid (di-n-propylacetic acid) is currently used in the treatment of types of epilepsy (Pinder et al 1977). The drug increases the brain content of γ-aminobutyric acid (Godin et al 1969) and this is generally considered to be the basis of its anticonvulsant effect (Hammond et al 1981). However, its suppression of seizures does not always appear to be mediated by cerebral GABA (Goldstein 1979), indicating that other neurotransmitters may also be involved. It has recently been suggested that spinal 5-hydroxytryptamine (5-HT) may play a role in reduction of clonic pentetrazol convulsions following treatment with valproic acid (Lazarova et al 1983). Although it increases brain content of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of 5-HT, valproic acid has no significant effect on cerebral 5-HT turnover in mice (Horton et al 1977) or rats (Chung Hwang & Van Woet 1979). We have found the drug to increase 5-HT synthesis in mouse brain following inhibition of monoamine oxidase (MAO) activity by pargyline.

Materials and methods

Experiments were on female CBA mice (22–28 g) which had free access to food and water. Drugs or vehicles were injected intraperitonealy (i.p.) in a volume of 10 ml kg^{-1}. Valproic acid (200 mg kg^{-1}; Apilepsin, Krka) was dispersed in Tween 80 and 0·9% NaCl (saline) and administered 90 min before death. The MAO inhibitor pargyline hydrochloride (120 mg kg^{-1} Sigma), dissolved in saline, was given 30 min after DPA injection. When MAO is inhibited the effect of a drug on brain 5-HT synthesis can be measured (Neff & Tozer 1978). Mice were killed by cervical dislocation after which whole brains were rapidly removed and analysed for their content of 5-HT and 5-HIAA with the method of Curzon & Green (1970) modified in that the volume of n-heptane was 50% smaller. This did not affect recovery of 5-HT and 5-HIAA. Statistical analysis was with Student's *t*-test.

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Results and discussion

Fig.1 shows the effect of valproic acid on cerebral 5-HT and 5-HIAA content under control conditions and during MAO inhibition by pargyline. Valproic acid increased brain 5-HIAA but did not alter 5-HT. Pargyline treatment led to an accumulation of 5-HT and an accompanying decrease in 5-HIAA content. When valproic acid was administered before pargyline, the accumulation of 5-HT was significantly augmented and 5-HIAA was also increased. This indicates the valproic acid caused an increase in synthesis of cerebral 5-HT. These data suggest that the drug increases 5-HT turnover in brain which may lead to an enhancement of 5-HT transmission.

Horton et al (1977) did not find valproic acid to have an effect on 5-HT turnover in the brain of mice given

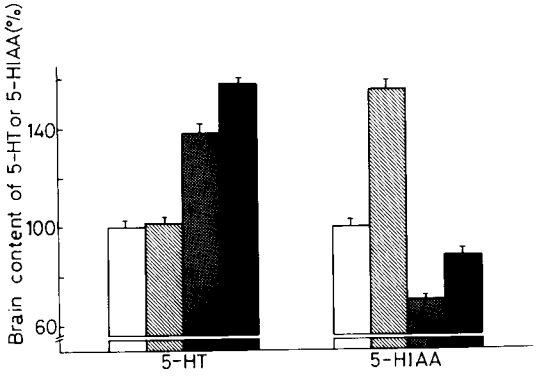

FIG. 1. Effect of valproic acid on brain 5-HT and 5-HIAA content in mice alone and following MAO inhibition by pargyline. In control animals (open columns) the content of cerebral 5-HT (759 ± 22 ng g^{-1}) and 5-HIAA (346 + 9 ng g^{-1}) was taken as 100%. The first injection (valproic acid 200 mg kg^{-1}, (striped columns) or vehicle) was given 30 min before the second injection (pargyline HCl 120 mg kg^{-1} (dotted columns) or vehicle). (Solid columns, both drugs), animals were killed 90 min after the first injection. Values represent mean ± s.e.m. for 6 mice per group. $^{a}P < 0·001$ vs control; $^{b}P < 0·01$ vs pargyline; $^{c}P < 0·01$ vs control; $^{d}P < 0·001$ vs pargyline.

probenecid, probably because of the variability of 5-HIAA values in their experiments (see Whitton et al 1983). Timing between valproic acid and pargyline application and decapitation could be the reason why Chung Hwang & Van Woet (1979) were unable to detect an increase of 5-HT turnover in rat brain after valproic acid (see Whitton et al 1983). Dipropylacetamide, the primary amide of valproic acid also increases the turnover of 5-HT in the brain of rat (Whitton et al 1983).

Lazarova et al (1983) have observed that treatments which reduce 5-HT transmission decrease the effectiveness of valproic acid against pentetrazol-induced convulsions. Our finding that the drug increased 5-HT turnover would appear to be consistent with assumption that the anti-convulsive effect of valproic acid is mediated by 5-HT at least in part. However, it has been observed (Horton et al 1977) that depletion of cerebral 5-HT did not affect the anticonvulsant action of valproic acid in mice exposed to audiogenic convulsions produced by 109 dB.

It has been postulated that a cerebral defficiency of 5-HT may be involved in the aetiology of some types of myoclonic epilepsy (Chadwick et al 1975), a condition in which valproic acid appears to be therapeutically useful (Pinder et al 1977). Fahn (1978) described a patient with severe post-anoxic intention myoclonus in whom 5-HIAA was undetectable in cerebrospinal fluid (CSF); valproic acid improved the patient during which time the CSF 5-HIAA level rose to normal. Current evidence suggests that 5-HT may play a role in protective effect of valproic acid in some types of seizure.

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The effect of indoramin on plasma lipids in hypercholesterolemic patas monkeys

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In patas monkeys fed a high cholesterol diet, chronic dosing with the antihypertensive agent indoramin increases the cholesterol ratio by raising the plasma HDL-C concentration. Epidemiological evidence suggests that increasing HDL-C reduces the incidence of coronary heart disease (CHD). If, therefore, indoramin is able to evoke these changes in man it may be expected to favourably influence the progress of CHD.

Epidemiological evidence from studies such as the Framingham Heart Study suggests that certain physiological parameters can be used to assess the risk of developing coronary heart disease (CHD) (Castelli 1984). Those physiological parameters of primary importance, known as risk factors, have been identified to be blood pressure and plasma lipid content. Elevation of either of these above the normal range predisposes towards the development of CHD.

Treatments to lower blood pressure have had beneficial effects upon the incidence of stroke and congestive heart failure in hypertensive patients, but despite this success it has proved difficult to show a concomitant reduction in CHD after treatment for hypertension. In some studies the treatment has been shown to increase the incidence of CHD. The reason for this finding is thought to be that current treatments aggravate one or more risk factors thereby negating the beneficial effect of lowering blood pressure (Ames 1983). One risk factor affected by drug therapy is the level and constituents of plasma lipids. The major plasma lipids, including cholesterol, are transported in the plasma in three main lipoprotein complexes: very low density (VLDL), low density (LDL) and high density (HDL).

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