A comprehensive review on current understanding of bradykinin in COVID-19 and inflammatory diseases

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Abstract

Bradykinin, a member of the kallikrein–kinin system (KKS), is a potent, short-lived vasoactive peptide that acts as a vasodilator and an inflammatory mediator in a number of signaling mechanisms. Bradykinin induced signaling is mediated through kinin B1 (BDKRB1) and B2 (BDKRB2) transmembrane receptors coupled with different subunits of G proteins (Gαi/Gαo, Gαq and Gβ1γ2). The bradykinin-mediated signaling mechanism activates excessive pro-inflammatory cytokines, including IL-6, IL-1β, IL-8 and IL-2. Upregulation of these cytokines has implications in a wide range of clinical conditions such as inflammation leading to fibrosis, cardiovascular diseases, and most recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In SARS-CoV-2 infection, bradykinin is found to be at raised levels and is reported to trigger a diverse array of symptoms. All of this brings bradykinin to the core point as a molecule of immense therapeutic value. Our understanding of its involvement in various pathways has expanded with time. Therefore, there is a need to look at the overall picture that emerges from the developments made by deciphering the bradykinin mediated signaling mechanisms involved in the pathological conditions. It will help devise strategies for developing better treatment modalities in the implicated diseases. This review summarizes the current state of knowledge on bradykinin mediated signaling in the diverse conditions described above, with a marked emphasis on the therapeutic potential of targeting the bradykinin receptor.

Keywords Bradykinin storm · Kinin receptors · Vasodilator · Inflammation · RAAS pathway · ARDS

Introduction

Bradykinin is a potent, transient vasoactive peptide that acts as a vasodilator and an inflammatory mediator in various signaling cascades. It is a member of the kallikrein–kinin system (KKS), associated with inflammatory response pathway mediating diverse functions in vascular permeability like thrombosis and blood coagulation [1]. Bradykinin induces vasodilation in peripheral circulation by decreasing the arterial tone of the smooth muscle and increasing blood flow [2]. Additionally, it initiates plasma extravasation by complying with capillary endothelium and vasoconstriction via the induction of venous smooth muscle fibers. During inflammatory conditions such as asthma, it promotes cellular movement from blood to tissues and activates mast cells, fibroblasts, macrophages and smooth muscles of organs [3, 4]. Bradykinin mediated signaling is also involved in chronic pain, vasculopathy, obesity, neuropathy, diabetes, and cancer [5–9].

Recently, it has been outlined that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disrupts KKS and renin–angiotensin–aldosterone system (RAAS), ushering in bradykinin storm, a process leading to heightened expression of bradykinin and consequent downstream signaling mediated effects. In such a state, bradykinin is at the core of many disparate symptoms of coronavirus disease...
(COVID-19), like loss of sense of smell and taste, leaky blood vessels, fluid accumulation in tissues and organs abnormal coagulation. The process impairs oxygen transfer from lungs to the blood, a common abnormality in COVID-19 patients [10]. Being a member of KKS, Bradykinin on its own components, and other components of its synthesis and sustenance. Rightly so, the biochemistry of these components, namely bradykinin receptors, bradykinin-related peptides, receptor agonists and antagonists and various other aspects, has been outlined in far more detail than bradykinin [5, 11, 12]. The evidence above casts a spotlight on bradykinin as a molecule of immense therapeutic potential that deservingly needs its due share of focused discussion fulfilled.

Here, we attempt an excursion into the currently available knowledge on bradykinin under the broad landscape of KKS, its signaling cascades and role in disease pathophysiology, both protective and deleterious, and bradykinin receptor targeting that can carve the premise of the therapeutic utilization of bradykinin in various conditions.

**Kallikrein–kinin system and bradykinin synthesis**

Kinins are low molecular weight peptides that get liberated from high molecular weight kininogens (HMWK) and low molecular weight kininogens (LMWK) by the action of plasma kallikrein (PK) or tissue kallikrein (TK), respectively, which makes up an integral part of KKS [13]. Distinct gene transcripts of plasma HMWK and tissue LMWK are derived from the kininogen gene (KNG1) located on chromosome 3q26 (in humans) by alternate splicing. This gene contains 11 exons, of which 9 and apart of exon 10 codes for the heavy chain of both kininogens. Full coding sequence of exon 10 makes 56 kDa light chain of HMWK and exon11 codes for 4 kDa light chain of LMWK [14, 15].

Plasma KKS are involved in constitutive anti-coagulant activity protecting endothelium, whereas the tissue system is essential in tissue repair and reaction to noxious or artificial stimuli [16]. HMWK is primarily expressed in the liver, whereas LMWK are widely distributed and expressed in endothelial cells of vasculature [17]. PK is produced as zymogen plasma pre-kallikrein, secreted primarily from hepatocytes into the blood. In the blood, it circulates as a complex with HMWK [18]. Normally, circulating PK is inactive but can be activated with a negatively charged surface like the basement membranes mediated blood clotting by factor XII (Hageman factor/FXII) and HMWK as cofactor. PK then processes HMWK (120 kDa) to release the nonapeptide bradykinin [19, 20].

Meanwhile, TK differs from PK as it can be encoded by various genes and secreted by many organs, including the pancreas, salivary glands and kidney [21]. There are 15 known TKs encoded by the genes named it from KLK1 to KLK15, the most prominent protease family in the human genome, which are located on 19q13 chromosome [22]. TK produces decapetide, kallidin or Lys-BK (LBK) mainly by its action on LMWK (70 kDa). In addition, TK can also act on HMWK to generate LBK [23] (Fig. 1). LBK can be converted into bradykinin in some circumstances by the action of plasma aminopeptidases upon removal of N-terminal lysine. These activated kinins can stimulate endothelial cells, increasing vasodilation, vascular permeability, nitric oxide (NO) production, and arachidonic acid mobilization [24]. Aminopeptidase B can act on LBK and release N-terminal lysine, thereby releasing bradykinin without further degradation [25].

Kinins are altered by a number of enzymes, including Carboxypeptidase M (CPM), a kininase I-type enzyme that modifies bradykinin and LBK into des-Arg⁹-BK and des-Arg¹⁰-LBK, respectively [26]. Further, C-terminal arginine residues of the kinins can be removed by carboxypeptidase N (CPN), a plasma carboxypeptidase. Angiotensin I converting enzyme (ACE) is a key kininase II that cleaves C-terminal dipeptides from kinins, rendering them inactive. Kinins are cleaved at internal phenylalanine (Phe5 in BK) by membrane-bound Neutral endopeptidase (NEP) [27, 28]. Therefore, given these factors, the circulating lifespan of bradykinin corresponds to only a few seconds following its transient activity with this consortium of digesting enzymes [29] (Fig. 2).

**Kinin receptors**

Regoli et al. have characterized kinin receptors through pharmacological studies [30]. The cell surface receptors such as kinin B1 and B2 are transmembrane G-protein coupled receptors with seven domains that mediate the biological effects of kinins [31]. BDKRB2 is widely expressed in many healthy tissues and stimulated by the binding of unaltered kinins. Unlike BDKRB2, BDKRB1 is inducible and present minimally in healthy tissues but expressed rapidly during inflammation and responded to kinin lacking C-terminal arginine residues [6].

BDKRB1 is scarcely detectable in peripheral tissues under normal physiology, but its mRNA was present constitutively in different brain regions and spinal cord [32, 33]. BDKRB1 is rapidly induced in almost all inflammatory and stressful conditions at transcriptional and post-transcriptional levels in the whole body [8, 34]. Pro-inflammatory mediators like interleukin-1β, IFNγ, TNFα, soluble gC1qR and epidermal growth factor at inflammatory sites can upregulate de novo synthesis of BDKRB1 in various cells especially, endothelial [35–37]. CPM binds to the external loop 2 of BDKRB1 increasing conformational activation and generates BDKRB1 agonists from kinins [38]. BDKRB2 is localized constitutively in the majority of inflammatory...
relevant cells, including endothelial cells, osteoblasts, epithelial cells and neurons in the brain. It is also expressed in different types of tumor cells and immune cells [33, 39–41].

BDKRB2 is activated by phosphorylation at serine (S339, S346, S348) and threonine (T342, T345) residues on the C-terminal region when an agonist binds, which leads to arrestin mediated internalization through clathrin-coated vesicles [42, 43]. When exposed to kinin for an extended period of time, BDKRB2 is secluded into the lysosome for degradation, whereas short-term stimulation results in dephosphorylation and, as a result, the receptor is recycled back to the surface. In contrast, agonist-induced internalization is not seen in BDKRB1. Unless BDKRB1 binds to agonist, its internalization occurs independent of beta-arrestin and is broken down in lysosomes [44, 45]. However, if a ligand binds to BDKRB1, the available number of receptors is increased by redirecting sequestered clathrin-coated BDKRB1 vesicle into the cell membrane [44] (Fig. 3).

In common, BDKRB1 and BDKRB2 receptors are involved in the progression and sustenance of chronic pain in complex regional pain syndrome type-I, vulvodynia and fibromyalgia-like pain symptoms [46–48]. Additionally, both receptors are activated in pathologies involving tissue damage due to oxidative stress, pro-inflammatory stimuli, vasoactive peptide stimuli such as those found in the renin-angiotensin system, lipopolysaccharides, and endotoxins. These receptors are also regulated by post-translational modifications (PTMs) [49–51]. Protective or pathological outcomes of receptors of kinin family (BDKRB1, BDKRB2) regulation and mediation by KKS in the events of both normal and pathophysiological states are discussed in multiple studies [52–54].

Bradykinin and its involvement in disease

Bradykinin-activated signaling pathways play a significant role in various pathological conditions such as

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**Fig. 1** The gene for KNG is present on q-arm of chromosome 3. Boxes 1–11 show the respective exons with intermittent introns. KNG gene undergoes alternative splicing to form HMWK and LMWK. Boxes 1–9 codes for signal peptide and heavy chain of HMWK and LMWK. Exon 10b encodes the bradykinin sequence. Exon 10b codes for the light chain of HMWK, whereas exon 11 contains sequences characteristic of the LMWK light chain.
COVID-19

COVID-19 is a highly contagious viral infection caused by the SARS-CoV-2 virus. The infection was first reported from Wuhan, China in December 2019 and advanced rapidly due to onward transmission [8]. It is hypothesized that bradykinin pathway is dysregulated in COVID-19 patients leading to various complicated respiratory conditions. Garvin et al. have reported that bronchoalveolar lavage fluid (BALF) of COVID-19 patients have reduced ACE gene expression and raised ACE2, renin, angiotensin, AT1 and AT2, kallikrein and kallikrein enzymes that activate BDKRB1 and BDKRB2 receptors [10] (Fig. 4). The expression of the BDKRB1 and BDKRB2 receptors was reported to be raised by 2945- and 207-folds, respectively. Kallikrein and kallikreins expression was undetected in controls but expressed in COVID-19. Although ACE gene expression reduced eightfold, resulting in enhanced activity of bradykinin, downregulation of ACE2 culminated in reduced degradation of des-Arg9-bradykinin. All of this along with the increased expression BDKRB1 and BDKRB2 receptors can lead to the bradykinin storm [10, 55]. Such ‘bradykinin storm’ leads to vasodilation, vascular permeability, and hypotension. It is possible that this bradykinin is produced by bronchiole and alveoli-resident mast cells. Tissue resident granulocytes and mast cells are known to generate bradykinin by synthesizing heparin, activating coagulation factor XII, and forming PK [56, 57]. Thus, the rise of bradykinin could be attributed to heightened mass cells density in the lungs of COVID-19 patients [58].

It is also hypothesized that bradykinin metabolite, des-Arg9-BK, could lead to inflammation, vasodilation, vascular permeability through bradykinin receptors [59]. This becomes important because des-Arg9-BK is cleaved by ACE2 [60] and is in contrary to the report by Garvin et al., it is established that SARS-CoV-2 infects target cells via its spike protein (S) antigen with ACE2 [61, 62]. The internalization of the resulting complex reduces the activity of ACE2. This increases its signaling via BDKRB1 leading to fluid extravasation and leukocyte movement to lungs [60].
Raised BALF ACE2 levels in the study by Garvin et al. could be because it was either membrane shed form (via ADAM17-mediated proteolytic cleavage) or soluble form and that the type of ACE2 was not exactly determined [10].

Dry cough as a COVID-19 symptom could be explained by bradykinin-mediated sensory nerve activity as a cascade for ACE-inhibitor modulated dry cough [64]. Further, bradykinin may have a role in gustatory and olfactory dysfunctions [65]; also, ACE-inhibitors can lead to olfactory dysfunction [66].

The loss of ACE2 function and the resulting raised Ang-II levels can also lead to decreased ACE activity via a negative feedback loop (renal ACE and renin gene is downregulated by Ang-II). This decrease in ACE levels can lead to a rise in bradykinin levels. Further, it is reported that Ang-II is involved in the raised expression of prolyl-carboxypeptidase, resulting in PK-induced generation of bradykinin [67]. Reduced ACE2 level outcomes like vasoconstriction [68], pro-inflammatory cytokine levels [69], C-reactive protein [70], pulmonary fibrosis [71], coagulopathy with increased plasma D-dimer, pulmonary thrombosis and venous thromboembolism [72, 73], dispersed intravascular coagulation [74] and ARDS [69, 75] are reported in COVID-19 patients. Reduced eNOS activity and NO levels are involved in COVID-19 patients with endothelial dysfunction, resulting in thrombosis and organ dysfunctions [76, 77]. It supports the hypotheses of reduced BDKRB2 stimulation (which initiates eNOS) and NO generation. Besides ACE-2, a lysosomal cysteine endopeptidase, cathepsin L, also assists SARS-CoV-2 cell entry via transmembrane protease serine-2 [61]. It forms kinins from LMWK and HMWK [78], and has kininogenase activity [79]. It can lead to bradykinin release and has hypertensive activities [80].

The rise in bradykinin, des-Arg<sup>9</sup>-BK, and Ang-II levels in the pulmonary vascular bed and peripheral vascular system by SARS-CoV-2 infection can lead to the onset of acute respiratory distress syndrome (ARDS) [81], a potentially fatal lung respiratory failure caused by inflammation and fluid build-up in the lungs, resulting in stiff lungs and hypoxemia [82]. It is proposed that BDKRB2 blockers and inhibition of PK might prevent the development of COVID-19 induced ARDS [59].

Cardiovascular complications

Prolonged hypertension is generally associated with renal dysfunction and tissue injury. Some studies suggest the protective function of bradykinin against hypertension-induced complications [83, 84]. For instance, salt-induced hypertensive and renal injured rats were infused subcutaneously with bradykinin showed protective effects against renal injury but not hypertension. In this way, bradykinin directly protects against salt-induced renal injury [84]. Bradykinin also has a proliferative effect on endothelial cells. Locally synthesized bradykinin takes part in neovascularization and helps repair vascular wall and remodeling after acute ischemia. It signals through BDKRB2/Pi3K/eNOS mediated employment of circulating progenitor cells having the regenerating capacity to the injury site [83]. Bradykinin has a key function in all cardiac conditioning mechanisms [85, 86]. Bradykinin infusion in isolated rat hearts provides intermittent protection through a pathway involving BDKRB2, PKG, NOS and mitochondrial K(ATP) channel [86]. Bradykinin also inhibits myocardial apoptosis through Akt and GSK-3β phosphorylation, improves antiapoptotic protein profile and plays a role in ventricular remodeling [87, 88].

Similarly, a pharmacological study reports the myocardial protective role of BDKRB1 and BDKRB2 in diabetic and nondiabetic patients, respectively, in acute coronary syndrome [89]. Cardioprotective drug-mediated augmentation of kinins’ half-lives, including bradykinin, has protective roles in cardiac remodeling, apoptosis and fibrosis, via BDKRB2-NO [90, 91]. However, bradykinin can have anti-fibrotic effects in pathogenic remodeling that surrounds cardiomyocytes leading to left ventricular enlargement and dysfunction [92]. In addition, bradykinin is involved in infarction triggered chest pain (angina) mediated through 12-lipoxygenase products, IP3 and TRPV1 channels. Bradykinin also acts as a cardiac nociceptor which stimulates BDKRB2 in upper thoracic spinal (sympathetic) sensory neurons [93, 94]. Thromboxane A2, a lipid family member with prothrombotic properties, reciprocally interacts with bradykinin during myocardial ischemia stimulating cardiac spinal afferents [94, 95]. Bradykinin agonists can be therapeutically used to counterbalance Bradykinin deficiency, which seems consistent with endogenous bradykinin-BDKRB2 mediated cardiac protection. However, deducing the right dosage, therapeutic window, and medication period will be significant determinants to control the balance.

Fibrosis

Fibrosis is the pathological wound healing condition in which connective tissue replaces normal parenchymal tissue to an extent that leads to substantial tissue remodeling and development of permanent scar tissue [96, 97]. Bradykinin has significant roles in diseases marked by tissue remodeling and chronic inflammation. In such states, bradykinin may have an anti-fibrogenic effect [98]. In cardiac and renal damage, stimulated BDKRB2 has protective effects. Overexpression of kallikrein gene reduces the onset of cardiac hypertrophy and renal fibrosis [98–100]. Bradykinin may induce such effects in heart and kidney via the beneficial role of RAAS inhibitors as the inhibition with pharmacologic agents of this system increases bradykinin levels [99,
(A) BDKRB1 mediated signaling

Inflammation/stress/tissue injury

Cytokine expression

p38 ERK JNK

Signaling cascade

TFs

BDKRB1

Increased expression

Des-Arg9-BK

Down stream signaling activated by Des-Arg9-BK

Inflammation

Leukocyte chemotaxis

EMT

Absence of agonist

BDKRB1 AP-2-Clathrin Complex

Resensitization and recycling

Prolonged absence of Des-Arg9-BK

Lysosomal Degradation

Nitric oxide (NO) and prostaglandins (PGs)

Nucleus

(B) BDKRB2 mediated signaling

Short exposure to Bradykinin

Dephosphorylation and recycling

Bradykinin

P Phosphorylation

β-arrestin

AP-2-Clathrin Complex

Long exposure to Bradykinin

Bradykinin

P Phosphorylation

P Phosphorylation

P Phosphorylation

P Phosphorylation

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101, 102]. Also, bradykinin has protective effects in models of ischemia–reperfusion, a condition characterized by the caused tissue damage owing to the return of the blood supply to tissue after a stretch of ischemia or anoxia (or hypoxia). This condition induces secretion of vasodilatory intermediates like NO and prostaglandins [103]. Further, bradykinin activates signaling molecules that safeguards parenchymal cells from apoptosis by NF-kB and AKT pathway [104, 105].

Targeting the bradykinin receptor

The proceeds in the cognizance of kinin roles, including BK and its receptors, stem from the progress made in chemically synthesized peptide and non-peptide selective receptor ligands [106–108]. Studies reporting compounds mediating their effects on B2R have been classified in three generations (Fig. 5). The first generation of B2R antagonists includes Vavrek and Stewart, who synthesized them by changing the C-terminal dipeptide Phe8-Arg9 of BK and substitution of Pro7 by D-Phe residue. This [D-Phe7] BK analogue is a weak antagonist and partial agonist of guinea pig and rabbit B2R [109]. Further, N-terminal addition of a D-Arg and the substitution of Pro5 by Hyp results in D-Arg- [Hyp3,D-Phe7] BK (NPC 567) with improved potency against degradation by proteases [110]. D-Arg- [Hyp3, Thi5,8, D-Phe7] BK is a homologue of NPC 567 with an unnatural amino acid. This replaces Phe at positions 5th and 8th, conceivably conferring resistance against degradation by proteases. In D-Arg- [Hyp3, D-Phe7, Leu5] BK, Phe8 is substituted by a Leu to eliminate aromaticity [109]. These antagonists are more potent in rabbit B2R than other study models (guinea pig, mouse) but inactive in humans because of rapid degradation by a battery of proteases [111, 112]. Additionally, they are converted to desArg9-metabolites (B1R agonists) by CPM, thereby making it non-selective [109].

The second generation of B2R antagonists was introduced by discovering HOE140 (Icatibant), which had rigidity, stability, increased binding, and potency without partial agonist activity [113]. In HOE140, D-Phe7 was substituted by the rigid analogue tetrahydrosquinooline-3-carboxylic acid (D-Tic) and Thi8 by octa hydro indole-2-carboxylic acid (Oic) (D-Arg-[Hyp3, Thi5, D-Tic7, Oic8] BK) [111, 114]. It could resist endo and exopeptidase activity by its tertiary amides D-Tic and Oic, similar to proline and hydroxyproline, along with D-Arg at the amino terminus. These characteristics give this molecule extreme stability and prolong its interaction with B2R [114]. In addition, these two unnatural amino acids and the beta-turn of the C-terminal region conferred extra rigidity, which marked the significance of the spatial orientation for optimal antagonist activity. Intra-arterial injection of HOE140 blocked the effect of exogenous bradykinin in rats and was found to be quite potent in humans as it competitively binds to B2R. HOE140 is very selective as it had almost no effect on other kinin receptors [115].

In addition, it is known as a non-equilibrium antagonist as it binds at the same site as BK but dissociates rather slowly, thereby preventing the complete occupation of agonist(s) [111, 116]. It has been employed in clinical trials to control acute rhinitis and asthma and gauge kinins’ function in pain and hyperalgesia [117–119]. Even though it failed to manage pollen-induced seasonal allergic rhinitis, it antagonised house dust-mite triggered nasal obstruction in allergic rhinitis patients [118]. Subcutaneous injection of HOE140 leads to local skin reaction caused by interaction with a mast cell GPCR which releases histamine [120]. Further, it has been certified for HAE treatment with acute attacks [121]. In order to improve stability, duration of action and flexibility in comparison to the previously described antagonists, dimeric peptides were explored. One such example is De-libant (CP-0127), a homodimer of D-Arg-[Hyp3, Thi5, Cys6, D-Phe7, Leu8] BK joined at Cys6 by bis-succinimidohexane (BSH) [122]. It has moderate potency as demonstrated in various assays and enhanced stability and efficacy in various in vivo models of trauma [4].

Later, non-peptide, orally active third-generation B2R antagonists including WIN64338 and FR173657 were synthesized. The former exerts moderate antagonism in the guinea pig but is inactive in humans [123–125]. However, later is highly potent on human B2R with pA2 value of 8.2 (pA2 value indicates the affinity of the antagonist to the receptor). FR173657 also inhibits bronchoconstriction in guinea pigs, reduces carrageenan-mediated paw edema, reduces caerulein-mediated pancreatitis in rats, and relieves kaolin-mediated pain in mice when administered orally [126, 127]. Anatibant (LF 16–0687; XY2405) is a synthetic non-peptide B2R antagonist with a characteristic pharmacological profile that meets essential criteria to be considered for clinical trials. Further, it is investigated in a clinical trial to brain edema after head injury [128–130].

Fasitibant (MEN16132) is also a nonpeptide selective antagonist for the B2R with high efficacy in several animal models of inflammation [131]. Based on the outcomes generated in various pharmacological investigations, it was
**Fig. 4** A schematic diagram of ACE2, ACE and Bradykinin regulation mechanisms. The enzyme ACE can act on Angiotensin I and Bradykinin to convert them into Angiotensin-(1–9) and inactive fragments, respectively, thus connecting the two pathways. The resulting products, Angiotensin-(1–7), Angiotensin II, and des-Arg9 bradykinin mediate their effects through Mas, AT1 and BDKRB1 receptors. (Notations: ACE- Angiotensin-converting enzyme, NEP-Neprilysin)

**Bradykinin 2 receptor antagonists**

**First generation antagonists**
- [D-Phe7] BK
- D-Arg-[Hyp3, D-Phe7]BK
- D-Arg-[Hyp3, Thi5, D-Phe7] BK
- D-Arg-[Hyp3, D-Phe7, Leu8]BK

**Properties:**
- Modified BK peptides
- Weak antagonists
- Vulnerable to degradation by proteases
- Potency: Rabbit > Guinea pig > Mouse
- Inactive in humans

**Second generation antagonists**
- D-Arg-[Hyp3, Thi5, D-Tic7, Oic8]BK (Hoe 140/Icatibant)
- D-Arg-[Hyp3, Thi5, Cys6, D-Phe7, Leu8]2-BK (Deltibant)

**Properties:**
- Stable altered BK peptides
- Competitive antagonists
- Prolonged binding with B2R
- No effect on other kinin receptors
- Active in humans

**Third generation antagonists**
- WIN64338
- FR173657

**Properties:**
- Non peptide
- WIN64338 active in guinea pig but not in humans
- FR173657 active in human

**Fig. 5** B2R receptor antagonists. Members and properties of the three generations of B2R antagonists are depicted.
taken up for phase II clinical trials for knee pain in osteo-
arthritis (NCT0109116) [132]. Lanadelumab (DX-2930) is
a Human monoclonal antibody-containing κ-light-chain of
immunoglobulin G1 against PK [133]. It binds to free solu-
table PK and HMWK bound PK. Further, it inhibits hydrolysis
of HMWK by PK, without inhibiting other serine-proteases,
like Factor XIIa and the zymogen PPK [133] (Table 1). It was
recently approved for the treatment of long-term prophy-
laxis for C1-INH-HAE attacks in patients aged 12 and above
[134]. However, European Medicines Agency designated it
as an orphan drug as it is not profitable to produce without
government assistance [135].

Future directions

The review summarizes pioneer research and recent updates
on bradykinin-induced effects in various diseases. Along
with bradykinin, we have also discussed distinctive role
of BDKRB1 and BDKRB2 in various conditions, which
are often involved in opposite and not always compensa-
tory or synergistic manner. Albeit under the limelight of
various KKS and RAAS components, the review showcases
the important role of bradykinins in the pathophysiology
of inflammatory conditions and recent COVID-19 burden.
Due to this conjoined nature of bradykinin signaling with
other mediators, the results of preclinical and clinical studies
aiming to manage the above diseases by pharmacological
targeting of bradykinin associated KKS components; mainly
kinin receptors need careful consideration to be devised.

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