

THE CORRELATION BETWEEN THE CENTRAL AND PERIPHERAL
CHOLINOLYTIC EFFECTS OF CERTAIN COMPOUND ESTERS
OF DIETHYLAMINOETHANOL AND AROMATIC ACIDS

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Certain substances with a calmative effect on the central nervous system have been classed as tranquilizers. Cholinolytics such as Diazyl [benzilic acid β -diethylaminoethyl ester hydrochloride], Aprophene [diphenylpropionic acid β -diethylaminoethyl ester hydrochloride], Methyldiazyl [benzilic acid β -diethylaminopropyl ester hydrochloride], Diphacyl [diphenylacetic acid β -diethylaminoethyl ester hydrochloride], Methyldiphacyl [diphenylacetic acid β -diethylaminoisopropyl ester hydrochloride], Pentaphene [phenylcyclopentacarboxylic acid β -diethylaminoethyl ester hydrochloride], etc. occupy a prominent place in this group.

That these substances have a central inhibitory effect is evident from their pronounced effect on the higher nervous activity of healthy people [4, 8] and animals [2, 5, 6, 7, 10, 11, 12, 13, 14, 15] and from the typical changes they cause in the spontaneous bio-electric activity of the brain [2, 3, 4, 9]. The cholinolytic nature of their effect is demonstrated by the mutual antagonism between their effect and the central effect of cholinomimetic substances such as nicotine and arecoline and anticholinesterase substances such as physostigmine, proserine [neostigmine], etc.

However, it is well known that these cholinolytics can block the cholinergic synapses of the peripheral, nervous system as well as those of the central, and a more definite idea of the correlation between the central and peripheral cholinolytic effects is of considerable theoretical and practical importance. Opinions on this correlation which have been based on comparisons of data obtained under conditions specially created to demonstrate either solely the central or solely the peripheral effects cannot be considered conclusive. The central and peripheral cholinergic systems are comparable up to a certain point, if only because of the obvious dissimilarity of the anatomicophysiological and biochemical conditions of their activity.

Scientists have been attempting to develop a test to demonstrate the properties of the central and peripheral cholinolytic effects by simultaneous registration of the latter, but the first to provide a solution to this problem was S. N. Golikov in 1954 [1]. His method has been acknowledged and used with creditable success as that best satisfying the given conditions.

S. N. Golikov is known to have successfully used N. V. Golyakhovskii's data on the central (tremor) and peripheral (salivation) cholinomimetic effects of arecoline to analyze the central and peripheral effects of atropine and Tropacine [ester of diphenylacetic acid hydrochloride]. He established that different doses of these cholinolytics are required to prevent the central and peripheral effects of arecoline. From the data he obtained, the author concluded that arecoline intoxication in mice could be used to assess the central and peripheral effects of cholinolytics, based on the ability of the latter to prevent or remove the central (tremor) or peripheral (salivation) symptoms of intoxication.

This method, however, despite its unquestionable merits, does not allow one to fully assess the effect of experimental cholinolytics. In the first place, it does not permit comparison of the central and peripheral effects of any cholinolytic, but only of those which block the m-cholinergic systems. In the second place, of the two aspects of a substance's effect — its strength and its duration — only one, the former, can be determined by means of this method. And finally, the method does not permit objective registration of all the visible effects (tremor and salivation).

In the course of a pharmacological study of certain new compound esters, derivatives of diethylamino-ethanol and aromatic acids, we developed a new method of determining the strength and duration of the central and peripheral effects of cholinolytics. As known, the classic method of studying peripheral synaptic transmission of nerve impulses is to compare the responses of the effector organ to stimulation of the peripheral section of the nerve recorded before and after administration of the experimental substance. The introduction of electrophysiological methods to pharmacological research has made it possible to record the changes in the bio-electric potentials of the brain during light, sound, tactile and other stimulations and during stimulation of individual nerves and internal organs. The electroencephalographic changes observed (waking symptom) are believed to reflect processes which occur in the cells in certain sections of the brain in response to the application of stimulation to the periphery.

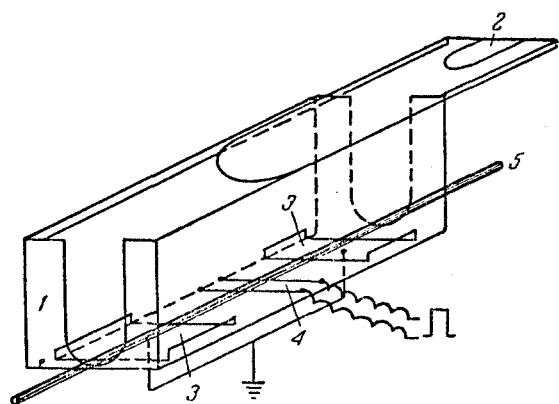


Fig. 1. Diagram of pencil case receptacle designed to hold nerve section during stimulation. Key: 1) Case frame; 2) case cover; 3) silver grounding plate; 4) stimulating electrodes; 5) nerve.

case and containing platinum electrodes for stimulating the nerve and silver grounding plates (Fig. 1). Silk thread was used to bind the receptacle to the deep muscles of the neck, after which the wound was closed with either silk or Kocher's forceps. The rabbit was then rolled on to its stomach and strapped to the bench until the end of the experiment. We recorded the ECG (lead II) and the EEG (frontal, parietal and occipital leads). The brain potentials were led off by means of platinum (30-70 μ) monopolar and bipolar electrodes. The vagus nerve was stimulated with square-wave pulses (250-400 cps, 0.1-1 m/sec, 6-10 volts) for 5-10 sec.

The parameters given for the stimulating stimuli are supraliminal for the central section of the vagus nerve and liminal for the peripheral. The relative disparity between the thresholds of the "central" and "peripheral" reactions in this case suited our purpose: this meant that any predominance observed of the central cholinolytic effect over the peripheral under these experimental conditions would be completely authentic. The sensitivity of the central and peripheral synapses to threshold stimulations was determined in control experiments.

A clear "waking" picture on the EEG and retardation of the heart rate on the ECG (Fig. 2) were observed in response to the experimental stimulation. These changes were evidence of the conduction of nerve impulses through the cholinergic synapses of the central and peripheral systems under normal conditions, while the absence of these effects demonstrated the blocking of these synapses following the administration of cholinolytics.

For example, Methyldiazyl (benzilic acid diethylaminoisopropyl ester racemate hydrochloride) removed the waking symptom when injected in a dose of 0.1-0.15 mg/kg, but a 0.2-0.3 mg/kg dose of this preparation was required to block the cholinergic systems of the heart. In the latter case, the peripheral blocking effect lasted 15-20 min, and the effect on the central nervous system lasted over an hour.

We have established that the waking symptom evoked by stimulation of the sciatic nerve, inflation of the stomach, stimulation of the vagus nerve, etc., is not apparent after the intravenous injection of central cholinolytics in specific doses. This is probably due to blockade of the synaptic cholinergic systems, according to data obtained in other investigations concerning the central effect of Diphacyl, Diazyl, and other substances of this series. It is known that these substances can block the peripheral as well as the central cholinergic synapses. The method we used to assess both the central and peripheral cholinolytic effects simultaneously was a combination of the method for recording the peripheral.

The vagus nerve, intact — not transected, of a rabbit under light urethan anesthesia (0.5 g/kg) was put into a moist receptacle fashioned from a pencil

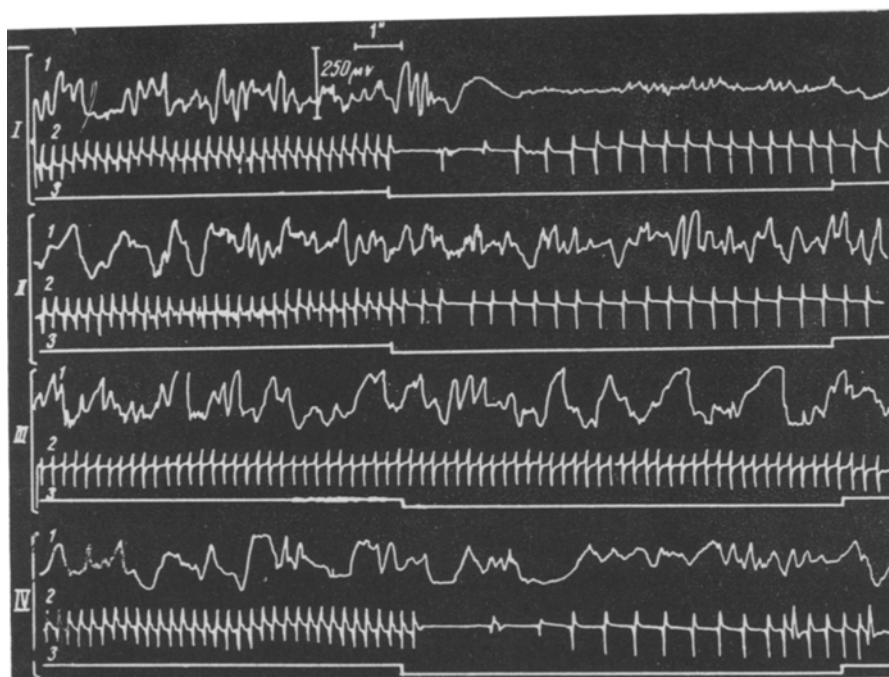


Fig. 2. Change effected by Methyldiazyl in the central and peripheral effects in response to stimulation of the vagus nerve (experiment performed on rabbit three hours after operation in which electrode was placed on vagus nerve and electrodes were fixed to the parietal region of the cerebral cortex). 1) EEG; 2) ECG; 3) stimulation of vagus nerve (dropped section of line); I) norm; II) 5 min after intravenous injection of Methyldiazyl in a dose of 0.1 mg/kg; III) 5 min after injection of preparation, this time in a dose of 0.3 mg/kg; IV) 30 min after second injection.

After the intravenous injection of the experimental substances, the response to stimulation of the vagus nerve was recorded every five minutes until the cholinolytic effect had completely disappeared. The strength and duration of the central and peripheral effects induced by several substances were determined in this way, making it possible to establish a correlation between the two effects.

This article cites data demonstrating the correlation between the central and peripheral cholinolytic effects of four known and two recently synthesized cholinolytics.

The substances we selected differ qualitatively in effect: Diazyl and Methyldiazyl are strong m-cholinolytics; Diphacyl and Pentaphene are relatively strong n-cholinolytics, and Methyldiphacyl and Aprophene block both the m- and n-cholinergic systems to an approximately equal degree.

The investigations conducted showed that all these substances possess both central and peripheral cholinolytic activity, which is fully corroborated by the specific literature data on the pharmacology of these preparations.

The correlations of the central and peripheral blocking effects of these substances in strength and duration are clear from the table.

The table shows that these substances exert a blocking effect on the central cholinergic synapses in doses which either do not effect or scarcely affect the peripheral cholinergic synapses. The central cholinolytic effect, moreover, lasts slightly longer than the peripheral.

Comparing the data obtained from the various preparations, one can note that the difference in their effects comprised an average of 400-1000%; when, however, the central and peripheral cholinolytic effects are determined separately under specially created conditions, the difference observed in the strength of the various preparations' effects runs from 2000-3000%. According to our data, for example, there is a difference of 1000% between Diazyl and Diphacyl in strength of central cholinolytic effect, while data obtained by other methods

Change of Central and Peripheral Cholinolytic Activity

| Preparation | Doses (in mg/kg) preventing | | Ratio of the doses inhibiting the central and peripheral effects | Duration of blocking action (in min) | |
|----------------|-----------------------------|--|--|--------------------------------------|------------|
| | waking reaction | bradycardia reaction (peripheral effect) | | central | peripheral |
| Diazyl | 0.1 | 0.2 | 1/2 | 60 | 30 |
| Methyldiazyl | 0.05 | 0.2 | 1/4 | 60 | 30 |
| Diphacyl | 1.8 | 3.0 | 3/5 | 45 | 20 |
| Pentaphene | 1.3 | 2.5 | 1/2 | 45 | 25 |
| Aprophene | 0.9 | 1.5 | 3/5 | 40 | 25 |
| Methyldiphacyl | 1.0 | 2.0 | 1/2 | 50 | 25 |

have defined this difference as 2000-3000%. The reason for the smaller difference observed in the strength of the different cholinolytics' effects is that, in our observations, we determined the general cholinolytic activity of the preparations instead of the specific m- or n-cholinolytic activity. Most of these substances are known to affect to some extent both m- and n-cholinergic systems. The method we propose makes it possible to determine the strength and duration of the central and peripheral cholinolytic effects of substances regardless of their qualitative peculiarities, since an impulse passes from the site of stimulation both centrally and peripherally through m- and n-cholinergic systems, making it possible for use to determine the total, or over-all, cholinolytic activity. The cholinolytic activity of the substances we investigated (Diazyl, Methyldiazyl, Pentaphene, Diphacyl, Methyldiphacyl and Aprophene) was found to be primarily central.

The duration of the central cholinolytic effect was longer than that of the peripheral.

This method of stimulating the intact vagus nerve and simultaneously recording the central (waking) and peripheral (retarded heart rate) effects can be used to simultaneously determine the strength and duration of both the central and peripheral cholinolytic effects.

SUMMARY

Synchronic determination of the strength and duration of the central and peripheral cholinolytic action of four known and 2 new preparations belonging to the ester group was carried out with the aid of a new method (stimulation of the intact vagus nerve with simultaneous registration of the central effect on the EEG and of the peripheral effect - slowing down of the cardiac rhythm - on the ECG). It was shown that Diazyl, Methyldiazyl, Diphacyl, Pentaphene, Methyldiphacyl and Aprophene produced mainly central cholinolytic activity; the strength and the duration of the central cholinolytic effect exceeded that at the periphery.

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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.
