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COMPARATIVE ANALYSIS OF EFFECTS OF IMIDAZOLINE DRUGS ON ISOLATED RAT HEART ATRIA

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Effects of cumulative concentrations of 16 known imidazoline and 2 imidazole drugs on amplitude and rate of spontaneously beating isolated rat heart atria were measured and related to the respective effects induced by norepinephrine. In addition, the effects of fixed concentrations of the agents on the responses evoked by cumulative concentrations of norepinephrine were determined. In general, imidazolines classified as α_1-adrenoceptor agonist showed positive inotropic activity providing evidence for involvement of the α_1-adrenoceptor in mediating cardiac contractility. Negative chronotropic effect was common for the imidazolines studied, including α_1-adrenoceptor agonists, α_2-adrenoceptor agonists, α_1/α_2-adrenoceptor antagonists and antazoline — an antihistaminergic imidazoline devoid of adrenoceptor affinity. On the other hand, the imidazole derivative, medetomidine, showed a weak positive chronotropic activity. Negative chronotropic properties appeared to be independent of the alpha-adrenoceptors and may result from the membrane stabilizing action, involving probably the sodium channel blockade.

K e y w o r d s: *Heart atria; Imidazolines; Alpha-adrenoceptors; Inotropic effect; Chronotropic effect; Membrane stabilizing agents.*

INTRODUCTION

The main sites of action of imidazoline drugs are probably located in brain and in peripheral vasculature. Recently, attention has been payed to the action of imidazolines on heart. However, no systematic comparative studies were reported regarding the activity of a representative set of imidazoline drugs towards heart preparations. On the other hand, single individual imidazolines are reported to elicit pronounced pharmacological effects mediated through cardiac receptors. Having the above in mind we designed an experiment in which the effects of 18 known azole drugs (16 imidazolines plus two imidazoles) would be compared.

Modification of beating rate and amplitude of isolated heart atria can be easily obtained by means of the β-adrenoceptor stimulating agents. Imidazoline drugs are commonly assumed to be devoid of any significant activity at the β-adrenoceptors (1). That chemical group of bioactive substances interacts strongly with adrenergic receptors of the α type. It has been suggested that stimulation of myocardial α-adrenergic receptors provides an input to the positive inotropic effect of sympathomimetic agents (2).

Selective radioligand binding studies demonstrated that the α-receptors of rat heart are predominantly of the α_1-subtype (3). The α_1-adrenoceptors identified in the perfused rat heart were reported to differ from those of isolated sarcolemma preparations but the difference may by explained as resulting from alterations occuring during the sarcolemma isolation (4). Studies employing selective blockers of α_1- and α_2-adrenoceptors proved the involvement of α_1-adrenoceptors in inotropic reaction of rat heart whereas the α_2-adrenoceptors were inactive with that respect (5, 6).

Supporting the hypothesis that α_2-adrenoceptors are of little importance, if any, for inotropic effects of imidazolines are the reports (7) on weak, positive inotropic activity of lofexidine and clonidine towards isolated guinea pig atria, and on the lack of any significant inotropic or chronotropic effects of medetomidine on spontaneously beating guinea pig atria (8). Based on the studies of the effect of a strong α_2-adrenoceptor imidazoline agonist, UK 14.304 on the heart of dogs it was concluded that there were no canine myocardial postjunctional α_2-adrenoceptors (9). On the other hand, the positive inotropic effects of clonidine on isolated atria of mice have been interpreted as resulting from stimulation of α_2-adrenoceptors in that specific preparation (10).

As far as the chronotropic activity is concerned the existing evidence (11, 12) implies that α-adrenoceptor mediates chronotropic effects in the rat. According to Flavahan and McGrath (13) α_1-adrenoceptors can mediate increases in heart rate independently of changes in acetylcholine release. Presynaptic α_1-adrenoceptor was suggested by McDonough et al. (14) to reduce acetylcholine owerflow from perfused rat atria. Also Starke (15) reported that bradycardia from stimulation of the vagus nerves was diminished by the α-adrenoceptor agonists (oxymetazoline and naphazoline) in the Langendorff-perfused rabbit hearts. There are also repors that α_1-adrenoceptors can mediate negative chronotropic responses (16). According to Rosé Meyer et al. (17) activation of presynaptic α_2-adrenoceptors resulted in inhibition of positive chronotropic responses to the low frequencies of cardiac nerve traffic. On the other hand Gorelik et al. (10) postulated the decrease in beating rate of isolated atria of mice, after either methoxamine or clonidine, to be independent of α-adrenoceptors and suggested it to be due to a muscarinic and nicotinic cholinergic stimulation.

MATERIALS AND METHODS

Materials

The following imidazolines were used for studies: cirazoline hydrochloride (gift of Dr. I. Cavero, Synthèlabo, Paris, France), UK 14.304 tartrate (gift of Pfizer Central Research, Sandwich, England), detomidine hydrochloride and medetomidine hydrochloride (gift of Dr. A. Karjalainen, Farmos — Group Ltd, Oulu, Finland), tiamenidine hydrochloride (gift of Hoechst AG, Frankfurt, FRG), oxymetazoline hydrochloride (gift of Schering Corporation, Bloomfield, USA), lofexidine hydrochloride (gift of Dr. H. Betzing, A. Nattermann and Cie, GmbH, Cologne, FRG), phentolamine methanosulfate (Regitine, Ciba-Geigy Ltd, Basle, Switzerland), clonidine hydrochloride (Haemiton, Germed, Dresden, FRG), xylazine hydrochloride (Rometar, Spofa, Praha, Czecho-Slovakia), tramazoline (Dr. Karl Thomae GmbH, Biberach an der Riss, FRG), moxonidine hydrochloride, (gift of Dr. B.I. Armah, BDF Research Laboratories, Hamburg, FRG). The remaining substances: xylometazoline hydrochloride, tymazoline, hydrochlorie, naphazoline nitrate, antazoline hydrochloride, tetryzoline hydrochloride, tolazoline hydrochloride and norepinephrine hydrotartrate (Levonor) were obtained from Polfa, Warszawa, Poland. The substances were dissolved in distilled water and added to the organ bath in volumes of 0.1 ml of solution.

Methods

Male albino Wistar rats weighing 220—260 g were anaesthetized with urethane 1.5 g/kg administered i.p. The hearts were removed after 20 min. After a short, gentle massage the atria were dissected free and suspended in a 15 ml jacketed organ bath containing a modified Krebs solution of the folowing composition (mM): NaCl (120.4), $CaCl_2$ (2.5), KCl (4.9), $MgCl_2 \times 6H_2O$ (0.6), $NaH_2PO_4 \times H_2O$ (1.0), $NaHCO_3$ (15.3) and glucose (11.5). The solution in the bath (37°C) was continuosly oxygenated and kept at pH 7.4. The spontaneous beating of the atria was measured with an isometric transducer (PIM-41-01B, COTM, Białystok, Poland), exerting an initial tension of 0.5 g. The rate and force of atrial beating were recordered by a pen receorder (TZ 21S, Laboratorní Pristroje, Praha, Czecho-Slovakia). Beating rate was additionally measured by means of a frequency digital counter (KZ 2026A-2, Zopan, Warszawa, Poland) and expressed as a number of pulses per minute. Amplitude was determined as a mean of the contractions measured (mm) after each concentration of an agent. After equilibration period of 60 min (during which the bathing solution was repeatedly exchanged with fresh portions every 5 min) a cumulative concentration-response curves were constructed with regard to the inotropic and chronotropic effects of norepinephrine at concentration ranging from 10^{-9} to 10^{-5}M. After each series of norepinephrine concentrations the atria were washed with a fresh bathing solution and equilibrated to the pre-drug reactivity. Next, the cumulative concentration-response curves were obtained for increasing concentrations of the imidazolines, studied. In the third stage of the experiment, the inotropic and chronotropic responses to norepinephrine were measured at the presence of fixed concentrations of the imidazolines. Effects were calculated as percent of atrial rate or amplitude preceding the administration of an agent. The results (means of at last 6 experiments $\pm$ S.D.) are given in Tables I and II and displayed graphically in Figs. 1—6. Statistical significance was calculated using the paired Student's *t-test* with respect to the control values obtained in the absence of any drug. The unpaired Student's *t-test* was used to detect significant changes of maximum NE effect in the presence of an indicated concentration of an imidazoline.

RESULTS

Effects of the imidazolines studied on amplitude and rate of spontaneously beating isolated rat heart atria are presented in Tables 1 and 2. Exemplary, representative results are also presented graphically in Figures 1—6.

Inotropic activity

As evident from Table 1, the drugs classified as α-adrenoceptor stimulating agents (first 6 agents listed), and especially tymazoline, xylometazoline, and naphazoline, exert statistically significant positive inotropic effects on spontaneously beating rat heart atria. At concentrations from 7.5×10^{-10}M to 7.5×10^{-6}M xylometazoline gives a concentration-dependent (up to 10^{-4}M) positive inotropic effect, up to 56% with respect to the control. Neither tymazoline nor xylometazoline in concentrations of 7.5×10^{-8}M affect significantly the inotropic effects of norepinephrine. Some activity in that test is observed for cirazoline. The effects of oxymetazoline did not attain statistical significance (*Fig. 1*). Naphazoline, classified as an α_1-stimulating agent, resembles in activity cirazoline.

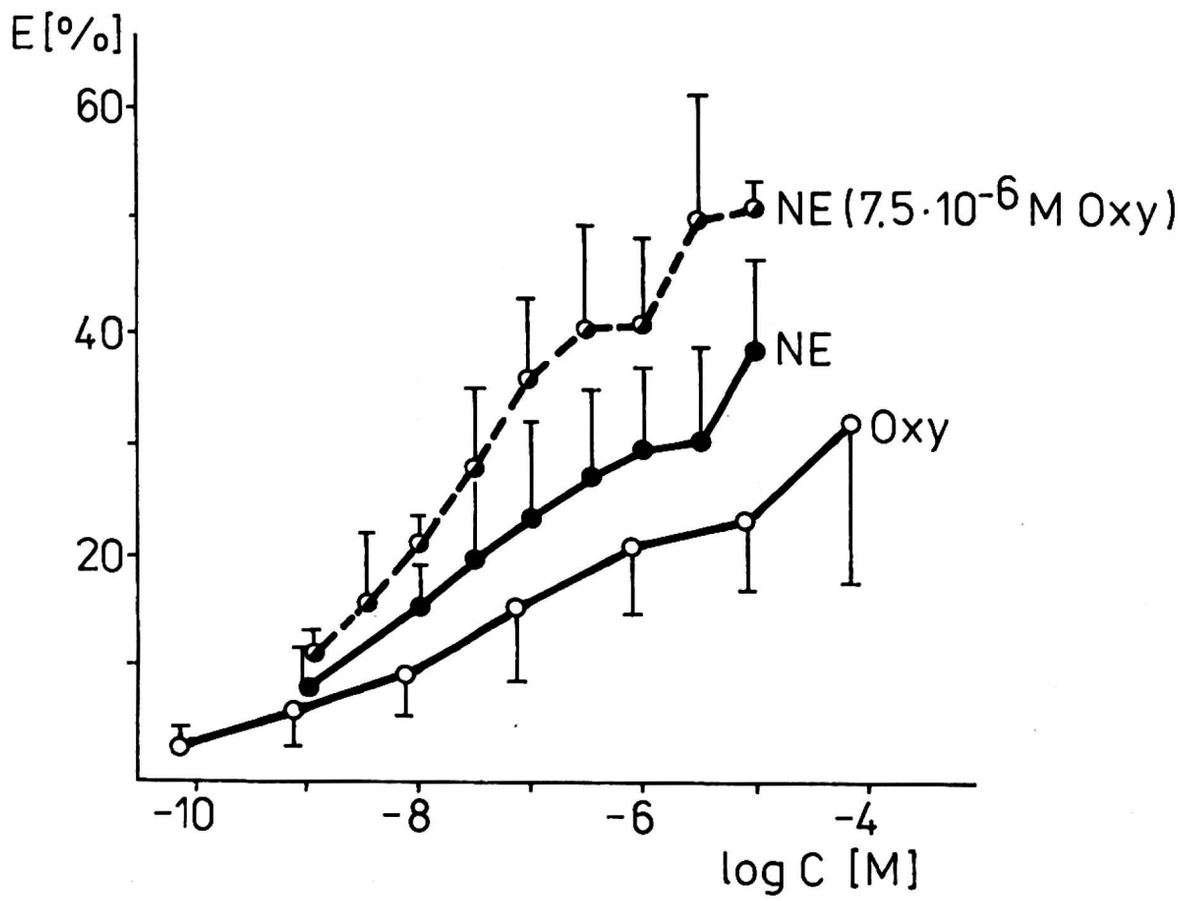

Fig. 1. Effect of norepinephrine (NE), oxymetazoline (Oxy) and norepinephrine in the presence of a fixed concentration of oxymetazoline on amplitude of isolated rat heart atria. Each point corresponds to mean ($n \geq 6$) values ±S.D.

A series of imidazoline derivatives classified as α_2-adrenoceptor agonists opens UK 14.304. The agent shows no statistically significant positive inotropic effect on atria. The inotropic effects evoked by cumulative concentrations of

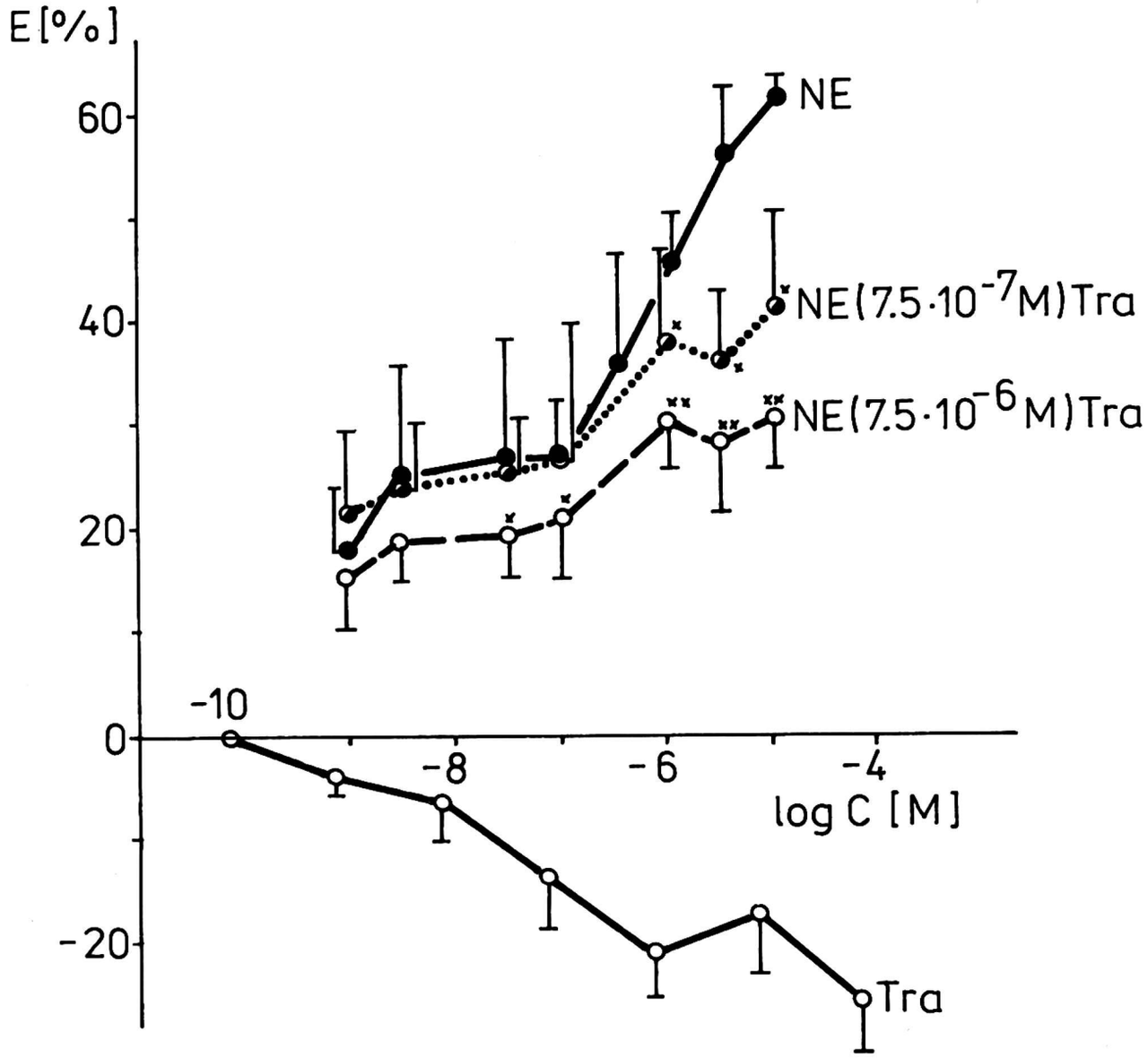

Fig. 2. Effect of norepinephrine (NE), tramazoline (Tra) and norepinephrine in the presence of fixed concentrations of tramazoline on amplitude of isolated rat heart atria. Each point corresponds to mean ($n \geqslant 6$) values $\pm$S.D. Asterisks indicate, * $p < 0.10$. ** $p < 0.05$ as determined by the *t-test*.

norepinephrine were not affected significantly by the presence of UK 14.304 at concentrations ranging from 7.5×10^{-8}M to 7.5×10^{-6}M. Similarly to UK 14.304, the two imidazoles medetomidine and detomidine have no significant inotropic activity.

The effect of xylazine, another α_2-adrenoceptor agonists, on amplitude of spontaneously beating rat heart atria appears somehow different from the effects of the compounds previously described. Xylazine elicits negative inotropic activity in concentration 7.5×10^{-6}M.

Tramazoline, classified (18) as a preferentially presynaptic α-adrenoceptor agonist, causes a stronger negative inotropic effect than xylazine and in concentration of 7.5×10^{-5}M markedly diminishes inotropic effects of norepinephrine (*Fig. 2*).

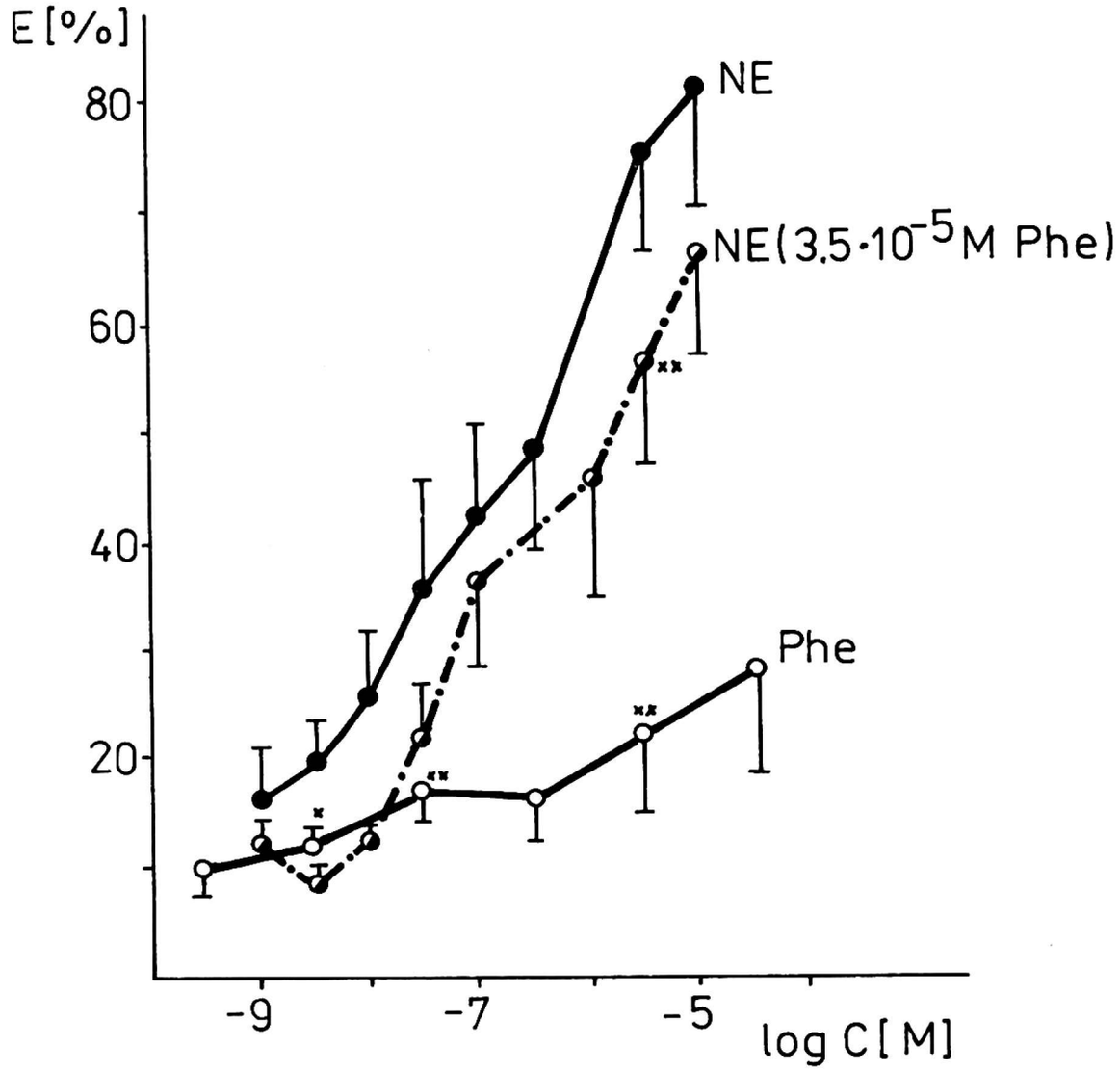

Fig. 3. Effect of norepinephrine (NE), phentolamine (Phe) and norepinephrine in the presence of fixed concentration of phentolamine on amplitude of isolated rat heart atria. Each point corresponds to mean ($n \geqslant 6$) values $\pm$S.D. Asterisks indicate, * $p<0.10$, ** $p<0.05$.

Moxonidine, new centrally acting α_2-adrenoceptor agonist has no effect on isolated, spontaneously beating rat atria, but in concentration of 7.5×10^{-6}M diminishes the response to the inotropic stimulation by norepinephrine.

The effect of clonidine on amplitude of spontaneously beating rat heart atria was ambigous. The effects of lofexidine did not attain statistical significance.

Tiamenidine, other α_2-adrenoceptor agonists at concentration 7.5×10^{-6}M has a more pronounced positive inotropic activity than the so far discussed α_2-adrenoceptor binding imidazolines. Still, however, this effect is weaker than those observed for the α_1-adrenoceptor stimulating imidazolines.

Phentolamine is an imidazoline derivative classified among the α_1/α_2-adrenoceptor antagonists (18). Its positive inotropic effect is lower than that of typical agonists of α_1-adrenoceptor (*Table 1, Fig. 3*).

Table 1. Effects of adrenergic drugs on amplitude of isolated heart rat atria

Drug	Percent change of control amplitude due to 7.5×10^{-6} M of drug	Maximum percent change of amplitude (concentration of the drug in M)	Percent change of maximum NE effect due to indicated concentration [M] of the drug
Tymazoline	$+50\pm14$**	$+56\pm6$ (7.5×10^{-5})	$+22$ (7.5×10^{-8})
Xylometazoline	$+44\pm26$**	$+57\pm16$ (7.5×10^{-4})	$+30$ (7.5×10^{-8})
Tetryzoline	$+43\pm3$	$+79\pm43$ (7.5×10^{-4})	$+31$ (7.5×10^{-7})
Oxymetazoline	$+23\pm3$	$+33\pm8$ (7.5×10^{-5})	$+12$ (7.5×10^{-6})
Cirazoline	$+34\pm11$	$+34\pm11$ (7.5×10^{-6})	$+20$ (7.5×10^{-6})*
Naphazoline	$+30\pm4$*	$+50\pm8$ (7.5×10^{-4})*	$+13$ (7.5×10^{-8})
UK 14.304	$+6\pm2$	$+8\pm6$ (7.5×10^{-4})	-14 (7.5×10^{-6})
Medetomidine	0 ± 0	$+5\pm2$ (7.5×10^{-5})	-13 (7.5×10^{-6})
Detomidine	$+5\pm1$	$+10\pm7$ (7.5×10^{-5})	-4 (7.5×10^{-6})
Xylazine	-9 ± 7	-16 ± 6 (7.5×10^{-5})*	-25 (7.5×10^{-6})
Tramazoline	-17 ± 2	-25 ± 2 (7.5×10^{-5})**	-31 (7.5×10^{-6})*
Moxonidine	-7 ± 2	-7 ± 2 (7.5×10^{-6})	-36 (7.5×10^{-6})**
Clonidine	$+3\pm2$	$+23\pm7$ (3.5×10^{-8})	$+15$ (3.5×10^{-6})
Lofexidine	$+23\pm14$	$+28\pm18$ (7.5×10^{-5})	$+14$ (7.5×10^{-6})
Tiamenidine	$+25\pm6$**	$+39\pm26$ (7.5×10^{-5})	$+6$ (7.5×10^{-6})
Phentolamine	$+22\pm18$	$+28\pm15$ (7.5×10^{-5})	-14 (7.5×10^{-5})
Tolazoline	-2 ± 4	$+83\pm22$ (7.5×10^{-4})*	$+15$ (7.5×10^{-8})
Antazoline	$+32\pm14$	$+35\pm17$ (7.5×10^{-5})	-28 (7.5×10^{-8})

All values were expressed as the mean ($n\geqslant6$) $\pm$ S.D. Significant differences from control as determined by the paired *t-test*: * $p<0.10$, ** $p<0.05$. Significant changes of maximum NE effect as determined by the unpaired *t-test:* * $p<0.10$, **$p<0.05$.

Another α-adrenoceptor antagonist, tolazoline, at concentrations higher than 10^{-8}M exceeds norepinephrine with respect to positive inotropic activity.

Antazoline is an antihistaminergic drug for which no activity towards adrenergic receptors was reported. Again, the positive inotropic activity of antazoline was below statistical significance level.

Chronotropic activity

As can be seen in Table 2 the negative chronotropic effect on isolated heart rat atria was demonstrated for four α_1-adrenoceptor agonist imidazolines: xylometazoline, oxymetazoline cirazoline and naphazoline. The concentrations of 7.5×10^{-6}M of oxymetazoline and cirazoline strongly decrease the positive chronotropic effects of norepinephrine (*Fig. 4*).

Cirazoline at concentration 7.5×10^{-6}M decreases the positive chronotropic effect of norepinephrine to the extent comparable to that observed for 7.5×10^{-6}M of naphazoline. When present at concentration 7.5×10^{-7}M cirazoline reverses the chronotropic effects of norepinephrine into negative.

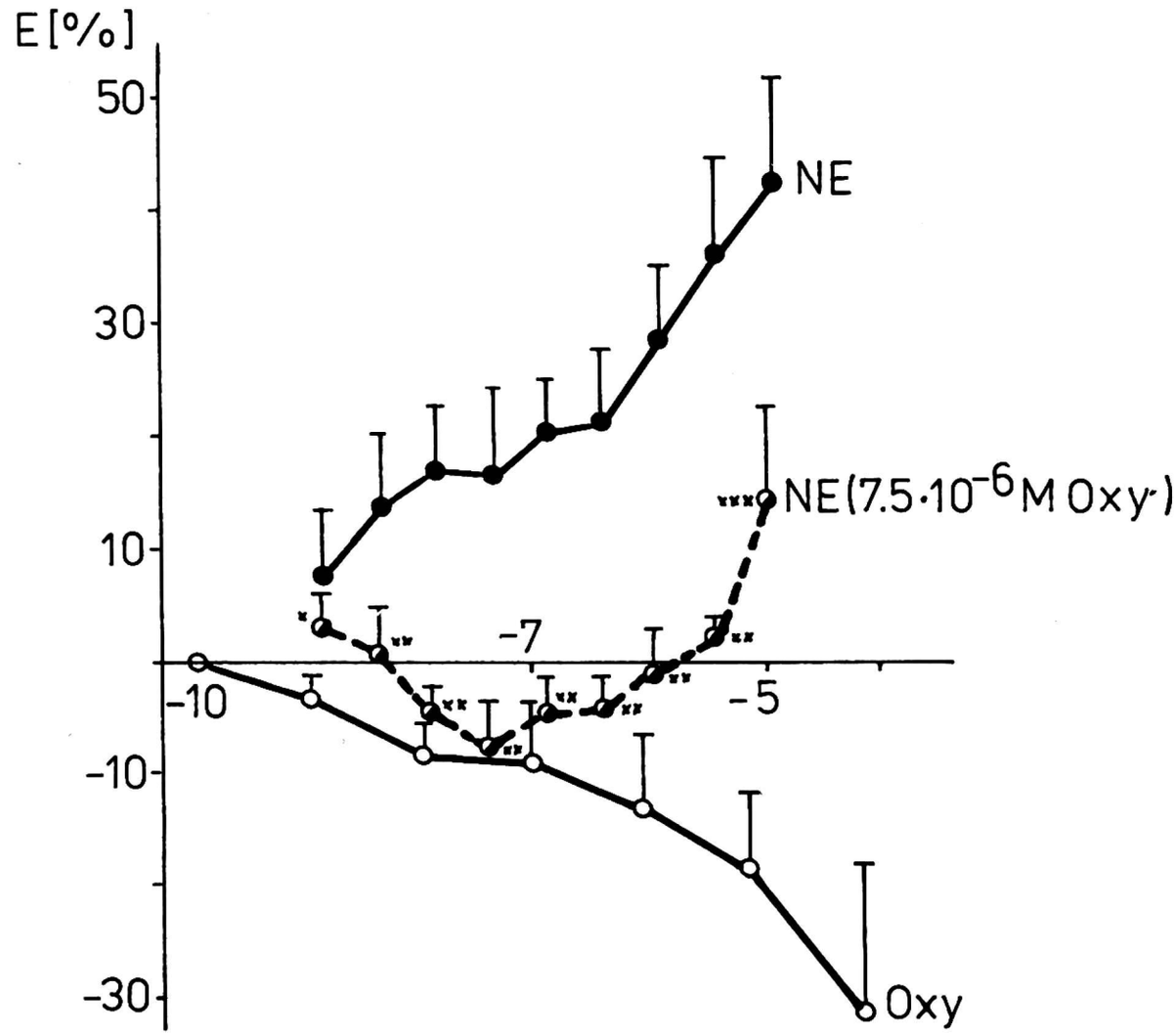

Fig. 4. Effect of norepinephrine (NE), oxymetazoline (Oxy) and norepinephrine in the presence of fixed concentration of oxymetazoline on rate of isolated heart atria. Each point corresponds to mean ($n \geqslant 6$) values $\pm$S.D. Asterisks indicate, ** $p<0.05$, *** $p<0.001$

Alpha$_2$-adrenoceptor agonist, UK 14.304, shows some bradycardic activity (*Table 2*). The maximum chronotropic effects of norepinephrine were significantly affected by the presence of UK 14.304 at concentration 7.5×10^{-6}M. Xylazine in concentration 7.5×10^{-5}M showed significant bradycardic effect.

The imidazole drug medetomidine, appeared to show no negative chronotropic activity but instead, the agent elicits a weak positive chronotropy.

Tramazoline, another α_2-adrenoceptor agonist, has no effect on rate of isolated rat atria up to its concentration of 7.5×10^{-6}M in the organ bath (*Fig. 5*).

The effects of clonidine on rate of spontaneously beating rat heart atria are weak at low concentrations of the agent. It induces a negative chronotropy at as high concentration as 3.5×10^{-4}M.

Bradycardic effects of lofexidine are similar to those of moxonidine. Neither lofexidine nor moxonidine induce stronger chronotropic effects than

those observed for the α_1-adrenoceptor stimulating imidazolines. An interesting feature of lofexidine, when applied at concentration 7.5×10^{-6}M, is a decreasing effect on chronotropic responses to norepinephrine.

Table 2. Effects of adrenergic drugs on beating rate of isolated heart rat atria

Drug	Percent change of control beating rate due to 7.5×10^{-6} M of drug	Maximum percent change of beating rate (concentration of the drug in M)	Percent change of maximum NE effect due to indicated concentration [M] of the drug
Tymazoline	−14±8	−17±7 (7.5×10^{-5})	−6 (7.5×10^{-8})
Xylometazoline	−17±6	−42±5 (7.5×10^{-4})***	−2 (7.5×10^{-8})
Tetryzoline	−13±5	−34±18 (7.5×10^{-4})	+12 (7.5×10^{-7})
Oxymetazoline	−18±5	−31±17 (7.5×10^{-5})	−28 (7.5×10^{-6})***
Cirazoline	−14±3**	−42±16 (7.5×10^{-5})*	−48 (7.5×10^{-6})***
Naphazoline	−10±3**	−30±9 (7.5×10^{-4})**	−4 (7.5×10^{-8})
UK 14.304	−2±2	−4±3 (7.5×10^{-4})	+8 (7.5×10^{-6})**
Medetomidine	+9±2**	+10±5 (7.5×10^{-5})*	+2 (7.5×10^{-6})
Detomidine	+5±2	+17±3 (7.5×10^{-5})	+4 (7.5×10^{-6})
Xylazine	−6±3	−26±4 (7.5×10^{-5})*	−13 (7.5×10^{-6})
Tramazoline	0±0	−7±1 (7.5×10^{-5})	−6 (7.5×10^{-6})
Moxonidine	−6±5	−13±8 (7.5×10^{-5})	+5 (7.5×10^{-6})
Clonidine	−7±3	−20±8 (3.5×10^{-4})***	−2 (3.5×10^{-6})
Lofexidine	−8±5	−8±5 (7.5×10^{-5})	−22 (7.5×10^{-6})**
Tiamenidine	−12±3*	−24±9 (7.5×10^{-5})*	−25 (7.5×10^{-6})***
Phentolamine	−4±1**	−31±13 (7.5×10^{-4})	−12 (7.5×10^{-5})
Tolazoline	+1±1	−6±2 (7.5×10^{-4})	+2 (7.5×10^{-8})
Antazoline	−11±5	−22±6 (7.5×10^{-5})**	−25 (7.5×10^{-8})***

All values were exspressed as the mean ($n \geq 6$) ±S.D. Significant differences from control as determined by the paired *t-test:* *$p<0.10$, ** $p<0.05$, *** $p<0.001$. Significant changes of maximum NE effect as determined by the unpaired *t-test*: ** $p<0.05$, *** $p<0.001$.

In contrast to other imidazoline α_2-adrenergic agents, tiamenidine evidently decreases beating rate of isolated rat heart atria. Also, highly pronounced is the inhibitory effect of tiamenidine with regards to the chronotropic activity of norepinephrine. At concentration 7.5×10^{-6}M tiamenidine reverses chronotropic activity of norepinephrine.

Within the class of α_1/α_2-adrenoceptor antagonists, the negative chronotropic activity of phentolamine is pronounced at the concentration of 7.5×10^{-6}M (*Fig. 6*).

Tolazoline, another α-adrenoceptor antagonist shows no significant negative chronotropic activity at the concentrations studied.

An antihistaminergic drug, antazoline reduces heart rate, at higher concentrations. It markedly decreases maximum chronotropic effects of norepinephrine if present at concentrations as low as 7.5×10^{-8}M.

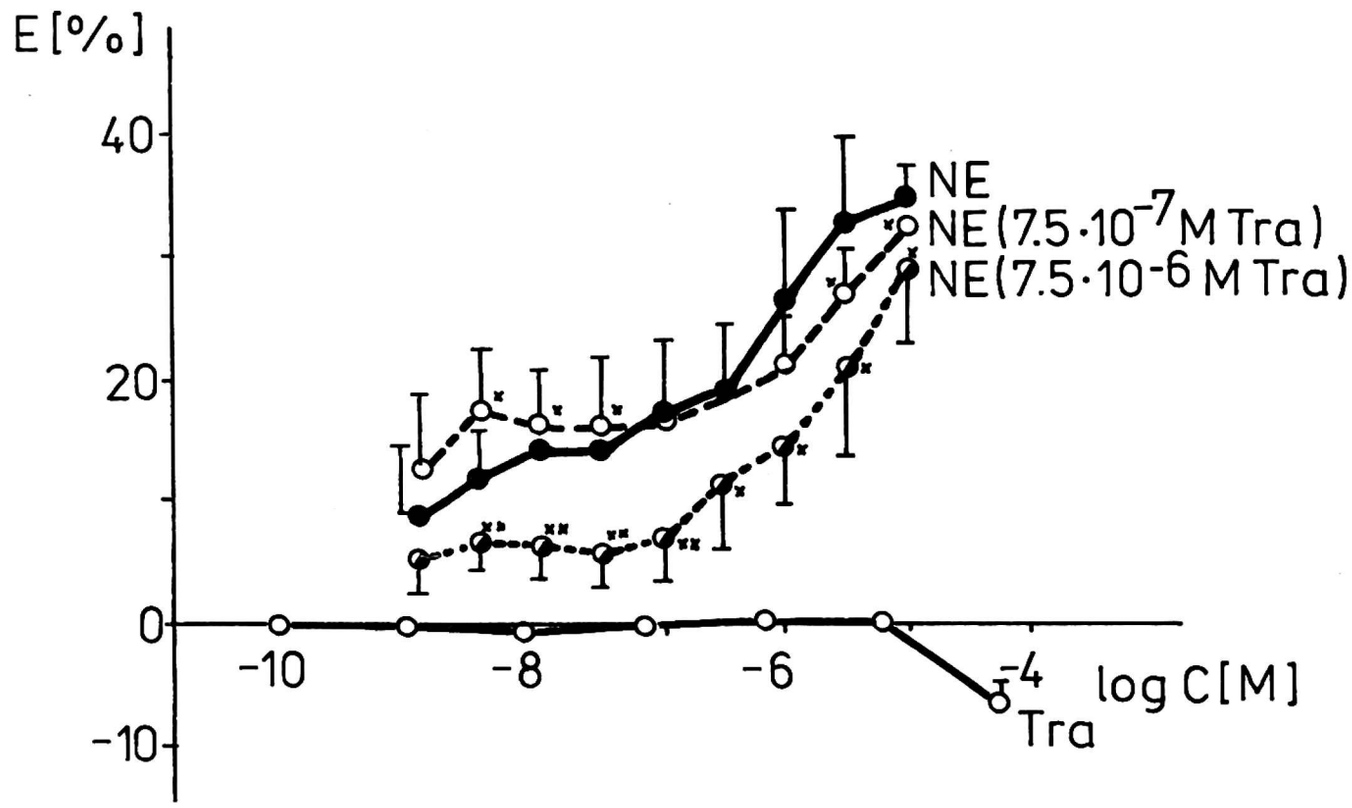

Fig. 5. Effect of norepinephrine (NE), tramazoline (Tra) and norepinephrine in the presence of fixed concentrations of tramazoline on rate of isolated rat heart atria. Each point corresponds to mean ($n \geq 6$) values $\pm$S.D. Asterisks indicate, * $p<0.10$, 0 ** $p<0.05$.

DISCUSSION

Such imidazoline drugs like tymazoline, xylometazoline, tetryzoline, oxymetazoline, cirazoline and naphazoline are commonly considered strong α_1-adrenoceptor agonists (18). As a matter of fact, some authors classify oxymetazoline among α_2-adrenoceptor agonists (19). Cirazoline, being a strong α_1-adrenoceptor agonist, is a the same time an α_2-adrenoceptor antagonist (20). In this work manifestations of positive inotropic activity were shown in case of tymazoline, xylometazoline, cirazoline and naphazoline. Thus, this study gives some evidences for agonistic properties of the above mentioned imidazolines towards α_1-adrenoceptors of rat heart atria. Our observations are also in agreement with the hypothesis that adrenergic receptors of the α_1 subtype are involved in inotropic reactions of isolated rat heart atria. However, in the positive inotropic effects of tolazoline, an α-adrenoceptor antagonist, one has to consider the stimulation of a histamine receptor. The positive inotropic effects of tolazoline, inhibited by the histamine receptor antagonists, have already been reported in guinea-pig atria (21, 22). Similarly, clonidine and related imidazoline derivatives have been classified as partial agonists at

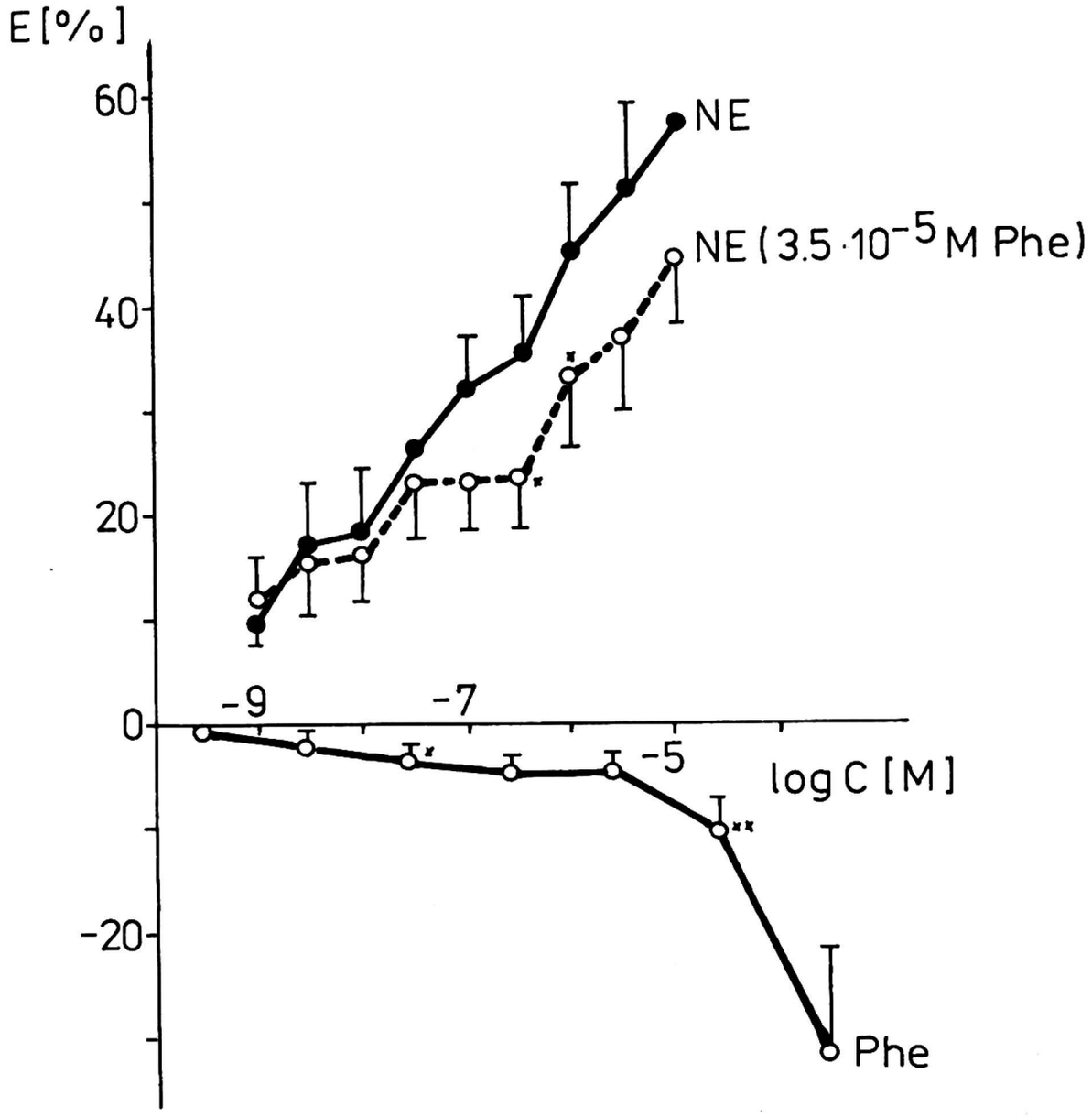

Fig. 6. Effect of norepinephrine (NE), phentolamine (Phe) and norepinephrine in the presence of fixed concentration of phentolamine on rate of isolated rat heart atria. Each point corresponds to mean ($n \geqslant 6$) values $\pm$S.D. Asterisks indicate, * $p<0.10$, ** $p<0.05$

histamine H_2-receptors in guinea-pig right atria (22, 23), although a lack of histamine-like activity for clonidine was reported in humans (24).

Such imidazoline derivatives like UK 14.304, detomidine, medetomidine, clonidine and lofexidine, typically classified among α_2-adrenoceptor agonists had no significant effect on amplitude of the atria. Positive inotropic effects elicited by some of α_2-adrenergic agents are negligible. Some exception may be tiamenidine at concentration of 7.5×10^{-6}M. Still, however, its positive inotropic activity is weaker than in the case of the α_1-adrenoceptor imidazoline agonists. Some α_2-adrenoceptor agonists like tramazoline, xylazine and moxonidine elicit negative inotropic effects. These compounds act both in the peripheral and the central nervous system. It is known, that these imidazolines are agonists of α_2-adrenoceptors in the cardiovascular system and specifically

in the anococcygeus muscle of the rat. On the other hand, these agents are generally known to diminish the responses to norepinephrine (17, 25, 26).

Phentolamine, an antagonist of α-adrenoceptor shows no significant inotropic activity. Effects of phentolamine on the norepinephrine and phenylephrine-induced responses of rat atria are similar to those reported by Martinez and McNeil (27).

The common feature in chronotropic responses of atria towards the imidazolines studied is bradycardia. This may be considered as a negative chronotropic effect resulted from positive inotropic action of the drugs according to the Starling law (28). In such a case a correlation between inotropic and negative chronotropic effect would be expected. There was no such a correlation for the drugs studied in this work. A strong inhibitory effect of cirazoline against the norepinephrine induced tachycardia calls the attention. In general α_2-adrenoceptor agonists seem to elicit weaker negative chronotropic effects than imidazolines classified as α_1-adrenoceptor agonists. It was demonstrated (29) that imidazolines classified as α_1-adrenoceptor agonists and/or antagonists are more lipophilic than those possessing stronger affinity towards α_2-adrenoceptors. Thus, the observed bradycardic effects of imidazolines might be of a lesser structural specifity. An exception among α_2-adrenoceptor agonists appears tiamenidine, significantly decreasing beating rate of atria and inhibiting chronotropic activity of norepinephrine. It is noteworthy that already Lindner and Kaiser (30) reported a marked reduction by tiamenidine of the heart rate in the intact dogs, cats and rabbits.

Summarizing the results of our studies we wish to stress the following:

1) Positive inotropic effects of imidazolines on isolated rat atria are due to stimulation of α_1-adrenoceptors. Imidazolines classified as α_1-adrenoceptor agonists, i.e., tymazoline, xylometazoline, naphazoline and cirazoline, evidently increase amplitude of rat atria and/or potentiate inotropic effects of norepinephrine. On the other hand typical agonists of α_2-adrenoceptor, i.e., UK 14.304, medetomidine, detomidine, clonidine, have much weaker (or not at all) amplitude-enhancing properties than the α_1-adrenoceptor agonists. Only tiamenidine and, to a lesser extent, xylazine, tramazoline and moxonidine, have positive inotropic effects. Supposedly, the positive inotropic effect of tolazoline at high concentrations does not result from α-adrenoceptor antagonist properties. In the case of tolazoline a stimulation of the histamine H_2-receptors may be involved.
2) Significant negative chronotropic effects, however of varying magnitude, were observed for majority of the imidazolines studied. The most pronounced bradycardic effects were elicited by α_1-adrenoceptor agonist: xylometazoline, cirazoline, oxymetazoline and naphazoline, α_2-adrenoceptor agonists medetomidine, tiamenidine, clonidine and xylazine, an α-adrenoceptor antagonists -phentolamine and an imidazoline derivative devoid

of adrenoceptor activity -antazoline. Excepting tiamenidine, the bradycardic activity of α_2-adrenoceptor agonists appears lower than that of α_1-adrenoceptor antagonists and agonists. Negative chronotropic activity elicits also antazoline, the agent devoid of adrenoceptor activity. One has to note that the agents considered here and classified as α_2-adrenoceptor agonists are less lipophilic than the α_1-adrenoceptor agonists. The imidazole derivative, medetomidine, has no bradycardic effect. Thus, the chronotropic effects on isolated rat atria of the imidazoline agents studied migh be mostly due to the membrane stabilizing properties. Those properties may result from the blockade of sodium channels. There is no a simple correlation between hydrophobicity and bradycardic effects, however, which implies that specific structural features of the agents are of importance for the effect observed.

3) Postive inotropic effects accompanied by negative chronotropic responses observed for some imidazoline agents alone and at the presence of norepinephrine are noteworthy as they cannot be explained exclusively by the Starling law. In present authors opinion the following imidazolines deserve analysis from the point of view of full therapeutic exploitation of their cardiovascular pharmacodynamic properties: tymazoline, xylometazoline, cirazoline and tiamenidine.

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