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ANTAGONISM BY SOME ANTIHISTAMINES OF THE AMINO ACID-EVOKED RESPONSES RECORDED FROM THE LOBSTER MUSCLE FIBRE AND THE FROG SPINAL CORD

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1 The effects of some antihistamines on the lobster muscle fibre and the frog spinal cord were investigated using intracellular and extracellular recordings, respectively.

2 On lobster muscle, histamine H_1-blockers reversibly antagonized responses to bath-applied glutamate, aspartate and quisqualate but not responses to γ-aminobutyric acid (GABA). Iontophoretic glutamate potentials were also reduced. Histamine (up to 1 mM) had no effect on this preparation.

3 The H_1-antagonists produced a small increase in muscle membrane conductance and a slight hyperpolarization. These effects were largely unchanged in a low Cl^- bathing solution. Procaine (1 mM) decreased membrane conductance and did not affect responses to GABA or glutamate.

4 The H_2-antagonist burimamide blocked both glutamate and GABA-evoked responses on the lobster muscle without affecting resting potential or conductance.

5 In the frog cord, bath-applied histamine produced ventral root depolarizations and dorsal root hyperpolarizations (sometimes biphasic responses). These effects were reduced by tetrodotoxin (TTX) but not by antazoline (H_1-blocker) or burimamide; the latter reversibly antagonized responses to both glutamate and GABA on TTX-treated cords while antazoline was ineffective.

6 It is suggested that antihistamines can act as non-specific amino acid antagonists by interacting at the level of the receptor-coupled ionophores.

Introduction

Histamine is a putative neurotransmitter in some areas of the mammalian brain (Green, 1970; Snyder & Taylor, 1972; Schwartz, 1975; Calcutt, 1976). Microiontophoretically applied histamine depresses the firing of feline brain and spinal neurones (Krnjević & Phillis, 1963; Phillis, Tebēcis & York, 1968a,b; Haas, Anders & Hosli, 1973); however, these effects are often non-specifically antagonized by histamine H_1- and H_2-receptor blockers (Phillis *et al.*, 1968a; Haas & Bucher, 1975; Haas, Wolf & Nussbaumer, 1975). This non-specificity has been tentatively attributed either to a blockade of axonal conduction (i.e. a local anaesthetic effect; Reuse, 1948; Phillis *et al.*, 1968a) or to a direct 'non-selective' action on the neuronal membrane (Haas, 1974); furthermore the ability of the antihistamines to block receptors other than the histamine receptor is well known (Goodman & Gilman, 1975).

In order to obtain more direct information on the non-specific membrane actions of the antihistamine drugs, we carried out a comparative study on two *in vitro* preparations, the lobster muscle fibre and the tetrodotoxin (TTX)-treated isolated spinal cord of the frog. The invertebrate tissue allowed a study of antihistamine action on resting membrane conductance using intracellular recordings; the experiments on the TTX-treated frog cord enabled the effect of antihistamines on responses to histamine to be investigated without possible interference from the local anaesthetic action of these compounds. Since L-glutamate and γ-aminobutyric acid (GABA) are putative neurotransmitters in both tissues

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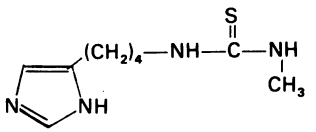
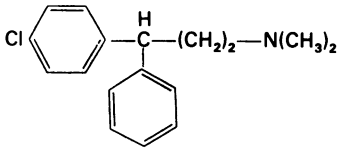
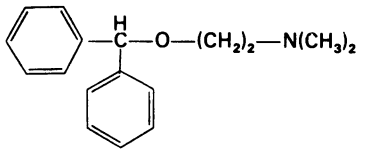
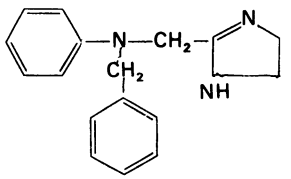
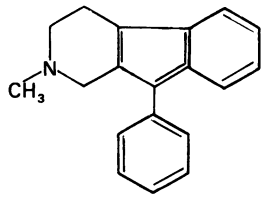
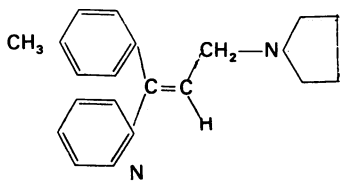
Table 1 Comparison of the potency of some antihistamines in antagonizing the depolarizing action of glutamate and in increasing the resting membrane conductance of lobster muscle fibre

Drug	*Chemical formula*	*Concentration (μM)*	*% Block of 100 μM glutamate response*	*% Increase in membrane conductance*
Burimamide		40	0	0
		100	7	*0*
Chlorpheniramine		40	19	*0*
		100	36	*5*
Diphenhydramine		40	38	*2*
		100	48	*4*
Antazoline		40	41	*0*
		100	85	*2*
Phenindamine		40	58	*7*
Triprolidine		40	71	*5*

(Gerschenfeld, 1973; Barker, Nicoll & Padjen, 1975; Onodera & Takeuchi, 1975; Nicoll, Padjen & Barker, 1976) a quantitative assessment of the action of antihistamines on two different populations of amino acid receptors was also possible.

Our results suggest that antihistamines can increase the resting membrane conductance and act as non-specific amino acid antagonists possibly by interacting at the level of the receptor-coupled ionophores.

Methods

Full details regarding the set-up of the lobster muscle and frog spinal cord preparations have recently been given (Constanti & Nistri, 1976a); therefore, only relevant descriptions of the methods will be presented here.

Lobster muscle fibre

The opener muscle of the first or second walking leg was superfused continuously with lobster saline solution of the following composition (mM): NaCl 522, KCl 12, $CaCl_2$ 21, $MgCl_2\,6H_2O$ 5, and Tris maleate 10, adjusted to pH 7.6 with 0.1 N NaOH. The membrane conductance of single superficial muscle fibres was measured by the method of Takeuchi & Takeuchi (1967) using three intracellular glass microelectrodes; one microelectrode filled with 0.6 M K_2SO_4 was inserted at the centre of the fibre in order to pass hyperpolarizing current pulses (0.25 Hz; 800 ms); the other two microelectrodes filled with 1.5 M K-citrate were inserted at the centre and at the end of the fibre, respectively, in order to record the resulting electrotonic potentials. GABA-evoked conductance changes (expressed as $\Delta g_m L$, where g_m is the conductance per unit length and L the half-length of the fibre) were calculated with respect to the resting conductance measured immediately before the application of GABA. To allow pooling of data from different fibres, the GABA responses in each experiment were normalized with respect to the 40 μM response. Membrane depolarizations evoked by bath-applied glutamate (expressed as ΔV; mV) were recorded at the centre of the muscle fibre. The current/voltage relation of the lobster fibre membrane under the present conditions was sufficiently linear in both depolarizing and hyperpolarizing directions (for potential changes $\leqslant 20$ mV) to allow depolarization responses to be taken as a quantitative measure of glutamate-receptor activation. Iontophoretic glutamate potentials were obtained by applying glutamate to single sensitive spots on the fibre membrane. Negative current pulses were passed through a microelectrode filled with 1 M L-Na glutamate (pH = 8 with NaOH; Takeuchi & Takeuchi, 1964). The retaining current was +20 nA. Iontophoretic potentials were recorded by an intracellular electrode placed about 500 μm away from the sensitive spot and photographed from the oscilloscope screen with a Polaroid camera.

Frog spinal cord

The spinal cord was hemisected and placed in a small bath containing a salt solution of the following composition (mM) NaCl 109, KCl 4, $CaCl_2$ 1.5, $NaHCO_3$ 1.27, and glucose 4, pH 7.2 gassed with 95% O_2 and 5% CO_2 and maintained at 13°C. Freshly prepared solutions of the substances to be tested were applied via the bathing medium. Recordings were made with extracellular Ag/AgCl electrodes (resistance 5–10 KΩ) from the VIIIth or IXth pairs of roots gently pulled into paraffin-filled side-chambers. Two types of potential were recorded: the ventral root potential (D-VRP) evoked by orthodromic stimulation of the adjacent dorsal root and the dorsal root potential (V-DRP) evoked by antidromic stimulation of the adjacent ventral root. Root potentials were displayed on a storage oscilloscope and a chart recorder.

Drugs

The following H_1-receptor antagonists were used: diphenhydramine hydrochloride (Parke-Davis), antazoline hydrochloride (Ciba Labs), chlorpheniramine maleate (Allen & Hanbury), phenindamine tartrate (Roche) and triprolidine hydrochloride (Wellcome). Burimamide was used as an H_2-antagonist (Black, Duncan, Durant, Ganellin & Parsons, 1972). All other substances were of reagent grade. All drug solutions were adjusted to the pH of the physiological solutions.

Results

Lobster muscle fibre

Effect of antihistamine drugs on bath-applied glutamate responses All the antihistamine compounds tested (concentration range 40 μM to 1 mM) reversibly depressed the depolarizations produced by bath-applied glutamate. The relative potencies were assessed by measuring the % reduction of the response to 0.1 mM glutamate applied for 2 minutes. This dose gave closely reproducible responses with little desensitization and a minimal tendency to evoke a contraction of the fibre (see Constanti & Nistri, 1976b). The results of an experiment in which 6 different antihistamines were tested on the same muscle fibre is shown in Table 1. Similar studies carried out on 5 other preparations

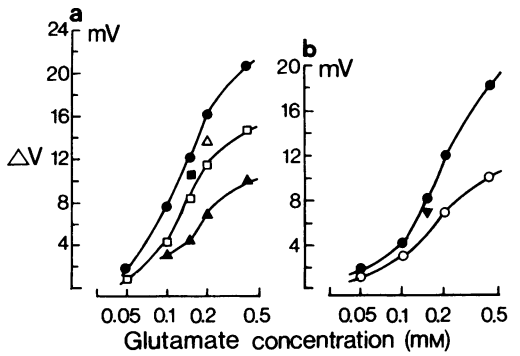


Figure 1 (a) Effect of antazoline on the dose-response curve to glutamate recorded from a single lobster muscle fibre: (●), glutamate-evoked membrane depolarization measured in control solution; (□), in 40 μM antazoline; (▲), in 100 μM antazoline. (■), and (△) represent recovery responses recorded 10 min after return from 40 μM and 100 μM antazoline respectively. (b) Effect of burimamide on the dose-response curve to glutamate (recorded from a different fibre from that in (a)). (●), Control glutamate curve measured in normal solution; (○), in 0.5 mM burimamide; (▼), recovery response recorded 10 min after return to normal solution. Ordinates represent depolarization (mV); abscissae give the concentration of glutamate added to the superfusing solution.

confirmed this order of activity. Triprolidine was the most potent antagonist of glutamate, and burimamide the least potent. Both H_1-blockers and burimamide also reduced the depolarizations evoked by L-aspartate (1 to 2 mM) or by quisqualic acid (1 to 6 μM), a powerful glutamate agonist (Shinozaki & Shibuya, 1974). However, the depolarizing responses produced by doubling the KCl content of the bathing solution were unaffected.

Histamine (1 mM) had no significant effect on membrane potential or conductance, nor did it antagonize the actions of bath-applied glutamate (0.1 mM) or GABA (40 μM) (cf. McGeer, McGeer & McLennan, 1961). This result contrasts with the action of the histamine metabolite, imidazoleacetic acid which increases lobster muscle membrane conductance (Constanti & Quilliam, 1974). The antihistamine drugs (up to 1 mM) also increased the resting membrane conductance (up to 10%; cf. Table 1 and Figure 4) often accompanied by a small membrane hyperpolarization. Triprolidine and phenindamine were particularly active in this respect although in comparison with GABA (10 μM) the effect of these compounds on the conductance was notably slow in onset and decline. At higher concentrations their effect on the conductance became irreversible. Burimamide was the exception in that it did not affect resting conductance or membrane potential even at a concentration of 2 mM. The glutamate-inhibitory action of the antihistamines was not merely due to their action on the membrane conductance since such a change of conductance was insufficient to account for the total reduction in glutamate responses. Moreover, there appeared to be no relation between the ability of a compound to antagonize glutamate and its ability to increase the resting conductance (Table 1). Of the present series, antazoline combined a high glutamate inhibitory action with a low effect on the conductance; this compound was thus selected for further study.

Figure 1a shows the effect of antazoline on the glutamate dose-response curve recorded in a single lobster muscle fibre. With a progressive increase in antazoline concentration there was a slight lateral shift of the curve to the right accompanied by a depression of the apparent maximum in a seemingly non-competitive manner. Recovery of the glutamate-evoked responses was obtained within 15 min of a return to the normal solution. A reversible depression of the glutamate dose-response curve was also seen in the presence of the weaker antagonist burimamide (Figure 1b).

At the frog neuromuscular junction the local anaesthetic compound, procaine, depresses the response of the end-plate to acetylcholine by a postsynaptic blocking mechanism (Katz & Miledi, 1975). As the antihistamine drugs are also known to possess local anaesthetic activity (Reuse, 1948) it was of interest to test whether the observed antagonism of the effects of glutamate by antihistamines on lobster muscle could be mimicked by procaine. In the presence of this compound (1 mM) there was no significant inhibition of glutamate-evoked responses and the resting membrane conductance was decreased by up to 5% (see also Fatt & Katz, 1953).

Effect on iontophoretic glutamate potential When the glutamate-filled microelectrode was placed over a sensitive spot on the fibre membrane and a 20 ms negative current pulse passed through it (pulse frequency 0.1 Hz to avoid desensitization), a brief depolarization (i.e. the iontophoretic glutamate potential) was recorded by the nearby intracellular electrode (Figure 2a). The amplitude and the time-course of this potential were comparable to those described by Takeuchi & Takeuchi (1964) and Onodera & Takeuchi (1975) in crayfish muscle, although the latter preparation is known to be more sensitive to iontophoretically applied glutamate (Ozeki, Freeman & Grundfest, 1966). After the bath solution had been changed to one containing 0.1 mM antazoline, the amplitude of the glutamate potential was markedly reduced (Figure 2b). This effect was fully reversible upon return to a normal solution (Figure 2c) indicating that the glutamate-containing electrode had not been displaced during the

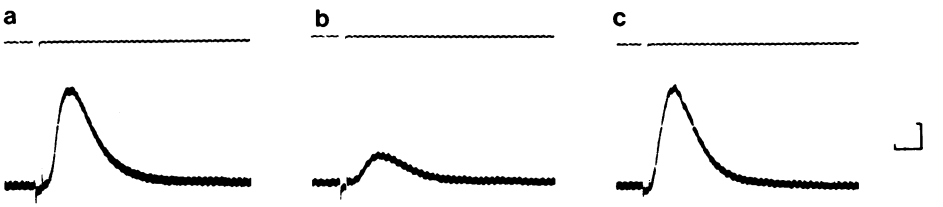


Figure 2 Effect of antazoline (100 μM) on the glutamate-evoked potential (lower beam) produced by the iontophoretic application of glutamate to a single sensitive site on the lobster fibre membrane. Upper beam shows the monitored glutamate ejection current. (a), Control glutamate-potential recorded in normal solution; (b) 2 min after changing to solution containing 100 μM antazoline; (c), recovery potential recorded 10 min after return to normal solution (superfusion system was operating throughout the experiment). Calibration: 2×10^{-7}A (upper beam), 0.5 mV (lower beam); 100 milliseconds.

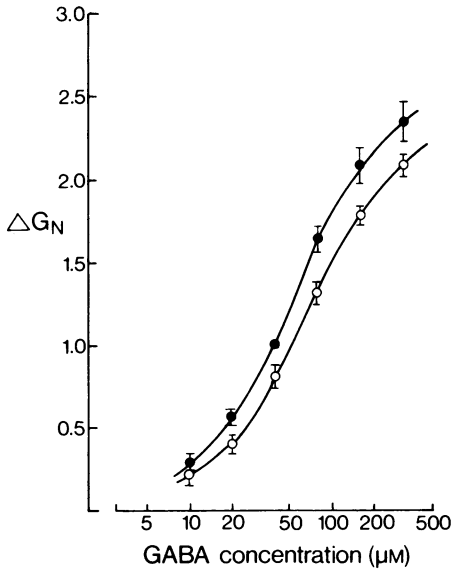


Figure 3 Effect of burimamide on the normalized γ-aminobutyric acid (GABA) log dose-conductance curve. (●), GABA-evoked increase in the membrane conductance of a lobster muscle fibre measured in normal solution; (○), in 1 mM burimamide. Ordinate scale represents normalized conductance increase (ΔG_N); abscissa scale gives the concentration of GABA added to the superfusing solution. ΔG_N was calculated with respect to the 40 μM response. Points represent mean of 3 measurements made on different fibres. Vertical lines show s.e. mean.

experiment. The resting conductance and resting potential were not affected by 0.1 mM antazoline in this preparation.

Effect on GABA dose-conductance curve All the H_1-receptor blocking drugs (up to 1 mM) failed to modify the GABA dose-conductance curve. However, burimamide (0.5 to 2 mM) showed a weak antagonistic effect towards GABA. Figure 3 shows the normalized log dose-conductance curve for GABA in control solution and in the presence of 1 mM burimamide. There was a slight shift of the curve to the right along the abscissa scale which was fully reversed upon returning to control solution. A similar shift of the dose-conductance curve for imidazoleacetic acid (Constanti & Quilliam, 1974) was also observed in the presence of burimamide (not shown).

Effect of Cl^- removal on the antihistamine-evoked conductance increase The GABA-evoked conductance change in crustacean muscle is known to be Cl^--mediated (Boistel & Fatt, 1958). In order to examine whether the antihistamine-induced conductance increase also involved a Cl^- permeability change, some experiments were carried out in a low Cl^--bathing solution (586 mM Cl^- reduced to 64 mM by replacement with Na isethionate); the changeover was first made to an intermediate low Cl^--isethionate solution (586 mM Cl^- reduced to 325 mM) and then after 15 min to the lower Cl^--containing solution. In the experiment illustrated in Figure 4, GABA (10 μM) in control solution, produced a rapidly developing conductance change with little effect on resting potential (Figure 4a). However, antazoline (1 mM) evoked a slowly developing conductance increase accompanied by a small hyperpolarization of about 1 mV (Figure 4b). After 40 min in low Cl^- (64 mM) medium, GABA depolarized the membrane (Figure 4c) in accordance with the positive shift in Cl^- equilibrium potential; the hyperpolarization produced by antazoline was slightly increased (Figure 4d). Twenty min after return to a normal solution GABA hyperpolarized the membrane (suggesting some loss of intracellular Cl^- during low Cl^- exposure; Figure 4e) whereas the response to antazoline was similar to control (compare Figures 4b and f). Similar results were obtained with high concentrations of the other H_1-antihistamine drugs. These findings suggest that the antihistamine-induced conductance increase was not dependent upon Cl^- and was therefore unlikely to involve an interaction with GABA receptors. The latter conclusion was supported by the finding that in

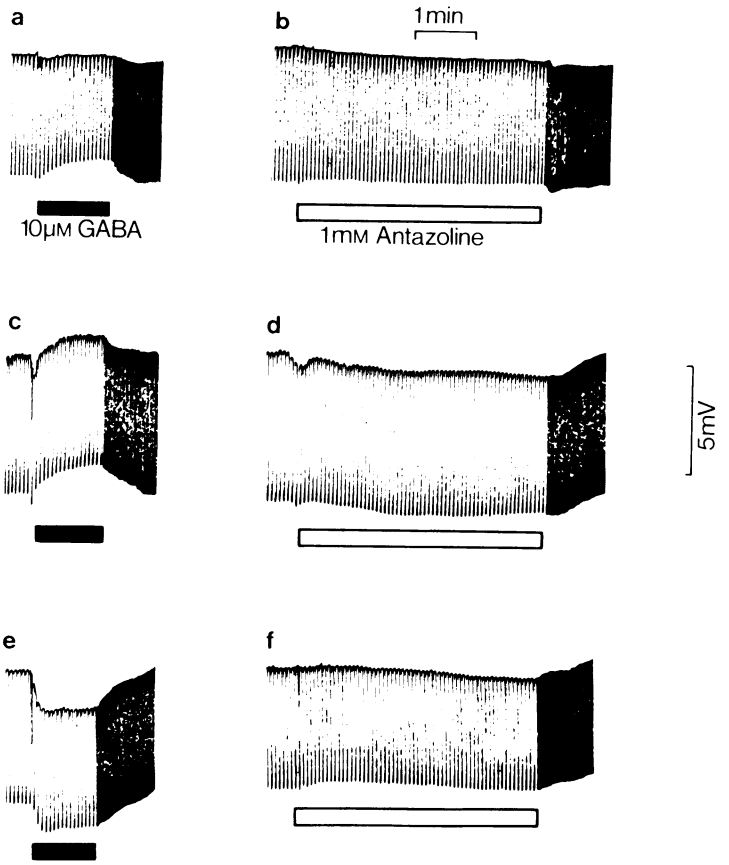


Figure 4 Effect on the membrane potential and conductance changes produced by γ-aminobutyric acid (GABA, 10 μM, filled bars) and antazoline (1 mM, open bars) on changing from a normal external solution (586 mM Cl^-) to a low- Cl^- (64 mM) solution (Cl^- replaced with isethionate- see text). Records show hyperpolarizing electrotonic potentials (downward deflections) recorded at the centre of a single lobster fibre in response to centrally applied intracellular current pulses (0.25 Hz; 800 ms; 1.5×10^{-7}A). (a) and (b) Control responses to GABA and antazoline, respectively, measured in normal solution. Note the slow onset/decline of action of antazoline and the accompanying small hyperpolarization (chart-speed was reduced by 1/3 during decline of responses); (c) and (d) 40 and 45 min respectively after changing to a low-Cl^- solution. GABA now depolarized the membrane whereas antazoline produced a slightly larger hyperpolarization relative to control (b); (e) and (f) 20 and 25 min, respectively, after returning to a normal bathing solution. GABA now hyperpolarized the membrane, whereas the antazoline response was similar to control (b).

the presence of picrotoxin, a potent GABA receptor antagonist (1 μM; see Constanti & Quilliam, 1974; Nistri, Constanti & Quilliam, 1974), the antihistamine-induced conductance change was unaffected.

Frog spinal cord

Effects of histamine on root potentials Histamine (3 mM) produced a slowly developing depolarization (0.5 to 0.7 mV) of the ventral root (onset 30 to 45 s after bath application) associated with an initial increase and subsequent decrease of the D-VRPs (Figure 5a-c); recovery was obtained after 20 min washing (Figure 5d). Histamine (3 mM) also slightly hyperpolarized the dorsal root (0.2 to 0.4 mV) and increased the V-DRPs (Figure 5f); this effect also had a slow onset and was reversed only after prolonged washing (Figure 5g). Occasionally, histamine produced biphasic responses (hyperpolarizations followed by depolarizations) of the dorsal roots. A noticeable property of the action of histamine on spinal root potentials was the tachyphylaxis which appeared after 3 or 4 applications of this substance.

In order to eliminate indirect actions of histamine due to propagated interneuronal activity, the spinal

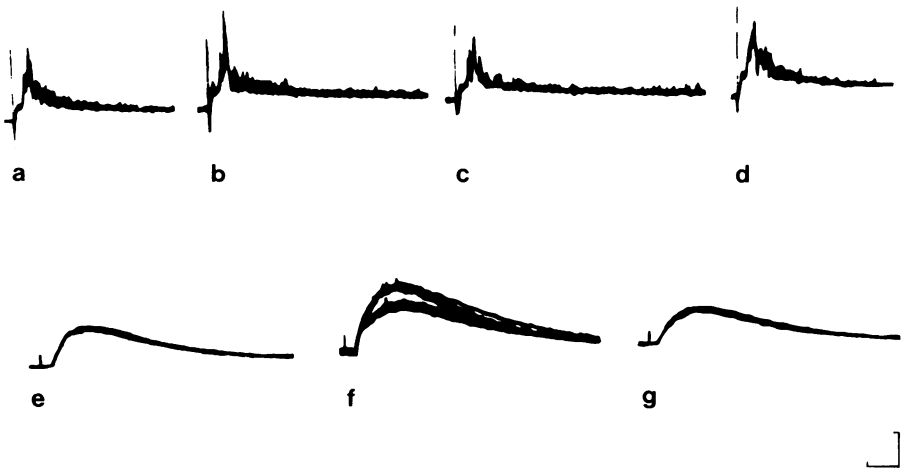


Figure 5 Effects of histamine on D-VRPs and V-DRPs of the frog spinal cord. Stimulation parameters for all the recordings (3 superimposed traces) were: 1 Hz; 0.1 ms; supramaximal voltage. Calibration bars: 0.5 mV (negativity upwards); 20 milliseconds. (a), control D-VRPs; (b) and (c) 50 s and 60 s, respectively, after the application of histamine (3 mM); (d), recovery after 20 min washing; (e), control V-DRPs; (f), 2 min after applying histamine (3 mM), note the increased size of the V-DRPs; (g), recovery after 22 min washing.

cord was bathed with TTX (3.1 μM; see also Evans & Watkins, 1975). In the presence of TTX, D-VRPs and V-DRPs were abolished; the drug-induced responses were thus seen as changes in the d.c. level of root polarization and represented the electrotonic spreading of the potential changes of motoneurones (for ventral root recordings) or of primary afferent terminals (for dorsal root recordings). In the presence of TTX, histamine-induced responses had the same polarity as those before the application of the toxin but were reduced in size by 50 to 60%. Antazoline (0.1 mM for 30 min), burimamide (0.5 mM for 30 min) or picrotoxin (10 μM for 30 min) did not affect these dorsal or ventral root responses to histamine, irrespective of whether TTX was present. Features of the action of histamine on the cord were, therefore: a slow onset and decline rate, tachyphylaxis, weak indirect actions mainly via interneurones and insensitivity to H_1- or H_2-blockers.

Effects of antazoline and burimamide on glutamate-evoked ventral root responses In the presence of TTX, dose-depolarization curves for glutamate, a putative excitatory transmitter of the afferents to motoneurone somata, were obtained by recording from a lumbar ventral root (cf. Constanti & Nistri, 1976b). Figure 6a shows that antazoline (0.1 mM for 30 min) had little effect on the glutamate dose-depolarization curve. Owing to the tissue desensitization following high doses of glutamate (Constanti & Nistri, 1976b), the small increase in the level of the apparent glutamate maximum in the presence of antazoline could not be reliably interpreted.

In contrast, burimamide (0.5 mM) produced a lateral shift of the glutamate curve and a reduction of the apparent maximum (Figure 6b). All these effects were reversible after washing (40–60 minutes).

Effects of antazoline and burimamide on GABA-evoked dorsal root responses In the presence of TTX, antazoline (0.1 mM for 30 min) did not affect the dose-depolarization curve for GABA (the putative transmitter released onto the primary afferent terminals; Barker *et al.*, 1975). However, burimamide (0.5 mM) reduced the GABA maximum and produced a lateral shift of the curve along the abscissa scale (Figure 7). Burimamide also depressed the dorsal root responses evoked by taurine (3 mM); thus, the blocking action of burimamide resembled that of picrotoxin on this preparation (Constanti & Nistri, 1976a; Nistri & Constanti, 1976).

Discussion

On lobster muscle, all the H_1-antagonists tested shifted the glutamate dose-depolarization curve in an apparently non-competitive manner but did not affect the GABA dose-conductance curve. These agents also produced a small increase in membrane conductance that was insensitive to picrotoxin and a membrane hyperpolarization relatively unaffected by a low Cl^- bathing solution. This effect was probably due to an increase in the passive ionic permeability of the membrane, possibly to K^+. In contrast, the H_2-antagonist burimamide was a weak antagonist of both

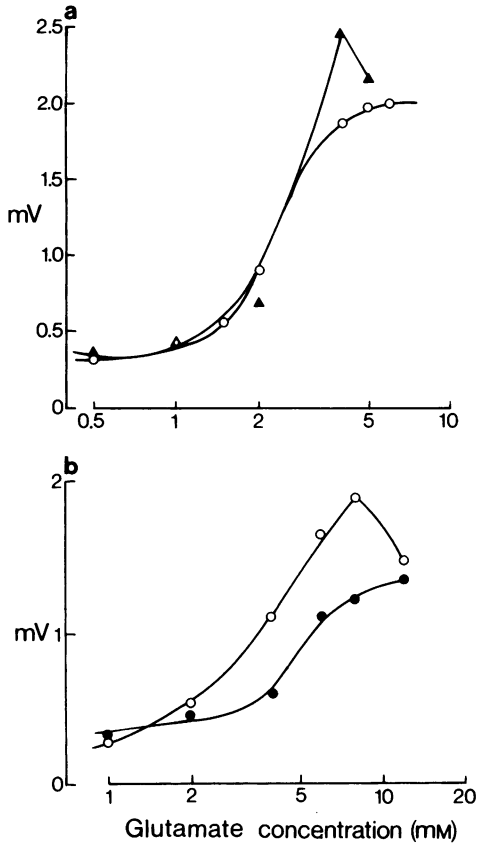


Figure 6 Effect of antihistamines on the glutamate dose-depolarization curve recorded from the frog spinal cord. Ventral root recordings in the presence of tetrodotoxin (TTX, 3.1 μM). (a) (O) Control glutamate curve; (▲), in the presence of antazoline (100 μM); (b) (O), control glutamate curve; (●), in the presence of burimamide (500 μM). Note that (a) and (b) were obtained from two different cords.

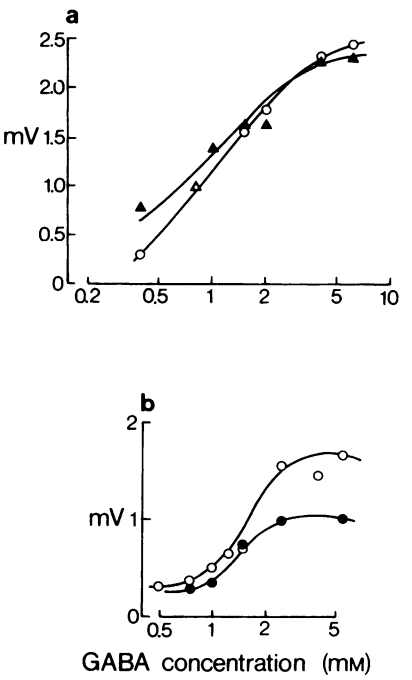


Figure 7 Effect of antihistamines on the γ-aminobutyric acid (GABA) dose-depolarization curve recorded from the frog spinal cord. Dorsal root recordings in the presence of tetrodotoxin (TTX, 3.1 μM). (a) (O), Control GABA curve; (▲), in the presence of antazoline (100 μM); (b) (O), Control GABA curve; (●), in the presence of burimamide (500 μM). Note that (a) and (b) were obtained from two different cords.

glutamate and GABA responses and did not affect the resting conductance. We cannot consider H_1-blockers as specific glutamate antagonists on lobster muscle since the effect of aspartate was also reduced; moreover, the lack of selectivity of burimamide towards glutamate and GABA responses indicated that this compound was a non-selective amino acid antagonist on this preparation.

On the frog spinal cord, histamine produced small and variable changes in the root potentials. The characteristic features for the action of histamine were: a slow onset and decline in rate of action compared to glutamate and GABA (see Constanti & Nistri, 1976a,b) and the occurrence of tachyphylaxis. Since the effects of histamine were mainly indirect and not antagonized by antazoline or burimamide it seemed unlikely that histamine had an important role in the transmission processes investigated. In the presence of TTX, a very potent local anaesthetic agent, antazoline (the most powerful glutamate antagonist on lobster muscle with a minimal effect on resting conductance) did not significantly affect the glutamate or GABA dose-depolarization curves whereas burimamide depressed both curves in a seemingly non-competitive manner.

It is possible that the H_1-antagonists on lobster muscle and burimamide on the frog spinal cord were interfering with amino acid responses by interacting with receptor-coupled ionophores (or with the coupling mechanism between receptor and ionophore); however, an additional small action on glutamate receptor binding sites cannot be excluded. The effect of these antihistamine agents on the receptor-coupled ionophores would explain the apparent non-competitive depression of the glutamate and GABA dose-response curve. Since glutamate and GABA responses on crustacean muscle are largely mediated by Na^+ and Cl^- respectively (Takeuchi & Takeuchi, 1967; Onodera & Takeuchi, 1975;

Constanti & Nistri, 1976b), the H_1-antagonists might block glutamate-activated Na^+ channels in the lobster muscle membrane, while burimamide might be a weaker and rather non-selective channel-blocking compound. A similar proposal was made by Barker & Gainer (1973) and Barker (1975a,b) to explain the action of pentobarbitone on lobster and crayfish muscles. Like the H_1-antihistamines on lobster muscle, pentobarbitone depressed the glutamate dose-depolarization curve in a seemingly non-competitive manner without effect on GABA responses. Barker (1975a) suggested that inhibition of the glutamate responses was dependent on the hydrophobic nature of the barbiturate molecule rather than on some steric factor. A similar proposal may be applicable to the antihistamines; however, the exact mechanism by which all these agents produce their effect has yet to be determined.

Blockade of receptor-coupled Na^+ conductance would also explain the action of burimamide on the frog spinal cord where the effects of glutamate and GABA seem to involve in part an increase in membrane Na^+ permeability (Barker & Nicoll, 1973; Constanti & Nistri, 1976a,b). The failure of antazoline (0.1 mM) to antagonize glutamate responses in the frog cord compared with the result of the experiments with lobster muscle remains unclear. Perhaps the glutamate-activated Na^+ channels of amphibian motoneurones are different in nature from those of the lobster muscle.

In view of the present findings, care must be exercised in the use of H_1-receptor blockers to study effects of histamine in the central nervous system. The antagonistic actions of these compounds towards amino acid-evoked responses and their ability to increase resting membrane conductance should be taken into consideration.

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