functional transmitter input leading to "supersensitive" responses to exogenous agonists. This resembles the supersensitivity demonstrated in cerebral tissue to isoprenaline after chemical denervation. (Nahorski & Rogers, 1975).

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References

NAHORSKI, S.R., REES, M.W. & ROGERS, K.J. (1975). Cyclic AMP in developing chick brain: changes with ischaemia and catecholamine administration. *Br. J. Pharmac.*, **54**, 255-256P.

NAHORSKI, S.R. & ROGERS, K.J. (1975). Altered sensitivity of β-adrenoceptor-mediated cyclic AMP formation in brain. *Br. J. Pharmac.* (in press).

A primate model of acute dystonic reaction to neuroleptics

G.M. ANLEZARK*, C.D. MARSDEN & B.S. MELDRUM

Department of Neurology, Institute of Psychiatry, London, SE5 8AF

A small proportion of patients (5% or less) treated with classical neuroleptic drugs of the butyrophenone and phenothiazine series develop acute dystonic reactions in the initial few days of therapy. The mechanism by which these reactions are produced is unknown, but the antipsychotic action of neuroleptics is thought to be due to blockade of central dopamine synapses.

In the course of testing the neuroleptics haloperidol (0.6-1.2 mg/kg i.v.) and pimozide (0.1-2.5 mg/kg i.v.) in the photosensitive Senegalese baboon, *Papio papio*, we discovered that three animals showed a dystonic response (Meldrum, Anlezark & Trimble, 1975). One animal showed the abnormal response only after the highest dose of pimozide and was not used in the subsequent experiments. The other two invariably showed the response with all doses tested. The normal response to neuroleptics in these baboons was sedation and a reduction in spontaneous motor behaviour lasting up to 5 hours. The abnormal response was characterized by episodes of compulsive gnawing, tongue protrusion, neck extension and trunk twisting and by licking accompanied by salivation and hyperventilation lasting up to 7 hours. This dystonic reaction was also produced by chlorpromazine (5 and 25 mg/kg i.m.), but not by thioridazine (3 and 7 mg/kg i.v.). It was abolished by the anticholinergics benztropine (0.2 mg/kg i.v.) and hyoscine (20 and 50 μg/kg i.v.). This is analogous to the situation in human patients, in whom anticholinergic drugs dramatically abolish acute dystonic reactions to neuroleptics. Thioridazine is a potent antipsychotic which has few extrapyramidal side effects, perhaps because it possesses high inherent anti-muscarinic activity (Miller & Hiley, 1974).

In acute experiments, the neuroleptics cause increased turnover and release of dopamine in the rat striatum (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970), and dystonic postures and movements are provoked by L-DOPA in some patients with Parkinson's disease. A possible explanation of dystonic reactions to neuroleptic drugs is that the dopamine release that they cause activates dopaminergic synapses not blocked by the neuroleptics. If this is so, depletion of central dopamine by reserpine or the tyrosine hydroxylase inhibitor, α-methyl-p-tyrosine (AMPT) should reduce or abolish the abnormal responses. Pretreatment with AMPT alone (200 mg/kg i.p. in a single dose or 150 mg/kg i.p. x 3) had little effect on the dystonic response to haloperidol (1 mg/kg i.v.), but pretreatment with reserpine (2 mg/kg i.p.) and AMPT (200 mg/kg i.p. or 150 mg/kg i.p. x 2) decreased the severity of the dystonic response to haloperidol and delayed its onset.

References

ANDÉN, N-E., BUTCHER, H., CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1970). Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.*, **19**, 303-314.

MELDRUM, B.S., ANLEZARK, G.M. & TRIMBLE, M. (1975). Drugs modifying dopaminergic activity and behaviour, the EEG and epilepsy in *Papio papio*. *Eur. J. Pharmac.*, **32**, 203-213.

MILLER, R.J. & HILEY, C.R. (1974). Anti-muscarinic properties of neuroleptics and drug-induced Parkinsonism. *Nature, Lond.*, **248**, 596-597.