EFFECT OF CERTAIN LOCAL ANESTHETICS ON CHEMOREFLEXES FROM THE HEART AND LUNGS

(UDC 612.815.1 : [612.17 + 612.2]-06 : 615.781)

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 60, No. 9, pp. 63-67, September, 1965
Original article submitted March 18, 1964

In 1953 Comroe and coworkers [15] showed that novocain, when injected intravenously, depresses the chemoreflexes from the receptors of the heart and lungs in response to serotonin. The mechanism of this depressant action has not been analyzed, and the presence of the depressant action has been interpreted as a special manifestation of the nonspecific effect of anesthetics on the interoceptive reflexes [15, 18]. In fact, anesthetics, when injected intravenously, depress many viscero-visceral reflexes [1, 4, 5, etc.]. However, further investigations showed that the mechanism of the blocking of most interoceptive reflexes by novocain differs significantly from the mechanism of depression of the chemoreflexes to serotonin. According to findings reported by A. P. Gilev [2], for instance, if novocain is injected intravenously into cats in a dose of 1-2 mg/kg it depresses the coronary chemoreflex to serotonin as a result of the blocking of the reaction of the cardiac receptors to this stimulus. Meanwhile, other viscero-visceral reflexes (reflexes from the mechanoreceptors of different regions, from the chemoreceptors of the carotid body, the spleen and the intestine to stimuli such as acetylcholine, cytisine, cyanides or nicotine) are depressed by the intravenous injection of novocain in a dose of 5-15 mg/kg as a result of its central cholinolytic and ganglion-blocking effect. The reaction of the interoceptors to the stimuli listed above remain unchanged following intravenous injection of novocain in nontoxic doses [3, 12, 14, 19, etc.].

Hence, in relation to the interoceptive reflexes novocain behaves as a typical anesthetic, depressing the receptors and the afferent nerve fibers only when injected locally. The receptors of the heart, reacting to serotonin, are an exception. Similar results have been obtained by the study of tipindole, a new serotonin antagonist, possessing weak anesthetic properties [8]. In A. P. Gilev's experiments [2], tipindole, even in a dose of 20 mg/kg, did not modify the reaction of the cardiac receptors to adequate mechanical stimulation. Hence, tipindole, like novocain, by its resorptive action, was capable in very small doses of causing selective depression of the reactions of the receptors of the heart and lungs to certain chemical stimuli. The presence of this marked selectivity of action suggested that no connection exists between the anesthetic properties of tipindole and novocain and their ability to depress the chemoreflexes from the heart and lungs.

In order to solve this problem, it was first necessary to find out whether all anesthetics, when injected intravenously, depress the chemoreflexes from the heart and lungs, and whether the local-anesthetic activity of these substances is dependent on their depressant action on the chemoreflexes. The study of the effect of local anesthetics on these chemoreflexes is not only of theoretical importance, but also of definite practical interest, because serotonin and guanidine derivatives are components of the body cells and, in certain pathological conditions, may enter the blood stream in large amounts and may produce a sharp fall in the arterial pressure and a slowing of the heart [13, 15, 16, 22, etc.]. In this investigation the effect of certain local anesthetics was studied on chemoreflexes from the heart and lungs caused by serotonin and phenylguanidine.

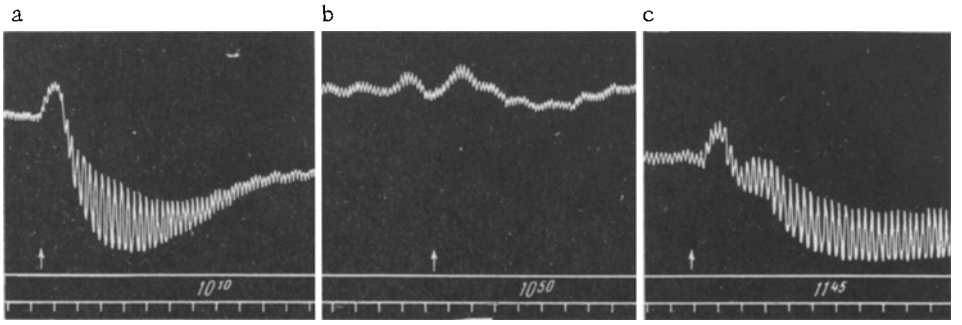

Fig. 1. Effect of novocain (1 mg/kg) on the chemoreflexes evoked by phenylguanidine (90 μg/kg intravenously). a) Reflex to phenylguanidine before injection of novocain; b) 1 min after injection of novocain; c) 56 min after injection of novocain. Significance of curves (from top to bottom): arterial pressure, marker of injection of stimulus, time marker 1 min.

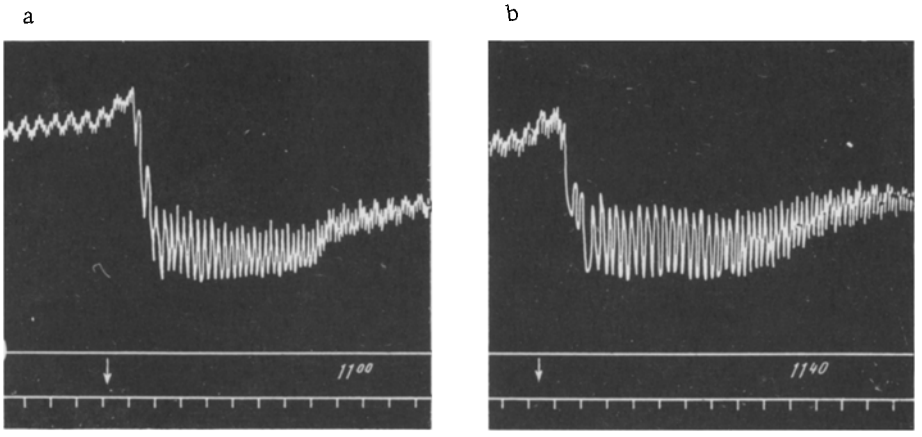

Fig. 2. Effect of trimecain (2 mg/kg) on the chemoreflex evoked by serotonin (serotonin injected into the left ventricle in a dose of 25 μg/kg). a) Reflex to serotonin before injection of trimecain; b) 1 min after injection of trimecain. Significance of the curves as in Fig. 1.

EXPERIMENTAL

Experiments were conducted on cats anesthetized with urethane (0.6 g/kg) and chloralose (0.04 g/kg). Serotonin and phenylguanidine were injected intravenously, and in some cases into the left ventricle by means of a polyethylene catheter, introduced through the subclavian artery and ascending aorta [7]. The changes in arterial pressure taking place in these circumstances were due not only to chemoreflexes from the heart and lungs, but also to a number of factors of nonreflex nature [15, 16, 21, etc.], and the intensity of the reflex reactions was therefore judged mainly from the degree of slowing of the heart rate. The slowing of the cardiac contractions following the intravenous injection of serotonin and phenlyguanidine is dependent on reflexes from the receptors of the heart and lungs, but if these substances are injected directly into the left ventricle, the slowing is due entirely to a reflex from the receptors of the heart [7, 15, 16]. The arterial pressure was measured in the carotid artery by means of a mercury manometer. The heart rate was determined from the tracing of the arterial pressure. Altogether 60 experiments were performed.

RESULTS

The experiments showed that novocain, in a dose of 1-2 mg/kg, has a marked depressant effect not only on reflexes evoked by serotonin, but also on the chemoreflexes produced by phenylguanidine (Fig. 1). For example, in a series of five experiments phenylguanidine slowed the heart rate before injection of novocain on the average by 64%, and after injection of novocain in a dose of 1 mg/kg, on the average by 24% (difference of means 40 ±8.4). In all the experiments novocain, in a dose of 2 mg/kg, caused complete depression of the chemoreflexes to phenylguanidine.

Comparison of Anesthetic Activity of Local Anesthetics and Their Influence on the Chemoreflexes from the Heart and Lungs

Local anesthetic	Anesthetic activity*	Effect on chemoreflexes (1-2 mg/kg)
Novocain	1	Marked depression
Trimecain	1-3	No effect
Lignocaine	1-3	"
Cinchocaine	20-200	"

*V. V. Zakusob [3], Goodman and Gilman [17], and N. T. Pryanishnikova [9, 10] found that the activity of these preparations in terminal, conduction, and infiltration anesthesia was as shown in the table.

Local anesthetics such as xylocain (lignocaine) and trimecain, whose activity is greater than that of adrenalin [9, 10, etc.], in doses of 1 and 2 mg/kg had no definite effect on the chemoreflexes from the heart and lungs (Fig. 2). In a series of eight experiments, for instance, lignocaine in a dose of 2 mg/kg did not change the reflex to phenylguanidine in 6 cases, in one case it depressed the reflex slightly, and in one case it increased it.

One of the most powerful local anesthetics, sovcain (cinchocaine), more than 20 times stronger in its action than novocain, in a dose of 1 mg/kg likewise did not depress the chemoreflexes to phenylalanine and serotonin. For example, in a series of seven experiments serotonin slowed the heart rate before injection of cinchocaine on the average by 57%, and after injection of cinchocaine by 52%. Cinchocaine was not injected in a dose of 2 mg/kg because of its high toxicity. Hence, the results obtained show that the anesthetic activity of these drugs is independent of their ability to depress the chemoreflexes from the heart and lungs (see table).

The absence of any connection between the anesthetic properties of novocain and of tipindole also is shown by an observation made by A. P. Gilev [2], In his experiments, the afferent impulses in the fibers of the vagus nerve arising in response to adequate mechanical stimulation of the cardiac receptors and to stimulation of the cardiac receptors with serotonin were recorded. Gilev found that novocain and tipindole depressed the "serotonin" impulses in the same doses. Impulses in response to mechanical stimulation of the receptors were depressed by novocain in a dose of 20 mg/kg. Tipindole, in a dose of 20 mg/kg, had no effect on the mechanoreceptor impulses. If the depression of the reaction of the receptors to serotonin was one of the early signs of the general depressant effect of the local anesthetics on the sensory nerve endings and the afferent fibers, novocain and tipindole would be expected to depress the impulses from the mechanoreceptors to an equal degree.

It may be concluded from the foregoing facts that the ability of novocain and tipindole to cause selective depression of the reaction of the receptors of the heart and lungs to chemical stimuli is due, not to the local anesthetic properties of these substances, but to other properties. It is difficult at present to decide what these properties are. However, a few suggestions may be made. Novocain is known to cause specific blocking of the serotonin reacting structures of the autonomic ganglia (the tryptamine M receptors [23]). Tipindole selectively depresses the reactions of the receptors of the ganglia and the D receptors of the muscles to serotonin. In our previous investigations [8] no direct relationship could be established between the effect of antagonists on the tryptamine M and the tryptamine D structures and the receptors of the cardio-pulmonary reflexogenic zone, also reacting to serotonin. The possibility is not ruled out, however, that tipindole and novocain possess a broad spectrum of antiserotonin action, and besides blocking the serotonin-reacting structures of the autonomic ganglia and the smooth-muscle organs, they also block the serotonin-reacting sensory nerve endings of the heart and lungs. The fact that novocain and tipindole depress the chemoreflexes not only to serotonin, but also to phenylguanidine, does not conflict with this hypothesis, since phenlyguanidine and serotonin, judging by data in the literature, excite the same receptors in the heart and lungs [20]. However, the final solution of this problem must await the results of further investigations.

Regardless of the conclusions to be deduced from these investigations, the results obtained are of considerable practical interest. At the present time novocain is being supplanted in clinical practice by local anesthetics such as lignocaine and trimecain [6, 11, 24, etc.]. This change is evidently undesirable in cases when depression of the chemoreflexes from the heart and lungs would be advantageous (in coronary insufficiency, operations on the heart and lungs, anaphylactic and blood-transfusion shock, pulmonary embolism and so on).

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. ***Some or all of this periodical literature may well be available in English translation.*** **A complete list of the cover-to-cover English translations appears at the back of this issue.**
