ABSTRACT
In protracted myocardial ischemia, sympathetic nerve endings undergo ATP depletion, hypoxia and pH reduction. Consequently, norepinephrine (NE) accumulates in the axoplasm, because it is no longer stored in synaptic vesicles, and intraneuronal Na⁺ concentration increases, as the Na⁺/H⁺ exchanger (NHE) is activated. This forces the reversal of the Na⁺-/Cl⁻/dependent NE transporter, triggering a massive carrier-mediated release of NE and thus, arrhythmias. Indeed, NE overflow in myocardial ischemia directly correlates with the severity of arrhythmias. Histamine H₃-receptors (H₃R) have been identified as inhibitory heteroreceptors in adrenergic nerve endings of the heart. In addition to inhibiting NE exocytosis from sympathetic nerve endings, selective H₃R agonists attenuate carrier-mediated release of NE in both animal and human models of protracted myocardial ischemia. Whereas H₃R-mediated attenuation of exocytotic NE release involves an inhibition of N-type Ca²⁺-channels, H₃R-mediated reduction of carrier-mediated NE release is associated with diminished NHE activity. In addition to inhibiting NE release, H₃R stimulation significantly attenuates the incidence and duration of ventricular fibrillation. Although other presynaptic receptors also modulate NE release from sympathetic nerve endings, H₃R stimulation reduces both exocytotic and carrier-mediated NE release, whereas α₂-adrenoceptor agonists attenuate NE exocytosis but enhance carrier-mediated NE release. Furthermore, unlike adenosine A₁-receptors, whose activation reduces both exocytotic and carrier-mediated NE release, H₃R stimulation is devoid of negative chronotropic and dromotropic effects (i.e., sinoatrial and atrioventricular nodal functions are unaffected). Because excess NE release can trigger severe arrhythmias and sudden cardiac death, negative modulation of NE release by H₃R agonists may offer a novel therapeutic approach to myocardial ischemia.

Myocardial Ischemia and Norepinephrine Release
In myocardial ischemia, sympathetic overactivity with excessive norepinephrine (NE) release is a prominent cause of cardiac dysfunction and arrhythmias. Indeed, severe ventricular arrhythmias are the main cause of sudden cardiac death in acute myocardial infarction and in postinfarct patients (Schöming et al., 1991). Animal and clinical studies indicate that reduction of NE release, or blockade of its effects, significantly attenuates ischemic cardiac dysfunction and associated arrhythmias (Schöming et al., 1991; Imamura et al., 1996a; Hatta et al., 1999). Changes in intracellular ion homeostasis, particularly Ca²⁺, are thought to play an important role in reperfusion arrhythmias. Once released from adrenergic nerve endings, NE acts on postsynaptic adrenoceptors to markedly alter the intracellular Ca²⁺ concentration of cardiac myocytes, pacemaker cells, and conducting tissue (see Fig. 1). It does so by increasing the open probability of voltage-dependent transmembrane Ca²⁺-channels and by stimulating IP₃ and Ca²⁺ mobilization via transductional cascades initiated by activation of β- and α-receptors, respectively (Schöming et al., 1991). In addition, NE enhances Na⁺ influx by stimulating the Na⁺/H⁺ exchanger (NHE), leading to a reversal of the Na⁺/Ca²⁺ exchanger (Kurz et al., 1991), and therefore, to more Ca²⁺ influx. Ca²⁺ overload eventually results in dysrhythmia and uncoordinated myocyte contraction.

³-Dependent exocytosis and Ca²⁺-independent carrier-
mediated efflux are the two major mechanisms of NE release from sympathetic nerve endings (Imamura et al., 1994; Kübler and Strasser, 1994). In protracted myocardial ischemia, the predominant mechanism of NE release is via a reversal of the neuronal NE uptake system (carrier-mediated release; see Fig. 1) (Schömig, 1990). This results in a massive efflux of NE, which triggers severe arrhythmias (Schömig, 1990; Imamura et al., 1996a; Hatta et al., 1999).

In protracted myocardial ischemia, sympathetic nerve endings undergo ATP depletion, hypoxia, and intracellular pH reduction (Kübler and Strasser, 1994). The first significant consequence of this altered axoplasmic environment is the inability of sympathetic nerve endings to store NE within synaptic vesicles. Vesicular storage of NE is dependent on the presence of a pH gradient across the vesicular membrane. In physiological conditions this gradient is maintained by an ATP-dependent H⁺-pump that acidifies the vesicular interior. Lack of ATP and reduced axoplasmic pH, both a consequence of anaerobic glycolysis (lactate production and reduced ATP synthesis), decreases the pH gradient and therefore, the driving force for NE storage (Kübler and Strasser, 1994). As a result, free axoplasmic NE accumulates and becomes available for efflux mediated by the Na⁺- and Cl⁻-dependent NE transporter (NET). The trigger for carrier-mediated efflux of free axoplasmic NE is the entrance of Na⁺ in exchange for axoplasmic H⁺ via the NHE (Schömig, 1990; Kurz et al., 1995; Imamura et al., 1996a; Hatta et al., 1997). Activation of the NHE is a compensatory response to the reduced axoplasmic pH. Accumulation of axoplasmic Na⁺ increases the availability of the NET to the inside of the axonal membrane and enhances the affinity of axoplasmic NE for the carrier (Sammet and Graefe, 1979). Once Na⁺, Cl⁻, and NE bind to the NET, carrier-mediated efflux of NE proceeds. That carrier-mediated NE release in protracted myocardial ischemia depends on Na⁺ entry via NHE activation, is supported by the evidence that NHE inhibitors are as effective as NET inhibitors in reducing NE release and ventricular arrhythmias (Imamura et al., 1996a).

Sympathetic nerve endings are endowed with a variety of cell-surface receptors. Among these, autoinhibitory α₂-adrenoceptors are effective modulators of depolarization-evoked NE release in the normoxic heart (Langer, 1977). In acute and protracted myocardial ischemia, several mediators, in addition to NE, are released or produced in the vicinity of sympathetic nerve endings, and subsequently interact with their specific receptors. Histamine, adenosine, angiotensin, and bradykinin all modulate exocytotic and carrier-mediated NE release in myocardial ischemia (Imamura et al., 1994; Imamura et al., 1996a; Hatta et al., 1997; Hatta et al., 1999; Maruyama et al., 1999). Regulation of intracellular Ca²⁺ concentration, which determines the ability of sympathetic nerve endings to store NE within synaptic vesicles. Vesicular storage of NE is dependent on Na⁺ accumulation triggers a massive release of free axoplasmic NE via a reversal of the NET. Released NE acts on postsynaptic adrenoceptors on myocytes, pacemaker cells, and conducting tissue. Stimulation of α₁- and β-adrenoceptors results in an increased intracellular Ca²⁺ concentration via IP₃ production and increased Ca²⁺ channel activity, respectively. Altered Ca²⁺ homeostasis ultimately leads to the development of arrhythmias. Compounds that inhibit the NHE (e.g., EIPA) or NET (e.g., DMI) markedly attenuate carrier-mediated release of NE. H₂R stimulation reduces NHE activity, thus inhibiting carrier-mediated NE release and the incidence of potentially fatal arrhythmias. ARR, arrhythmias; SNE, sympathetic nerve ending; VMAT, vesicular monoamine transporter.

**Fig. 1.** Scheme illustrating the events that trigger carrier-mediated NE release, and consequently, the development of ventricular arrhythmias, in protracted myocardial ischemia. Lack of O₂ results in a switch from aerobic respiration to anaerobic glycolysis. Consequently, ATP is depleted and axoplasmic pH is reduced (due to lactate production). This diminishes vesicular storage of NE, leading to a large increase in free axoplasmic NE. Compensatory activation of NHE by axoplasmic acidification causes the influx of Na⁺ in exchange for H⁺. The resulting Na⁺ accumulation triggers a massive release of free axoplasmic NE via a reversal of the NET. Released NE acts on postsynaptic adrenoceptors on myocytes, pacemaker cells, and conducting tissue. Stimulation of α₁- and β-adrenoceptors results in an increased intracellular Ca²⁺ concentration via IP₃ production and increased Ca²⁺ channel activity, respectively. Altered Ca²⁺ homeostasis ultimately leads to the development of arrhythmias. Compounds that inhibit the NHE (e.g., EIPA) or NET (e.g., DMI) markedly attenuate carrier-mediated release of NE. H₂R stimulation reduces NHE activity, thus inhibiting carrier-mediated NE release and the incidence of potentially fatal arrhythmias. ARR, arrhythmias; SNE, sympathetic nerve ending; VMAT, vesicular monoamine transporter.

**H₃R:** From Negative Feedback Autoreceptors in Central Histaminergic Pathways to Inhibitory Heteroreceptors in Peripheral Adrenergic Nerve Endings

The classification of histamine receptors into three subtypes (H₁, H₂, and H₃) was recently reviewed by Hill et al.
(1997). Briefly, all three receptor subtypes are seven transmembrane-spanning proteins (Hill et al., 1997; Lovenberg et al., 1999), with histamine $K_D$ values of 160 nM, 1 $\mu$M, and 40 nM for $H_3$, $H_2$, and $H_1$ receptors, respectively (Malinowska et al., 1998). $H_3$-receptor activation involves the activation of the phosphoinositide pathway through a pertussis-toxin-insensitive G-protein most likely of the $G_{11}$ class. $H_2$-receptors are coupled to adenyl cyclase via the $G_s$ protein and thus enhance intracellular cyclic AMP concentrations (Hill et al., 1997). $H_3$-receptors are coupled to a pertussis-toxin-sensitive $G_i$ or $G_o$-protein (see below).

The third ($H_3$) histamine receptor subtype was discovered by Schwartz and colleagues as an inhibitory autoreceptor in central histaminergic pathways (Arrang et al., 1983). Subsequently, $H_3$R activation was found to depress adrenergic neurotransmission in the mesenteric artery (Ishikawa and Sperelakis, 1987) and to attenuate the pressor and tachycardic responses to stimulation of the spinal cord and the medulla oblongata (Hey et al., 1992; Malinowska and Schlicker, 1993). Accordingly, in addition to their inhibitory autoreceptor role in histaminergic neurons, $H_3$R appear to function as inhibitory heteroreceptors and, thus, modulate transmitter release from adrenergic endings (for a recent review refer to Malinowska et al., 1998).

**$H_3$R and Cardiac Function**

That $H_3$R may modulate sympathetic neurotransmission in the heart was first suggested by Luo and associates (1991). They demonstrated that the selective histamine $H_3$R agonist (R)-$\alpha$-methylhistamine inhibits the positive inotropic response to field stimulation in the isolated guinea pig right atrium, possibly by a presynaptic action. Our laboratory provided the definitive demonstration that $H_3$R are present on adrenergic nerve endings in the guinea pig heart. Once activated by selective ligands such as (R)-$\alpha$-methylhistamine and imetit (Hill et al., 1997), $H_3$R inhibit NE release elicited by sympathetic nerve stimulation and the associated inotropic and chronotropic responses (Endou et al., 1994; Imamura et al., 1994; Seyedi et al., 1997). Notably, $H_3$R agonists do not affect the response to exogenous NE, indicating an exclusive prejunctional location of $H_3$R. By functional and pharmacological identification, it was furthermore determined that heteroinhibitory $H_3$R are present in sympathetic nerve terminals of the canine (Seyedi et al., 1996) and human heart (Imamura et al., 1995). Recently, selective $H_3$R activation in the dog heart in vivo was shown to decrease the inotropic and chronotropic responses to cardiac sympathetic nerve stimulation and to diminish NE overflow into the coronary sinus (Mazenot et al., 1999a).

The presence of modulatory $H_3$R on adrenergic nerve terminals in the heart infers their possible activation by an endogenous ligand, probably histamine. In support of this notion, the administration of exogenous histamine in combination with $H_1$- and $H_3$R antagonists, significantly inhibits the tachycardia and NE release elicited by sympathetic nerve stimulation in isolated guinea pig hearts, an effect prevented by the $H_3$ antagonist thioperamide (Imamura et al., 1994). Nonetheless, although sympathetic nerve stimulation causes a moderate increase in histamine overflow, this is probably insufficient to activate $H_3$R, because thioperamide affects neither the tachycardia nor the NE release (Imamura et al., 1994). Thus, in physiological conditions cardiac $H_3$R appear to be quiescent, yet available for activation by exogenous ligands. Compared with $H_3$R, other prejunctional modulatory receptors, such as adenosine $A_1$, and $\alpha_2$-adrenoceptors, were found to be quiescent and tonically activated, respectively (Imamura et al., 1994). Indeed, similar to thioperamide, the selective adenosine $A_1$-receptor antagonist N-0861 failed to modify the chronotropic and NE-releasing effects of sympathetic nerve stimulation, whereas the $\alpha_2$-adrenoceptor antagonist yohimbine markedly potentiated the adrenergic responses (Imamura et al., 1994). Collectively, this evidence suggests that in normal conditions, NE released by depolarization of sympathetic nerve terminals is sufficient to activate the $\alpha_2$-mediated negative feedback loop, whereas both $H_3$- and $A_1$-receptors mediate redundant negative modulatory mechanisms of NE release.

**$H_3$R and Ischemic Cardiac Dysfunction**

Short-Lived Myocardial Ischemia: Guinea Pig Model.

Although redundant in normal physiological conditions, $H_3$R might play an important modulatory role in cardiac dysfunction (Imamura et al., 1994). We tested this hypothesis in acute myocardial ischemia, which is characterized by enhanced NE exocytosis (Haass et al., 1989; Schömig, 1990) and increased histamine spillover (Levi et al., 1991). The isolated guinea pig heart subjected to a 10-min period of global ischemia followed by reperfusion was chosen as an initial experimental model. This model closely resembles the state of enhanced NE exocytosis, which occurs in the early phases of myocardial ischemia (Imamura et al., 1994). Typically, the NET inhibitor desipramine enhances NE overflow at reperfusion, confirming the exocytotic nature of this NE release process (Imamura et al., 1994). In this setting, the selective $H_3$R antagonist thioperamide doubled the overflow of NE at reperfusion, indicating that $H_3$R become activated during the ischemic period and control exocytotic NE release from sympathetic nerve endings. In fact, $H_3$R are plausibly fully activated in these ischemic conditions, because the selective $H_3$R agonist (R)-$\alpha$-methylhistamine did not modify NE overflow at reperfusion. This interpretation presupposes the enhanced availability of an endogenous $H_3$ ligand during ischemia. Indeed, histamine spillover into the coronary effluent was increased more than 3-fold at reperfusion, suggesting that during ischemia noradrenergic terminals were exposed to a high concentration of this amine. In contrast, the enhancement in histamine spillover on sympathetic nerve stimulation in normal conditions was only half as large as in ischemia/reperfusion, indicating that local histamine concentrations attained as a result of sympathetic nerve stimulation are insufficient to activate $H_3$R on adrenergic endings. Indeed, blockade of $H_3$R with thioperamide failed to modify NE release in response to adrenergic nerve stimulation, but caused a 2-fold increase in NE release during reperfusion after 10-min of global ischemia (Imamura et al., 1994).

Analogous to $H_3$R, $\alpha_2$- and $A_1$-receptors also appear to become fully activated during the ischemic period. Neither the $\alpha_2$-adrenoceptor agonist UK 14,304 nor the adenosine $A_1$-receptor agonist N6-cyclopentyl-adenosine modified the magnitude of NE overflow at reperfusion. Moreover, similar to thioperamide, the selective $\alpha_2$-adrenoceptor antagonist yohimbine and the $A_1$-receptor antagonist N-0861 each markedly enhanced NE overflow at reperfusion (Imamura et al.,...
More effective than either $\alpha_2$-adrenoceptors or H$_3$R, a likely indication that in these experimental conditions adenosine accumulates in greater local concentrations than either histamine or NE (Imamura et al., 1994).

**Protracted Myocardial Ischemia: Guinea Pig Model.**

Because prejunctional H$_3$R down-regulate NE exocytosis in the early phases of myocardial ischemia (Imamura et al., 1994), H$_3$R may also modulate carrier-mediated NE release during protracted myocardial ischemia. Carrier-mediated NE release is accompanied by reperfusion arrhythmias, whose severity increases with increasing amounts of released NE (see Fig. 2) (Imamura et al., 1996a). Characteristic of carrier-mediated NE release, NE overflow during reperfusion following a 20-min period of global ischemia in isolated guinea pig hearts is blocked by the NET and NHE inhibitors, desipramine and 5-(N-ethyl-N-isopropyl)-amiloride (EIPA), respectively (Figs. 1 and 2). This indicates that an activation of NHE creates the conditions that favor a reversal of the NET. Notably, desipramine and EIPA also prevent the occurrence of reperfusion arrhythmias, thus implicating NE as a major cause of reperfusion arrhythmias (Fig. 2) (Imamura et al., 1996a). Indeed, the selective H$_3$R agonist imetit markedly attenuated the NE overflow during reperfusion, an effect prevented by the selective H$_3$R antagonist thioperamide. Remarkably, imetit acted synergistically with EIPA, suggesting that activation of H$_3$R may lead to inhibition of NHE (Imamura et al., 1996a). In fact, $\alpha_2$-adrenoceptor activation, which is known to stimulate NHE, enhanced NE release, whereas $\alpha_2$-adrenoceptor blockade attenuated it. Furthermore, activation of adenosine A$_1$-receptors markedly attenuated NE release, whereas their inhibition potentiated it (Fig. 2) (Imamura et al., 1996a).

H$_3$R activation markedly reduced the incidence of ventricular fibrillation during reperfusion, and greatly shortened its duration in the remaining cases, demonstrating that these modulatory receptors mitigate the dysfunctional consequences of prolonged myocardial ischemia. $\alpha_2$-Adrenoceptor blockade and adenosine A$_1$-receptor activation also prevented reperfusion arrhythmias. As these antiarrhythmic effects coincided with a marked reduction in NE overflow, our findings highlight the importance of nonexocytotic NE release in the generation of reperfusion arrhythmias (Fig. 2) (Imamura et al., 1996a).

Although H$_3^-$ and adenosine A$_1$-receptor stimulation, as well as $\alpha_2$-adrenoceptor blockade, all reduced carrier-mediated NE release, H$_3$R stimulation may be more advantageous than adenosine A$_1$-receptor activation or $\alpha_2$-adrenoceptor blockade. Unlike adenosine A$_1$-receptor stimulation (Baldardini et al., 1994), H$_3$R activation has no negative chronotropic and dromotropic effects. Furthermore, H$_3$R negatively modulate both exocytotic and carrier-mediated NE release associated with acute and protracted myocardial ischemia, respectively. In contrast, $\alpha_2$-adrenoceptor blockade inhibits carrier-mediated NE, but enhances NE exocytosis (Imamura et al., 1996a).

**Protracted Myocardial Ischemia: Human Model.**

Carrier-mediated NE release was recently described in a human model of myocardial ischemia (Kurz et al., 1995). We used a similar technique to test the hypothesis that H$_3$R activation will inhibit carrier-mediated NE release in the human heart (Hatta et al., 1997). 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 Ca$^{2+}$-independent and inhibited by the NET inhibitor desipramine. Furthermore, the NHE inhibitors EIPA and HOE 642, and the Na$^+$-channel blocker tetrodotoxin, inhibited NE release, whereas the Na$^+$-channel activator aconitine potentiated it. The selective H$_3$R agonist imetit decreased NE release, an effect which was blocked by each of the H$_3$R antagonists thioperamide and clobenpropit (see Fig. 3). Notably, imetit acted synergistically with EIPA, HOE 642, and tetrodotoxin to reduce anoxic NE release (see Fig. 3). Thus, activation of H$_3$R 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 by itself increased NE release, indicating that H$_3$R become activated in myocardial ischemia by the natural ligand (Fig. 3) (Hatta et al., 1997).

Unlike the definite modulatory role of H$_3$R in caviian and human hearts, no attenuation of NE release was observed with H$_3$R stimulation in a protracted ischemia-reperfusion model in the rat heart (Mazenot et al., 1999b). This has been attributed to the well known insensitivity of the rat to histamine (McLeod et al., 1994; Mazenot et al., 1999b).

**Sensory-Adrenergic Nerve Ending Cross-Talk and Myocardial Ischemia.**

Stimulation of sensory neurons in the heart with capsaicin or bradykinin causes the local release of neuropeptides, such as CGRP and Substance P, which stimulate specific receptors on sympathetic nerve terminals and thus release NE (Seyedi et al., 1999). Histamine released from local mast cells by CGRP (Imamura et al., 1996b) activates H$_3$R on both adrenergic (Imamura et al., 1994) and sensory (Imamura et al., 1996b) nerve endings and thus attenuates NE release. In contrast, a decrease in pH potentiates NE release by sensitizing C-fiber endings (Seyedi et al., 1999). Thus, in myocardial ischemia, when protons accumulate, sensory C-fibers become activated, and bradykinin release is enhanced, the H$_3$R-mediated negative feedback

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**Fig. 2.** Correlation between duration of ventricular fibrillation and magnitude of NE overflow into the coronary effluent of isolated guinea pig hearts subjected to 20-min global ischemia followed by 45-min reperfusion. Each point is the mean of 4 to 6 experiments, except for the control point, which is the mean of 14 experiments. The line was calculated by regression analysis ($r =$ correlation coefficient). DMI (10 nM; NET inhibitor); EIPA (10 uM; NHE inhibitor); CPA, $N^\omega$-cyclopropyl-adenosine (100 nM; $\alpha_1$-receptor agonist); Yoh, yohimbine (1 uM; $\alpha_2$-adrenoceptor antagonist); Im, imetit (100 nM; H$_3$R agonist); UK, UK 14,304 (10 uM; $\alpha_2$-adrenoceptor agonist); CPA, 8-cyclopentyladenosine (100 nM; $\alpha_2$-adrenoceptor agonist); Yoh, yohimbine (1 uM; $\alpha_2$-adrenoceptor antagonist); Im, imetit (100 nM; H$_3$R agonist); UK, UK 14,304 (10 uM; $\alpha_2$-adrenoceptor agonist); and N,N,0861 (5 uM; $\alpha_1$-receptor antagonist). Figure modified from Imamura et al., 1996a.
H₃R: Signal Transduction

Until the recent cloning of the human H₃R (Lovenberg et al., 1999), little was known about the intracellular signal transduction pathway initiated by H₃R activation. Several investigators suggested that the H₃R is a Gᵢ- or Gᵢₐ-coupled receptor, because both functional and binding studies with selective H₃R agonists demonstrate a sensitivity of the receptor to pertussis toxin (Endou et al., 1994; Hill et al., 1997). Reduction of NE exocytosis from sympathetic nerves in the normoxic heart by H₃R stimulation is associated with an inhibition of N-type Ca²⁺ channels (Endou et al., 1994). The inhibitory action of H₃R stimulation on N-type Ca²⁺ channels has been verified by direct channel current measurements in central histaminergic fibers (Takeshita et al., 1998).

It is less well understood how H₃R stimulation inhibits carrier-mediated release of NE in protracted myocardial ischemia. H₃R stimulation is associated with a reduced NHE activity (Imamura et al., 1996a; Hatta et al., 1997), but the second messengers mediating this response remain unclear. Because protein kinase C is known to stimulate the NHE, the inhibitory action of H₃R on carrier-mediated NE release might result from a reduction in protein kinase C activity (Imamura et al., 1996a). This proposal was motivated in part by the report that H₃R stimulation inhibits phospholipase C in the HGT-1 gastric tumor cell line (Cherifi et al., 1992). This finding, however, has yet to be confirmed by other laboratories. Only now, with the cloning of the H₃R, has a direct coupling of H₃R stimulation to adenylyl cyclase been demonstrated. Lovenberg and colleagues (1999) cloned an H₃R from a human thalamus cDNA library. When the receptor was transfected into a variety of cell lines, the ability to inhibit forskolin-stimulated cAMP formation with a selective H₃R agonist (R-α-methylhistamine) was confirmed. In SK-NMC human neuroblastoma cells (Biedler et al., 1973) expressing this cloned H₃R cDNA, we recently observed the same potent, dose-dependent, inhibitory action of R-α-methylhistamine on forskolin-stimulated cAMP formation (R.L. and N.C.E.S., unpublished observation). Interestingly, before H₃R cloning, several research groups had failed to see H₃R-mediated inhibition of adenylyl cyclase (Hill et al., 1997). How H₃R inhibit NHE and, thus, carrier-mediated NE release in protracted myocardial ischemia remains to be determined. Hopefully, with the availability of H₃R cDNA, this and other important questions will be answered.

Acknowledgments

We thank Paul A. Moench and Christina J. Mackins for helpful editorial suggestions.

References


Conclusions

Excessive NE release is characteristic of myocardial ischemia and is associated with severe arrhythmias and sudden cardiac death. In protracted myocardial ischemia, free NE accumulates in the axoplasm of adrenergic terminals, due to diminished vesicular storage, whereas intraneuronal Na⁺ increases, secondary to NHE activation. This triggers the reversal of the NET and, hence, a massive release of NE, which disturbs Ca²⁺ homeostasis in myocytes, pacemaker cells, and conducting tissue, causing arrhythmias and cardiac dysfunction (see Fig. 1). Activation of H₃R significantly inhibits carrier-mediated NE release and alleviates reperfusion arrhythmias (see Fig. 2). Stimulation of H₃R most likely leads to a reduction in NHE activity (see Fig. 3), although the signal transduction pathway mediating this response remains to be determined. Unlike other presynaptic negative modulatory receptors (e.g., adenosine A₁-receptors) H₃R activation is devoid of negative chronotropic and dromotropic effects. Furthermore, although α₂-adrenergic receptor stimulation reduces NE exocytosis, it actually enhances carrier-mediated NE release. Because H₃R stimulation decreases carrier-mediated NE release in the human heart, selective H₃R agonists may represent a new therapeutic frontier in myocardial ischemia.

Fig. 3. Human model of protracted myocardial ischemia: inhibition of anoxic NE release from right atrial tissue by the selective H₃R agonist imetit (100 nM) (A) and subthreshold concentrations of the NHE blocker, HOE 642 (3 μM) and imetit (30 nM) in combination (B). Human atrial tissue was incubated without any drug (control) or with (A) imetit and the selective H₃R antagonist clobenpropit (CBP; 25 nM), either alone or in combination, (B) subthreshold concentrations of imetit (30 nM) and HOE 642 (3 μM), either alone or in combination. Bars are mean ± S.E. values of total NE released into the incubation medium during 70 min of anoxia (n = 5–12; *P < .05 and **P < .01 from control, respectively; †P < .05 and ††P < .01 from imetit, respectively, by ANOVA followed by post hoc Bonferroni’s test). Figure modified from Hatta et al., 1997.


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