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Concentrations of desipramine in the vas deferens and potentiation of noradrenaline response

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Previous investigations have shown that a concentration of $3{\cdot}3 \times 10^{-7}$ g/ml of desipramine potentiates *in vitro* the contraction of the rat vas deferens induced by noradrenaline (Benvenuti, Bonaccorsi & Garattini, 1967). Since further experiments established that the potentiation decreased in relation to the time of exposure of the vas deferens to desipramine, a study was conducted to measure the level of desipramine in this preparation.

Vas deferens were isolated from Sprague-Dawley rats (200 ± 10 g) and suspended in a 20 ml organ bath at 37 C°. Krebs-Hucovič solution bubbled with carbogen was used for two parallel sets of experiments for obtaining cumulative dose response curves to noradrenaline (10^{-8}–10^{-4}M) and concentrations of desipramine after various periods (from 10 to 180 min) of exposure. Desipramine was measured by adapting the method of Hammer & Brodie (1967) consisting of the extraction of the drug with hexane from vas deferens homogenate and the successive acetylation with ^{3}H-acetyl anhydride. The sensitivity of the method was around 10 ng/vas deferens (weight 30–40 mg).

TABLE 1. *Effect of desipramine on noradrenaline activity and concentrations of desipramine in the rat vas deferens*

Desipramine (10 min) M	Noradrenaline ED50 before ED50 after	Concentration ng/mg
$3{\cdot}3 \times 10^{-9}$	2·4	<0·2
$1{\cdot}6 \times 10^{-7}$	4·7	<0·2
$3{\cdot}3 \times 10^{-7}$	4·5	$0{\cdot}42 \pm 0{\cdot}13$
$6{\cdot}6 \times 10^{-7}$	6·2	$1{\cdot}69 \pm 0{\cdot}09$
$1{\cdot}6 \times 10^{-6}$	2·2	$4{\cdot}54 \pm 0{\cdot}12$
$3{\cdot}3 \times 10^{-6}$	1·8	$6{\cdot}10 \times 0{\cdot}54$
$6{\cdot}6 \times 10^{-6}$	1·5	$13{\cdot}20 \pm 1{\cdot}32$

Table 1 summarizes the results obtained; the potentiation of noradrenaline by desipramine increased up to a certain concentration in tissues and then decreased with further increases in desipramine concentration.

The concentration of desipramine in the vas deferens was proportional to the concentration present in the medium and, when the concentration exceeded 10^{-6} g/ml, there was an inhibition of noradrenaline effect.

These studies suggested an uptake of desipramine by the vas deferens since the tissue/medium ratio ranged from 10 to 40. Other studies showed that the accumula-

tion of desipramine (0·2 μg/ml) was progressive with time (from 1·54 μg/g tissue after 10 min of exposure to 15·00 μg/g after 180 min). Furthermore, accumulation of desipramine in the vas deferens was temperature dependant for the concentration was $0{\cdot}51 \pm 0{\cdot}05$ μg/g at 4° C, $1{\cdot}19 \pm 0{\cdot}1$ at 18° C and $3{\cdot}44 \pm 0{\cdot}07$ at 37° C (30 min exposure).

Surgical denervation of the vas deferens as well as previous incubation with oubain (10^{-5}M), cocaine (10^{-4}M) or imipramine (10^{-5}M) did not change the accumulation of desipramine ($6{\cdot}6 \times 10^{-7}$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.

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

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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 μg/kg) in arachis oil (1 mg/ml) subcutaneously daily for 4 days. The isolated uteri were suspended in 25 ml Krebs, solution at 37°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 α- and β-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.