References

ARREGUI, A., EMSON, P.C. & SPOKES, E.G. (1978). Angiotensin-converting enzyme in substantia nigra: reduction of activity in Huntington's disease and after intra-striatal kainic acid in rats. *Eur. J. Pharmac.*, **52**, 121–124.

BARBEAU, A. (1975). Potentiation of levodopa effect in man. *Lancet*, **2**, 683–684.

CROSSMAN, A.R., WALKER, R.J. & WOODRUFF, G.N. (1974). Problems associated with iontophoretic studies in the Caudate nucleus and Substantia nigra. *Neuropharmac.* **13**, 547–552.

DAVIES, J. & DRAY A. (1976). Substance P in the Substantia nigra. *Brain Res.*, **107**, 623–627.

MIYAMOTO, M. & NAGAWA, Y. (1977). Mesolimbic involvement in the locomotor stimulant action of TRH in rats. *Eur. J. Pharmac.*, **44**, 143–152.

MROZ, E.A. & LEEMAN, S.E. (1977). Substance P. *Vitam & Horm.*, **35**, 209–281.

Effects of dopamine receptor agonists and antagonists in the rat nucleus accumbens

S.B. FREEDMAN, CHRISTINE P. WAIT & G.N. WOODRUFF

Department of Physiology and Pharmacology, University of Southampton, Bassett Crescent East, Southampton, SO9 3TU

ADTN (2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene) is a potent dopamine receptor agonist and a powerful locomotor stimulant (Woodruff, 1978). We have studied the effects of the (+)- and (−)-enantiomers of ADTN and of some other potential dopamine receptor agonists in the nucleus accumbens using two techniques.

First we have evaluated the activity of these compounds on the dopamine-sensitive adenylate cyclase in nucleus accumbens homogenates. Secondly, we have investigated their locomotor-stimulant activity following injections into the nucleus accumbens of conscious rats. For both sets of experiments we used previously-described methods (Woodruff, Watling, Andrews, Poat & McDermed, 1977).

On the dopamine-sensitive adenylate cyclase in the nucleus accumbens, (+)-ADTN was approximately 125 times more active than (−)-ADTN in increasing cyclic AMP production, the EC_{50} values (concentrations producing 50% of maximum response) being 120 nM and 15 μM respectively.

Dopamine and 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine (SKF 38393) were also active agonists on the adenylate cyclase, with EC_{50} values of 6.2 μM and 110 nM respectively, although the latter compound produced only 70% of the maximal response. SKF 38393 is also active in the striatum (Setler, Sarau, Zirkle & Saunders, 1978).

The ADTN analogue 2,3-dihydroxy-9-amino-9,10-dihydrophenanthrene, which is inactive on other dopaminergic systems (Nichols, Toth, Kohli & Kotake, 1978), was similarly inactive in the nucleus accumbens.

The effects of dopamine, ADTN and SKF 38393 on cyclic AMP production were blocked by fluphenazine (1 μM), but were unaffected by tiapride (100 μM) or sulpiride (100 μM).

The bilateral injections of (±)-ADTN (116 nmol each side) or of SKF 38393 (197 nmol each side) into the nucleus accumbens caused an intense stimulation of locomotor activity, with durations of action of 21 h and 13 h respectively. 2,3-dihydroxy-9-amino-9,10-dihydrophenanthrene (142 nmol) was inactive as a locomotor stimulant.

The locomotor stimulant actions of ADTN was blocked by fluphenazine, sulpiride or tiapride, the antagonists being injected directly into the nucleus accumbens 3 h after the ADTN injection. The ID_{50} values (dose in nmol required on each side of the nucleus accumbens to produce 50% inhibition of the ADTN response) were: (±)-sulpiride 1.7; fluphenazine 2.4; tiapride 4.7. A similar pattern of antagonist activity was found using SKF 38393 as the agonist.

Our results support the concept of dopamine receptor involvement in drug-induced hyperactivity, and suggest that the nucleus accumbens dopamine receptors are similar to those in the striatum. Sulpiride and tiapride, which differ from classical neuroleptics in that they are inactive as antagonists on the dopamine-sensitive adenylate cyclase, are nevertheless potent antagonists of the behavioural actions of ADTN and SKF 38393.

We thank Dr Carl Kaiser, SK&F, Dr John McDermed, Burroughs Wellcome, and Dr David Nichols for gifts of drugs. S.B.F. is a S.R.C. Case student in conjunction with Chemitechna.

References

NICHOLS, D.E., TOTH, K.E., KOHLI, J.D. & KOTAKE, C.K. (1978). 2,3-dihydroxy-9-amino-9,10-dihydrophenanthrene, a rigid congener of dopamine and isoapomorphine. *J. Med. Chem.*, **21**, 395–397.

SETLER, P., SARAU, H.M. ZIRKLE, C.L. & SAUNDERS, H.L. (1978). The central effects of a novel dopamine agonist. *Eur. J. Pharmac.*, **50**, 419–430.

WOODRUFF, G.N. (1978). Biochemical and pharmacological aspects of dopamine receptors. In: Dopamine, *Adv. Biochem. Psychopharmac.* **19**, Ed. Roberts, P.J., Woodruff, G.N. & Iversen, L.L., pp. 89–118. New York: Raven Press.

WOODRUFF, G.N., WATLING, K.J., ANDREWS, C.D., POAT, J.A. & MCDERMED, J.D. (1977). Dopamine receptors in rat striatum and nucleus accumbens; conformational studies using rigid analogues of dopamine. *J. Pharm. Pharmac.* **29**, 422–427.

Differential rotational behaviour after unilateral 5,7-dihydroxytryptamine induced lesions of the dorsal raphé nucleus

T.P. BLACKBURN, G.A. FOSTER, C.G. HEAPY & J.D. KEMP
(introduced by D.T. GREENWOOD)

Research (Biology) Department, ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TG

Rats with unilateral lesions of the dopamine containing neurones, of the ascending nigrostriatal pathway exhibit behavioural asymmetry (Andén, Dahlström, Fuxe & Larsson, 1966) and a functional imbalance in locomotor control expressed as a characteristic form of 'rotational' behaviour when administered drugs which facilitate dopaminergic neurotransmission (Ungerstedt, 1971).

However, the relationship between dopamine dependent rotational behaviour and the possible involvement of other neurotransmitter systems is far from clear since lesions outside the nigrostriatal pathway induce similar behavioural phenomena (Glick, Jerussi & Fleischer, 1976). Recent evidence suggests that 5-HT afferents from the dorsal (DRN) and medial (MRN) raphe nuclei modulate nigrostriatal function (Dray, Conye, Oakley & Tanner, 1976; Haigler & Aghajanian, 1974; Pasquier, Kemper, Forbes & Morgane, 1977). The aim of the present study was to assess the effect of unilateral dorsal raphé lesions on nigrostriatal function as might be revealed by rotational behaviour.

Adult male rats of the Alderley Park SPF strain (180–200 gm) were pretreated with pargyline HCl (50 mg/kg i.p.) one hour before the injection of 5,7-dihydroxytryptamine (5,7-DHT), dissolved in 2 μl of 0.9% saline (8 μg base/μl). The neurotoxin was injected under halothane anaesthesia over a period of 5 min through the cerebellum at an angle of 47° to the vertical plane in a Kopf stereotaxic instrument (DRN coordinates: 5.4 caudal to lambda, 1.0 lateral to the midline and 9.4 ventral to the surface of the skull, according to the Skinner stereotaxic atlas). Sham operated controls received 2 μl of saline with and without ascorbate antioxidant (0.2 mg/ml).

Unilateral DRN lesions induced transient spontaneous tight ipsiversive rotation following surgery which had disappeared by the second post-operative day. On the third post-operative day all rats were tested for rotational behaviour by challenging with either apomorphine or 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT); rotational behaviour being assessed in automated rotometers (Barber, Blackburn & Greenwood, 1973). When challenged with apomorphine, lesioned animals displayed a dose-related ipsilateral rotational response (0.3 turns/min at 0.5 mg/kg s.c. to 4.5 turns/min at a dose of 1.0 mg/kg s.c.). In contrast, administration of 5-MeODMT to these animals produced a dose related contraversive rotational response (1.4 turns/min at a dose of 1.0 mg/kg s.c. to 4.2 turns/min at a dose of 7.5 mg/kg s.c.). All drug induced rotations were completely blocked by haloperidol (0.3 mg/kg i.p.), and significantly reduced by methysergide (10 mg/kg i.p.).

Following rotational studies, groups of lesioned animals were sacrificed and regional neurochemical assays revealed a significant reduction in striatal, anterior cortical and nigral 5-HT concentration on the lesioned side (67%, $P < 0.001$; 34%, $P < 0.005$ and 45%, $P < 0.001$ respectively). A significant and selective decrease in the uptake of [^{3}H]-5-HT was also observed in cortical and striatal tissue on the lesioned side.

Our observations are consistent with other studies in which L-5-hydroxytryptophan evoked contralateral rotation in rats with unilateral 5,7-DHT induced lesions of the DRN-forebrain tract at the level of the medial forebrain bundle (Jacobs, Simon, Ruimy & Trulson, 1977; Azmitia & Segal, 1978). The available neurochemical data suggests that the main effect of unilateral lesions of the DRN is to cause a loss of forebrain 5-HT possibly resulting in supersensitivity on the denervated side; an effect revealed by contralateral rotation in response to 5-HT agonists.

References

ANDÉN, N.E., DAHLSTRÖM, A., FUXE, K. & LARSSON, K. (1966). Functional role of the nigro-striatal dopamine neurones. *Acta pharmac.*, **24**, 263–274.