THE BLOCKING EFFECT OF CHOLINOLYTIC SUBSTANCES AT THE PARASYMPATHETIC GANGLIA*

S.N. Golikov and Iu.G. Fedorchuk

From the All-Union Scientific Research Sanitary-Chemical Institute

(Director – Doctor of Medical Sciences S.N. Golikov), Leningrad

(Received September 24, 1956. Presented by Active Member Acad. Med. Sci. USSR, S.V. Anichkov)

In the pharmacological investigations of cholinolytic medicinals, their blocking effects are of considerable interest. To study the effect of cholinolytic substances upon sympathetic ganglia is a relatively simple matter; to do the same with parasympathetic ganglia is a much more difficult procedure. One of the difficulties lies in the fact that the parasympathetic postganglionic fibers are very short. This anatomic peculiarity practically excludes perfusion of the parasympathetic ganglia, even when this method is the most satisfactory one known for studying the ganglionic actions of various substances. Besides this, in parasympathetic nerves both the pre- and postganglionic fibers are cholinergic. This adds to the difficulties in the determination of the blocking effects of cholinolytic substances at the parasympathetic ganglia. While it is relatively easy to study pure gangliolytics (such as hexonium**) as they do not exert a practical influence upon the effector cells innervated by the postganglionic fibers, it is much more difficult to examine the ganglionic actions of substances blocking both the M- and the N-cholinergic systems*** as in these instances the M-cholinergic effect tends to mask the action on the ganglia.

While studying the pharmacological properties of cholinolytic substances having both nicotinolytic as well as atropine-like properties, we became convinced that the methods so widely employed for the studies of the blocking effects upon the parasympathetic ganglia of these substances (arterial pressure, bowel in situ and others) are far from satisfactory. In these experiments the absence of a reaction to stimulation of the preganglionic fibers of the parasympathetic nerves in the presence of a response to acetylcholine is taken to prove a ganglionic cholinolytic block. However, the lack of a response to electric stimulation may also depend largely on the atropine-like properties of the preparation. In connection with this, it is interesting to evaluate the relative merits of methods used to investigate the effects of cholinolytic substances upon parasympathetic ganglia. We correlated experiments upon arterial pressure, the heart and intestine in situ. In this study we present the results obtained when we used atropine-like substances, specifically, the chlorhydrate ester of diphenylglycolic acid and diethylamino-ethanol (ester 22).

Experiments recording cat arterial pressure showed that small doses of ester 22 removed first the effects of vagal stimulation while it took much larger doses to remove the acetylcholine effects (Figure 1). This gives reason to believe that ester 22 has a powerful ganglion-blocking effect while having only weak atropine-like properties. However, the results of experiments with a cat heart in situ were somewhat different. The inotropic and chronotropic effects of acetylcholine (10-20 gamma/kg intravenously) and electric stimulation of the peripheral end of the cut vagus were abolished by the use of approximately the same doses. In many of the experiments the

*Presented at the 646th session of the I.M. Sechenov Physiological Society, April 17, 1956.

**Transliterated – probably hexamethonium.

***That is, substances possessing ganglion-blocking as well as atropine-like properties.

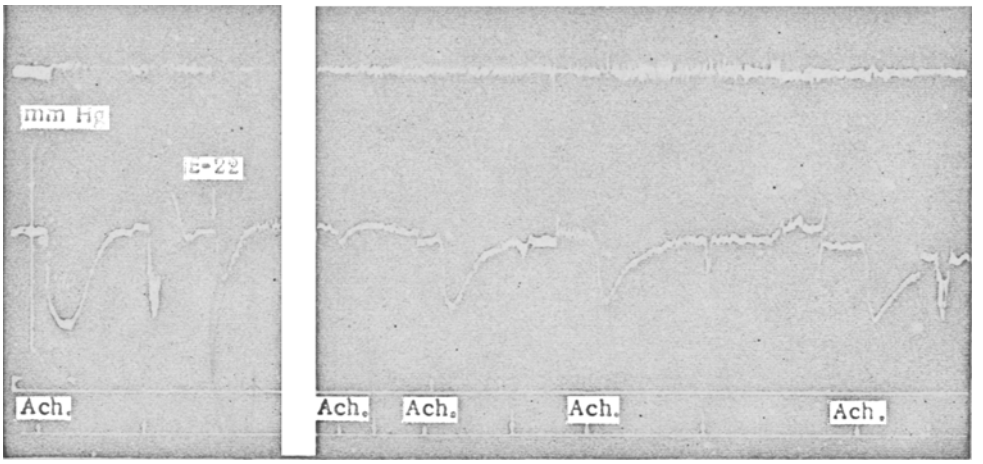

Fig. 1. Effect of ester 22 upon respiration and arterial pressure in a cat when the vagus nerve is stimulated with electric current and acetylcholine. Significance of curves (from above down): respiration, arterial pressure, time marker (1 second); stimulus marker: ↑) acetylcholine (1 gamma per 1 kg intravenously); ↓) vagus stimulation; E-22) ester 22 (0.2 mg/kg intravenously).

acetylcholine effects were abolished with somewhat smaller doses than were the electrical effects of stimulating the peripheral end of the cut vagus (Figure 2). Analogous data were obtained also in experiments done upon the bowel in situ. Bowel contractions produced by acetylcholine in most instances disappeared with smaller amounts of the preparation than were needed to abolish the contractions following the stimulation of the peripheral end of the severed vagus nerve.

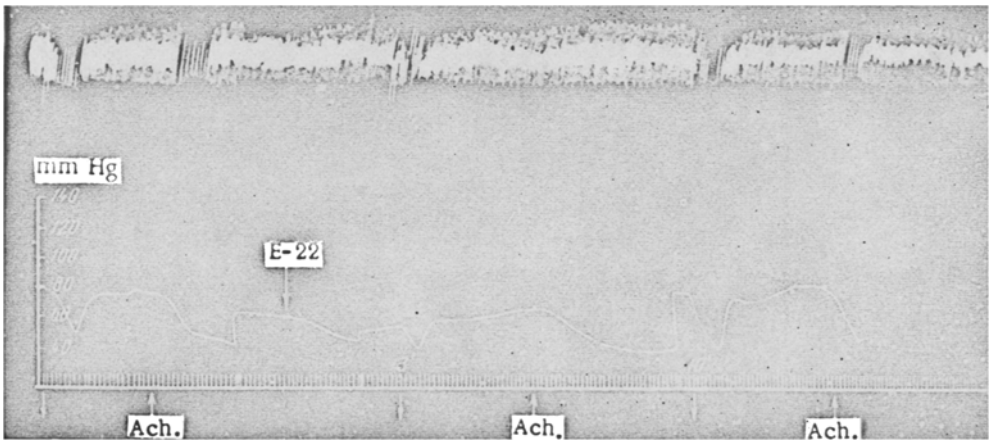

Fig. 2. Influence of ester 22 upon the arterial pressure and frequency and rhythm of cardiac contractions after vagus stimulation and acetylcholine action. Significance of curves (from above down): heart action in situ, arterial pressure, time marker (1 second); ↓)vagal stimulation; E-22) ester 22 (0.1 mg/kg intravenously); ↑) acetylcholine.

Thus, on the basis of cardiac and intestinal experiments in situ one might conclude that ester 22 has mainly atropine-like properties while, at the same time, one could interpret the arterial pressure experiments as in-

dicating that the preparation has mainly a ganglion-blocking action. This shows that the three most widely used methods in the determination of atropine-like and ganglion-blocking effects of substances fail to give an adequate concept of ester 22 actions.

In the experiments upon the heart in situ, simultaneously with the cardiac contractions, we recorded the arterial pressure. The results of our experiments showed that the cardiac and arterial pressure effects of electrical vagal stimulation disappeared with small dosages while the acetylcholine effects were abolished from the heart first while the arterial pressure required much larger doses (see Figure 2). These data indicate that the hypotensive effects evoked by electric stimulation of the vagus and acetylcholine are not equivalent and that removal of the vagal hypotensive effect during the response to acetylcholine is not evidence for the ganglion-blocking action of the given preparation. In this regard, the experiments on the heart and intestine are much more conclusive. But even here it is rather difficult to decide whether the removal of the vagal effect is due to ganglionic block by the given substance or whether it is due to its atropine-like properties.

To study the blocking action of cholinolytic substances on parasympathetic ganglia we chose the ganglia of the pelvic nerve. It turned out that our method of recording in situ the cat urinary bladder contractions was the method of choice for our investigation.

The studies were conducted as follows. By means of a catheter inserted into a dissected urethra the bladder was filled with warm Ringer solution and then, using a water manometer, it was connected with a Marey capsule. Bladder contractions were induced by stimulating the preganglionic parasympathetic fibers of the bladder branch of the pelvic nerve, using for this purpose either an induction current or intravenous injection of nicotine (0.02 mg/kg).

In these experiments it was established that atropine in doses of 5-10 mg/kg had almost no effect upon bladder contractions induced by intravenous nicotine or electric stimulation of the urinary branch of the pelvic nerve. Hexonium and nicotine (the first in doses of 1-2 mg/kg intravenously, the second in doses of 0.1-0.5 mg/kg) completely abolished urinary bladder contractions caused by electric stimulations of the pelvic nerve. Insofar as the bladder contractions caused by electric stimulation of the pelvic nerve or by nicotine remained stable in relation to atropine, this method presented many conveniences in the investigation of the action of cholinolytic substances having atropine-like qualities in their effects upon the parasympathetic ganglia of the pelvic nerve. Ester 22 in these experiments did not abolish bladder contractions even when administered in doses of 10 mg/kg (Figure 3). Thus, it is evident that the atropine-like preparation, ester 22, has almost no effect upon the parasympathetic ganglia of the pelvic nerve. When this preparation was used to study arterial pressure and the heart and intestinal actions in situ, it abolished the effects of electrical stimulation of the parasympathetic nerves even when used in doses of 0.1-0.8 mg/kg. Apparently, in these experiments the suppression of the effects of the electrical stimulation is the consequence of a block of the M-cholinergic system.

Fig. 3. Influence of ester 22 upon the parasympathetic ganglia of the pelvic nerve. Significance of curves (from above down): bladder contractions in situ; time marker (5 seconds); N) nicotine (0.02 mg/kg intravenously); E-22) ester 22 (10 mg/kg intravenously).

Our pharmacological analysis has demonstrated that the M-cholinergic system of the urinary bladder displays very little sensitivity to choline mimetic substances. Thus, pilocarpine, which is a selective stimulator of the M-cholinergic system [1], could produce only sporadic urinary bladder contractions when given intravenously in large doses such as 1-10 mg/kg. When repeated, pilocarpine as a rule failed to produce an effect. In favor of our hypothesis is the fact that bladder contractions caused by acetylcholine are prevented completely by intravenous use of nicotine (0.1-0.5 mg/kg) and by hexonium (1 mg/kg). Most likely, acetylcholine produces bladder contractions by stimulating the N-cholinergic system of the parasympathetic ganglia and not the M-cholinergic system of the muscle fibers. Otherwise nicotine, which acts selectively upon the ganglia, would not inhibit bladder contractions evoked by acetylcholine.

The lack of sensitivity displayed by the M-cholinergic system of the urinary smooth musculature to choline mimetic and cholinolytic substances makes the method we have described above quite useful for the evaluation of the blocking actions of cholinolytics upon parasympathetic ganglia.

The above discussion attests to the fact that there is no single method which, by itself, gives a complete picture of the ganglion-blocking actions of various substances. The most complete and trustworthy picture of the blocking actions of cholinolytic substances upon parasympathetic ganglia may be obtained by using all the known methods including experiments upon the urinary bladder.

SUMMARY

The most authentic data on the blocking effect of cholinolytics on the parasympathetic ganglia may be obtained only when different methods, including experiments on the urinary bladder, are employed.

LITERATURE CITED

[1] S.V. Anichkov and M.L. Belen'kii, Text of Pharmacology [in Russian] (Moscow, 1954).

[2] S.S. Krylov, Farmakol. i Toksikol. 19 (3), 21 (1956).