Bradykinin Activates a Cross-Signaling Pathway between Sensory and Adrenergic Nerve Endings in the Heart: A Novel Mechanism of Ischemic Norepinephrine Release?1

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ABSTRACT

We had shown that bradykinin (BK) generated by cardiac sympathetic nerve endings (i.e., synaptosomes) promotes exocytotic norepinephrine (NE) release in an autocrine mode. Because the synaptosomal preparation may include sensory C-fiber endings, which BK is known to stimulate, sensory nerves could contribute to the proadrenergic effects of BK in the heart. We report that BK is a potent releaser of NE from guinea pig heart synaptosomes (EC50; 20 nM), an effect mediated by B2 receptors, and almost completely abolished by prior C-fiber destruction or blockade of calcitonin gene-related peptide and neurokinin-1 receptors. C-fiber destruction also greatly decreased BK-induced NE release from the intact heart, whereas tyramine-induced NE release was unaffected. Furthermore, C-fiber stimulation with capsaicin and activation of calcitonin gene-related peptide and neurokinin-1 receptors initiated NE release from cardiac synaptosomes, indicating that stimulation of sensory neurons in turn activates sympathetic nerve terminals. Thus, BK is likely to release NE in the heart in part by first liberating calcitonin gene-related peptide and Substance P from sensory nerve endings; these neuropeptides then stimulate specific receptors on sympathetic terminals. This action of BK is positively modulated by cyclooxygenase products, attenuated by activation of histamine H3 receptors, and potentiated at a lower pH. The NE-releasing action of BK is likely to be enhanced in myocardial ischemia, when protons accumulate, C fibers become activated, and the production of prostaglandins and BK increases. Because NE is a major arrhythmogenic agent, the activation of this interneuronal signaling system between sensory and adrenergic neurons may contribute to ischemic dysrhythmias and sudden cardiac death.

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ABBREVIATIONS: BK, bradykinin; CGRP, calcitonin gene-related peptide; NE, norepinephrine.
Materials and Methods

NE Release from Cardiac Synaptosomes. Male Hartley guinea pigs (Harlan Bioproducts for Science, Inc., Indianapolis, IN) weighing 250 to 300 g were sacrificed by cervical dislocation under light anesthesia with CO2 vapor in accordance with institutional guidelines. The rib cage was dissected away, and the heart was rapidly excised, freed from fat and connective tissue, and transferred to a Langendorff apparatus (Park et al., 1992). Spontaneously beating hearts were perfused through the aorta for 15 min at constant pressure (40 cm of H2O) with Ringer's solution at 37°C saturated with 100% O2 (pH 7.5; Park et al., 1992). This procedure ensured that no blood traces remained in the coronary circulation. When indomethacin was used, hearts were perfused with indomethacin (10 μM) for an additional 10 min. In either case, at the end of the perfusion, hearts were minced in ice-cold 0.32 sucrose containing 1 mM EGTA, pH 7.4. Synaptosomes were isolated as previously described (Seyedi et al., 1997). Minced tissue was digested with 40 mg collagenase (type 2; Worthington Biochem. Corp., Freehold, NJ) per 10 ml of HEPES-buffered saline solution (HBS) per gram of wet heart weight for 1 h at 37°C. HBS contained 1 mM pargyline to prevent enzymatic destruction of synaptosomal NE. After low-speed centrifugation (10 min at 120g at 4°C), the resulting pellet was suspended in 10 volumes of 0.32 M sucrose and homogenized with a Teflon/glass homogenizer. The homogenate was spun at 650g for 10 min at 4°C and the pellet rehomogenized and respun. The pellet containing cellular debris was discarded, and the supernatants from the last two spins were combined and equally subdivided into 10 to 12 tubes. Each tube was centrifuged for 20 min at 20,000g at 4°C. This pellet, which contained cardiac synaptosomes, was resuspended in HBS to a final volume of 500 μl in the presence or absence of pharmacological agents for a total of 20 min in a water bath at 37°C. Each suspension functioned as an independent sample and was used only once. In every experiment, one sample was untreated (control, basal NE release), and others were incubated with drugs for 20 min. When antagonists were used, samples were incubated with the antagonist for 20 min before incubation with the agonist. Controls were incubated for an equivalent length of time without drugs. At the end of the incubation period, each sample was centrifuged for 20 min (20,000g at 4°C). The supernatant was assayed for NE content by HPLC with electrochemical detection (Seyedi et al., 1997). The pellet was assayed for protein content by a modified Lowry procedure (Seyedi et al., 1997).

Capsaicin Pretreatment In Vivo. Guinea pigs were anesthetized with pentobarbital sodium (25 mg/kg i.p.) and artificially ventilated with a rodent respirator (Harvard Apparatus), according to institutional guidelines. Theophylline (100 mg/kg i.p.) was given to counteract respiratory impairment. Capsaicin (total dose, 50 mg/kg s.c.) was administered 6 h before in vitro experimentation; this has been shown to cause a total loss of CGRP-containing nerves within the heart (Imamura et al., 1996b). Control animals received the same treatment except for capsaicin. Hearts from control and capsaicin-treated animals were excised and perfused in the Langendorff apparatus as described above. Most hearts were used for the preparation of synaptosomes. Others were perfused with BK (1 μM) for 20 min to determine whether C-fiber destruction affects the ability of BK to elicit NE release from the intact heart. Destruction of C fibers in capsaicin-pretreated hearts was ascertained by measuring NE overflow in response to a 20-min capsaicin (1 μM) perfusion. NE availability in capsaicin-pretreated hearts was assessed by measuring NE overflow in response to a 20-min tyramine (1 μM) perfusion. NE overflow into the coronary effluent was assayed by HPLC (as described above) before and during perfusions with capsaicin, BK, and tyramine.

Statistics. Values are expressed as mean percent increases above basal NE release (synaptosomes) or basal NE overflow (isolated hearts) ± S.E. There were no statistically significant differences in basal NE release among the various experiments. Analysis by one-way ANOVA was used, followed by post hoc testing (Dunnett’s test). In two instances (see Figs. 7 and 8), paired and unpaired Student’s t tests were used, respectively. A value of p < .05 was considered statistically significant. The EC50 for BK-induced NE release was calculated by nonlinear regression curve fitting with the GraphPad Prism program (GraphPad Software, Inc., San Diego, CA).

Drugs and Chemicals. CGRP, CGRP8–37, and Substance P were purchased from Peninsula Labs., Inc. (Belmont, CA). Capsazepine, Hoe 140, imetit dihydrobromide, and thioperamide maleate were purchased from Research Biochemicals International (Natick, MA). Atrpine sulfate, BK, [des-arg9leu8]BK, capsaicin, indomethacin, theophylline, and tyramine hydrochloride were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO). CP 99,994 was a gift from Pfizer Central Research. Capsazepine was dissolved in 100% ethanol. Capsazepine and indomethacin were dissolved in dimethyl sulfoxide. Further dilutions were made with distilled water; at the concentration used, dimethyl sulfoxide and ethanol did not affect mediator release.

Results

Release of Synaptosomal NE by BK and Capsaicin. Incubation of the cardiac synaptosomal fraction with 1 to 100 nM BK caused a concentration-dependent NE release that reached a maximum of ∼32% above basal level (EC50 ~20 nM; Fig. 1). The concentration-response curve was not modified in the presence of atropine (1 μM; Fig. 1). The BK B2-receptor antagonist HOE 140 (3 nM; ~pA2) caused a marked downward shift in the BK concentration-response curve. In contrast, the B1-receptor antagonist [des-arg9leu8]BK (1 μM; 2.5 × pA2) failed to shift the BK concentration-response curve (Fig. 1).

Fig. 1. As a function of its concentration (EC50 ~20 nM), BK elicits the release of endogenous NE from guinea pig heart synaptosomes. The BK B2-receptor antagonist Hoe 140 (3 nM) blocks the effect of BK, whereas the BK2-receptor antagonist [des-Arg9-Leu8]BK (1 μM) does not. Atropine (1 μM) does not modify the BK concentration-response curve. Points are mean increases in NE release above basal level (±S.E.) in the presence of BK alone (n = 16) or together with atropine (n = 8), Hoe 140 (n = 6), or [des-Arg9-Leu8]BK (n = 16). Basal NE release was 1.46 ± 0.11 pmol/mg of protein before BK and 1.53 ± 0.09 pmol/mg of protein before BK in the presence of atropine or the BK-receptor antagonists. *p < .01 versus BK-evoked NE release, by ANOVA followed by post hoc Dunnett’s test.
reduced by ~60% in the presence of the capsaicin-receptor antagonist capsazepine (10 μM). When synaptosomes were isolated from hearts of guinea pigs pretreated in vivo with capsaicin (50 mg/kg, 6 h earlier) to destroy sensory C fibers (Imamura et al., 1996b), NE release in response to a subsequent incubation with capsaicin was reduced by ~60% as compared with cardiac synaptosomes from sham-treated animals (Fig. 3A). Similarly, capsaicin pretreatment in vivo reduced the response of cardiac synaptosomes to BK by ~75% (Fig. 3B).

**Release of Synaptosomal NE by CGRP and Substance P.** Incubation of the synaptosomal fraction with capsaicin or BK in the presence of antagonists of the sensory neuropeptide transmitters CGRP and Substance P greatly diminished the effects of capsaicin and BK. The CGRP-receptor antagonist CGRP<sub>8-37</sub> (1 μM; pK<sub>i</sub>, 6.5–8.0; Bell and McDermott, 1996) decreased the NE-releasing effects of capsaicin and BK by 50 to 60% (n = 6 + 6, p < .01). The Substance P/tachykinin neurokinin-1 (NK<sub>1</sub>)-receptor antagonist CP 99,994 (100 nM; pK<sub>i</sub>, 7.3–9.3; Regoli et al., 1994) decreased the NE-releasing effects of capsaicin and BK by ~60% (n = 6 + 6, p < .01). As shown in Fig. 4, A and B, when these neuropeptide-receptor antagonists were used in combination, at 5- and 10-fold greater concentrations (i.e., CGRP<sub>8-37</sub> 5 μM and CP 99,994 1 μM), the blockade of the NE-releasing effect of capsaicin and BK remained at a 60 to 65% level.

CGRP (100 nM) and Substance P (1 μM) each induced NE release from cardiac synaptosomes. As shown in Fig. 4, C and D, CGRP and Substance P caused a ~40% and ~30% increase in NE release above basal levels, respectively. The NE-releasing effect of CGRP was antagonized by the CGRP-

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**Fig. 2.** The sensory neuron excitotoxin capsaicin elicits the release of endogenous NE from guinea pig heart synaptosomes. The synaptosomal fraction was incubated with capsaicin (100 nM) in the absence or presence of the capsaicin-receptor antagonist capsazepine (10 μM). Bars represent mean values (± S.E., n = 6–10). Basal NE release was 1.26 ± 0.07 pmol/mg of protein; **p < .01 versus basal NE level; ††p < .01 versus capsaicin-evoked NE release, by ANOVA followed by post hoc Dunnett’s test.

**Fig. 3.** Release of endogenous NE from guinea pig heart synaptosomes on incubation with capsaicin (100 nM; A) or BK (50 nM; B). Prior destruction of sensory C fibers by the in vivo administration of capsaicin to guinea pigs (50 mg/kg, 6 h earlier; capsaicin pretreated) markedly attenuates the effects of the subsequent administration of capsaicin and BK to cardiac synaptosomes. Columns represent means ± S.E. (n = 6–10). Basal NE release from cardiac synaptosomes from control and capsaicin-pretreated animals was 1.54 ± 0.08 and 1.84 ± 0.13 pmol/mg of protein, respectively. **p < .01 versus basal NE release; ††p < .01 versus control, by ANOVA followed by post hoc Dunnett’s test.

**Fig. 4.** Top, release of endogenous NE from guinea pig heart synaptosomes on stimulation of C-fiber endings with capsaicin (100 nM; A) or BK (50 nM; B). The effects of capsaicin and BK are both inhibited by a combination of CGRP- and Substance P-receptor antagonists [CGRP<sub>8-37</sub> (5 μM) and CP 99,994 (1 μM), respectively]. Bottom, incubation of the synaptosomal fraction with the sensory neuropeptide transmitters CGRP (100 nM; C) and Substance P (SP, 1 μM; D) elicits the release of endogenous NE. This effect is inhibited by the CGRP and SP antagonists (C and D, respectively). Columns are means ± S.E. (n = 12 for A and B and 7 or 8 for C and D). Basal NE release was 1.40 ± 0.13 pmol/mg of protein for A and B and 1.54 ± 0.08 pmol/mg of protein for C and D. **p < .01 versus basal NE level; ††p < .01 versus capsaicin- and BK-evoked NE release; †p < .05 versus CGRP- and SP-evoked NE release, by ANOVA followed by post hoc Dunnett’s test.
receptor blocker CGRP

Modulation of BK- and Capsaicin-Induced Release of NE from Cardiac Synaptosomes. Inhibition of cyclooxygen-

The histamine H3-receptor agonist imetit (100 nM) diminish-

Acidosis greatly potentiated the NE-releasing effect of BK. As shown in Fig. 7, a reduction in pH from 7.4 to 7.0, 6.5, and 5.5 caused a progressive leftward and upward shift of the concentration-response curve for the BK-induced NE release. Thus, at pH levels between 7.0 and 5.5, the effect of any given BK concentration was ~20 to 90% greater than at pH 7.4. Basal NE release was unaffected by lowering the pH from 7.4 to 6.5 (basal NE release was 1.50 ± 0.06, 1.53 ± 0.06, and 1.59 ± 0.06 pmol/mg protein at pH 7.4, 7.0, and 6.5, respectively; n = 8–20; not significant). In contrast, at pH 5.5, basal NE release was ~40% greater than at pH 7.4 (p < .01); addition of BK further increased NE release by ~50%.

BK-Enhanced NE Overflow from Isolated Guinea Pig Hearts: Modification by Capsaicin Pretreatment. We next determined whether C-fiber destruction affects the ability of BK to elicit NE release from the intact heart. As shown in Fig. 8A, the overflow of NE from isolated guinea pig hearts increased by 48% during a 20-min perfusion with BK (1 μM). In contrast, in hearts from capsaicin-pretreated animals, NE overflow increased only by 17% in response to BK (p < .001, by unpaired Student’s t test; Fig. 8A). Not shown in Fig. 8 is that NE overflow increased by 45.8 ± 12.2% in response to a 20-min perfusion with capsaicin (1 μM) but only by 10.5 ± 5.0% in capsaicin-pretreated hearts (p < .05; n = 4 + 4). In contrast, the increase in NE overflow elicited by a 20-min perfusion with tyramine (1 μM) was unaffected by capsaicin pretreatment (Fig. 8B), indicating that the diminished BK and/or capsaicin response in capsaicin-pretreated hearts was not caused by a loss in NE availability.

Discussion

Our findings demonstrate that stimulation of cardiac sensory C fibers with BK elicits the release of NE from sympathetic nerve endings, an action attenuated by prior C-fiber destruction or by CGRP- and Substance P-receptor antagonists. This suggests that BK, at least in part, initiates the release of CGRP and Substance P from C fibers; these neu-

Fig. 5. Pretreatment with the cyclooxygenase inhibitor indomethacin (10 μM; see Materials and Methods) markedly attenuates the capsaicin (100 nM; A)– and BK (50 nM; B)–induced release of endogenous NE from guinea pig heart synaptosomes. Columns represent means ± S.E. (n = 6 for both A and B). Basal NE release was 2.31 ± 0.18 pmol/mg of protein for control. **p < .01 versus basal NE release; ††p < .01 versus capsaicin- and BK-evoked NE release, by ANOVA followed by post hoc Dunnett’s test.

Fig. 6. The histamine H3-receptor agonist imetit (100 nM) attenuates the capsaicin (100 nM; A)– and BK (50 nM; B)–induced release of endogenous NE from guinea pig heart synaptosomes. The effect of imetit is abolished by the histamine H3-receptor antagonist thioperamide (Thiop; 0.3 μM). Columns represent means ± S.E. (n = 16 for both A and B). Basal NE release was 1.06 ± 0.03 pmol/mg of protein. **p < .01 versus basal NE level; †p < .01 and ††p < .05 versus capsaicin- and BK-evoked NE release (for A and B, respectively), by ANOVA followed by post hoc Dunnett’s test.
Ropeptides subsequently act on adrenergic nerve endings to promote NE release. This action of BK is mediated by B_2 receptors; positively and negatively modulated by cyclooxygenase products and histamine H_3 receptors, respectively; and greatly potentiated at a lower pH.

We had previously reported that BK promotes NE release from adrenergic nerve endings in a preparation of cardiac synaptosomes (Seyedi et al., 1997). This synaptosomal fraction is likely to contain other types of nerve endings, such as cholinergic terminals and unmyelinated sensory C fibers. Inasmuch as atropine does not modify the NE-releasing effects of BK (Seyedi et al., 1997; see also Fig. 1), cholinergic nerves are not likely to contribute to these effects. In contrast, sensory C fibers are known to be highly sensitive to BK (Franco-Cereceda, 1988; Geppetti, 1993; Wood and Docherty, 1997). Thus, we questioned whether the cardiac sympathomimetic effects of BK might be initiated in part by an action on sensory nerves, subsequently relayed to adrenergic terminals.

First, we established that, in addition to its proexocytotic effects (Kurz et al., 1997; Seyedi et al., 1997; Chulak et al., 1998), BK elicits the release of endogenous NE from cardiac adrenergic nerves even in the absence of K⁺-induced depolarization. We found this action to be as potent (EC_{50} ≈ 20 nM) as the proexocytotic effect of BK (EC_{50} ≈ 17 nM; Seyedi et al., 1997) and mediated by B_2 receptors. In fact, B_2 receptors have been consistently found to mediate the proadrenergic effects of BK (McDonald et al., 1994; Minshall et al., 1994; Chulak et al., 1995, 1998; Poxton, 1995; Dendorfer et al., 1996; Boehm and Huck, 1997; Rump et al., 1997; Seyedi et al., 1997).

Next, we sought to demonstrate that chemical stimulation of cardiac sensory C fibers results in NE release from adrenergic terminals. For this we used capsaicin, a highly specific sensory neuron excitotoxin and vanilloid-receptor agonist (Caterina et al., 1997; Wood and Docherty, 1997). We found that incubation of the cardiac synaptosomal fraction with capsaicin caused the release of endogenous NE, and this effect was inhibited by the vanilloid-receptor blocker capsazepine (Bevan et al., 1992; Caterina et al., 1997; Wood and Docherty, 1997). Moreover, prior destruction of sensory C fibers by pretreatment with capsaicin in vivo (Imamura et al., 1996b) greatly reduced NE release in response to a subsequent capsaicin administration to the intact heart and cardiac synaptosomes. This is the first demonstration that stimulation of cardiac sensory neurons in turn activates sympathetic nerve terminals.

Most important, we found that, analogous to capsaicin, nearly complete destruction of sensory C fibers markedly decreased the NE-releasing activity of BK, both in the intact heart and in the synaptosomal fraction. This decreased BK response was not caused by NE depletion. Indeed, we found that tyramine released the same amount of NE from control and capsaicin-pretreated hearts. These findings clearly indicate that sensory nerve terminals play an important role in the sympathomimetic effects of BK in the heart.

To identify the chemical signals by which sensory terminals may communicate with adrenergic fibers, we used two neuropeptide-receptor antagonists, CGRP_{8-37} and compound CP 99,994, that specifically block the effects of CGRP and

![Fig. 7. Acidosis potentiates the BK-induced release of endogenous NE from guinea pig heart synaptosomes. The synaptosomal fraction was incubated in control (pH 7.4) or acidic (pH 7.0, 6.5, and 5.5) conditions. Points are mean ± S.E. increases in NE release above basal level (n = 8–20). Basal NE release was 1.50 ± 0.06, 1.53 ± 0.06, 1.59 ± 0.06, and 2.15 ± 0.13 pmol/mg of protein, for pH 7.4, 7.0, 6.5, and 5.5, respectively. *p < .05 versus pH 7.4 by paired Student’s t test. ††p < .01 versus pH 6.5 by unpaired Student’s t test.]

![Fig. 8. Sensory C-fiber destruction by in vivo capsaicin pretreatment decreases the ability of BK but not of tyramine to elicit NE release from the intact guinea pig heart (see Materials and Methods for details). Columns represent mean ± S.E. increases above basal NE overflow (n = 5 for each column). Basal NE overflow was 0.50 ± 0.05 pmol · g⁻¹ · min⁻¹ (n = 20). **p < .01 versus control overflow by unpaired Student’s t test.]

To identify the chemical signals by which sensory terminals may communicate with adrenergic fibers, we used two neuropeptide-receptor antagonists, CGRP_{8-37} and compound CP 99,994, that specifically block the effects of CGRP and
Substance P with $K_D$ in the high and low nanomolar range, respectively (Regoli et al., 1994; Bell and McDermott, 1996). We found that the administration of exogenous CGRP and Substance P elicited the release of synaptosomal NE and that these effects were inhibited by CGRP$_{8-37}$ and CP 99,994, respectively. Furthermore, we found that the NE-releasing effects of capsaicin and BK were markedly reduced by blockade of CGRP and Substance P receptors. This suggests that BK ultimately releases NE in the heart by first liberating CGRP and Substance P from sensory nerve endings; these neuropeptides then stimulate specific receptors on sympathetic nerve endings. Indeed, BK is known to release CGRP from capsaicin-sensitive nerves in guinea pig atria (Geppetti et al., 1990). We found that the NE-releasing effect of BK was not further reduced when CGRP$_{8-37}$ and CP 99,994 were used in combination at 5- and 10-fold greater concentrations. Similarly, a small portion of the NE-releasing effect of BK persisted even after destruction of C fibers. Thus, BK appears to act for the most part on sensory C fibers and to a lesser extent directly on sympathetic nerve endings.

Prostaglandins are known to enhance the actions of BK on sensory nerves. Indeed, sensory neurons are endowed with cyclooxygenase activity, and indomethacin attenuates the BK-stimulated release of CGRP and Substance P from sensory neurons in culture (Vasko et al., 1994) and of CGRP from guinea pig atria (Geppetti et al., 1990). Furthermore, the BK-induced release of Substance P in the kidney is a prostaglandin-dependent phenomenon (Kopp et al., 1997), and the cyclooxygenase system contributes to enhanced BK responsiveness of chemosensitive nerve endings in heart failure (Schultz et al., 1997). Accordingly, we assessed whether endogenous prostaglandins play a role in the C-fiber-dependent sympathomimetic effects of BK in the heart. We found that pretreatment of isolated guinea pig hearts with indomethacin markedly reduced the ability of BK to release NE from the synaptosomal fraction. Analogous to BK, the NE-releasing effect of capsaicin was also significantly decreased. Thus, the C-fiber-initiated release of NE from cardiac sympathetic nerve terminals comprises a cyclooxygenase-dependent step. Conceivably, cyclooxygenase products could augment the release of neuropeptide transmitters from activated sensory fibers (Vasko et al., 1994). Also, prostaglandins may play a role in the BK-stimulated release of CGRP and Substance P from sensory nerve endings; these effects were inhibited by CGRP$_{8-37}$ and CP 99,994, respectively (Regoli et al., 1994; Bell and McDermott, 1996). Furthermore, we found that the NE-releasing effect of BK persisted even after destruction of C fibers. Thus, BK appears to act for the most part on sensory C fibers and to a lesser extent directly on sympathetic nerve endings.

In conclusion (see Fig. 9), our data suggest that BK initiates the antidromic release of CGRP and Substance P by activating B$_2$ receptors on afferent sensory C fibers (Maggi, 1995); these neuropeptides subsequently act on CGRP and NK$_1$ receptors at adrenergic endings and promote NE release. In addition, but probably to a smaller extent, BK releases NE by directly stimulating B$_2$ receptors at adrenergic terminals (Seyedi et al., 1997). Because BK can be generated by cardiac sympathetic nerve endings (Seyedi et al., 1997), our findings identify a novel paracrine cross talk between adrenergic and sensory nerve endings in the heart, whereby BK formed at sympathetic endings activates sensory fibers that in turn stimulate sympathetic endings via neuropeptide release. Histamine released from local mast cells by BK (Imamura et al., 1996b) acts at inhibitory histamine H$_3$ receptors located at both adrenergic (Imamura et al., 1995) and sensory (Imamura et al., 1996b) nerve endings as part of a BK-initiated negative-feedback loop that ultimately limits NE release. In contrast, cyclooxygenase...
products appear to augment the sympathomimetic action of BK in the heart. Because the effect of BK is potentiated at a lowered pH, the NE-releasing action of BK is likely to be greatly enhanced in the setting of myocardial ischemia, where protons accumulate (Hirche et al., 1980; Ichihara et al., 1991; Opie, 1991). C fibers become activated (Franco-Cereceda, 1988; Milner et al., 1989; Franco-Cereceda and Lundberg, 1992; Wood and Docherty, 1997), and the production of prostaglandins (Berger et al., 1976, 1977; Kraemer et al., 1976) and BK (Kimura et al., 1973; Matsuki et al., 1987; Lamontagne et al., 1985) increases. Because NE is a major arrhythmogenic agent (Schömig, 1990; Schömig et al., 1991; Imamura et al., 1996a), the activation of this sensory/adrenergic interneuronal cross-talk system may contribute to ischemic dysrhythmias and sudden cardiac death.

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References


Fig. 9. Proposed cross talk between sympathetic nerve terminals (SNE) and capsaicin-sensitive sensory C-fiber endings (SCFE) in the guinea pig heart. The kallikrein-kinin system in adrenergic nerve endings generates enough BK to activate B2 receptors in an autocrine (SNE) and paracrine (SCFE) fashion. BK-stimulated C fibers release CGRP and Substance P in an antidromic mode. CGRP and Substance P then act at CGRP_3,7-sensitive CGRP receptors and CP 99,994-sensitive NK1 receptors on SNE to evoke NE release. Protons potentiate BK’s action on SCFE. Negative modulatory histamine (HIST) H2 receptors are present on both SNE and SCFE. Cyclooxygenase products (PG) enhance the NE-releasing effect initiated by BK or capsaicin. Capsazepine inhibits the effect of capsaicin on SCFE.


Imamura M, Smith NC, Garbarg M and Levi R (1996b) Histamine H2-receptor-


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