ANNAL. BIOL. TIHANY	42	99–113	HUNGARIA 1975

PHARMACOLOGICAL PROPERTIES OF THE RECEPTORS AT THE HEART MUSCLE MEMBRANE OF *LOCUSTA MIGRATORIA MIGRATORIOIDES* R. F. (INSECTA)

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Received: 15th March, 1975

In recent years while studying the sites of actions of different substances the analysis of their effect on the membrane prevailed both on the nerve and muscle cells, in order to discover the pharmacological properties as well as the ion-mechanisms of the receptors (GERSCHENFELD, 1973; TRAUTWEIN, 1973; MILLER, 1973). Recent results proved the membrane effect of transmitters on the heart of numerous invertebrate and vertebrate species and in some cases even their sites of action and ion-dependence were described (MILLER, 1973; HOLLEY and DELALEU, 1972; WILKENS and GREENBERG, 1973; IRISAWA et al., 1973). In *Locusta* heart our previous results verified the transmitter role of acetylcholine (Ach), 5-hydroxytryptamine (5HT) and gamma-aminobutyric acid (GABA), as well as the Na- and Ca-ion dependence of the effect of Ach and 5HT (S.-RÓZSA and V.-SZŐKE, 1973; S.-RÓZSA et al. 1973). To pursue these studies the investigations of the site of action of transmitters were emphasized for clearing up whether on the heart muscle membrane of insects the receptors of Ach, 5HT and GABA can be compared to the structures known for other classes of animals or whether they had some distinguishable properties. The present paper summarizes the results of these experiments.

Material and method

Experiments were carried out on the adults of 2—7 weeks old *Locusta migratoria migratorioides* R. F., both male and female specimens were used. The animals were obtained from breeding, kept at a temperature of 28—32°C with 12 hours photoperiodism. The experiments were made at room temperature (22—26°C).

The experiments were performed on the half-isolated heart, it was described earlier in detail (S.-Rózsa and V.-SZŐKE, 1970). The recording of action potentials was made by conventional glass microelectrodes filled with 2.5 M KCl using the equipment described earlier (S.-RÓZSA and V.-SZŐKE, 1972).

In the experiments the physiological saline prepared for insect hearts (LUDWIG et al., 1975) was used and the investigated substance was dissolved in the same solution immediately before application. The substances were studied at concentrations 10^{-10}—10^{-3} M observing their effect over a period

of 10 minutes. The pretreatment with inhibitors took 5—15 minutes, then the transmitter was added together with the blocking substance. In case of biphasic effect of the transmitter the blocking of both effects was studied.

The following substances were used: acetylcholine chloride (Sigma); 5-hydroxytryptamine creatinine sulphate (Reanal); gamma-amino-butyric acid (Reanal); nicotine hydrogen (t)-tartrate (BDH); d-tubocurarine dichloride (Schuchardt); atropine sulphate (BDH); benzoquinonium chloride, mytolon (St. W. Res. Inst); bromo-d-lysergic acid diethylamide, BOL-148 (Sandoz); methysergide bimaleate (Sandoz); ergometrine (Fluka); picrotoxin (Fluka); bicuculline (Pierce chemical Co).

Results

1. *Effect of antagonists on the membrane of Locusta heart*

According to our data, the antagonists possess own effects on the heart varying from an insignificant decrease or increase in frequency and sometimes in amplitude to the stopping of heart beats.

TABLE I

Effects of receptor antagonists on the spontaneous action potentials of Locusta heart

Antagonists and concentration used (M)		Changes in spontaneous action potentials	
		frequency	amplitude
Antagonists of Ach receptors			
d-Tubocurarine	10^{-6}—10^{-4}	decrease, increase	slight decrease
	10^{-3}	decrease, stopping	ceased
Atropine	10^{-8}—10^{-6}	decrease, increase	unchanged
	10^{-5}—10^{-3}	decrease	unchanged
Nicotine	10^{-8}—10^{-6}	increase, decrease	unchanged
	10^{-5}—10^{-3}	increase, decrease	unchanged
Mytolon	10^{-7}—10^{-6}	increase, decrease	unchanged
	10^{-5}—10^{-3}	decrease	unchanged
Antagonists of 5HT receptors			
BOL-148	10^{-5}	increase, decrease	decrease
	10^{-4}—10^{-3}	increase, decrease stopping	ceased
Methysergide	10^{-6}—10^{-4}	decrease, stopping	decrease, ceased
Ergometrine	10^{-9}—10^{-4}	increase, decrease	decrease
Antagonists of GABA receptors			
Picrotoxin	10^{-9}—10^{-7}	decrease	unchanged
	10^{-6}—10^{-4}	increase, decrease unchanged	unchanged
Bicuculline	10^{-9}—10^{-7}	increase, decrease stopping	unchanged
	10^{-6}—10^{-5}	decrease	unchanged
	10^{-4}	decrease, increase stopping	unchanged

Note: The lowest concentration seen in the *Table* reflects the threshold concentration of the pharmacons. The effect demonstrated at the first place shows the effect of drugs on the action potentials at the first minute of application, then the change of effect is seen if occurred few minutes after the application of the drugs

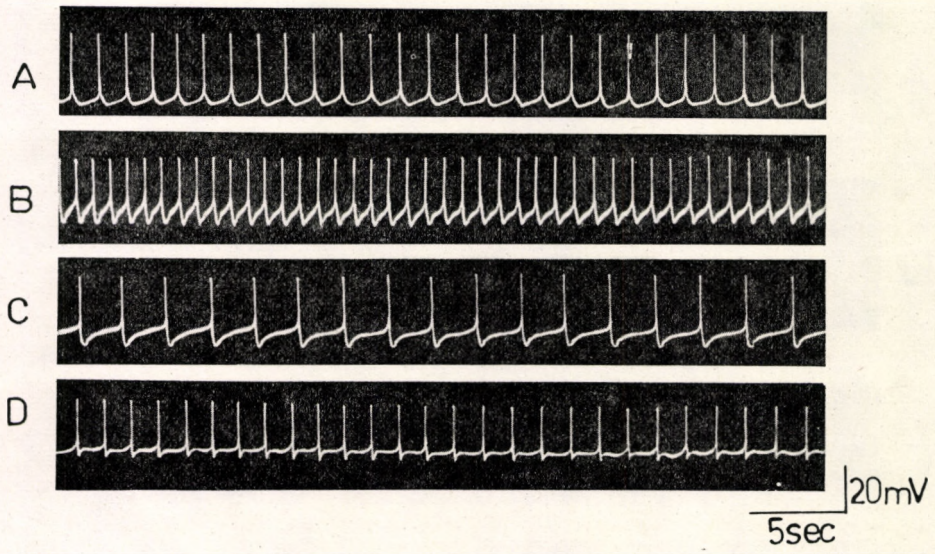

Fig. 1. Effect of nicotine on the generation of action potentials on *Locusta* heart. *A* — control; *B* — effect of nicotine (10^{-3}M) 1 minute after application; *C* — same as *B* but 5 minutes after application of drug; *D* — activity after washing out nicotine

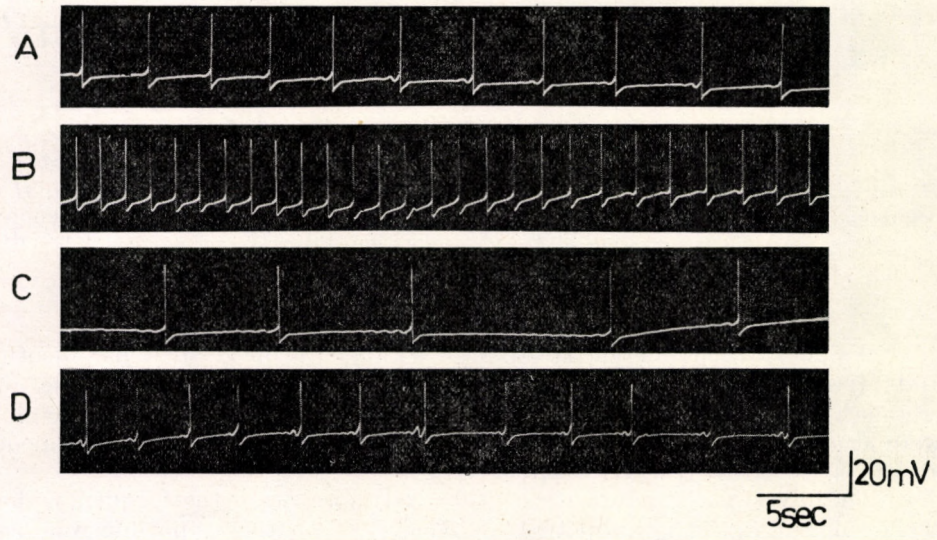

Fig. 2. Effect of mytolon on spontaneous action potentials. *A* — control; *B* — applying 10^{-3} M mytolon; *C* — effect of mytolon 2.5 minutes after application; *D* — activity after washing out the drug

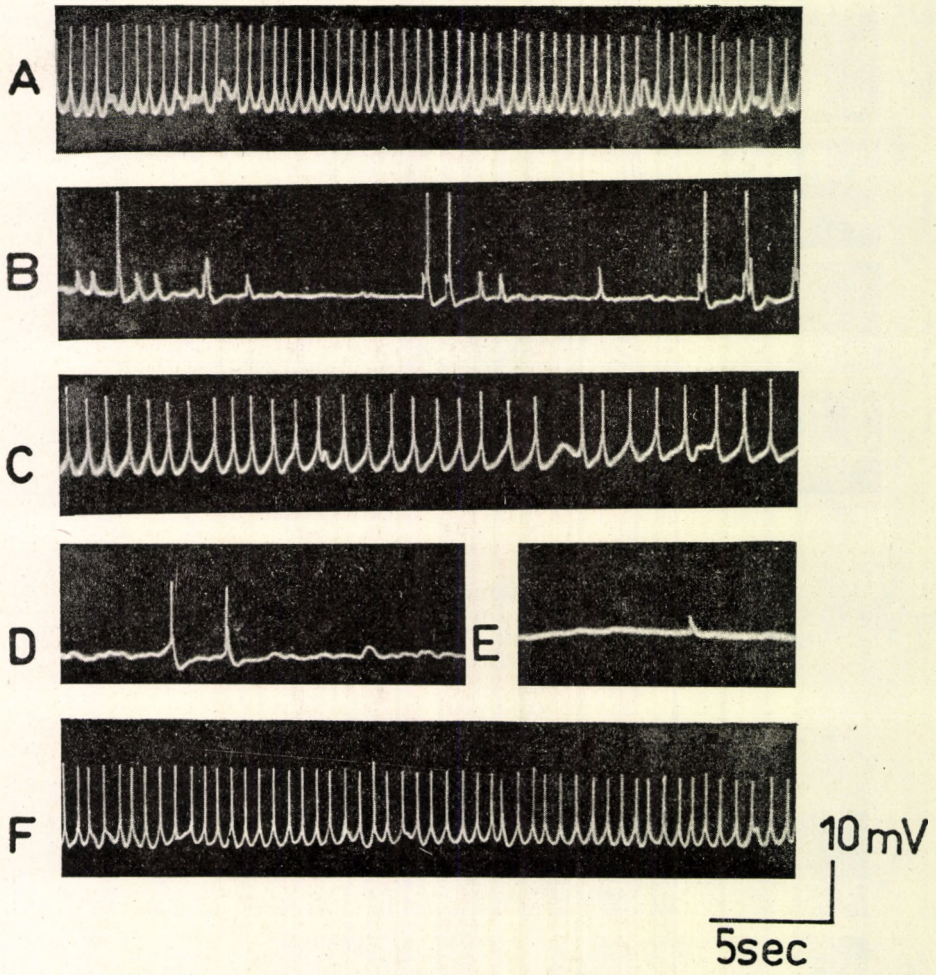

Fig. 3. Effect of d-tubocurarine on the membrane of *Locusta* heart. *A* —ontrol; *B* — beginning of the action of d-tubocurarine (10^{-4}M); *C* — same as *B* after 3.5 minutes; *D* — same as *B* after 5 and 6 minutes of application, respectively; *E* — activity after washing out d-tubocurarine

Among anticholinergic substances d-tubocurarine, atropine, nicotine and mytolon, among antagonists of the 5HT, BOL-148, methysergide and ergometrine, while among antagonists of GABA picrotoxin and bicuculline were studied. The results can be seen in *Table I* regarding the spontaneous action potentials of the *Locusta* heart.

The investigated substances influenced more often the frequency than the amplitude fo the action potentials. The effect on the amplitude was negligible with the exception of the antagonists of 5HT *(Table I)*. Using antagonists the biphasic effect can often be observed indicating the time-dependent appearance of the inhibitory or excitatory influences in the same concentration

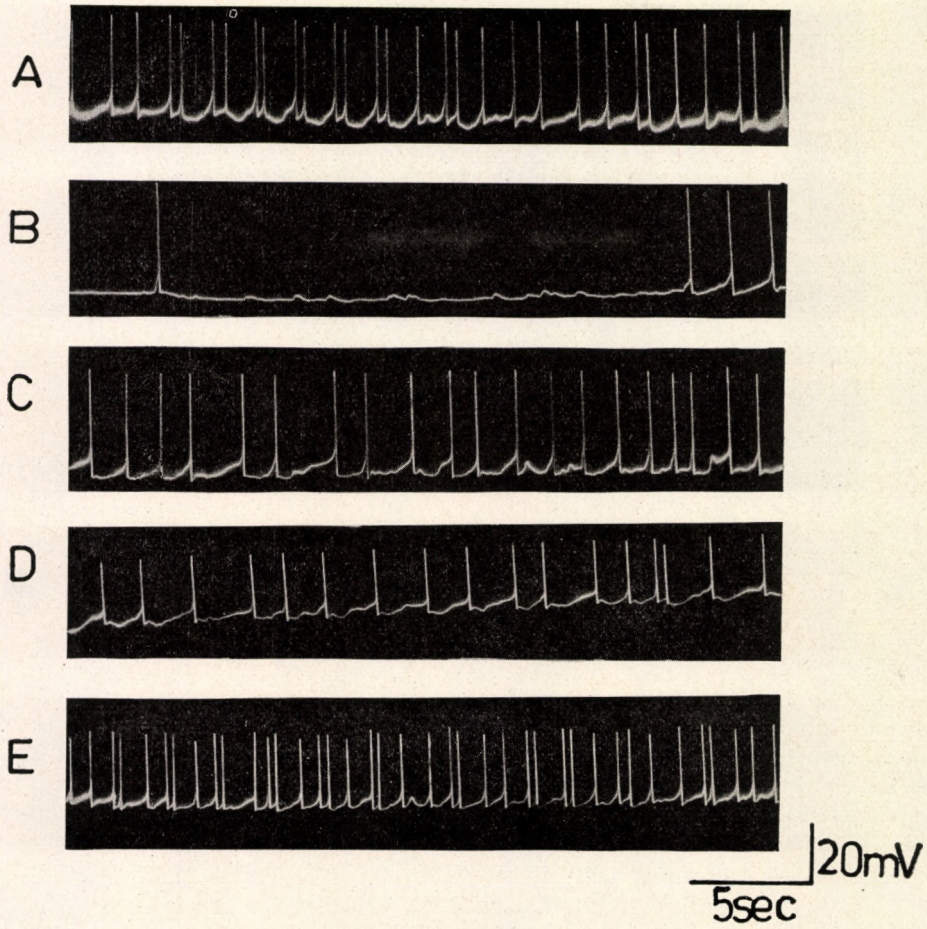

Fig. 4. Effect of atropine on the sponatneous action potentials of *Locusta* heart. *A* — control; *B* — applying atropine at 10^{-6}M; *C* — effect of atropine 1 minute after application; *D* — effect of atropine 2 minutes after application; *E* — activity after removing atropine

of the drugs. In *Table I* both the first and secondary effects of the pharmacons are shown.

Using cholinergic antagonists the changes in frequency were fairly small. Thus, nicotine at 10^{-3} M at the beginning of its application increased frequency by 50 per cent then decreased it by 30 per cent *(Fig. 1)*. At the same concentrations mytolon, at the beginning, doubled the initial frequency but after 2.5 minutes it failed to achieve even half of the control value *(Fig. 2)*. The time-dependent changes were the same in sign using nicotine or mytolon, but nicotine influenced mainly the diastolic depolarization of action potentials which appeared even during the decrease of frequency *(Fig. 1C)*, while mytolon caused oscillation in the membrane potential *(Fig. 2B, C)*. During its application d-tubocurarine influenced the synaptic potentials *(Fig.3)* and

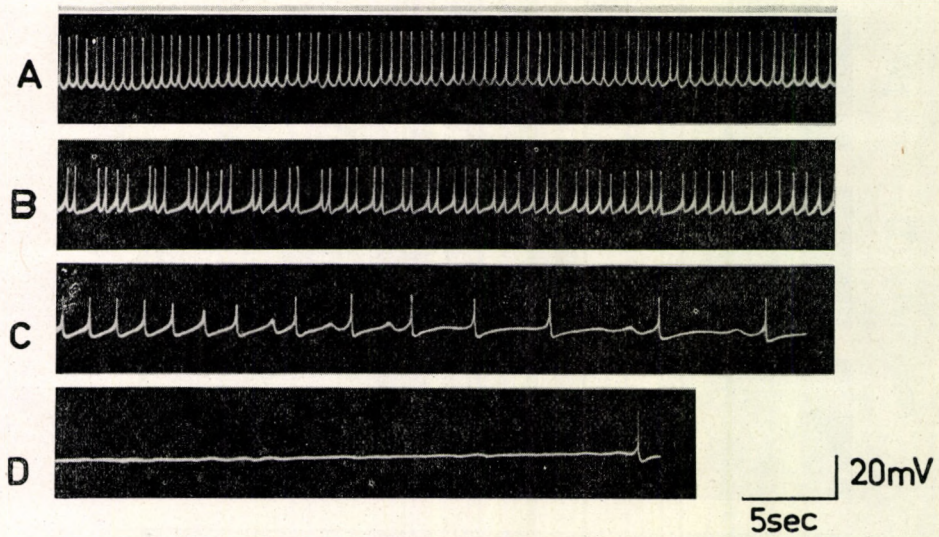

Fig. 5. Effect of BOL-148 on the membrane of *Locutsa* heart; *A* — control; *B* — application of 10^{-3}M BOL-148; *C* — effect of BOL 148 5 minutes after application; *D* — same as *C* after 8 minutes

periodically abolished potential generation *(Fig. 3)*. The inhibition of the spontaneous activity appeared at the beginning and even after 5 and 6 minutes interrupted with the periods of firing *(Fig. 3C)*. At the beginning of its application atropine caused strong inhibition, then step by step the generation of action potentials was restored *(Fig. 4)*. Here also during diastolic depolarization the significant increase in synaptic potentials was observed prevailing even after the stopping of spike generation *(Fig. 4B)*. High concentrations (10^{-4}—10^{-3} M) of atropine sometimes caused slight temporary increase in frequency but it was followed by a decrease. The effect of cholinergic antagonists was eliminated easily by washing out.

Among receptor inhibitors of 5HT, BOL-148 exerted effect from a concentration of 10^{-5} M. At this concentration BOL-148 caused slight increase in frequency but at 10^{-4}—10^{-3} M it gradually slowed the firing and ceased the geneartion of the action potentials at 8—10 minutes after application *(Fig. 5D)*, this latter was slow or irreversible. Methysergide eliminated the generation of action potentials without excitatory phase in lower than 5HT threshold concentration *(Fig. 6)*, but this inhibition ceases after washing out. The effect of ergometrine was variable, beginning with 10^{-9}M after 4—5 minutes of application it increased frrequency by 8—10 per cent by simultaneously lowering the amplitude to 50 per cent of the control. However, in other cases ergometrine caused only inhibition. The effect of ergometrine was hardly reversible.

Among the receptor antagonists of GABA the effect of picrotoxin was very variable, it caused inhibition and excitation alike or was even ineffective. In this variation no concentration dependence was ascertained, although at low concentrations the increase in frequency was more usual *(Table I)*.

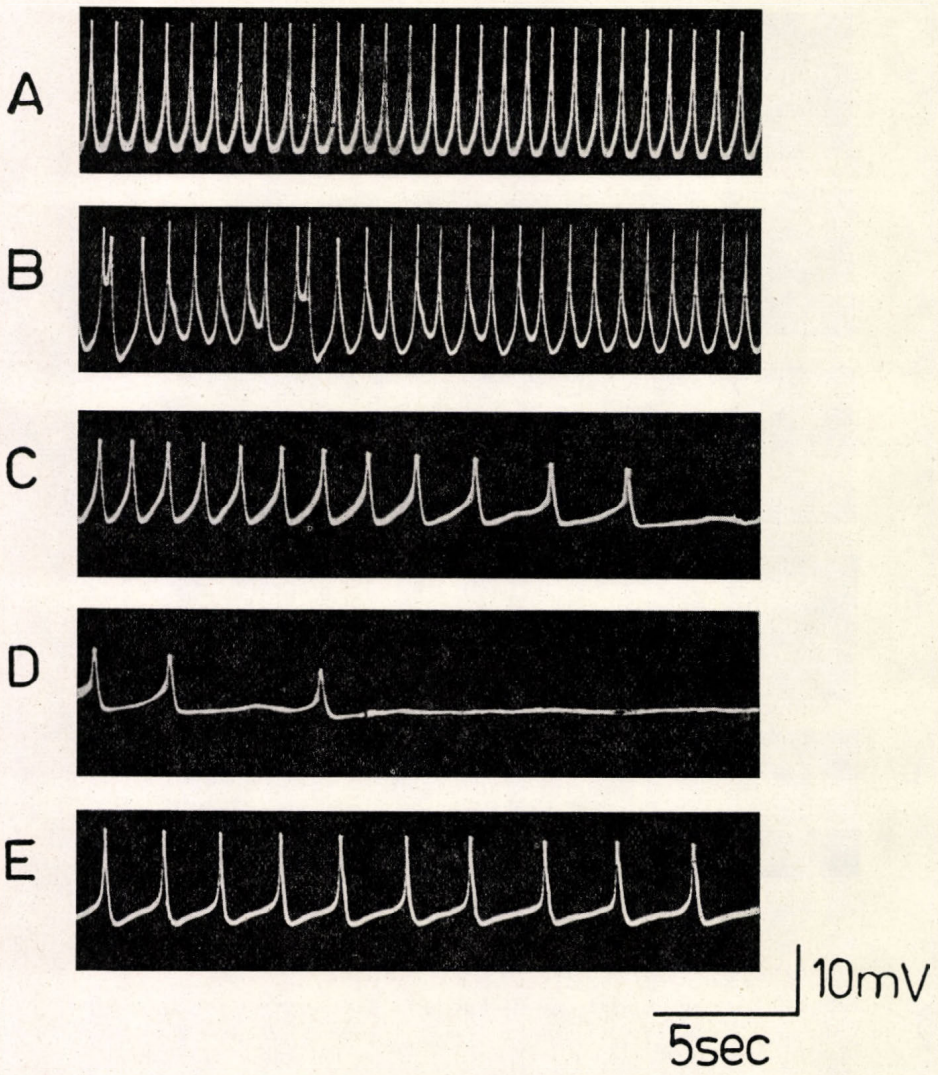

Fig. 6. Effect of methysergide on the membrane of *Locusta* heart. *A* — control; *B* — effect of methysergide (10^{-6}M) immediately after application; *C* — effect of methysergide 2 minutes after appliation; *D* — same as *C* after 3 minutes; *E* — after methysergide removal

This effect was reversible. Bicuculline at concentrations 10^{-9}—10^{-7} M first increased the frequency of spontaneous firing then inhibited it, while at 10^{-6}—10^{-5} M only decreased the frequency of action potentials, but at 10^{-4} M, similarly to the d-tubocurarine, inhibition was interrupted from time to time by firing *(Fig. 7)*. Inhibition took place within 5 minutes of application. Using bicuculline, the secondary stopping of the generation of action potentials was not regular. The synaptic potentials become more frequent, prevailing

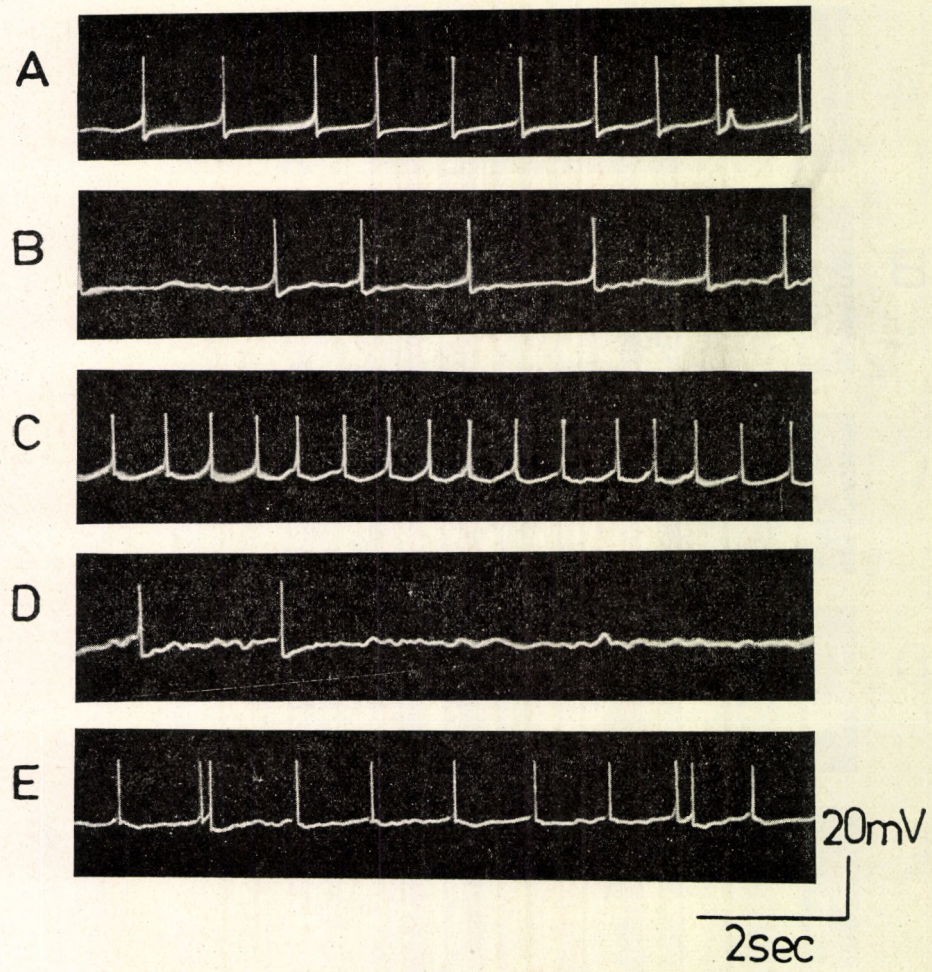

Fig. 7. Effect of bicuculline on the membrane of *Locusta* heart. *A* — control; *B* — effect of bicuculline (10^{-4}M) 30 se after application; *C* — same as *B* after 2.5 minutes; *D* — same as *B* after 3.5 minutes; *E* — after bicuculline removal

also during the stopping of the heart by bicuculline *(Fig. 7D)*. The effect of bicuculline was slowly reversible even after repeated washing out. The amplitude of the spontaneous action potentials was not influenced by the two antagonists of GABA receptors.

2. The sites of action of Ach, 5HT and GABA

According the our previous results in the spontaneous action potentials of *Locusta* heart Ach and 5HT caused both the inhibitory and excitatory effects, while GABA produced partial or complete inhibition (*S.*-Rózsa and

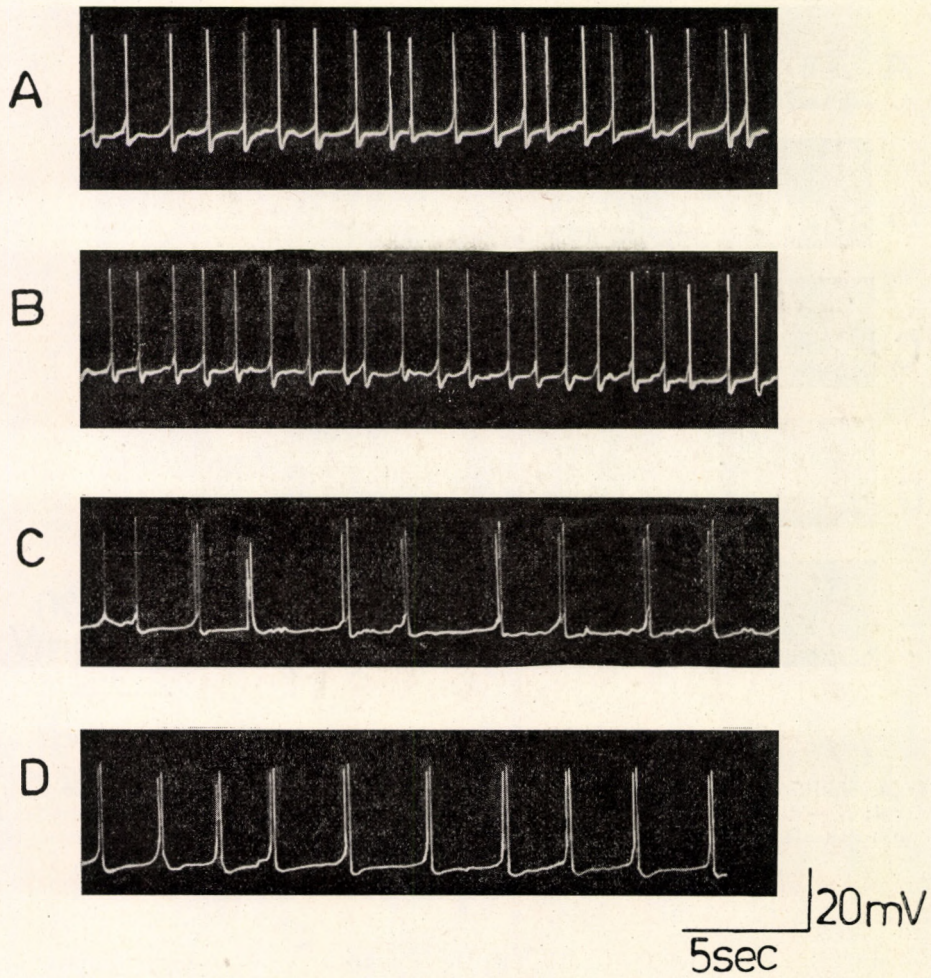

Fig. 8. Modification of Ach effect after pretreatment of *Locusta* heart by atropine. *A* — control; *B* — first minute of the atropine (10^{-5} M) treatment; *C* — effect of simultaneous application of atropine (10^{-5} M) and Ach (10^{-3} M); *D* — activity after washing out atropine and Ach

V.-Szőke, 1972; S.-Rózsa et al, 1973). The abolishment of these effects was studied here by using the above pharmacons.

The results are summarized in *Table II*, referring to the wide limits of antagonists used, since most of them eliminated or turned the effect of transmitter applied to the opposite. The antagonistic properties of pharmacons were more obvious in the blocking effect at low concentrations of transmitters. On the Ach receptors of the heart membrane of *Locusta* d-tubocurarine possessed somehow low activity, because it failed to block the inhibitory effect of Ach, and also its excitatory effect was turned into the opposite in some of the cases, mainly in old animals. The inhibitory effect of Ach (10^{-9} M) normally was

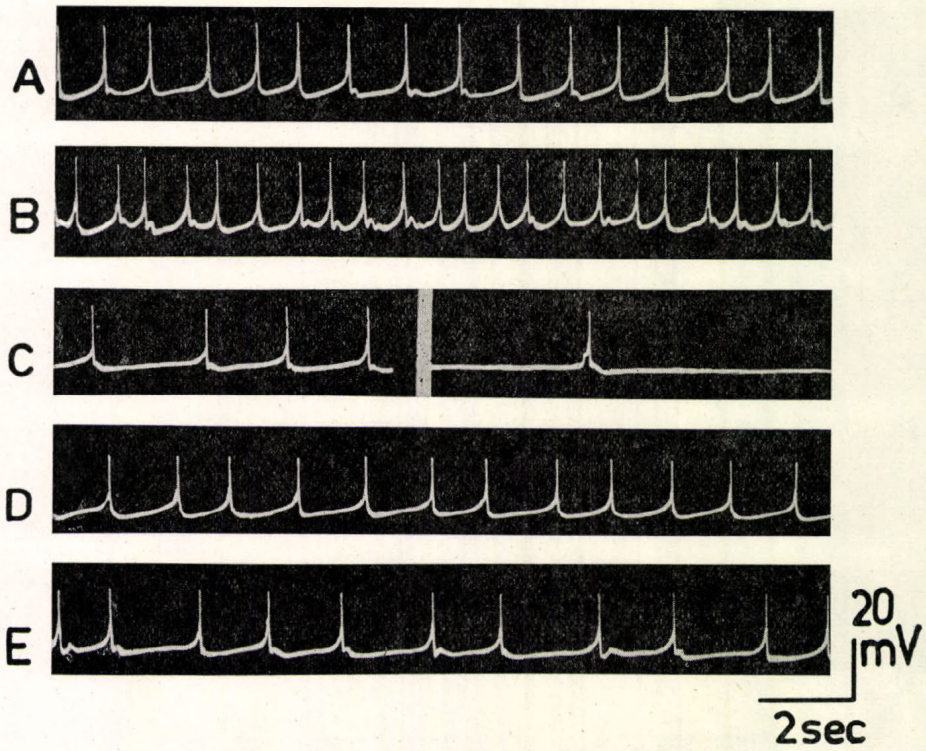

Fig. 9. Modification of 5HT effect by pretreating *Locusta* heart with BOL-148. *A* — control; *B* — beginning of the pretreatment of the heart with BOL-148; *C* — same as *B* 15 minutes after pretreatment; *D* — effect of simultaneous application of BOL-148 (10^{-4} M) and 5HT (10^{-4} M)

abolished by atropine (10^{-4} M) but the synaptic potentials appeared more frequently and the heart beats became arrhythmic. After pretreatment with atropine the excitatory influences, of Ach was eliminated but the arrhythmic heart beats were characteristic too *(Fig. 8)*. In some cases following the pretreatments with atropine the high concentration of Ach caused an inhibition *(Table II)*. Both the inhibitory and excitatory effects of Ach were abolished by nicotine on young animals, while on older ones the inhibitory effects prevailed or instead of the usual excitatory response at 10^{-6} M Ach the inhibition occurred. Mytolon ($10^{-6}-10^{-3}$ M) failed to influence the effect of Ach.

Among the antagonists of 5HT both BOL-148 and methysergide abolished the excitatory influences of 5HT. At most of the cases BOL-148 ($10^{-4}-10^{-5}$ M) not only eliminated the excitation caused by 5HT but stopped the heart beats *(Table II)*. BOL-148 applied alone caused also a decrease in the frequency of action potentials which could not be completely compensated by adding 5HT *(Fig. 9)*. The effect of ergometrine was variable on the receptors of 5HT, sometimes at $10^{-4}-10^{-5}$ M it abolished the excitation caused by 5HT but in other cases it remained ineffective *(Table II)*.

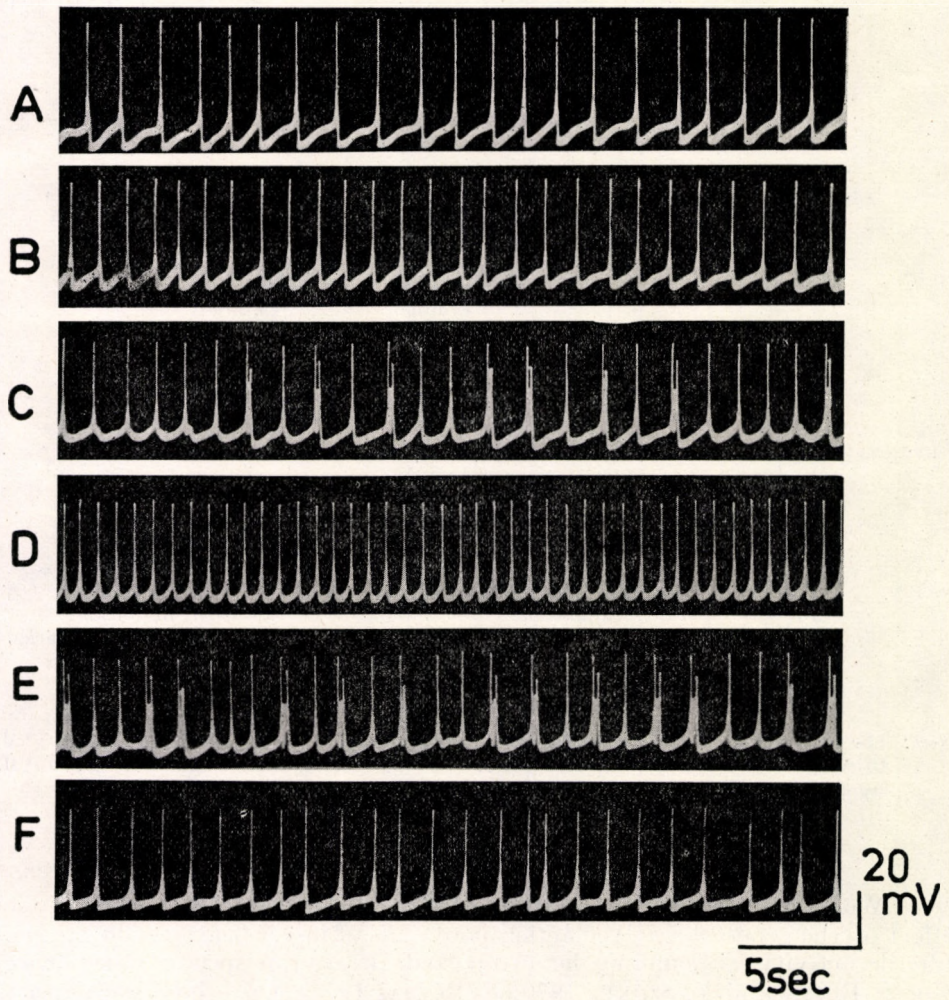

Fig. 10. Modification of GABA effect by treating the heart with bicuculline. *A* — control; *B* — 7 minutes after pretreating the heart with bicuculline (10^{-7} M); *C* — same as *B* after 20 minutes; *D* — effect of simultaneous adding of bicuculline (10^{-7} M) and GABA (10^{-5} M); *E* — same as *D* after 5.5 minutes; *F* — after removing the drugs

From the receptor antagonists of GABA picrotoxin abolished the inhibition caused in low concentrations (10^{-7}, 10^{-6} M), while in high concentrations (10^{-5}—10^{-4} M) decreased in degree but without a complete elimination *(Table II)*. The bicuculline proved to be a more effective antagonist on the GABA receptors because, beginning with 10^{-8} M, it completely or partially abolished the inhibitory effect of GABA *(Table II)*. In some of the cases, after treatment with the bicuculline, the inhibition caused ba GABA turned to excitation which persisted throughout application *(Fig. 10 D, E)*. During GABA application the heart beats became arrhythmic but they were quickly restored after the drug was washed out *(Fig. 10F)*.

TABLE II

Modification of the effects of Ach, 5HT and GABA applying specific inhibitors to the receptors of the heart of Locusta

Transmitter (M)	The effect of the transmitters on AP (control)	Antagonist	Effect of transmitter after pretreatment of the heart with antagonists
Acetylcholine			
10^{-9}	inhibition	d-TC	ineffective or inhibition
	inhibition	atropine	ineffective or inhibition
	inhibition	nicotine	ineffective or inhibition
10^{-6}	excitation	atropine	inhibition
	excitation	mytolon	excitation
10^{-4}	excitation	d-TC	excitation, stopping
	excitation	atropine	ineffective, inhibition
	excitation	nicotine	excitation
	excitation	mytolon	excitation
5-hydroxytryptamine			
10^{-6}	excitation	BOL-148	inhibition (to stopping)
10^{-5}	excitation	BOL-148	inhibition (to stopping)
	excitation	methysergide	inhibition
	excitation	ergometrine	excitation, ineffective
GABA			
10^{-6}	inhibition	bicuculline	excitation, inhibition
	inhibition	picrotoxin	ineffective, slight inhibition
10^{-5}	inhibition	picrotoxin	inhibition
10^{-4}	inhibition	bicuculline	excitation

Note: The concentrations of antagonists: d-TC 10^{-5} M, atropine 10^{-6}—10^{-4} M, nicotine 10^{-9} M, 10^{-4} M; mytolon 10^{-6} M, 10^{-4} M; BOL-148 10^{-6} M, 10^{-5} M, methysergide 10^{-5} M, 10^{-4} M, ergometrine 10^{-5}, 10^{-4} M, bicuculline 10^{-8}, 10^{-5} M, picrotoxin 10^{-6}, 10^{-4} M

Discussion

We have shown that the antagonists of different receptors exert also an effect on the generation of the action potentials of insect hearts as on the contractile activity, although we have reported already on specific dependence, too (S.-Rózsa and V.-Szőke, 1970; S.-Rózsa, 1974). On other insect hearts the effect of the antagnoists of Ach have been described earlier, according to this nicotine caused excitation on the heart of several species (Jaeger and Gahan, 1937; Davenport, 1949; Naidu, 1955), while atropine and curare abolished the Ach effect (Hamilton, 1939; Metcalf et al., 1964; Jones, 1964). According to our earlier data regarding the contractile activity of *Locusta* heart, mytolon, nicotine and methysergide exerted biphasic effect (excitation, inhibition), while BOL-148 caused only inhibition (S.-Rózsa, 1974). The action potentials of the heart were affected with these pharmacons in a similar way exepting BOL-148 which also causes excitation *(Table I)*. The other pharmacons used here have not been studied, as far as contractile activity of the heart is concerned. The changes in the action potentials of *Locusta* heart showed the temporary character of the excitation arising during the first minutes of the application of pharmacons reversing soon to inhibition which often stopped potential generation. This latter phenomenon is connected with the adaptation and desensitization of receptors. The significant increase in the amplitude of the

action potentials was found only under the influence of antgonists of 5HT receptors *(Table I)*.

All the antagonists used, exept mytolon, abolished the effect of certain transmitters in different degrees or turned it to a response opposite in sign. In abolishing the generation of action potentials on *Locusta* heart among cholinergic antagonists atropine and nicotine, among the inhibitors of 5HT receptors BOL-148 and methysergide, while among GABA antagonists bicuculline were the most effective agents. The above correspond to the data obtained on the contractile activity of the heart exepting the efficiency of methysergide (S.-Rózsa, 1974). Our results emphasized the presence of similar structures in *Locusta* heart to the vertebrate receptors. The specificity of the receptors cannot be discussed here since the antagonists were tested only on one kind of receptors, when our earlier data showed the mixedtype of the sites of action of the transmitter in insect hearts (S.-Rózsa and V.-Szőke, 1970, S.-Rózsa, 1974).

Although systematic studies have not been carried out to prove the dependence of the effects of receptor antagonists on the age of the animals, still some decrease was found in the efficiency of these drug in older *Locusts*. Age-dependence in Ach and 5HT effects was not obvious in our earlier studies although it was ascertained by several authors (McFarlane, 1967; McFarlane and Ting-Ya Fong, 1971; Roussel, 1974). The changes in receptor sensitivity observed during the application of the pharmacons also directed attention to the importance of the age of th animals.

On the heart membrane of arthropods and especially insects only limited amount of data is available regarding the receptor properties. The effect of GABA was analyzed only on *Periplaneta* and *Porcellio* hearts being abolished by picrotoxin (Holley and Delaleu 1973; Miller, 1973; Richter, 1973). Although our present data added some further information to the sites of the action of transmitters on insect heart the exact localization may be found only on completely isolated hearts. On semi-isolated hearts both the tranmitter and pharmacons can act on the heart and nerve tissues alike, and the separation of the two sites involves some difficulties.

Summary

The effect of receptor antagonists of Ach, 5HT and GABA were studied on the membrane of the heart muscle cells of *Locusta* and their interactions with the transmitters. The used antagonists of cholinergic (d-tubocurarine, atropine, nicotine), serotoninergic (BOL-148, methysergide, ergometrine) and GABA-ergic (picrotoxine, bicuculline) receptors had effect on the membrane of *Locusta* heart. In the majority of the cases the initial excitatory or inhibitory effects turned to opposite in sign at the 5th minute of the application. Among cholinergic antagonists d-tubocurarine, atropine and nicotine abolished both the excitatory and inhibitory effects of Ach partially or completely, while mytolon was ineffective. Among the inhibitors of 5 HT receptors BOL-148 and methysergide eliminated the excitatory effect of 5HT moreover, BOL-148 turned it to inhibition but the ergometrine only partially blocked 5HT effect. Picrotoxin abolished the effect of low concentrations of GABA, however, the effect of high concentrations of GABA (10^{-4} M) was antagonized only by bicuculline.

According to these results the receptors of the heart membrane of *Locusta* may be characterized with the same phycological properties as known for vertebrates, so that they may be regarded similar to each other.

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TRANSMITTEREK RECEPTORAINAK FARMAKOLÓGIAI TULAJDONSÁGAI *LOCUSTA MIGRATORIA MIGRATORIOIDES* R. F. (INSECTA) SZIVÉNEK MEMBRÁNJÁN

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Összefoglalás

Vizsgálták kolinerg, serotoninerg és GABA-erg receptor bénítók hatását *Locusta* szívizomsejtjeinek membránján és azok kölcsönhatását transzmitterekkel. Megállapították, hogy a kolinerg (d-tubocurarine, atropine nicotine), serotoninerg (BOL-148, methysergide, ergometrine) és GABA-erg (picrotoxine, bicuculline) bénítók *Locusta* szív membránján saját hatással is rendelkeznek. Az esetek többségében a kezdeti serkentő vagy gátló hatás ellenkező előjelűvé válik a kezelés 5. perce körül. Kolinerg bénítók közül a d-tubocurarine, atropine és nicotine különböző mértékben antagonizálják az acetylcholine gátló és sekentő hatását, a mytolon hatástalan. A serotoninerg blokkolók közül a BOL-148 és methysergide az 5HT serkentő hatását megszüntetik, a BOL-148 gátlóvá alakítja azt, míg az ergometrin részleges 5HT-hatás kivédést eredményez. A picrotoxin GABA hatását alacsony koncentrációk alkalmazásakor kivédi, de magasabb (10^{-4}M) BAGA koncentrációk hatását csak a bicuculline antagonizálja.

Az eredmények szerint rovar szívek membránján a receptorok farmakológiai blokkolása magasabbrendűeken ismert bénítókkal valósítható meg, így azokkal azonos tulajdonságúaknak tekinthetők.