Sensitivity of isolated atria from reserpine-treated rats to noradrenaline

SIR,—Chronic sympathetic postganglionic denervation reduces the noradrenaline content of smooth or cardiac muscle (Goodall, 1951; von Euler & Purkhol, 1951; Burn & Rand, 1959) increases its sensitivity to injected noradrenaline and decreases its reactivity to tyramine (Bulbring & Burn, 1938). Pretreatment with reserpine causes similar changes (Burn & Rand, 1958a). Burn & Rand (1959) therefore suggested the possibility of an inverse relationship between tissue stores of noradrenaline and sensitivity to exogenous noradrenaline. Recent observations failed to support such a view, since pretreatment of short duration (24 to 48 hr) with large doses of reserpine failed to cause supersensitivity (Fleming & Trendenburg, 1961). These authors pointed out that the time factor must also be considered, although this factor seemed to be more important for the appearance of supersensitivity of the nictitating membrane than of the cardiovascular system. In the present study, sensitivity to exogenous noradrenaline was reinvestigated in isolated atrial preparations made from rats treated with reserpine at various times.

Male albino rats of the Holtzman strain, weighing 225 to 250 g, were used in all experiments. Animals were killed by a blow at the base of the neck, decapitated and the heart rapidly removed. Atria were freed of ventricular muscle, connective tissue, fat and blood vessels, then placed in a modified Tyrode's solution (Bhagat & Shideman, 1963b) maintained at 28° and containing $2{\cdot}9 \times 10^{-8}$M atropine sulphate. A mixture of 95% oxygen and 5% carbon dioxide was bubbled through the bathing fluid via a sintered glass plate at the bottom of the bath. Isometric contractile amplitude (resting tension of approximately 0·5 g) and rate of spontaneous beat were recorded. Drugs were added to the bath after the preparation had attained a constant amplitude of contraction and responses were calculated as percentage changes relative to the amplitude existing just before the addition of the drug.

The concentrations of catecholamines in the ventricular myocardium were determined by the trihydroxyindole fluorimetric procedure of Shore & Olin (1958) and are expressed as μg of noradrenaline per g of fresh tissue.

Noradrenaline bitartrate monohydrate and reserpine (Serpasil, Ciba) are expressed as base and cocaine hydrochloride as the salt. In one group, rats were given 1·5 mg/kg of reserpine intramuscularly 24 hr before the experiment, while in another group, 0·5 mg/kg of reserpine was administered every 18 hr and the animals were used 72 hr after the first injection.

TABLE 1. POSITIVE INOTROPIC EFFECT OF NORADRENALINE ON ISOLATED RAT ATRIA

Treatment	Catecholamine concentration (μg/g of fresh tissue) mean ± s.e.	Sensitivity to noradrenaline (0·5 μg/ml) Increase in size of contraction mean % change ± s.e.	
			in presence of cocaine 5 μg/ml
Control	1·06 ± 0·04 (8)	98 ± 11·4 (12)	132 ± 12·6 (6)
Reserpine 1·5 mg/kg 24 hr before experiment	0·06 ± 0·03 (10)	89 ± 6·8 (10)	128 ± 9·5 (5)
Reserpine 0·5 mg every 18 hr (3 doses) rats killed at 72 hr ..	0·08 ± 0·04 (10)	105 ± 9·8 (10)	136 ± 8·7 (6)

Results in Table 1 show that the sensitivity to noradrenaline of isolated atria obtained from rats pretreated with reserpine was normal. This confirms the

findings of Bhagat & Shideman (1962a, b) who did not find any supersensitivity to noradrenaline in atria from rats depleted of their catecholamines with reserpine or guanethidine. Perhaps organ and species differences may be of importance, since the hearts of spinal cats (Fleming & Trendelenburg, 1961) and isolated atria from reserpinised rabbits are supersensitive (MacMillan, 1959), whereas those from reserpine-pretreated rats are not. Crout, Muskus & Trendelenburg (1962) also reported that isolated atria from reserpine-pretreated guinea-pigs are normal in their sensitivity to noradrenaline. They attributed this difference to the schedule of treatment with reserpine, but this could not be so in our experiment, since reserpine was injected in small doses and 72 hr were allowed for the development of supersensitivity.

Reserpinised atria not only behaved like normal tissues in their sensitivity to noradrenaline but also to the sensitising effect of cocaine. Similar findings with cocaine have been reported by Trendelenburg, Muskus, Fleming, & Gomez (1962) with the nictitating membrane of the cat. The ability of cocaine to potentiate the effects of adrenaline on blood pressure and on sympathetically innervated organs was first reported by Frohlich & Loewi (1910). Since then, several studies have been made to explain this phenomenon. The most generally accepted hypothesis is that cocaine impairs the rapid uptake of noradrenaline by storage sites in tissues thereby increasing the amount of exogenous noradrenaline available for reaction with sympathetic receptors (Whitby, Hertting & Axelrod, 1960; Hertting, Axelrod, Kopin & Whitby, 1961; Bhagat, 1964). Similarly, reserpine is known to block the uptake of noradrenaline. But recent chemical investigation by Kopin & Gordon (1963) suggest that reserpine-treated animals can take up noradrenaline but they disposed of it primarily by enzymatic inactivation rather than by storage. With such a system, the potentiating action of cocaine could then be attributed to an impairment of uptake of catecholamines into the structures rather than to blockade of either subsequent storage (predominant in normal tissues) or subsequent enzymatic degradation (predominant in reserpinised tissues).

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