Release of Histamine by Sympathetic Nerve Stimulation in the Guinea Pig Heart and Modulation of Adrenergic Responses

A Physiological Role for Cardiac Histamine?

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SUMMARY. Histamine has been reported to attenuate adrenergic responses in cardiovascular tissues. In guinea pig atria preloaded with [3H]norepinephrine, histamine diminishes the field stimulation-induced efflux of radioactivity; this effect has been attributed to an inhibition of norepinephrine release from nerve endings. To assess the possible physiological relevance of these findings, we have reinvestigated the effects of histamine on cardiac sympathetic responses and on the release of endogenous norepinephrine in the guinea pig heart isolated with its intact sympathetic innervation. Heart rate, left ventricular contractile force, and perfusion pressure all increased with increasing frequencies of sympathetic nerve stimulation (2-8 Hz). Histamine (3 × 10^-8 to 3 × 10^-7 M) caused dose-dependent attenuation of the responses to sympathetic stimulation. The ability of histamine to modulate nerve stimulation-induced norepinephrine overflow into the coronary effluent was dependent on whether the heart had been preloaded with norepinephrine. Whereas histamine did not cause a significant reduction in nerve stimulation-induced norepinephrine overflow in hearts from untreated animals, histamine significantly reduced stimulation-induced norepinephrine overflow in hearts from guinea pigs that had been pretreated with norepinephrine before sacrifice. Histamine also attenuated the increases in left ventricular contractile force, perfusion pressure, and heart rate, which result from the intracardiac administration of norepinephrine (0.16-μg bolus injection). In this respect, histamine was as effective as it was in inhibiting the responses elicited by nerve stimulation. Thus, in normal animals, the negative modulatory effect of histamine on adrenergic responses can be attributed largely, if not totally, to a postjunctional mechanism. In contrast, a prejunctional action of histamine may contribute significantly to the negative modulation observed in norepinephrine-preloaded hearts. Since we have observed a large increase in the amount of endogenous histamine present in the coronary effluent after sympathetic stimulation (930 pg during the 30 seconds poststimulation vs. 240 pg during 30 seconds prestimulation), as well as a prolongation of nerve stimulation-induced cardiac responses in the presence of the H2 receptor antagonist tiotidine, we postulate that histamine plays a physiological role as a modulator of sympathetic responses in the heart. (Circ Res 54: 516-526, 1984)
Although there is evidence for a modulatory action of histamine on adrenergic responses in the heart and vasculature, the physiological significance of these findings remains to be determined. Direct evidence that histamine modulates stimulation-induced NE release from nerve terminals derives from field-stimulated preparations preloaded with radiolabeled NE. These experiments create conditions that are not present in vivo, and may lead to artifacts.

The present study attempts to clarify the physiological role of histamine as a modulator of sympathetic nerve activity in the heart. We used as an experimental model the isolated guinea pig heart (Langendorff preparation) with intact bilateral sympathetic innervation. In this preparation, we measured stimulation-induced cardiac responses (i.e., left ventricular contractile force, heart rate, and coronary perfusion pressure) and the simultaneous release of endogenous transmitter.

**Methods**

Male Hartley guinea pigs (250-300 g) were killed by cervical dislocation and, in each, the ribcage was dissected away, exposing the heart. After removal of the pericardium, the pulmonary artery was severed and a cannula was inserted into the ascending aorta. With a peristaltic pump (Buchler Instruments), the heart was perfused through the aorta, in situ, at constant flow (3.5-4.0 ml/min) with Krebs-Henseleit solution equilibrated with 95% O2-5% CO2 and maintained at 32°C. The composition of the perfusion solution was (mM): Na+, 142.5; K+, 5.4; Ca++, 2.5; Mg++, 1.2; Cl-, 128; HCO3-, 24.9; H2PO4-, 1.0; SO4-, 1.2; and glucose, 10.0. Both right and left stellate ganglia were carefully isolated under a dissecting microscope, and the underlying tissue was dissected free from the spinal column (Hukovic and Muscholl, 1962). The heart with sympathetic nerves attached was removed from the thorax and transferred to a specially designed Langendorff apparatus, where it was suspended via the aortic cannula. The right and left postganglionic sympathetic nerves were placed over bipolar platinum electrodes and stimulated simultaneously with a Grass stimulator (model S44) coupled to a Grass stimulus isolation unit (model SIU5). Sinus rate was determined from surface electrograms recorded from the right atrium and left ventricle, amplified on a Tektronix 410 physiological monitor, and recorded at a paper speed of 50 mm/sec on a Texas Instruments oscillograph. Isometric left ventricular contractile force (Grass FT03C force-displacement transducer) and coronary artery perfusion pressure (Statham pressure transducer, model P23AA) were continuously recorded on a Grass model 7D polygraph. The cardiac effluent was collected for 15-second intervals before, during, and after nerve stimulation and was subsequently analyzed for norepinephrine (NE) and/or histamine content.

NE was assayed in the coronary perfusate by high performance liquid chromatography. Perchloric acid and EDTA were added to samples to achieve final concentrations of 0.01 N and 0.025%, respectively. After short-term storage (<2 weeks) at −70°C, the samples were thawed, centrifuged, and 20- to 50-μl aliquots were injected directly onto a reverse-phase C18 column (Altex Ultrasphere Ion Pair, 25 × 0.46 cm) by an automated sample injector (Wisp 710B; Waters Associates). A reference concentration of NE was frozen with each group of samples as a control.
fur possible degradative losses occurring prior to assay. Phosphate-EDTA buffer containing octane sulfonate and methanol (Hegstrand and Eichelman, 1981) was pumped through the chromatographic column at 1.0 ml/min. The oxidation current of NE was measured at a glassy carbon electrode, set to +0.72 V, with an LC-4 electrochemical detector (Bioanalytical Systems Inc.).

Samples of the coronary perfusate to be analyzed for histamine content were stored at -20°C immediately upon collection and were assayed within 1 week. A reference concentration of histamine was frozen with each group of samples to serve as a control for degradative loss prior to the assay. Analysis by the microradioenzymatic method of Beaven et al. (1982) was performed on triplicate 10-μl aliquots of each sample. No significant loss of either NE or histamine occurred during storage.

Heart preparations were equilibrated in the Langendorff apparatus for 30 minutes, during which time all physiological parameters (contractile force, heart rate, and coronary perfusion pressure) attained stable values.

Both right and left cardiac sympathetic nerves were stimulated at the desired frequency for 30 seconds with square wave pulses, 1 msec in duration, and of supramaximal intensity (12 V). A 15-minute recovery period was provided between successive nerve stimulations and, unless otherwise noted, not more than three stimulation periods were applied to a given heart preparation.

In some experiments, hearts were pretreated (pre-loaded) with NE by in vivo intravenous administration of 83 μg/kg of L-NE bitartrate. Fifteen minutes later, the animals were killed, and the heart-sympathetic nerve preparation was isolated in the usual manner (described above).

In the experiments designed to study the effect of histamine on cardiac responses to sympathetic nerve stimulation, histamine was added to the perfusion medium to give the desired concentration. Hearts were perfused with the histamine-containing solution for 5 minutes prior to stimulation and, unless otherwise noted, not more than three stimulation periods were applied to a given heart preparation.

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Table 1: Consistency of Cardiac Responses to Successive Series of Sympathetic Nerve Stimulation

<table>
<thead>
<tr>
<th>Stimulus series</th>
<th>Cardiac contractility (%)</th>
<th>Heart rate (beats/min)</th>
<th>Perfusion pressure (%)</th>
<th>Norepinephrine overflow during stimulation (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>121.7 ± 10.4†</td>
<td>36.0 ± 6.8‡</td>
<td>25.4 ± 2.7‡</td>
<td>3.5 ± 0.5§</td>
</tr>
<tr>
<td>2</td>
<td>123.3 ± 13.3</td>
<td>34.8 ± 5.2</td>
<td>22.5 ± 5.6</td>
<td>3.2 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>133.6 ± 10.0</td>
<td>34.6 ± 5.7</td>
<td>25.8 ± 6.5</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>4</td>
<td>124.3 ± 12.6</td>
<td>34.8 ± 3.4</td>
<td>26.6 ± 6.7</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>5</td>
<td>99.8 ± 8.7</td>
<td>33.0 ± 4.6</td>
<td>24.9 ± 5.9</td>
<td>2.9 ± 0.4</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM (n = 5).

* Sympathetic nerves were stimulated bilaterally for 30 seconds at 8 Hz. A 15-minute recovery period was provided between successive series of stimuli.
† Measured during a 30-second period of nerve stimulation.
‡ Maximum increase.
§ The basal NE concentration in the coronary effluent was <0.1 ng/ml.

Results

Cardiac Sympathetic Nerve Stimulation: Effects on Contractility, Rate, Coronary Resistance, and Norepinephrine Overflow

Electrical stimulation of postganglionic sympathetic nerves in the spontaneously beating isolated guinea pig heart caused an increase in left ventricular contractile force (LVCF), heart rate (HR), perfusion pressure (PP), and norepinephrine overflow (NEO) into the coronary effluent. Representative tracings from one experiment are shown in Figure 1. LVCF and PP increased as a function of the frequency of stimulation and reached a maximum
Sympathetic Stimulation

**FIGURE 2.** Time course of stimulation-induced responses and norepinephrine overflow in isolated guinea pig hearts in the absence or presence of histamine. Maximum increases in left ventricular contractile force (LVCF), coronary perfusion pressure (PP), heart rate (HR), and norepinephrine overflow (NEO) were recorded during four consecutive 15-second intervals commencing with nerve stimulation (8 Hz; 30 sec), in control preparations (closed circles) or in the presence of 3 × 10⁻⁷ M histamine (open circles). Before stimulation, LVCF, HR, and PP were 3.3 ± 0.3 g, 209 ± 6 beats/min, and 52.6 ± 4.4 mm Hg, respectively. Points and bars represent means (±SE) of 4–6 experiments. ** = significant depression of responses by histamine at the 0.05 and 0.01 level, respectively, as determined by paired t-test.

at 8 Hz. Thus, a frequency of 8 Hz or less was used in subsequent experiments. The consistency of responses to successive cycles of nerve stimulation at 8 Hz is shown in Table 1. Constant increases in contractility, heart rate, perfusion pressure, and NE overflow were observed in response to five successive stimulation periods separated by 15-minute intervals. Time courses of the changes in LVCF, PP, HR, and NEO elicited by sympathetic nerve stimulation are shown in Figure 2. LVCF, HR, and NEO increased almost concomitantly, and reached a peak at about 30 seconds. The change in PP was biphasic; PP rapidly rose to a peak by 15 seconds, and decreased progressively thereafter to below control levels by 60 seconds.

**Modification by Histamine of Cardiac Responses to Sympathetic Nerve Stimulation**

In the absence of nerve stimulation, histamine (3 × 10⁻⁷ M) caused relatively small changes in LVCF, PP, and HR which reached maxima of +26.4 ± 12.6%, −23.5 ± 5.3%, and +12.5 ± 1.9% (mean ± SEM; n = 5), respectively. The histamine-induced increase in LVCF reverted during the equilibration period before nerve stimulation. In opposition to its small direct cardiac effects at this concentration, histamine markedly depressed the responses to sympathetic nerve stimulation. Tracings from one experiment are shown in Figure 3. It is evident that the stimulation-induced increases in LVCF and PP were much reduced in the presence of histamine (compare panels A and B); this depression was reversed after histamine washout (panel C). Time courses of changes in LVCF, PP, HR, and NEO elicited by sympathetic nerve stimulation in the presence of histamine (3 × 10⁻⁷ M) are shown in Figure 2. Histamine reduced the maximal stimulation-induced increases in LVCF, PP, and HR by 58%, 55%, and 43%, respectively, relative to control values. In contrast, histamine did not significantly attenuate NEO at this and at lower concentrations (Fig. 4), which, nonetheless, markedly reduced the responses to sympathetic stimulation (data shown later in Fig. 9A).

Since auto-inhibition of NE release is most pronounced at low frequencies of stimulation (Yamaguchi et al., 1977), we questioned whether we had failed to detect a prejunctional modulatory effect of histamine on NEO because we had used a relatively high frequency of stimulation (8 Hz), at which prejunctional mechanisms may be less apparent. To test this possibility, we studied the effect of histamine on NEO also at lower frequencies of nerve stimulation. The bar graphs shown in Figure 5 demonstrate that LVCF, PP, HR, and NEO all increased as a function of increasing stimulation frequency. However, even at nerve stimulation frequencies of 2 and 4 Hz, histamine did not reduce NEO, whereas it potently attenuated the increases in LVCF, PP, and HR.

**Amplification of Norepinephrine Overflow by Drugs, and Effects of Exogenous Histamine**

Our finding that histamine attenuated cardiac responses to adrenergic stimulation without reducing NEO was at variance with the view held by others
(Rand et al., 1982; McGrath and Shepherd, 1976; Kimura and Satoh, 1983; Lockhandwala, 1978) that histamine inhibits NE release from sympathetic nerve endings. We reasoned that, since NEO represents a small fraction of the NE actually released from sympathetic nerves, the uptake of released NE by various sites might have contributed to our inability to detect a significant reduction of NEO by histamine. Therefore, we performed experiments in which hearts were perfused with a combination of drugs selected to enhance the fraction of neuronally released NE which appears in the coronary perfusate. These included $10^{-8}$ M desipramine (DMI) to inhibit neuronal uptake of NE (uptake1) and $10^{-5}$ M hydrocortisone (HC) to inhibit extraneuronal uptake of NE (uptake2). In addition to DMI and HC, $10^{-7}$ M yohimbine (Y) was added to diminish prejunctional auto-inhibition of NE release. Concentrations of all three drugs were selected to approximate the EC50 values for their respective activities (Babulova et al., 1973; Kaumann, 1972; Sullivan and Drew, 1980). Time courses of the changes in LVCF, PP, HR, and NEO elicited by sympathetic nerve stimulation in hearts treated with the DMI + HC + Y combination, both in the absence and in the presence of $3 \times 10^{-7}$ M histamine are shown in Figure 6. The drug combination potentiated and prolonged the responses to sympathetic nerve stimulation; this coincided with a 6-fold increase in NEO (compare Fig. 6 with Fig. 2). Interestingly, the increase in NEO was associated with a large increase in LVCF but only minor changes in PP and HR. Histamine greatly depressed the LVCF, PP, and HR responses to sympathetic stimulation in hearts perfused with the DMI + HC + Y combination by 87%, 54%, and 47%, respectively. However, in spite of the large enhancement of NEO induced by the drug combination, histamine caused only a modest reduction in NEO, clearly insufficient to account for the attenuation of cardiac responses by histamine. The small depression of NEO by histamine did not attain a level of statistical significance except during the 15- to 30-second period of sympathetic stimulation.

Modification by Histamine of Norepinephrine Overflow in Hearts Preloaded with Exogenous Norepinephrine

Our experiments had failed to demonstrate a significant attenuation of NEO by histamine, even when losses of released NE were minimized by
inhibition of NE uptake. Whereas we had studied the release of endogenous NE, other investigators who had reported a histamine-induced reduction in NE release (Rand et al., 1982; McGrath and Shepherd, 1976) had measured the efflux of radioactivity from tissues that were preloaded with [3H]-NE (i.e., exogenous NE). Accordingly, we investigated the effects of histamine on nerve stimulation-induced NE release from hearts preloaded with exogenous NE (i.e., hearts from guinea pigs that had been injected with NE, 83 μg/kg, iv, 15 minutes prior to sacrifice). The effect of histamine on sympathetic nerve stimulation-induced NEO, in control and NE-pretreated hearts, is shown in Figure 7. It is clear that histamine reduced NEO only in NE-pretreated hearts. Furthermore, Figure 7 suggests that it is only the release of the additional NE, made available by preloading, that is sensitive to histamine inhibition.

**Modification by Histamine of Cardiac Responses to the Administration of Norepinephrine**

Since we found that histamine depresses the responses to sympathetic stimulation without affect-
FIGURE 7. Effect of preloading the heart with NE on the ability of histamine to modulate nerve stimulation-induced NEO. Hearts were isolated from either untreated guinea pigs (triangles) or from animals that were pretreated with 83 μg/kg NE 10 minutes before sacrifice (circles). The hearts were perfused either in the absence or in the presence of 3 × 10⁻⁷ M histamine. Cumulative NEO is plotted as a function of time from the initiation of sympathetic stimulation (8 Hz). During the 15-second period before stimulation, the cumulative NEO was below the limit of detection with our assay (i.e., <0.1 ng). * = significant depression of NEO by histamine at the 0.05 level. The asterisks in the figure refer to the open circles.

ing to any significant extent the release of endogenous NE, we tested the alternate possibility, i.e., that histamine attenuates the effects of released NE. Increases in LV CF, PP, and HR caused by the intra-aortic administration of 0.16 μg NE (approximate ED₅₀ for these three responses) are shown in Figure 8. It can be seen that, in the presence of histamine (3 × 10⁻⁷ M), these increases were greatly reduced, but were largely restored following histamine washout. The dose-response curves for histamine-induced attenuation of cardiac responses to either sympathetic stimulation (8 Hz, 30 seconds) or NE administration (0.16 μg) are shown in Figure 9. It is apparent that histamine, as a function of its concentration, reduces both types of adrenergic responses, and that histamine is a more potent modulator of the LVCF and PP responses (IC₅₀ = 10⁻⁸-10⁻⁷ M) than of the HR response (IC₅₀ = 10⁻⁷-10⁻⁶ M). From a comparison of the curves in panel A with that in panel B (Fig. 9), it readily appears that histamine is as effective in attenuating cardiac responses to sympathetic stimulation as it is in attenuating the responses to administered NE. These findings indicate that a postjunctional mechanism is completely sufficient to account for the attenuation of cardiac sympathetic responses by histamine.

Release of Endogenous Histamine by Sympathetic Nerve Stimulation

When sympathetic nerves to guinea pig hearts were stimulated at 8 Hz for 30 seconds, we found that, in addition to NE, the concentration of endogenous histamine increased in the coronary effluent (Fig. 10). During the 30-second poststimulation period, there was a 3-fold increase in histamine concentration relative to that present in the perfusate prior to stimulation. Maximum release of both histamine and NE occurred during the 30-second poststimulation period.

Recent data from our laboratory (Gross et al., 1984) indicate that the histamine-induced attenuation of sympathetic responses is mimicked by the
specific H2 agonist, dimaprit, and inhibited by the specific H2 antagonists, cimetidine and tiotidine. Analysis of results obtained with cimetidine are complicated by its cardiac depressant action at concentrations lower than those necessary to antagonize H1-mediated histamine responses completely; this depressant effect of cimetidine is unrelated to its antihistaminic action (R. Levi, unpublished observations). Tiotidine, on the other hand, is a specific H2-blocker that does not exhibit such cardiac depressant effects (Trzeciakowski and Levi, 1980). Results displayed in Table 2 demonstrate that the modulation of sympathetic responses by histamine is completely antagonized by tiotidine 10^{-7} M. Thus, in an attempt to determine whether enough endogenous histamine is released as a result of sympathetic stimulation to attenuate adrenergic responses, we stimulated cardiac sympathetic nerves in the presence of tiotidine. If histamine serves a physiological role as a modulator of adrenergic responses, one would expect that tiotidine would potentiate and/or prolong the time course of responses to sympathetic stimulation. Figure 11 illustrates how tiotidine modified the time-course of sympathetic responses. The findings from a typical experiment are shown in panels A–C; time courses of nerve stimulation-induced responses (8 Hz for 30 seconds) were determined in the presence and absence of 10^{-7} M tiotidine. A slight but short-lasting attenuation of the increases in LVCF and PP occurred with tiotidine during nerve stimulation, whereas a more prolonged potentiation occurred after stimulation was terminated. On the other hand, HR was potentiated by tiotidine both during and after nerve stimulation. Results of several experiments such as the one shown in panels A–C are combined in panels D–E. The systematic deviation from control LVCF, PP, and HR responses, in the presence of tiotidine, provides strong evidence that sympathetic stimulation induces the release of physiologically relevant quantities of histamine.
**Discussion**

Our findings clearly indicate that histamine is a potent inhibitor of the increases in contractile force, heart rate, and coronary resistance which result from sympathetic nerve stimulation in the isolated guinea pig heart. These modulatory effects of histamine are independent of its direct cardiac actions. Indeed, the direct effects of histamine are either in the opposite direction (HR, LVCF) or of lesser magnitude (PP) than the modulatory effects. Histamine’s effects on sympathetic responses could involve a prejunctional
mechanism, whereby histamine acts to decrease the neuronal release of NE, a postjunctional mechanism in which histamine modulates the effects of released NE, or a combination of the two.

The results that we have obtained provide strong evidence that histamine's effect on adrenergic responses in the normal heart is postjunctional. This conclusion is supported by two major pieces of evidence. First, we have observed that histamine does not cause a significant reduction in the sympathetic stimulation-induced overflow of endogenous NE into the coronary perfusate. Second, responses to intracardiac administration of NE are depressed by histamine in the same concentration range in which histamine attenuates responses to nerve stimulation. Although histamine-induced attenuation of responses to directly administered NE may be explained only by a postjunctional action, this finding would not rule out the contribution of a prejunctional action for the depression by histamine of cardiac responses to sympathetic stimulation. However, our inability to detect a reduction in neuronally released NE—under conditions in which histamine was found to reduce sympathetically evoked responses (i.e., a range of histamine concentrations and a range of stimulation frequencies)—indicates that if a prejunctional component is present at all, it plays a relatively minor role.

Since the NE which we measure in the coronary perfusate represents only a fraction of that actually released by the nerve terminals, we addressed the possibility that transmitter loss may have contributed to our inability to detect a histamine-induced depression of NEO. To test this possibility the recovery of released NE was enhanced by addition of uptake1 and uptake2 inhibitors to the cardiac perfusion medium in the presence of yohimbine. The reasoning behind the use of yohimbine was that, in the presence of uptake inhibitors, the synaptic NE concentration may be large enough that auto-inhibition of NE release may mask the inhibition due to histamine action. Yet, even with a 6-fold increase in NEO, histamine greatly depressed the LVCF, PP, and HR responses without significantly reducing NEO (see Fig. 6).

Our conclusion that histamine modulates sympathetic transmission in cardiovascular tissue via a post- rather than a prejunctional mechanism is in conflict with results obtained by several other groups (Rand et al., 1978; McGrath and Shepherd, 1976; Powell, 1979). However, researchers who reported a reduction of neuronal NE release by histamine have measured radioactivity efflux from tissues that had been pretreated with [3H]-NE (Rand et al., 1978; McGrath and Shepherd, 1976), whereas we have assessed the release of endogenous NE. Interestingly, when we studied nerve stimulation-induced NEO in hearts from guinea pigs that were preinjected with NE, we also found that histamine depressed NE release. In fact, it appears that only the release of the additional NE, made available by preloading the tissue, is sensitive to inhibition by histamine (see Fig. 7). Although we do not know the tissue site from which exogenous NE is released subsequent to loading, our results indicate that it may be distinct from that of endogenous NE.

Two independent groups have proposed that histamine acts by a prejunctional mechanism to reduce the tachycardia which results from sympathetic nerve stimulation in the dog (Lockhandwala, 1978; Kimura and Satoh, 1983). The basis for their suggestion is that tachycardia induced by direct intravenous administration of NE is unaffected by histamine. Lack of agreement between our results in the guinea pig and those obtained in the dog may stem from species differences, or the fact that we used bilateral sympathetic stimulation, whereas in the dog only the right nerve was stimulated. Interpretation of these findings in the dog requires caution, since Lockhandwala found the sympathetic modulatory action of histamine to be H2-receptor dependent, whereas Kimura and Satoh found this effect to be mediated by H1-receptors.

We have observed that, in addition to NE, the concentration of histamine in the cardiac perfusate increases significantly subsequent to sympathetic nerve stimulation. This intriguing finding favors the notion that histamine serves a physiological role as a modulator of sympathetically induced cardiac responses. The concentration of histamine observed in the cardiac perfusate rose to 4.2 nM in the 30-second period following nerve stimulation (8 Hz; 30 sec). Since we observed depression of sympathetic responses with 30 nM histamine, the concentration of histamine measured in the coronary perfusate is merely one order of magnitude short of that necessary to antagonize sympathetic responses under our experimental conditions. Although the volume of distribution of the released histamine within the heart is unknown, and therefore the local concentrations achieved cannot be evaluated, it is almost certain that concentrations of histamine are attained that are sufficient to play a physiological role in the modulation of sympathetic responses.

Further support of our hypothesis that released histamine plays a physiological role in the regulation of sympathetic responses is provided by the finding that the H2-antagonist, tiotidine (Yellin et al., 1979; Trzeciakowski and Levi, 1980), depresses or potentiates (as a function of time) the cardiac responses to sympathetic stimulation (see Fig. 11). We postulate that histamine released as a result of nerve stimulation acts on the heart, not only directly, but also indirectly, by modulating adrenergic responses. The H2-antagonist tiotidine blocks both direct (Trzeciakowski and Levi, 1980) and indirect cardiac effects (see Table 2), thus altering the normal kinetics of cardiac responses to sympathetic stimulation. Indeed, we may account for tiotidine's potentiation of HR, as well as for its potentiation of LVCF and PP.
following cessation of nerve stimulation, by tiotidine’s antagonism of the modulatory effects of endogenously released histamine. On the other hand, the early depression by tio-
tidine of the stimulation-induced increases in contractile force and perfusion pressure (see Fig. 11) probably results from tio-
tidine’s inhibition of the direct cardiac H2-dependent actions of released histamine. In fact, histamine has both positive (H2-mediated) and negative (H1-med-
iated) inotropic effects in the guinea pig heart (Zavecz and Levi, 1978). Thus, blockade of H2-
receptors by tio-
tidine may unmask an H1-dependent negative inotropic response to the histamine which is released during nerve stimulation. This would contribute to the early depression of contractility, and in turn, of perfusion pressure, which follows nerve stimulation in the presence of tio-
tidine.

Although it is clear that H2-blockade alters the kinetics of cardiac responses to sympathetic stimu-
lulation (see Fig. 11), we might have observed a greater potentiation of these responses if it were not for the fact that histamine release is markedly enhanced when sympathetic nerves are stimulated in the pres-
ence of tio-
tidine (Gross et al., 1984). This additional histamine is likely to compete with tio-
tidine at the vari-
ously distributed H2-receptors, thus partly off-
setting the potentiating effects of tio-
tidine.

In conclusion, we have shown that histamine attenuates cardiac adrenergic responses in the intact heart and that this is achieved predominantly by a postjunctional mechanism. The finding that cardiac histamine is released together with NE upon sym-
pathetic nerve stimulation, and that the kinetics of the cardiac responses to adrenergic nerve stimulation are modified by an H2-receptor antagonist, sug-
gests for the first time a physiological role for his-
tamine. Thus, histamine may no longer be a “mediator in search of a function” (Trzeciakowski and Levi, 1981).

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