and by atropine. The response to opiates, but not that to atropine, was antagonized by naloxone.

The receptors involved were then characterized using the μ and δ-receptor classification of Lord *et al.*, (1977). The opiate μ-receptor, as found in the guinea-pig ileum, is equally sensitive to the enkephalins and the classical opiate agonist, normorphine, whilst the δ-receptor, as found in the mouse vas deferens, is considerably less sensitive to normorphine than to the enkephalins. In addition, the concentration of naloxone required to antagonize the enkephalins is ten times higher in the mouse vas deferens than in the guinea pig ileum whilst normorphine is reversed by low concentrations of naloxone in both tissues.

From Table 1 it is clear that the rat rectum is considerably more sensitive to the enkephalins than to normorphine and that the effect of the enkephalins, but not that of normorphine, is relatively resistant to antagonism by naloxone. Thus, in both these respects, the rectum is similar to the mouse vas deferens. The opiate receptors in the rat rectum would thus appear to be of the δ-type.

References

LORD, J.A.H., WATERFIELD, A.A., HUGHES, J. & KOSTERLITZ, H.W. (1977). Endogenous opioid peptides: multiple agonists and receptors. *Nature, Lond.* **267**, 495–499.

NIJKAMP, F.P. & VAN REE, J.M. (1978). Effects of endorphins on different parts of the gastro-intestinal tract *in vitro* in: *Characteristics and Function of Opioids*, ed. J.M. van Ree and L. Terenius p. 179–180, Elsevier/North Holland, Amsterdam.

SHAW, J.S. & TURNBULL, M.J. (1978). *In vitro* profile of some opioid pentapeptide analogues. *Eur. J. Pharmac.* **49**, 313–317.

Effects of peptides on neurones in the substantia nigra and nucleus accumbens

R.D. PINNOCK, M.J. TURNBULL & G.N. WOODRUFF

Department of Physiology and Pharmacology, University of Southampton, Bassett Crescent East, Southampton, SO9 3TU and Department of Biology, I.C.I. Pharmaceuticals Division, Alderley Park, Macclesfield

It is now clear that peptides play an important role in the brain. Indirect evidence suggests that TRH (pyroglutamyl-histidyl-prolineamide) and MIF (prolyl-leucyl-glycineamide) might influence the activity of the nigro-striatal and mesolimbic dopaminergic pathways (Barbeau, 1975; Miyamoto & Nagawa, 1977). Both Substance P (Mroz & Leeman, 1977) and angiotensin-converting enzyme (Arregui, Emson & Spokes, 1978) occur in the substantia nigra and Substance P has been shown to have direct effects on neurones in the substantia nigra (Davies & Dray, 1976). In the present investigations we have studied the effects of substance P, TRH, MIF and angiotensin II on neurones in the rat substantia nigra and nucleus accumbens.

Female Wistar rats (150–200 g) were anaesthetised with urethane (1.5 g/kg). Action potentials were recorded extracellularly and drugs were applied microiontophoretically using 6-barrelled micropipettes as previously described (Crossman, Walker & Woodruff, 1974). The recording barrel contained pontamine sky blue (2%) in NaCl soln. (0.2 M). The other barrels each contained one of the following: Substance P (0.7 mM); angiotensin II (10 mM) (each in 20 mM acetic acid, pM 4.5); TRH (48 mM, pH 4.5); MIF (55 mM, pH 4.5); dopamine HCl (200 mM, pH 4.0). All peptides were ejected as positive ions. In the case of MIF, experiments were carried out to ensure that the drug was expelled from the micropipette under the conditions used. Each peptide was tested on between 14 and 96 neurones.

Both MIF and TRH (up to 100 nA for 120 s) failed to influence the activity of neurones in either the nucleus accumbens or in the zona compacta (SNC) or the zona reticulata (SNR) of the substantia nigra. The inhibitory of dopamine in the nucleus accumbens was unaffected by MIF or TRH. Angiotensin II was similarly inactive on substantia nigra neurones when applied with currents of up to 100 nA for 160 seconds. Substance P, on the other hand, caused a powerful, dose-dependent, stimulation of neurones in the substantia nigra. The excitations produced by Substance P were of slow onset and long duration and were apparent both in the SNC and in the SNR. A total of 65 of the 96 cells tested were excited by Substance P.

Our results are consistent with a functional role for Substance P in the substantia nigra but provide no evidence to support the hypothesis that TRH, MIF or angiotensin II might be transmitters in the areas investigated.

We are grateful to Dr J. Morley, I.C.I. for carrying out the MIF measurements. R.D.P. is a S.R.C. Case student in conjunction with I.C.I.

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.