Table 1 Effects of drugs on paired hemibladder preparations at different temperatures

Drug	Concentration (μM)	n	Temperature °C (s.e. mean)	Response % control (s.e. mean)	P
Hyoscine	0.3	7	33.7 (0.4)	67 (5)	
			21.4 (0.8)	92 (5)	<0.01
Hyoscine	0.3	4	33.1 (0.5)	56 (12)	
			38.5 (0.5)	47 (12)	>0.05
Hexamethonium	300	4	33.5 (0.5)	45 (9)	
			21.6 (0.6)	85 (5)	<0.01
Eserine	8	6	33.1 (0.4)	162 (17)	
			23.1 (0.5)	120 (6)	<0.01

The pelvic nerves were stimulated maximally with 0.5 ms duration pulses at 8 Hz for 7 s every 2 minutes. Drug-induced changes in the response of the tissues were measured when they became maximal.

with 5% CO_2: 95% O_2. The pelvic nerve was stimulated with bipolar platinum electrodes at 8 Hz for 7 s every 2 min, and contractions of the longitudinal muscle were recorded on a Grass RPS 7C8A polygraph via Grass FTO3C force-displacement transducers.

Hyoscine (0.3 μM) produced a maximum blockade of the response to nerve stimulation that was greatest at 38°C, and least at room temperature (21°C, Table 1). Doubling the stimulation period to 14 s or increasing the concentration of hyoscine to 3 μM did not increase the magnitude of the blockade ($n=3$). In contrast with this, hyoscine (0.3 μM) did block the effects of exogenous acetylcholine at room temperature ($n=4$). Hexamethonium (0.3 mM) was also ineffective against the response to nerve stimulation at room temperature, but not at 33°C. Eserine (8 μM) increased the responses to nerve stimulation more at 33°C than at room temperature (Table 1). The response to electrical stimulation at 21°C was probably due to excitation of nervous elements because tetrodotoxin (0.3 μM) abolished the contractions ($n=2$).

These results indicate that the parasympathetic innervation to the bladder exhibits the pharmacological characteristics of a mixed nerve, the cholinergic component of which is only effective above room temperature. At room temperature the innervation is almost entirely non-cholinergic.

References

WEETMAN, D.F. (1972). The guinea-pig isolated, innervated bladder preparation: the effects of some autonomic drugs. *Archs int. Pharmacodyn. Ther.*, **196**, 383–392.

WEETMAN, D.F. & TURNER, N. (1973). The effects of ganglion blocking agents on the isolated, innervated bladder of the guinea-pig. *Archs int. Pharmacodyn. Ther.*, **201**, 100–105.

Evidence for two distinct types of postsynaptic α-adrenoceptor

SUSAN M. BENTLEY, G.M. DREW & SUSAN B. WHITING

Department of Pharmacology, Allen & Hanburys Research Ltd., Ware, Hertfordshire SG12 0DJ, U.K.

Prazosin lowers blood pressure in animals (Constantine, McShane, Scriabine & Hess, 1973) and man (Cohen, 1970). Its primary mode of action is thought to be blockade of vascular α-adrenoceptors (Wood, Phelan & Simpson, 1975; Cavero, 1976). Moulds & Jauernig (1977) showed that prazosin antagonized the contractile effect of noradrenaline in isolated spiral strips of human visceral arteries but, in contrast to phentolamine, was inactive against noradrenaline on peripheral arteries. We have investigated the α-adrenoceptor blocking action of prazosin in more detail by determining its ability to antagonize responses to exogenous phenylephrine and noradrenaline and to sympathetic nerve stimulation *in vivo*. Phentolamine was included in the study for comparison. All drugs were given intravenously.

In pithed rats phentolamine competitively antagonized the vasopressor responses to phenylephrine and noradrenaline. The doses of phentolamine required to produce phenylephrine and noradrenaline dose-ratios of 10 (DR_{10}) were 0.24 and 0.46 mg/kg respectively. Prazosin was a competitive antagonist of phenylephrine; its DR_{10} was

0.0125 mg/kg. In contrast, prazosin had little or no effect on the pressor responses to low doses of noradrenaline (30–300 ng/kg) but reduced those to higher doses (>1 μg/kg). Pretreatment with propranolol or cocaine did not markedly alter the interaction between prazosin and noradrenaline.

The α-adrenoceptor blocking actions of phentolamine and prazosin were also examined in chloralose anaesthetized cats, from which the right adrenal gland had been removed. In these experiments, matched submaximal pressor responses to single doses of phenylephrine and noradrenaline and to right splanchnic nerve stimulation were obtained before and after administration of the antagonist. Phentolamine caused a dose-related reduction in the response to each stimulus; the mean doses of phentolamine which reduced by 50% (ED_{50}) the responses to phenylephrine, noradrenaline and nerve stimulation were 0.20, 0.38 and 1.22 mg/kg respectively. The corresponding ED_{50} values for prazosin were 0.04, 2.69 and >10 mg/kg respectively. Thus prazosin was about 5 times more potent than phentolamine against phenylephrine, but was much less potent against noradrenaline and nerve stimulation.

The results of these experiments suggest that there maybe two types of postsynaptic α-adrenoceptors. Phenylephrine stimulates only one type and prazosin blocks only this type. Low doses of noradrenaline stimulate the prazosin-insensitive type and high doses stimulate both types. Phenotolamine blocks both types of α-adrenoceptor. The general distribution of these two types of receptors is not known but those innervated by the right splanchnic nerve in the cat seem to be predominantly of the prazosin-insensitive type. The prazosin-insensitive receptors may resemble the presynaptic α-adrenoceptors located on the terminals of the adrenergic nerves supplying the rabbit pulmonary artery (Cambridge, Davey & Massingham, 1977) and rat heart (Cavero, Lefèvre & Roach, 1977) at which prazosin is a weak antagonist and phenylephrine is a weak agonist.

References

CAMBRIDGE, D., DAVEY, M.J. & MASSINGHAM, R. (1977). Prazosin, a selective antagonist of postsynaptic α-adrenoceptors. *Br. J. Pharmac.*, **59**, 514P–515P.

CAVERO, I. (1976). Cardiovascular effects of prazosin in dogs. *Clin. Sci. mol. Med.*, **51**, 609s–612s.

CAVERO, I., LEFÈVRE, F. & ROACH, A. (1977). Further studies on cardiovascular effects of prazosin. *Fed. Proc.*, **36**, 955.

COHEN, B.M. (1970). Prazosin hydrochloride (CP-12, 299-1), an oral antihypertensive agent; preliminary clinical observations in ambulatory patients. *J. clin. Pharmac.*, **10**, 408–417.

CONSTANTINE, J.W., McSHANE, W.K., SCRIABINE, A. & HESS, H-J. (1973). Analysis of the hypotensive action of prazosin. In *Hypertension: Mechanisms and Management*, ed. Onesti, G., Kim, K.E. and Moyer, J.H., pp. 429–444. Grune and Stratton Inc.

MOULDS, R.F.W. & JAUERNIG, R.A. (1977). Mechanism of prazosin collapse. *Lancet*, **i**, 200–201.

WOOD, A.J., PHELAN, E.L. & SIMPSON, F.O. (1975). Cardiovascular effects of prazosin in normotensive and genetically hypertensive rats. *Clin. exp. Pharmac. Physiol.*, **2**, 297–304.

Calcium, cyclic amp and the response of rat descending colon to angiotensin, to prostaglandin E_2 and to potassium chloride

ANN D. CROCKER, I.M. MAYEKA & K.A. WILSON

The Pharmacological Laboratories, The Department of Pharmacy, University of Aston, Birmingham B4 7ET

The increased intracellular calcium for muscle contraction may arise from intracellular or extracellular sources (Van Bremmen, Farinas, Casteels, Gerba, Wuytack & Deth, 1973) perhaps associated with altered cyclic AMP levels (Marshall & Kroeger, 1973). Smooth muscle responses to angiotensin (Khairallah, Vadaparampil & Page, 1965) and prostaglandins (Coceani & Wolfe, 1966) are sensitive to changes in extracellular calcium. The role of calcium and cyclic AMP in the response of rat descending colon to angiotensin, Prostaglandin E_2 and potassium has now been investigated.

Isotonic contractions were recorded of muscle preparations from male Wistar rats suspended in aerated Tyrode solution. Preparations were exposed to a calcium-free Tyrode containing EDTA (0.025 mmol). Half-maximal responses to angiotensin were reduced to $7.8 \pm 1.3\%$ ($n=6$) after 15 min whereas half-maximal responses to prostaglandin E_2 and potassium were reduced to $50.8 \pm 4.9\%$ ($n=6$) and $39.2 \pm 5.6\%$ ($n=6$) respectively. The reduction of angiotensin responses was significantly greater than those of prostaglandin E_2 or potassium ($P<0.001$). SKF525A inhibits calcium influx associated with depolarization (Kalsner, Nickerson & Boyd, 1970). Preparations were exposed to calcium free Tyrode containing 2.6×10^{-5} mol SKF525A for 60 minutes. On reintroduction of calcium the tonic responses to angiotensin and prostaglandin E_2 were reduced and potassium was inactive. Subsequent removal of SKF525A allowed recovery of