Journal of Pharmaceutical Research International

Volume 34, Issue 57, Page 1-15, 2022; Article no.JPRI.94547
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Plasma Kinins- A Pharmacological Perspective

Jefry Winner G. [a++] and Anusha N. [a#*]

[a] *Department of Pharmacology, JIPMER, India.*

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i577254

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/94547

Review Article

Received: 08/10/2022
Accepted: 14/12/2022
Published: 17/12/2022

ABSTRACT

Background: Plasma kinins are known for decades but the understanding of them is not up-to the mark and the complexity is the reason. There are many drugs and trials undertaken with these as drug targets but only very few have been successfully marketed and used. Rest all others have resulted in failure during various phases of the trial.
Purpose: The purpose of this review is to explain and explore the complexity of plasma kinins and explore the relations between Kinins, and analyze the failures in drug development with these receptors as targets.
Implication: This extensive review might help in understanding the complexity and ensure the reduction of drug development failures in these molecules as drug targets
Conclusion: Kinins have an important role in the homeostatic functions of the body physiologically. The pathophysiological roles in inflammation are also known. The complexity of these systems is well established.

Keywords: Bradykinin; tissues; tachykinins; neurokinin; plasma; neurons; kinins.

[++]*Postgraduate student;*
[#]*Assistant Professor;*
**Corresponding author: E-mail: anushanatarajan29@gmail.Com;*

1. INTRODUCTION

The plasma that constitutes more than half of the circulating extracellular volume is of utmost importance in sustaining life. But the fact to be understood here is that even such a vital component has ironical characteristics. These are undeniably true in the case of peptides in the blood, which culminates both peptides and peptidases side by side. This means that the kinins in plasma, ubiquitous throughout kininases [1]. Even though their absolute roles are yet to be established, their definitive roles are brought to light by the extensive research which is being done today [2]. This has become an area of interest in the fields of physiology, pharmacology, pathology, and therapeutics in recent years. This review narrates about the kinins commencing from their discovery to their physiological roles and their implications in drug development, and tries to analyze the most noted part, which is the failures that overshadow the drug development in the case of kinins.

2. HISTORY OF PLASMA KININS

Kinins in Greek means “to move” and their role is also such that it moves or takes forward the process of inflammation. Bradykinin one of the most important kinin and extensively studied has its roots originating from 1948 from biological institute at Sao Paulo which was discovered by a team of physiologists and pharmacologists led by Dr. Mauricio Rocha e silva [3]. This research later on continued and led to the development of captopril initially referred as “Bradykinin potentiating factor “. The discovery of bradykinin has led to a new understanding of many physiological and pathological phenomena including circulatory shock induced by venoms and toxins.

The next in this group is referred as Tachykinins as the name suggests and in contrary to Bradykinins, they cause rapid action and also homologous to bradykinin it also helps to sustain inflammation. The discovery of this substance came during the early 20^{th} century. In 1931, while investigating the tissue distribution of the newly characterized transmitter acetylcholine, Von Euler and Gaddum noted in acid ethanol extracts of equine intestine a hypotensive and spasmogenic activity that differed from acetylcholine in that it contracted the rabbit jejunum in the presence of atropine. The activity of this preparation, first referred to as P on kymograph tracings, was distinct from the biologically active principles known at that time. The active component was soon termed substance P (P for preparation), and early experiments suggested that SP was peptide or protein in nature [4]. Tachykinins include 10-12 amino acid containing peptides that include Neurokinin k, Neurokinin A, substance P and Neuropeptide gamma. So, these kinins have an important role in various physiological processes and thereby they could be manipulated to produce various pharmacological effects.

3. PHYSIOLOGY OF BRADYKININ

The synthesis of bradykinin takes place in plasma and tissues by proteolytic cleavage of HMWK (High Molecular Weight Kininogen) and LMWK (Low Molecular Weight Kininogen) respectively. The synthesis of Kinins is triggered by various factors one of them includes endothelial injury which is hence the name contact system which is accompanied by Factor XII to XI. Factor XIIa converts pre-kallikrein into plasma kallikrein, and they autoactivate through a positive feedback loop. Plasma kallikrein cleaves high-molecular-weight kininogen (HMWK) into bradykinin [5]. Bradykinin then binds to B2-receptors, inducing vasodilation and increased endothelial permeability, leading to the characteristic swelling of an angioedema attack [6]. Their actions are mainly mediated through B1 and B2 receptors. Bradykinin receptors are cell surface, G-protein coupled receptors of the seven-transmembrane domain family. The existence of two subtypes of bradykinin receptor, B1 and B2, has been confirmed through the use of high affinity peptide and nonpeptide receptor antagonists, radioligand binding studies and, recently, receptor cloning and expression studies [7]. For synthesis and functional roles of bradykinin.

In vitro studies show stimulation of endogenous B1R promotes cell growth, migration, and invasion [8]. A study found that, when B2 is inhibited or absent, receptor B1 is upregulated and might develop some B2 hemodynamic properties, which indicates that they both play a role in the maintenance of normal Vaso regulation or the development of hypertension [9]. The vascular effects of B1 receptor activation may be a result of the release of endothelial NO, prostaglandins, and possibly endothelium-derived hyperpolarizing factors [10,11].

B_2 bradykinin receptors are present in neurons of the brain stem, basal nuclei, cerebral cortex, thalamus, and hypothalamus. B_2 immunolabelling

was also observed in the endothelial lining of the lateral and third ventricles' superior sagittal Dural sinus and ependyma. B_1 kinin receptors have been localized on neurons of the thalamus, spinal cord, and hypothalamus [12]. In studies that investigated the role of the FGF-2 pathway in the BK-mediated human endothelial cell permeability and migration, and the role of the B2 receptor (B2R) of BK in this cross-talk. Is established. B2R blockade by the selective antagonist, fasitibant, significantly inhibited FGF-2/FGFR-1 signaling, and in turn, BK-mediated endothelial cell permeability and migration [13]. The B_2 receptor is believed to play an important role in the beneficial effects of angiotensin- 1 converting enzyme inhibitors used in the treatment of cardiovascular diseases, yet it is involved in the acute phase of inflammation and of somatic and visceral pain. An additional role was introduced for the B_2 BK receptor, demonstrating its proliferative effects [14]. Some studies also show that bradykinin can also induce anti-mitogenic effects in proliferating cells using an alternative signal transduction pathway involving a protein tyrosine phosphatase [15]. Thus, the role of bradykinin as a homeostatic plasma kinin is undeniable, as the available literature suggests.

4. PHYSIOLOGY OF TACHYKININS

The tachykinins are a group of plasma kinins that play a major role in inflammation and neurotransmission hence most of them are referred to as neuropeptides [16-19]. The two human tachykinin genes are called TAC1 and TAC3 [20].

The major source of tachykinins is in the gut are enteric neurons, followed by nerve fibers from dorsal root and vagal ganglia. Tachykinin-containing fibers surround enteric ganglia, ramify through muscle, form a perivascular mesh around submucosal arteries, and supply the mucosa. This explains the fact of isolation of substance P from the Gut [4]. The important roles of tachykinins include Neuro-neuronal transmission, Protective secretory responses to infection [21,22]. Tachykinins also participate in the inflammatory responses to infection, including the formation of granulomas, and sites of chronic inflammation that prevent the spread of infectious agents [23]. Tachykinins stimulate smooth muscle contraction of the human ureter, mostly by activating the NK_2R [24]. *Tac1*, *Tac3*, and *Tac4* are expressed by human sperm, and tachykinins increase sperm motility by NK_1R- and NK_2R-dependent mechanisms [25]. Mouse and human keratinocytes express NK_1R and NK_2R. The consensus of multiple studies is that SP and NKA control the capacity of keratinocytes to serve as cytokine factories by regulating the production of proinflammatory cytokines [26]. Thus tachykinins are involved in a vast array of physiological functions that makes them a potential target for drug development.

5. THE ROLE OF PLASMA KININS IN DISEASES

5.1 Bradykinins

The role of bradykinin in various disease states is indisputable. Studies in a mouse strain with a targeted disruption of the BK_2 receptor gene have given important new insights into the role of the kallikrein/kinin system in the pathogenesis of hypertension and heart failure [27]. Neuropathic pain is a leading debilitating morbidity resulting from Spinal Cord Injury, and it remains an unmet medical demand. In a rat model of contusion SCI, more than a twofold increase was observed for the expression of B1BKR and vanilloid-1 (TRPV-1) receptor genes in the injured segment dorsal horn region of the spinal cord in rats manifesting hyperalgesia behavior compared with SCI rats that did not show hyperalgesia [28]. Bradykinin may be a competitive substrate of DPP-4, and decreased bradykinin levels may enhance protective effects against ischemia/reperfusion injury during Leukotrienes [29]. There is a well-established role of Bradykinin in Hereditary angioedema and some forms of acquired angioedema which are especially due to increased bradykinin levels [30].

5.2 Tachykinins

Many types of tumor cells express NKRs, and tachykinins from tumor cells or infiltrating nerves or immune cells can influence proliferation, apoptosis, and metastasis of tumor cells in an autocrine, paracrine, or neurocrine manner [31,32,33]. In the case of pulmonary diseases that affect the lungs by inducing inflammation, substance P has a substantial role as elucidated by various animal studies [34]. SP stimulates the generation and release of cytokines, chemokines, matrix metalloproteases, and ROS from neutrophils, thus playing a major role in inflammation [35,36]. Tachykinins also stimulate secretion from airway seromucous glands and thus play an important role in airway inflammation [37]. The role of tachykinins in

Postoperative nausea and vomiting is undisputable, and the respective antagonists are highly effective in treating and preventing this aspect [38].

6. PHARMACOLOGICAL IMPLICATIONS OF BRADYKININS

With such important roles in various physiological and pathological processes the role of Bradykinins and their receptors as drug targets is quite justifiable. The signalling of bradykinin receptors is mediated by kinins. Following ligand-binding, B1R and B2R signal through associated G proteins to activate signalling molecules like protein kinase C and phospholipases, and secondary messengers like inositol-1,4,5, -triphosphate, diacylglycerol, calcium, and arachidonic acid. These secondary messengers go on to modulate other signalling processes (e.g., nitric oxide or prostaglandin production) [39]. Following the discovery of bradykinin by Roche et al there are various research that has been undertaken to exploit its role in drug development. The invitro synthesis of BK peptide was introduced by solid phase preparation strategy by Merrifield [40]. Since then, many kinin derivatives have been synthesized and investigated. These sequences include modifications (e.g., amino acid substitutions, reduction of amide bonds, N-terminal capping) that are aimed at conferring selectivity, stability to peptidases, agonist/antagonist properties and prolonging in vivo pharmacological effects [41]. Icatibant, a B2R antagonist, is the only kinin to receive U.S. Food and Drugs Administration approval. It is indicated for the treatment of acute attacks of hereditary angioedema in adults with C1-esterase inhibitor deficiency [42]. Anatibant and fasitibant, B2R antagonists, advanced into clinical testing for treatment of traumatic brain injury and knee osteoarthritis, respectively. However, their development was discontinued due to the lack of efficacy [43,44]. The hope is that new scaffolds will be able to find clinical utility in other disease setting. All drug molecules developed are listed in Table 1.

7. PHARMACOLOGICAL IMPLICATIONS OF TACHYKININS

Tachykinins have got some important implications as pharmacological agents since the approval of their first agent Aprepitant by FDA in 2003 which is now widely used CINV [53].

Various other congeners of Aprepitant were also approved subsequently. Casopitant, Netupitant, and Rolapitant were approved later on [54,55,56]. Apart from vomiting Aprepitant was also tried as an agent for Depression [57]. This compound has also shown antiproliferative properties in tumoral cell lines of glioma, neuroblastoma, retinoblastoma, pancreas, larynx, colon, and gastric carcinoma [58,59,60, 61]. Experimental studies in the rabbit colon suggest that NK2 receptors antagonist MEN 11420 (Nepadutant) may also dose-dependently modulate colonic transit [62]. The selective inhibition of peripheral NK3 receptors by SB-235375 (Talnetant) reduced the nociceptive response to colorectal distension in the rat model [63,64]. According to these studies, specific NK3 receptor antagonists exhibit potential as analgesic agents for visceral pain in IBS patients. Recombinant NEP and NK1 receptor antagonist SR140333 prevented the exacerbated inflammation in NEP knockout mice [65,66,67]. Selective tachykinin receptor antagonists tested on guinea pigs have been shown to inhibit late allergic and airway hyperresponsiveness and reduce eosinophilic infiltration and vascular permeability [68,69,70]. However, all these studies were preliminary, and little therapeutic benefit could be inferred for humans. Some of the important clinical indications for which tachykinin antagonists are tried are listed in the Table 2.

Among the drugs mentioned in the table only aprepitant and fosaprepitant could be marketed. Many others have been discontinued in the developmental stage itself. Some trials are ongoing like Aprepitant for Advanced small cell carcinoma(NCT04840004). Aprepitant was also tried for Alcohol craving and PTSD(NCT00896038) which was completed but trial results were not available. Interestingly aprepitant was also tried for HIV infection which failed to show viral load reduction [71]. DNK-333 which was tried for IBS in two trials [(NCT00699166) and (NCT00394173)] produced significant subjective relief of symptoms in IBS but not with stool consistency which was the primary endpoint of the trial. Vestipitant was another agent tried for Tinnitus but showed no clinically significant results [72]. Vofopitant was another drug tried for PTSD but showed efficacy not better than placebo [73]. Ibodutant another drug which was evaluated for IBS showed better efficacy when compared to placebo in symptomatic improvement when compared to placebo [74]. TA-5538 was tried for overactive bladder in a trial in Japan and was discontinued for undisclosed reasons. SSR 240600 was tried

in a trial called BILADY for which results were not published (NCT00564226). LY-686017 which was tried for social anxiety disorder showed no significant difference in Leibowitz social anxiety scale (LSAS) when compared to placebo (NCT00191002) [75]. Orvepitant was tried for MDD but the trial was terminated since seizures occurred in patients during the trial period (NCT00880399). Rolapitant was studied for its effects in PONV but the results of the trial were not published (NCT00539721). Casopitant was another drug which was tried for a number of conditions, its efficacy for overactive bladder was evaluated but terminated due to undisclosed reasons (NCT00332319). The same drug was tried for fibromyalgia and this trial was completed but results were not published (NCT00264628). Similar is the case with primary insomnia [(NCT00280423), (NCT00280436), (NCT00354809)]. For CINV the manufacturers approached European medicines agency for marketing authorisation application but withdrawn in September 2009 by the manufacturers [76]. So again as like bradykinins the modalities to target tachykinins were also not so straightforward other than cases of PONV and CINV Even though research continues in this field and successful drug development for other indications might become feasible.

8. APREPITANT ANTICIPATION

This was the first drug to be approved as a Tachykinin antagonist [52]. Since then this has been tried in numerous clinical trials for numerous indications. There are various trials that have tried the role of aprepitant as an antiemetic drug for the treatment of highly emetogenic conditions like following cancer chemotherapy and some following surgical procedures for PONV. The trial done with aprepitant in HIV infected individuals showed no viral load reduction despite reduction in biological activity [71]. A few trials were successful but for many trials the information was not available and some were terminated. Aprepitant was tried in germ cell tumours and was found to have a complete remission rate as compared to placebo (NCT00572572). Another study that involved aprepitant in its well-known indication for CINV following cisplatin chemotherapy (NCT00619359). Again, trials involving Aprepitant in PONV and with other drugs like granisetron, dexamethasone, prochlorperazine and palonosetron (NCT00475085 and NCT00819039) showed it to be an effective drug for antiemesis, but still its effect in other indications is still in the line and yet to be established this might become feasible in the near future if research continues to flourish.

9. SAREDUTANT FOR DEPRESSION AND ANXIETY

This is a tachykinin antagonist with a higher selectivity for NK2 receptor which was assumed to be effective from the preclinical data [77]. The results of a double-blind, randomized, placebo- and fluoxetine-controlled multicentre Phase IIb clinical trial performed with saredutant in patients which showed a good sustained response in the treatment group compared to placebo [78]. The favourable safety and tolerability profile of saredutant was also confirmed in the elderly (INDIGO study) as well as in long-term treatment (MAGENTA study) [79, 80]. But still the drug was not found to affect the outcome significantly as compared to existing standard of care and placebo. This was also tried for GAD but the results were inconclusive and the drug was yet to show its impact to be used clinically.

10. NK3 RECEPTOR ANTAGONISTS

These are found exclusively in brain and spinal cord but their location is quite restricted and this also possess challenges in development of NK3 antagonists which are limited comparitivley [81, 82]. Osanetant was the first non-peptide NK3 antagonist described; it was derived from the known NK2 antagonist saredutant. Osanetant was compared with three other potential antipsychotics such as the 5-HT2a/5-HT2c receptor antagonist SR-46349B, the cannabinoid CB1 receptor antagonist rimonabant and the neurotensin receptor antagonist SR-48692, as well as with the classical antipsychotic haloperidol and with placebo. There was no significant difference between the efficacy of Osanetant and haloperidol in that study [83].Talnetant in a placebo-controlled trial showed a reduction in clinical symptoms not better than risperidone however the study showed a good tolerability as compared to risperidone [84]. But this drug has been abandoned by the researchers for undisclosed reasons. With all these inconclusive and a bit contradictory evidences long-term trials of further improved NK3 antagonists may confirm the positive results obtained so far with regard to efficacy and tolerability.

11. THE PATHWAY OVERWHELMED WITH FAILURES

Failure is a common pathway, especially when it comes to drug development. Even though we have understanding of these Kinins long back like decades ago the drug development targeting these kinins possess a humongous task and still challenging. Till this date we could successfully develop and market only a single bradykinin antagonist Icatibant [41]. All others were unable to produce clinical benefit to be approved for marketing.

In case of tachykinins the story is little bit different although the first one among the class Aprepitant has been approved in 2003 [52]. There are some congeners of it that are marketed but still despite their varied and ubiquitous roles they don't show any clinical benefit in other conditions that are good enough to be marketed. We tried to analyse the reasons behind the failures of these drugs. The important reason being the complexity of the systems in maintaining the bodily homeostasis and its interconnections with various pathways accounts for its complexity. One of the well-established inter-connections is with RAAS and this is thought to compensate for the effect of Bradykinin Receptor blockers and lead to sub-optimal therapeutic or clinical response. Some studies suggest that Synergistic vasodilatory effect of AT and Bradykinin in Kininogen knockout rat models [85]. C5-9 induced vascular leakage is blocked by B1R antagonist which again shows the interconnection between complement system and Kinins [86]. Similarly such issues are alongside tachykinins also their diverse nature is also evident. There are studies that show interconnections between both kinins itself, both of them are in fact linked with release of Cys-LT in asthma [87]. Tachykinins are also known to induce the broncho constrictive effects of Captopril thereby shows its potentiating effect via bradykinins [88].

Following this historical evidence, there is also numerous recent research in the field of plasma kinins. Bradykinin agonists have been shown to reduce the progression of diabetic retinopathy in animal models of streptozotocin-induced diabetes mellitus [89]. Bradykinin potentiating agents present in the three-finger toxin of snake venom Bothrops jararaca have been investigated and are under research for coronary artery disease and peripheral artery disease. The experimentations using snake venom since the identification of captopril decades back are still in the continuum [90]. Receptor modeling and molecular docking studies for understanding the various pharmacological roles of bradykinin receptors are on the rise [91]. Bradykinin is also considered an important component in the pathophysiology of chronic pain and itch [92]. The major area of research in hereditary angioedema concerns the bradykinin receptors and their pharmacology [93]. Recently, a new monoclonal antibody, Lanaledumab, has been developed against bradykinin and blocked its action. The approval for Lanaledumab was obtained on 23 August 2018 by the FDA [94]. Recently numerous studies have shown good insights into the role of Kinins in various diseases like myocardial infarction, hypertension, and inflammatory pathways. All these studies are still in the pre-clinical stages and need to go a long way for clinical translation. Recent trends in drug development are moving towards biotechnology compounds that have largely replaced small molecules in recent years. All this evidence suggests that these peptides are more complex to comprehend than anticipated. This warrants further research to elucidate the exact mechanisms that might fuel up drug development in a more organized and successful pathway.

Table 1. Clinical phase of bradykinins antagonists

Drug	Target	Clinical phase	Indications	Comments	Reference
HOE-140 (Icatibant)	B2R antagonist	Approved	Hereditary angioedema	Shortened the duration of acute attacks	[44]
		Phases I-IV	Cardiopulmonary bypass, inflammation, fibrinolysis, surgery, ischaemic heart diseases, ischaemic	Many completed and ongoing studies. Decreased intraoperative fibrinolytic capacity in	[45]

Drug	Target	Clinical phase	Indications	Comments	Reference
			reperfusion, heart failure, ACE inhibitor associated angioedema, angioneurotic edema	cardiopulmonary bypass. No efficacy demonstrated for angioedema and ischemia-reperfusion injury	
		Phase II	Mitochondria and chronic kidney disease	Completed, no evidence of efficacy	NCT03177798
		Phase II	Knee pain in osteoarthritis	Completed, results not available	NCT00303056
MEN16132 (Fasitibant)	B2R antagonist	Phase II	Knee pain in osteoarthritis	Two studies completed. No direct evidence of efficacy, treated patients used less rescue medication.	NCT01091116 NCT02205814
CP-0127 (Deltibant)	B2R antagonist	Phase II	Severe traumatic brain injury sepsis	Ineffective for sepsis. Discontinued due to unexpected preclinical findings.	[46]
LF16-0687 (Anatibant)	B2R antagonist	Phase II	Severe traumatic brain injury	Inconclusive results and possible safety issues. Trial halted.	[47]
RMP-7 (Lobradimil)	B2R agonist	Phase II	Childhood brain tumors	Completed. No improved efficacy	[48]
		Phase I	HIV infection and cryptococcal meningitis	Completed, results not available	NCT00002316
FOV-2304 (Safotibant)	B1R antagonist	Phase II	Diabetic macular edema	Discontinued, results not available.	[49,50]
MK-0686	B1R antagonist	Phase II	Postherpetic neuralgia, postoperative dental pain, osteoarthritis Terminated for postherpetic neuralgia, completed for dental pain and osteoarthritis.	No results disclosed	[51]
BI-113823	B1R antagonist	Phase I	Osteoarthritis	Terminated	NCT01207973
SSR-240612	B1R antagonist	Phase II	Inflammation and neuropathic pain	Halted for undisclosed reasons.	[52]
B9870 (Breceptin) Phase I	Dual B1R and B2R antagonist	Phase I	Small cell lung cancer	No information available.	[50]

ACE- Angiotensin Converting Enzyme; B1R- Bradykinin Receptor; B2R- Bradykinin Receptor; NCT- National Clinical Trial

Table 2. Clinical indications for which tachykinin antagonists are tried

Drug molecule	TK receptors	Clinical condition
Aprepitant	NK1	CINV PONV HIV Hot flashes Alcohol craving/PTSD
Fosaprepitant	NK1	CINV PONV
Casopitant	NK1	CINV PONV Primary insomnia Fibromyalgia Overactive bladder
Rolapitant	NK1	PONV
Orvepitant	NK1	MDD
LY-686017	NK1	SAD Alcohol craving
Vofopitant	NK1	Social phobia Primary insomnia PTSD
Vestipitant	NK1	SAD Primary insomnia Tinnitus/hearing loss
AZD-2624	NK1	Schizophrenia
SSR-240600	NK1	Overactive bladder/urge urinary incontinence
TA-5538	NK1	Overactive bladder
Saredutant	NK2	MDD GAD Asthma
Nepadutant	NK2	IBS Asthma POI
Ibodutant	NK2	IBS
DNK-333	NK1/NK2	Asthma IBS
AVE-5883	NK1/NK2	Asthma
CS-003	NK1/NK2/NK3	Asthma
Osanetant	NK3	Schizophrenia Panic disorder Depression
Talnetant	NK3	Schizophrenia IBS
SSR-241586	NK2/NK3	Schizophrenia

Table 3. Aprepitant anticipation

S.No	Trial no	Title	Phase
1	NCT00428519	Effects of treatment with aprepitant (Emend_) in HIV-infected individuals	I
2	NCT00835965	Oral aprepitant and lower dose dexamethasone versus aprepitant alone for preventing postoperative nausea and vomiting (PONV) after elective laparoscopic surgeries	IV
3	NCT00738621	Combination antiemetic regimen for prevention of PONV in breast surgery	IV
4	NCT00717054	Comparison of oral aprepitant alone versus oral aprepitant and transdermal scopolamine for preventing postoperative nausea and vomiting	III
5	NCT00572572	Aprepitant + 5HT3 + dexamethasone in patients with germ cell tumours (there is significant increase in CR rate)	IV
6	NCT00659737	A randomized, double-blind comparison of oral aprepitant alone versus oral aprepitant and transdermal scopolamine for preventing postoperative nausea and vomiting	II
7	NCT00869310	Aprepitant in the prevention of cisplatin-induced delayed emesis	IV
8	NCT00651755	Aprepitant effect on drug metabolism in multi-day combination (CHOP/R-CHOP) chemotherapy regimen in lymphoma patients	IV
9	NCT00659945	Effectiveness of aprepitant in the treatment of postoperative nausea and vomiting (PONV) in patients undergoing outpatient plastic surgery	III
10	NCT01534637	Aprepitant in preventing nausea and vomiting in patients undergoing chemotherapy and radiation therapy for pancreatic cancer	III
11	NCT00415103	Aprepitant plus palonosetron versus granisetron in the prevention of nausea and the emesis induced by chemotherapy in patients treated with hematopoietic progenitors	II
12	NCT00734929	Aprepitant with dexamethasone versus ondansetron with dexamethasone for postoperative nausea and vomiting (PONV) prophylaxis in patients having craniotomy	II
13	NCT00869973	Aprepitant in the prevention of delayed emesis induced by cyclophosphamide plus anthracyclines in breast cancer Condition: nausea, vomiting	II
14	NCT00619359	Emesis Prevention of chemotherapy-induced nausea and vomiting (CINV) associated with cisplatin chemotherapy noninferior	II
15	NCT00719173	Effect of aprepitant on cyclophosphamide pharmacokinetics in patients with breast cancer	II
16	NCT00736073	A trial of aprepitant for prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis	II
17	NCT00631930	Palonosetron, aprepitant, and low-dose dexamethasone in preventing nausea and vomiting in patients undergoing high-dose chemotherapy and stem cell transplant for multiple myeloma or lymphoma	II
18	NCT00895245	Fosaprepitant dimeglumine, palonosetron hydrochloride, and dexamethasone in preventing nausea and vomiting caused by cisplatin in patients with stage III or stage IV head and neck cancer undergoing chemotherapy and radiation	II
19	NCT00293384	Aprepitant, granisetron, and dexamethasone in preventing nausea and vomiting in patients receiving cyclophosphamide before a stem cell transplant	II

20	NCT00314743	Oral neurokinin-1 antagonist, aprepitant, in combination with ondansetron and dexamethasone in patients undergoing autologous peripheral blood stem cell transplantation	IV
21	NCT00588835	Pharmacokinetic study on the addition of aprepitant to cisplatin–etoposide treatment in lung cancer patients	III
22	NCT00571168	Efficacy and safety of aprepitant in subjects with multiple myeloma during and after high-dose chemotherapy	III
23	NCT00475085	Granisetron, dexamethasone, prochlorperazine, aprepitant, and palonosetron in preventing nausea in women undergoing chemotherapy for breast cancer	III
24	NCT00888329	Aprepitant for prevention of postoperative nausea and vomiting in elective hysterectomy Condition: postoperative nausea and vomiting	I
25	NCT00819039	A study of aprepitant (MK0869) in paediatric patients undergoing surgery condition: postoperative nausea and vomiting	I
26	NCT00818259	Recruiting a study of aprepitant (MK0869) and fosaprepitant (MK0517) in paediatric patients receiving chemotherapy Condition: chemotherapy-induced nausea and vomiting	II
27	NCT00896038	The effect of NK1R antagonism on alcohol craving and PTSD symptoms in alcohol dependent patients with PTSD Conditions: alcoholism; alcohol dependence; post-traumatic stress disorder; FMRI	II

Terminated Trials *Completed trials*

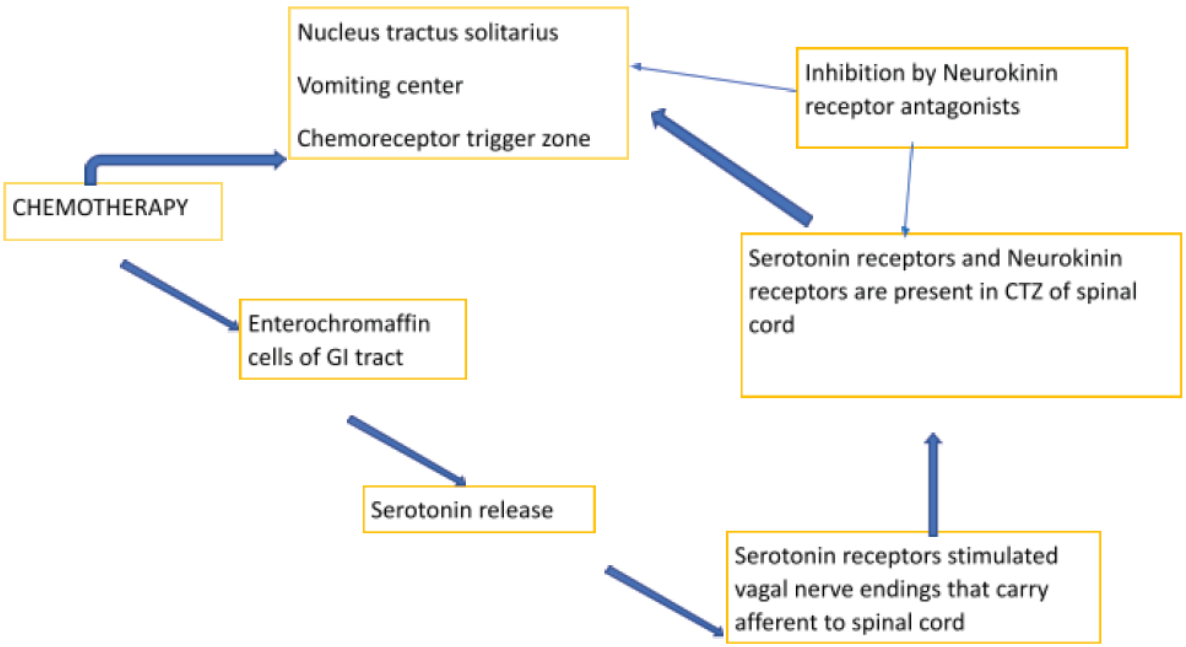

Fig. 1. The proposed mechanism of chemotherapy induced nausea and vomiting

12. CONCLUSION

With this comprehensive review, it is evident that these kinins have an important role in the homeostatic functions of the body physiologically. Again, the pathophysiological roles in inflammation and most important being sustainability of inflammation rather than inciting itself is evident. These makes them a potential target for drug development and the drugs developed were extensively discussed and the failures with respective clinical trials. The complexity of these systems and interconnections are evident and sounds like we are still “scratching the surface” of a complicated puzzle. The time to explore the complexity and fit the puzzle would be in the near future with advancements in the field of research day by day. Still, this seems to be an evolving science and an area to be explored to pave a way for upcoming drug discoveries.

DISCLAIMER

This paper is an extended version of a preprint document of the same author.

The preprint document is available in this link: https://d197for5662m48.cloudfront.net/documents/publicationstatus/83681/preprint_pdf/53d7d6f20f3077326dcfdb38732ed7ba.pdf
[As per journal policy, preprint article can be published as a journal article, provided it is not published in any other journal]

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Beraldo Wilson, Silvia T, Andrade P. “1 - Discovery of bradykinin and the kallikrein—kinin system.” In The Kinin System, edited by Stephen G. Farmer, 1–8. Handbook of Immunopharmacology. London: Academic Press; 1997.
2. Hall Judith M, Ian K. M. Morton. “2 - The pharmacology and immunopharmacology of kinin receptors.” In The Kinin System, edited by Stephen G. Farmer, 9–43. Handbook of Immunopharmacology. London: Academic Press; 1997.
3. Rocha e Silva M, Beraldo WT, Rosenfeld G "Bradykinin, a hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin". American Journal of Physiology. 1987;156(2):261–73.
4. Almeida, Teresa & Rojo, Javier & Nieto, Pedro & Pinto, Francisco & Hernandez Ferrer, Mariano & Martín, et al. Tachykinins and tachykinin receptors: Structure and activity relationships. Current Medicinal Chemistry. 2004;11:2045-81.
5. Björkqvist J, Sala-Cunill A, Renné T. Hereditary angioedema: A bradykinin-mediated swelling disorder. Thromb Haemost. 2013;109:368–74
6. Kaplan AP, Ghebrehiwet B. The plasma bradykinin-forming pathways and their interrelationships with complement. Mol Immunol. 2010;47:2161–9
7. Hall JM. Bradykinin receptors. Gen Pharmacol. 1997;(1):1-6.
8. Taub JS, Guo R, Leeb-Lundberg LM, Madden JF, Daaka Y. Bradykinin receptor subtype 1 expression and function in prostate cancer. Cancer Res. 2003 ;63(9):2037-41.
9. Duka A, Duka I, Gao G, Shenouda S, Gavras I, Gavras H. Role of bradykinin B1 and B2 receptors in normal blood pressure regulation. Am J Physiol Endocrinol Metab. 2006;291:E268–74.
10. Emanueli C, Bonaria Salis M, Stacca T, Pintus G, Kirchmair R, Isner JM, et al. Targeting kinin B (1) receptor for therapeutic neovascularization. Circulation. 2002;105:360–6
11. Lagneux C, Adam A, Lamontagne D. A study of the mediators involved in the protection induced by exogenous kinins in the isolated rat heart. Int Immunopharmacol. 2003;3:1511–1518
12. Golias Ch, Charalabopoulos A, Stagikas D, Charalabopoulos K, Batistatou A. The kinin system--bradykinin: biological effects and clinical implications. Multiple role of the kinin system--bradykinin. Hippokratia. 2007 ;11(3):124-8.
13. Terzuoli E, Corti F, Nannelli G, Giachetti A, Donnini S, Ziche M. Bradykinin B2

Receptor Contributes to Inflammatory Responses in Human Endothelial Cells by the Transactivation of the Fibroblast Growth Factor Receptor FGFR-1. Int J Mol Sci. 2018 ;19(9):2638.

14. Duchêne J, Schanstra J, Cellier E, Bascands JL, Girolami JP [30 years: Happy birthday, GPCR. The bradykinin B2 receptor: an alternative and antiproliferative pathway]. Nephrologie. 2002; 23(1):39-41.
15. Maggio JE. "Tachykinins". Annu. Rev. Neurosci. 1998; 11: 13–28.
16. Helke CJ, Krause JE, Mantyh PW, Couture R, Bannon MJ. "Diversity in mammalian tachykinin peptidergic neurons: multiple peptides, receptors, and regulatory mechanisms". FASEB J. 1990; 4 (6): 1606–15.
17. Avanov AIa. "Tachykinins and conformational aspects of their interactions with receptors". Mol. Biol. (Mosk). 1992; 26 (1): 5–24.
18. Boot JD, de Haas S, Tarasevych S, "Effect of an NK1/NK2 receptor antagonist on airway responses and inflammation to allergen in asthma". Am. J. Respir. Crit. Care Med.2007; 175 (5): 450–7.
19. Dornan WA, Vink KL, Malen P, Short K, Struthers W, Barrett C. "Site-specific effects of intracerebral injections of three neurokinins (neurokinin A, neurokinin K, and neurokinin gamma) on the expression of male rat sexual behavior". Physiol. Behav. 1993;54 (2): 249–58.
20. Grady EF, Gamp PD, Jones E, Baluk P, McDonald DM, Payan DG, Bunnett. Endocytosis and recycling of neurokinin 1 receptors in enteric neurons. NW Neuroscience. 1996; 75(4):1239-54.
21. Southwell BR, Seybold VS, Woodman HL, Jenkinson KM, Furness. Quantitation of neurokinin 1 receptor internalization and recycling in guinea-pig myenteric neurons. JB Neuroscience. 1998; 87(4):925-31.
22. Tachykinins and their functions in the gastrointestinal tract. Shimizu Y, Matsuyama H, Shiina T, Takewaki T, Furness JB Cell Mol Life Sci. 2008; 65(2):295-311.
23. Deiteren A, De Winter BY, Nullens S, Pelckmans PA, De Man JG. Role of tachykinin receptors in the modulation of colonic peristaltic activity in mice. Eur J Pharmacol. 2011; 667(1-3):339-47.
24. Hernandez J, Lackner A, Aye P, Mukherjee K, Tweardy DJ, Mastrangelo MA, Weinstock J, Griffiths J, D'Souza M, Dixit S, Robinson P. Substance P is responsible for physiological alterations such as increased chloride ion secretion and glucose malabsorption in cryptosporidiosis. Infect Immun. 2007; 75(3):1137-43.
25. The role of substance P, hemokinin and their receptor in governing mucosal inflammation and granulomatous responses. Weinstock JV Front Biosci. 2004;9:1936-43.
26. Jerde TJ, Saban R, Bjorling DE, Nakada SY. NK-2 is the predominant tachykinin receptor subtype in the swine ureter. BJU Int. 1999; 83(3):312-8.
27. Pinto FM, Ravina CG, Subiran N, Cejudo-Román A, Fernández-Sánchez M, Irazusta J et al. Autocrine regulation of human sperm motility by tachykinins. Reprod Biol Endocrinol. 2010; 8:104.
28. Song IS, Bunnett NW, Olerud JE, Harten B, Steinhoff M, Brown JR et al. Substance P induction of murine keratinocyte PAM 212 interleukin 1 production is mediated by the neurokinin 2 receptor (NK-2R). Exp Dermatol. 2000; 9(1):42-52.
29. Madeddu P, Varoni MV, Palomba D, Emanueli C, Demontis MP, Glorioso N et al. Cardiovascular phenotype of a mouse strain with disruption of the bradykinin B2-receptor gene. Circulation.1997; 96:3570–8.
30. DomBourian, M. G. Turner, N. A. Gerovac, T. A. Vemuganti, R. Miranpuri, G. S. Türeyen et al. B1 and TRPV-1 receptor genes and their relationship to hyperalgesia following spinal cord injury. Spine. Phila. Pa. 1976. 2006; 31: 2778–282;
31. Tang Z, Wang Z, Hu Z, Zhang M, Li L, Li B. The role of bradykinin in lung ischemia-reperfusion injury in a rat lung transplantation model. Acta Cir Bras. 2016;(12):807-812.
32. Bas, M., V. Adams, T. Suvorava, T. Niehues, T. K. Hoffmann, and G. Kojda. “Nonallergic Angioedema: Role of Bradykinin.” Allergy 62, 2007; (8): 842–56.
33. Roper M, Ham RG, Stewart JM. Biosynthesis of substance P in cultured mouse neuroblastoma and rat glioma cells. Harkins J, Brain Res. 1978; 147(2):405-9.
34. Akazawa T, Kwatra SG, Goldsmith LE, Richardson MD, Cox EA, Sampson JH, Kwatra MM. A constitutively active form of neurokinin 1 receptor and neurokinin 1

receptor-mediated apoptosis in glioblastomas. J Neurochem. 2009;(4): 1079-86.

35. Rosso M, Robles-Frías MJ, Coveñas R, Salinas-Martín MV, Muñoz M. The NK-1 receptor is expressed in human primary gastric and colon adenocarcinomas and is involved in the antitumor action of L-733,060 and the mitogenic action of substance P on human gastrointestinal cancer cell lines. Tumour Biol. 2008; (4):245-54.
36. Kradin R, MacLean J, Duckett S, Schneeberger EE, Waeber C, Pulmonary response to inhaled antigen: neuroimmune interactions promote the recruitment of dendritic cells to the lung and the cellular immune response to inhaled antigen. Pinto C Am J Pathol. 1997(5):1735-43.
37. Augustyniak D, Jankowski A, Mackiewicz P, Skowyra A, Gutowicz J, Drulis-Kawa Z. Innate immune properties of selected human neuropeptides against Moraxella catarrhalis and non-typeable Haemophilus influenzae. BMC Immunol. 2012;(13):24.
38. Okaya T, Holthaus R, Kato A, Lentsch AB, Involvement of the neuropeptide substance P in lung inflammation induced by hepatic ischemia/reperfusion. Inflamm Res. 2004;(6):257-61.
39. Rogers DF. Motor control of airway goblet cells and glands. Respir Physiol. 2001 Mar; 125(1-2):129-44.
40. Horn CC, Wallisch WJ, Homanics GE, Williams JP. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. Eur J Pharmacol. 2014; (722): 55-66.
41. Kakoki M, Smithies O. The kallikrein kinin system in health and in diseases of the kidney. Kidney Int. 2009;(75):1019–30.
42. Merrifield RB. solid-phase peptide synthesis. III. An improved synthesis of bradykinin. Biochemistry. 1964;(3):1385–90.
43. Marceau F, Bawolak MT, Fortin JP, Morissette G, Roy C, Bachelard H, et al. Bifunctional ligands of the bradykinin B 2 and B 1 receptors: An exercise in peptide hormone plasticity. Peptides 2018;(105): 37–50.
44. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N. Engl. J. Med. 2010;(363):532–41.
45. Shakur H, Andrews P, Asser T, Balica L, Boeriu C, Quintero JDC, et al. The brain trial: A randomised, placebo-controlled trial of a Bradykinin B2 receptor antagonist (Anatibant) in patients with traumatic brain injury. Trials 2009;(10):1-10.
46. Tenti S, Pascarelli NA, Cheleschi S, Guidelli, GM, Fioravanti A. The emerging role of bradykinin in the pathogenesis of osteoarthritis and its possible clinical implications. Curr. Rheumatol. Rev. 2016;(12):177–84.
47. Balaguer JM, Yu C, Byrne JG, Ball SK, Petracek MR, Brown NJ, et al. Contribution of endogenous bradykinin to fibrinolysis, inflammation, and blood product transfusion following cardiac surgery: A randomized clinical trial. Clin. Pharmacol. Ther. 2013;(93):326–34.
48. Straka BT, Ramirez CE, Byrd JB, Stone E, Woodard-Grice A, Nian H, et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. J. Allergy Clin. Immunol. 2017;(140):242–8.
49. Pedersen CM, Schmidt MR Barnes G, Bøtker HE, Kharbanda RK, Newby DE, et al. Bradykinin does not mediate remote ischaemic preconditioning or ischaemia-reperfusion injury in vivo in man. Heart 2011;(97):1857–61.
50. Whalley ET, Figueroa CD, Gera L, Bhoola KD. Discovery and therapeutic potential of kinin receptor antagonists. Expert Opin. Drug Discov. 2012;(7):1129–48.
51. Warren K, Jakacki R, Widemann B, Aikin A, Libucha M, Packer R, et al. Phase II trial of intravenous lobradimil and carboplatin in childhood brain tumors: A report from the Children's Oncology Group. Cancer Chemother. Pharmacol. 2006;(58): 343–7.
52. Da Costa PLN, Sirois P, Tannock IF, Chammas R. The role of kinin receptors in cancer and therapeutic opportunities. Cancer Lett. 2014, (345), 27–38.
53. Pruneau D, Bélichard P, Sahel JA, Combal JP. Targeting the kallikrein-kinin system as a new therapeutic approach to diabetic retinopathy. Curr. Opin. Investig. Drugs. 2010;(11):507–14.
54. Bozó É, Éles J, Keser, GM. Bradykinin B1 receptor antagonists: A patent update 2009–2012. Expert Opin. Ther. Pat. 2012; (22):1443–52.
55. Quartara L.; Altamura, M. (August 2006), "Tachykinin receptors antagonists: From

research to clinic", Current Drug Targets. 7 (8):975–992,

56. Lohr L (2008). "Chemotherapy-induced nausea and vomiting". Cancer Journal. 14 (2):85–93.
57. "FDA approves Akynzeo for nausea and vomiting associated with cancer chemotherapy". Food and Drug Administration; 2014. Archived from the original on February 1, 2017. Retrieved march 17,2022.
58. Duffy RA, Morgan C, Naylor R, Higgins GA, Varty GB, Lachowicz JE et al. "Rolapitant (SCH 619734): a potent, selective and orally active neurokinin NK1 receptor antagonist with centrally-mediated antiemetic effects in ferrets". Pharmacology, Biochemistry, and Behavior. 2012;102(1):95–100.
59. M. S. Kramer,N.Cutler, J. Feighner et al., "Distinctmechanism for antidepressant activity by blockade of central substance P receptors," *Science*, 1998;281(5383):1640 –5.
60. Mu˜noz M, Berger M, Rosso M, Gonzalez-Ortega A, Carranza A, Cove˜nas R. "Antitumor activity of neurokinin-1 receptor antagonists in MG-63 human osteosarcoma xenografts," International Journal of Oncology. 2014;44(1):137–46.
61. Munoz M, Gonzalez-Ortega A, Salinas-Martin MV, et al., "The neurokinin-1 receptor antagonist aprepitant is a promising candidate for the treatment of breast cancer." International Journal of Oncology. 2014;45:1658–72.
62. Berger M, Neth O, Ilmer M, et al., "Hepatoblastoma cells express truncated neurokinin-1 receptor and can be growth inhibited by aprepitant *in vitro* and *in vivo*," Journal of Hepatology. 2014;60(5):985–94.
63. M. Mu˜noz and M. Rosso, "The NK-1 receptor antagonist aprepitant as a broad-spectrum antitumor drug," *Investigational* New *Drugs*, 2010, 28, (2), pp. 187–93.
64. Onori L, Aggio A, Taddei G, Tonini M. Contribution of NK (2) tachykinin receptors to propulsion in the rabbit distal colon. Am J Physiol. 2000;(278):G137–47.
65. Fioramonti J, Gaultier E, Toulouse M, Sanger GJ, Bueno L. Intestinal anti-nociceptive behaviour of NK3 receptor antagonism in conscious rats: Evidence to support a peripheral mechanism of action. Neurogastroenterol Motil. 2003;15:363–9.
66. Shafton AD, Bogeski G, Kitchener PD, Lewis VA, Sanger GJ, Furness JB. Effects of the peripherally acting NK receptor antagonist, SB-235375, on intestinal and somatic nociceptive responses and on intestinal motility in anaesthetized rats. Neurogastroenterol Motil 2004;16:223–31.
67. Hwang L, Leichter R, Okamoto A, Payan D, Collins SM, Bunnett NW. Downregulation of neutral endopeptidase (EC 3.4.24.11) in the inflamed rat intestine. Am J Physiol. 1993;264:G735–43.
68. Sturiale S, Barbara G, Qiu B, Figini M, Geppetti P, Gerard N et al: Neutral endopeptidase (EC 3.4.24.11) terminates colitis by degrading substance P. Proc Natl Acad Sci USA 1999; 96:11653–8.
69. Barbara G, De Giorgio R, Stanghellini V, Corinaldesi R, Cremon C, Gerard N et al: Neutral endopeptidase (EC 3.4.24.11) downregulates the onset of intestinal inflammation in the nematode infected mouse. Gut. 2003;52:1457–64.
70. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al: GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64(4):401-6.
71. Joos GF, Pauwels RA: Tachykinin receptor antagonists: potential in airways diseases. Current Opinion in Pharmacology. 2001;1 (3): 235-41.
72. Schuiling M, Zuidhof AB, Zaagsma J, Meurs H: Involvement of tachykinin NK1 receptor in the development of allergen-induced airway hyperreactivity and airway inflammation in conscious, unrestrained guinea pigs. Am J Respir Crit Care Med. 1999;159(2):423-30.
73. Tebas P, Tuluc F, Barrett JS, Wagner W, Kim D, Zhao H et al. A randomized, placebo controlled, double masked phase IB study evaluating the safety and antiviral activity of aprepitant, a neurokinin-1 receptor antagonist in HIV-1 infected adults. PLoS One. 2011;6(9):e24180.
74. Roberts, Claire; Inamdar, Amir; Koch, Annelize; Kitchiner, Pauline; Dewit, Odile; Merlo-Pich, Emilio et al. A randomized, controlled study comparing the effects of vestipitant or vestipitant and paroxetine combination in subjects with tinnitus, otology & neurotology. 2011;32;(5): 721-7.
75. Mathew SJ, Vythilingam M, Murrough JW, Zarate CA Jr, Feder A, Luckenbaugh DA,et al. A selective neurokinin-1 receptor antagonist in chronic PTSD: a randomized, double-blind, placebo-controlled, proof-of-

concept trial. Eur Neuropsychopharmacol. 2011;21(3):221-9.
76. Tack J, Schumacher K, Tonini G, Scartoni S, Capriati A, Maggi CA; Iris-2 investigators. The neurokinin-2 receptor antagonist ibodutant improves overall symptoms, abdominal pain and stool pattern in female patients in a phase II study of diarrhoea-predominant IBS. Gut. 2017; 66(8):1403-13.
77. Tauscher J, Kielbasa W, Iyengar S, Vandenhende F, Peng X, Mozley D et al. Development of the 2nd generation neurokinin-1 receptor antagonist LY686017 for social anxiety disorder. Eur Neuropsychopharmacol. 2010;20(2):80-7.
78. "Glaxo Smith Kline withdraws its marketing authorisation application for Zunrisa" (PDF). London: EMEA; 2009. Archived from the original (PDF) on 15 October 2009.
Access on 21 December 2009
79. Saffroy M, Torrens Y, Glowinski J, et al. Autoradiographic distribution of tachykinin NK2 binding sites in the rat brain: comparison with NK1 and NK3 binding sites. Neuroscience 2003; 116:761-73
80. Le Fur G. In: Sanofi-Synthe´labo Information Meeting, February 16, 2004, 53-6
81. Hopkins CR. ACS chemical neuroscience molecule spotlight on Saredutant. ACS Chemical Neuroscience. 2010 Oct;1(10):653-4.
82. Rayes, N., Bowen, D.J., Coffin, T. *et al.* MAGENTA (Making Genetic testing accessible): a prospective randomized controlled trial comparing online genetic education and telephone genetic counseling for hereditary cancer genetic testing. BMC Cancer. 2019;19: 648.
83. Almeida TA, Rojo J, Nieto PM, et al. Tachykinin and tachykinin receptors: structure and activity relationships. Curr Med Chem 2004; 11:2045-81.
84. Rigby M, O'Donnell R, Rupniak NM. Species differences in tachykinin receptor distribution: further evidence that the substance P (NK1) receptor predominates in human brain. J Comp Neurol 2005; 490:335-53
85. Couture R, Toma N, Barbot L. SR142801 behaves as a tachykinin NK-3 receptor agonist on a spinal nociceptive reflex in the rat. Life Sci 2000; 66:51-65
86. Meltzer HY, Arvanitis L, Bauer D, et al. A placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorders. Am J Psychiat.2004; 161:975-84
87. GSK R&D Day 2003. Psychiatry update.
88. Gorelik, G., Carbini, L. A. & Scicli, A. G. Angiotensin 1–7 induces bradykinin-mediated relaxation in porcine coronary artery. J. Pharmacol. Exp. Ther. 1998; 286:403–10.
89. Cheng Y, Yu X, Zhang J, Chang Y, Xue M, Li X, Lu Y, Li T, Meng Z, Su L, Sun B, Chen L. Pancreatic kallikrein protects against diabetic retinopathy in KK Cg-A^y/J and high-fat diet/streptozotocin-induced mouse models of type 2 diabetes. Diabetologia. 2019;62(6):1074-1086.
90. Kini RM, Koh CY. Snake venom three-finger toxins and their potential in drug development targeting cardiovascular diseases. Biochem Pharmacol. 2020 Nov;181:114105.
91. Shen JK, Zhang HT. Function and structure of bradykinin receptor 2 for drug discovery. Acta Pharmacol Sin. 2022;8:1–10.
92. Li C, Kim HJ, Back SK, Na HS. Common and discrete mechanisms underlying chronic pain and itch: Peripheral and central sensitization. Pflugers Arch. 2021;473(10):1603-1615.
93. Khan DA, Kocatürk E, Bauer A, Aygören-Pürsün E. What's New in the treatment of urticaria and angioedema. J Allergy Clin Immunol Pract. 202;9(6):2170-2184.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/94547