Short communications

The absence of cocaine- and 6-hydroxydopamine-induced supersensitivity to oxymetazoline in the rat anococcygeus muscle

A. GIBSON AND D. POLLOCK

Department of Pharmacology, University of Glasgow, Glasgow, G12 8QQ, Scotland

Neither cocaine nor 6-hydroxydopamine potentiated the responses of the anococcygeus muscle to oxymetazoline, suggesting that the specific supersensitivity to noradrenaline produced by these drugs is due to abolition of neuronal uptake mechanisms.

Both cocaine and 6-hydroxydopamine (6-OHDA) produce a specific increase in the sensitivity of the rat anococcygeus muscle to noradrenaline (NA), with no effect on the responses to acetylcholine (ACh) or potassium chloride (Gibson & Pollock, 1973). It has been suggested that at least part of the supersensitivity produced by cocaine in other tissues is due to a direct action on the postsynaptic cell (Kalsner & Nickerson, 1969; Maxwell, Wastila & Eckhardt, 1966; Varma & McCullough, 1969). However, the specificity of the supersensitivity following both cocaine and 6-OHDA in the anococcygeus suggests a presynaptic site of action such as inhibition or destruction of the neuronal uptake processes for catecholamines (Iversen, 1967). If the latter is indeed the mechanism then neither procedure should potentiate the responses of an adrenoceptor agonist which is not a substrate for the uptake processes. In this study, the effects of cocaine and 6-OHDA on the responses of the anococcygeus muscle to oxymetazoline, an α-adrenoceptor agonist not taken up by adrenergic nerve terminals (Birmingham, Paterson & Wojcicki, 1970; Mujic & van Rossum, 1965) were examined.

Methods.—Anococcygeus muscles from male Wistar rats (200–250 g) were dissected and set up in organ baths as described previously (Gibson & Pollock, 1973). Dose/% response curves for oxymetazoline were obtained from not less than 6 muscles in each experimental group. The pD_2 value (Ariens & van Rossum, 1957) for each dose/% response curve was calculated, and mean pD_2 values for each experimental group were compared using the Student's t test.

Cocaine was added to the Krebs bathing medium to give a concentration of 3 μM.

6-OHDA was administered intraperitoneally (2×50 mg/kg on day 1; 2×100 mg/kg on day 4; muscles were examined on day 6).

Drugs used were cocaine hydrochloride (Cockburns), 6-hydroxydopamine chloride (Calbiochem), and oxymetazoline hydrochloride (Allen & Hanburys).

Results.—The anococcygeus muscle responded to very low concentrations of oxymetazoline, the threshold dose (0·1 nM) being 100 times less than that for noradrenaline. The responses were completely abolished by phentolamine (10 nM). The effects of cocaine and 6-OHDA on the pD_2 values for oxymetazoline are shown in Table 1.

TABLE 1. *Effects of cocaine and 6-hydroxydopamine (6-OHDA) on pD_2 values and maximum responses of the anococcygeus muscle to oxymetazoline*

	$pD_2 \pm$S.E. (M)	Max ± S.E. (g)	n
Control	8·87±0·24	7·0±0·2	11
Cocaine	8·65±0·18	7·0±0·6	8
6-OHDA	8·48±0·22	7·0±0·4	8

Neither cocaine nor 6-OHDA significantly altered the pD_2 value for oxymetazoline in the anococcygeus. Neither treatment had any effect on the maximum response of the muscle to the agonist.

Discussion.—Kalsner & Nickerson (1969) found that cocaine potentiated the responses of the aortic strip to methox-

amine; methoxamine is not taken up by adrenergic nerves. However, Trendelenburg, Maxwell & Pluchino (1970) found that cocaine did not potentiate the effects of methoxamine on the nictitating membrane, and suggested that cocaine-induced supersensitivity to NA in this tissue resulted from inhibition of neuronal uptake. The present results suggest that the same is true in the rat anococcygeus muscle, since cocaine failed to potentiate the response of the muscle, to oxymetazoline.

6-Hydroxydopamine has been shown to produce a chemical sympathectomy of the anococcygeus muscle (Gibson & Gillespie, 1973), and also to produce a specific supersensitivity to NA (Gibson & Gillespie, 1973; Gibson & Pollock, 1973). Since 6-OHDA did not produce supersensitivity to oxymetazoline it appears that the specific supersensitivity to NA was due to destruction of the adrenergic nerve terminals and hence the neuronal uptake processes. The results confirm that chemical sympathectomy of the anococcygeus fails to produce the unspecific postsynaptic type of supersensitivity which follows surgical denervation (Trendelenburg, 1966). This type of supersensitivity was also absent in the heart following chemical sympathectomy (Haeusler, Haefely & Thoenen, 1969).

In conclusion, the failure of both cocaine and 6-OHDA to potentiate the responses of the rat anococcygeus muscle to oxymetazoline suggests that the specific supersensitivity produced by these procedures is due to abolition of the uptake processes of adrenergic nerves.

The authors wish to express their gratitude to Dr. D. Jack of Allen & Hanburys for the gift of oxymetazoline. A. Gibson is an MRC scholar.

REFERENCES

ARIENS, E. J. & VAN ROSSUM, J. M. (1957). pD_x, pA_x, and pD'_x values in the analysis of pharmacodynamics. *Archs. int. Pharmacodyn. Ther.*, **110**, 275–299.

BIRMINGHAM, A. T., PATERSON, G. & WOJCICKI, J. (1970). A comparison of the sensitivities of innervated and denervated rat vasa deferentia to agonist drugs. *Br. J. Pharmac.*, **39**, 748–754.

GIBSON, A. & GILLESPIE, J. S. (1973). The effect of immunosympathectomy and of 6-hydroxydopamine on the responses of the rat anococcygeus to nerve stimulation and to some drugs. *Br. J. Pharmac.*, **47**, 261–267.

GIBSON, A. & POLLOCK, D. (1973). The effects of drugs on the sensitivity of the rat anococcygeus muscle to agonists. *Br. J. Pharmac.* **49**, 506–513.

HAEUSLER, G., HAEFELY, W. & THOENEN, H. (1969). Chemical sympathectomy of the cat with 6-hydroxydopamine. *J. Pharmac. exp. Ther.*, **170**, 50–61.

IVERSEN, L. L. (1967). The uptake and storage of noradrenaline. Cambridge University Press.

KALSNER, S. & NICKERSON, M. (1969). Mechanism of cocaine potentiation of responses to amines. *Br. J. Pharmac.*, **35**, 428–439.

MAXWELL, R. A., WASTILA, W. B. & ECKHARDT, S. B. (1966). Some factors determining the response of rabbit aortic strips to dl-norepinephrine-7-H^3 hydrochloride and the influence of cocaine, guanethidine and methylphenidate on these factors. *J. Pharmac. exp. Ther.*, **151**, 253–261.

MUJIC, M. & VAN ROSSUM, J. M. (1965). Comparative pharmacodynamics of sympathomimetic imidazolines; studies on intestinal smooth muscle of the rabbit and the cardiovascular system of the cat. *Archs. int. Pharmacodyn. Ther.*, **155**, 432–449.

TRENDELENBURG, U., MAXWELL, R. A. & PLUCHINO, S. (1970). Methoxamine as a tool to assess the importance of intraneuronal uptake of l-norepinephrine in the cats' nictitating membrane. *J. Pharmac. exp. Ther.*, **172**, 91–99.

TRENDELENBURG, U. (1966). Mechanisms of supersensitivity and subsensitivity to sympathomimetic amines. *Pharmac. Rev.*, **18**, 629–640.

VARMA, D. R. & MCCULLOUGH, H. N. (1969). Dissociation of supersensitivity to norepinephrine caused by cocaine from inhibition of ^{3}H-norepinephrine uptake in cold-stored smooth muscle. *J. Pharmac. exp. Ther.*, **166**, 26–34.

(*Received June* 18, 1973)