Drugs of the Kallikrein–Kinin System

Subjects: Pharmacology & Pharmacy

Contributor: François Marceau

The kallikrein–kinin system consists of the two kininogen substrates present in the blood plasma, and two serine proteases: the plasma and tissue kallikreins. The action of the latter on kininogens produces small peptides, the kinins, short-lived, but endowed by powerful pharmacologic actions on blood vessels and other tissues. Several classes of drugs alter kinin formation or action at their receptors for a therapeutic benefit.

kallikrein–kinin system | kininogens | bradykinin | B1 receptor | B2 receptor

1. Kallikrein–Kinin Systems: The Formation and Clearance of Kinins

Both protective and pathogenic effects are mediated by two largely separate kallikrein–kinin systems (KKS; abbreviations are defined in **Table 1**) via the formation of small and unstable peptides, the kinins (**Figure 1**, schematic representation). Thus, vascular effects (vasodilation, increased microvascular permeability), inflammatory manifestations (edema, pain, increased local blood flow), smooth muscle contraction, and epithelial cell stimulation are potentially initiated by kinins [1]. The nonapeptide bradykinin (BK; H-Arg^{1}-Pro^{2}-Pro^{3}-Gly^{4}-Phe^{5}-Ser^{6}-Pro^{7}-Phe^{8}-Arg^{9}-OH) is the reference kinin sequence found in domain 4 of two circulating proteins, the high-molecular-weight and low-molecular-weight kininogens (HK, LK; about 20 and 80% molar proportions, respectively). The hepatic synthesis of both kininogen forms is based on the alternative splicing of a single gene product, *KNG1*.

Table 1. List of abbreviations.

Abbreviation	Standing for	Corresponding Gene
ACE	angiotensin-I-converting enzyme	*ACE*
	angiopoietin 1	*ANGPT1*
APN	aminopeptidase N	*ANPEP*
Arg-CP	arginine carboxypeptidase	
B1R	bradykinin B1 receptor	*BDKRB1*
B2R	bradykinin B2 receptor	*BDKRB2*
BK	bradykinin	

Abbreviation	Standing for	Corresponding Gene
C1INH	C1-esterase inhibitor	*SERPING1*
D6	domain 6 of HK	
FXII	coagulation factor XII	*F12*
FXIIa	activated factor XII	
HAE	hereditary angioedema	
HAE-C1INH	HAE caused by C1INH haplodeficiency	
HK	high-molecular-weight kininogen	*KNG1*
KKS	Kallikrein–kinin system	
KLK-1	tissue kallikrein	*KLK1*
LK	low-molecular-weight kininogen	*KNG1*
Lys-BK	kallidin	
mAb	therapeutic monoclonal antibody	
NPA	non-peptide antagonist	
	plasminogen	*PLG*
tPA	tissue plasminogen activator	*PLAT*
uPA	urokinase-type plasminogen	*PLAU*

HK (110 kDa) circulating in a complex form with prekallikrein (85 kDa) and factor XI is part of the contact system (**Figure 1**), along with coagulation factor XII (FXII, Hageman factor, 80 kDa). When exposed to negatively charged surfaces, such as the basal membrane of denuded vascular endothelial cells, all these components assemble into a tetramolecular complex with ensuing proteolytic reactions: the mutual activation of FXII and prekallirein into their proteolytically active forms factor XIIa (FXIIa) and plasma kallikrein, respectively, the cleavage of HK releasing BK and the cleavage of factor XI that initiates the intrinsic coagulation pathway [2]. The contact system is tightly controlled by a circulating serpin inhibitor, C1-esterase inhibitor (C1INH, 105 kDa), that is also part of the complement cascade. FXIIa and plasma kallikrein are irreversibly inhibited by C1INH [3]. Blood clots are cleared by the fibrinolytic system which is connected to the contact system (**Figure 1**): plasmin, the fibrinolytic enzyme, activates FXII into FXIIa to a certain extent, indirectly promoting BK production via secondarily activated plasma kallikrein. C1INH is a secondary inhibitor of plasmin [3]. Whether HK is directly cleaved by additional proteases has been suggested, but not well established in whole blood, where endogenous inhibitors are present: plasmin and the complement-associated protease, MASP-1, may directly release BK from HK [4][5]. There is no evidence of BK release when platelets or neutrophils are activated in human whole blood [6], casting a doubt about previously suggested activation pathways demonstrated using purified components of the contact system (e.g., triggered by the polyphosphate nanoparticles from platelets [7]).

Tissue kallikrein (KLK-1; kallidinogenase) is a member of a family of 15 secreted proteases encoded on human chromosome locus 19q13.4 [8]. These serine proteases assume different, often uncertain, physiological functions. Only KLK-1 is a relevant kininogenase in this family. This was verified with two KLKs, normally found in the prostate, as they release no or very little kinins from purified HK (KLK-3) (KLK-2 is 1000-fold less active than KLK-1 in this respect) [9]. KLK-1 releases the biologically active decapeptide Lys–BK (= kallidin) from both forms of kininogen, but mostly from the more abundant LK. KLK-1 is widely expressed and abundant in the kidney, pancreas, salivary glands, lungs, blood vessels, and other tissues; its secretion and activation via the removal of an N-terminal sequence are not well understood. KLK-1 is regulated by its own irreversible inhibitor, kallistatin (*SERPINA4* gene product). The previously claimed direct agonist effect of KLK-1 on human BK B2 receptor (B2R) has been disproved using the pure recombinant enzyme in its active form [10].

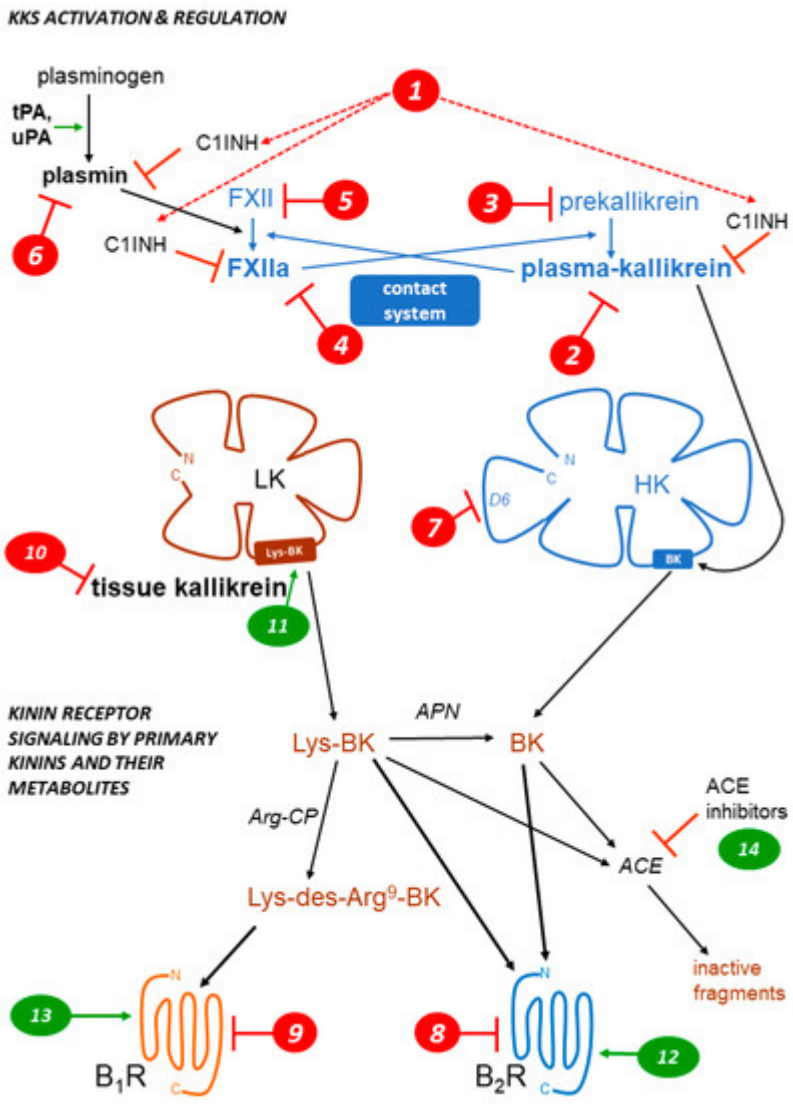


Figure 1. Schematic representation of the KKS, featuring the two validated pathways of kinin generation: that of plasma kallikrein (part of the contact system) releasing bradykinin (BK) from high-molecular-weight kininogen (HK), and that mediated by secreted tissue kallikrein (KLK-1), generating Lys–BK mainly from low-molecular-weight kininogen (LK). Two G-protein-coupled receptors (B1R, B2R) mediate the cellular effects of kinins. Three types of metallopeptidases that hydrolyze kinins are indicated (APN, Arg–CP, ACE). Numerical markers indicate the mode

of action of the inhibitory (red) or stimulatory drugs (green) of the KKS and are referred to in **Table 2** and the main text. See **Table 1** for abbreviations. Modified from [11][12].

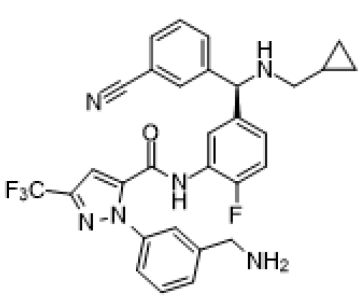
Kinins are inherently unstable, with a half-life well under 1 min [11], and are metabolized by several metallopeptidases. An in vivo study showed that angiotensin-converting enzyme (ACE, kininase II) is the dominant BK-inactivation pathway in rats, followed by aminopeptidase P [13]. Both peptidases inactivate BK, initially producing fragments $BK_{1–7}$ and $BK_{2–9}$, respectively. Fragment $BK_{1–5}$ is a relatively stable product of a second cycle of $BK_{1–7}$ cleavage by ACE. Lys–BK is also inactivated by ACE. Aminopeptidase N (APN, CD13) can remove the N-terminal Lys residue from Lys–BK to produce BK [1]. The arginine carboxypeptidases (Arg–CPs), plasma carboxypeptidase N, and glycosylphosphatidylinositol-linked carboxypeptidase M remove the C-terminal Arg residue from BK and Lys–BK, producing des-Arg^9–BK ($BK_{1–8}$) and Lys-des–Arg^9–BK, respectively, also the subsequent substrates of ACE [1]. Arg–CPs represent only a minor metabolic pathway when circulating kinins are considered [13][14], but may be important in inflammatory exudates. Crucially, Arg–CPs connect the KKS with the pharmacological profile of the kinin B1 receptor (B1R) selectively responsive to the des-Arg^9 metabolites of kinins (see below).

The biomarkers of kinin-mediated disorders include the consumption of kininogen(s) and the detection of circulating kinin metabolites such as fragments $BK_{1–5}$ and $BK_{2–9}$, and the detection of plasma kallikrein activity, for instance, using the synthetic substrate based on the C-terminal BK sequence HD-Pro-Phe-Arg-*pNA*. These assays are technically challenging, but one or more of them have been applied to hereditary angioedema (HAE), either during attacks or in remission [15][16] to other edematous conditions such as ascites, secondary to liver cirrhosis [17] and chronic urticaria [18][19], and to animal models of sepsis and sickle cell disease [20][21].

2. Kinin Receptors

Before the era of molecular biology, the number and identity of kinin receptor subtypes in each mammalian species were uncertain. Historically, the first proposed kinin receptor subtype, B1R, was discovered as the one mediating contraction in isolated rabbit aorta in response to kinins based on classical pharmacologic criteria, a typical order of potency for agonists and antagonism by newly discovered peptide antagonists [22]. Native kinins (BK and Lys–BK) from which the Arg^9 residue has been removed by Arg–CPs (des-Arg^9–BK, Lys–des-Arg^9–BK, respectively) are the optimal agonists of the B1R, even if this kinin metabolic pathway is not prominent. Only Lys–des-Arg^9–BK, also called des-Arg^{10}–kallidin, has a subnanomolar affinity for the human (and rabbit) B1R [1]; this agonist is presumably generated from Lys–BK (kallidin), itself derived from the cleavage of kininogens by tissue kallikrein (**Figure 1**), and hence independently from the contact system. Early peptide antagonists, such as [Leu^8]des-Arg^9-BK, consolidated the pharmacological identity of B1R; the other pharmacologic preparations, directly responsive to BK and Lys–BK, but insensitive to the des-Arg^9 metabolites, were said to possess the still not fully defined B2R subtype. The first B2R antagonists were discovered in the early 1980s; they featured a constrained peptide backbone and were more or less protected from peptidases. Icatibant (Hoe 140; D-Arg–[Hyp^3, Thi^5, D-Tic^7, Oic^8]BK) is the success story among these early drugs [1][23] (**Table 2**). Selected modern nonpeptide antagonists (NPAs) of both kinin receptor subtypes are presented in **Figure 2**. It is very typical that BK receptor antagonists exhibit species-dependent

alterations of affinity and competitive behavior for their pharmacological targets [1]; thus, clinically developed antagonists have gone through a structural optimization process to the human forms of B1R or B2R [1][24].



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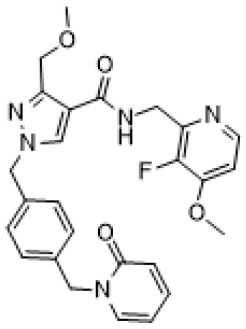

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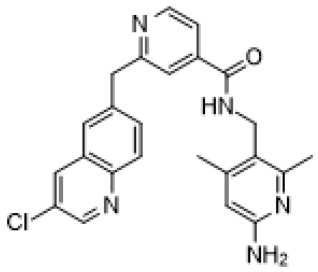

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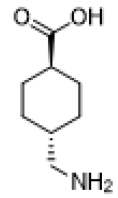

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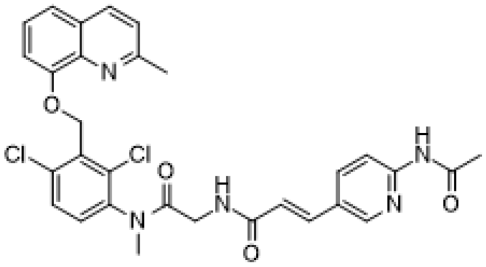

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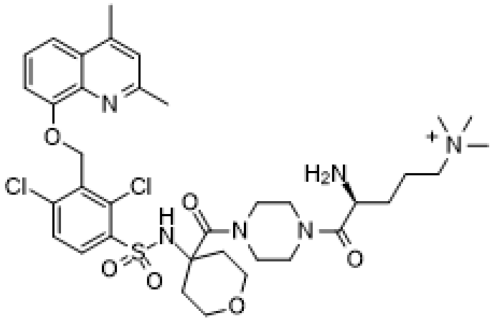

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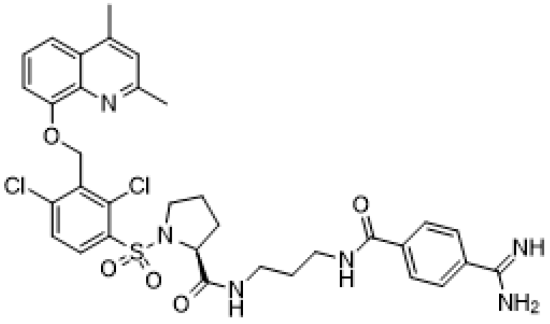

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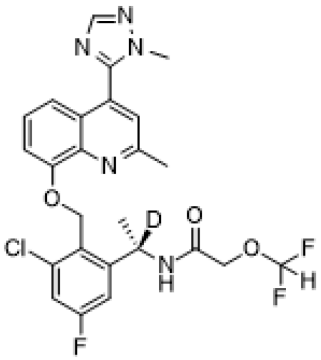

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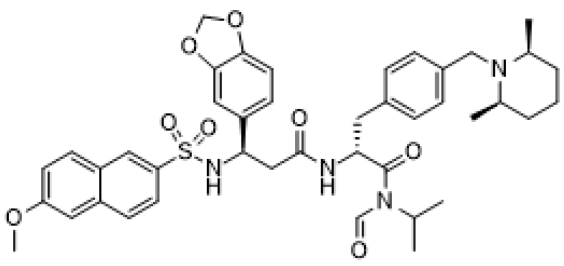

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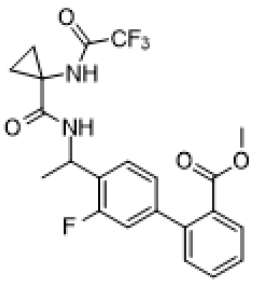

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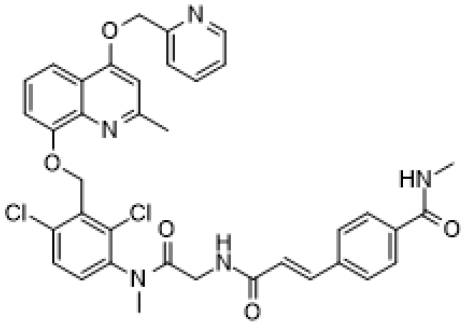

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Figure 2. Structure of small-molecule drugs cited in **Table 2** and text (except for KV998086 and BI1026706, currently undisclosed). The *numerical markers* indicate the mode of action, as in **Figure 1**. The structure of the antagonists of kinin receptors is optimized for the human forms of these receptors. Note the structural similarities of the B2R antagonists (marker *8*). Only deucrictibant is developed as an orally administered drug in this class.

The receptor classification was confirmed by the discovery of a kinin receptor locus: in human chromosome region 14q32, genes encoding G-protein-coupled receptors B2R and B1R, respectively termed *BDKRB2* and *BDKRB1*, are found in tandem [25]; a similar organization is found in the genome of other mammals. While the expression of both genes is regulated, B2R generally accounts for the in vivo effects of kinins in healthy laboratory animals. This receptor subtype is constitutively expressed in many cell types, including vascular endothelial cells, smooth muscle cells, some epithelia, sensory neurons, and other cell types [1]. B1R, initially discovered in rabbit isolated blood vessels maintained in vitro for several hours, is not generally detectable in healthy animals. The paradox was resolved when B1R was found to be expressed following tissue trauma, inflammation (such as the injection of bacterial lipopolysaccharide to animals) under the control of inflammatory cytokines (e.g., interleukin-1, tumor necrosis factor-α, interferon-γ), and signaling pathways (e.g., mitogen activated protein kinases, NF-κB, Jak/Stat) [25][26][27][28]. While B1R and B2R are structurally related, only the latter is phosphorylated, internalized, and recycled following agonist stimulation [1][25]. Thus, the B1R is potentially important in sustained inflammatory states and infectious disease. For instance, treatment with a B1R antagonist decreased mortality and mitigated cardiac inflammation and dysfunction in an experimental Chagas disease model in mice [29]. However, it does not follow that B1R should be systematically blocked in tissue injury situations; for instance, the development of an adaptative collateral circulation is mediated by this receptor subtype following arterial occlusion in a rodent model [30].

Both kinin receptor subtypes are coupled mainly to the protein G_q and calcium signaling pathways. These trigger smooth muscle contraction and vascular endothelial cell stimulation, including calcium-dependent prostanoid and nitric oxide release and plasma extravasation, secondary to the opening of endothelial junctions [1][25].

Figure 1 is a schematic representation of the kinin-generating pathways and their receptors; numerical markers indicate the mode of action of the numerous drugs of the KKS. Earlier achievements, such as the early peptide receptor antagonists, are reviewed else-where [31]. The present emphasis is on drugs that are currently in use, have reached clinical development (successfully or not), or are in preclinical development.

3. Drugs of the KKS in therapeutics

The therapeutic showcase of the KKS is presently hereditary angioedema (HAE), a rare disease most often caused by the haplodeficiency of C1INH: numerous mutations transmitted in an autosomal dominant manner are known in the corresponding gene *SERPING1* [32]. HAE is characterized by recurrent episodes (attacks) of swelling due to fluid extravasation; limbs, the orofacial and genital areas, and the intestine can be affected. Attacks may be life-threatening (suffocation), painful and incapacitating. The physio-pathology of HAE and its management have been recently reviewed [32][33][34][35]. While C1INH inhibits several proteases in the contact, fibrinolytic and complement systems, bradykinin is believed to be the ultimate mediator of HAE-C1INH attacks.

Drugs and biotechnological treatments are used or proposed for attack prevention (prophylaxis), to abort attacks ("on demand" treatments), or both. Several HAE therapies that affect the KKS are approved or under development (Table 2). The parenteral administration of C1INH, or gene therapy to increase the hepatic biosynthesis of normal C1INH, is physiologically sound for HAE-C1INH. This approach is supported by multiple clinical trials for C1INH concentrates. The heart of the contact system is also targeted in HAE (Fig. 1, Table 2): plasma kallikrein or its proenzyme prekallikrein, FXIIa or its proenzyme FXII can be suppressed or pharmacologically inhibited by several pharmacological or biotechnological interventions. The proof of concept for a further level of intervention on the contact system has been recently reported in a preclinical study: the mAb 3E8 targets domain 6 (D6) of HK, thus inhibiting the assembly of the trimolecular complex HK-prekallikrein-factor XI (mode of action *7* in Fig. 1). In transgenic mice that express human HK, mAb 3E8 inhibits dextran sulfate-induced BK formation and FXII activation [36].

Table 2. Inhibitors of the KKS for treating or preventing attacks of hereditary angioedema.

Type of Agent *Mode of Action Marker in Figure 1*	Drug or Intervention	Development Status	Ref.
Parenteral replacement of C1INH ***1***	various C1INH concentrates, natural or recombinant	approved, widely used	[37]
Gene therapy to increase the endogenous synthesis of C1INH ***1***	BMN 311 HAE	clinical trials	[38]
	OTL-105 HAE	preclinical	[39]
Kunitz-domain-based peptide inhibitor of plasma kallikrein ***2***	ecallantide	approved	[40]
Small molecule inhibitors of plasma kallikrein ***2***	berotralstat (BCX7353)	approved	[41]
	sebetralstat (KVD-900)	clinical trials	[42]
	ATN-249, ATN-111	clinical trials	[43]
Anti-plasma kallikrein mAb ***2***	lanadelumab	approved	[44]
	STAR-0215	clinical trials	[45]
Transfer of a gene encoding an anti-plasma kallikrein mAb ***2***	RegenxBio undisclosed	preclinical	[46]
Antisense suppressor of hepatic plasma prekallikrein production ***3***	donidalorsen (PKK-L Rx)	clinical trials	[47]
Gene therapy to disrupt hepatic plasma prekallikrein production ***3***	NTLA-2002	clinical trials	[48]
Small molecule inhibitor of factor XIIa ***4***	KV998086	preclinical	[49]

Type of Agent ***Mode of Action Marker in Figure 1***	Drug or Intervention	Development Status	Ref.
Anti-factor XII mAb ***4***	garadacimab (CSL312)	clinical trials	[50]
Small interfering RNA targeting factor XII mRNA ***5***	ALN-F12	preclinical, halted?	[51]
	ARC-F12	preclinical, halted?	[52]
Plasmin/tPA inhibitor ***6***	tranexamic acid	approved, 2nd line prophylactic agent	[53]
Bradykinin B2R antagonists ***8***	peptide icatibant	approved	[54]
	NPA deucrictibant (PHA-022121, PHA-121)	clinical trials	[24] [55]

On the effector side, the BK B2R antagonists inhibit the vascular manifestations of HAE (Table 2, Fig. 1). The injectable and rapidly cleared peptide antagonist icatibant is widely used to abort HAE attacks. The nonpeptide B2R antagonist deucrictibant [24] (Fig. 2) is orally bioavailable, more potent, and longer lived than icatibant in vivo; it is currently developed for on demand treatment of HAE attacks (a potentially convenient substitute to subcutaneous icatibant, Table 2). Chronically administered deucrictibant will also be tested for prophylaxis. Both icatibant and deucrictibant are competitive and reversible antagonists at the human B2R [24]. There is clear evidence of fibrinolytic system activation during HAE attacks [56]. Tranexamic acid, an inhibitor of plasmin and tissue plasminogen activator, has been approved as a second line prophylactic treatment of HAE.

Other ongoing or terminated therapeutic projects exploited inhibitors of the KKS. Some comments are offered here concerning specific indications. Pain is one of the cardinal signs of inflammation; despite good preclinical evidence, the clinical development of nonpeptide and orally bioavailable B1R antagonists SSR240612 and MK0686 (Fig. 2, mode of action 9) has failed due to their lack of efficacy in phase 2 trials (Table 3, Fig. 2) [57]. Fasitibant, a B2R antagonist injected in an intraarticular manner, has also failed to relieve pain associated with knee osteoarthritis (Fig. 2, mode of action *8*) [58]. The B1R antagonist BI1026706 (Fig. 2, mode of action *9*) failed to prevent diabetic macular edema [59] and the B2R antagonist anatibant (Fig. 2, mode of action *8*) was ineffective to prevent post-traumatic cerebral edema [60]. The unsuccessful clinical research concerning the B1R as a druggable target could benefit from the repurposing of potent and specific antagonists that have passed successfully clinical phase 1 development (Fig. 2), for instance for the prevention of COVID-19 complications [61]. An efficient monoclonal antibody that blocks the enzymatic action of tissue kallikrein, DX-2300, has been developed and shown of potential interest in preclinical research [62] (mode of action *10*). Other therapeutic investigations of the KKS antagonists are reviewed elsewhere [63].

Whether KKS stimulation can be of therapeutic value is generally a debate at an early stage (modes of action *11* to *14*, Fig. 1) [63]. It is already well supported that ACE inhibitors, widely prescribed anti-hypertensive drugs, mediate a part of their beneficial effects via a potentiation of the vasodilator effects of kinins mediated by the B2R [64] (mode of action *14*). On the other hand, a nonpeptide and long-acting B2R agonist structurally related to antagonists,

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FR190997 (Fig. 2, mode of action 12) is clearly pro-inflammatory in animals [65]. Let us mention here the clinical development of tissue kallikrein (KLK-1, mode of action *11*). Endogenous tissue kallikrein promotes reparative neovascularization following experimental ischemia and protects the heart in animal models of pathologies [66][67]. This enzyme, produced in a regulated manner in the kidney, is released in urine and protects from sodium overload and salt-sensitive hypertension [68]. Tissue kallikrein also participates to flow-dependent vasodilation, a local circulatory adaptative mechanism [69]. So, why not consider the parenteral administration of tissue kallikrein in therapeutics? In China, active KLK-1 purified from human urine has reached clinical use for acute ischemic stroke. When added to standard thrombolytic therapy, parenteral tissue kallikrein improved the neurological recovery in a significant manner [70]. A pharmaceutically refined recombinant tissue kallikrein, DM199, is being clinically developed for cerebrovascular and renal dysfunctions [71][72].

The medicinal chemistry related to the KKS has reached maturity, with the development of modern drugs, injectable biotechnological proteins, and advanced gene therapy projects. In addition to C1INH replacement therapy, HAE has been the focus of intense drug development efforts based on a limited number of validated targets (plasma kallikrein, FXIIa and their respective zymogens, the B2R). The recent transition to oral therapies is also noted. Although drug targeting of KKS in animal models provided promising therapeutic leads, disappointing clinical outcomes followed, as in other therapeutic areas. The existence of orally bioavailable drugs that have at least passed clinical phase 1 development (B1R and B2R antagonists, plasma kallikrein inhibitors) could facilitate their repurposing for additional therapeutic indications.

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