

Bradykinin Signal Pathways Modulate Neurohypophyseal Hormones Secretion

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Abstract

Afferent renal nerves stimulate vasopressin (VP) secretion by activation of VPergic neurons of supraoptic (SON) and paraventricular nuclei (PVN). Therefore, intrarenal infusion of bradykinin (BK), which excites afferent renal nerves, increases VP release. However, BK is also a potent intrarenal vasodilator hence BK may modulate VP secretion not only by stimulating its release via afferent renal nerves, but also inhibiting its renal effects as intrarenal vasodilator via a paracrine control. Furthermore, BK impairs the mechanism of phosphorylation that induces the translocation of aquaporin 2 containing vesicles to the apical plasma membrane thus inhibiting the osmotic water permeability of the collecting duct cells induced by VP via its V2 receptor, a Gs protein-coupled receptor. In addition, BKB2 receptor knockout mice exhibit decreased urine volume and increased urine osmolality following water deprivation.

Oxytocin (OT) increases urine output and sodium excretion in rats. Icatibant, a BKB2 antagonist, suppresses these effects showing that BK mediates diuresis and natriuresis induced by OT.

Infusion of OT down-regulates myometrial OT and BK receptors indicating the existence of a common final pathway of OT and BK in the contractile responsiveness of uterine myometrial cells. The frequency of uterine contractions induced by OT and BK are stimulated by nitric oxide via prostaglandins release.

Keywords: Neurohypophyseal; Hormone; Receptor; Antagonist

Introduction

Bradykinin (BK) is a peptide of the kinin group of proteins with potent endothelium-dependent vasodilator activity via the release of prostacyclin, nitric oxide and endothelium-derived hyperpolarizing factor.

The BK receptors are a group of G-protein-coupled receptors (GPCRs). Two BK receptors have been reported: the B1 and B2 receptor. They stimulate phospholipase C to increase intracellular calcium ion concentration and mitogen-activated protein kinase pathways.

BK also causes natriuresis, modulating the mechanism of VP action at the renal level, as well as contraction in rat uterus via the same signal pathway of OT.

The neurohypophyseal hormones VP and OT are synthesized by magnocellular neurosecretory neurons (MCNs) in the supraoptic (SON) and paraventricular nuclei (PVN) and transported down the axons to the posterior pituitary and released into the circulatory system. VP is released following increased plasma osmolality via osmoreceptor activation or hypovolemia via baroreceptor activation. OT is released following cervical stretch (Ferguson reflex) or milk let-down reflex of Ely-Petersen [1].

Vasopressin (VP)

There is evidence that the kidneys can regulate VP secretion. It has been observed that electrical stimulation of afferent renal nerves stimulates, in different animal models, VP release and the activity of MCNs in the SON and PVN where VP is synthesized [2]. Intrarenal infusion of BK, which is known to excite afferent renal nerves, increases the activity of VPergic neurons in the SON of rats and increases VP release in rabbits. These effects are significantly suppressed following renal denervation indicating that the kidneys can influence VP secretion via afferent renal nerves [3]. On the other hand, BK is a potent

endothelium-dependent intrarenal vasodilator, as well as nitric oxide (NO) and prostaglandins (PGs), an effect mainly expressed in the inner medulla. Therefore, BK might modulate VP secretion not only by stimulating its release via afferent renal nerves but also inhibiting VP release by its action as intrarenal vasodilator. We can hypothesize that osmotic and non-osmotic mechanisms activating reno-renal reflexes via afferent renal nerves reach the spinal cord and transport renal information to the brain via the medullary reticular formation and dorsal medulla oblongata where is located the nucleus of the solitary tract (NTS) that is involved in the control of VP secretion [4-6]. This sequence of events that induce VP release and activation of vasopressor factors, such as renin-angiotensin-aldosterone system and renal sympathetic inputs, provokes the release of intrarenal vasodilators, such as BK, NO and PGs, that counteract the vasopressor action of these hormones via a paracrine control.

BK and other autacoids, such as PGE2 and endothelin-1, antagonize the intrarenal VP mechanism of action. VP, released from the neurohypophysis (NH) following osmotic stimuli, binds to its V2 receptor (a Gs protein-coupled receptor) on the basolateral membrane of collecting duct epithelial cells triggering an intracellular cAMP signaling cascade which phosphorylates a serine residue of the membrane water channel aquaporin-2 (AQP2) [7,8]. This phosphorylation is essential

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for trafficking of AQP2 containing vesicles to the apical plasma membrane [9-12] thus increasing reabsorption of water through AQP2 water channels. When plasma VP concentration decreases, AQP2 vesicles are internalized from the plasma membrane, consequently plasma membrane returns watertight. BK plays an inhibitory role on VP-induced AQP2 activation [13]. Indeed BK pretreatment impaired the mechanism of phosphorylation that induces the translocation of AQP2 to the apical plasma membrane thus inhibiting the osmotic water permeability of the collecting duct (CD) cells [14].

In *in vivo* studies, infusion of BK provokes diuresis and natriuresis. These effects are mediated by BKB2 receptors because icatibant, an antagonist of these receptors, suppresses the diuretic and natriuretic response induced by BK. In addition, BK inhibits VP-induced water flow in microperfused rabbit cortical CD cells. Also in these conditions are involved BKB2 receptors because these effects are antagonized by icatibant and not by BKB1 antagonists. Furthermore, BK increases Ca(2+) in cortical CD cells via a BKB2 receptor mechanism [15]. Cytosolic Ca(2+) increase in CD cells is mediated via the G proteins Gq and G α 13, that are coupled to BKB2. This Ca(2+) increase is suppressed by the BKB2 antagonist icatibant. In CD cells BK provokes an increase of Rho activity. This Rho protein plays an inhibitory role on trafficking of vesicles containing AQP2 to the apical membrane via stabilization of actin filaments. Therefore, BK inhibits the urinary concentrating effects of VP by stimulation of Rho activity thus impairing AQP2 trafficking [14].

BKB2 receptor knockout mice (B2-KO) exhibit decreased urine volume and increased urine osmolality following 24 h of water deprivation. It has been observed that dehydration or administration of a VP V2-receptor agonist showed increased urinary concentration in B2-KO mice than in controls, thus indicating that BK acting on its B2 receptor plays an antagonistic role on the antidiuretic effects of VP [16].

Intra-aortic administration of BK induces in dose-dependent manner, a reduction in blood pressure (MAP) and renal blood flow (RBF), and an increase in renal vascular resistance (RVR). Similar responses have been observed following intrarenal administration of BK, even if the increase of RVR was significantly pronounced. These actions are not prevented by antagonists of VP V1-receptors or α 1-adrenoceptors, while the antagonist of BKB2 receptors icatibant is able to prevent the hemodynamic responses to BK. These data indicate that BK shows renal vasoconstrictor and vasodilator properties both mediated by BKB2 receptors [17].

BKB2 receptors are located also in the brain [18], mainly in the nuclei of the medulla oblongata that are involved in the control of cardiovascular functions. Intracerebroventricular administration of BK increases MAP and heart rate, effects completely prevented by the specific BKB2 antagonist icatibant [19], thus showing that centrally administered BK induces cardiovascular responses by activation of brainstem catecholamine neurons of A1 and A2 noradrenergic cell group via signal to the sympathetic nervous system.

Oxytocin (OT)

In rats, intravenously injected OT is able to increase urine volume and natriuresis, with increased urinary excretion of kinins. Aprotinin, a kallikrein inhibitor, and icatibant, a BKB2 antagonist, significantly suppress diuresis and urinary excretion of sodium induced by OT, thus showing that kallikrein and BK mediate the diuresis and natriuresis induced by OT [20].

In rat uterine slices a compound with BK agonist activity and OT

antagonist activity, L-366,811, stimulates phosphatidylinositol turnover and, in dose-related manner, contractions of the isolated rat uterus.

OT infusion induces a significant decrease of maximal binding of [³H]-OT and OT receptor concentration in myometrial plasma membranes. BK infusions down-regulated BK receptor concentration. Long-term treatment with OT down-regulated myometrial BK receptors. Therefore, the down-regulation of OT and BK receptors observed following long-term treatment with OT may indicate the existence of a common final pathway in the contractile responsiveness of uterine myometrial cells [21].

Inhibitors of NO synthase suppress PGF 2α and PGE 2 synthesis induced by BK in the uterus of estrogen-primed rats. Therefore, frequency of uterine contraction provoked by BK and OT is modulated by NO via PGs release (Chaud et al., 1997) [22]. In addition, BK and OT activate phospholipase C which provokes the release of Ca(2+) from intracellular stores. This event is critical for BK- and OT-induced contraction of uterine smooth muscle [23].

Adrenomedullin (AM), a potent endogenous vasodilator peptide, plays an inhibitory role on the spontaneous uterine periodic contraction. This effect is prevented by antagonist of AM receptors or calcitonin gene-related peptide (CGRP) receptors. AM inhibits BK-induced periodic uterine contraction, but is unable to counteracts periodic contraction induced by OT or PGF 2α , thus showing that AM is able to inhibit both spontaneous and BK-induced periodic contraction of uterus via activating receptors for AM and CGRP [24].

Conclusions

The neurohypophyseal hormones VP and OT are submitted to a large number of afferent pathways regulating their mechanism of action. The interactions that these neural pathways form utilize neurotransmitters and neuropeptides as ATP, noradrenaline, serotonin, acetylcholine, taurine, glycine, neurokinins, neuropeptide Y, angiotensin II and substance P, that act on their own membrane receptors. BK modulates these mechanisms acting on intracellular signaling cascade, triggered by VP and OT, as phosphorylation in CD cells and phospholipase C in uterine smooth muscle.

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