Desensitization of the rat aortic strip to vasopressin by infusions of noradrenaline

G.J.S. ABRAHAM & P.A. NASMYTH

Department of Biochemical and Experimental Pharmacology, St. Mary's Hospital Medical School, London W2 1PG.

Eden & Nasmyth (1974) showed that when noradrenaline (400 ng kg^{-1} min^{-1}) was perfused for 30 min through an organ bath containing a rat aortic strip bathed in Krebs solution, it desensitized the tissue to noradrenaline. In order to determine whether or not the desensitization was specific for noradrenaline, the experiment was repeated using vasopressin as the agonist.

Responses of the rat aortic strip to vasopressin (1.5–2.5 mU ml^{-1}) were established before and after perfusing the organ bath with noradrenaline (400 ng kg^{-1} min^{-1}) for 30 min, the rate of infusion being based upon the weight of the animal from which the aorta had been removed. In four experiments the responses to vasopressin were reduced by 65–80% with a mean of 74%.

To determine if the β-adrenoceptors were involved in the phenomenon, the experiment was repeated with propranolol (3.3 μM) in the Krebs solution bathing the tissue. It was without effect on the responses to vasopressin and it did not prevent the desensitization produced by the infusion of noradrenaline. When phentolamine (5–7 μg kg^{-1} min^{-1}) was infused together with the noradrenaline, the response to the latter was blocked. Thirty minutes after stopping the infusion of both drugs, but continuing to perfuse Krebs solution through the organ bath at the rate of 10 ml min^{-1}, the responses to noradrenaline were fully restored and those to vasopressin were unaffected. Thus blockade of the α-adrenoceptors prevented the desensitization.

It was established that clonidine, which stimulates presynaptic α-adrenoceptors preferentially (Starke, Montel, Gayk & Merker, 1974), was 100 times less effective than noradrenaline on post-synaptic α-adrenoceptors in this tissue. Phenylephrine, which stimulates post-synaptic α-adrenoceptors preferentially (Starke, Endo & Taube, 1975) was equipotent with noradrenaline on these receptors.

When infusions of clonidine varying from 450 ng to 2.5 μg kg^{-1} min^{-1} were employed the responses to vasopressin in 5 experiments were reduced by 43–77% with a mean of 56%. Infusions of phenylephrine (52 μg kg^{-1} min^{-1}) reduced the responses to vasopressin by 24–40% with a mean of 32% in 4 experiments.

References

EDEN, E. & NASMYTH, P.A. (1974). The cardiovascular effects of L-dopa in the pithed rat. *Br. J. Pharmac.*, **51**, 473–480.

STARKE, K., ENDO, T., TAUBE, H.D. (1975). Pre- and post-synaptic components in effect of drugs with α adrenoceptor affinity. *Nature*, **254**, 440–441.

STARKE, K., MONTEL, H., GAYK, W. & MERKER, R. (1974). Comparison of the effects of clonidine on pre- and post-synaptic adrenoceptors in the rabbit pulmonary artery. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **285**, 133–150.

Effects of catecholamine antagonists on the milk-ejection reflex of the anaesthetized rat

G. CLARKE & D.W. LINCOLN

Department of Anatomy, University of Bristol.

The 'oxytocinergic' neurones of the supraoptic and paraventricular nuclei of the lactating rat display a rapid burst of action potentials (> 40 Hz, 2–4 s) every 5–15 min during suckling (Lincoln & Wakerley, 1975). This burst of neuronal activity releases a pulse of oxytocin (~ 1 mU) from the neurohypophysis; this circulates to the mammary glands, contracts the myoepithelial cells and ejects the milk. Catecholamines may be involved in the central control of this neuroendocrine reflex for both noradrenaline and dopamine release oxytocin and vasopressin when placed in the lateral ventricles of the brain (Kuhn, 1974; Bridges, Hillhouse & Jones, 1975). This study examines the effects of antagonists of noradrenaline and dopamine upon the milk-ejection reflex of the rat, for with the exception of the ergot alkaloids which prevent milk ejection in the conscious rat (Grosvenor & Turner, 1957) no such study has been reported.

Rats, from day 7–10 of lactation and separated from their young for 16 h, were anaesthetized with urethane (1.1 g/kg, i.p.) and the teat ducts of two mammary glands were cannulated to record intramammary pressure. Three hours later, and whilst the animals were still deeply anaesthetized, 10 pups were applied to the uncannulated nipples. Each milk ejection in the subsequent 3 h period of suckling was recorded; each ejection was associated with an abrupt rise in intramammary pressure and a concomitant

behavioural response from the pups. The antagonists were given i.v. after 60–90 min, i.e. after the occurrence of 5–8 milk ejections. In this control period, and after saline treatment, milk ejections were observed at regular intervals of 6.5 ± 2.3 min (s.d.).

The α-adrenergic blocking drug phentolamine (0.4 mg/kg) caused a three-fold increase in the interval to the first milk ejection following its administration. Higher doses were more effective, and at 1.6 mg/kg this milk ejection interval increased to about 120 minute. By contrast, the β-adrenergic antagonist propranolol (5 mg/kg) failed to block the reflex. Haloperidol, pimozide and metoclopramide, all considered as dopamine antagonists, also prevented milk ejection. Haloperidol and pimozide were equi-effective, causing a three-fold increase in the latency at 1.5 mg/kg, whereas 7.0 mg/kg metoclopramide was required for the same result. A six-fold increase in latency (i.e. 39 min) was obtained with 4.0 mg/kg haloperidol, 4.5 mg/kg pimozide and 12 mg/kg metoclopramide; the period of antagonism was related linearly to the dose. Partial responses, associated with the release of small pulses of hormone, were rarely observed. Further, the milk-ejection intervals which followed the initial delay were within the control range. A direct action of the drugs on the neurohypophysis or mammary glands was unlikely, since the milk-ejection responses to exogenous oxytocin and electrical stimulation of the neurohypophysis were not decreased. Hexamethonium (2 mg/kg) did not inhibit milk ejection, though it caused a similar reduction in blood pressure to that observed with the antagonists.

This work was supported by a grant from the Medical Research Council.

References

BRIDGES, T.E., HILLHOUSE, E.W. & JONES, M.T. (1975). The effect of dopamine on neurohypophysial hormone release *in vivo* and *in vitro*. *J. Physiol.*, **246**, 107P.

GROSVENOR, C.E. & TURNER, C.W. (1957). Evidence for adrenergic and cholinergic components in milk let-down reflex in lactating rat. *Proc. Soc. exp. Biol. Med.*, **95**, 719–722.

KUGH, E.R. (1974). Cholinergic and adrenergic release mechanism for vasopressin in the male rat: a study with injections of neurotransmitters and blocking agents into the third ventricle. *Neuroendocrinology*, **16**, 255–264.

LINCOLN, D.W. & WAKERLEY, J.B. (1975). Factors governing the periodic activation of supraoptic and paraventricular neurosecretory cells during suckling in the rat. *J. Physiol.*, **250**, 443–461.

The effects of prostaglandins E_1 and E_2 on heart rate responses to cervical sympathetic nerve stimulation and ganglion stimulant drugs in the anaesthetized mouse

W. FENIUK (introduced by B.J. LARGE)

Department of Pharmacology, School of Medicine, Thoresby Place, Leeds LS2 9NL.

Prostaglandins E_1 and E_2 inhibit the bradycardia caused by vagal stimulation in anaesthetized mice (Feniuk & Large, 1975). Their effect has now been studied on the tachycardia produced by either cervical sympathetic nerve stimulation (Large, 1975) or administration of drugs.

Anaesthetized mice were prepared as described by Feniuk & Large (1975). Following section of the left cervical sympathetic and both vagi, the intact right cervical sympathetic nerve was stimulated through bipolar electrodes (rectangular pulses; 0.5 ms duration; supramaximum voltage). Prostaglandins were injected i.v. when the tachycardia to a given frequency of stimulation had levelled and % changes were measured. In assessing the reduction of drug-induced tachycardia, prostaglandins were given 30–60 s prior to the third successive injection of the stimulant drug.

Initial mean arterial pressure was 52 ± 3 mm Hg and heart rate was 430 ± 9 bts/minute. Frequency-dependent tachycardia occurred with nerve stimulation, the maximum usually at 10 Hz ($\Delta HR = 208 \pm 11$ bts/min). Prostaglandins E_1 and E_2 caused dose-dependent inhibition of the tachycardia which seemed more pronounced at the lower frequencies of stimulation. There was also marked inhibition by the prostaglandins of the tachycardia produced by the muscarinic stimulant McN-A-343 (4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltri methyl ammonium chloride), but virtually no modi fication of the responses elicited by either DMPP (1,1 dimethyl-4-phenyl piperazinium) or by noradrenaline (Table 1). Similar results were obtained with the prostaglandins when nerve stimulation or DMPP injection was made in the presence of atropine (0.5 mg/kg) or when McN-A-343 injection was made after hexamethonium (2.5 mg/kg).

Although the results demonstrate that the prostaglandins can modify sympathetic transmission to the heart *in vivo*, their site of action is still unknown.