Activation of Histamine H₃ Receptors Inhibits Carrier-Mediated Norepinephrine Release in a Human Model of Protracted Myocardial Ischemia¹, ²

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ABSTRACT

During protracted myocardial ischemia, ATP depletion promotes Na⁺ accumulation in sympathetic terminals and prevents vesicular storage of norepinephrine (NE). This forces the reversal of the neuronal uptake transporter, and NE is massively released (carrier-mediated release). We had shown that histamine H₃ receptors (H₃Rs) modulate ischemic NE release in animals. We have now used a human model of protracted myocardial ischemia to investigate whether H₃Rs may control carrier-mediated NE release. Surgical specimens of human atrium were incubated in anoxic conditions. NE release increased ~7-fold within 70 min of anoxia. This release was carrier mediated because it was Ca²⁺ independent and inhibited by the uptake₁ inhibitor desipramine. Furthermore, the Na⁺/H⁺ exchanger (NHE) inhibitors ethyl-isopropyl-amiloride and HOE 642, and the Na⁺ channel blocker tetrodotoxin inhibited NE release, whereas the Na⁺ channel activator aconitine potentiated it. The selective H₃R agonist imetit decreased NE release, an effect that was blocked by each of the H₃R antagonists thioperamide and clobenpropit. Notably, imetit acted synergistically with ethyl-isopropyl-amiloride, HOE 642 and tetrodotoxin to reduce anoxic NE release. Thus, activation of H₃R appears to result in an inhibition of both NHE- and voltage-dependent Na⁺ channels. Most importantly, endogenous histamine was released from the anoxic human heart, and thioperamide and clobenpropit each alone increased NE release, indicating that H₃R become activated in myocardial ischemia. Our findings indicate that H₃Rs are likely to mitigate sympathetic overactivity in the ischemic human heart and suggest new therapeutic strategies to alleviate dysfunctions associated with myocardial ischemia.

Previous work in our laboratory established the presence of heteroinhibitory H₃Rs on adrenergic nerve endings in the heart of the guinea pig (Endou et al., 1994; Imamura et al., 1994), dog (Seyedi et al., 1996) and humans (Imamura et al., 1995). Once activated, these receptors attenuate NE exocytosis. The mechanism of this effect involves a G₂/G₃ protein and a decreased entry of Ca²⁺ through N-type channels (Endou et al., 1994). A decreased PKC activity, resulting from a decreased phosphoinositide turnover (Cherifi et al., 1992) and diacylglycerol formation, may also play a role in the modulation of NE release associated with H₃R activation (Imamura et al., 1995).

H₃R activation also inhibits NE release in animal models of acute and protracted myocardial ischemia (Imamura et al., 1994, 1996). In the acute ischemia model, NE release is exocytotic and Ca²⁺ dependent. In the protracted ischemia model, NE release is Ca²⁺ independent, carrier mediated and much greater than that with acute ischemia (Imamura et al., 1994, 1996). During protracted myocardial ischemia, ATP depletion promotes Na⁺ accumulation in sympathetic nerve endings and prevents the vesicular storage of NE. This forces the reversal of the neuronal uptake transporter from an inward to an outward direction, and NE is massively released (carrier-mediated release) (Dart and Du, 1993; Schönig, 1990). The mechanism of the H₃R-induced attenuation of carrier-mediated NE release probably involves an inhibition of the NHE (Imamura et al., 1996). Such inhibition would reduce the intraneuronal accumulation of Na⁺ and therefore decrease the activity of the NE transporter in the outward direction.

Carrier-mediated NE release was recently described in an ischemic model in human cardiac tissue (Kurz et al., 1995). We used this model to test the hypothesis that H₃R activa-

ABBREVIATIONS: DMI, desmethylimipramine (desipramine); EIPA, 5-(N-ethyl-N-isopropyl)-amiloride; H₃R, histamine H₃ receptor; NE, norepinephrine; NHE, Na⁺/H⁺ exchanger; PKA, protein kinase A; PKC, protein kinase C; TTX, tetrodotoxin; KHS, Krebs-Henseleit Solution; DMSO, dimethylsulfoxide.
tion will inhibit carrier-mediated NE release in the human heart. Moreover, we were intrigued by the possibility that as in animal models (Imamura et al., 1994, 1996; Levi et al., 1991; Wolff and Levi, 1986, 1988), endogenous histamine would also be released in the ischemic human heart, and, if so, in sufficient concentrations to activate H₂R. Thus, the purpose of this investigation was to determine whether in the ischemic human heart, carrier-mediated NE release can be negatively modulated by activation of H₂R by both exogenous and endogenous ligands and whether this action may be related to an inhibition of intraneuronal Na⁺ accumulation.

Materials and Methods

Source of human cardiac tissue. Specimens of right atrium (i.e., cardiovase waste tissue) were obtained from 209 patients undergoing cardiopulmonary bypass (144 men and 65 women, age 64.9 ± 0.8 years; coronary artery bypass graft surgery, 173; valve replacement, 23; both, 13), following a protocol approved by our institutional review board. Seventy-three of the 186 bypass patients were chronically treated with beta adrenoceptor-blocking agents. Preoperative treatment with beta blockers did not affect the anoxic release of NE and/or histamine. At the time of surgery, a piece of atrial appendage measuring ~1 cm² was removed from the atriotomy site.

Incubation conditions. The specimen was immediately transported to the laboratory in ice-cold oxygenated KHS of the following composition (mM): NaCl 118.2, KCl 4.83, CaCl₂ 2.5, MgSO₄ 2.37, KH₂PO₄ 1.0, NaHCO₃ 25 and glucose 11.1. After removal of fat and connective tissue, the specimen was divided into several fragments (each weighing 23.3 ± 0.8 mg wet weight, measured at the end of incubation). Each fragment was incubated for 45 min at 37.5°C in 2 ml of KHS gassed with 95% O₂ and 5% CO₂ and containing the reducing agent sodium dithionite (3 mM; PO₂ 95%). After the 45-min stabilization period, fragments were incubated for an additional 20 min in oxygenated KHS in the absence or presence of one or more pharmacological agents. When thiorperamide or clofenaport was used, it was added 15 min after the beginning of the stabilization period.

Induction of anoxia. Anoxia was induced by incubating the atrial fragments for 10 to 70 min in glucose-free KHS gassed with 95% N₂ and 5% CO₂ and containing the reducing agent sodium dithionite (3 mM; PO₂ 5–95 mm Hg; pH 7.4) containing the monoamine oxidase inhibitor pargyline (1 mM). After the 45-min stabilization period, fragments were incubated for an additional 20 min in oxygenated KHS in the absence or presence of one or more pharmacological agents. When thiorperamide or clofenaport was used, it was added 15 min after the beginning of the stabilization period.

NE assay. Incubating media were assayed for NE by high-pressure liquid chromatography with electrochemical detection (Imamura et al., 1994). Perchloric acid and EDTA were added to samples to achieve final concentrations of 0.01 N and 0.025%, respectively. After a short period of storage (<2 weeks) at ~70°C, the samples were thawed. The NE present in the effluent was adsorbed on acid-washed alumina adjusted at pH 8.6 with Tris-2% EDTA buffer and then extracted into 150 μl of 0.1 N perchloric acid. These final sample aliquots were kept frozen until injected onto a 3-μm ODS reverse-phase column (3.2 × 100 mm; Bioanalytical System, West Lafayette, IN) with an applied potential of 0.85 V. The mobile phase consisted of monochloroacetic acid (75 mM), Na₂EDTA (0.5 mM), sodium octylsulfate (0.5 mM) and acetoniitride (1.5%) at pH 3.0. The flow rate was 1.0 ml/min. Dihydroxybenzylamine was added to each sample as an internal standard before alumina extraction and used for recovery calculation. The recovery of NE was 77%, and the detection limit was ~0.2 pmol.

Histamine assay. Incubating media containing SKF-91,488 (10 μM), a histamine N-methyltransferase inhibitor (Beaven and Shaff, 1979), were stored for a short period (<2 weeks) at ~70°C. Samples were then thawed and assayed for histamine content with the use of a commercial enzyme immunoassay kit (Immunotech International, Westbrook, ME) (Imamura et al., 1994). The recovery of histamine was ~100%, and the detection limit was ~0.02 pmol.

Statistics. Values are expressed as mean ± S.E. Analysis by analysis of variance was used followed by post hoc testing (Bonferroni’s test). Student’s t test was performed for paired observations. A value of P < .05 was considered statistically significant.

Drugs. HOE 642 (4-isopropyl-3-methylsulfonylbenzoyl-guanidine methanesulfonate) was a gift of Hoechst Marion Roussel (Frankfurt, Germany). DMI hydrochloride (desipramine), histamine dihydrochloride, pargyline hydrochloride and sodium dithionite (Na₂S₂O₄) were purchased from Sigma Chemical (St. Louis, MO). Aconitine, clobenpropit dihydrobromide, EIPA, imetit dihydrobromide, L-(-)-norepinephrine bitartrate, SKF-91,488 dihydrochloride, TXT and thiorperamide maleate were purchased from Research Biochemicals International (Natick, MA). EIPA was initially dissolved in 99.8% DMSO; TXT and aconitine were initially dissolved in 95% ethanol, and further dilutions were made in KHS. At the concentrations used, DMSO and ethanol had no effect on any preparation in these studies. All other drugs were dissolved in KHS.

Results

Carrier-mediated NE release from the human myocardium. The incubation of human right atrial tissue in glucose-free KHS in anoxic conditions (PO₂ ~0 mm Hg; pH 7.3), caused a pronounced time-dependent release of endogenous NE. As shown in figure 1, after 50 min of anoxia, NE release increased ~4.5-fold above basal level and reached a ~7-fold maximum plateau after 60 to 70 min of anoxia. Maximum anoxic NE release was not modified in Ca⁺⁺-free conditions (fig. 2A). Furthermore, maximum anoxic NE release was also inhibited in the presence of the neuronal uptake 1 inhibitor DMI (100 nM) (see Materials and Methods). NE release in normoxic conditions is shown for comparison. Points are mean ± S.E.M. values of NE released into the incubation medium at the time indicated on the abscissa (n = 5–9; ** P < .01 from normoxic control; † P < .05 from both anoxic and normoxic control by analysis of variance followed by post hoc Bonferroni’s test).

Fig. 1. Time course of NE release from human right atrial tissue in anoxic conditions in the presence and absence of the neuronal uptake inhibitor DMI (100 nM) (see Materials and Methods). NE release in normoxic conditions is shown for comparison. Points are mean ± S.E.M. values of NE released into the incubation medium at the time indicated on the abscissa (n = 5–9; ** P < .01 from normoxic control; † P < .05 from both anoxic and normoxic control by analysis of variance followed by post hoc Bonferroni’s test).
lease was not modified by 1 μM atropanine (648 ± 676 vs. 676 ± 614 pmol/g in the absence and presence of atropanine, respectively; n = 5).

Because Ca^{++}-independent NE release is consistent with a reversal of the NE transporter in an outward direction, we next assessed whether NE release would be affected by inhibition of the transporter. As shown in figures 1 and 2B, anoxic NE release was markedly reduced (i.e., by ~40%) when human atrial tissue was incubated with the NE neuronal uptake inhibitor DMI (100 nM). Interestingly, after 20 min of anoxia, when NE release was only slightly greater than its normoxic control, DMI enhanced anoxic NE release by ~35%.

**Intracellular Na^{+} balance and carrier-mediated NE release.** Because the desipramine-induced inhibition suggested that anoxic NE release was carrier-mediated, a condition associated with increased intracellular Na^{+}, we next investigated whether NE release would be affected by agents capable of interfering with intracellular Na^{+} accumulation. As shown in figure 3, maximum anoxic NE release was markedly reduced (i.e., by ~40%) when atrial tissue was incubated with the NHE inhibitors EIPA (10 μM; fig. 3A) and HOE 642 (10 μM; fig. 3B).

Because voltage-dependent Na^{+} channels may also contribute to increase intracellular Na^{+} in anoxic conditions, we subsequently determined whether NE release would be influenced by TTX. As shown in figure 4A, TTX (1 μM) significantly decreased maximum anoxic NE release (i.e., by ~35%). Conversely, aconitine (100 nM), which prolongs Na^{+} channel conductance, markedly potentiated anoxic NE release (i.e., by ~40%, fig. 4B).

**Activation of H₃Rs and carrier-mediated NE release.** Because the previous findings implied that anoxic NE release was carrier mediated and likely associated with accumulation of Na^{+}, we next investigated whether activation of prejunctional modulatory receptors would affect NE release in anoxic conditions. As shown in figure 5, the selective H₃R agonist imetit (100 nM) markedly reduced maximum anoxic

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**Fig. 2.** A, Anoxic NE release from human right atrial tissue in Ca^{++}-free conditions. Bars represent the total NE released into the incubation medium during 70 min of anoxia in the absence (Ca^{++}-free) and presence (Control) of 2.5 mM Ca^{++} (mean ± S.E.M.; n = 10; NS by paired t test). B, Blockade of anoxic NE release from human right atrial tissue by the NE uptake inhibitor DMI. Bars represent the total NE released during 70 min of anoxia in the absence (Control) and presence of DMI (100 nM) (mean ± S.E.M.; n = 9; * P < .05 by paired t test).

**Fig. 3.** A, Blockade of anoxic NE release from human right atrial tissue by the NHE inhibitor EIPA. Bars represent the total NE released during 70 min of anoxia in the absence (Control) and presence of EIPA (10 μM) (mean ± S.E.M.; n = 13; * P < .05 by paired t test). B, Blockade of anoxic NE release from human right atrial tissue by the NHE inhibitor HOE 642. Bars represent the total NE released during 70 min of anoxia in the absence (Control) and presence of HOE 642 (10 μM) (mean ± S.E.M.; n = 6; ** P < .01 by paired t test).

**Fig. 4.** A, Blockade of anoxic NE release from human right atrial tissue by the Na^{+} channel blocker TTX. Bars represent the total NE released during 70 min of anoxia in the absence (Control) and presence of TTX (1 μM) (mean ± S.E.M.; n = 10; ** P < .01 by paired t test). B, Potentiation of anoxic NE release from human right atrial tissue by the Na^{+} channel activator aconitine. Bars represent the total NE released during 70 min of anoxia in the absence (Control) and presence of aconitine (100 nM) (mean ± S.E.M.; n = 9; ** P < .01 by paired t test).
NE release (i.e., by 40–45%). The selective H$_3$R antagonists thioperamide (300 nM) and clobenpropit (25 nM) each blocked the effect of imetit (fig. 5, A and B). Furthermore, thioperamide and clobenpropit each alone increased maximum anoxic NE release by 25% to 30% (fig. 5, A and B). In contrast, neither imetit nor thioperamide or clobenpropit modified NE release in normoxic conditions. NE release was 138.6 ± 21.4; 132.9 ± 16.8; 138.9 ± 24.5 and 135.1 ± 22.1 pmol/g in control normoxia and in normoxia in the presence of imetit, thioperamide and clobenpropit, respectively (mean ± S.E.M.; n = 6–12; * P < .05 and ** P < .01 vs. control; † P < .05 and †† P < .01 vs. imetit by analysis of variance followed by Bonferroni’s test).

Because inhibition of the antipporter and blockade of the Na$^+$ channels, as well as activation of H$_3$R, attenuated anoxic NE release, we subsequently tested whether H$_3$R stimulation might be coupled to inhibition of the NHE and/or to blockade of the Na$^+$ channel. For this, we evaluated the effects of subthreshold concentrations of EIPA, HOE 642, TTX and imetit, alone and in combination. As shown in figure 6, imetit at 30 nM (fig. 6, A–C), EIPA at 3 μM (fig. 6A), HOE 642 at 3 μM (fig. 6B) and TTX at 0.3 μM (fig. 6C) each failed to diminish anoxic NE release when tested alone. In contrast, when imetit was combined with EIPA (fig. 6A), HOE 642 (fig. 6B) or TTX (fig. 6C), maximum anoxic NE release was significantly decreased (i.e., by ~50%).

**Anoxia and histamine release from the human myocardium.** As shown in figure 5, A and B, the selective H$_3$R antagonists thioperamide and clobenpropit each alone increased maximum anoxic NE release by 25% to 30%. Because this suggested that H$_3$R become activated in anoxic conditions, we next assessed whether anoxia promotes histamine release from the human myocardium. To prevent histamine destruction, human right atrial tissue was incubated with the histamine N-methyl transferase inhibitor SKF-91,488 (10 μM; Imamura et al., 1994). After 70 min of anoxia, histamine release into the incubation medium increased by 33% over matched normoxic controls (929 ± 121 vs. 698 ± 65 pmol/g; n = 15, P < .05 by paired t test). SKF-91,448 did not influence NE release: anoxic NE release was ~7-fold greater than in normoxic conditions, whether in the presence (data not shown, n = 15) or absence (fig. 1) of SKF-91,448.

**Discussion**

Our findings indicate that activation of prejunctional H$_3$R suppresses carrier-mediated NE release in a human model of protracted myocardial ischemia and suggest that this action is associated with an inhibition of Na$^+$ accumulation in sympathetic nerve endings.

Exposure of human atrial myocardium to protracted anoxia, instituted by replacement of oxygen with nitrogen, lack of glucose and introduction of a reducing agent (Kurz et al., 1995), elicited a massive release of endogenous NE, which progressively increased in a time-dependent fashion, reaching a maximum plateau after 70 min of exposure. The neu-
nal NE transporter blocker DMI inhibited the anoxic NE release, a strong indication that this release was carrier mediated (Imamura et al., 1996). Notably, when NE release is exocytotic, DMI potentiates it (Imamura et al., 1994); in fact, we found that DMI potentiated NE release only at the beginning of anoxia (see fig. 1). In contrast to NE exocytosis, which is associated with acute myocardial ischemia (Imamura et al., 1994), carrier-mediated NE release occurs in protracted ischemia, when metabolically deprived ion pumps fail and protons accumulate in sympathetic nerve endings, leading to a compensatory NHE activation and intracellular Na\(^+\) accumulation (Dart and Du, 1993; Schömig, 1990). This, coupled with a decreased vesicular storage of NE and its consequent accumulation in the axoplasm, causes a reversal of the NE neuronal uptake (uptake\(_1\)), such that large amounts of NE are actively transported out of the sympathetic nerve terminal (carrier-mediated NE release) (Dart and Du, 1993; Imamura et al., 1996; Kurz et al., 1995; Schömig, 1990).

We found that two different NHE inhibitors, EIPA (Vigne et al., 1983) and HOE 642 (Russ et al., 1996), inhibited anoxic NE release, suggesting that activation of the antiporter was involved in the Na\(^+\) accumulation in sympathetic nerve endings. Also, voltage-dependent Na\(^+\) channels most likely contributed to the intraneuronal accumulation of Na\(^+\) in anoxic conditions, and thus to the reversal of the NE transporter. Accordingly, the Na\(^+\)-channel blocker TTX (Hille, 1992) decreased anoxic NE release, whereas aconitine, which is known to prolong Na\(^+\) channel conductance (Hille, 1992), potentiated it. The fact that anoxic NE release was sensitive to TTX does not necessarily imply that exocytosis played a role in the anoxic release process (Münch et al., 1996). Indeed, as previously indicated, if an exocytic process had been involved, DMI would have potentiated it (Imamura and Levi, 1995). We found that DMI enhanced NE release only at the beginning of anoxia, when exocytosis is known to play a role (Imamura et al., 1994). In contrast, DMI markedly antagonized NE release after 50 and 70 min of anoxia (figs. 1 and 2B). Thus, in this ischemic human model, exocytosis plays only a minor, initial role in the release of NE, whereas reversal of the neuronal transporter in an outward direction is the predominant long-term mechanism of the massive NE release that characterizes protracted anoxia.

The selective H\(_3\)R agonist imetit (Garbarg et al., 1992) markedly attenuated anoxic NE release, an effect that was prevented by the H\(_3\)R antagonists thioperamide (Arrang et al., 1987) and clobenpropit (Barnes et al., 1993; Kathmann et al., 1993). Thus, our findings indicate that activation of H\(_3\)R inhibits carrier-mediated NE release. Having previously demonstrated that H\(_3\)R are located on sympathetic nerve endings in the human heart (Imamura et al., 1995), we suggest that the adrenergic nerve terminal is the site at which H\(_3\)Rs inhibit carrier-mediated NE release in this human model of protracted myocardial ischemia. Because H\(_3\)R activation, unlike DMI, does not inhibit the neuronal uptake of NE (Imamura et al., 1994), the inhibition of carrier-mediated NE release by H\(_3\)R must involve other mechanisms—possibly, a reduction in intraneuronal Na\(^+\) accumulation.

Such reduction could result from an association between H\(_3\)R activation and inhibition of NHE. Indeed, we found that subthreshold concentrations of imetit and EIPA, as well as subthreshold concentrations of imetit and HOE 642, acted synergistically to significantly reduce anoxic NE release when added in combination. Furthermore, subthreshold concentrations of imetit and TTX also acted synergistically to inhibit anoxic NE release. Thus, activation of H\(_3\)R appears to result in an inhibition of both NHE and voltage-dependent Na\(^+\) channels.

H\(_3\)Rs are likely coupled to a pertussis toxin-sensitive G\(_i\)/G\(_o\) protein and effect a reduction in Ca\(^{++}\) current in cardiac sympathetic nerve endings, thus attenuating NE exocytosis in acute myocardial ischemia (Endou et al., 1994; Imamura et al., 1994). Because exocytosis is PKC dependent (Greengard, 1987; Imamura et al., 1995) and H\(_3\)R activation seemingly inhibits phosphoinositide metabolism (Cherifi et al., 1992), this would in turn decrease PKC activity. Thus, PKC inhibition could play an important role in the H\(_3\)-mediated attenuation of NE release in acute myocardial ischemia. Furthermore, because PKC activation is known to stimulate NE (Wakabayashi et al., 1997), an H\(_3\)-mediated decrease in PKC activity would be expected to inhibit NHE. Accordingly, we had proposed that in protracted myocardial ischemia in the isolated guinea pig heart, the reduction of carrier-mediated NE release associated with H\(_3\)R activation may result from an inhibition of NHE in sympathetic nerve endings, secondary to phosphoinositide turnover inhibition and consequent decrease in PKC activity (Imamura et al., 1996). The same mechanism could apply to the H\(_3\)-mediated inhibition of carrier-mediated NE release in the present human model of protracted myocardial ischemia.

It is conceivable that a reduction in PKC activity may also mediate the H\(_3\)-induced inhibition of voltage-dependent Na\(^+\) channels. PKC activation, which is likely to occur with hypoxia (Ju et al., 1996), is known to slow Na\(^+\) current inactivation rate and increase Na\(^+\) channel open probability (Numann et al., 1994). Accordingly, PKC inhibition would decrease the intraneuronal accumulation of Na\(^+\) in anoxic conditions. Another possibility is that G\(_i\)-coupled H\(_3\)Rs reduce intraneuronal cAMP levels by inhibiting adenyl cyclase; this would likely decrease PKA activity. Because PKA stimulates NHE-1 and NHE-2 (Kandasamy et al., 1995) and enhances Na\(^{+}\) current through voltage-operated Na\(^+\) channels (Levitan, 1994), a decrease in PKA activity could reduce the intraneuronal accumulation of Na\(^+\) and, thus, carrier-mediated NE release. Notably, HOE 642 is a selective inhibitor of NHE-1 (Scholz et al., 1995), the predominant NHE isoform in the heart (Loh et al., 1996), whereas NHE-3, which is inhibited by PKC (Tse et al., 1993) and PKA (Moe et al., 1995), is not expressed in the heart (Tse et al., 1993).

Because thioperamide and clobenpropit each alone potentiated anoxic NE release, H\(_3\)Rs must become activated in anoxic conditions. This presupposes the enhanced availability of an endogenous H\(_3\)-ligand in protracted ischemia. Indeed, we found that histamine release was significantly increased in anoxic conditions, suggesting that cardiac adrenergic nerve endings are exposed to functionally significant concentrations of this amine in protracted ischemia, which is in keeping with the very high affinity of H\(_3\)R for histamine (KD = 5 nM) (Hill et al., 1997). Inasmuch as H\(_1\) and H\(_2\) histamine receptors have a relatively low affinity for histamine (KD \(\sim\) 10 \(\mu\)M) (Hill et al., 1997), it is conceivable that depending on the amounts released, endogenous histamine may have antiarrhythmic or arrhythmogenic effects due to H\(_3\)-mediated decrease of NE release (Imamura et al., 1996).
or activation of H3/H2 receptors (Levi et al., 1991), respectively.

Although an enhanced histamine release in myocardial ischemia/reperfusion had already been described in cavian and canine hearts (Imamura et al., 1994, 1996; Levi et al., 1991; Wolff and Levi, 1986, 1988), and an increase in mast cell number and histamine content had been reported in the human heart as a result of ischemia (Forman et al., 1985; Kalsner and Richards, 1984), this is the first demonstration that sufficient histamine is released in the ischemic human heart to activate H3R on sympathetic nerve endings and thus attenuate carrier-mediated NE release.

In view of our previous findings in the guinea pig heart (Imamura et al., 1994, 1996), dog ventricular myocardium (Seyedi et al., 1996) and human atrium (Imamura et al., 1995), H3Rs are most likely present on sympathetic nerve endings in human ventricle. Therefore, our discovery that endogenous histamine, released in a human model of protracted myocardial ischemia, activates H3Rs on sympathetic nerve endings may be clinically relevant. In an ischemia/reperfusion model in the guinea pig, we previously found that NE release directly correlates with the severity of reperfusion arrhythmias and H3R activation reduces NE release and the incidence of ventricular fibrillation by 50% (Imamura et al., 1996). In humans, myocardial infarction is often accompanied by arrhythmias that can be fatal (Braunwald and Sobel, 1988). Sympathetic overactivity and excessive NE release may increase metabolic demand, thus aggravating the primary ischemia and initiating a vicious cycle leading to further myocardial damage (Kübler and Strassier, 1994). Indeed, increased plasma NE levels are a powerful predictor for the development of cardiac failure, angina, myocardial infarction and mortality (Benedict et al., 1996). Therefore, reduction in NE release from cardiac sympathetic nerves is a pivotal protective mechanism. Our findings indicate that H3Rs are likely to mitigate the consequences of sympathetic overactivity in the ischemic human heart and suggest new therapeutic strategies to alleviate dysfunctions associated with myocardial ischemia.

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This article is dedicated to Emeritus Professor Alberto Giotti.

References


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