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Editorial

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IS BRADYKININ (BK) A PHYSIOLOGICAL VASODILATOR IN THE GUT?

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The physiological role of bradykinin (BK) as a mesenteric vasoregulator was explored. This nonapeptide is a potent vasodilator substance when administered exogenously in multiple *in vivo* models and is a smooth muscle relaxant when added to *in vitro* preparations. BK is naturally occurring in the gut wall. The substrate for BK, as well as the biosynthetic and metabolizing systems are present in the blood, the vascular wall, immunological cells, and perivascular neurons. BK B_2 and B_1 receptors have been characterized with sympathetic agonist and antagonist substances, and the receptors are present on mesenteric endothelial cells and myocytes. BK interacts with multiple endogenous mesenteric vasodilator mediators, such as nitric oxide, prostacyclin, and neuropeptides. Taken together this evidence supports the functional importance of BK as a normal vasodilator in the gut.

Key words: *bradykinin, mesenteric circulation, vasodilation, B_2 receptors, endothelium, nitric oxide, prostacyclin, vascular smooth muscle*

Bradykinin (BK) is a nonapeptide (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) synthesized by the action of serine proteases, the kallikreins, on precursor proteins, the kininogens (1). Kallikreins are present in most tissues as well as in the plasma, neutrophils, and other body fluids (2), and different kininogens are present in the blood (3). Plasma kallikrein forms BK from a high molecular weight form of kininogen which is also blood borne (2). Additionally, kallikreins have been found in much of the vascular wall with higher concentrations in small vessels (4, 5). Protein synthesis in vascular smooth muscle is utilized to maintain a pool of kallikreins (4), and there is mRNA coding for the enzymes in vascular tissue (6).

The major BK degrading enzyme in plasma is angiotensin coverting enzyme (7–11). Other enzyme systems which may be involved in hydrolyzing BK include carboxypeptidase A and N and aminopeptidase P (11–13). Furthermore, mesenteric endothelium removal does not abolish angiotensin converting enzyme activity (14).

Thus, the circulation contains both the biosynthetic and the metabolic systems needed to generate and to hydrolyse BK. These systems are present in both the blood and the vascular wall. Furthermore, BK also interacts with the vascular endothelium, with immunological cells in the interstitium, and with nerve cells to cause release of multiple vasodilator mediators (2). Some other important effects of BK include inflammation, hypotension, increased microvascular permeability, stimulation of chloride and glucose transport and activation of phospholipase A_2 (2).

The vasodilator response to BK may be due to some combination of the following suggested mechanisms: endothelial NO production and guanosine 3',5' monophosphate accumulation (15, 16), endothelial prostanoid generation (17–19), endothelium dependent but NO independent vascular muscle hyperpolarizing factor (20–23), inhibition of sympathetic nerve release of norepinephrine (24), neuronal release of vasodilator peptide neurotransmitters, such as calcitonin gene-related peptide and substance P (25–28), stimulation of beta adrenoceptors via adrenal medullary release of catecholamines (29), and formation of intracellular inositol phosphates (17, 19).

BK influences cellular function by binding to receptor subtypes located on the cell surface (1,30–33). Identification of BK B_1 and B_2 subtypes is based primarily upon the relative potency of various agonists and antagonists (1, 30, 33–37), although a human BK B_2 receptor has been sequenced and cloned (32). The B_2 receptor is the predominant physiological mediator of the fundamental vascular actions of BK (1, 2, 34, 38, 39). Thus, BK B_2 receptor antagonism prevented the BK induced rapid increase in intracellular calcium (Ca^{2+}) and the release of nitric oxide (NO) from endothelial cells (40–43). Other basic cellular actions of BK have included increasing second messengers such as guanosine 3'5' cyclic monophosphate (16, 41, 44), inositol 1,4,5-triphosphae (19, 45, 46), and prostaglandins (19, 44, 45, 47–51), as well as interacting with angiotensin converting enzyme (9).

In early studies it was found that exogenously administered BK was a general vasodilator agent (52) and BK was specifically shown to dilate the circulations of the stomach (53), pancreas (54), and gut (55). BK vasodilation of the *in vivo* mesenteric circulation was documented repeatedly in human (56–59) and several animal (29, 55, 60–68) models. Accordingly, intra-arterial BK evoked visible arterial dilation and angiographic evidence of enhanced blood flow in the human mesenteric circulation (57, 59). BK also increased human and canine portal vein caliber and pressure (56, 59, 69),

probably as a result of arterial vasodilation and augmented intestinal blood flow. In the anesthetized rat model intra-arterial BK increased mesenteric blood flow (60, 61, 65, 66, 67, 70), and the dilator effect was mediated by BK B_2 receptors and NO (67). Additional rat studies documented that some but not all of the splanchnic vasodilator actions of BK were mediated by NO (15, 61, 71–74). Thus, there were findings that endothelial prostaglandin synthesis also contributed to the BK induced vascular relaxation (18, 75–78). In anesthetized dogs (59, 63, 79), cats (80), and calves (81) BK also increased mesenteric arterial inflow, portal vein diameter, and/or splanchnic venous pressure. BK elicited release of the potent vasodilator neurotransmitter, calcitonin gene-related peptide, from the mesenteric circulation of rats (25–28), prompted adrenal medullary stimulation of beta adrenoceptors (29), and inhibited norepinephrine release (24).

BK infusion either evoked dilator responses or antagonized norepinephrine induced constrictor responses in rat (10, 82–85), cat (62, 86), and rabbit (47) isolated perfused gut preparations. In isolated mesenteric vascular strips or rings, BK was a potent relaxing agent (15, 39, 87–91).

In cultured endothelial cells from human (40, 45, 92), porcine (31, 41), and bovine (42, 45, 48) aortae or umbilical veins, BK binding to the B_2 subtype receptor evoked an abrupt accumulation of cytosolic [Ca^{2+}] (92). This Ca^{2+} accumulation was probably mediated by a G-protein at the endothelial cell surface with consequent opening of plasma membrane Ca^{2+} channels (31). The increased cytosolic Ca^{2+} would then activate NO synthase and lead to NO release from endothelial cells which would relax adjacent vascular smooth muscle cells (31, 40–42, 48, 61, 71, 93–97). In addition, BK was shown to release vasodilator prostaglandins (50, 51) and prostacyclin (45, 48) from cultured endothelial cells and vascular myocytes. BK also released NO from vascular smooth muscle (73) and nerve (96) cells. The multiple mechanisms involved in BK induced vasodilation are depicted in *Fig. 1*.

Topically applied BK relieved norepinephrine induced vasoconstriction of rat mesenteric microvessels under microscopic observation (97, 98). BK released adrenal medullary catecholamines via a Ca^{2+} dependent mechanism (99, 100); however, this effect did not attenuate BK induced mesenteric vasodilation (29).

The mesenteric vasodilator response to BK was abolished in glucopenic animals and was restored by administering insulin (97, 98), suggesting that BK induced relaxation of blood vessels depends upon either intracellular glucose or insulin. In mice, BK stimulated release of tumor necrosis factor and interleukin-1 from macrophages (101). The BK-cytokine interaction may be mediated by BK B_1 receptors which are known to be induced by interleukin-1 and endotoxin (1, 34). Furthermore, interleukin-1 induced NO production in vascular smooth muscle (102).

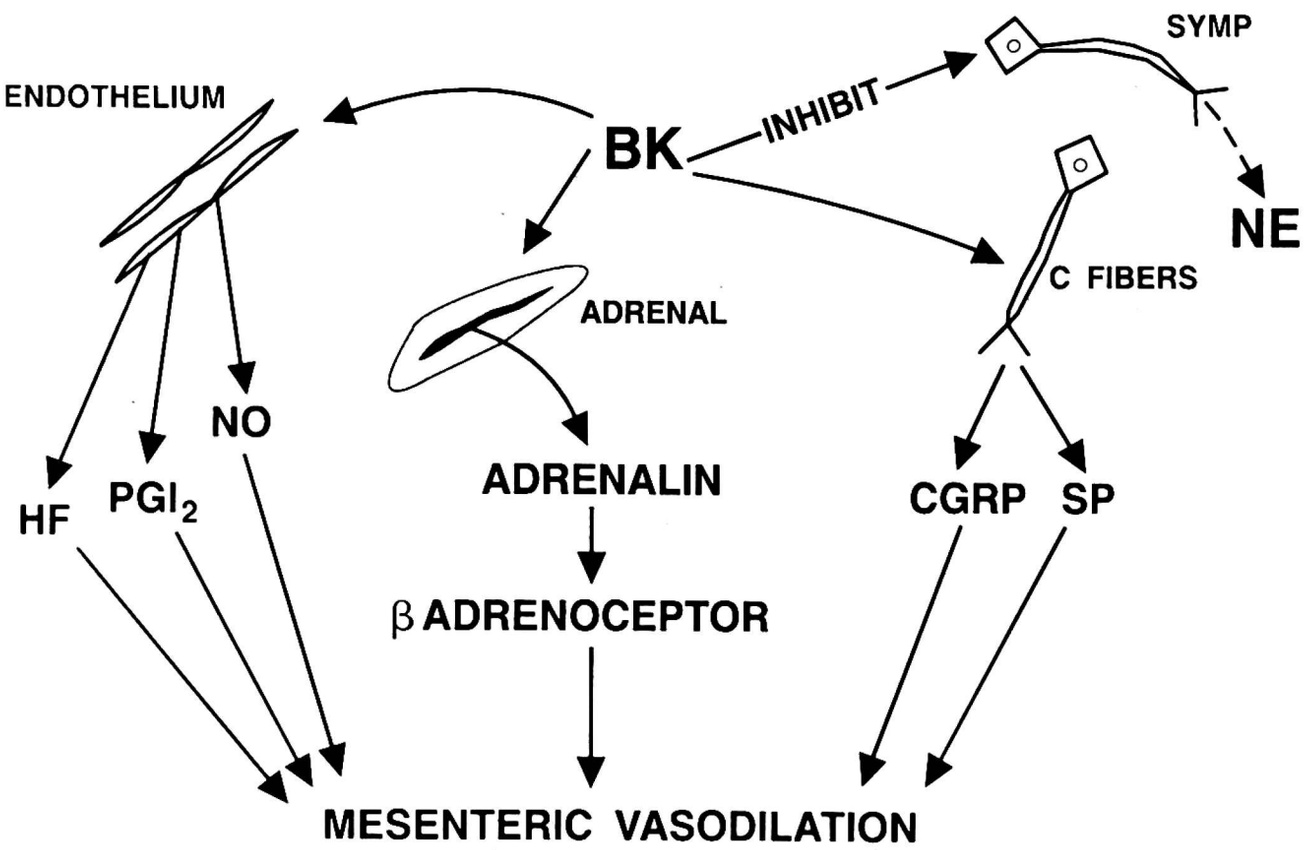

Fig. 1. Mechanisms by which BK elicts mesenteric vasodilation. Abbreviations: HF = hyperpolarizing factor, PGI_2 = prostacyclin, NO = nitric oxide, CGRP = calcitonin gene-related peptide, SP = substance P, SYMP = sympathetic nerves, NE = norepinephrine.

There is also some evidence against BK acting as a physiological vasodilator agent in the enteric circulation. Thus, in conscious rats with chronic catheterization of systemic vessels, low doses of BK diminished mesenteric blood flow (103). In addition, in the norepinephrine precontracted rat mesenteric circulation, low doses of BK either contracted (104) or did not relax (105) the intestinal vasculature.

In isolated perfused preparations BK released dilator eicosanoids (44, 45, 47, 48, 50, 51), although there are conflicting reports about prostaglandin mediation of BK induced intestinal vasodilation (60). Indomethacin was shown to inhibit BK induced mesenteric relaxation of rabbit mesenteric vessels (87, 89, 106), whereas indomethacin was ineffective in mitigating BK evoked relaxation of rat mesenteric vascular rings (85). In guinea pig gut BK contracted mesenteric veins via its B_2 receptors (107), and in rabbits BK vascular relaxation was blocked by a B_1 receptor antagonist (108). BK proved to be a less potent relaxant of rabbit mesenteric arterial rings than either kallidin (88) or $DesArg^9$-BK (89, 108). In non mesenteric vascular ring preparations BK caused a contractile response from endothelium denuded rabbit vessels which was mediated by B_1 receptors and intracellular bound Ca^{2+} release (108).

The foregoing discussion suggests that the physiological role of BK and the mechanisms of its vasoactivity vary between animal species and experimental

preparations. However, the bulk of evidence supports a physiological role for BK as a paracrine vasodilator in the gut. Information which ranges from suggestive to convincing provides several essential features upon which this conclusion is based:

- BK is released by cells located near vascular smooth muscle, namely endothelial, immunological, and neural cells;
- The biosynthetic and metabolizing machinery is present in the mesenteric vasculature to regulate BK availability;
- BK B_2 and B_1 receptors are located on the surface of mesenteric endothelial cells and myocytes;
- BK interacts with other endogenous vasodilator mediators, e.g., NO, prostacyclin, neuropeptides, beta adrenoceptors; and
- Exogenously administered BK is a potent mesenteric vasodilator agent.

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