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Adrenoceptors mediating metabolic responses in the greyhound

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Studies on the metabolic effects of catecholamines have suggested that the receptors mediating liver and muscle glycogenolysis and lipolysis in the dog are β-receptors (Mayer, Moran & Fain, 1961). Not all species behave similarly, as liver glycogenolysis is mediated by α-receptors in the rat (Fleming & Kenny, 1964) and in man (Antonis, Clark, Hodge, Molony & Pilkington, 1967). Recently, Lands, Arnold, McAuliff, Luduena & Brown (1967) have suggested that β-adrenoceptors could be divided into two groups, $\beta 1$ and $\beta 2$. This classification has been supported by the development of drugs such as salbutamol, which mainly stimulates $\beta 2$ adrenoceptors (Cullum, Farmer, Jack & Levy, 1969), and practolol, which selectively blocks $\beta 1$ adrenoceptors (Dunlop & Shanks, 1968). The subdivisions of β-adrenoceptors mediating the metabolic responses to catecholamines have not been investigated using these two drugs.

The present work examines some of the metabolic responses to isoprenaline, salbutamol and phenylephrine in the dog and the effects of propranolol and practolol on these responses to isoprenaline. A series of increasing doses of isoprenaline, phenylephrine and salbutamol were given as 10 min intravenous infusions to greyhounds anaesthetized by intravenous injection of pentobarbitone (30 mg/kg). Heart rate was recorded and blood samples were analysed for free fatty acids, lactic acid and glucose. In the experiments in which phenylephrine was given, arterial pressure was recorded.

Phenylephrine in doses sufficient to cause an appreciable increase in arterial pressure did not elevate any of the metabolic parameters but isoprenaline increased heart rate, free fatty acid, lactic acid and glucose concentrations. Salbutamol increased heart rate, fatty acid and glucose concentrations having activities relative to isoprenaline of 1/30, 1/10 and 1/1, respectively. Minimal increases in lactic acid were produced by salbutamol.

Intravenous administration of propranolol reduced the heart rate and metabolic responses to isoprenaline to the same extent. Practolol (3 mg/kg), reduced heart rate and free fatty acid responses to isoprenaline but did not significantly alter lactic acid or glucose responses. Practolol (9 mg/kg), caused significant reduction of the lactic acid response although it did not affect the glucose response.

The above results are consistent with the hypothesis that the receptors mediating lipolysis and muscle glycogenolysis in the dog are similar to those for heart rate, that is, $\beta 1$, while the receptors mediating liver glycogenolysis are $\beta 2$.

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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-