Bradykinin-Mediated Angioedema:
Pathways, Physiology, and Disease Mechanism

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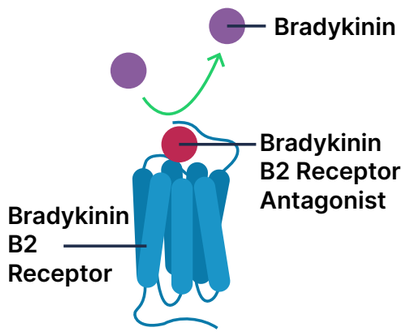
Bradykinin Production

BK

BK is formed through several biological pathways, which can be either kallikrein-dependent or -independent.[1-3] Bradykinin exerts its effects by converging on and activating specifically the bradykinin B2 receptor.[4,5]



The dysregulation of bradykinin B2 receptor signalling can contribute significantly to a range of inflammatory disorders[6,7]

Bradykinin B2 Receptor Antagonism

Consequently, B2 receptor antagonism represents a potential therapeutic target for AE-BK, characterised by vascular leakage and tissue swelling.[6,7]

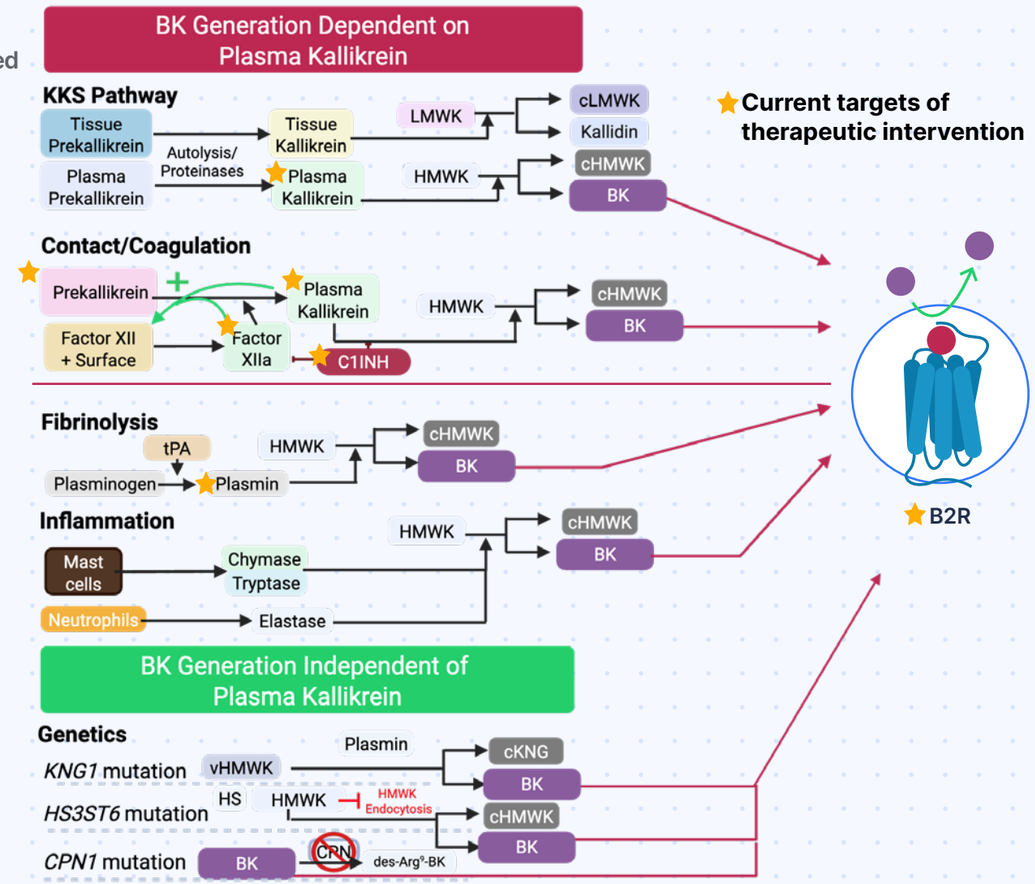
Based on their pathophysiology, bradykinin B2 receptor antagonism has been investigated for potential therapeutic effects in:

HEREDITARY ANGIOEDEMA
Had significant therapeutic effects in the acute treatment setting[8]

CHRONIC SEVERE ASTHMA
Improvement in measured pulmonary function vs placebo; however, there was no significant clinical benefit[9]

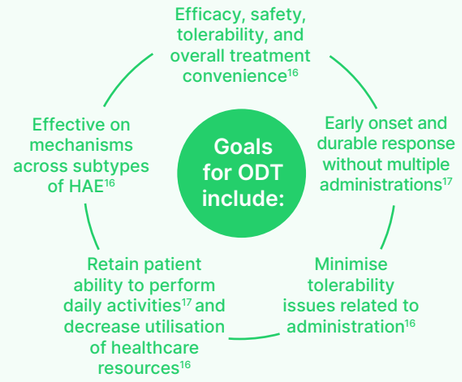
INTRADIALYTIC HYPOTENSION
Reduced the reduction in blood pressure in patients with IDH, and had no evident effects in patients without IDH[10]

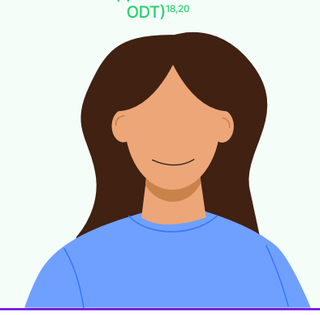
COLD-INDUCED URTICARIAL SYNDROME
Had effects on cold-induced urticarial symptoms including rash and headache[11]



Unmet Needs in AE-BK

Unmet needs in AE-BK for ODT and LTP management approaches should address underlying mechanisms from all subgroups of AE-BK, as well as patient needs and expectations.





Characterising AE-BK

The WAO/EAACI guidelines, and more recently the DANCE consensus, were developed to provide global consensus in defining different subtypes of AE.[6,12]

The differential diagnosis of AE subtypes remains **complex and time-consuming**, driving ongoing efforts to identify measurable biomarkers to facilitate the **diagnosis and classification** of AE-BK and AE subtypes.[13]

Moreover, access to testing procedures varies between clinics, causing delays in diagnosis.[6] **Pathway-specific testing is limited**, with current diagnostic indicators unable to distinguish between AE-BK and other AE types.[14,15]

Abbreviations: **AE:** angioedema; **Arg:** arginine; **BK:** bradykinin; **cHMWK:** cleaved high molecular weight kininogen; **cLMWK:** cleaved low molecular weight kininogen; **CPN:** carboxypeptidase N; **CPN1:** carboxypeptidase N 1 gene; **cKNG:** cleaved kininogen; **DANCE:** Definition, Acronyms, Nomenclature, & Classification of Angioedema; **FXII:** Factor 12; **HAE:** hereditary angioedema; **HMWK:** high molecular weight kininogen; **HS:** heparan sulfate; **HS3ST6:** heparan sulfate 3-O-sulfotransferase 6 gene; **IDH:** intradialytic hypotension; **KKS:** kallikrein–kinin system; ***KNG1:*** *kininogen 1 gene*; **LMWK:** low molecular weight kininogen; **LTP:** long-term prophylactic; **ODT:** on-demand; **QoL:** quality-of-life; **tPA:** tissue plasminogen activator; **v:** variant; **WAO/EAACI:** World Allergy Organization/European Academy of Allergy and Clinical Immunology.

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