THE ROLE OF BRAIN 5-HYDROXYTRYPTAMINE IN THE ANALGESIC ACTION OF CENTRALLY ACTING SYMPATHOMIMETICS

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Brain concentrations of 5-hydroxytryptamine are important in the analgesic actions of opiates and sympathomimetics, but not in that of cholinomimetics (Major & Pleuvry 1970; Pleuvry & Tobias 1971).

Some of amphetamine's undesirable actions (notably excitation) can be reduced by rendering the molecule stereochemically more rigid, and we have recently reported the activities of two contrasting rigid amphetamine derivatives, the exo and endo-isomers of 2-aminobenzonorbornene and their N-methyl derivatives (Burn et al 1980). The possible importance of 5-HT in the analgesic effects of the N-methyl derivatives is now reported.

Groups of female mice, 25-35 g, were used. Analgesia was assessed by counting the number of writhing movements during the 20 min following intraperitoneal injection of a 0.75% solution of acetic acid (100mg/kg). Locomotor activity of groups of 5 mice was measured using an Animex meter for the 2 h following drug dose. DL-p-chlorophenylalanine methyl ester, 150 mg/kg, (pCPA) was given twice daily for 3 days, drug challenge being 2 h after the last injection. Previous measurements of brain amines following p-chlorophenylalanine (cf the ester) showed that this pretreatment causes a selective reduction in whole brain 5-HT by 70%. 5-Hydroxytryptophan, 75 mg/kg, (5-HTP) was injected subcutaneously 10 min prior to drug challenge. This pretreatment more than doubles brain 5-HT concentration.

In the writhing test the ID_{50} values (mg/kg) were morphine sulphate 0.14, d-amphetamine sulphate 1.41, 2-aminoindane hydrochloride 0.70, exo N-methyl-2-aminobenzonorbornene fumarate 2.2 and endo N-methyl-2-aminobenzonorbornene fumarate 79.4.

5-HTP pretreatment decreased and pCPA increased the incidence of writhing following injection of acetic acid. The analgesic activity of d-amphetamine (4mg/kg) was virtually abolished by pCPA pretreatment. Whilst the analgesic activity of the rigid derivatives was also reduced by pretreatment with pCPA, the changes were much less, and in some instances were not statistically significant. In complementary experiments whilst the analgesic activity of amphetamine was greatly potentiated by 5-HTP pretreatment the potentiation of the rigid derivatives was not significant. Droperidol (0.5 mg/kg), though inhibiting writhing itself, had no significant effect on the analgesic action of amphetamine.

On the activity meter, the excitatory action of amphetamine (5 mg/kg), and the inhibitory action of 2-aminoindane (5 mg/kg) were unaffected by pCPA pretreatment. The excitatory action of amphetamine was abolished by droperidol, as was the depressant action of 2-aminoindane.

That tryptaminergic rather than dopaminergic mechanisms are involved in sympathomimetic analgesia is confirmed, but curiously the amphetamine derivatives which are more selective, in that they lack amphetamine's excitatory actions, seem less dependent on brain 5-HT concentrations.

Burn, P. et al (1980) J. Pharm. Pharmac. 32: 87-91
Major, C.T & Pleuvry, B.J. (1970) Br. J. Pharmac. 40: 143-144p
Pleuvry, B.J. & Tobias, M.A. (1971) Ibid. 43: 706-714