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ANALYSIS OF THE ACTION OF SOME CHOLINERGIC COMPOUNDS ON THE HEART OF FRESH-WATER MUSSEL (*ANODONTA* sp.)

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In the heart of fresh-water mussel, similarly to several other molluscs (PROSSER 1940, WELSH and TAUB 1948, TEN CATE 1955, NISTRATOVA and YUZHANSKAIA 1966) acetylcholine is a mediator of inhibitory nervous impulses. In this respect the heart of molluscs does in no way differ from those of vertebrate animals. The investigation of pharmacological reactions has, however, shown that the muscles of molluscs, including those of the heart, exhibit specific peculiarities (see KRIJGSMAN and DIVARIS 1955, CRESCITELLI and GEISSMAN 1963). So eserine and other cholinesterase inhibitors in many cases do not change the reaction of the heart to ACh (PROSSER 1940, GHIRETTI 1948, GADDUM and PAASONEN 1955, SAKHAROV and NISTRATOVA 1963). Nicotine has an excitatory effect on heart activity to which the heart responds with increased amplitude (YUNG 1881, CHONG and PHILLIS 1965). Atropine, which is an ACh antagonist in the heart of vertebrates does not influence the effect of ACh in the case of molluscan heart (BACQ 1934, PROSSER 1940, GADDUM and PAASONEN 1955, FREDERICQ 1947, WELSH and TAUB 1953, SAKHAROV and NISTRATOVA 1963, CHONG and PHILLIS 1965).

On the other hand, in contrast to vertebrates, in the heart of molluscs a curare-like compound, mytolon, is known to be the most potent ACh antagonist (LUDUENA and BROWN 1952, WELSH and TAUB 1953, CHONG and PHILLIS 1965).

These data point to the fact that ACh receptors in the heart of molluscs differ from those in vertebrates. The investigation of some pecularities of these receptors greatly helps us to understand the mechanism of the action of mediators.

For this purpose in this paper we attempted to study the effect of some cholinergic compounds on the heart of a bivalve mollusc *(Anodonta cygnea)* in normal state and also when ACh was applied or when the visceral ganglion was being stimulated.

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Methods

Our experiments were conducted on a fresh-water mussel *(Anodonta cygnea L.)* in the Biological Research Institute of the Hungarian Academy of Sciences in Tihany and in the Institute of Animal Morphology, Academy of Sciences USSR, Moscow. Before the experiments the mussels were kept in aerated aquariums at temperatures of 7—10° C. The experiments were conducted at room temperature both in the case of isolated and in situ ventricles.

Visceral ganglion was stimulated by a series of square wave impulses (1—3 V, 10 Hz, 30 sec) using an Alvar stimulator. All compounds were injected into the interior of the ventricle by means of a cannula. For this reason the in situ preparation was made as follows: the dorsal part of the shell was removed, the pericardium cut up, the anterior and posterior aortas and also one of the auricles at the atrioventricular junction were loosely tied down without damaging the nerves. The cannula was inserted into the ventricle through the auricle and special care was taken to keep its fluid-level constant.

The isolated ventricle was prepared according to the method described earlier (SAKHAROV and NISTRATOVA 1963). The perfusion fluid was taken out of the ventricle immediately or one minute after the end of the stimulation of visceral ganglion, and was tested on an isolated mussel heart and on an isolated frog heart prepared according to the Straub method. In the latter case the obtained perfusion fluid was adjusted to the ionic concentration of frog RINGER solution. To 3 volumes of perfusion fluid one volume of solution was added with the following ionic content: NaCl 21.5 g, KCl 0.44 g, $CaCl_2$ 0.8 g, $NaHCO_3$ 0.28 g to 1 litre distilled water (SAKHAROV and NISTRATOVA 1963). The mussel-physiological solution suggested by MARCZYNSKI (1959) was used.

In the course of experiments the following agents were used: acetylcholine chloride, arecoline iodmethylate, nicotine, trimethylammonium chloride, trimethylammonium iodide (TMA), tetraethylammonium iodide (TEA), mixed mononitrogenic cholinolytics — mesphenal and arpenal — and mytolon (2,5-bis—(3-diethylaminopropylamino)-benzoquinon-bis-benzylchloride) (WIN 2747) (HOPPE 1950).

In addition to these the effect of 5-hydroxytryptamine (serotonin) and that of its antagonist 2-bromo-d-lysergic acid diethylamide or BOL-148 was examined.

Results

The isolated ventricle of *Anodonta* responds to the applied ACh with an increase in tone and a decrease in amplitude. With the increase of ACh concentration the above mentioned effects become more and more explicit. Still in the case of very high ACh concentrations causing a complete arrest the heart gets over this stoppage and overcomes the inhibition. In the case of the stimulation of visceral ganglion similar results have been obtained.

It is interesting to note that ACh of about threshold concentration or a weak electric stimulation of short duration of the visceral ganglion may cause an excitatory effect on the heart.

Arecoline at $1 \cdot 10^{-6}$—$1 \cdot 10^{-3}$ g/ml concentrations stimulates heart activity whereas at $1 \cdot 10^{-3}$ g/ml a small tonic effect is also observable. But after an arecoline treatment of the heart ACh produces its usual effect.

Nicotine about in the same concentrations as ACh almost completely repeats the effect of the latter. Thus low nicotine concentrations ($1 \cdot 10^{-8}$—$5 \cdot 10^{-9}$ g/ml) result in an increase of amplitude and the activity of heart muscles improves *(Fig. 1a)*. At high concentrations (10^{-6}—10^{-5} g/ml) a sharp increase in tone and the fall of amplitude to zero can be observed and consequently

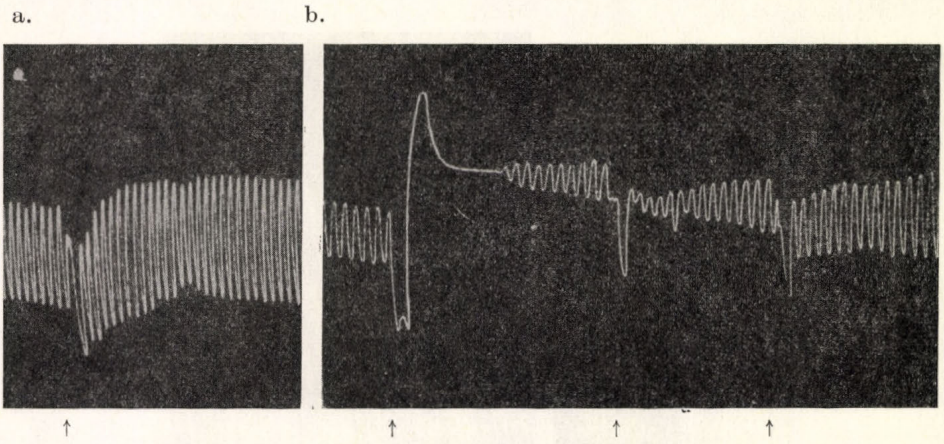

Fig. 1. The effect of nicotine at $1 \cdot 10^{-8}$ g/ml (a) and at $1 \cdot 10^{-5}$ g/ml (b) on the isolated ventricle of the mussel. Arrows indicate the moment of nicotine applying. In the case of repeated treatment with nicotine the "desensitization" is clearly observable.

1. ábra $1 \cdot 10^{-8}$ g/ml (a) és $1 \cdot 10^{-5}$ g/ml (b) koncentrációjú nicotin hatása a kagyló izolált szívén. A nyílak a nicotin applikálás pillanatát mutatják. Ismételt nicotin adásakor jól megfigyelhető a "desensitisatio".

the heart overcomes the inhibition. A repeated application of nicotine of the same concentration leads to „desensitization" or even to a slight increase of the amplitude *(Fig. 1b)*. At this stage ACh has no inhibitory effect.

Trimethylammonium chloride and tetramethylammonium iodide at $1 \cdot 10^{-5}$ — $1 \cdot 10^{-4}$ g/ml have an effect similar to ACh, although they are much weaker cholinomimetics. As a contrast, tetraethylammonium iodide (TEA) at $1 \cdot 10^{-4}$ — $1 \cdot 10^{-3}$ g/ml produces a slight decrease in tone and a considerable increase in amplitude. If the concentration of ACh is lower than that of TEA — the difference being of one order of magnitude — ACh produces only an increase in amplitude, i. e. no inhibition is observable. In the case of equal concentrations of TEA and ACh the effect of the latter becomes weaker but does not disappear completely.

Mesphenal does not influence the heart activity. At $1 \cdot 10^{-5}$ g/ml it diminishes the effect of ACh at a concentration of $1 \cdot 10^{-6}$ g/ml. A great difficulty is produced by the fact that mesphenal does not easily dissolve in water. Arpenal at $1 \cdot 10^{-5}$ g/ml stimulates the work of heart and reduces the inhibitory effect of ACh at a concentration of $1 \cdot 10^{-6}$ g/ml easily and for a long time. After arpenal treatment ACh produces a considerable stimulation of heart activity *(Fig. 2)*. In equimolar concentrations arpenal reduces the effect of ACh almost completely.

Mytolon at $1 \cdot 10^{-5}$ — $1 \cdot 10^{-4}$ g/ml brings about a considerable increase in amplitude without any observable change in tone during the first 10—20 minutes. On the other hand, after repeated mytolon treatments of 1.5—2

hours, the strength of contractions diminishes slightly but the tone of the heart rises.

After a treatment of isolated mussel heart with mytolon at $1 \cdot 10^{-5}$ g/ml for a period of 20—30 minutes, the heart does not show any symptoms of being inhibited by ACh of the same concentration, but rather exhibits an

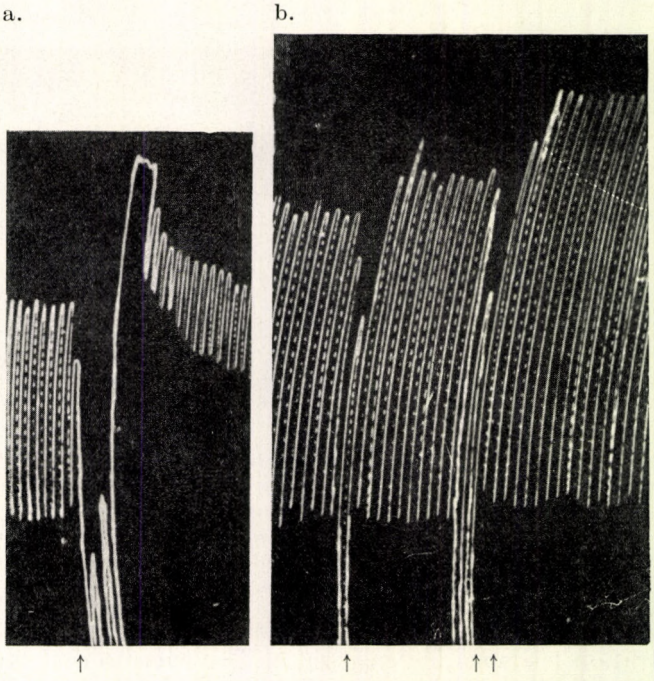

Fig. 2. Reaction of the isolated mussel heart to ACh at $1 \cdot 10^{-6}$ g/ml before (a) and after (b) arpenal treatment of the heart at the concentration of $1 \cdot 10^{-5}$ g/ml ↑ ↑ = acetylcholine; ↑ = arpenal. ACh was given after 15 min. subsequent to the treatment of the heart with arpenal (b)

2. ábra Az izolált kagylószív reakciója az $1 \cdot 10^{-6}$ g/ml koncentrációjú ACh-ra a szív arpenallal ($1 \cdot 10^{-5}$ g/ml) való kezelése előtt (a) és után (b).
↑ ↑ = acetylcholin ↑ = arpenal Az ACh 15 perccel az arpenallal való kezelés (b) után adva.

increase in amplitude *(Fig. 3b)* If, however, the concentration of ACh was 10 times as high as that of mytolon, the normal reaction of the heart to ACh returned *(Fig. 3c)*. But when the concentration of mytolon is also raised to $1 \cdot 10^{-4}$ g/ml, the sensitivity of the heart to ACh of the same concentration diminishes again.

It seems probable that there is a competition between mytolon and ACh for receptors as the affinity of mytolon to the receptor is about 10 times greater than that of ACh. An analogous phenomenon has been observed by several authors between ACh and atropine in the case of vertebrate hearts (Clark 1926, Cullis and Lucas 1936, Jacob 1956, Hall 1959, Takenaka 1959, Nistratova 1961).

In contrast to the heart of *Venus mercenaria* and *Tapes watlingi* mytolon can be washed out of the heart of *Anodonta cygnea* fairly easily with the help

of mussel-physiological solution, after which the heart becomes sensitive to ACh again.

Similar results were obtained with electric stimulation of visceral ganglion. Indeed, injecting mytolon of a concentration of $1 \cdot 10^{-5}$ g/ml into the in situ mussel's ventricle for 20 minutes created a considerable positive inotropic

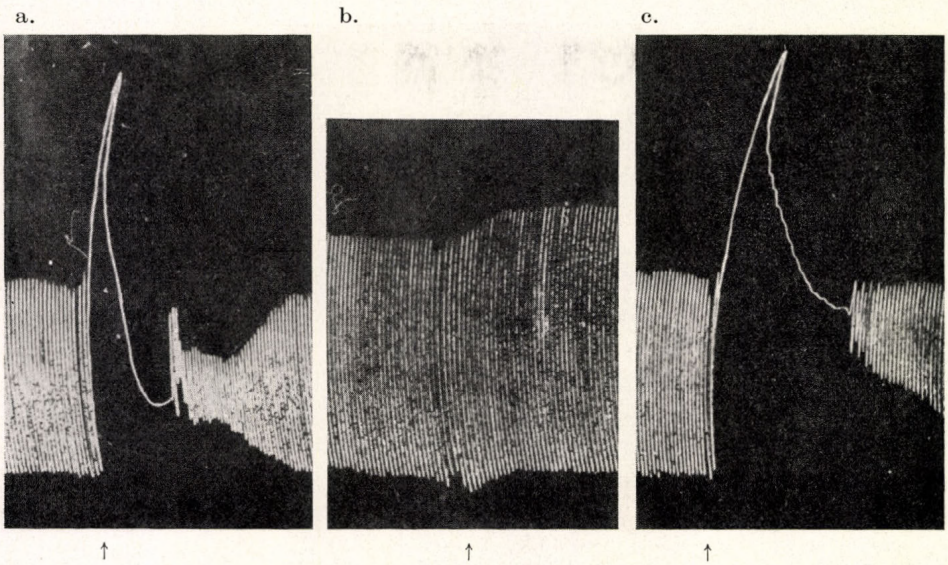

Fig. 3. The influence of mytolon to ACh effect on the isolated ventricle of mussel. a = Reaction of the heart to ACh at $1 \cdot 10^{-5}$ g/ml; b = Reaction of the heart after its treatment with mytolon at $1 \cdot 10^{-5}$ g/ml for 20 min. c = The effect of ACh at $1 \cdot 10^{-4}$ g/ml after the treatment of the heart with mytolon at $1 \cdot 10^{-5}$ g/ml

3. ábra A mytolon hatása az acetylcholin hatásra az izolált kagyló szíven. a = A szív válasza az $1 \cdot 10^{-5}$ g/ml ACh-ra. b = A szív válasza az $1 \cdot 10^{-5}$ g/ml ACh-ra 20 perces mytolon ($1 \cdot 10^{-5}$ g/ml) előkezelés után. c = Az $1 \cdot 10^{-4}$ g/ml ACh hatása a szív mytolonnal ($1 \cdot 10^{-5}$ g/ml) való előkezelése után.

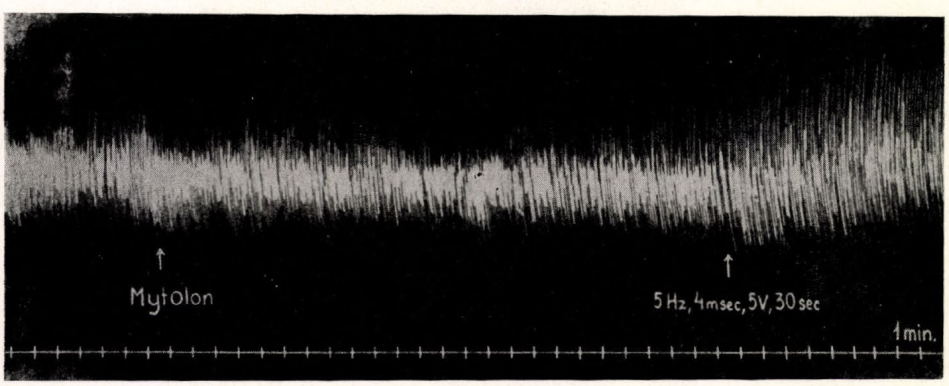

Fig. 4. Response of the in situ mussel heart to the electrical stimulation of the visceral ganglion after the treatment of the heart with mytolon at $1 \cdot 10^{-5}$ g/ml. Mytolon was left to act in the ventricle for 20 min.

4. ábra Az in situ kagylószív válasza a visceralis ganglion elektromos ingerlésére mytolonnal ($1 \cdot 10^{-5}$ g/ml) való előkezelés után. A mytolont 20 percig hagytuk hatni a szíven.

effect and a subsequent stimulation of visceral ganglion brought a further increase of the strength of contraction without any change in tone *(Fig. 4)*. What can be the cause of this increased amplitude if the treatment of the heart with mytolon is followed by another treatment with ACh? In order to solve this problem the perfusion fluid obtained from a donor mussel heart

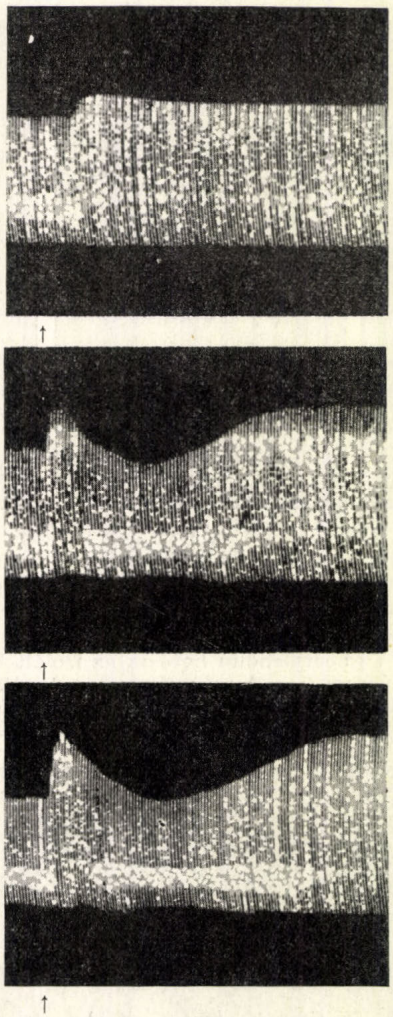

Fig. 5. Effect of perfusates obtained from the isolated mussel heart on the atropine-treated isolated frog heart. a = control, b = after the treatment of the heart with mytolon at $1 \cdot 10^{-5}$ g/ml, c = after ACh applied to the mytolon-treated ($1 \cdot 10^{-5}$ g/ml) heart
All perfusates were gained after 5 min. following the treatment. Arrow indicates the moment of fluid exchange

5. ábra Az izolált kagylószívből nyert perfuzátumok hatása az atropinnal előkezelt izolált békaszíven. a = kontroll, b = a szív mytolonnal ($1 \cdot 10^{-5}$ g/ml) való kezelése után, c = a mytolonnal előkezelt szíven való ACh adás után. Mindegyik perfuzátumot 5 perccel a kezelés után vettük le. A nyíl mutatja a folyadékcsere pillanatát.

was tested on an atropine-treated recipient frog heart isolated by STRAUB's method. Both the control and experimental perfusates were collected after equal periods of time. It appeared that the control perfusates exercised a slight excitatory effect on the frog heart *(Fig. 5a, 6a)*.

The perfusion fluid originating from the mussel heart treated with mytolon, produced a greater excitatory effect on the frog heart which response,

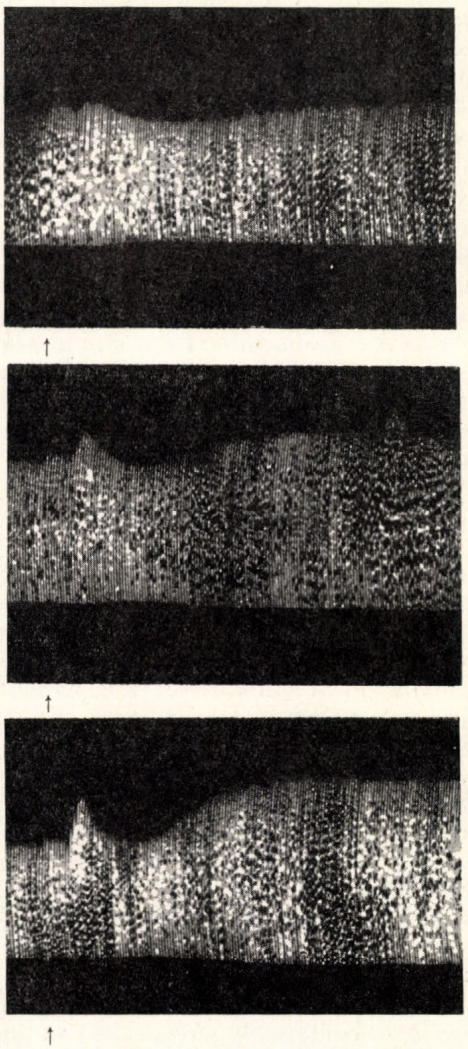

Fig. 6. Effect of perfusates obtained from in situ mussel heart on the atropine-treated isolated frog heart. a = control, b = after the treatment of the heart with mytolon at $1 \cdot 10^{-5}$ g/ml, c = after the electrical stimulation of visceral ganglion. Perfusates were collected after 90 sec. subsequent to the treatment of the heart with mytolon.

6. ábra Az in situ kagylószívből nyert perfuzátumok hatása az atropinnal előkezelt béka szíven. a = kontroll, b = a szív mytolonnal. ($1 \cdot 10^{-5}$ g/ml) való kezelése után, c = a visceralis ganglion elektromos ingerlése után. A perfuzátumokat 90 másodperccel a szív mytolonnal való kezelése után vettük le.

by its character, resembles the effect of macroergs of the adenilic or uridinic type *(Fig. 5b, 6b)*. But the greatest increase in amplitude was observed in the case of perfusion fluid gained after the stimulation of visceral ganglion *(Fig. 6c)* or after the injection of ACh into the mytolon-treated heart *(Fig. 5c)*. This effect on frog heart, in its form, is similar to that of ATP in a considerable degree. In every case the excitatory effect caused by ACh cannot be attributed to serotonin because the heart of frog is not sensitive to this compound. In addition to this the simultaneous treatment of mussel heart with BOL-148 of the concentration of $1 \cdot 10^{-5}$ g/ml and with mytolon of the same concentration did not diminish the excitatory effect on mussel heart subsequent to the stimulation of visceral ganglion either. In our control experiments, however, BOL-148 blocked completely the action of serotonin of a concentration of $1 \cdot 10^{-5}$ g/ml.

In the course of experiments the investigation of the effect of various compounds revealed that nicotine, trimethylammonium chloride and tetramethylammonium iodide act on the heart of *Anodonta* in a similar way as ACh. Mytolon, tetramethylammonium iodide and arpenal increase the amplitude of heart beat and are ACh antagonists. After the treatment of the heart with these compounds ACh is responsible for a stimulating effect which arises from the release of a macroerg compound (or compounds). Mesphenal also diminishes the effect of ACh without changing the amplitude.

And lastly arecoline, which is known as a M-cholinomimetic compound in vertebrates, does not influence the effect of ACh even in high concentrations.

Discussion

The effect of cholinergic compounds on *Anodonta* heart has not been thoroughly investigated so far. But recently there has been a gradual growth in experimental material and on the basis of these findings the following classification of investigated compounds seems to be possible:

1. Compounds similar in action to ACh, i. e. which increase the tone of heart muscles and diminish the amplitude of contractions. In the case of their repeated application "desensitization" sets in with a simultaneous increase of the strength of contractions. The following compounds are included in this group: choline, carbocholine, nicotine, trimethylammonium chloride, tetramethylammonium iodide. With the exception of nicotine these compounds, however, are much weaker cholinomimetics than ACh itself.

2. Compounds having no or very little effect on the activity of heart muscles which do not influence the effect of ACh. The following compounds belong to this group: atropine, arecoline, hexamethonium and d-tubocurarine.

3. And at last a fairly large group of pharmacological agents exists which are able to increase the amplitude on their own and in addition to this block the inhibitory effect of ACh completely. After the treatment of heart muscles with these compounds ACh displays a strong excitatory effect. The following compounds may be mentioned here: TEA, mytolon, arpenal and nicotine. It is interesting to note that either ACh itself of about threshold concentration or the slight stimulation of the visceral ganglion may produce a positive inotropic effect, but it does not come about so often as the inhibitory one. The excitatory effect of ACh and some other cholinergic compounds has been observed both in normal condition and after a treatment of the heart with mytolon

and has been reported also for other species of molluscs (WELSH and TAUB 1948, CORDA 1955, LOVELAND 1963, DITADI 1964, CHONG and PHILLIS 1965, GREENBERG 1965, TURPAEV, NISTRATOVA and PUTINTSEVA 1966).

What is the explanation of this phenomenon? It has been demonstrated in earlier investigations that under the influence of ACh (SAKHAROV and NISTRATOVA 1963) or following the stimulation of visceral ganglia (NISTRATOVA and YUZHANSKAIA 1966) a macroerg compound is released into the perfusion fluid, which was identified later as ATP (NISTRATOVA and MALINOVSKAIA, in preparation). In the ventricle of the mussel heart where according to some authors there is no cholinesterase (TURPAEV, NISTRATOVA and PUTINTSEVA 1966; NISTRATOVA and YUZHANSKAIA 1966) — but recently with Hestrin's method was revealed (HIRIPI, VARANKA and SALÁNKI 1966) — this stimulating compound is able to cease the inhibition of the heart since it is a competetive antagonist of ACh (NISTRATOVA 1965, NISTRATOVA and TURPAEV 1965).

It has been demonstrated in this paper that the stimulatory effect of mytolon is also connected with the release of the above mentioned compound. After a treatment with mytolon, ACh has an additional increasing effect on the amplitude of heart beat because of the great amount of this released macroerg compound. Similar results were obtained after a treatment of the heart with mytolon if the visceral ganglion was stimulated. Only the inhibitory phase of the ACh effect was lost, whereas its excitatory effect was accompanied by the accumulation of a large amount of macroerg compounds in the perfusion fluid.

On the basis of these data it may be concluded that the inhibitory and excitatory phases involved in the ACh effect are connected with not only one but with at least two different systems and that the release of the excitatory compound is not caused by the interaction of ACh with "inhibitory" cholinoreceptors of the mussel heart. It seems possible that both in the case of injecting sufficently high ACh concentrations into the heart and also when the visceral ganglion was stimulated the mediator reacts with the cholinoreceptor on the one hand producing a rise in tone and an inhibition of contractions, or influences some sort of an enzymatic system which leads to the accumulation of excitatory compounds in the perfusion fluid on the other. If the accumulation of this compound is of a sufficiently high concentration, it can be considered as a competetive ACh antagonist which is able to cease the inhibition of the heart.

The possibility of finding two types of ACh receptors in the heart of molluscs is not totally excluded, since the interrelation of one of them with ACh leads to inhibition and the reaction of ACh with the other one creates a positive inotropic effect. This possibility was pointed out by FRAY (cit. KRUTA 1936), WELSH (1948), DITADI (1964), CHONG and PHILLIS (1965), etc.

Several authors also observed the excitatory effect of ACh and of the stimulation of visceral ganglion after a treatment of the heart with mytolon, and explained this effect with the release of serotonin (WELSH 1953, LOVELAND 1963, PHILLIS 1966). This suggestion, however, does not seem to be the only possible explanation in our case, since the simultaneous treatment of the in situ ventricle with mytolon and BOL-148 did not eliminate the excitatory effect, they did not even change its magnitude. In the control experiments at the same time BOL-148 completely blocked the effect of serotonin (PÉCSI 1966).

An analysis of published data and of our results prove the specific peculiarities of ACh receptors both in the heart of *Anodonta* and in other molluscs On the basis of their nature they seem to be very near to "nicotinic" receptors and also to those of autonomic ganglia of vertebrates (WELSH and TAUB 1953). The analogy, however, is not complete, since mytolon, for example, influences, the synapses of autonomic ganglia only to a small degree. But, on the other hand, it is one of the most active ACh antagonist in the case of molluscan heart. Considering some characteristics of cholinoreceptors of the heart, they appear to be different from those of other molluscan muscles, including the most investigated ABRM of *Mytilus* (CAMBRIDGE, HOLGATE and SHARP 1959, TWAROG 1960, MAGAZHANIK and MIKHELSON 1963, MIKHELSON and KHROMOV–BORISOV 1964). It seems also probable that connections between receptor and ACh or its antagonists can be of other types as well since the latter can be washed out fairly easily (CAMBRIDGE, HOLGATE and SHARP 1959, MAGAZHANIK and MIKHELSON 1963).

Although similar features can be observed in the structure and peculiarities of ACh receptors of both vertebrates and invertebrates, still there are also great differences between them the investigation of which will enable us to understand the mechanism of ACh effect better.

Summary

The effect of various cholinergic compounds on the in situ heart of *Anodonta cygnea* and also on the isolated heart of this mollusc was studied.

It was found that nicotine, trimethylammonium chloride and tetramethylammonium iodide have an effect similar to ACh: in low concentrations they increase the amplitude of contractions, in high concentrations they increase the tone and diminish the amplitude completely. In the case of repeated application of these compounds "desensitization" sets in both to themselves and also to ACh injected from outside.

Mytolon, tetraethylammonium iodide and arpenal increase the amplitude of contractions of the heart and work as ACh antagonists. After a treatment of the heart with these compounds, ACh or the stimulation of the visceral ganglion produce a stimulatory effect in consequence of released macroerg compound (or compounds).

Mesphenal also diminished the effect of ACh but did not change the strength of contractions of the ventricle.

M-cholinomimetic arecoline produced a slight increase in amplitude but did no influence the effect of ACh.

The pecularities of ACh receptors in the heart of molluscs are discussed in comparison with cholinoreceptors of vertebrates.

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BIZONYOS CHOLINERG TÍPUSÚ VEGYÜLETEK HATÁSÁNAK ANALÍZISE A TAVIKAGYLÓ *(ANODONTA* sp.*)* SZÍVÉN

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Összefoglalás

Az *Anodonta sp.* in situ és izolált szívén különböző cholinerg típusú anyagok hatását vizsgáltuk.

Megállapítást nyert, hogy a nicotin, trimethylammoniumklorid és a tetramethylammoniumjodid az acetylcholinhoz (ACh) hasonlóan hatnak: kis koncentrációkban növelik az amplitudót, míg nagy koncentrációkban a tónust növelik, viszont az amplitudót egészen a leállásig csökkentik. Ezen anyagok ismételt bevitelére „desensitisatio" lép fel mind a saját, mind a kívülről bevitt ACh-ra.

A mytolon, tetraethylammoniumjodid és az arpenal növelik az amplitudót és mint ACh antagonisták szerepelnek. A szív ezen anyagokkal való kezelése után az ACh, illetve a visceralis ganglion elektromos ingerlése stimuláló hatást eredményez a szíven makroerg természetű anyag (vagy anyagok) kiszabadulása következtében.

A mesphenal szintén blokkolja az ACh hatást, de az amplitudót nem változtatja meg.

Az M-cholinomimetikus arecolin kis amplitudónövekedést eredményez, de az ACh hatására nem hat.

Megbeszéltük a molluszkasziv ACh receptorának sajátosságait, összevetve a gerincesek cholinoreceptorával.

АНАЛИЗ ДЕЙСТВИЯ НЕКОТОРЫХ ВЕЩЕСТВ ХОЛИНЕРГИЧЕСКОГО РЯДА НА СЕРДЦЕ БЕЗЗУБКИ *(ANODONTA* sp.*)*

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На сердце пластинчатожаберного моллюска *Anodonta* in situ, а также на изолированном сердце этого моллюска было испытано действие различных веществ холинергического ряда.

Никотин, триметиламмоний хлорид и тетраметиламмоний иодид действуют подобно ацетилхолину: в малых концентрациях увеличивают амплитуду сокрашений, а в больших — повышают тонус и снижают амплитуду вплоть до полной остановки. При повторном введении этих веществ наступает «десенситизация» как ним самим, так и к внесенному извне ацетилхолину.

Митолон, тетраэтиламмоний иодид и арпенал увеличивают амплитуду сокращений сердца и являются антагонистами ацетилхолина. После обработки сердца этими веществами ацетилхолин или раздражение висцерального ганглия начинают оказывать стимулирующее действие за счет высвобождения вещества (или веществ) макроэргической природы.

Месфенал также снимает ацетилхолиновый эффект, но не изменяет силы сокращений желудочка.

М-холиномиметик ареколин вызывает небольшее увеличение амплитуды, но не влияет на ацетилхолиновый эффект.

В статье обсуждается вопрос об особенностях рецептора ацетилхолина в сердце моллюсков по сравнению с холинорецепторами позвоночных.