Effect of Ganglionic Blocking Agents on Pressor Responses Induced by Splanchnic Faradization. (22435)

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The efferent components of the greater splanchnic nerve of mammals are generally considered to be largely preganglionic with only a small postganglionic representation (1-5). Synapses of these preganglionic fibers occur primarily in the celiac and aorticorenal ganglia except for those fibres which go directly to the adrenal medullae, this innervation being considered a modified "ganglionic" junction. Stimulation of the peripheral end of the divided splanchnic nerve leads to a sympatho-adrenal discharge which is associated with an arterial pressor response. It might be anticipated that ganglionic blocking agents would markedly reduce this pressor response.

Recently reports(6,7) have appeared which indicate that ganglionic blocking agents have effects on the visceral circulation of the dog which are inconsistent with the decrease in peripheral resistance and increase in flow which would be expected following interruption of sympathetic vasomotor tone. The following study was carried out to determine some of the effects of ganglionic blocking agents on visceral circulation.

Materials and methods. A total of 25 cats of both sexes, anesthetized with Dial-urethane, were used in this study. The left splanchnic nerve was exposed through a lateral incision in the abdominal wall and transected near its exit from the diaphragm. Operative procedures generally resulted in a 20 mm Hg drop in arterial pressure. A platinum electrode was placed on the peripheral end of this nerve and stimulation applied with an Electrodyne stimulator at 5 v, 100 u sec duration, at 30 per second for 15 seconds. The carotid pressure was recorded with an Anderson glass capsule manometer(8). All drugs were administered intravenously from 5 to 15 minutes prior to stimulation, depending upon their duration of action. Stimulations were spaced 30 to 45 minutes apart. Each stimulation was followed by an injection of 70% epinephrine—30% norepinephrine (epi + n-epi) mixture. According to Mirkin and Bonnycastle(9), this approximates adrenal effluent proportions following splanchnic stimulation. Doses (2-6 μg/kg) were selected to give a pressor response equivalent to that obtained by the control splanchnic stimulation.

Results. Effect of ganglionic blocking agents on pressor responses induced by left splanchnic nerve faradization. Four ganglionic blocking agents were tested for their capacity to antagonize the pressor response due to splanchnic stimulation: tetraethylammonium bromide (TEA), hexamethonium chloride, pentapyrrolidinium bitartrate and chlorisondamine chloride (Ecolid™, Ciba). TEA, hexamethonium and pentapyrrolidinium yielded essentially the same results. In two animals for each compound, doses of 1, 5 and 10 mg/kg failed to obliterate or antagonize the pressor response; on the contrary, they provided a clear-cut augmentation of the response to stimulation and to injected epi + n-epi (Fig. 1). Chlorisondamine chloride in doses of 320 μg, and 1, 5 and 10 mg/kg, similarly failed to antagonize the response to stimulation but did not augment it, nor did this compound potentiate the response to injected epi + n-epi.

Interpretation of the results is complicated by the presence of the left adrenal gland in this series of experiments. For, while ganglionic blockade may have reduced the neural vasoconstrictor components of the pressor response, the release of epinephrine and norepinephrine from the adrenal medulla may not have been blocked, and under the simulated denervation of ganglionic blockade may have given rise to a markedly enhanced pressor effect. To eliminate this possibility, another group of cats was run in which the left

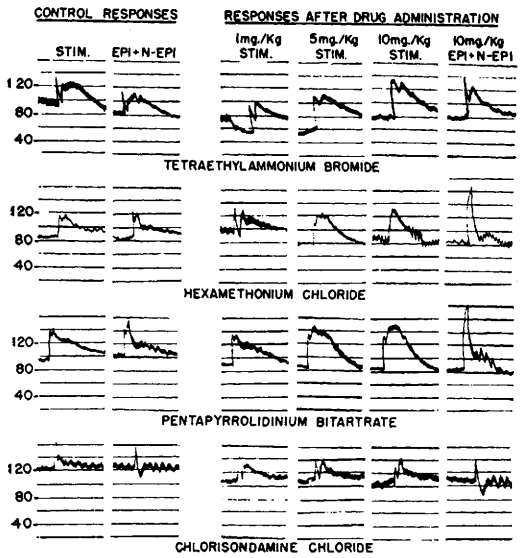

FIG. 1. Arterial pressor responses elicited by left splanchnic nerve faradization in presence of ganglionic blocking agents.

splanchnic was stimulated following removal of the ipsilateral adrenal gland.

Effect of ganglionic blocking agents on pressor response induced by left splanchnic nerve faradization with left adrenal ablated. The procedure outlined above was followed except that the left adrenal was removed. In 2 animals for each compound, TEA, pentapyrrolidinium and chlorisondamine chloride in doses of 1 to 10 mg/kg did not block or antagonize the pressor response concomitant with splanchnic stimulation, but, on the contrary, augmented it. Hexamethonium neither antagonized nor augmented the response to stimulation. All four compounds potentiated the response to injected epi + n-epi (Fig. 2). To substantiate the fact that we were dealing with vasoconstrictor impulses and thus a response mediated peripherally by norepinephrine, 2 mg/kg of the adrenergic blocking agent, phentolamine, was injected intravenously at the end of each experiment and followed by a stimulation and an injection of epi + n-epi. Phentolamine acts to lessen the pressor effect of norepinephrine and reverses the effect of epinephrine to a depressor effect. In these experiments this substance always reduced, but did not reverse, the pressor response to splanchnic nerve stimulation. The pressor effect following the injection of epi + n-epi, however, was reversed.

Discussion. Since the efferent composition of the greater splanchnic nerve is generally taken to be largely preganglionic, the evidence presented in this paper tends to cast doubt upon the capacity of high doses of ganglionic blocking agents to block effectively transmission of vasoconstrictor impulses through certain collateral sympathetic ganglia in the cat. An alternative view is that these ganglia are blocked and that the pressor response induced by splanchnic stimulation is due to a potentiation of the vasoconstrictor activity carried by the numerically small complement of postganglionic efferents. But since complete blockade at the ganglia would produce a very marked reduction in the total number of impulses reaching visceral arterioles, it would be necessary to postulate that ganglionic blockade produces an enormous potentiation of the activity of the neurohumoral substances released by the few postganglionic fibers. The responses to injected epi + n-epi are potentiated only two to three times at most by ganglionic blocking agents and thus make this alternative view seem unlikely.

These findings may well help to explain

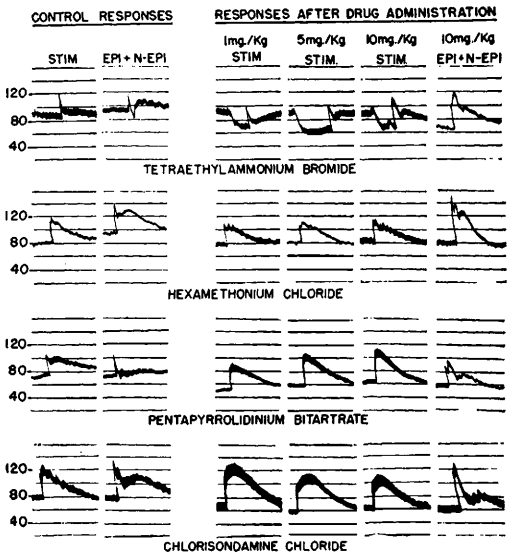

FIG. 2. Arterial pressor responses elicited by left splanchnic nerve faradization in presence of ganglionic blocking agents and with the left adrenal ablated.

the observations in the dog by Plummer *et al.* (6) with chlorisondamine chloride and those of Trapold(7) with chlorisondamine chloride, hexamethonium and pentapyrrolidinium, that peripheral resistance of the mesenteric bed is not greatly decreased after administration of such agents.

That certain sympathetic pathways should not be affected by ganglionic blocking agents is not a novel concept. Freyburger *et al.*(10) and Pardo *et al.*(11) have presented evidence to this effect, and Moe and Freyburger(12) have discussed the subject at length. Cicardo and Dutrey(13) have also presented evidence indicating the ineffectiveness of ganglioplegic agents to block certain ganglionated pressor pathways.

Evidence has been presented by Freyburger *et al.*(14) and Morrison and Farrar(15) that TEA can block the release of epinephrine from the adrenal medulla following splanchnic nerve stimulation. It is not known whether the other blocking agents possess this activity. Apparently, however, epinephrine released from the medulla plays a subsidiary part in the pressor response elicited by faradization of the splanchnic nerve(16).

Summary. The effects of the ganglionic blocking agents, TEA, hexamethonium, pentapyrrolidinium and chlorisondamine chloride on the pressor responses induced by peripheral splanchnic faradization have been determined in 16 cats. These agents did not antagonize the pressor responses when the ipsilateral adrenal gland was present or after it had been ablated. The significance of these findings is discussed.

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Effects of Reserpine on Urinary Bladder Tension. (22436)

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The most prominent actions of reserpine are its "tranquilizing" and blood pressure lowering effects(1-3). Both of these responses are slow in onset, generally commencing from one to several hours after intravenous injection. However, slowness of onset is not characteristic of all the pharmacological responses to this compound. The present communication deals with the response of the urinary bladder to reserpine, an action which begins within 5 minutes after administration.

Methods. Twenty female dogs anesthetized with 30 mg/kg intraperitoneally, plus a continuous intravenous infusion of 0.1 mg/kg/