Plasma noradrenaline levels as a measure of noradrenaline release

C.R. BENEDICT, MARIANNE FILLENZ, CLARE STANFORD & INMACULATA VALERO

Department of Clinical Pharmacology, University Laboratory of Physiology and Department of Psychology, Oxford

In order to monitor noradrenaline (NA) release over extended periods, cannulae were inserted into the right atrium of rats through the superior vena cava under anaesthesia. Tubing connected to the cannula runs subcutaneously and is brought to the surface in the midscapular region. Rats were allowed to recover from the anaesthesia and were kept on a standard laboratory diet. Blood samples of 0.25 ml were withdrawn and replaced with an equal volume of sterile saline. The blood was put into heparinized tubes containing 1.6 mg glutathione/ml blood and centrifuged; the serum was diluted 1:4 with distilled water and stored deep frozen. The NA content of the samples was assayed using a radioenzymatic method (Hörtnagl, Benedict, Grahame-Smith & McGrath, 1977). The NA content of plasma in untreated rats was 1.88 ± 0.08 ng/ml ($n=16$, C.V.$=0.58$). When desmethylimipramine (DMI; 10 mg/kg) and normetanephrine (NMN; 50 mg/kg) were given in a single intraperitoneal injection, to block neuronal and extraneuronal NA uptake mechanisms respectively, plasma NA rose to 5.26 ± 0.51 ng/ml ($n=9$). In order to discover whether there were changes related to the time of day, plasma NA was measured in a group of rats at hourly intervals between 1100 and 1700 hours. There were no statistically significant variations in plasma NA level throughout this period and the mean coefficient of variation for the 6 h period was 0.50, similar to that for the control value, which represents individual variation. Experiments were next carried out to measure the effect of the administration of NA. Plasma NA was measured at various time intervals after the intravenous administration of 100 μg/kg of NA; calculations carried out on the basis of these measurements showed that 1 min after NA administration only 4% of the administered dose was found in the circulation. There followed an approximately exponential decline in plasma NA levels with a $T_{\frac{1}{2}}$ of 1.5–2 minutes. In order to compare the fate of exogenous and endogenous NA rats were subjected to a 1 min swim stress. Blood samples taken before and at the end of the swim stress (water temperature 17°C) showed a rise in plasma NA from 2.33 ± 0.13 ng/ml to 9.44 ± 2.06 ng/ml. After the termination of the swim stress plasma NA levels fell steeply within the first 2 minutes. This initial rate of decline was affected very little by the administration of DMI (10 mg/kg) and NMN (50 mg/kg).

These preliminary experiments suggest that plasma NA in rats shows little variation between individuals or with time of day; although only a fraction of the released NA escapes uptake and reaches the blood stream, even short-lasting changes in release rate are reflected in plasma NA levels. NA in plasma has a very short half-life and even in the presence of DMI and NMN mechanisms for the rapid removal of NA remain.

Reference

HÖRTNAGL, H., BENEDICT, C.R., GRAHAME-SMITH, D.G. & McGRATH, B. (1977). Sensitive radioenzymatic assay for adrenaline and noradrenaline in plasma. *Br. J. clin. Pharmac.* (in press).

Effects of uptake blockade on cardiac responses of anaesthetized dogs to isoprenaline, noradrenaline, and sympathetic nerve stimulation

R.A. BROWN, ANNE M. SOLCA & J. WILSON

Department of Pharmacology, Fisons Ltd., Pharmaceutical Division, R. & D. Laboratories, Bakewell Road, Loughborough, Leicestershire

The greater muscle mass of the ventricular myocardium relative to that of the atria suggests that extraneuronal uptake (uptake 2) of catecholamines may perform a more substantial role in the termination of inotropic rather than chronotropic responses of the heart to catecholamines. In contrast, the higher density of sympathetic innervation in the sino-atrial and atrial tissues raises the possibility that neuronal uptake (uptake 1) may be more important in the termination of chronotropic than inotropic responses.

Accordingly, we have investigated the effects of differential and combined blockade of uptake 1 and uptake 2 on cardiac responses of anaesthetized dogs to (±)-isoprenaline, (−)-noradrenaline and electrical stimulation of the left ansa subclavia nerve.