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Long term effects of p-chloroamphetamine on hippocampal 5-hydroxytryptamine release

C.A. MARSDEN

Department of Physiology and Pharmacology, Medical School, Queens Medical Centre, Nottingham, NG7 2UH

ρ-Chloroamphetamine (PCA) produces a long lasting depletion of brain 5-hydroxytryptamine (5-HT) which may be associated with a cytotoxic effect on brain 5-HT neurones (Sanders-Bush & Massari, 1977). An initial effect of PCA however is a rapid and short lasting release of brain 5-HT (Sanders-Bush & Massari, 1977) accompanied by a characteristic behavioural response consisting of forepaw treading, lateral headweaving, hind limb abduction and straub tail (Curzon, Fernando & Marsden, 1978). It is possible to monitor this release in the unrestrained unanaesthetized rat using *in vivo* voltammetry (Marsden, Conti, Strope, Curzon & Adams, 1979). The present communication concerns the long term effects of PCA administration on 5-HT release.

Release was monitored in male Wistar rats (220–280 g) using electrochemical electrodes implanted chronically into the dorsal hippocampus (Adams, Conti, Marsden & Strope, 1978). A potential (+0.7 V) was applied and the current changes which followed oxidation of electroactive compounds by the working electrode were recorded. Behavioural effects were scored using a 0-3 rating scale (Curzon, Fernando & Marsden, 1978).

PCA (5.0 mg/kg i.p.) produced a marked behavioural response ($n = 6$) and a concurrent increase in current (i) values ($n = 4$) which did not occur in rats pretreated with ρ-chlorophenylalanine (200 mg/kg) so probably reflects increased release of 5-HT. When L-tryptophan (50 mg/kg i.p.) was given 30 min before PCA (5 mg/kg) there was a significant increase in both the behavioural score ($P<0.001$) and 5-HT release ($P<0.01$). A second dose of PCA (5 mg/kg) given 24 h after the first significantly reduced the behavioural score and 5-HT release ($P<0.001$) compared to the response produced by the first dose. The behavioural and 5-HT release effects were restored by pretreating rats with L-tryptophan (50 mg/kg) 30 min before the second PCA injection. This result indicates that at 24 h the effects of PCA on 5-HT turnover are still reversible. When the second dose of PCA was given 10 days after the first there was still a significant reduction in both the behavioural score and 5-HT release compared with the response after the first injection. However, L-tryptophan (50 mg/kg) pretreatment failed to restore either the behavioural effects or the release of 5-HT, indicating at this stage that the effects of PCA on 5-HT turnover are largely irreversible. When the MAO inhibitor tranylcypromine (20 mg/kg i.p.) was given in place of L-tryptophan at 10 days the administration of PCA did result in a delayed and very exaggerated behavioural response but only a small increase in current (i) values indicating marked 5-HT receptor stimulation accompanied by relatively low 5-HT release.

The results are consistent with the suggestion that PCA has a long term cytotoxic action on 5-HT neurones and indicate that this may be accompanied by the development of post-synaptic receptor supersensitivity.

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