Supersensitivity of cerebral dopamine receptors during on-going chronic (six months) administration of trifluoperazine to rats

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Tardive dyskinesias occurring during chronic antipsychotic drug therapy are thought to be due to the development of overactivity of striatal dopamine (DA) function (Marsden, Tarsy & Baldessarini, 1975). Repeated administration of antipsychotic drugs to rodents for 1–2 weeks results in a decrease of the evidence for DA receptor blockade seen on acute administration (Asper, Baggiolini, Burki, Lauener, Ruch & Stille, 1973). Withdrawal of antipsychotic drugs after a few weeks of therapy is associated with development of apparent supersensitivity of DA receptors (Tarsy & Baldessarini, 1973). We now report changes in indices of cerebral DA receptor activity in rats during continuous six months chronic administration of trifluoperazine.

Male Wistar rats (200 $\pm$ 10g) received either trifluoperazine hydrochloride (approximately 3 mg kg^{-1} day^{-1}; stabilised in distilled water) or distilled water alone for 6 months. In the first 2 weeks, animals receiving trifluoperazine showed decreased spontaneous locomotor activity, mild catalepsy, and loss of stereotypy to apomorphine (0.5 mg/kg s.c.). This evidence for functional blockade of cerebral DA receptors was accompanied by an increase in DA turnover (as judged by the elevation of striatal and mesolimbic dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) levels; $P < 0.05$) and by inhibition of DA (1–150 μM) stimulation of striatal adenylate cyclase activity *in vitro* (DA EC50 for animals receiving trifluoperazine being 462% of that for control animals).

Three months from the beginning of drug administration the initial behavioural and biochemical effects of trifluoperazine had disappeared, the animals being indistinguishable from controls. After 6 months animals exhibited a greater stereotyped response to apomorphine (0.5 mg/kg s.c.) than observed in the control group ($P < 0.05$). At this time dopamine stimulation of striatal adenylate cyclase was enhanced in animals receiving trifluoperazine (DA EC50 for drug treated animals being 83% less than for control animals). Furthermore, at this time binding of [^{3}H]-spiperone (0.125–4.0 nM) to striatal preparations in the presence and absence of DA (10^{-4} M) showed an increase in receptor affinity but no change in the number of striatal binding sites compared to controls.

This data provides evidence to suggest that changes in at least some cerebral DA receptors occur in the course of continued antipsychotic drug administration. Such changes may be of relevance to the production of tardive dyskinesias in man.

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