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The mechanism underlying potentiation of the pressor action of noradrenaline by some drugs which depress sympathetic tone

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The potentiation of the action of noradrenaline on the blood pressure of spinal cats by intravenously injected hexamethonium or bretylium and intrathecally injected procaine, all of which depress sympathetic tone, was accompanied by an increase in cardiac output but no significant change in total peripheral resistance. Acute cardiac sympathectomy itself caused increases in cardiac output and in the pressor action of noradrenaline which were similar to those produced by the drugs. After cardiac sympathectomy or after treatment of spinal cats with pronethalol, the blood pressure responses to noradrenaline were not further modified by bretylium, hexamethonium, or intrathecal procaine. It is concluded that potentiation of the pressor action of noradrenaline by these drugs in the spinal cat results from inhibition of cardiac sympathetic tone.

THE potentiation of blood pressure responses to noradrenaline by a variety of drugs which affect sympathetic tone is well recognised. It is known to occur after administration of adrenergic neurone blocking drugs such as bretylium and guanethidine (Maxwell, Plummer, Schneider, Povalski & Daniel, 1960; Laurence & Nagle, 1963); after ganglion blocking agents (Corcoran & Page, 1947; Paton, 1951; Page & Taylor, 1950); and after total spinal anaesthesia (Hilton & Reid, 1956). While the increased sensitivity to adrenaline and noradrenaline following the administration of ganglion blocking drugs has been attributed by some early workers to blocking of compensatory baroreceptor reflexes (Moe, 1948; Page & Taylor, 1950); other investigators have realised that such a potentiation cannot be attributed only to the abolition of normal compensatory nervous mechanisms since it occurs after bilateral vagotomy (Page & Taylor, 1950); after denervation of the carotid sinus and aortic arch baroreceptors (Maengwyn-Davies, Walz & Koppanyi, 1958); and also after section of the spinal cord at a high level (Bartorelli, Capri & Cavalca, 1954).

According to Wilber & Brust (1958), and Hodge & Whelan (1962), potentiation of the pressor action of noradrenaline by ganglion blocking drugs is not accompanied by a change in peripheral resistance. Similar findings with bretylium have been reported by Laurence & Nagle (1963).

The present investigation was designed to determine whether the cardiac stimulant action of noradrenaline is involved in the potentiation of its pressor action by drugs and procedures which lower the sympathetic tone.

Experimental

Cats were anaesthetised with ether and rendered spinal by Dale's method as described by Burn (1952). Blood pressure was recorded from

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a cannulated femoral artery by means of a mercury manometer. Drugs were injected via a cannulated femoral vein.

The chest was opened, when necessary, at the beginning so that the whole experiment was made under uniform conditions.

The routine was as follows. Three doses of noradrenaline, all of which produced sub-maximal effects, were administered at 5 min intervals until responses had become constant. Intravenous injection of bretylium (5 mg/kg); hexamethonium (10 mg/kg); or procaine hydrochloride (2·5 ml/kg of 2% procaine hydrochloride), injected intrathecally between fourth and fifth lumber vertebrae was then made and 30 min later responses to noradrenaline redetermined. In some experiments the above routines were followed after injecting pronethalol (5 mg/kg) or after cardiac sympathectomy by removing the sympathetic chain from the stellate ganglia to the fifth thoracic vertebra, or by cutting all the postganglionic cardiac sympathetic nerves.

The effect of noradrenaline on the cardiac output in spinal cats was estimated in open chest cats under positive artificial respiration by the Fick method. Noradrenaline, 0·5 μg/kg/min was infused until the increased arterial blood pressure had attained constant level. Mixed venous blood samples were withdrawn into slightly heparinised syringes through a fine bore polythene cannula placed into the right atrium via the right external jugular vein. Arterial blood samples were obtained from a polythene cannula inserted in a carotid artery. The oxygen content of arterial and mixed venous blood samples was determined by the method of Roughton & Scholander (1943). The rate of oxygen consumption was measured with a Benedict-Roth spirometer filled with 100% oxygen and running for at least 5 min before sampling.

Total Peripheral Resistance, T.P.R. was calculated using the following formula.

$$\text{T.P.R.} = \frac{\text{Arterial blood pressure in mm Hg}}{\text{Cardiac output (ml/kg/min)}}$$

Cardiac Output (C.O.) was calculated using the following formula.

$$\text{C.O.} = \frac{\text{Oxygen consumption ml/min}}{\text{A-V oxygen difference ml/litre}}$$

Drugs used. (−)-Noradrenaline bitartrate; bretylium tosylate; hexamethonium bromide; procaine hydrochloride; pyrogallol; pronethalol.

Results

THE EFFECT OF DRUGS AND PROCEDURES WHICH ABOLISH THE SYMPATHETIC TONE ON THE PRESSOR ACTION OF NORADRENALINE IN SPINAL CATS

The result of the first series of experiments, in which the effects of bretylium (5 mg/kg), hexamethonium (10 mg/kg), spinal anaesthesia (2·5 ml/kg of 2% procaine hydrochloride), and of cardiac sympathetic denervation on the pressor responses to three different doses of noradrenaline were investigated, are presented in Fig. 1. All these drugs and

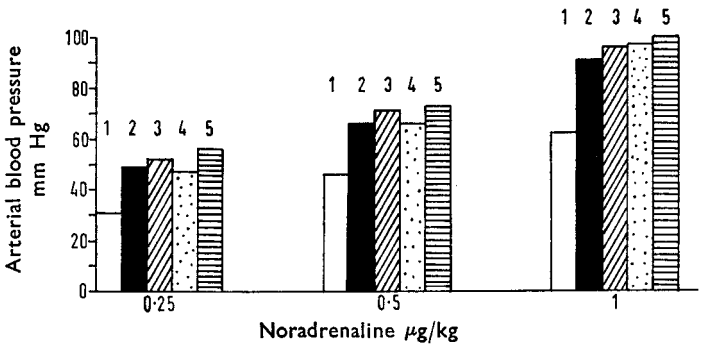

FIG. 1. The effects of hexamethonium (10 mg/kg), bretylium (5 mg/kg), total spinal anaesthesia (procaine 2·5 ml/kg, 2% solution), and acute cardiac sympathetic denervation on the pressor responses to noradrenaline (0·25, 0·5 and 1·0 μg/kg) injected intravenously in spinal cats. 1. Control. 2. Hexamethonium. 3. Bretylium. 4. Spinal anaesthesia. 5. Acute cardiac sympathetic denervation. Control columns represent the means of 16 animals. All other columns represent the means of 4 animals. Hexamethonium, bretylium, spinal anaesthesia and cardiac sympathetic denervation significantly potentiated the pressor actions of all doses of noradrenaline.

Significance of difference between means (control and treated) was examined by '*t*' test. The difference between the treated and the control responses was significant in all instances ($P = <0{\cdot}05$).

procedures significantly potentiated the effect of noradrenaline on the blood pressure of cats. Each value in Fig. 1 represents a mean of four experiments except for the control values which represent a mean of 16 experiments. There is no statistically significant difference between degrees of potentiation produced by bretylium, hexamethonium, spinal anaesthesia and cardiac sympathectomy.

SPINAL CATS WITH SYMPATHETICALLY DENERVATED HEART

Sympathetic denervation of the heart itself potentiated responses to noradrenaline (Figs 1 and 3) while bretylium (5 mg/kg), hexamethonium (10 mg/kg) or spinal anaesthesia then failed to produce any further potentiation of the pressor action (Figs 2 and 3). In spinal cats previously injected with pronethalol (5 mg/kg), sympathetic denervation, as well as hexamethonium, bretylium and spinal anaesthesia failed to potentiate the pressor response to noradrenaline (Fig. 4).

In cats with denervated hearts and in pronethalol-pretreated cats pyrogallol potentiated the pressor action of noradrenaline (Fig. 5).

CARDIAC OUTPUT MEASUREMENTS

The effect of infusion of 0·5 μg/kg/min of noradrenaline on the cardiac output, before and after intravenous injections of bretylium (5 mg/kg), hexamethonium (10 mg/kg), spinal anaesthesia or cardiac sympathetic denervation, was investigated in open-chest cats under artificial respiration. Before the potentiating drug or procedure, the infusion of noradrenaline produced an increase in arterial blood pressure with an increase in peripheral resistance and no change in cardiac output. After administration of bretylium, hexamethonium, cardiac sympathectomy or after

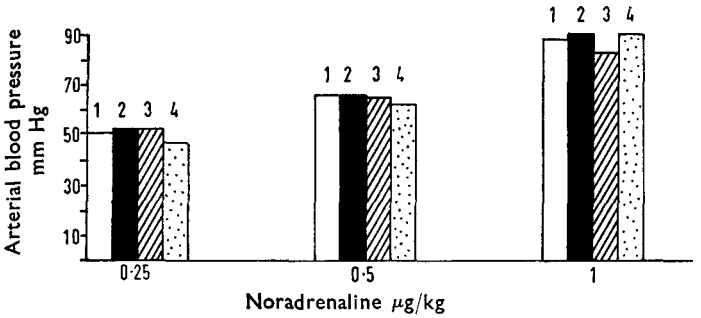

FIG. 2. The effect of drugs and procedures as described in Fig. 1 on spinal cats with sympathetically denervated hearts. 1. Control. 2. Hexamethonium. 3. Bretylium. 4. Spinal anaesthesia. Control columns represent the means of 12 animals. All other columns are the means of 4 animals. Hexamethonium, bretylium and spinal anaesthesia did not significantly potentiate the pressor actions of any doses of noradrenaline. Significance of difference between means (control and treated) was examined by '*t*' test; P = <0·05.

spinal anaesthesia, the pressor action of the same dose of noradrenaline was potentiated; the increase in peripheral resistance remained the same but there was now an increase in cardiac output (Table 1).

Administration of pyrogallol also potentiated the pressor action of noradrenaline but in this case the potentiation was accompanied by an increase in peripheral resistance without any change in cardiac output. Detailed results of these experiments are given in Table 1.

TABLE 1. THE EFFECT OF INFUSION OF NORADRENALINE (NA; 0·5 μg/min) ON THE ARTERIAL BLOOD PRESSURE, CARDIAC OUTPUT AND TOTAL PERIPHERAL RESISTANCE IN SPINAL CATS BEFORE AND AFTER BRETYLIUM, HEXAMETHONIUM, SPINAL ANAESTHESIA OR CARDIAC SYMPATHETIC DENERVATION

	Average arterial blood pressure mm Hg		Average cardiac output ml/kg/min		Total peripheral resistance		
Treatment	Before NA	Change produced by NA	Before NA	Change produced by NA	Before NA	Change produced by NA	% change
Control	85	+22·5	153	+2	0·55	+0·14	25·4
After bretylium 5 mg/kg i.v.	70	+50·0*	117*	+38*	0·60	+0·17	28·0
Control	80	+20·0	165	+5	0·48	+0·10	20·8
After hexamethonium 10 mg/kg i.v.	65	+30·0*	117*	+24*	0·55	+0·12	21·8
Control	90	+29·0	140	−4	0·64	+0·23	35·9
After spinal anaesthesia ..	47	+41*	88*	+32*	0·53	+0·20	37·7
Control	100	+25	170	0	0·59	+0·14	23·7
After cardiac sym. denerv.	80	+51*	106*	+36*	0·75	+0·17	22·6
Control	90	+28	138	+3	0·65	+0·19	29·2
After pyrogallol	95	+48*	136	0	0·70	+0·35*	50·0*

(+) Indicates an increase and (−) a decrease in cardiac output. Each value in the table represents a mean of four experiments. Significance of differences between means was examined by "*t*" test and is indicated by asterisk; P = <0·05.

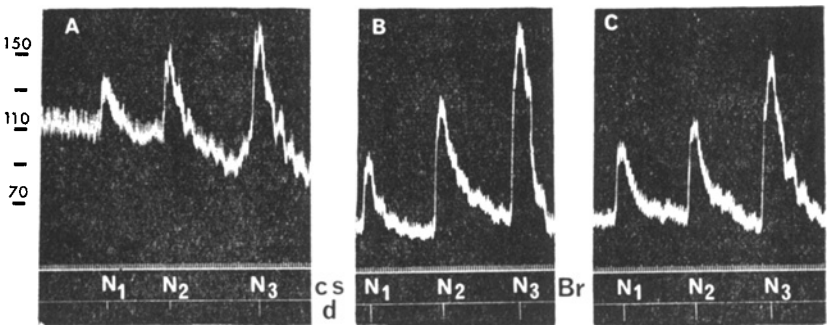

FIG. 3. The effect of cardiac sympathetic denervation followed by bretylium on the pressor responses to intravenous noradrenaline in the spinal cat (2·8 kg). A. Responses to noradrenaline 0·25 (N_1) 0·5 (N_2) 1·0 (N_3) μg/kg. B. 15 min after acute sympathetic cardiac denervation (csd). C. 30 min after the intravenous bretylium (Br) (5 mg/kg). Time trace: 10 sec intervals.

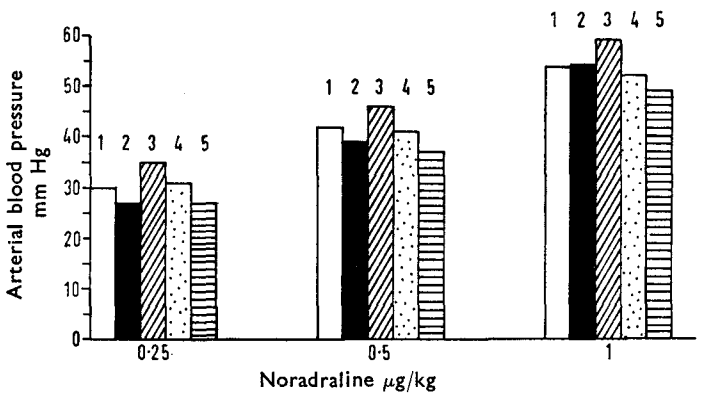

FIG. 4. Spinal cats pretreated with pronethalol (5 mg/kg i.v.) injected 15 min before the beginning of the experiments. Drugs and procedures and control and test animals as described in Fig. 1. Hexamethonium (2), bretylium (3), spinal anaesthesia (4) or cardiac sympathetic denervation (5) did not potentiate the pressor action of any doses of noradrenaline. Significance of difference between means (control and treated) was examined by 't' test; $P = <0{\cdot}05$.

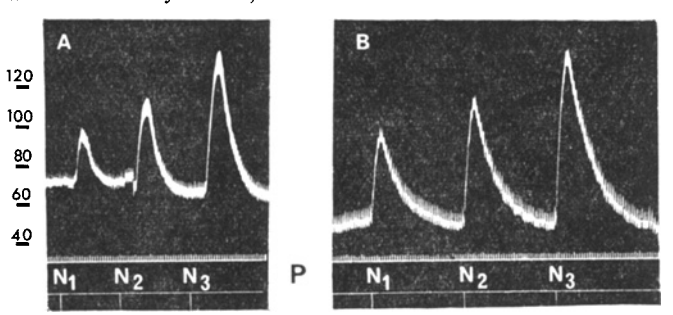

FIG. 5. The effect of pyrogallol (10 mg/kg i.v.) on the pressor responses to intravenous noradrenaline (0·25 (N_1), 0·5 (N_2) and 1·0 (N_3) μg/kg i.v.) in a spinal cat (2·2 kg) with a sympathetically denervated heart. Acute cardiac sympathectomy was made 15 min before beginning the experiment. A. Responses to noradrenaline. B. 15 min after the administration of pyrogallol (P). Time trace: 10 sec interval.

Discussion

The degree of potentiation produced by bretylium, hexamethonium, spinal anaesthesia and cardiac sympathetic denervation was similar in all experiments. These results agree with those of Hilton, Arellano & Fenner (1963) who found that ganglion blocking drugs and spinal anaesthesia produced equal potentiation of the pressor action of adrenaline in dogs. When potentiation was produced by one drug or procedure, the other three drugs or procedures failed to increase the pressor action of noradrenaline any further. These results indicate a similar mode of action for bretylium, hexamethonium, cardiac sympathectomy and spinal anaesthesia in potentiating the increase in blood pressure produced by noradrenaline and suggest that the drugs act by producing a "chemical sympathectomy." Pyrogallol, which potentiates the pressor action of sympathomimetic catecholamines by protecting them from enzymatic destruction (Bacq, 1936a, b), further potentiated the pressor action of noradrenaline after bretylium, hexamethonium, cardiac sympathectomy or spinal anaesthesia.

However, Mantegazza, Tyler & Zaimis (1958) have shown potentiation of the vasoconstrictor action of noradrenaline, and the potentiation of the actions of adrenaline, noradrenaline and of post ganglionic sympathetic nerve stimulation on the nictitating membrane of the cat has been demonstrated by Shimamoto, Kanauchi & Uchizuim (1955). According to these authors such a potentiation does not involve the abolition of the sympathetic tone.

By whichever of the four methods the potentiation was produced, it was accompanied by an increase in cardiac output with no further increase in peripheral resistance. These findings support those of Laurence & Nagle (1963) who have shown that the pressor potentiation of noradrenaline by bretylium and guanethidine in man is not due to increased peripheral resistance. Hodge & Whelan (1962) and Wilber & Brust (1958) have reported similar findings for the potentiation of noradrenaline by ganglion blocking drugs.

Eckstein & Horsley (1961) and Zimmerman, Brody & Beck (1960) have shown that removal of sympathetic tone to the heart causes a reduction in heart rate, cardiac output and ventricular work. Thus it is hardly surprising that noradrenaline injected under these conditions increases cardiac output. The question as to why noradrenaline does not increase cardiac output in animals with intact sympathetic innervation is difficult to explain although it has been demonstrated before. Thus according to Eckstein & Horsley (1961), in the presence of intact sympathetic innervation, the heart fails to increase its rate and output when atrial pressure is increased, whereas after denervation it responds to an increase in filling pressure by increasing its rate and output.

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