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INVESTIGATION OF THE ROLE AND MECHANISM OF EFFECT OF NUCLEOTIDES ON THE ISOLATED HEARTS OF MOLLUSCS

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Nucleotides as constituents of nucleic acids, synaptic membranes and receptors of cell surfaces perform many functions in the organism. Although their direct participation in the generation, conduction and transmission of the nerve impulse has not been proved, the number of authorities indicating the importance of the change in the free nucleotide level during excitatory processes is continuously increasing (ROBB 1956, POSKONOVA 1961, KOSHTOYANTS 1963, KUPERMAN et al. 1964, FORRESTER 1966). The adenine and uracil nucleotides also play a part in liberation of the heart of lower vertebrates and molluscs from inhibitory nervous effects (POSKONOVA 1961, S.-RÓZSA 1966). In addition to this a concurrent antagonism has been demonstrated in the effect of ATP and an inhibitory transmitter on the heart of molluscs (SAKHAROV and NISTRATOVA 1963). Such antagonism between uracil nucleotides and acetylcholine was described earlier on the heart of frogs (PUTINTZEVA 1962).

Data showing that stimulatory transmitters (catecholamines, 5-HT) are stored bound to ATP (EULER 1966, ROBERTS 1966) indicate that nucleotides released together with transmitters may also have some connection with the generation and elimination of the nerve impulse. The importance of nucleotides is also emphasized by the data showing the realization of the effect of stimulatory transmitters passing through nucleotide metabolism on the heart of vertebrates (STAN and HONIG 1965, SUTHERLAND and ROBINSON 1966) and molluscs (S.-RÓZSA 1967).

On the heart of invertebrates the effect of nucleotides has not yet been studied except in the case of ATP, and because it seems that they are of major importance in the regulation of heart activity, their systematic investigation becomes necessary. The present article contains the data obtained in the course of investigating adenine, guanine, uracil and cytosine nucleotides. The aim of our experiments was particularly to find out which of the above mentioned nucleotides influence the function of molluscan heart and the effect of the excitatory transmitters.

Method

The experiments were performed on the isolated hearts of *Helix pomatia* L. and *Anodonta cygnea* L. The isolated organ was obtained as described in a previous article (S.-Rózsa and Pécsi 1967). In case of *Helix* hearts Meng's solution was used (Meng 1958), while for *Anodonta* hearts we applied that proposed by Marczynski (Marczynski 1959).

During the experiments the following agents were used: adenosine triphosphate (ATP), adenosine diphosphate (ADP), Reanal; adenosine monophosphate (AMP), guanosine triphosphate (GTP), guanosine diphosphate (GDP), guanosine monophosphate (GMP), uridine triphosphate (UTP), uridine diphosphate (UDP), uridine monophosphate (UMP), cytidine monophosphate (CMP), Koch-Light; cytidine triphosphate (CTP), cytidine diphosphate (CDP), Sigma; 5-hydroxytryptamine (5-HT), Fluka.

The agents were applied in Meng and Marczynski solution respectively in concentrations of 10^{-10}—10^{-2} M. They were passed into the cannula by means of a pipette, and care was taken to return the same quantity of fluid to the heart as had been taken from it.

The experiments were conducted in the spring, summer and autumn months at room temperatures (20—25 °C). All the agents investigated had been tested both in the autumn and spring.

Results

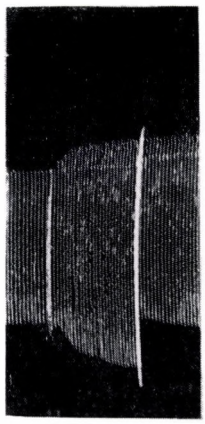
1. *Effect of nucleotides on the isolated Helix and Anodonta hearts*

Adenine nucleotides

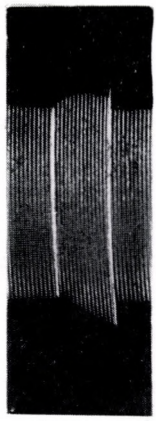
At low concentrations AMP, ADP and ATP produced on a *Helix* heart a moderate stimulatory effect which was indicated by an increase of amplitude *(Fig. 1)*. The threshold concentration proved to be 10^{-6} M in case of AMP and ADP. The degree of stimulatory effect was independent of the concentration between 10^{-6}—10^{-4} M, appearing with unchanged intensity with both nucleotides. ATP produced a stronger stimulation *(Fig. 1)* than the two other adenine nucleotides, the threshold concentration being 10^{-9} M. When applying higher concentrations the stimulatory effect of adenine nucleotides ceased. With concentrations between 10^{-3}—10^{-2} M, ATP and ADP have a negative inotropic effect, while AMP turns the regularly functioning heart into an arhythmic one. The effect of adenine nucleotides ceases quickly after washing out, only an increase of tone being observable in the case of ATP *(Fig. 1)* as an after-effect.

Fig. 1. Effect of adenine and guanine nucleotides on the isolated *Helix* heart
A — Type of effect of AMP, ADP and ATP; B — Seasonal change of GDP effect. GMP effect; C — Seasonal change of GTP effect

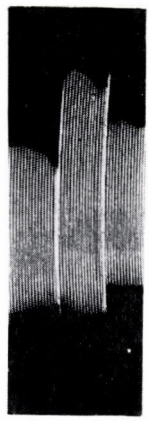
1. ábra. Adenin és guanin nukleotidok hatása izolált *Helix* szíven
A — AMP, ADP és ATP hatástípusa; B — GDP hatásának szezonális változása, GMP effektus; C — GTP hatásának szezonális ingadozása



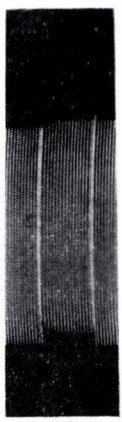
AMP 10^{-4}



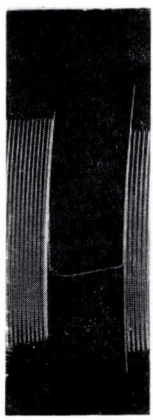
ADP 10^{-4}



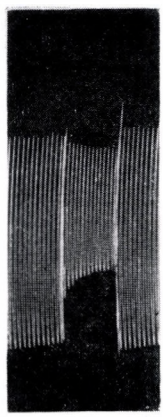
ATP 10^{-9}



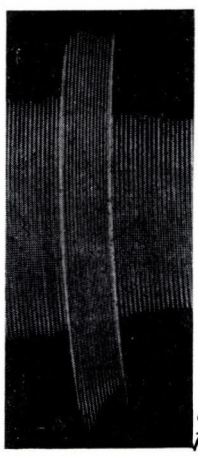
GDP 10^{-4}



GDP 10^{-4}



GMP 10^{-5}



GTP 10^{-6}

GTP 10^{-6}

On the *Anodonta* heart the above mentioned nucleotides produce their effects with considerably higher concentrations. The threshold concentration of ATP was between 10^{-5}—10^{-4} M, so that a concentration of 10^{-5}M was inactive, while that of 10^{-4} M was of positive inotropic effect and it turned an arhythmic heartbeat into a regular one. With hearts of weak activity and a concentration of 10^{-3} M, the initial positive inotropic effect was transformed gradually into systolic contraction by a continuously decreasing amplitude, but strongly beating *Anodonta* hearts were not affected at that concentration. A further increase of the concentration (10^{-2} M) results in an immediate systolic contraction of all hearts. If we leave the hearts for a while after washing out, then the heartbeat started again automatically. The frequency of heart activity was not significantly influenced by the adenine nucleotides.

The effect of ADP is like that of ATP, but its threshold concentration is higher (10^{-4}—10^{-3} M). An ADP concentration of 10^{-2} M results in an immediate systolic contraction. Its effect can be washed out and the *Anodonta* heart responds repeatedly to further ADP dosing.

The effect of AMP is even more weak on the heart of *Anodonta*. The threshold concentration is 10^{-3}—10^{-2} M. The concentration of 10^{-2} M produced a weak decrease in amplitude which was easily eliminated by washing out.

Guanine nucleotides

Contrary to the adenine nucleotides the effect of two guanine nucleotides, namely that of GDP and GTP, has a seasonal change on the *Helix* heart. As with the adenine nucleotides the effect of GMP does not show any seasonal change, but unlike those it does not produce any stimulation, but only inhibition.

In the course of our experiments on the *Helix* heart, the GMP proved to be the least effective, producing only an inhibition with a concentration of 10^{-3}—10^{-5} M and above, without causing a decrease of amplitude greater than 30%. A systolic arrest of the heart was, however, never observed. GDP was inactive in the spring and summer months (from March on), while in autumn it caused a complete arrest of the heart from 10^{-8} M onwards. GTP produced an increase in amplitude up to 90% in the spring and summer periods from 10^{-7} M on, while causing an inhibition at the same concentration from the autumn months (October to November). The inhibition was easily washed out in the case of GDP and GTP and the activity of the heart remained undamaged for a longer time *(Fig. 1)*.

As to the *Anodonta* heart GMP proved to be less effective. A concentration of 10^{-2} M resulted in a decrease in amplitude and increase in frequency, but a systolic arrest of the heart was never observed.

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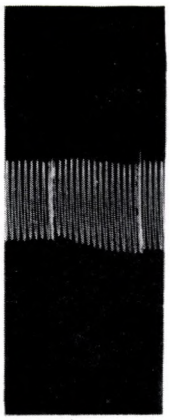
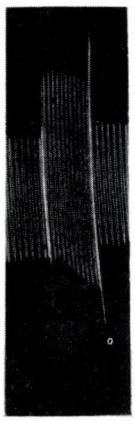
Fig. 2. Effect of uracil and cytosine nucleotides on the isolated *Helix* heart
A — Effect of UMP and seasonal change of UDP effect; B — Seasonal change of UTP effect; C — Effect of CMP, CDP and CTP

2. ábra. Uracil és citozinnukleotidok effektusa izolált *Helix* szíven
A — UMP hatása és az UDP effektus szezonális változása; B — UTP hatás szezonális ingadozása; C — CMP, CDP és CTP effektus

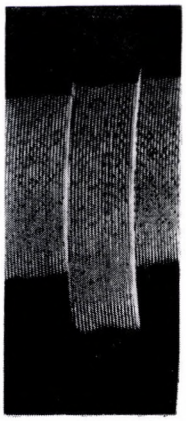
UMP 10^{-8}



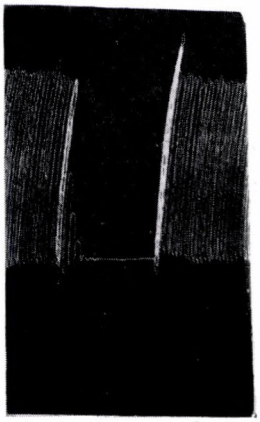
UDP 10^{-8}



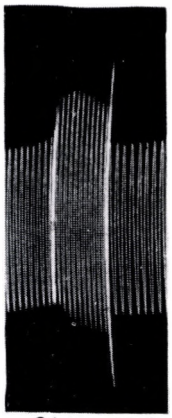
UDP 10^{-8}



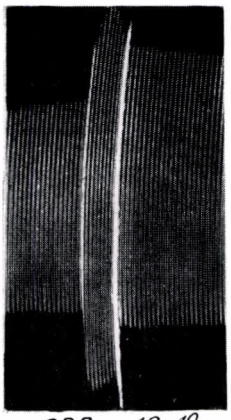
UTP 10^{-9}



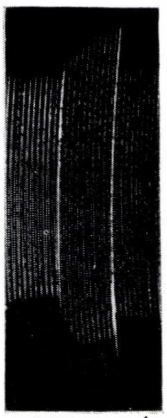
UTP 10^{-9}



CMP 10^{-7}



CDP 10^{-10}



CTP 10^{-4}

A concentration of 10^{-3} M of GDP caused only a slight increase in tone-level, while after 10^{-2} M a systolic contraction developed, but the arrest of the heart followed only after some minutes.

The GTP threshold of the *Anodonta* heart was around 10^{-4} M. The concentration of 10^{-4} M produced a decrease of amplitude and increase of tone, while 10^{-2} M caused a gradually developing systolic contraction. The effect of GTP is like that of ATP—ADP, but its effect is weaker, as the high concentration of the latter (10^{-2} M) resulted in an immediate systolic arrest.

The effect of guanine nucleotides on the *Anodonta* hearts can also be washed out easily and the heart reacts again to a repeated nucleotide application. No seasonal change of the effect of guanine nucleotides was experienced with the *Anodonta* hearts.

Uracil nucleotides

Among the uracil nucleotides UMP is ineffective in all seasons on the *Helix* heart. UDP has a stimulatory effect in spring and summer (from March onwards) with a concentration of 10^{-8} M on. UTP produces a considerable increase of amplitude in spring and summer, but with an increased concentration (10^{-8}—10^{-2} M) there is no increase in intensity, while the same concentration of UTP on the *Helix* hearts in autumn (from November on) results in all cases in a complete arrest of the heart *(Fig. 2)*. The effect of uracil nucleotides can be washed out quickly and the heart does not adapt to these agents. UTP produces in the same season exactly the opposite effect to the guanine nucleotides.

On *Anodonta* hearts UMP proved to be ineffective in all concentrations used. A seasonal change of effect with the application of uracil nucleotides could not be observed on *Anodonta* hearts.

The threshold concentration of UDP was around 10^{-4} M and this produced a weak positive inotropic and chronotropic effect. Higher concentrations (10^{-3}—10^{-2} M) resulted in a pronounced increase of amplitude and frequency and the tone was also increased, but no arrest of heart activity was observed.

The threshold concentration of UTP on *Anodonta* hearts was between 10^{-6}—10^{-5} M. 10^{-5} M has a weak, 10^{-4} M a pronounced positive inotropic effect. At 10^{-3} M concentration it produces an increase of amplitude around 25%, and an increase of tone can also be observed. A concentration of 10^{-2} M causes a systolic arrest of the heart, but unlike ATP of similar concentration the heart begins to beat again in a short time without washing out *(Fig. 3)*. The heartbeat thus spontaneously restored was of a lower amplitude and higher frequency (an increase of 50%), but after a few minutes of functioning the original level is restored again.

Effects produced by UTP and UDP can be quickly eliminated by washing out and the heart reacts again to a repeated application of nucleotide.

Cytosine nucleotides

Cytosine nucleotides, like the adenine nucleotides, do not show a seasonal change in their effect on *Helix* hearts. CMP caused a positive inotropic effect from a threshold concentration of 10^{-10} M onwards and even at high concentrations (10^{-3}—10^{-2} M) it had no inhibitory effect. Among all the nucleotides

investigated, CDP proved itself to be the most effective stimulatory factor, producing at concentrations of 10^{-10}—10^{-2} M a pronounced stimulatory effect which was hardly to be washed out and manifested itself in an increase of amplitude *(Fig. 2)*. CTP has also a stimulatory effect at concentrations of 10^{-5}—10^{-2} M *(Fig. 2)* and the effect manifests itself also in an increase of amplitude, the frequency remaining constant.

Between *Anodonta* and *Helix* hearts we observed the most conspicuous divergence in relation to cytosine nucleotides. Thus with *Anodonta* hearts two cytosine nucleotides proved themselves to be completely ineffective (CDP, CMP). Only a concentration of 10^{-2} M of CTP resulted in a weak negative inotropic and positive chronotropic effect, which was easily washed out.

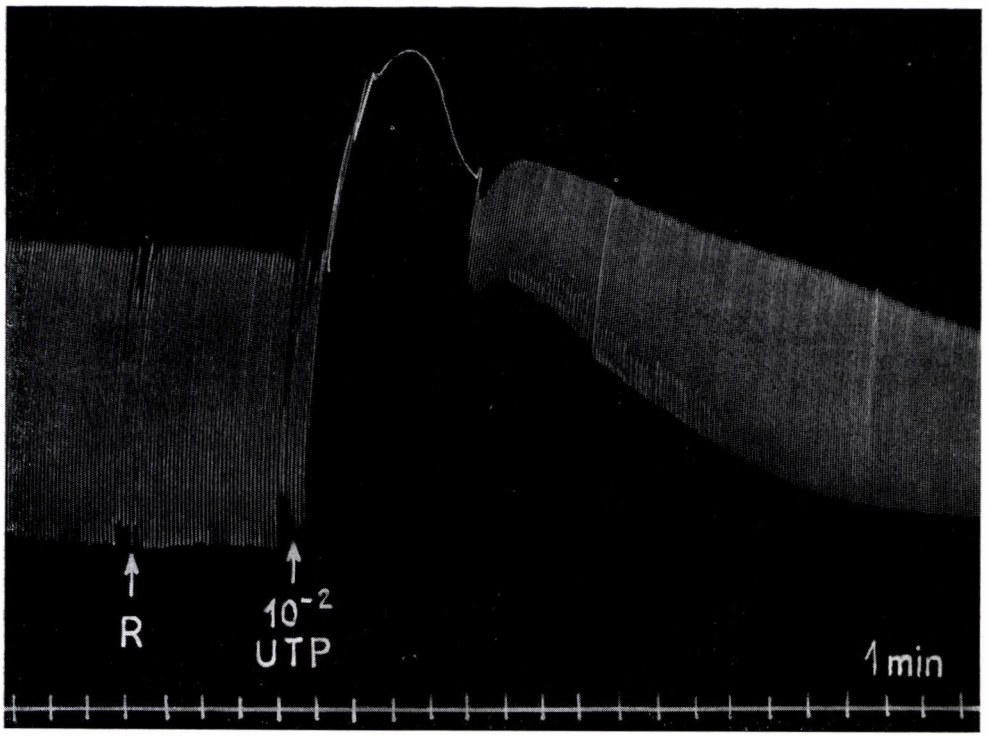


Fig. 3. Effect of 10^{-2} M uridine triphosphate on the isolated *Anodonta* heart

3. ábra. 10^{-2} M UTP hatása izolált *Anodonta* szíven

2. *Influence of nucleotides on the stimulatory effect of 5-HT*

In order to clear up whether the above mentioned nucleotides have a role in realizing the effect of stimulatory transmitters, we investigated the effect of 5-HT on hearts previously treated with nucleotides. These experiments

were conducted on *Helix* hearts because these proved themselves to be several times more sensitive to both the nucleotides and 5-HT.

Our experiments showed that none of the adenine nucleotides (ATP, ADP, AMP) and the monophosphates (AMP, GMP, UMP, CMP) had any influence on the 5-HT effect. Even after a long (30—60 minutes) preincubation with a high concentration (10^{-4}—10^{-2} M) of the above agents, 5-HT produced an unchanged stimulatory effect with the threshold concentration(10^{-10}—10^{-9}M) and intensity. GDP proved itself also to be ineffective in influencing the effect of 5-HT.

After pretreatment with a solution of UDP of a concentration of 10^{-6}—10^{-5} M lasting for 25—30 minutes, the 5-HT caused no further rise in the stimulatory effect produced by the UDP, the amplitude remaining constant even with 5-HT concentrations of 10^{-6}—10^{-5} M. If the heart was repeatedly washed out with physiological solution after the UDP treatment, then 5-HT produced again its stimulatory effect corresponding to the control. CDP had the same effect. These mutual effects appeared most clearly around the threshold concentrations of UDP, CDP and 5-HT.

Pretreatment with the triphosphates (GTP, UTP and CTP) reversed the effect of 5-HT. Preincubation was effected in the season when these nucleotides produced a stimulatory effect. In *Fig. 4* the effect of UTP and CTP on the 5-HT response is shown. After a treatment of 15 minutes with UTP with a concentration of 10^{-9} M, 5-HT arrests the heart. Later on the heart was liberated from the inhibitory effect, but the original level of amplitude was not reached *(Fig. 4B)*. 10^{-5} M CTP has a similar effect *(Fig. 4C)*. In the same season 5-HT always produces a stimulatory effect on the control hearts *(Fig. 4A)*.

Carrying out incubation in the season when UTP and GTP have an inhibitory effect (i.e. in autumn for GTP and spring for UTP) 5-HT starts the heart stopped by the two nucleotides, but this effect is not worth measuring since the same can be established by applying a physiological solution too. The capacity of CTP to modulate the effect of 5-HT remains unchanged in every season, i.e. 5-HT produces an inhibitory effect on a heart pretreated with CTP both in autumn and spring.

Discussion

In the case of hearts of vertebrates the effectivity and type of influence of nucleotides is connected with the OH group positioned at the sixth carbon atom of the pyrimidine ring (positive inotropic effect), or else with the group NH_2 of the purine base (negative inotropic effect) (Drury and Szent-Györgyi 1923, Versprille 1964). In our case we have to look for an other explanation, partly because some of the nucleotides investigated showed reactions on the

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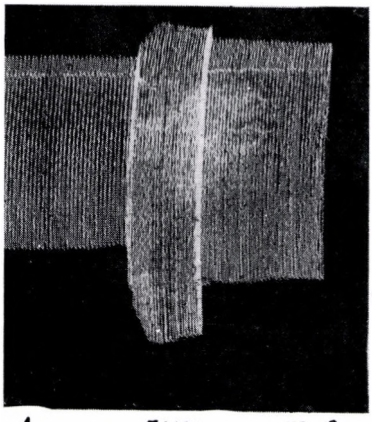
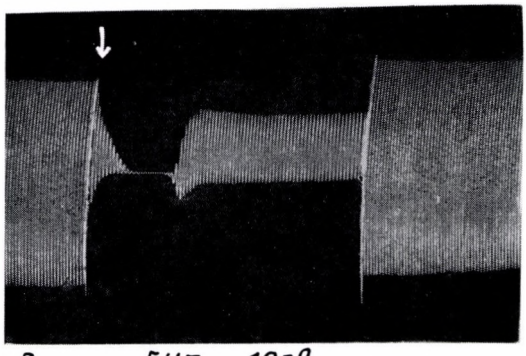
Fig. 4. Effect of triphosphonucleotides modulating the 5-HT effect
A — Effect of 5HT on the control heart; B — Effect of 5HT on a heart pretreated with UTP; C — Effect of 5HT after preincubation with CTP

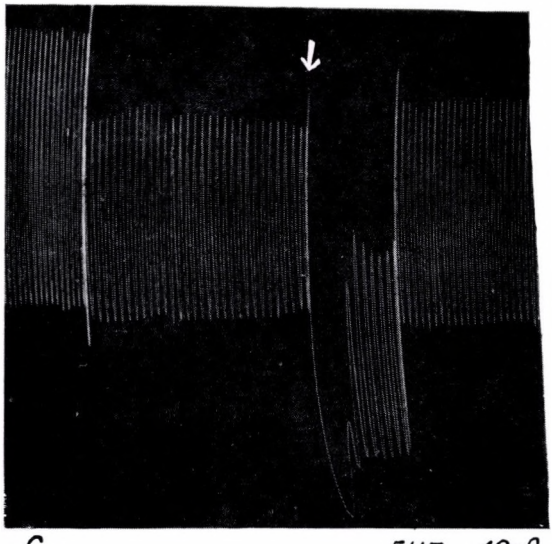
4. ábra. Trifoszfonukleotidok 5HT hatást moduláló effektusa
A — 5HT effektus kontroll szíven; B — 5HT effektus UTP-vel előkezelt szíven; C — 5HT hatás CTP előinkubálás után



A. 5HT 10^{-9}



B. 5HT 10^{-9}



C. 5HT 10^{-9}

heart of molluscs deviating from those observed with the hearts of vertebrates, and partly because in the effects of a series of nucleotides seasonal changes could be observed which cannot at all be explained by the purely stable physico-chemical characteristics of the nucleotides investigated. For the sake of comparison we compared our data with the results gained in the course of experiments on frog hearts (VERSPRILLE 1963, 1964, PUTINTZEVA and BOBROVA 1964), since between *Helix* and *Anodonta* hearts — apart from the seasonal changes — up to a concentration of 10^{-3} M only threshold concentration differences were obtained, without any deviation in the type of effect. The *Anodonta* heart reacted to nucleotide concentration 30—40 times higher than the *Helix* heart and proved itself to be practically insensitive to cytosine nucleotides. The *Anodonta* heart has already been shown to have a lower sensitivity to amines too (S.-RÓZSA and PÉCSI 1967), and our present results corroborate our previous observation that it is less suited for biotesting than the *Helix* heart.

The adenine nucleotides have a positive inotropic effect with concentrations of 10^{-9}—10^{-4} M which can be regarded as physiological. This effect is not preceded by the negative chronotropic response which characterizes the effect of all three adenine nucleotides and particularly that of ATP on frog hearts (VERSPRILLE 1963, 1964, PUTINTZEVA and BOBROVA 1964). AMP and ADP have a weaker effect on *Helix* and *Anodonta* hearts and the effect of ATP is distinct from the former ones only in that it manifests itself with a dosage of lower concentrations *(Fig. 1)*.

Among the guanine nucleotides GMP has no effect on frog hearts, while on *Helix* and *Anodonta* hearts it causes inhibition. GTP and GDP produce a weak stimulation on frog hearts, corresponding to the spring stimulatory effect of GTP on *Helix* hearts. In the other seasons of the year GDP and GTP inhibit both *Helix* and *Anodonta* hearts. For the GDP effect it is characteristic that we have a change from a stimulatory to an inhibitory effect depending on season, but only with *Helix* hearts.

UMP is ineffective with all three kinds of hearts. The UTP and UDP effects show a seasonal change on *Helix* hearts, inhibiting in spring and stimulating in autumn. Their effect is thus exactly opposite to that of GTP. On frog hearts both have a stimulatory effect. Cytosine agents are ineffective with *Anodonta* hearts, while with frog hearts they have a stimulatory effect — except CMP —, and the same is true for *Helix* hearts in all seasons. On *Helix* hearts CDP is the most effective stimulant among all the nucleotides.

In connection with the effect of the above mentioned nucleotides two problems must be dealt with:

1. What are the causes of the inhibitory or stimulatory effects?
2. How can we explain the seasonal change observed in the effects of guanine and uridine nucleotides?

As to the first question, we can take into account only the effect around the threshold concentration, since an inhibition produced by a concentration of 10^{-2} M could hardly be taken as a physiological one. The stimulatory effect can be explained only in the case of adenine (ATP, ADP, AMP) and cytosine (CTP, CDP, CMP) nucleotides by the structure of these agents, since in the effect of these no seasonal change is present. Nevertheless — unlike the vertebrates (VERSPRILLE 1964) — the cytosine nucleotides are more effective stimulators on *Helix* hearts, CDP being the most effective of them.

This is in contradiction to the previous observation that polyphosphates have in general the highest effectivity (PUTINTZEVA and BOBROVA 1964, VERSPRILLE 1964). On vertebrates the order of triphosphates concerning their positive inotropic effect was ATP > UTP > GTP > CTP. For explaining of the positive inotropic effect of ATP and CTP we may suppose that the effect is connected with the configuration. In any case we have to exclude the possibility that the effect takes into account the existence of purine or pyrimidine base, since one of the nucleotides contains the former, the other the latter of these; thus the adenine nucleotides have the character of electrondonors, while for the cytosine nucleotides the quality of electronacceptor is characteristic. The effect does not show a correlation to these properties. ATP cannot in this case be taken into account as a phosphate-donor, it is more probable that it takes a part in the process as the substrate of the regulatory enzyme systems (adenylcyclase, cyclic 3'5'-AMP system). The effect of CTP may be related to its role in the lipid synthesis (BRADY and TOWER 1960). It is well known that lipids are important structural elements of all membranes on which the excitatory effects take place. So the effect of cytosine nucleotides in case of the isolated heart can be explained by their effect on the cell surface.

The effect of guanine and uracil nucleotides may be connected with their role in metabolism. It is well known that guanine nucleotides play a specific part in brain metabolism and that among all the nucleotides only the content of GTP and GDP increases with a stimulatory effect in the brain. The uracil nucleotides are connected with the carbohydrate metabolism of the brain and the same connection has been proved also for muscles (BRADY and TOWER 1960).

Thus it is clear why the effect of these two nucleotides changes from a stimulatory into an inhibitory one or vice versa depending on the season. It has been established that the spring period in case of gastropods coincides with the end of hibernation, while the autumn is the period of preparation for hibernation, and both states are accompanied by a change in the type of metabolism (RAGHUPATHIRAMIREDDY and SWAMI 1967). The guanine and uracil nucleotides may balance the inhibitory and stimulatory effects in the myocardial elements through their effect in influencing metabolism. So we are able to explain the fact that their effect on the heart of these animals may change before and after hibernation depending on the changes of type of metabolism.

Data showing a connection between the realization of the nucleotides and type of transmitter effect prove that nucleotides are connected with the formation of the type of the effect of transmitters too. The two diphosphonucleotides (UDP, CDP) only cease the stimulatory effect of 5-HT, while the three triphosphonucleotides (GTP, UTP, CTP) convert it into an inhibitory one.

The change in the type of the effect of transmitter on *Helix* heart preincubated by nucleotides may be taken as analogous to the seasonal change of the stimulatory effect obtained by the stimulation of the extracardial nerve. According to our previous data (S.-RÓZSA and GRAUL 1964) on *Helix* heart, no stimulatory effect can be produced by the stimulation of the extracardial nerve before hibernation, while in spring, after waking up from hibernation the stimulatory effects prevail. Supposedly the change of configuration of those receptor structure may be responsible for the modulation of the 5-HT effect, through which this effect realizes under normal conditions. Similar changes can be produced as a result of seasonal changes too. Considering that a lipide

nature is attributed to the 5-HT receptors (WOOLLEY and GOMMI 1966) the role of the CTP in this process should be cleared first of all. As to the two other nucleotides (GTP, UTP), we may connect their capacity to convert the 5-HT effect into an inhibitory one with their effect on general metabolism.

Summary

1. All the four groups of nucleotides investigated (adenine, guanine, uracil and cytosine) influence the functioning of the isolated *Helix* hearts. On *Anodonta* hearts cytosine nucleotides proved themselves to be ineffective. On the isolated *Anodonta* hearts the threshold concentration of the above nucleotides is 30—40 times higher than on *Helix* hearts.

2. In the effects of adenine and cytosine nucleotides no seasonal changes appeared either on *Helix* or *Anodonta* hearts. Adenine nucleotides had a positive inotropic effect on *Helix* hearts with concentrations between 10^{-9}—10^{-4} M and on *Anodonta* hearts with concentrations between 10^{-5}—10^{-4} M, while with concentrations of 10^{-3}—10^{-2} M they produced a decrease in frequency and a systolic arrest on both hearts. Cytosine nucleotides on *Helix* hearts have a stimulatory effect up to a concentration of 10^{-2} M, CDP being the most effective with a threshold concentration of 10^{-10} M.

3. Guanine and uracil nucleotides have different effects in spring and autumn on *Helix* hearts, but not on *Anodonta* hearts. This change in the effect is characteristic for nucleotides containing di- and triphosphates. CTP has a stimulatory effect in spring with concentrations of 10^{-7}—10^{-2} M, while the same concentrations lead to a complete inhibition in autum. UTP (10^{-9}—10^{-2} M) and UDP (10^{-8}—10^{-2} M) exert a reversed effect, i.e. inhibitory in spring and stimulatory in autumn. The seasonal changes can be connected to the change in types of metabolism before and after hibernation. On *Anodonta* hearts the guanine nucleotides proved to have an inhibitory effect (10^{-4}—10^{-2} M), while the uracil nucleotides have a stimulatory character (10^{-6}—10^{-3} M).

4. The *Helix* hearts are protected by UDP and CDP against the stimulatory effect of 5-HT, while GTP, UTP and CTP transform it into an inhibitory one. Adenine nucleotides and those containing monophosphate are ineffective as regards modulation of the 5-HT effect. The CTP effect can be connected to the influence exerted on the 5-HT receptors of lipid nature, while the effect of UTP and GTP influencing the 5-HT effect should be connected with effects exerted on metabolic processes.

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NUKLEOTIDOK SZEREPÉNEK ÉS HATÁSMECHANIZMUSÁNAK VIZSGÁLATA MOLLUSZKÁK IZOLÁLT SZIVÉN

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Összefoglalás

1. Mind a négy vizsgált nukleotida (adenin, guanin, uracil és citozin) befolyásolta az izolált *Helix* szív működését. *Anodonta* szíven a citozin nukleotidok hatástalannak bizonyultak. Az izolált *Anodonta* szíven, a fenti nukleotidok küszöbkoncentrációja 30—40 nagyságrenddel magasabb mint *Helix* szíven.

2. Az adenin és citozin nukleotidok hatásában sem a *Helix*, sem az *Anodonta* szíven nem észleltünk szezonális változásokat. Az adenin nukleotidok *Helix* szíven 10^{-9}—10^{-4} M, *Anodonta* szíven pedig 10^{-5}—10^{-4} M koncentrációkban pozitív inotróp hatásúak voltak. 10^{-3}—10^{-2} M koncentrációban mindkét szíven frekvencia-csökkenést és systolés leállást hoztak létre. A citozin nukleotidok *Helix* szíven 10^{-2} M koncentrációig bezárólag serkentő hatásúak, leghatásosabb a CDP, melynek küszöbkoncentrációja 10^{-10} M.

3. A guanin- és uracil nukleotidok tavasszal és ősszel eltérő hatásúak *Helix* szíven, de *Anodonta* szíven nem. Ez a változás a di-és trifoszfát tartalmú nukleotidokra jellemző. A GTP tavasszal 10^{-7}—10^{-2} M koncentrációkban serkent, ugyanez a koncentrációsor ősszel teljes gátlást okoz. Az UTP (10^{-8}—10^{-2} M) és UDP (10^{-9}—10^{-2} M) fordítva, tavasszal vált ki gátlást és ősszel serkentést. A szezonális változások a téli álom előtti és utáni anyagcsere-típus változásokkal hozhatók összefüggésbe. *Anodonta* szíven guanin nukleotidok gátló (10^{-4}—10^{-2} M), az uracil nukleotidok serkentő (10^{-6}—10^{-3} M) hatásúaknak bizonyultak.

4. *Helix* szíven az UDP és CDP kivédik az 5HT serkentő hatását, a GTP, UTP és CTP pedig gátlóvá alakítják át. Az adenin nukleotidok és a monofoszfátot tartalmazó nukleotidok hatástalanok az 5HT modulálása tekintetében. CTP hatást a lipid-természetű 5HT receptorokra kifejezett hatással, az UTP és GTP 5HT-effektust befolyásoló hatását pedig anyagcserefolyamatokra kifejtett változásokkal hozzák összefüggésbe.

ИССЛЕДОВАНИЕ РОЛИ И МЕХАНИЗМА ДЕЙСТВИЯ НЕКОТОРЫХ НУКЛЕОТИДОВ НА ИЗОЛИРОВАННОМ СЕРДЦЕ МОЛЛЮСКОВ

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При изучении влияния ряда нуклеозидфосфатов на сердце виноградной улитки и беззубки установлено следующее:

1. Все изученные нуклеотиды эффективны в отношении сердца улитки, а на сердце беззубки производные цитидина оказались неэффективными.

2. Не наблюдались сезонные изменения в эффектах адениловых и цитидиновых нуклеотидов на обоих сердечных препаратах. Адениловые нуклеотиды первые оказывали на оба сердца стимулирующее действие, но на сердце улитки пороговая концентрация была на 30—40 порядка ниже. В высокой концентрации (10^{-3}—10^{-2} М) адениловые нуклеотиды тормозили биения сердца как улитки, так и беззубки. Производные цитидина на сердце улитки оказывали стимулирующее действие в концентрациях 10^{-10}—10^{-2} М. Наиболее сильным из них оказался ЦДФ.

3. Гуанидин- и уридинфосфаты оказывают на сердце улитки весной и осенью противоположное действие, но на сердце беззубки такие сезонные изменения эффектов не наблюдались. ГТФ 10^{-7}—10^{-2} М весной стимулирует, а осенью тормозит сердце улитки. УТФ и УДФ, напротив, весной вызывают торможение, а осенью стимуляцию сердцебиений. Обсуждается связь этих сезонных изменений с изменениями типа обмена веществ до и после зимней спячки. На сердце беззубки гуанидинфосфаты вызывают торможение, а уридинфосфаты стимуляцию.

4. УДФ, ЦДФ, ГТФ, ЦТФ и УТФ видоизменяют реакцию сердца улитки на медиаторы, превращая при некоторых условиях стимулирующее действие (серотонина) в тормозное. Монофосфорные производные и аденозинфосфаты не играют роли в модуляции ответа на серотонин.