Plasma adrenaline concentrations in rats: influence of anaesthetics and heart rate response to pronethalol

The response of the heart rate of anaesthetized rats to β-adrenoceptor antagonists depends in part on the choice of anaesthetic and the presence or absence of partial agonist activity in the antagonist. For example, under urethane anaesthesia pronethalol (a β-adrenoceptor antagonist with partial agonist activity) produces a marked bradycardia whereas under pentobarbitone there is a modest increase in heart rate (Barrett, 1971). There is evidence that urethane produces a hypothalamic (or general limbic) activation with an increased level of autonomic discharge (Reinert, 1964). In contrast, the level of autonomic activity during pentobarbitone anaesthesia is very low. From estimates of blood glucose concentrations which were abnormally high during urethane anaesthesia, Reinert (1964) suggested the presence of elevated adrenomedullary secretion of adrenaline in the circulation. Against such a background the dramatic bradycardia in response to pronethalol under urethane anaesthesia could be readily understood.

The present study repeats some of the experiments of Barrett (1971) but adds to those experiments the assay of plasma adrenaline and blood glucose concentrations. Female rats (200–250 g) of an albino Wistar strain, in groups of 6, were anaesthetized with either pentobarbitone (50 mg kg^{-1}, i.p.) or urethane (1·5 g kg^{-1}, i.p.). Heart rate was monitored using a cardiotachometer (Devices) triggered by the QRS complex of the electrocardiogram, from needle electrodes inserted subcutaneously. Pronethalol (20 mg kg^{-1}, i.p.) was given 1·5 h after the induction of anaesthesia and whole blood samples (5·0–6·0 ml) were withdrawn from the abdominal aorta 30 min later. Control animals received a saline injection at 1·5 h and were also bled 30 min later. A sample of whole blood was set aside for glucose assay (Morley, Dawson & Marks, 1968) and the remainder centrifuged for plasma separation. Catecholamines were adsorbed from plasma onto alumina (Weil-Malherbe, 1968), eluted with 0·1 N HCl and the adrenaline content of the eluate determined by bioassay using a methacholine-stimulated rat uterus preparation (de Jalon, Bayo & de Jalon, 1945). Recovery of adrenaline was checked by addition of [^{14}C]adrenaline to plasma samples immediately before addition of alumina and subsequent scintillation counting of eluate fractions. The adrenaline recovery averaged 70%.

The mean heart rate of rats anaesthetized with pentobarbitone 1·5 h after injection was 307 ± 9 beats min^{-1} (mean ± s.e.) compared with 362 ± 12 beats min^{-1} for those receiving urethane. No significant change in rate occurred over the succeeding 30 min for animals given saline at 1·5 h. Pronethalol, however, produced an increase in heart rate of 38 ± 8 beats min^{-1} in the pentobarbitone-anaesthetized rats, whereas it decreased cardiac frequency by an average of 174 ± 20 beats min^{-1} in the urethane injected animals (Table 1). These results are in close agreement with the earlier observations of Barrett (1971). The blood glucose concentration of rats anaesthetized with urethane were approximately double those of animals given pentobarbitone ($P < 0{\cdot}01$) and the concentrations correlate closely with those reported by Reinert (1964) in his urethane-anaesthetized animals (168 ± 8 mg dl^{-1}). The administration of pronethalol had no significant effect on the blood glucose concentration under either anaesthetic. The estimates of plasma adrenaline concentrations showed significant differences under the influence of pentobarbitone and urethane (Table 1). The injection of pronethalol did not appear to alter the plasma adrenaline concentrations significantly. Pooling the results gives a mean value of 6·1 μg $litre^{-1}$ for pentobarbitone anaesthetized rats compared with 14·2 μg $litre^{-1}$ for rats receiving urethane. The difference is significant at the 1% level. The only other estimate of

Table 1. *Heart rate, blood glucose and plasma adrenaline concentrations in rats anaesthetized with urethane or pentobarbitone 30 min after administration of saline* (2·0 mg kg^{-1}) *or pronethalol* (20 mg kg^{-1}) i.p. All values expressed as mean ± standard error for groups of 6 rats.

	Urethane anaesthesia		Pentobarbitone anaesthesia	
	After saline	After pronethalol	After saline	After pronethalol
Change in heart rate (beats min^{-1})	+7 ± 4	—174 ± 20	—4 ± 3	+38 ± 8
Blood glucose (mg dl^{-1})	159 ± 15	153 ± 16	85 ± 3	78 ± 4
Plasma adrenaline (μg $litre^{-1}$)	13·8 ± 1·4	14·5 ± 1·1	6·2 ± 0·6	6·0 ± 0·5

rat plasma adrenaline concentrations we could find the in literature (Anton & Sayer, 1962) gives a value of 10·8 μg $litre^{-1}$ by a trihydroxyindole chemical method. The present values obtained by bioassay are comparable although there is no information given as to how Anton & Sayre treated their animals before blood sampling. The concentrations observed in the present study may bear no relation to resting concentrations of adrenaline in undisturbed conscious rats.

The results clearly demonstrate both an increased sympathoadrenal activity and sensitivity to β-adrenoceptor blockade in rats anaesthetized with urethane compared with those given pentobarbitone. The estimates of plasma adrenaline concentrations provide direct evidence of this state, confirming that of earlier indirect indices. A twofold difference in the plasma adrenaline concentrates is, however, unlikely to account for the dramatic difference between a bradycardia of 174 beats min^{-1} and tachycardia of 38 beats min^{-1} in response to pronethalol under the influence of the two anaesthetics. It is improbable therefore that a difference in circulating adrenaline concentrations can alone account for the difference in response. β-Blocking drugs decrease the effect of sympathetic tone on the heart, and in rats anaesthetized with urethane this would show as a decrease in heart rate. Previous studies (Barrett 1971) have shown an equally marked difference in the response of the heart rate to atropine under the two anaesthetics, which implied a major contribution of unopposed vagal action in the bradycardia observed after pronethalol in rats anaesthetized with urethane. These experiments suggest that the estimation of plasma adrenaline concentrations will not provide a reliable prediction of the cardiac response to β-adrenoceptor blockade.

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Department of Pharmacology,
School of Medicine,
Leeds LS2 9NL, U.K.

H. G. DEAN
P. A. RYLETT

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