Do Ganglion-Blocking Agents and Reserpine Affect Central Vasomotor Activity?

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In a majority of experiments on both dogs and cats, hypotensive doses of tetraethylammonium chloride or mecamylamine caused no change or moderate increase in efferent electric activity in the largely preganglionic thoracic portion of the splanchnic nerve, and caused complete and prolonged elimination of efferent activity in the postganglionic inferior cardiac and renal nerves. Both drugs failed to suppress changes in splanchnic nerve activity that were elicited reflexly. These results imply strongly that both ganglion-blocking drugs, in dosage used intravenously to induce hypotension, act mainly through their peripheral effects rather than through one on central vasomotor synapses. In both dogs and cats, reserpine caused slowly progressive and marked diminution in efferent splanchnic nerve activity, which supports the hypothesis that the central action of this agent contributes to its hypotensive effect.

Several quaternary compounds are able to interrupt impulse transmission through autonomic ganglia, and it has generally been assumed that the hypotensive effects of these agents depend largely upon this activity. Lately, however, evidence has been presented which indicates the hypotensive response depends, at least in part, upon central synaptic blockade. Lape and Hoppe,1 employing cross-circulation technics in dogs, showed that the hypotensive response to tetraethylammonium chloride (TEAC) depended equally on central and peripheral blockade, while the response to hexamethonium and azamethonium (Pendiomide) depended predominantly upon a peripheral effect. Dontas and Nickerson2 have also demonstrated a central effect of ganglion-blocking agents in cats by use of the electro-neurogram, and they concluded that hypotensive responses to large doses of these agents are probably due mainly to central blockade. Hart and Marrazzi3 had previously demonstrated the ability of TEAC to block some central synapses but did not correlate this activity with arterial pressure responses. On the other hand, Heymans and colleagues4 found TEAC, hexamethonium and other ganglion-blocking agents to have no effect on cardio-inhibitory reflexes, even when injected directly into a carotid artery.

In view of the wide clinical and experimental uses of ganglion-blocking agents, it is desirable to know precisely their basic mechanisms of action. We have re-examined the central effects of a prototype ganglion-blocking agent, TEAC. Mecamylamine, a secondary amine and ganglion-blocking agent, has been studied also, since it presumably penetrates the blood-brain barrier much more readily than do quaternary ammonium compounds.5, 6 The central action of reserpine has been reinvestigated since, though Bein7 showed it to inhibit efferent activity in the postganglionic inferior cardiac nerve, Dontas8 found it not to affect efferent activity in the mainly preganglionic splanchnic nerve.

METHODS

Adult dogs were anesthetized with morphine (2 mg./Kg. intramuscularly) and pentobarbital sodium (15 mg./Kg. intravenously) and cats with pentobarbital sodium (30 mg./Kg. intraperitoneally) or with urethane (40 to 60 mg./Kg.) and chloralose (200 to 300 mg./Kg.) intravenously after induction with ether. Carotid arterial pressures were measured with a strain gage manometer and carrier wave amplifier, and recorded, both on a direct writing instrument and photographically from the face of a cathode ray tube.
The supradiaphragmatic portion of the left greater splanchnic nerve was used to estimate preganglionic vasomotor discharge. It was cut above the diaphragm, and above any discernible ganglion, and then dissected free, 1 to 2 cm. towards the sympathetic trunk. Adequate exposure was obtained by resecting the lowest 2 or 3 ribs. An intermittent positive pressure respirator maintained adequate ventilation. A dissecting microscope was used to remove the connective tissue from the central end of the cut nerve. The nerve was placed on silver-wire electrodes connected to capacity-coupled amplifiers. Electrical activity was recorded photographically on moving paper from the face of a cathode ray tube simultaneously with arterial pressure. Drying of the nerve was prevented by humidification of surrounding air and by covering the preparation with mineral oil. This made it possible to record from the same nerve for as long as several hours without change in electric activity from deterioration of the preparation. In most experiments, records were also made from small bundles of the whole nerve after teasing it apart. In experiments where a drug could be given but once, as with reserpine, experiments were alternated by using the whole nerve in one and a small bundle in the next. Technical procedures were essentially the same in both cats and dogs.

Postganglionic activity was measured either from the left inferior cardiac nerve or from a renal nerve. The former was exposed by resecting the first 2 or 3 ribs. In cats the left inferior cardiac nerve was identified at its origin from the stellate ganglion; in dogs, it was usually found to arise from the inferior cervical ganglion. In either case, the nerve was cut midway in its course towards the heart, the central end freed of connective tissue and sheath and then placed on silver-wire electrodes as was the splanchnic nerve. Renal nerves were exposed through a paravertebral, retroperitoneal excision and freed from the surface of the renal artery. The cut central ends of several of these small nerves were tried until one was found that showed clear-cut efferent activity.

The vagus-depressor-sympathetic trunks were cut in all experiments in order that reflex activity during the carotid occlusion response be maximal. All test drugs were given intravenously: TEAC in dosage of 5 mg./Kg.; mecamylamine (Inversine), 1 to 2 mg./Kg.; serotonin, 60 µg. of base total; histamine, 40 µg. total; levarterenol, 5 µg. total; and reserpine (Serpasil), 1 mg./Kg.

RESULTS

Effect of Ganglion-Blocking Agents on Splanchnic Nerve Activity. As described by Maes and by Gernandt, Liljestrand and Zotterman, efferent activity in the cat's splanchnic nerve was mainly intermittent, showing grouped bursts of impulses corresponding with heart rate and, often, a superimposed respiratory rhythm as well. Dogs' splanchnic nerves showed the same pattern of activity. In both dogs and cats, there was a variable amount of continuous background activity in addition to the pulsatile component. Carotid occlusion, hypotension due to intravenous injection of histamine, and chemoreceptor stimulation by intravenous injection of serotonin caused pronounced increase in activity, characterized not only by greater total electric potential but by a change in the pattern of response, from mainly pulsatile to mainly continuous. This is illustrated in figure 1. If anesthesia was deep, or if the animal's arterial pressure was below a fairly wide normal range, nerve activity was apt to be mainly continuous, showing only a faint pulsatile component. Pressor responses to intravenous injection of levarterenol or release of clips on the common carotid were associated with quick, transient decrease or elimination of nerve activity, and one or both of these procedures was used in each experiment to ensure that the potentials recorded were not spurious.

In the majority of experiments employing TEAC, records were made from the cut central end of the whole nerve and then from several small bundles separated from it. TEAC was given intravenously, usually in a dose of 5 mg./Kg. which is considered large enough ordinarily to produce its maximum hypotensive effect. In 10 of 17 experiments, total activity in bundles of fibers from the splanchnic nerve, or in the whole nerve, was slightly to moderately increased during hypotensive responses to TEAC, and the pattern of activity changed regularly from largely intermittent to mainly continuous, as during hypotensive responses to histamine or during carotid occlusion (fig. 2). In 3 experiments, nerve activity was essentially unchanged; in 4 experiments, activity decreased slightly or moderately. These 17 experiments included
5 dogs and 12 cats, and there was no discernible species difference in neural responses to TEAC.

When arterial pressure had returned to normal and nerve activity again showed a normal pattern, TEAC would again elicit similar arterial pressure and neural responses. Usually, at least 30 min. elapsed between injections. Different strands from the same nerve ordinarily showed qualitatively similar responses to TEAC. The exceptions were in 2 of the 3 experiments in which activity decreased: other bundles in each nerve showed increased activity during hypertensive responses to TEAC. The exceptions were in 2 of the 3 experiments in which activity decreased: other bundles in each nerve showed increased activity during hypertensive responses to TEAC.

In the majority of preparations, increased nerve activity following TEAC was less than when comparable hypotension was due to intravenous injection of histamine, and also less than during the carotid occlusion response. This implies that TEAC induces either a degree of central blockade, or peripheral blockade of the few postganglionic fibers traveling in the intrathoracic portion of the splanchnic nerve. Blockade of these fibers may balance increased activity in others so that the total effect is no change, or relatively small increase, in activity. Should the blockade be central, it must be rather minor, since it was possible to evoke clear-cut reflex changes in splanchnic nerve activity even during large and prolonged hypotensive responses to TEAC. Figure 2, for example, shows nearly complete inhibition of nerve activity during the initial rise in pressure due to injection of levarterenol during a hypotensive response to TEAC. TEAC also failed to prevent increase in splanchnic nerve activity when the common carotid arteries were occluded.

To avoid reflex increase in sympathetic discharge during hypotension—which might mask a partial central blockade—TEAC was given during the already increased discharge due to exclusion of the carotid sinus and aortic buffer mechanisms. In 3 experiments (2 cats, 1 dog), there was no change or minor decrease in splanchnic nerve activity (fig. 3), indicating that, in the presence of increased vasomotor discharge at least, the central blocking action of TEAC, if present, is slight, and probably of little importance in determining cardiovascular response.

Mecamylamine (1 to 2 mg./Kg.), like TEAC, failed to show prominent central blocking activity in 6 of 7 experiments. The
exception was a dog, in which records were made from a bundle of the splanchnic nerve, and activity disappeared slowly over a period of 40 min. This could have been due to deterioration of the preparation. Since mecamylamine is long-acting, it was not possible to determine whether nerve activity would have returned. In 2 other dogs there was essentially no change in splanchnic nerve activity after mecamylamine; in cats, nerve activity was essentially unchanged in 3 experiments and increased in one experiment (fig. 4).

The type of anesthesia employed did not modify importantly the effect of TEAC on splanchnic nerve activity. When chloralose-urethane, instead of pentobarbital, was used in cats, pressures were usually lower, total nerve activity less, and reflex responses reduced, but the effect of TEAC on nerve activity was qualitatively the same. In several experiments with both cats and dogs, response to TEAC was the same before and after decamethonium was given in doses sufficient to cause immobilization.

**Effect of TEAC on Activity of Postganglionic Sympathetic Nerves.** Efferent activity was recorded from the cut central end of either the inferior cardiac nerve arising from the stellate ganglion, or from a renal nerve freed from the surface of a renal artery. The response to 5 mg./Kg. of TEAC intravenously was strikingly different in these postganglionic preparations. In 3 cats and 2 dogs, nerve activity disappeared promptly, entirely, and for prolonged periods of time. Reappearance of nerve activity lagged behind recovery of arterial pressure. Figure 5 shows

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**Fig. 2.** *Top record,* normal splanchnic activity. *Middle record,* increased activity during hypotension 3 min. after TEAC, 5 mg./Kg. I.V. *Bottom record* (immediately after preceding record), reflex inhibition nerve activity with beginning of pressor response to 5 μg levartenol I.V. Cat. Pentobarbital anesthesia.
a typical effect on activity in a renal nerve. Total activity in this small postganglionic nerve is considerably less than that found in the inferior cardiac nerve. Increased activity during carotid occlusion, also illustrated in figure 5, implies that renal hemodynamics may be influenced by carotid sinus baroreceptor reflexes. The inferior cardiac nerve also showed increased activity during the carotid occlusion response, and both nerves, like the splanchnic, showed reflex increase in activity during hypotensive responses to histamine and decreased activity during pressor responses to levarterenol.

Effect of Reserpine on Splanchnic Nerve Activity. Reserpine (1 mg./Kg.) was given intravenously to 9 cats and 2 dogs. No other drugs had been tested beforehand. It caused pronounced diminution in splanchnic nerve activity in all experiments, though it failed
to completely eliminate activity in any. Definite decrease in vasomotor discharge usually appeared after 10 to 20 min. Thereafter, electric activity continued to diminish slowly and progressively along with arterial pressure until, after 40 to 70 min., the effect was maximum. Total activity at this time was usually 1/4 to 1/3 the control, and ordinarily continued to show pulse modulation.

DISCUSSION

The effect of TEAC on preganglionic is quite different from its effect on postganglionic efferent sympathetic nerve activity. The complete and prolonged disappearance of all activity in the postganglionic inferior cardiac or renal nerve contrasts with the usual small increase in activity in the largely preganglionic splanchnic nerve. Thus there is the strong implication that the hypotensive effect of TEAC depends in large measure upon its ability to interrupt ganglionic transmission rather than upon a central effect.

On the other hand, the increased splanchnic activity usually observed after intravenous injection of TEAC contrasted with the much larger reflex increases in activity during hypotension due to injection of histamine, and an occasional small bundle from the splanchnic nerve showed decreased activity after TEAC. Thus TEAC apparently causes a partial inhibition of impulse transmission in this largely preganglionic nerve. The point of blockade is not clear. It could be central or it could be at the ganglionic synapses of the few postganglionic fibers in the thoracic portion of the splanchnic nerve. Possible support for the latter view comes from the observation that, while an occasional small bundle from the splanchnic nerve shows sharp decrease in activity following TEAC, other bundles from the same nerve respond with increase in activity.

Strongest support for central activity of the ganglion-blocking agents comes from the cross circulation experiments of Lape and Hoppe. However, in these experiments the blocking agents were given directly into the vertebral artery, and in dosage adequate to cause hypotension when given intravenously. Thus, vasomotor centers were subjected transiently to concentrations of blocking agent much higher than those following intravenous administration, and it is not known whether central blockade would have resulted with the latter method of administration. The authors did not report whether hypotensive doses of ganglion-blocking agents, given to the donor
animal, perfusing the recipient's brain, had an effect on the recipient animal's arterial pressure. In the absence of this information, the sum of the data would seem to continue to indicate that ganglion-blocking agents cause fall in arterial pressure largely by peripheral blockade, central blockade contributing to a slight degree, if at all. Presently unknown differences in technic probably account for the different results of the electromyographic experiments by Dontas and Nickerson. The anesthetic agents employed or the use of decamethonium are apparently not responsible.

Since mecamylamine presumably penetrates the blood-brain barrier more readily than the quaternary ammonium compounds, it was anticipated that this agent might well show central blocking activity. This was not the case, however—at least if such blockade is reflected in efferent splanchnic nerve activity. Reserpine, on the other hand, caused a slow, progressive and marked decrease in splanchnic nerve activity in all experiments, and this observation supports the hypothesis that reserpine's hypotensive activity depends, at least in part, upon a central effect.

**Summary**

The largely preganglionic efferent electric activity in the thoracic portion of the splanchnic nerve was, in a large majority of experiments on both cats and dogs, either unchanged or increased after intravenous administration of doses of TEAC or mecamylamine that elicited large and sustained falls in arterial pressure. Both drugs failed to suppress reflexly elicited changes in splanchnic nerve activity.
Postganglionic activity in the inferior cardiac or renal nerve was, on the other hand, promptly and completely eliminated for long periods of time after administration of TEAC. There is, therefore, the strong implication that ganglion-blocking agents, in dosage used intravenously to induce hypotension, act mainly through their peripheral ganglion-blocking activity rather than through an effect on central vasmotor synapses.

Grouping of impulses to correlate with heart rate and respiration, along with a variable amount of continuous activity, characterized normal electric activity in the splanchnic nerve in both dogs and cats. Carotid occlusion, hypotension due to histamine, or chemoreceptor stimulation by serotonin, caused increase in total activity, and the pattern of activity to change from pulse and respiratory modulated to mainly continuous. Hypotension due to ganglion-blocking agents was associated with the same changes, but increase in activity was not as great, and an occasional bundle from the splanchnic nerve showed decrease in activity. Since other bundles from the same nerve showed increased activity in response to TEAC, it was assumed that these occasional bundles may have contained the few postganglionic fibers occurring in the thoracic portion of the splanchnic nerve. Blockade of impulse transmission in these bundles may have balanced increased activity in other fibers, thus accounting for the lesser increase in nerve activity with hypotension due to ganglion-blocking agents than with hypotension due to histamine.

In both dogs and cats, reserpine caused slow, progressive and marked diminution in splanchnic nerve activity, supporting the hypothesis that the central action of this agent is a major contributor to its hypotensive effect.

**Summario in Interlingua**

Le efferente activitate electrica, que es primarimente preganglionic in le portion thoracic del nervo splanchnic, se monstrava, in un grande majoritate del experimentos executate in cattos e canes, inalterate o augmentate post administrationes intravenose de chloruro de tetraethylammonium o de mecamylamina que evocava considerabile e perdurative reductiones del pression arterial. Ni le un ni le altre droga supprimeva alterationes reflexemente evocate in le activitate del nervo splanchnic. Del altere latere, le activitate postganglionic in le nervo infero-cardiac o renal esseva prompte—e completamentemente eliminate pro longe periodos de tempore post le administration de chloruro de tetraethylammonium. Per consequente il ha un forte suggestion que agentes de blocage ganglionic—in le dosages usate pro inducer hypotension—age principally per lor effecto de peripheric blocage ganglionic e non per un effecto super le synapses vasmotori central.

Un gruppage del impulsos in correlation con le frequentia cardiac e le respiration—in-simul con un quantitate variabile de activitate continue—characterisava le normal activitate electric del nervo splanchnic in canes et etiam in cattos. Oclusion carotidic, hypotension induce per histamina o stimulation chimoreceptor per medio de serotonina causave un augmento del activitate total e le transition de illo ab un configuration modulate per pulso e respiration a un configuration principalmente continue. Hypotension causate per agentes de blocage ganglionic esseva associate con le mesme alterationes, sed le augmento del activitate esseva minus marcate, e il occurreva de tempore a tempore que un fasce ab le nervo splanchnic monstrava un reduction de activitate. Proque altere fasces ab le mesme nervo monstrava augmentate activitate in responsa a chloruro de tetraethylammonium, il esseva postulate que iste sporadic fasces contineva possibilemente alicun fibras postganglionic occurrente in le portion thoracic del nervo splanchnic. Il es possibile que le blocage del transmission de impulsos in iste fasces contraballanciava le augmentate activitate in altere fibras, lo que explicarea le minus pronuncia augmento del activitate nervose in hypotension causate per agentes de blocage ganglionic que in hypotension causate per histamina.

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