CURARE-LIKE DRUGS AND CARDIOVAGAL SYNAPSES: COMPARATIVF STUDY *IN VITRO* ON ISOLATED GUINEA-PIG VAGUS-HEART PREPARATION

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Received November 9, 1960

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Isolated vagus-heart preparations from guinea-pigs have been used for a comparative study of the ability of curare-like drugs to block the effects of preganglionic stimulation of the vagi on the heart, *in vitro*. The following drugs all had this property and have been arranged in order of decreasing potency in this respect: hexafluorenium, gallamine, laudexium, decamethonium, tubocurarine, suxamethonium and succinyldisulphocholine.

THOUGH observed for a long time and considered by some workers to be a general property, the ganglion blocking effect of drugs which interrupt the transmission at the level of neuromuscular junctions of striated muscle has not received much study (Bovet, 1959; Paton, 1954; Paton and Perry, 1953; Rosenblueth, 1950).

It was felt that a direct demonstration of this side-effect of curare-like drugs could prove of indubitable interest in adding to our knowledge of the cardiovascular troubles sometimes occuring in a curarised patient (Foldes, 1957).

Using the isolated guinea-pig vagus-heart preparations, we assessed the anti-vagal action of the following curare-like drugs: tubocurarine, decamethonium, suxamethonium, succinyldisulphocholine, gallamine, hexafluorenium and laudexium.

METHODS

The guinea-pigs weighed 300–350 g. The isolated vagus-heart preparations were made from them as previously described (Della Bella, Rognoni and Villani, 1959). The apex of the perfused heart was connected to an isotonic lever which recorded contractions on a kymograph. The preganglionic fibres of the intact vagus were placed on a pair of platinum electrodes, near the heart, to avoid any stretching. Rectangular pulses of 1 millisec. duration, 15 to 20/sec. were applied for 5 sec. at 10 min. intervals of these fibres from an electronic stimulator. Drugs were dissolved in Ringer solution and were injected into the perfusion fluid close to its entry into the heart, 2 min. before a period of vagal stimulation.

RESULTS

Table I shows the minimum doses of the curare-like drugs required to modify the effects on the heart of preganglionic stimulation of the vagus. Hexamethonium has been included as an example of a drug which has nearly pure ganglionic blocking effect. The doses of these drugs required

to produce "head drop" in rabbits have been collected from the literature (Bovet, 1957; Foldes, 1957; Della Bella and others, 1959; Della Bella, Villani and Zuanazzi, 1956) and are included for comparison.

It was found that the most active compound was hexafluorenium, which proved even more active than hexamethonium in blocking the effects of preganglionic vagal stimulation on the heart *in vitro*. This is

TABLE I

GANGLION BLOCKING AND CURARE-LIKE ACTIVITIES OF DRUGS TESTED

Drugs	Minimum active dose on the cardiovagal synapses (*in vitro*) mg.	"Head-drop" dose in rabbits, mg./kg.
Hexamethonium iodide	0·075	—
Hexafluorenium bromide	0·025	0·08
Gallamine iodide	0·050	0·50
Laudexium methylsulphate	0·075	0·03
Decamethonium iodide	0·250	0·15
Tubocurarine chloride	0·300	0·15
Suxamethonium chloride	0·500	0·20
Succinyldisulphocholine iodide.. ..	2·500	2·00

of interest because hexafluorenium produces a marked fall of blood pressure when injected intravenously in rabbits (Fig. 1) and in dogs (Macri, 1954) resembling that caused by the intravenous injection of hexamethonium. Hexafluorenium does not, however, block the effects of preganglionic stimulation of the vagi on the heart either in the rabbit (Fig. 1) or in the dog (Macri, 1954). Fig. 1 shows that hexafluorenium potentiates both the vagal responses the action of acetylcholine: this may be attributed to inhibition of cholinesterases by the drug (Rizzi, 1957; Foldes, Molloy, Zsigmond and Zwartz, 1958). Gallamine and laudexium also have high *in vitro* action in blocking the effects on the heart of

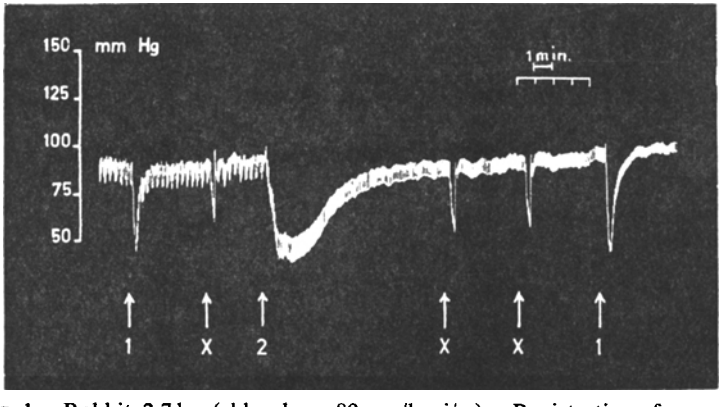

FIG. 1. Rabbit, 2·7 kg. (chloralose: 80 mg./kg. i/v.). Registration of pressure at the carotid. It can be seen that after the administration of hexafluorenium (0·5 mg./kg., i.v. at 2), the response to electrical stimulation of the vagus appears to be potentiated (at X: electrical stimulation of the peripheral trunk of the right vagal nerve for 5 sec.; frequency, 15 pulses/sec.; duration of each pulse: 1 millisec.). Also, the response to the administration of acetylcholine (at 1) is more potentiated (0·5 μg./kg., i.v.).

preganglionic vagal stimulation (Fig. 2) and are almost as active as hexamethonium (Table I). This observation in the case of gallamine (Fig. 3) is in agreement with the clinical and experimental findings that the drug has an inhibitory action on the cardiac effects of vagal stimulation (Bovet, Depierre, Courvoisier and Lestrange, 1949; Jacob and

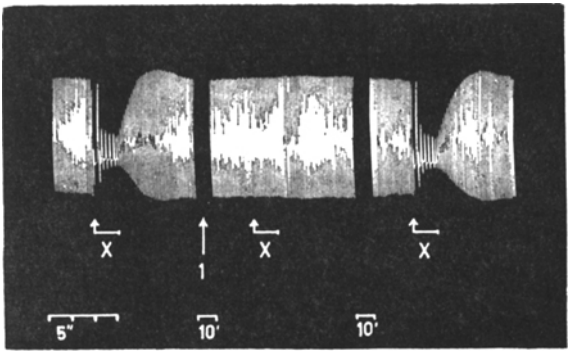

FIG. 2. Isolated guinea-pig vagus-heart preparation. Registration of the responses to electrical stimulation (at X) of the cardiovagal fibres for 5 sec. (frequency, 20 pulses/sec.; duration of each pulse, 1 millisec.). The blocking effect due to hexamethonium treatment (75 μg. at 1) carried out 2 min. before stimulation, is evident.

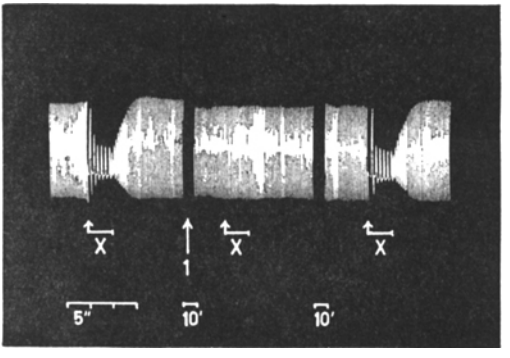

FIG. 3. Isolated guinea-pig vagus-heart preparation. Registration of the responses to electrical stimulation (at X) of the cardiovagal fibres for 5 sec. (frequency, 20 pulses/sec.; duration of the single pulse, 1 millisec.). Treatment with gallamine (50 μg. at 1) causes a vagal block practically identical to that obtained with hexamethonium in the experiment described in Fig. 2.

Depierre, 1950; Riker and Wescoe, 1951). The vagal blocking action of laudexium appears to be approximately three times that of tubocurarine (Table I). But when their activities were compared using isolated guinea-pig intestine stimulated with nicotine, tubocurarine was found the more potent (Collier and Macauley, 1952). Finally, suxamethonium had only slight *in vitro* vagal blocking action (Table I). This has already been noted *in vivo* by workers using electrocardiographic methods of recording

in cats; its neuromuscular blocking activity is also of short duration (Purpura and Grundfest, 1956). The disulphonium analogue—succinyldisulphocholine proved even less active (Fig. 4).

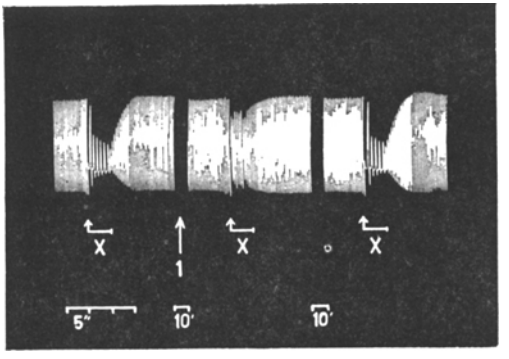

FIG. 4. Isolated guinea-pig vagus-heart preparation. Recording of the responses to electrical stimulation (at X) of the cardiovagal fibres for 5 sec. (frequency, 20 pulses/sec., duration of each pulse, 1 millisec.). Partial disappearance of the vagal response, following succinyldisulphocholine treatment (2 mg. at 1), is evident.

DISCUSSION

It is not possible to determine the nature of the anti-vagal effect shown by the drugs tested with the isolated vagus-heart preparations used. However, since it is well known that these drugs do not possess atropine-like properties and do not interfere with the liberation of the cholinergic mediator, it may well be assumed that the anti-vagal effect recorded is a result of the inhibitory action exerted on the cardiovagal synapses.

Table I shows that the ganglion blocking effect of curare-like drugs *in vitro* has a very close relationship to their curare-like action *in vivo* except for gallamine. On the contrary, the same relationship does not persist when the *in vivo* ganglion blocking activity is considered. For example, hexafluorenium which is found to have a very high ganglion blocking activity *in vitro*, does not have any such activity *in vivo*. Instead, the suxamethonium activity *in vitro* is still retained *in vivo*. It is difficult at the present moment to give a satisfactory explanation for these differences.

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