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NUTS AND BOLTS

A modular map of Bradykinin-mediated inflammatory signaling network

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Abstract

Bradykinin, a member of the kallikrein-kinin system (KKS), is associated with an inflammatory response pathway with diverse vascular permeability functions, including thrombosis and blood coagulation. In majority, bradykinin signals through Bradykinin Receptor B2 (B2R). B2R is a G protein-coupled receptor (GPCR) coupled to G protein family such as $G\alpha_{qs}$, $G\alpha_q/G\alpha_{11}$, $G\alpha_{i1}$, and $G\beta1_\gamma2$. B2R stimulation leads to the activation of a signaling cascade of downstream molecules such as phospholipases, protein kinase C, Ras/Raf-1/MAPK, and PI3K/AKT and secondary messengers such as inositol-1,4,5-trisphosphate, diacylglycerol and Ca^{2+} ions. These secondary messengers modulate the production of nitric oxide or prostaglandins. Bradykinin-mediated signaling is implicated in inflammation, chronic pain, vasculopathy, neuropathy, obesity, diabetes, and cancer. Despite the biomedical importance of bradykinin, a resource of bradykinin-mediated signaling pathway is currently not available. Here, we developed a pathway resource of signaling events mediated by bradykinin. By employing data mining strategies in the published literature, we describe an integrated pathway reaction map of bradykinin consisting of 233 reactions. Bradykinin signaling pathway events included 25 enzyme catalysis reactions, 12 translocations, 83 activation/inhibition reactions, 11 molecular associations, 45 protein expression and 57 gene regulation events. The pathway map is made publicly available on the WikiPathways Database with the ID URL: https://www.wikipathways.org/index.php/Pathway:WP5132. The bradykinin-mediated signaling pathway map will facilitate the identification of novel candidates as therapeutic targets for diseases associated with dysregulated bradykinin signaling.

Keywords Bradykinin storm · Post-translational modifications · Protein–protein interactions · Signaling pathways

Abbreviations

BK	Bradykinin
KKS	Kallikrein-kinin system
RAS	Renin-angiotensin system
B1R	Bradykinin receptor B1
B2R	Bradykinin receptor B2
PK	Plasma kallikrein
GPCR	G-protein coupled receptor
PIP2	Phosphatidylinositol 4, 5-bisphosphate
ACE	Angiotensin-converting enzyme
NO	Nitric oxide

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PGI2 Prostaglandin I2
eNOS Endothelial nitric oxide synthase

Introduction

Bradykinin is a potent, short-lived vasoactive peptide, which acts as an inflammatory mediator. It is a constituent of the kallikrein-kinin system (KKS). Kinins are released from high molecular weight kininogens (HMWK) and low molecular weight kininogens (LMWK) by the action of plasma kallikrein (PK) or tissue kallikrein (TK). HMWK and LMWK are the two components of KKS and play a major role in the synthesis of bradykinin (Leeb-Lundberg et al. 2005; Vandell et al. 2008; Hofman et al. 2016a, b; Nokkari et al. 2018). The LMWK is cleaved by tissue kallikrein into a 10-amino-acid peptide, lysyl-bradykinin (kallidin), with a sequence Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg (Kaplan et al. 2002). The action of a plasma amino-peptidase on kallidin cleaves the N-terminal Lys and liberates bradykinin as a 9-amino-acid peptide. The other arm of the cascade comprises factor XII, an initiating protein that binds to charged surface macromolecules and forms factor XIIa, which converts prekallikrein into active plasma kallikrein. Further, HMWK is cleaved by plasma kallikrein into nonapeptide bradykinin (Kaplan et al. 2002; Kenniston et al. 2014). Degradation of bradykinin occurs by the action of kininase I and kininase II enzymes. Kininase I, also known as plasma carboxypeptidase, removes the C- terminal Arg from bradykinin and kallidin to form Des-Arg9-bradykinin and Des-Arg10-kallidin, respectively. Kininase II is similar to angiotensin-converting enzyme (ACE) in function and metabolizes bradykinin into two C- terminal dipeptides and a heptapeptide (Kaplan et al. 2002).

Bradykinin is released in pathological conditions such as trauma and inflammation, which binds to its kinin receptors. It is encoded by exon 10 of the kininogen gene located on chromosome 3 (3q26) in humans (Fong et al. 1991). Bradykinin activates several second messenger systems, thereby regulating blood–brain barrier permeability, blood pressure, pain perception, glutamate release from astrocytes, neuronal differentiation, and nitric oxide production (Whalley et al. 2012).

The action of bradykinin is mediated through an interaction with cell surface bradykinin receptors. Bradykinin Receptor B1 (B1R) and Bradykinin Receptor B2 (B2R) are the two subtypes of bradykinin receptors, which belong to the GPCR family (Leeb-Lundberg et al. 2005; Marceau et al. 2020). B1R encoded by the gene BDKRB1 has minimal expression in healthy tissues, and its expression is induced only under special conditions such as injury and inflammation (Couture et al. 2001; Qadri and Bader 2018). In most cases, bradykinin acts through the B2R, which is encoded by the gene BDKRB2. B2R is ubiquitously expressed and implicated in vasodilation, osmoregulation, smooth muscle contraction, and nociceptors' activation (Leeb-Lundberg et al. 2005). B2R expression upregulated under pathological conditions of tissue injury due to oxidative stress, pro-inflammatory stimuli such as exposure to lipopolysaccharides, endotoxins, cytokines (IL-1beta and TNF-alpha) and vasoactive peptide stimuli as it is seen in the renin-angiotensin system (RAS) (Marceau et al. 2002; Tschope et al. 2002; Bossi et al. 2009; Jaffa et al. 2012; Naffah-Mazzacoratti Mda et al. 2014).

Bradykinin stimulates B2R coupled with G proteins and activates signaling molecules such as protein kinase C (PKC), phospholipase C (PLC), mitogen-activated protein kinases (MAPKs), phosphoinositide-3 kinase (PI3K)/AKT and second messengers IP_3 (inositol triphosphate), diacylglycerol (DAG) and Ca^{2+} ions (Kakoki and Smithies 2009; Dong et al. 2015; Wang et al. 2017). These second messengers mediate signaling mechanisms (e.g., nitric oxide or prostaglandin production) (Kakoki and Smithies 2009). Besides, bradykinin is also known to be involved in the activation of inflammatory cytokines. Previous studies have demonstrated that bradykinin-induced activation of MAPKs is involved in the upregulation of several cytokines such as *IL-6*, *IL-1β*, *IL-8* and *IL-2* (Paegelow et al. 1995; Pan et al. 1996; Huang et al. 2003; Meini et al. 2011; Yang et al. 2018) which are implicated in inflammation, respiratory, gastrointestinal, cardiac, neuronal, ophthalmologic and dermatological problems. Recent reports have shown that bradykinin storm may be responsible for the more severe symptoms of Coronavirus disease (COVID-19) (Garvin et al. 2020; Roche and Roche 2020; Wilczynski et al. 2021). Some reports suggest that B2R forms a complex with ACE, and this is thought to play a role in cross-talk between the RAS and the KKS (da Costa et al. 2014). Accumulation of bradykinin is implicated in angioedema by genetic defects and ACE inhibitors (Bas et al. 2007). Besides, bradykinin also plays a major role in cancer progression mechanisms (Stewart et al. 2002), for instance, with increased lung cancer risks (Kmietowicz 2018) and proliferation and migration in gastric cancers (Wang et al. 2017), in addition to allergic rhinitis, asthma, and anaphylaxis (Kaplan et al. 2002).

Recent computational analyses suggested that genes related to the bradykinin were up-regulated in bronchoalveolar lavage (BAL) samples of COVID-19 patients. The system implicates the core of the mechanisms triggering the adverse array of symptoms such as muscle pain, fatigue, nausea, vomiting, diarrhoea, headaches, and reduced cognitive function (Garvin et al. 2020). Recent reports show that SARS-CoV-2 employs its spike protein (S) antigen to interact with ACE2 and invade target cells (Astuti and Ysrafil 2020; Zhang et al. 2020). The loss of ACE2 activity and subsequent rise in Angiotensin-II

leads to a fall in ACE function through a negative feedback loop, ultimately resulting in raised bradykinin levels (Zhu et al. 2010). The increase of bradykinin may be due to the increases in the density of mast cells in the lungs of COVID-19 patients (Motta Junior et al. 2020). Even though several studies have been conducted at the molecular level to deduce the bradykinin signaling pathways, an organized network of molecular reactions induced by bradykinin is not publicly available. Therefore, we curated bradykinin-induced reactions from the literature and organized them into a dataset of molecular reactions. We developed a resource of signaling events mediated by bradykinin, similar to the previously published signaling pathways of IL-18, IL-10, IL-33, endothelin, oncostatin M and AXL, available in the NetPath and Wikipathways database (Dey et al. 2013; Soman et al. 2013; Verma et al. 2016; Pinto et al. 2018; Rex et al. 2020; Dagamajalu et al. 2021a, 2021b).

Methodology

We carried out a literature survey of articles related to bradykinin-mediated signaling. The articles were fetched from PubMed using query terms ("Bradykinin" OR "BK" OR "BK receptor" OR "B_1receptor" OR "BK receptor B1" OR "BDKRB1" OR "B1R" OR"B_2 receptor" OR "BK receptor B2" OR "BDKRB2" OR "B2R") AND ("pathway" OR "signaling" OR "signalling" OR "induced pathway" OR "induced signaling" OR "induced signalling"). The research articles were screened manually to evaluate the presence of bradykinin-induced signaling events. The systematic manual curation of signaling events was done based on the previously described PathBuilder tool, NetSlim and NetPath annotation criteria (Kandasamy et al. 2009, 2010; Raju et al. 2011). Accordingly, molecular events induced or influenced by bradykinin were included in the pathway. Further, curated downstream molecules were categorized into activation/inhibition, post-translational modifications (PTMs), translocation, molecular association, gene regulation and protein expression events. Additionally, information about cell lines used in the experiment, type of experiment, gene and protein regulation type (upregulation/downregulation) and PTMs (site and residue wherever available) were also curated. The curated information was further subjected to quality control through an internal review by a couple of experienced curators. Each described signaling event in the pathway was hyperlinked to the abstracts of corresponding articles from where it was retrieved.

PathVisio software used to depict pathway map of bradykinin mediated molecular signaling events (Kutmon et al. 2015).

Results

In the current study, the PubMed search using query terms fetched 4444 articles related to the bradykinin signaling pathway until September 2020. These articles were carefully reviewed based on our NetPath annotation criteria and shortlisted into 400 articles. The annotated articles provided several molecular reactions such as 11 molecular interactions, 25 enzyme catalysis events, 12 translocations, 83 activation/inhibition reactions, 45 protein expressions and 57 gene regulation events (Supplementary Data S1). These events were further incorporated into the corresponding signaling pathway map (Fig. 1). Information regarding bradykinin signaling events can be obtained from the WikiPathways database (https://www.wikipathways.org/index.php/Pathway:WP5132). The signaling pathway map can be freely downloaded in png, pdf and gpml formats from this database.

Description of the bradykinin signaling pathway

Bradykinin, a pro-inflammatory nonapeptide, is released by the action of plasma or tissue kallikreins on kininogens (Drouin et al. 1979; Kakoki and Smithies 2009). Signaling by bradykinin is mainly mediated through B2R, a receptor of the seven-transmembrane GPCR family, which are capable of generating a broad spectrum of physiological responses such as vasodilation, fluid balance and retention, smooth muscle contraction, and algesia on target cells (Khasar et al. 1995; Virych et al. 2017). Bradykinin/B2R induces the activation of MAPK1/3 via PKC and c-Src pathways, which up-regulates matrix metalloproteinase (MMP)-9 and increases the conventional outflow facility in human trabecular meshwork cells (Webb et al. 2011). Furthermore, bradykinin enhance cell proliferation by the activation of cytosolic calcium, PKC-alpha (α), -beta (β), -delta (δ), -epsilon (ε) and -eta (η) and MAPK1/3 mediated signaling in primary culture of breast cancer cells, pheochromocytoma PC12 cells and ventricular myocytes (Clerk et al. 1996; Graness et al. 1997; Greco et al. 2005). In addition, c-Src phosphorylates FRS2 at Tyr196, leading to the activation of MAPK1/3 and nuclear translocation of STAT3, which ultimately results in the release of FGF-2 protein. The release of FGF-2 mediates various biological effects, including permeability, migration and inflammation in human HREC and HUVEC cell lines (Terzuoli et al. 2018).

Bradykinin mediates signaling modules in various cells such as cardiomyocytes, epithelial cells, fibroblasts and

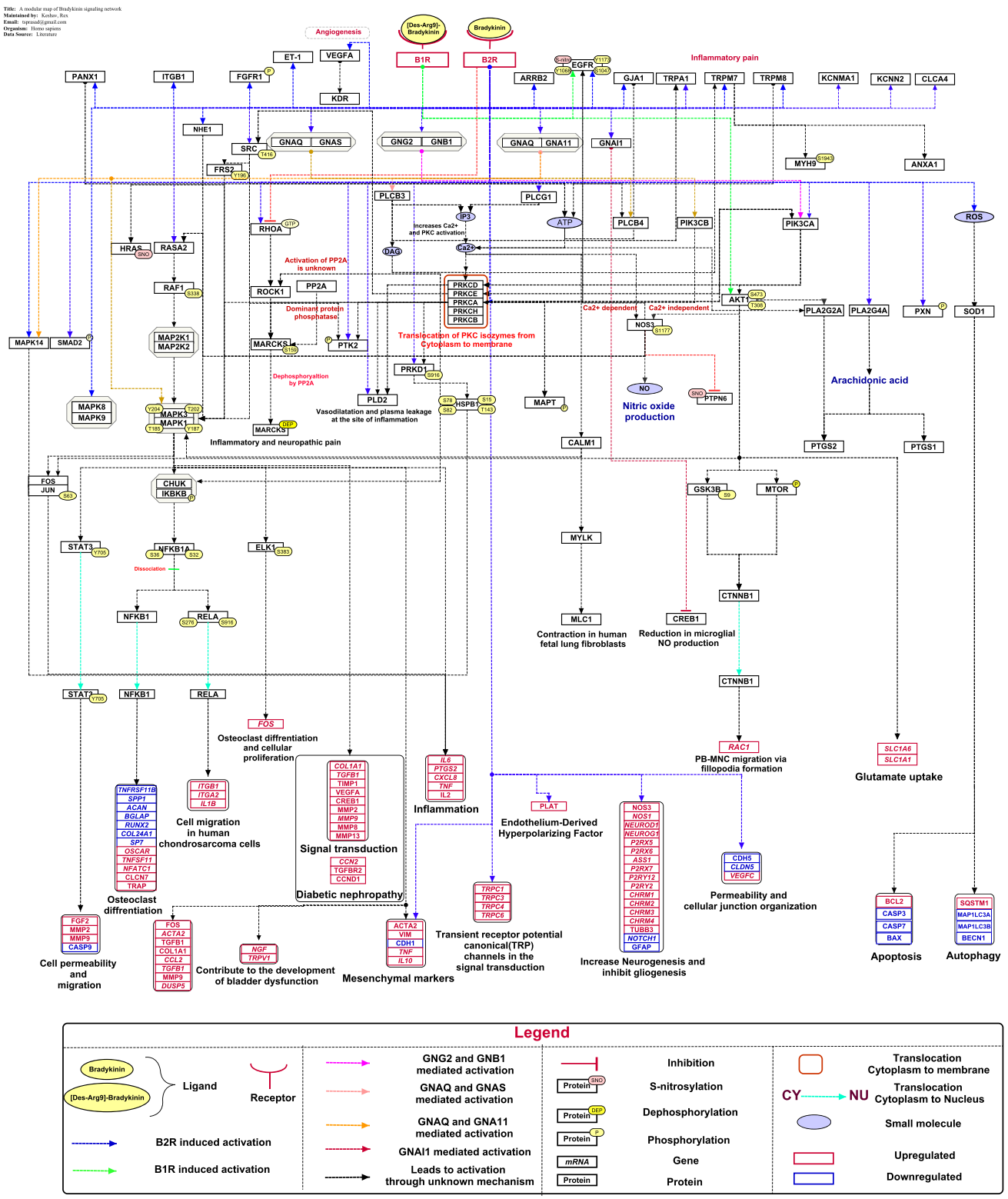

Fig. 1 Schematic representation of bradykinin mediated signaling pathway. The signaling pathway map represents molecules involved in ligand-receptor interactions and bradykinin-activated downstream molecular events including molecular association, catalysis, translocation, and gene regulation events. Information regarding the post-translational modification site and the residue is also shown in the pathway.

neuroblastoma cells. In synovial fibroblasts, bradykinin stimulates B2R and activates IKKα/β (IKK alpha/beta) via the activation of PLC, PKC-δ (PRKCD) and increases the binding of RELA and NFKB1 to the NF-κB element, which leads to the increased production of *IL-6* in rheumatoid arthritis (Lee et al. 2008). In addition, B2R stimulation by bradykinin activates EGFR mediated PI3K activation and translocation of PRKCD from the cytoplasm to the plasma membrane to induce MAPK1/3 activation and FOS protein expression, which lead to cell proliferation in human breast epithelial cells (Greco et al. 2004). In human cardiac c-kit+ progenitor cells, B2R activation by bradykinin releases Ca^{2+} from the endoplasmic reticulum and influx through store-operated Ca2+ entry (SOCE) complex activates AKT, MAPK1/3 phosphorylation and cyclin D1 protein expression leads to cell proliferation and migration to promote myocardial repair (Li et al. 2017). In human neuroblastoma SH-SY5Y cells, bradykinin promotes neurite outgrowth through rapid transient MARCKS phosphorylation through PKC dependent RhoA/ROCK pathway followed by dephosphorylation with the help of protein phosphatase 2A (PP2A) (Tanabe et al. 2012). Bradykinin stimulates myofibroblast migration through Hsp27 phosphorylation and cyclooxygenase 2 (COX2) expression via PKD in the CCD-18Co cell line (Chu et al. 2017). In human ciliary muscle (CM) cells, bradykinin/B2R leads to expression of COX1, and COX2 via MAPK signaling pathway. Subsequent release of PGE2 and PGF2α to the extracellular space is involved in the modulation of intraocular pressure (IOP) (Sharif et al. 2013).

In addition to MAPK activation, PI3K/AKT/mTOR/GSK3β is another major signal transducer involved in bradykinin mediated signaling. In human cardiac c-Kit + progenitor cells, PLC-mediated Ca^{2+} influx through the SOCE channel initiates AKT phosphorylation and CCND1 expression, leading to cell cycle progression and migration (Li et al. 2018). In human retinal pigment epithelial (ARPE) cells, bradykinin stimulates PI3K/AKT pathway via B1R and B2R to activate PLA2/COX2-mediated up-regulation of *SLC1A6* and *SLC1A1*, which triggers glutamate uptake (Lim et al. 2008). Bradykinin/B2R/PI3K/eNOS signaling exerts a potent chemoattractant activity on CD133(+) and CD34(+) circulating angiogenic progenitor cells (CPCs) associated with neovascularization potential (Krankel et al. 2008).

Bradykinin signaling pathway in diseases

Bradykinin is a potent pro-inflammatory mediator, neutrophil chemoattractant and angiogenic factor, which acts through B1R and B2R in many inflammatory diseases such as chronic pain, vasculopathy, asthma, allergic rhinitis, neuropathy, obesity, rheumatoid arthritis, diabetes, cancer and infectious disease (Barnes 1992; Couture et al. 2001; Wang et al. 2008; Dagnino et al. 2020; Lau et al. 2020). Lys-des[Arg9]-bradykinin/B1R induces the epidermal growth factor receptor (EGFR) and downstream signaling via the MAPK1/3 activation mechanism modulate neutrophils migration by upregulating MMP-2 and MMP-9 in estrogen-sensitive and -insensitive breast cancer cells (Ehrenfeld et al. 2011). B1R activation upregulates chemokine CXCL5A expression involved in neutrophil recruitment at sites of inflammation (Duchene et al. 2007).

Inflammation

Bradykinin induced pro-survival and proliferative intracellular signaling in human hepatic stellate cells and rat hepatocytes through AKT mediated NF-κB translocation and downregulation of *TGFB1* and *COL1A1* expression attenuate liver damage and fibrosis (Sancho-Bru et al. 2007). Further, in human airway epithelial cells, bradykinin activates the Ras/Raf-1/MAPK pathway, which in turn leads to the activation of IKKα/β and NF-κB and up-regulation of COX2, which is involved in the transition of acute allergic reactions to chronic airway inflammatory diseases, such as asthma (Chen et al. 2004).

Bradykinin triggers the activation of TRPA1 via the PLC and PKA pathways in response to tissue inflammation, which might trigger the sensation of pain in rat DRG neurons (Wang et al. 2008). Bradykinin receptors induce the overexpression of inflammatory cytokines, including *TNF-α* and *IL-10*, which are involved in inflammation in the human salivary gland cells (Lee et al. 2017). Bradykinin induces the expression of *IL-8* via the binding of transcription factors AP-1, nuclear factor (NF)-IL-6 and NF-κB to the *IL-8* promoter via prostaglandin E2 dependent and independent activation in human airway smooth muscle cells (Zhu et al. 2003). Recent studies have reported that bradykinin-induced COX-2 expression and PGE2 release via PKC-δ-dependent activation of MAPK1/3 and NF-κB pathways may lead to brain injury and inflammatory diseases in human CM cells, podocytes, rat astrocytes and A549 cells (Chen et al. 2004; Hsieh et al. 2007; Sharif et al. 2013; Saoud et al. 2020). In vulvar vestibule fibroblasts, bradykinin/B2R induces NF-κB activation, which increases the *IL-6* release and causes pain (Falsetta et al. 2016). In human articular chondrocytes and renal epithelial cells, bradykinin induces the release of inflammatory cytokines such as *IL-6* and *IL-8* via NF-κB signaling mechanism (Meini et al. 2011; Yang et al. 2018).

Cancer

The bradykinin-mediated B2R triggers NF-κB activation via $G\alpha_{qs}$, $G\beta_1\gamma_2$, PI3K, AKT and IKK2 pathway in HeLa cells (Xie et al. 2000). In A549 lung epithelial cells, bradykinin

requires $G_{q/11}$ to activate MAPK1/3 and MAPK14, which induces the phosphorylation of EGFR at Ser 1047 and upregulates the transcription of dual-specificity MAPK phosphatase 5 (DUSP5) (Izumi et al. 2018). Bradykinin mediated B2R activation leads to cell proliferation in human renal carcinoma A498 cells through MAPK1/3 and NHE1 pathways (Kramarenko et al. 2012). Also, bradykinin/B2R promoted the proliferation, migration, and invasion of cervical cancer cells via the STAT3 signaling pathway by upregulating the expression of MMP-2, MMP-9 and downregulating the expression pro-apoptotic protein cleaved caspase-9 (Yang et al. 2009; Wang et al. 2019). Bradykinin enhances cell migration in human prostate cancer cells through B2R/PKCδ/c-Src-dependent signaling by regulating the expression of MMP-9 via the NF-κB pathway (Yu et al. 2013). In head and neck squamous cell carcinomas, the bradykinin/B2R activation upregulates COX-2 through the MAPKs pathway in tumorigenesis (Zhang et al. 2008). Bradykinin promotes cell proliferation, migration, invasion, and tumor growth of gastric cancer by upregulation of MMP-2, MMP-9, COX-2 and downregulation of E-cadherin via MAPK pathway (Wang et al. 2017).

In various breast cancer cells, bradykinin-induced proliferation through PKC mediated MAPK, PI3K and AKT pathways (Greco et al. 2004, 2005, 2006). Bradykinin/B2R induced PI3K activation mediates the translocation of PRKCE from the cytosol to plasma membrane in the human colon carcinoma cell line SW-480 (Graness et al. 1998). In human prostate cancer cells, bradykinin/B2R signaling induces VEGF expression leads to angiogenesis through AKT/mTOR/NF-kB/AP-1 pathway (Yu et al. 2014). In the human colorectal cancer cell line SW480, bradykinin increases *IL-6* production via B2R and the MAPK pathway, contributing to invasion and migration (Wang et al. 2014).

Other diseases

In mesangial cells, c-Src/MAPK activation by bradykinin induces CTGF, TGF-beta RII, and collagen I expression, which contributes to the development of diabetic nephropathy (Tan et al. 2005). SARS-CoV-2 infection activates inflammatory cytokine storm, which leads to multi-organ injury in the host (Rex et al. 2021). Recent studies reported that dysregulated bradykinin signaling is at the core of most of the symptoms of the SARS-CoV-2 infection. A vicious positive bradykinin feedback loop has been suspected in the progression of the cytokine storm mediated by *IL-6* and *IL-8* (Garvin et al. 2020; Roche and Roche 2020). The bradykinin/B2R mediated signaling induces NO production and S-nitrosylation of RAS and EGFR, which activates MAPK1/3 and up-regulates VEGF protein expression leading to angiogenesis in HUVEC cells (Moraes et al. 2014). Several studies reported that bradykinin has an important role in a broad range of human diseases. Therefore, an organized integrative pathway map of bradykinin will provide a platform for accelerating scientific investigation on the role of bradykinin in various diseases.

Drugs that target Bradykinin signaling

Bradykinin is known to play a role in certain cardiovascular conditions (Blaes and Girolami 2013). In such a state, B2R agonists or ACE inhibitors are employed to enhance bradykinin lifetime and its downstream effects (Jalowy et al. 1998; Campbell et al. 2004). However, the pathological state of chronic inflammation witnessed in Alzheimer's disease due to the elevated levels of bradykinin (Singh et al. 2020a, 2020b). Similarly, overexpression of bradykinin was observed in hereditary angioedema, asthma and COVID-19 patients (Hofman et al.2016a, 2016b; Ricciardolo et al. 2018; Garvin et al. 2020). In such conditions, bradykinin effects countered using antagonists like Hoe140, which competitively antagonizes B2R (Wirth et al. 1991). Alternatively, kallikrein inhibitors such as Lanadelumab, Garadacimab, Ecallantide (DX-88), and Berotralstat were used to interfere with PK activity, which hinder HMWK cleavage (Farkas and Varga 2011; Davoine et al. 2020; Manning and Kashkin 2021; Wedner et al. 2021; Zuraw et al. 2021). A recent study reported that a new chemical, compound 3, can antagonize B2R even at a picomolar concentration (Lesage et al. 2020).

Conclusions

Bradykinin-mediated signaling implicated in inflammation, chronic pain, vasculopathy, neuropathy, obesity, diabetes, and cancer. However, the role of the bradykinin-mediated signaling pathway in inflammatory diseases is still unclear. In-depth data mining and depiction of molecular reactions induced by bradykinin into a spatiotemporally organized signaling network will help the future biomedical investigation in bradykinin signaling. The comprehensive network map of bradykinin signaling will provide several peripheral novel proteins with undefined functionality in the signaling pathway, providing new hypotheses for future research. In addition, an increase in the number of proteins in the bradykinin signaling network will make this pathway linked to various new physiological events when future datasets subjected to gene set enrichment analyses.

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Declarations

Conflict of interest The authors report no conflicts of interest.

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