

tion of desipramine ( $0.2 \mu\text{g/ml}$ ) was progressive with time (from  $1.54 \mu\text{g/g}$  tissue after 10 min of exposure to  $15.00 \mu\text{g/g}$  after 180 min). Furthermore, accumulation of desipramine in the vas deferens was temperature dependant for the concentration was  $0.51 \pm 0.05 \mu\text{g/g}$  at  $4^\circ \text{C}$ ,  $1.19 \pm 0.1$  at  $18^\circ \text{C}$  and  $3.44 \pm 0.07$  at  $37^\circ \text{C}$  (30 min exposure).

Surgical denervation of the vas deferens as well as previous incubation with ouabain ( $10^{-5}\text{M}$ ), cocaine ( $10^{-4}\text{M}$ ) or imipramine ( $10^{-5}\text{M}$ ) did not change the accumulation of desipramine ( $6.6 \times 10^{-7}\text{M}$  for 30 min) in the vas deferens. These studies indicate that desipramine is stored in high concentrations in the vas deferens and suggest that only a fraction of this concentration is required for blocking the membrane pump which is of importance in explaining the potentiation of noradrenaline response.

#### REFERENCES

- BENVENUTI, F., BONACCORSI, A. & GARATTINI, S. (1967). Potentiation of noradrenaline isomers by cocaine and desipramine in the isolated vas deferens of the rat. *J. Pharm. Pharmac.*, **19**, 477-478.  
HAMMER, W. & BRODIE, B. B. (1967). Application of isotope derivative technique to assay of secondary amines: estimation of desipramine by acetylation with  $\text{H}^3$ -acetic anhydride. *J. Pharm. exp. Ther.*, **157**, 503-508.

#### Effects of catecholamines on the uteri of adult, immature and ovariectomized rabbits

K. R. BUTTERWORTH and M. J. RANDALL\*†, *Department of Pharmacology, St. Mary's Hospital Medical School, Paddington, London, W2*

In 1933 Gruber, talking about the uterus, stated "No single organ in the body has been studied as thoroughly by experimenters with more conflicting results and opinions . . .". Marshall (1969) states "Unfortunately, what was true in 1933 is still true in 1969, particularly with regard to the actions of the sympathomimetic amines". Thus the early investigations have now been extended and include immature rabbits and ovariectomized adult rabbits, both before and after oestrogen treatment. The modifications of the effects of adrenaline, noradrenaline and isoprenaline by adrenoceptor blocking agents also have been investigated.

Dutch (2.2-3.4 kg) and New Zealand White (3.8-5.1 kg) rabbits were used. The smaller strain of rabbit matures more quickly and hence immature Dutch rabbits were used at an earlier age (4-8 weeks, 0.57-1.235 kg) than the New Zealand White ones (7-11 weeks, 0.62-1.85 kg). The ovariectomized animals were used 28-35 days after removal of the ovaries. The immature and the ovariectomized rabbits which were treated with oestrogen received oestradiol benzoate ( $100 \mu\text{g/kg}$ ) in arachis oil (1 mg/ml) subcutaneously daily for 4 days. The isolated uteri were suspended in 25 ml Krebs, solution at  $37^\circ\text{C}$  and aerated with 5% carbon dioxide in oxygen.

Uteri of mature rabbits contract to adrenaline and noradrenaline and relax to isoprenaline. These are the well known responses which were used by Ahlquist in 1948 to demonstrate the presence of  $\alpha$ - and  $\beta$ -adrenoceptors in the uterus of this species. Using the uteri of immature rabbits, isoprenaline still had the same type of effect as in the adult but adrenaline and noradrenaline also caused an inhibition. Acetylcholine still caused a contraction. Similarly the uteri of ovariectomized rabbits responded by inhibition to adrenaline, noradrenaline and isoprenaline. When immature and ovariectomized animals were treated with oestrogen, the responses of these uteri then reverted to the type seen in the mature rabbit; namely contraction to adrenaline and noradrenaline and relaxation to isoprenaline.

After treatment of the uteri from untreated mature, oestrogen treated immature and ovariectomized rabbits with the  $\alpha$ -adrenoceptor blocking agent, phentolamine (0.1–1.0  $\mu\text{g/ml}$ ), all three catecholamines caused relaxation. Treatment of uteri from immature and ovariectomized animals with the  $\beta$ -adrenoceptor blocking agent propranolol (10–40 ng/ml) caused the inhibitory responses to adrenaline and noradrenaline to be converted to the excitatory type seen in the adult.

Thus it is concluded that both  $\alpha$ - and  $\beta$ -adrenoceptors are present in the uteri of mature and immature rabbits. The type of response obtained can be altered by choosing a catecholamine with a greater or lesser degree of  $\alpha$ - or  $\beta$ -agonist activity, by varying the level of oestrogen influence, or by the use of the appropriate type of adrenoceptor blocking agent.

† Present address: Pfizer Ltd., Sandwich, Kent.

#### REFERENCES

- AHLQUIST, R. P. (1948). A study of adrenotropic receptors. *Am. J. Physiol.*, **153**, 586–600.  
GRUBER, C. M. (1933). The autonomic innervation of the genito-urinary system. *Physiol. Rev.*, **13**, 497–609.  
MARSHALL, JEAN M. (1969). Adrenergic innervation of the female reproductive tract: anatomy, physiology and pharmacology. *Ergebn. Physiol.*, **62**, 6–67.

#### Effect of adrenalectomy upon some rat heart enzymes

B. A. CALLINGHAM and LAURA DELLA CORTE\*, *Department of Pharmacology, University of Cambridge*

One effect of adrenalectomy in the rat is an increase in the monoamine oxidase (MAO) activity of the heart (Avakian & Callingham, 1968) and, to a lesser extent in other organs (Caesar, Collins & Sandler, 1970). This increase in activity can be prevented by the administration of hydrocortisone to the adrenalectomized animals.

In an attempt to determine the nature of this effect, we have examined some of the enzymes found in rat heart homogenates, particularly those in the mitochondrial fraction where the bulk of the MAO is found. The possibility that morphological changes occur has been examined by means of electron microscopy of tissue sections and of mitochondrial pellets.

Adrenalectomized rats were maintained on sodium chloride solution (0.9% w/v) following operation and were killed between 10 and 42 days later. The hearts of these animals and of controls were homogenized in modified Chappell-Perry medium (Chappell & Perry, 1954) in which the editic acid (EDTA) is replaced by ethyleneglycol bis aminoethyl tetra acetic acid (EGTA) and magnesium ions omitted. Oxygen electrode measurements of the resulting mitochondrial fractions following differential centrifugation showed little or no uncoupling of phosphorylation when either succinate or pyruvate and malate were used as substrates. The mitochondria were therefore largely undamaged. Electron microscopy confirmed this.

MAO and NADH<sub>2</sub>-cytochrome-C reductase, both located in the outer membrane of the mitochondrion, significantly increased activity in whole homogenates and in mitochondria from the hearts of adrenalectomized rats. In our experiments MAO activity was 100% and NADH<sub>2</sub>-cytochrome-C-reductase 32% higher than control values in mitochondrial fractions. The increase in MAO activity was seen using several substrates, e.g. tyramine, dopamine and benzylamine. In contrast there was no