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Bradykinin B_2 receptors in nodose ganglia of rat and human

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Abstract

The present study has employed in vitro electrophysiology to characterise the ability of bradykinin to depolarise the rat isolated nodose ganglion preparation, containing the perikarya of vagal afferent neurons. Both bradykinin and kallidin elicited a concentration-dependent (1–100 nM) depolarisation when applied to the superfusate bathing the nodose ganglia, whereas the bradykinin B_1 receptor agonist, des-Arg^9-bradykinin, was only effective in the micromolar range. Furthermore, the electrophysiological response to bradykinin was antagonised by the bradykinin B_2 receptor antagonist, D-arginyl-L-arginyl-L-prolyl-*trans*-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2α,3β,7aβ)-octahydro-1*H*-indole-2-carbonyl-L-arginine (Hoe 140), in a concentration-related manner. To determine the anatomical location of functional bradykinin B_2 receptors, in vitro autoradiography with [^{125}I] *para*-iodophenyl Hoe 140 was performed on sections of rat and human inferior vagal (nodose) ganglia and confirmed the presence of binding over vagal perikarya. Collectively, these data provide evidence for functionally relevant bradykinin B_2 receptors on vagal afferent neurons, which are apparently also present on human vagal perikarya.

Keywords: Bradykinin; Bradykinin B_2 receptor; Nodose ganglion; Electrophysiology; Autoradiography

1. Introduction

The nonapeptide bradykinin, and related kinins such as kallidin result from enzymatic cleavage of kininogens by kallikreins (Margolius, 1989). The physiological actions of kinins are mediated via actions at bradykinin B_1 and B_2 receptors that have been cloned (McEachern et al., 1991) and shown to be encoded by distinct mRNAs (Webb et al., 1994). Numerous pharmacological studies have implicated a role for bradykinin in cardiovascular control mechanisms. Thus, activation of bradykinin B_2 receptors on sympathetic afferent terminals innervating the heart mediates sympathetic cardiac chemoreflexes in the dog (Kaufman et al., 1980; Staszewska-Woolley et al., 1988). Similarly, both the hypertension induced by intrasplenic injection of bradykinin and the hypotension induced by intravenous bradykinin are bradykinin B_2 receptor-mediated (Louttit and Coleman, 1993). Central pressor actions of bradykinin on the cardiovascular system were demonstrated following intracerebroventricular (i.c.v.) (Privitera, 1992) and intrathecal (Lopes et al., 1993) administration. Specific microinjection studies indicated that the nucleus of the solitary tract (Fior et al., 1993) and the ventrolateral medulla (Privitera et al., 1994) represented likely sites of action for bradykinin to modulate cardiovascular regulation via bradykinin B_2 receptor activation.

A more recent study has characterised the peripheral and central cardiovascular components of bradykinin microinjected into the nucleus of the solitary tract of the anaesthetised rat, and concluded that both bradykinin B_1 and B_2 receptors are involved in cardiovascular responses at this level of the brain stem (Caligiorne et al., 1996). Furthermore, both bradykinin B_1 and B_2 receptor antagonists caused a significant attenuation of the baroreceptor heart-rate reflex, whereas bradykinin facilitated the reflex (Caligiorne et al., 1996). Arterial baroreceptor afferents ultimately project centrally through the vagus and glossopharyngeal nerves, with their perikarya located in the nodose and petrosal ganglia respectively, and terminate in the medial nucleus of the solitary tract (Lawrence and Jarrott, 1996). Considering the ability of bradykinin to modulate blood pressure and heart rate by acting in the nucleus of the solitary tract, the present study was de-

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signed to ascertain whether bradykinin receptors were located on vagal afferents. The isolated rat nodose ganglion–vagal trunk preparation was employed to determine whether activation of bradykinin receptors on the soma membranes of nodose ganglia could evoke an electrophysiological response. This methodology also gives an indication of the presence and properties of receptors on central vagal afferent terminals (Round and Wallis, 1986). The association of bradykinin receptors with vagal perikarya in rat and human was also examined by autoradiography using the bradykinin B_2 radioligand [^{125}I]*para*-iodophenyl-D-arginyl-L-arginyl-L-prolyl-*trans*-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-D-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-L-(2α,3β,7aβ)-octahydro-1*H*-indole-2-carbonyl-L-arginine ([^{125}I]PIP-Hoe 140) (Brenneret al., 1993).

2. Materials and methods

All experiments described herein were performed in accordance with the Prevention of Cruelty to Animals Act 1986, under the guidelines of the Code of Practice for the Care and Use of Animals for Experimental Purposes in Australia. In addition, human inferior vagal ganglia were obtained from cadavers within $\sim$18 h of death at the Victorian Institute of Forensic Pathology (VIFP). Donors were of either sex with no previous history of neurological disease. Ethical permission for the use of human tissue was granted by the Ethics and Integrity in Research Committees of both Monash University and VIFP.

2.1. In vitro electrophysiology

Electrophysiological experiments were performed as previously described (Castillo-Meléndez et al., 1994; Lawrence et al., 1995a, 1996). In brief, male Sprague–Dawley rats (250–350 g) were killed by cervical dislocation and the nodose ganglia with attached distal vagal trunk were removed and desheathed. The tissue was then placed in a twin-chambered perspex bath with the nodose ganglion placed in one compartment of the bath and isolated from the vagal nerve trunk in an adjacent compartment by a silicone grease seal, as previously described (Widdop et al., 1990). The preparation was superfused with Krebs buffer (36°C, 2 ml/min) of the following composition (in mM): NaCl 118, $NaHCO_3$ 24.9, KH_2PO_4 1.3, KCl 4.7, $CaCl_2$ 2.6, glucose 11, $MgSO_4$ 1.2, gassed with 95% O_2/5% CO_2, pH approximately 7.4. The d.c. potential between the two compartments following drug administration to the nodose ganglion was recorded by calomel electrodes connected to the preparation through agar-KCl bridges. The potential changes were amplified and displayed on a Grass Polygraph (Model 79D). Drugs were applied non-cumulatively and remained in contact with the tissue until apparent equilibrium was reached. In experiments involving bradykinin or other peptide analogues, drug superfusates also included the peptidase inhibitors (*N*-[*N*-[1-(*S*)-carboxyl-3-phenylpropyl]-(*S*)-phenyl-alanyl-(*S*)-isoserine (SCH 39370, 1 μM) and either captopril or enalaprilat (10 μM) to prevent peptide degradation. This was followed by a washout and recovery period (10–20 min) to allow full repolarisation prior to another drug addition. When used, antagonists were added to the superfusate 20 min prior to agonist application. This method allowed stable responses to be measured over a 5–6 h period. The magnitude of an observed depolarisation was measured from a projection of the baseline preceding the response to take account for any drift in potential difference.

At the beginning and end of each experiment a positive control of a previously determined maximal concentration of 5-hydroxytryptamine (5-HT, 3 μM) (Widdop et al., 1992) was applied to the nodose ganglia in order to check the viability of the preparations. Concentration-response curves for bradykinin were compared by performing paired *t*-tests of the depolarisations evoked by bradykinin in the absence and presence of antagonists for each preparation.

2.2. Receptor autoradiography

Cryostat-cut sections of fresh-frozen human inferior vagal ganglia (12 μm) or rat nodose ganglia (10 μm) were thaw-mounted onto gelatin/chrome-alum coated slides and stored at -80°C until further process. On the day of autoradiography experiments, rat and human tissue was allowed to equilibrate to room temperature prior to a preincubation in TES buffer (25 mM, pH 6.8) for 30 min at room temperature. Slide-mounted sections were then incubated in TES buffer (25 mM, pH 6.8) containing 1,10-phenanthroline (1 mM), enalaprilat (1 μM), bacitracin (140 μg/ml) and bovine serum albumin (0.1%) with [^{125}I]PIP-Hoe 140 (10 pM) for 90 min at room temperature. After the assay incubation, sections were washed in TES buffer (10 mM, pH 6.8; 3×6 min), followed by distilled water (2×10 s) and then dried under a gentle stream of cool air. Non-specific binding was defined with bradykinin (3 mM).

2.3. Materials

[^{125}I]*para*-Iodophenyl Hoe 140 ([^{125}I]PIP-Hoe 140) was radiolabelled as described (Brenner et al., 1993). Bradykinin was obtained from Auspep (Australia). Des-Arg^9-bradykinin, kallidin, bacitracin, 1,10-phenanthroline, TES buffer ((*N*-tris[hydroxymethyl]methyl-2-aminoethane-sulfonic acid), polyethyleneimine and bovine

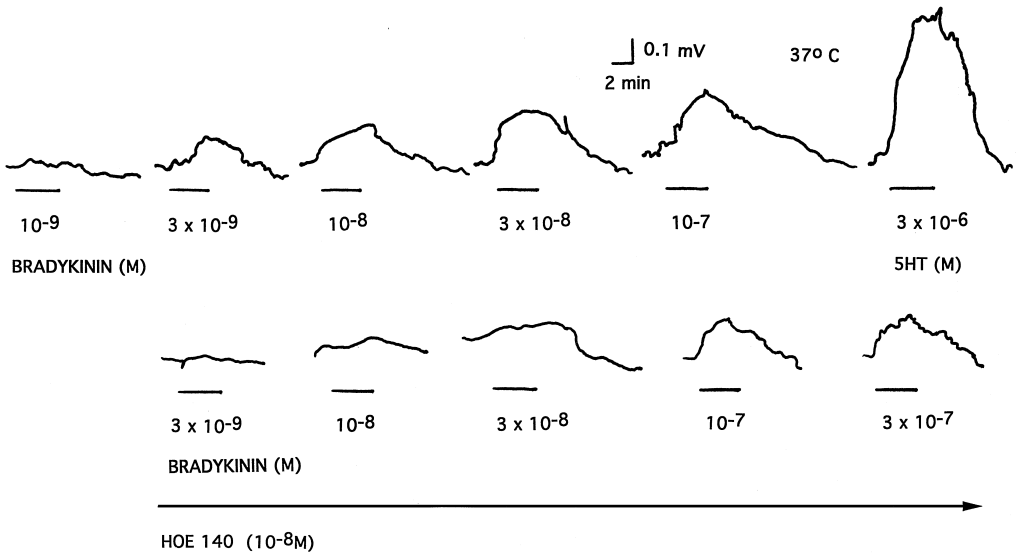

Fig. 1. Polygraph trace showing a representative series of responses to different concentrations of bradykinin applied to the rat isolated nodose ganglion preparation. The top row shows bradykinin alone and also a positive control of 5-HT (3 μM). The bottom row shows the effect of Hoe 140 (10 nM) on the responses to bradykinin. Drug superfusions occur during the periods indicated by the solid bars. Scales as shown.

serum albumin were all obtained from Sigma Chemical, USA. Enalaprilat was obtained from Merck Sharp and Dohme. Hoe 140 was a gift from Hoechst and SCH 39370 was a gift from Schering. All other chemicals were either analytical or laboratory grade from various suppliers.

Dried sections were then apposed to X-ray film (Kodak X-omat) and finally dipped in nuclear emulsion (Amersham LM1). After developing, sections were counterstained with thionin (0.1%) and examined on an Olympus microscope (BH2) employing both dark- and light-field condensers.

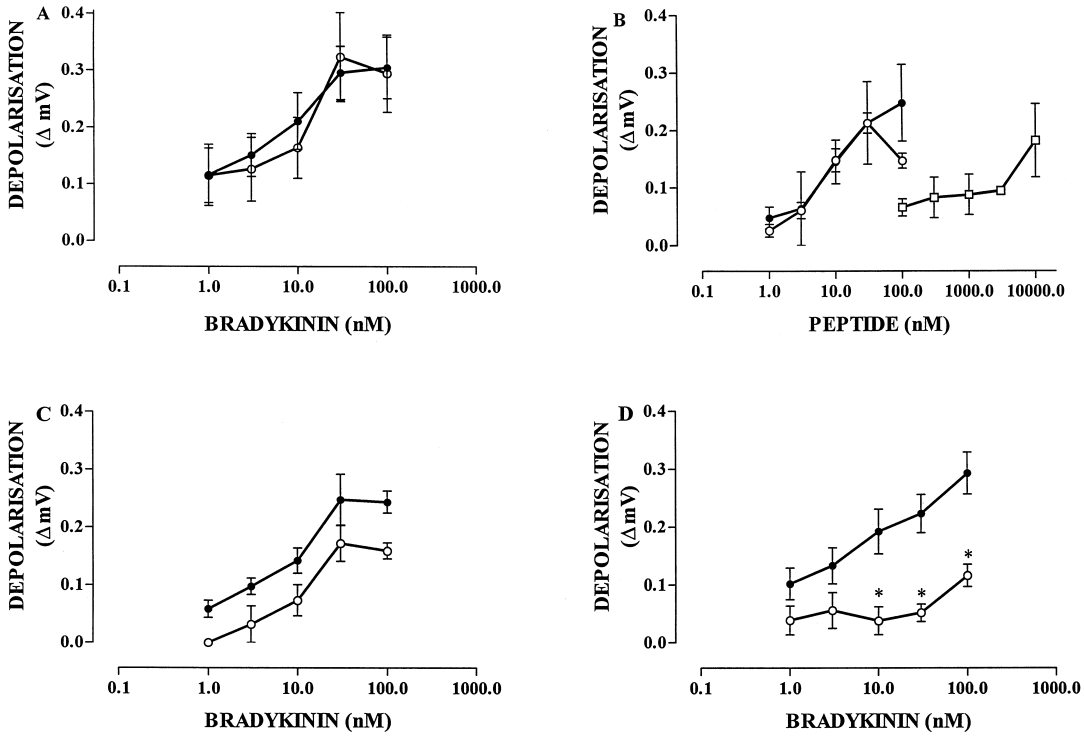

Fig. 2. Concentration-response curves to bradykinin and related analogues on the rat isolated nodose ganglion preparation. Data are expressed as mean ± S.E.M. (A) Bradykinin (closed symbols), followed by a washout and a repeat bradykinin (open symbols) concentration-response curve ($n = 5$). (B) Bradykinin (closed circles, $n = 4$), kallidin (open circles, $n = 6$) and des-Arg^9-bradykinin (open squares, $n = 4$). (C) Bradykinin in the absence (closed symbols) and presence (open symbols) of Hoe 140 (3 nM, $n = 3$). (D) Bradykinin in the absence (closed symbols) and presence (open symbols) of Hoe 140 (10 nM, $n = 3$). $*$ $p < 0.05$, paired t-test, response of bradykinin (10–100 nM) significantly reduced in the presence of Hoe 140 (10 nM).

3. Results

3.1. In vitro electrophysiology

Addition of bradykinin to the superfusate bathing the isolated nodose ganglia elicited a concentration-dependent depolarisation (Fig. 1). While the responses obtained are robust, we cannot exclude the possibility that a longer incubation time may have resulted in increased responses. Furthermore, the ability of bradykinin to depolarise the rat isolated nodose ganglia was reproducible, and not apparently subject to tachyphylaxis (Fig. 2A). The peptide kallidin was also capable of evoking electrophysiological responses over a similar concentration range to bradykinin (1–100 nM) whilst the truncated B_1 receptor agonist, Des-Arg^9-bradykinin (Regoli et al., 1981) was only active at concentrations in the micromolar range (Fig. 2B). Furthermore, the ability of bradykinin to depolarise the rat isolated nodose ganglia was attenuated by the bradykinin B_2 receptor antagonist, Hoe 140 (Hock et al., 1991; Wirth et al., 1991). As can be seen in Fig. 1, the magnitude of depolarisations elicited by bradykinin is markedly reduced in the presence of Hoe 140. Due to the inability of bradykinin to consistently reach a maximal effect over the concentration range employed, concentration-response curves for bradykinin have been analysed by comparing the observed depolarisations evoked by bradykinin in the absence and presence of Hoe 140. Thus, while 3 nM Hoe 140 ($n = 3$) reduced the efficacy of bradykinin, this effect did not reach statistical significance (Fig. 2C). Increasing the concentration of Hoe 140 by half a log unit to 10 nM ($n = 3$) resulted in a more robust shift in the bradykinin concentration-response curve such that the evoked depolarisations elicited by 10, 30 and 100 nM bradykinin were significantly reduced ($P < 0.05$, paired t-tests) in the presence of the bradykinin B_2 antagonist (Fig. 2D).

3.2. Receptor autoradiography

[^{125}I]PIP-Hoe 140 (10 pM) bound topographically to sections of rat and human inferior vagal (nodose) ganglia. Examination of emulsion-dipped sections at the light microscope level indicated that binding was predominantly

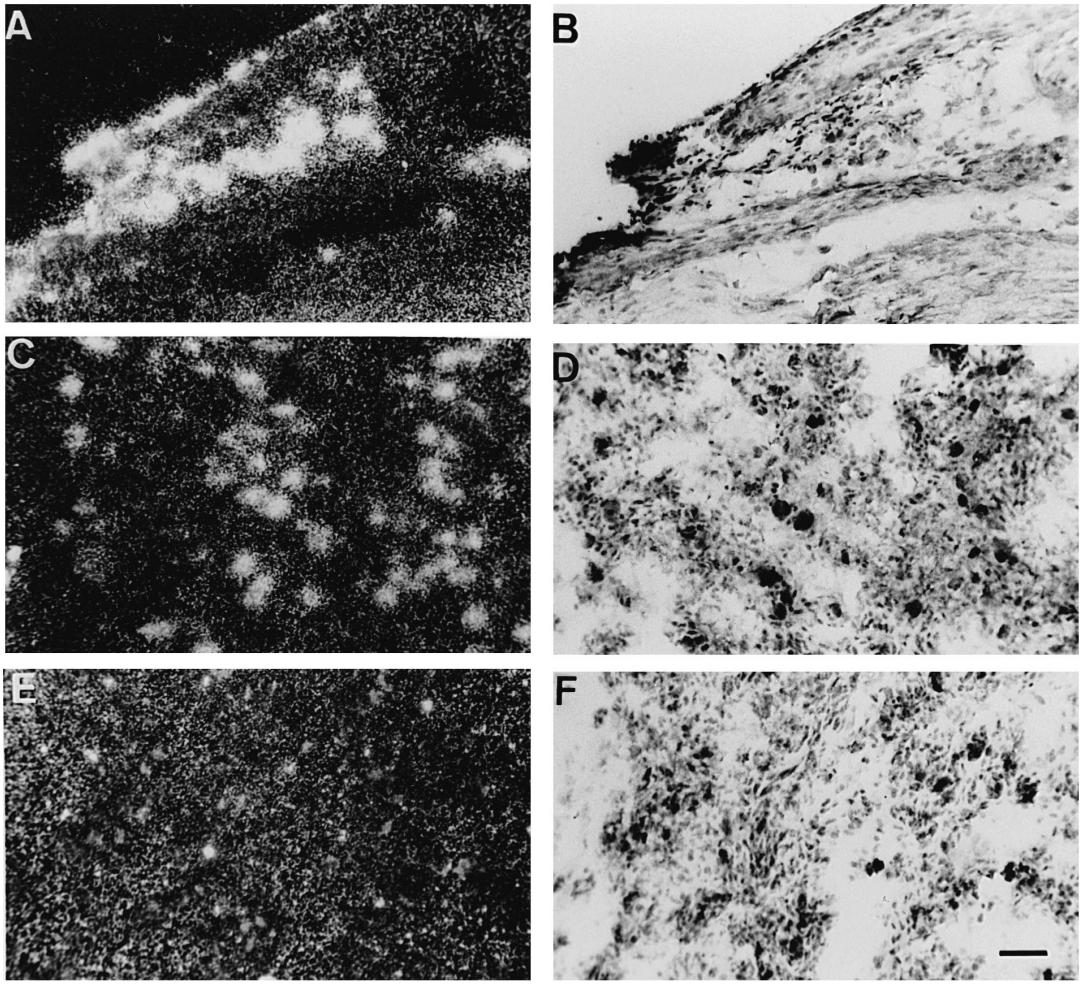

Fig. 3. Photomicrographs of [^{125}I]PIP-Hoe 140 (10 pM) binding in rat and human nodose ganglia. (A) Rat nodose ganglion, total binding, dark field. (B) Light field corresponding to A. Scale bar = 50 μm. (C) Human nodose ganglion, total binding, dark field. (D) Light field corresponding to C. Scale bar = 100 μm. (E) Human nodose ganglion, non-specific binding, dark field. (F) Light field corresponding to E. Scale bar = 100 μm.

associated with vagal perikarya in both rat and human (Fig. 3).

4. Discussion

The present study clearly demonstrates the presence of functional bradykinin B_2 receptors on rat vagal afferent neurons. Furthermore, complementary anatomical and biochemical evidence is provided indicating that bradykinin B_2 receptors are likely to be present on central vagal afferent terminals within the rat nucleus of the solitary tract. By analogy, the data obtained from human tissues is in agreement with the rat data, suggesting that bradykinin and bradykinin receptors may have a role in modulation of neurotransmission at central vagal afferent terminals, for example those concerned with cardiorespiratory control mechanisms. It has been previously hypothesised that bradykinin may be important in the pathogenesis of hypertension as both spontaneously hypertensive rats and DOCA-salt hypertensive rats exhibit higher levels of kallikrein activity compared to normotensive rats (Khan et al., 1994). Considering the ability of bradykinin to elicit depressor responses and facilitate the baroreflex at the level of the nucleus of the solitary tract (Caligiorne et al., 1996), one would surmise that alterations in bradykinin levels in other brain regions, such as the rostral ventrolateral medulla where bradykinin mediates a pressor response (Privitera et al., 1994), may be more likely associated with the pathogenesis of hypertension.

The rat isolated nodose ganglion preparation is a convenient model to characterise the presence of soma membrane-bound receptors on vagal perikarya, and also to predict the presence of receptors with similar properties on central vagal terminals (Round and Wallis, 1986). This technique has recently been employed to characterise the ability of dopamine (Lawrence et al., 1995a), nitric oxide (Lawrence et al., 1996) and γ-aminobutyric acid (GABA, Ashworth-Preece et al., 1997) to depolarise rat vagal afferents. The observation that both bradykinin and kallidin could elicit depolarisations in the nanomolar range while des-Arg^9-bradykinin was only active in the micromolar range suggested a bradykinin B_2 receptor-mediated response. Such a conclusion was further strengthened by the ability of the selective bradykinin B_2 receptor antagonist, Hoe 140 (Hock et al., 1991; Wirth et al., 1991) to shift the bradykinin concentration-response curve to the right in a concentration-related manner. The reduction in the maximum response to bradykinin in the presence of Hoe 140 may indicate a non-competitive action of the antagonist in this preparation. Both competitive and non-competitive modes of action have been reported for Hoe 140 (Griesbacher and Lembeck, 1992). In similar studies, bradykinin B_2 receptors have been demonstrated on the superior cervical ganglion of mouse and rat (Seabrook et al., 1995). In that particular study, the authors also demonstrated a potentiation of responses to bradykinin and [des-Arg^{10}]-kallidin following prolonged incubation with interleukin 1β; however, such a strategy was not employed in the present study. The possibility therefore exists that cytokines may induce bradykinin receptors on vagal perikarya.

While the electrophysiological data reported herein represent a population response, with no characterisation of neuron-type involved, there are cogent reasons to surmise that bradykinin B_2 receptors are present on cardiovascular-related vagal innervation to the brain stem. Thus, bradykinin has profound effects upon the cardiovascular system when administered directly into the nucleus of the solitary tract of the rat (Caligiorne et al., 1996; Fior et al., 1993), and activation of bradykinin B_2 receptors increases the sensitivity of the baroreceptor heart-rate reflex (Gerken and Santos, 1992; Madeddu et al., 1994). Furthermore, autoradiographic studies have visualised a high density of bradykinin B_2 receptors in the guinea-pig nucleus of the solitary tract (Fujiwara et al., 1989; Privitera et al., 1992).

In addition to characterising the bradykinin receptor types present on rat vagal afferent neurons functionally, the present study has also developed autoradiographic methods to examine bradykinin receptors in nervous tissue of rat and human. The bradykinin B_2 receptor radioligand [^{125}I]PIP-Hoe 140 has been characterised in guinea-pig tissue (Brenner et al., 1993), and in our hands bound avidly to slide mounted sections of rat and human nodose ganglia. Light microscopic examination revealed the binding to be punctate and predominantly associated with vagal perikarya in both species, therefore providing anatomical confirmation of the functional observations. One would expect that following ligation of the rat vagus nerve, binding of [^{125}I]PIP-Hoe 140 to accumulate adjacent to the ligature sites, indicating the likelihood of antero- and retrograde axonal transport of bradykinin B_2 receptors along the rat vagus nerve. By analogy, one could expect a similar occurrence in humans. Previous studies using surgical ligation techniques have demonstrated axonal transport along the rat vagus nerve of vasopressin V_1 receptors (Gao et al., 1992), glutamate receptors (Lewis et al., 1987), cholecystokinin receptors (Mercer and Lawrence, 1992), opioid receptors (Young et al., 1980), muscarinic receptors (Laduron, 1980), β-adrenoceptors (Lawrence et al., 1995b) and adenosine transport sites (Castillo-Melendez et al., 1996).

In summary, the present study has found evidence of functionally relevant bradykinin B_2 receptors on rat vagal afferent neurons. In contrast, under the present experimental conditions, no evidence was found for the presence of bradykinin B_1 receptors on vagal afferents. Therefore, previous reports of bradykinin B_1 receptor-mediated events in the rat nucleus of the solitary tract (Caligiorne et al., 1996) are likely to occur postsynaptic to vagal afferent terminals. These observations indicate that the cardiovascular effects of bradykinin in the rat nucleus of the solitary tract are likely, at least in part, to be mediated by

activation of bradykinin B_2 receptors on vagal afferent (possibly baroreceptor or chemoreceptor afferent) terminals within the nucleus of the solitary tract. Furthermore, a similar scenario could be expected in humans, as bradykinin B_2 receptors are located on a population of human vagal afferent cell bodies. It is clearly possible that bradykinin may also modulate vagal functioning with respect to other sensory information in addition to cardiovascular.

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