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Supersensitivity of central noradrenaline receptors after reserpine

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In a recent series of experiments the effects of (−)-noradrenaline (NA), applied by microiontophoresis, on the activity of spontaneously firing cells in the brain stem of rats anaesthetized with halothane have been studied in untreated animals and in animals pretreated with reserpine, α-methyl-*p*-tyrosine (AMPT) or bis(1-methyl-4-homopiperazinylthiocarbonyl)-disulphide (FLA 63). The doses of these drugs and the pretreatment times are given in Table 1. The communication presents data concerning the firing rates of the brain stem neurones in each group and their responses to iontophoretically applied NA.

TABLE 1. *Effects of monoamine depletion by pretreatment with different drugs on neuronal firing rates and neuronal sensitivities to noradrenaline (NA) in the brain stem*

	Neuronal firing rates			Magnitudes of NA excitations	
Drug, dose and pretreatment time	Median (spikes s^{-1})	Mode	(No. of neurones studied)	Mean no. of spikes elicited by 0·75 μC NA	(Sample size)
None	14·9	8·0	(113)	2322	(12)
Reserpine (5 mg/kg) 20 h pretreatment	11·7	2·0	(113)	4242†	(13)
α-Methyl-*p*-tyrosine base (500 mg/kg) 20 h pretreatment	14·4	8·0	(113)	3455‡	(15)
FLA 63 (25 mg/kg) 4 h pretreatment	14·4	12·0	(56)	2270‡	(14)

†Significantly different from untreated values ($P<0·001$). ‡Not significant (Student's *t* test).

The neurones in the untreated animals had median firing rate of 14·9 spikes s^{-1}, and a mode firing rate of eight spikes s^{-1}. The firing rates of the neurones in the animals pretreated with AMPT and FLA 63 were similarly distributed (Table 1). The firing rates of the neurones in the animals pretreated with reserpine were significantly differently distributed, with lower median and mode frequencies (Table 1).

The responses of the brain stem neurones in the rats anaesthetized with halothane resembled those observed in the unanaesthetized decerebrate cat (Boakes, Bradley, Brookes, Candy & Wolstencroft, 1971). The responses to NA in the animals pretreated with AMPT and FLA 63 were similar to those in the untreated animals. In the reserpinized animals the excitatory responses to NA were much greater than those in the other groups, both in magnitude and duration. Table 1 shows an analysis of the responses to NA of a sample of neurones in each group. Few inhibitory responses were observed in the reserpinized animals but these were similar to those observed in the other groups.

The increased sensitivity to NA in the reserpinized animals is similar to the supersensitivity of peripheral structures to NA after reserpine pretreatment (Trendelenburg, 1963). The absence of any change in the responses of the neurones in animals pretreated with AMPT or FLA 63 suggests that the increased responses to NA observed

after reserpine pretreatment is due to a blockade of NA uptake and storage rather than a change in the sensitivity of the postsynaptic receptor. The increased neuronal responses to iontophoretically applied NA which have been observed after iontophoretic application of imipramine and of desipramine and after destruction of adrenergic terminals with 6-hydroxydopamine (Avanzino, Ermirio & Zummo, 1971; Hoffer, Siggins & Bloom, 1971) support this suggestion.

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Microinjection study of the rôle of adrenergic transmission in the control of the secretion of antidiuretic hormone

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Particularly abundant supplies of noradrenaline-containing nerve-terminals have been demonstrated by histochemical methods in the hypothalamic nuclei concerned with antidiuretic hormone (ADH) release, namely the supraoptic nucleus (SON) and paraventricular nucleus (PVN) (Fuxe, 1965). However, comparatively little is known about the rôle of adrenergic transmission in ADH release. In a series of experiments on cats anaesthetized with chloralose, we studied the effects of the microinjection of noradrenaline (NA) and adrenoceptor blocking drugs into the SON on ADH secretion. The drug solutions, adjusted to plasma pH and osmolarity, were injected in volumes not larger than 1 μl through stereotactically placed steel cannulae.

The position of the cannulae tips was determined from frozen sections, stained with cresyl violet and luxol blue. Control injections of normal saline were made to ensure that experimental procedures had no effect on the concentrations of blood ADH.

Blood samples (4 ml) were withdrawn from an external jugular vein and extracted according to the method of Bisset, Hilton & Poisner (1967). The extracts were assayed for antidiuretic activity on rats anaesthetized with alcohol (Bisset, 1962). Arterial blood pressure was monitored during the injection sampling sequences. Noradrenaline (5–30 μg), invariably caused release of ADH. In the same cat, the response was dose dependent, although it varied considerably in size between different animals. In six experiments (in which NA (20 μg) was administered) the percentage increase of ADH in samples taken 2 min after the injection of 20 μg NA, compared with samples taken 2 min before, varied between 80% and 400%. The effects of two adrenergic blocking agents, phentolamine and propranolol, on the release of ADH by NA were studied. Pretreatment with phentolamine did not always prevent the NA-induced release of ADH. In the dose used (75 μg) phentolamine itself caused a release of ADH in four experiments out of five. The percentage increase varied between 67 and 525%.