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ACTIVATION OF THE ADDUCTOR IN *ANODONTA*-GLOCHIDIA BY N, N-DIALKYL-TRYPTAMINES, 5-METHOXY-TRYPTAMINE, β-ADRENERG-ANTAGONISTS, COCAINE, SCOPOLAMINE AND OTHER PHARMACONS

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Earlier it has been described by us that tryptamine, contrary to other indole compounds, is a relatively selective activator of the adductor in *Anodonta*-glochidia (LÁBOS et al. 1964; LÁBOS, 1966). It was found also that the most of the α- and β-adrenergic agonists and antagonists potentiate the tryptamine rhythm, moreover dichloroisoproterenol (DCI) is solely able to evoke rhythmic activity (LÁBOS, 1966). On the basis of these facts tryptamine was suspected as excitatory (LÁBOS et al. 1964) and some kind of adren ergic substance as inhibitory and/or excitatory mediators in the chemical control of adductor activity (LÁBOS, 1966). This supposition was supported by a chemical analysis according to which tryptamine and phenyl-alanine have been found in the extracts gained from the whole glochidial organism (S.-RÓZSA and LÁBOS, 1967). Electron microscopic observations of glochidia have shown nerve endings containing dense core vesicula (ZS.-NAGY and LÁBOS, 1969), the connection of which to catecholamines and tryptamines is presumed and disputed in mollusc (DAHL et al. 1963; COTTRELL and LAVERACK, 1968).

Tryptamine-sensitivity of the glochidia is variable, perhaps it is in connection with ontogenesis (LÁBOS et al. 1964). However, it has become clear, that certain non-specific factors able to modify the uptake and the effect of drugs also have to be taken into account (LÁBOS and LUKACSOVICS, 1968). Differences in the activiting effects of tryptamine, serotonin and different alkyl-tryptamines often are explained by their different permeation (VANE et al. 1069; MARLEY and VANE, 1963; OFFENMEIER and ARIENS, 1966). In other instances, the central excitatory effects of alkyl-tryptamines are considered as specific (LESSIN et al. 1965; SZARA, 1964; GERSCHON and BELL, 1963; OFFENMEIER and ARIENS, 1966).

By all means, therefore, it seemd to be reasonable to extend the experiments to substances with alkyl-indol-amine structure and of sympathetic type. Thus, the pronethalol and propanolol appeared to be important as being more selective-adrenolytic drugs as DCI (BLACK and STEPHENSON, 1962; KOCH-WESER, 1964) and also the N,N-diethyl-tryptamine (DET) was chosen, because it is one of the most complex central excitant indole-compound (SZARA, 1964). Among others, yohimbine (α-adrenolytic), cocaine (adrenaline-sensistor) and scopolamine (cholinolytic) were tested, to get complementary information to the pharmacology of glochidia.

Methods

By a method which has been described elsewhere (LÁBOS et al. 1964; LÁBOS, 1966), groups consisting of 10—25 larvae have been gained from the external gill of *Anodonta* were observed. We habe noted the number of rhythmic contractions in each minute and the ratio of glochidia being in closed state. The results were obtained from experiments (at least) on 100 animals or they refer to 100 animals. The total number of the glochidia used for the experiments was about 15.000. Only glochidia originating from the same population and tested in the same day were taken for comparisons.

Lake water of Balaton (BW) or distilled water (DW) were utilized as solvents. In general the concentrations of the applied materials refer to salts.

List of the applied substances: tryptamine HCL (TA; Schuchardt), N,N-diaethyltryptamine bioxalate (DET; Koch-Light), N,N-diaethyl (DET; Serva), serotonin-creatinine-sulphate (5HT; Sandoz), N,N-dimethyl-tryptamine-H-oxalate (DMT; EGA), 5-methoxytryptamine (5MeOTA; Mann Ltd), bufotenine H oxalate (5-OH-DMT; Fluka), melatonin purum (Fluka), cocaine HCl (Fluka), L-scopolamine (Fluka), atropin sulphate (Fluka), N-Br-methyl-atropine, Halidor (EGYT-201; 1-benzyl-1-3'-di-methylamino-propoxy cyclo-heptane), tetracaine HCl (EGYT), procaine HCL, ergometrine-H-tartarate (BDH), papaverine HCl (EGYT), γ-amino butiryc acid (Reanal; GABA), ergotoxine-methane-sulphonate (BDH), brom-lysergic acid-diethylamide (BOL-148, Sandoz), methysergide (UML-491, Sandoz), yohimbine HCl (Merck), chlorpromazine HCl (CPZ; EGYT), L-adrenaline-D-H-tartarate (EGA), L-noradrenaline-bitartarate (Serva), dopamine HCl (DA; Sigma), DL-isoproterenol (IPNA; Fluka), tyramine HCl (Fluka), ephedrine sulphate, dibenamine HCl, di-chloro-isoproterenole HCl (DCI, Eli et Co. Ltd.), alderlin HCl (nethalide, pronethalol; Wilmslow Ltd) propranolol HCl (Inderal; ICI), nicotinic acid, Vitamin B_6, pyrydoxale-5'-phosphate (Py-5'PO_4; Sigma), isonicotinicacid hydrazide (INH), iproniazide, actomol (ICI Ltd; Spinks and Whittle, 1966) carbamide, LiCl (BDH), NaCl, $CaCl_2$, $MgCl_2$, NaN_3, KCN, 2,4-DNP, ouabaine, α,α-dipirydyl (Chinoin), NaF, $CdCl_2$, cyclic-3',5'-adenosine monophosphate dibutyrate (cAMP); Boehringer Co), caffeine, theophylline, histamine HCl (Fluka), histidine, cystamine, acetylcholine Cl (Sandoz, ACh), d-tubocurare (d-TC), nicotine tartarate, reserpine (NCCo).

Results

1. Effects of pronethalol, DCI and propranolol

Already in 50—100 μM concentrations, pronethalol evokes a detectable rhythmic activity. Both in water of Balaton or distilled one, the activity often reaches 500 cmp maximal frequency *(Fig. 1)*. For higher concentrations (250 μM) it was typical that the activity stops suddenly after about 5 min. In DW the response is more prolonged. A tonic closure was not characteristic of a predominant majority of the populations even after applying 500 μM. However, sometimes such populations were found, which hardly responded by rhythmic actvity and after a certain pause a closure has taken place.

The pattern of individual rhythm follows the reaction observable in groups but there are glochidia whose maximal activity reaches a peak-frequency of 40—60 cpm/glochidium for 1/2—2 min. It is often noticeable that the maximal activity is followed by contractions organized in groups.

Approximately the same concentrations of DCI evoke a rhythm of similar degree and time-course as those of pronethalol. The attainable peak-frequency

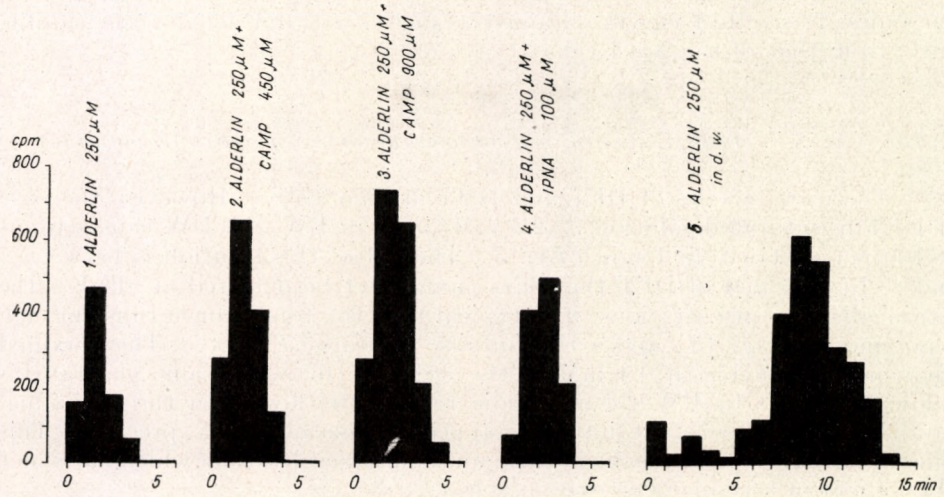

Fig. 1. Effect of pronethalol alone and in the presence of cAMP and IPNA. 100—100 glochidia. The solvents are distilled water (5th diagram) or Balaton-water (1st—4th diagrams)

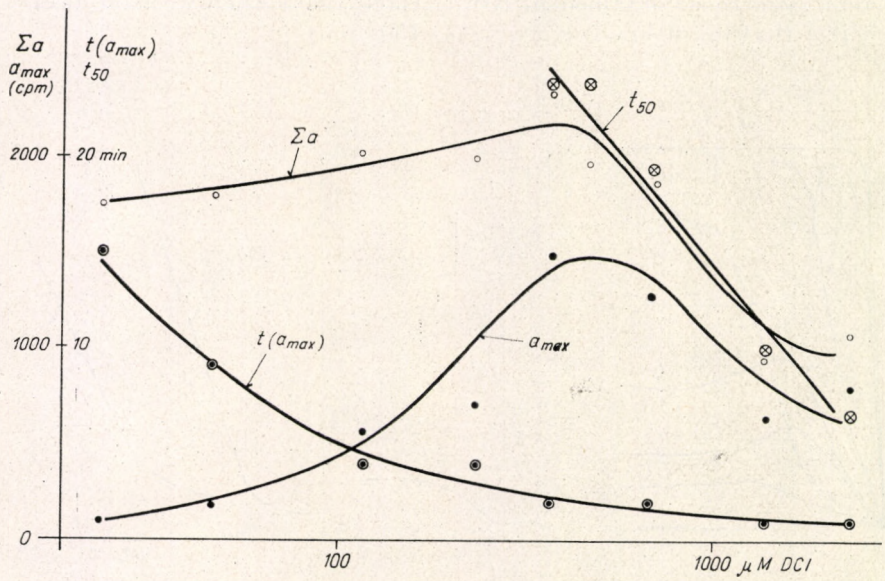

Fig. 2. DCI-effects. 100—100 animals. *Abscisse:* concentration; *ordinates:* total number of observed contractions (Σa), maximal frequency (a_{max}, cpm), time required for closure of 50 per cent (t_{50}) and time of maximum frequency ($t(a_{max})$)

is 400—1000 cpm. The sudden stop of activity is more typical. Independently from the rhythm following the stop by a considerable delay closure may appear *(Fig. 2)*. The time between the rhythm of maximal frequency and the closure can be even 10—20 min. In the individual cases it could not be observed that the activity of high frequency would damp gradually or by grouping activity (that is by an appearance of pauses).

The effect of propanolol was tested by diluting the content of Inderal ampoules. Dose-effect curves obtained in such a way did not deviate significantly from that of the NaCl vehicle.

2. *Effect of N,N-dialkyl-tryptamines, bufotenine and 5-methoxy-tryptamines*

The oxalate salts of DET and DMT are ineffective. However, the base of DET in saturated solution (~2.5 mM) both in BW and DW causes tonus of 100 per cent within 1 min *(Fig. 3)*. The pH of this solution is between 7 and 8. In 0.25 mM of DET the tonus cannot yet be detected at all. For the intermediated concentrations, it is typical that the tonus-curve runs through a maximum *(Fig. 3/1)* and a rhythm also appears *(Fig. 3/2)*. The maximal frequency attainable in 0.4 mM at the 3rd—5th min. Its value generally is below 200 cpm. In DW the rhythmic response is lower. In the individual rhythm patterns constant intervals appear, sometimes very precisely. This constant frequency is reached by monotonous acceleration which does not always end in a similar decrease in speed.

In DW, by lower concentrations of 5-methoxy-tryptamine a quick tonic closure can be elicited, almost without rhythmic activity. For example 250 μM leads to a closure of 50 per cent within 6—7 min. These results are different from those obtained in BW (LÁBOS, 1966) when we have been able to elicit a rhythm of low frequency (< 150 cpm).

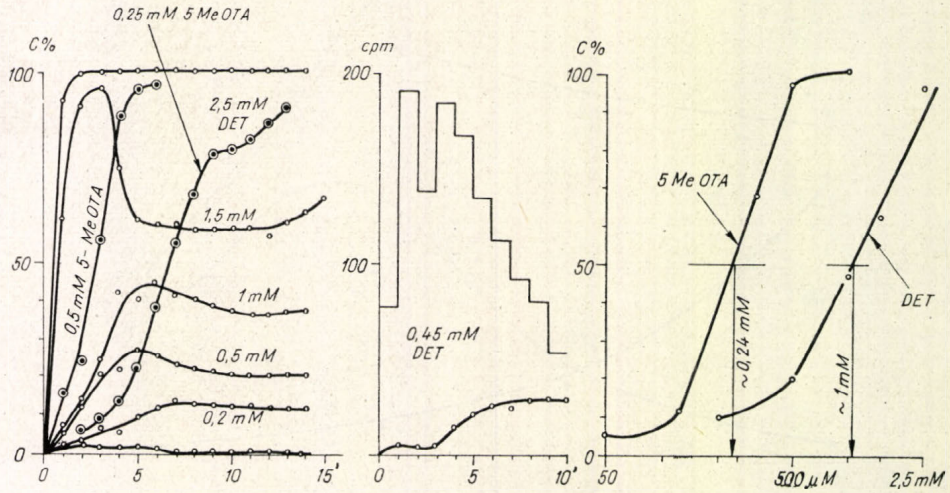

Fig. 3. DET (○) and 5-MeOTA (⊙) effects. 1. Tonus-time diagrams; 2. Frequency and tonus-time diagrams; 3. Dose-response (tonus-ratio)-curves. 100-100 animals. Solvents: lake-water (DET) and distilled water (5-MeOTA)

Earlier it has been published by us that 150—300 μM concentrations of bufotenine, examining for 20 min, were not effective (LÁBOS, 1966). Because of the effectiveness of DET a testing of higher concentrations for a longer time of incubation seemed to be reasonable. Indeed, it has become clear that already 160 μM can evoke a low-frequency rhythm, however only after about 1 hour of incubation. But when the concentration has been increased above 1 mM, the rhythmic activity was elicited in the 10th min, the frequency

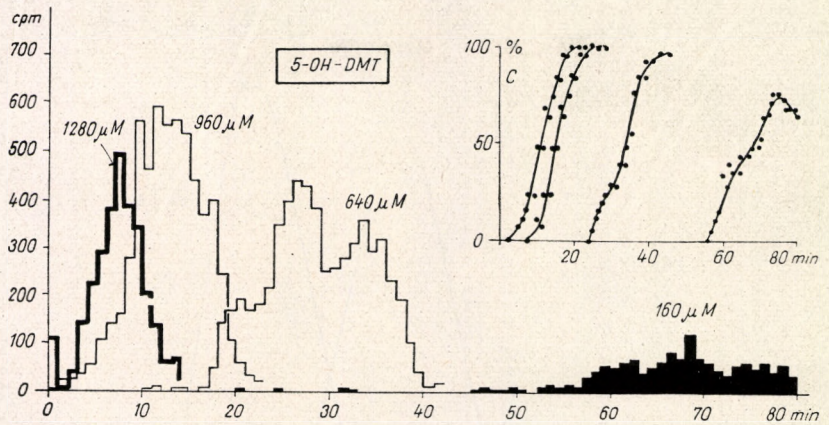

Fig. 4. Bufotenine-response. Frequency- and tonus-time diagrams. 100-100 animals. Balaton-water

of which is near to that of the tryptamine. The required concentrations of bufotenine are yet higher by 2—3 than those of the equipotent tryptamine (LÁBOS et al. 1964; LÁBOS, 1966). Also a further difference is, that bufotenine may lead to a closure of 100 per cent *(Fig. 41)*. In lower concentrations the closure-time curves have inflection or maximum.

3. *Effects of cocaine, scopolamine, atropine, novatropine, yohimbine, ergometrine, ergotoxine*

Both cocaine and scopolamine evoke a considerable and long-lasting rhythmic activity *(Fig. 5, 6,* and *7)*. Neither of them lead to tonus even in very high doses. The contractions are more complete in scopolamine than in cocaine, but in both compounds they become gradually of fibrillation-like. L-scopolamine causes an increase of activity already in 300 μM concentration. In higher concentrations the rhythm is of lower frequency and ceases earlier without any closing. A consequence of this that the dose-response curve shows a maximum. The threshold concentration of cocaine is about 150 μM. However its dose-response curve is similar to that of the scopolamine *(Fig. 5)*. The maximum of cocaine-curve is at 700 μM and that of the scopolamine s at 1600 μM. These values refer to BW. In DW a shift to right is observable. The dose-effect curve of atropine is comparable with those of the cocaine and scopolamine, except that its maximum is significantly lower than those of the

former ones. For the position or amplitude of dose-response curve-maxima the following is valid, respectively *(Fig. 5)*:

cocaine < atropine < scopolamine
or cocaine, scopolamine > atropine

The effect of atropine cannot be influenced by ACh.

In experiments for 50 min, novatropine is not effective even in concentrations above 1 mM.

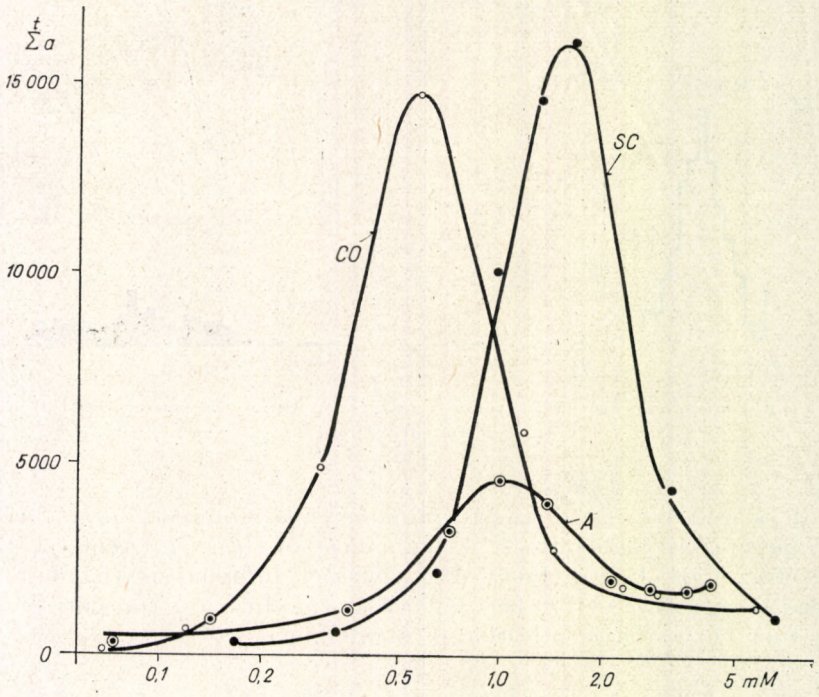

Fig. 5. Cocaine (CO), scopolamine (SC) and atropine (A) dose-effect curves. *Abscisse:* concentration (mM base); *ordinate:* number of produced rhythmic contractions in a given period. Summation has been carried out for 40, 80 and 20 min for the three drugs respectively, as it was necessary. Each points: 100 glochidia. Solvent: Balaton-water

Both in cocaine and scopolamine the time course of the individual patterns are rather variable. In lower concentrations, the rhythm accelerates gradually but slows down periodically. The periodicity of the slowing down is often very definite and even during observations of groups is detectable. Contractions organized in bursts or recurring in precise intervals have been observed only in cocaine. The scopolamine rhythm includes periods of less exact and its periodic modulation is less explicit.

250—500 μM yohimbine evokes a low-frequency rhythm, a tonus running through a maximum. Ergotoxine evokes a tonus while ergometrine does a rhythm of low frequency *(Fig. 8)*.

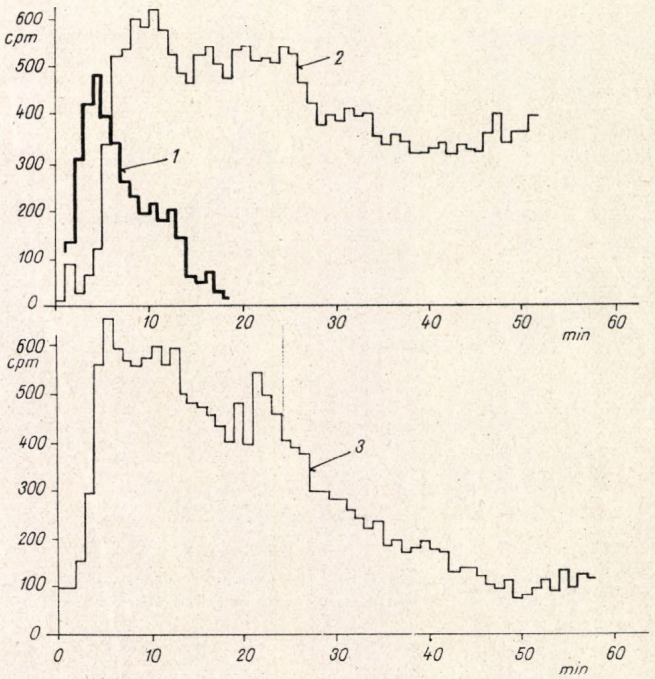

Fig. 6. Noradrenalin on scopolamine rhythm. 100-100 animals. 1. 1 mg/ml L-scopolamine; 2. 1 mg/ml L-scopolamine + 100 μg/ml noraderenaline; 3. 500 μg/ml scopolamine

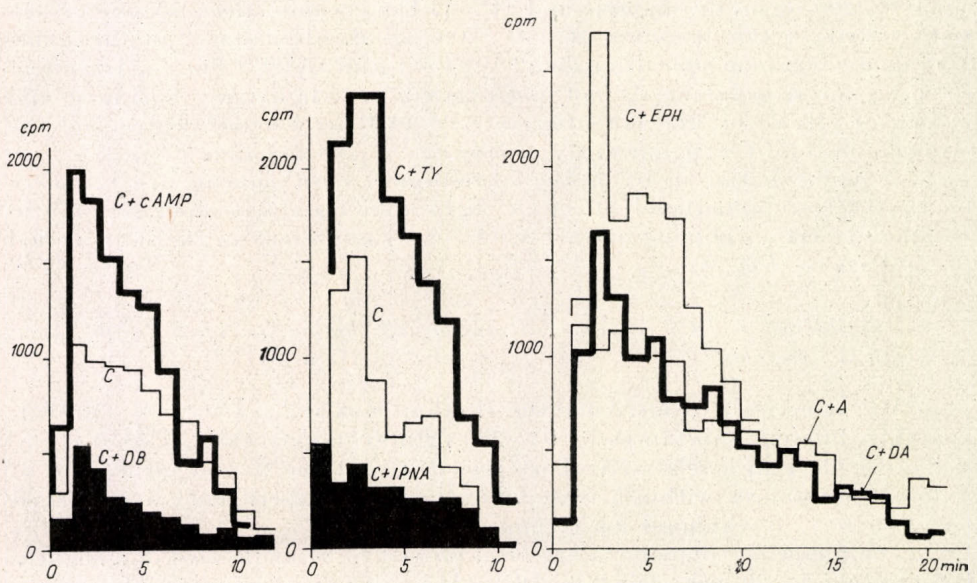

Fig. 7. Susceptibility of cocaine-response. Frequency-time curves. 100-100 animals. Balaton-water. C = cocaine; DB = dibenamine; EPH = ephedrine; DA = dopamine; A = adrenaline; IPNA = isoproterenol; cAMP = cyclic AMP; TY = tyramine

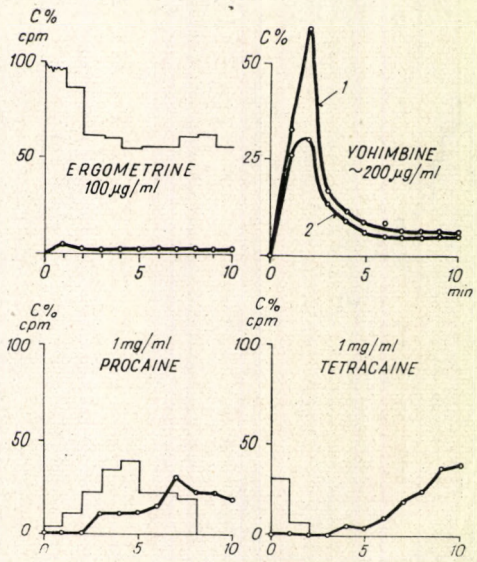

Fig. 8. Yohimbine, ergometrine, procaine and tatracaine effects
Frequency and tonus-time curves. 100-100 animals

4. Effects of scopolamine and cocaine in the presence of sympathomimetica, cAMP and dibenamine. Influence of reserpine preincubation

The effects of 200 µg/ml cocaine and 1 mg/ml scopolamine are inhibited by 100—200 µg/ml dibenamine and IPNA. The cocaine effect is more or less potentiated in the presence of 100—200 µg/ml adrenaline, noradrenaline, tyramine, dopamine, ephedrine and 200—400 µg/ml cAMP *(Fig. 7)*. The effect of 1 mg/ml scopolamine is not potentiated by adrenaline, dopamine and ephedrine. However, the potentiation by cAMP is of small degree and the scopolamine-effect is significantly prolonged by noradrenaline *(Fig. 6)*.

A preincubation in 10—20 µg/ml reserpine is not showing any influence on the DCI or pronethalol effect. A slight inhibition was observed only in cocaine at certain populations. This inhibition is present in the later period of activation *(Fig. 9)*.

5. Susceptibility of DCI-response. Pronethanol rhythm in cAMP and pyridoxale-5'-phosphate

We attempted to influence the rhythm evoked by 150—600 µM DCI, applying different substances in 10—200 µg/ml concentrations. This rhythm, as taking place in a relatively short period, is suitable to test on it a lot of different substances within a reasonable time. The experiments were carried out with 100—100 animals for 10 min.

The following compounds has been proved to be ineffective or a slightly potentiating (±20 per cent) on DCI: ACh, atropine, nicotine, dopamine, adrenaline, ephedrine, INH, tyramine, cystamine, GABA, ouabaine, $CaCl_2$, carbamide, creatinine.

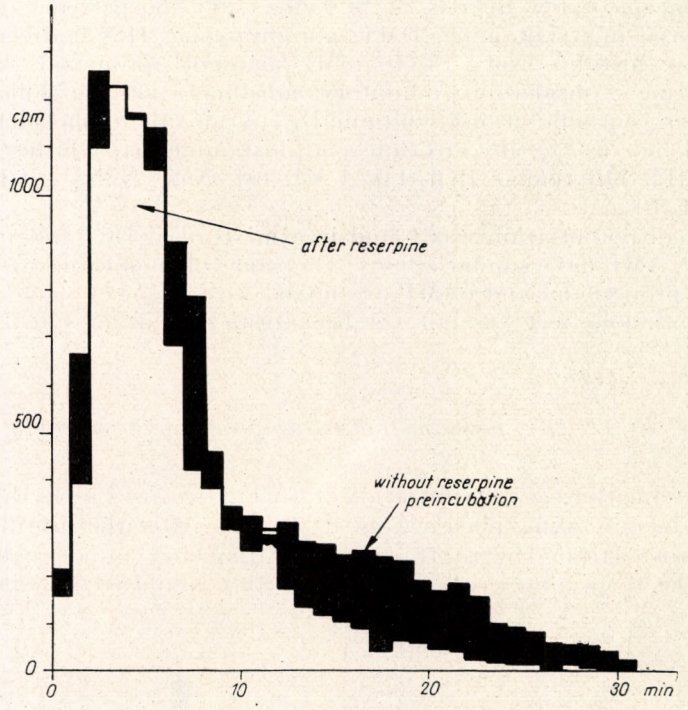

Fig. 9. Reserpine preincubation on the cocaine-rhythm. 100-100 animals. 200 μg/ml cocaine; 50 μg/ml reserpine preincubation for 3 hours. Solvent: Balaton-water

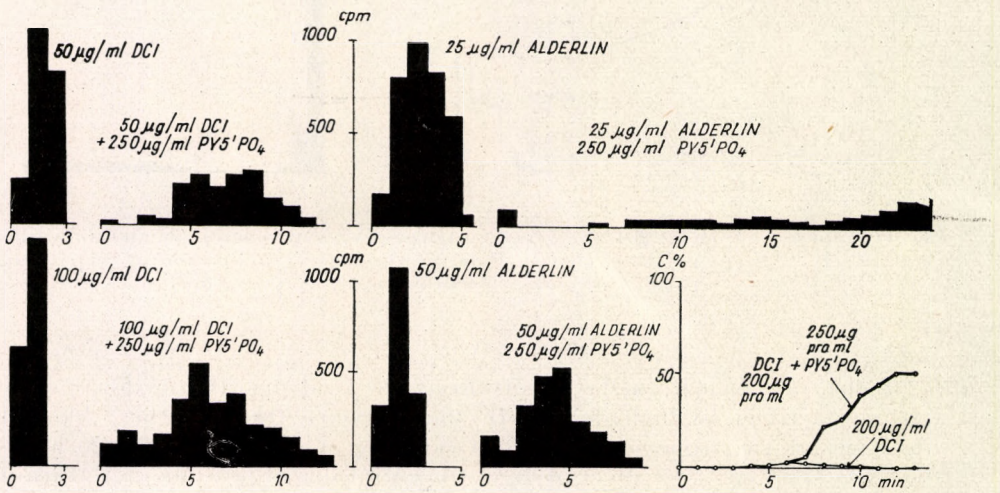

Fig. 10. DCI and pronethalol-rhythm in pyridoxale-5'-phosphate. Frequency-time curves. 100-100 animals. Balaton-water

Inhibition of low degree on DCI-effect (30—50 per cent decrease) has been observed in: tryptamine, DMT, noradrenaline, IPNA, dibenamie, CPZ, ergometrine, histidin, NaCl ($\leq$ 10 mM), actomol, iproniazid, $MgCl_2$ ($\leq$ 10 mM), creatine. Considerably inhibitory substances are the following (more than 80 per cent inhibition): vitamin B_6, pyridoxale-5'-phosphate (see also for pronethalol in *Fig. 10)* nicotinic acid, histamine, papaverine, theophyllin, caffeine, 5HT, bufotenine, BOL-148, UML-491, NaF, NaN_3, 2,4-DNP, $CdCl_2$, KCN, LiCl (10 mM).

A small potentiation was found in a mixture of DCI and 1 mM cAMP. ATP, ADP, AMP have similar effects. The same phenomenon can be observed also when pronethalol and cAMP are mixed.

Pronethalol-effect has not yet been tested by other substances.

6. *Effects of EGYT-201, procaine and tetracaine (Fig. 8 and 11)*

Depending on the concentration, EGYT-201 causes a rhythmic activity of high frequency taking place within 1—10 min. After the rhythm the larvae rest in opened state. The rhythm of peak frequency is noticeable at 100—200 μM. The tryptamin rhythm is considerably inhibited by this substance.

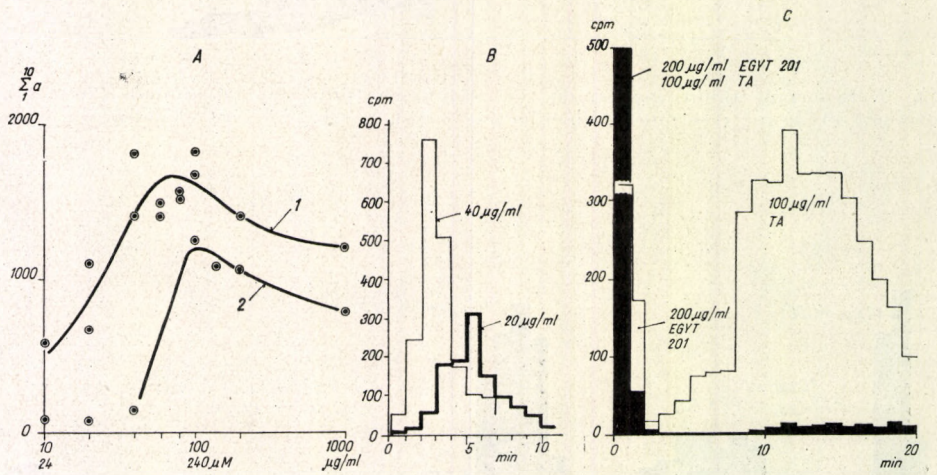

Fig. 11. Effects of EGYT—201. A — dose-response curves in Balaton (1) and in distilled water (2); B — frequency-time curves (Balaton-water); C — inhibition of tryptamine-rhythm (Balaton-water)

In 0.45 or even in 4.5 mM concentrations, the local anaesthetics do not evoke rhythmic activity of high degree. In similar concentrations, the β-blocking substances or the tropeine compounds can elicit an activity of 5—20 higher frequency. In *Fig. 8* the effect of high concentrations of procaine or tetracaine are demonstrated. A closure of low degree and a negligible rhythmic activity is typical (see *Table 1* and *Fig. 8).*

TABLE 1

Pharmacon	Threshold μM	Optimal μM	Tonus	Σa_{max}	a_{max}	Time course min	Rhythm	Pattern, modulation or timecourse of individual rhythm
DCI	10	500	late	2 000	1000	3—10	short, high	sudden stop
Pronethalol ...	50	350	late	3 000	500—800	5—15	short, high	clock-like accuracy of intervals, later periodic
Cocaine	150	600	Ø	15 000	500—1000	10—35	long, high	clock-like accuracy of intervals, later bursts
Scopolamine ...	350	1700	Ø	15 000	500—1000	10—80	long, high	slightly periodic
Atropine	150	1000	Ø	4 500	500—700	5—20	medium,high	irregular
Yohimbine			two phases	~100	<50	5—10	very low	Ø
Ergometrine ...			Ø	400	100	5—10	very low	Ø
DET	350	1000	two phases	2 000	200	10—15	low	clock-like accuracy
5MeOTA	150	240	sudden	Ø	Ø	3—10	Ø	Ø
Bufotenine	150	1000	synchron	6 000	600	15—80	high	regular
EGYT—201	20	100	late	1 700	800	3—10	short	short-lasting, regular
Procaine			low		Ø	1	Ø	Ø
Tetracaine			low		50	5	very small	Ø
Tryptamine ...	10	500	Ø	4 000	1000	5—50	high	regular

Explanations see in the text and legenda

Discussion

Before analyzing the possible specific effects of the tested substances we have to discuss the most important phenomena regarded to be non-specific.

As cocaine, yohimbine, atropine, ephedrine and EGYT-201 have an accessory effect of local anaesthetic (HAUSCHILD, 1961, p. 698), this possibility seems to be important. As that the true local anaesthetica are not activator *(Fig. 8)*, for this reason the activator effects cannot be considered as coming from such a property of the compounds even in the case of EGYT-201 which proved to be a potent local anaesthetic agent on Anodonta nerve (unpublished). Exclusively the cessation of the rhythm and perhaps the late and not consequent tonus evoked by pronethalol may originate from this. However, the descending parts of the dose-response and those of the frequency-time curves of cocaine, scopolamine or atropine may originate from a conduction block as well.

One may interpret the non specific origin for example as a "general membrane activation". But this term is too much undifferentiated and the fact that the effects are generally distinguishable from each other contradicts this possibility *(Table 1)*. Therefore, their points of attack may be different in the different groups of substance (cocaine-scopolamine-atropine or DCI-pronethalol). During the experiments showing the heterogenous susceptibility of DCI-effect, several sympathetic pharmacons have proved to be more or less effective as potentiating or inhibitory agents.

These facts require to discuss the question of specificity for DCI and pronethalol in detail and also for similar reasons the possible effects of cocaine, scopolamine and atropine have to be raised and discussed as well.

As two of the examined β-antagonists (DCI and pronethalol) cause rhythmic activity ending by a relatively sudden stop without closure we do not think that the possibility of an adrenergic control (LÁBOS, 1966) may be out of question when considering these factors playing a role in the adductor activity. The effect of propranolol in NaCl-milieu cannot be compared to these effects as simply attributed to the different conditions. Consequently further experiments are desirable.

It is known that DCI and pronethalol have properties of β-agonists (POWELL and SLATER, 1958; BLACK and STEPHENSON, 1962; KOCH-WESER, 1964; BLOOM and GOLDMAN, 1966; ARIENS, 1967). For this reason it is difficult to decide whether the observed activity — if it is specific — is a consequence of a β-agonist or β-antagonists property. The IPNA itself is not an activator but it inhibits the DCI rhythm (LÁBOS, 1966). Applying solely, cAMP is also ineffective, nevertheless, it potentiates slightly the effects of DCI and pronethalol. However this latter fact have to be considered as non-specific for cAMP, in accord with the observations of KIM et al. (1968), that AMP, ADP and ATP also can elicit similar effects. All these circumstances support an interpretation that the effects would originate — if they are specific — from "antagonist-activation". This would correspond with the findings of POWELL and SLATER (1958) concerning DCI and with the AHLQUIST's definition (1948) of the β-agonist which includes inhibitory effect.

The specificity concerning the influences evoked by different substances on DCI rhythm can be proved only by a quantitative method, testing the competitive mode of interrelations which may be a severe criterium (ARIENS,

1967) for each substances separately. Nevertheless, it is presumable, that IPNA inhibits the DCI response acting at the same point, where DCI evokes its effect. On the other hand, the non-competitive character (as an aspect of non-specificity) is evident for several substances (for example indole-compounds, metabolic inhibitors, cations, etc. . . .) influencing the DCI-response.

The activation evoked by the cholinolytic L-scopolamine which lasts for an exceptionally long time and is of high frequency is conspicious. It has been noticed before that atropine also causes a rhythmic response but this has considerably lower frequency (LÁBOS et al. 1964). A comparison of the dose-response curves in *Fig. 5* supports this observation. In higher animals scopolamine is mainly but not always (MÉHES, 1927), tranquillant and atropine is excitant (BRADLEY and ELKES, 1953; FORREZ, 1951; RINALDI and HIMWICH, 1955; RINALDI, 1965; ISBELL et al. 1964; WADA et al.1963).

As cocaine, scopolamine and atropine have similar structure and cocaine is adrenomimetic agent it may be raised that the effect of these drugs somehow is related to the presumed adrenergic control, because their local anaesthetic and cholinolytic activator effects are less probable or even can be excluded.

This is not surprizing for cocaine, but scopolamine or atropine are generally not considered as agents with direct sympathomimetic effect. However in our case the cholinergic control is not probable (LÁBOS et al. 1964; LÁBOS, 1966). This is supported also by the fact, that ACh does not inhibit the atropine-rhythm. On the other hand we must take into account that quaterner substances as ACh or novatropine may be ineffective because of their retarded permeation. Finally the sympathomimetic effect is just which cannot be excluded in interpreting the effect of the three tropeine-like pharmacons. Whether these effects are really sympathomimetic or other receptors being able to respond to these agents are responsible — it is an open question.

It is interesting to consider a recent paper of KALSNER and NICKERSON (1969). They explain the cocaine-potentiation of responses to amines by a direct hyperresponsive influence of cocaine on the effectors which is not related to uptake or storage of amines and at the same time the potentiation deviates from the procaine-like properties of cocaine. A possibility of a purely pharmacological interpretation without any endogenous sympathetic or adrenerg system is also possible.

The presence of an "adrenergic" control may be supported by the results showing that dibenamine, IPNA and perhaps reserpine inhibit the cocaine rhythm. But there are differences between scopolamine and cocaine concerning to the potentiation of their effects by catecholamines and ephedrine. These differences may be in connection also with the high concentrations of scopolamine required to attain an equipotent effect with cocaine *(Fig. 5)*.

It is more difficult to make these activating and potentiating effects consistent with the similar activating character of DCI and pronethalol. It is not impossible that an undifferentiated receptor system plays a role in the two groups of phenomenon. This is supported by the inhibition of cocaine-rhythm by dibenamine and IPNA and also by its potentiation by adrenaline, dopamine, noradrenaline, tyramine, ephedrine. In this respect numerous examples are known from the literature when α- and β-effects cannot be well distinguished (ARIENS, 1967; PATIL et al. 1968; GOVIER, 1968; LÁBOS, 1966). Furthermore the fact that ineffective sympathomimetics (for example ephedrine) are of MAO-inhibitor and are able to prolonge the effect of others

(MÉHES, 1927) also may be responsible for potentiations. On the other hand certain metabolites or metabolic inhibitors (nicotinic acid, vitamin B_6, INH, iproniazide, actomol, pyridoxale-5'-phosphate) are more or less effective on the DCI or pronethalol rhythm. An interpretation of such phenomena is rather complex, as for example, β-adrenolytic drugs also can inhibit MAO (GREEF and WAGNER, 1966).

Connection of the activations with an adenyl-cyclase system (BUEDING et al. 1966; BLOOM and GOLDMAN, 1966) does not seem to be close if it exists at all, as cAMP effect is of small degree.

The hallucinogen and central excitant DET and bufotenine (SZARA, 1964; LESSIN et al. 1965; DOWNING, 1964) are activators as it has been expected. It must be mentioned that besides the specific differences in the effects of indole compounds or their different permeation (VANE et al. 1960; WOOLEY and SHAW, 1962; MARLEY and VANE, 1967) — because of the ineffectivity of DMT and DET-oxalate — disturbing influence of counter-anion may also play a role. Numerous examples have been given here that even the solvent itself is not neutral. Thus, the distilled and Balaton-water have different influences on the effects of drug. The latter is rich in ions and it is possible that different cations are responsible for the observed differences.

Summary

Effects of activator substances were compared which elicit rhythmic or tonic adductor activity of *Anodonta* glochidia (see *Table 1).*

It can be stated that:

1. DCI and pronethalol evoke a rhythm in 100 μM concentration cessing suddenly. A late tonus was observed independent from the rhythm. Propanolol in NaCl does not evoke proper rhythmic activity.

2. DET leads to rhythm and a tonus of medium degree; 5-MeOTA evokes tonus almost without rhythm. Bufotenine in 1 mM concentration elicits a rhythm of high frequency.

3. The rhythm evoked by DCI can be influenced by indole compounds, secale-alkaloids, metabolic inhibitors (KCN, NaN_3, 2,4-DNP), cations (Na^+, Li^+, Ca^{2+}). Typical inhibitions are caused by pyridoxale-5'-phosphate. nicotinic acid, vitamin B_6, INH and actomol. The cAMP potentiates slightly.

4. Cocaine evokes in 100—2000 μM concentrations a high frequency rhythm which is sometimes periodic; maximal activity is at 600 μM.

5. Scopolamine can produces a long-lasting rhythm (80 min). It is effective in 500—5000 μM concentration; maximum is at 1700 μM.

6. IPNA and dibenamine inhibits, 0.5—1 mM cAMP and catecholamines ($\sim$0.5 mM) potentiates the cocaine- or scopolamine-effects. A reserpine-preincubation slightly inhibits the late phase of cocaine-effect.

7. Yohimbine and ergometrine causes a low-frequency rhythm; the latter evokes a transient tonic closure as well.

8. EGYT-201 (spasmolyticum and local anaestheticum) elicits a short-lasting and very frequent rhythmic activity. True local anaesthetica (procaine and tetracaine) do not activate.

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N, N-DIALKIL TRIPTAMINOK, 5-METOXI-TRIPTAMIN, β-ADRENERG-ANTAGONISTÁK, KOKAIN, SZKOPOLAMIN ÉS EGYÉB FARMAKONOK AKTIVÁLÓ HATÁSA *ANODONTA*-GLOCHIDIUMOK ZÁRÓIZOM-TEVÉKENYSÉGÉRE

Lábos Elemér

Összefoglalás

Anodonta glochidiumok ritmusos és tónusos záróizom-tevékenységét aktiváló anyagok hatását hasonlítottuk össze. Megállapítottuk, hogy

1. a DCI és nethalide 100 μM koncentrációban általában hirtelen leálló magas frekvenciájú ritmikus választ váltanak ki; tónust nem észleltünk;
2. a DET ritmikus választ és közepes fokú tónust hoz létre, míg az 5MeOTA tónust és igen kisfokú ritmust okoz. A bufotenin 1 mM koncentrációban igen nagy frekvenciájú ritmust vált ki;
3. a DCI és Alderlin-ritmus befolyásolható indolvázas vegyületekkel, anyarozs-alkaloidákkal, anyagcseregátlókkal (KCN, NaN_3, 2,4-DNP), kationokkal (Na^+, Li^+, Ca^{2+}). Jellegzetes gátlást piridoxál-5'foszfát, nikotinsav okoz a B_6-vitamin és INH. A cAMP kissé potencíroz;
4. a kokainnal 50—2000 μg/ml koncentrációban magas frekvenciájú — esetenként periodikus — ritmikus tevékenységet lehet kiváltani; maximális tevékenység 700 μM-nál észlelhető;
5. a szkopolamin igen hosszan (80 perc) elnyúló, magas frekvenciájú ritmust hoz létre 200—2000 μg/ml koncentrációban; maximális a ritmus 1,6 mM-nál;
6. IPNA és dibenamin gátolja, 200—400 μg/ml cAMP és katecholaminok (100 μg/ml) általában fokozzák (egyes esetekben hatástalanok) a kokain és szkopolamin hatását. Reszerpin-előinkubáció gátolja a kokain-hatást;
7. a yohimbin, ergometrin alacsony frekvenciájú ritmust okoz; előbbi átmeneti tónusos zárást is kivált;
8. az EGYT—201 (spazmolitikum és lokalanesztetikum) rövid lefolyású igen magas frekvenciájú ritmikus aktivitást vált ki.

ВОЗБУЖДАЮЩЕЕ ВОЗДЕЙСТВИЕ N—N ДИАЛКИЛ ТРИПТАМИНОВ, 5-МЕТОКСИТРИПТАМИНА, β-АДРЕНЕРГИЧЕСКИХ АНТАГОНИСТОВ, КОКАИНА, СКОПОЛАМИНА И ДРУГИХ ФАРМАКОЛОГИЧЕСКИХ ВЕЩЕСТВ НА АКТИВНОСТЬ ЗАПИРАТЕЛЬНОЙ МЫШЦЫ ГЛОХИДИЕВ БЕЗЗУБКИ

Э. Лабош

Возбуждающее действие веществ было сравнено в отношении тонической и ритмической деятельностей глохидиев беззубки. Было установлено, что:

1. ДЦИ и нефалид в концентрации 100 μм вызывают быстро развивающийся ритмический ответ высокой частоты. Наблюдается и поздний, независящий от ритма тонус.

2. ДЕТ вызывает ритмическую реакцию и тонус средней величны, а 5-метокситриптамин вызывает тонус и слабое увеличение ритма. Буфотенин в концентрации I mм вызывает ритм высокой частаты.

3. Ритм вызванный под влиянием ДЦИ и алдерлина видоизменяется при даче индольных соединений, алкалоидов, спорыньы, инхибиторов обмена веществ (KCN, NaN_3, 2,4-DNP) и катионов (Na^+, Li^+, Ca^{++}). Характерное торможение наступало под действием пиридоксал-5-фосфата, никотиновой кислоты, витамина $Б_6$, INH и актомола. Цикличный АТФ некоторое усиление ответа.

4. Кокаин в концентрации 50—2000 μг/мл вызывает ритмическую деятельность высокой частаты и иногда-периодическую реакцию; максимальный эффект был регистрирован при 700 μм.

5. Скополамин вызывает ритм высокой частоты и продолжительности (80 мин) в концентрации 200—2000 μг/мл; максимальное увеличение ритма наблюдалось в концентрации 1,6 мМ.

6. Изопропилнорадреналин и дибенамин тормозят, цикличный АТФ (200—400 μг/мл) и катеколамины (≈100 μг/мл) вообще увеличивают эффект кокаина и скополамина, или иногда неэффективны. Обработка резерпином предотвращает позднюю стадию эффекта кокаина.

7. Йохинбин и эргометрин вызывают ритм низкой частоты. Первое из них вызывает и временное тоническое закрывание.

8. EGYT—201 (спазмолитическое и локаланастетическое средство) вызывает кратковременную ритмическую активность очень высокой частоты.