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Bradykinin – an undervalued mediator?

Bradykinina – niedoceniany mediator?

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S u m m a r y

The paper aims to analyse basic mechanisms of pathological processes in various tissues and organs that apparently are not related but may be associated with bradykinin, a poorly known component of the kinin system. Bradykinin is commonly known to be involved in the aetiology of cough present in millions of patients receiving treatment with angiotensin-converting enzyme inhibitors. Results of numerous studies suggest an important role of bradykinin in the formation of symptoms that apparently are not related and that are present in tissues and organs that are functionally remote. Bradykinin not only is responsible for adverse drug reactions but also has beneficial effects as it has anticoagulant and nephroprotective properties. The paper analysed involvement of bradykinin in the pathomechanism of acute and chronic inflammation, allergic reactions, angioedema, neuropathic pain, intercellular signal transduction, accelerated development and formation of metastases. Data regarding a role of bradykinin in such processes in the central nervous system as memory consolidation, neurodegenerative processes and control of sleep-wake rhythm were analysed. Moreover, the authors presented potential involvement of bradykinin in the pathogenesis of symptoms associated with burning mouth syndrome that used to be considered as an idiopathic syndrome, hardly treatable. Possibilities to expand therapy options for conditions mentioned above using substances affecting bradykinin metabolism were presented. Currently, treatment includes icatibant – a selective, competitive antagonist of the B2 bradykinin receptor, and the following agents are at various stages of development: bradykinin synthesis inhibitor and three recombinant C1-esterase inhibitors.

S t r e s z c z e n i e

Celem pracy jest przeanalizowanie podstawowych mechanizmów procesów patologicznych w różnych tkankach i narządach, które pozornie nie mają ze sobą związku, a mogą być związane z bradykininą, słabo poznaną składową układu kininowego. Powszechnie uznany jest udział bradykininy w powstawaniu kaszlu występującego u milionów pacjentów w przebiegu leczenia inhibitorami enzymu konwertującego angiotensynę. Wyniki licznych badań sugerują znaczącą rolę bradykininy w powstawaniu objawów pozornie ze sobą niezwiązanych, w odległych od siebie funkcjonalnie tkankach i narządach. Bradykinina nie tylko odpowiada za objawy niepożądane leków, ale także działa korzystnie, np. przeciwzakrzepowo, nefroprotekcyjnie. W pracy analizowano udział bradykininy w patomechanizmach ostrego i przewlekłego zapalenia, w reakcjach alergicznych, obrzęku naczynioruchowym, bólu neuropatycznym, przekazywaniu sygnałów między komórkami, przyspieszaniu rozwoju i tworzenia przerzutów nowotworowych. Przeanalizowano dane dotyczące udziału bradykininy w procesach centralnego układu nerwowego: konsolidacji pamięci, procesach neurozwyrodnieniowych i kontroli rytmu sen-czuwanie. Omówiono także potencjalny udział bradykininy w patogenezie objawów zespołu piekącej jamy ustnej, uważanego za zespół idiopatyczny, rzadko poddający się leczeniu. Przedstawiono możliwości rozszerzenia terapii wymienionych stanów z wykorzystaniem substancji wpływających na metabolizm bradykininy. Obecnie w terapii stosowany jest ikatybant – selektywny, kompetencyjny antagonista receptora bradykininy B2, a w różnych fazach badań są inhibitor syntezy bradykininy oraz trzy rekombinowane inhibitory C1-esterazy.

Conflict of interest
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Many data suggest that symptoms associated with pathologies of numerous tissues and organs that used to be described as separate entities, not related to each other, may have a common background, namely bradykinin. Bradykinin may be responsible for a vast majority of symptoms and they will be initially reported to general practitioners.

The paper aims to analyse various phenomena with regard to the isolation of common features associated with bradykinin and to present new medications that are available as well as directions of pharmacotherapy development.

Bradykinin has become a subject of significant attention when it has been found that it is responsible for adverse drug reactions observed during treatment with angiotensin-converting enzyme inhibitors – routine agents used in patients with arterial hypertension and/or chronic heart failure. Consequently, it has been observed that symptoms associated with bradykinin have been present in dozens of millions of people. Angiotensin-converting enzyme inhibitors (ACEIs) inhibit the conversion of angiotensin I to angiotensin II, and angiotensin II has the most potent properties to contract smooth muscles in the blood vessels, therefore when its production is inhibited, vascular muscles relax, peripheral resistance and blood pressure are reduced. As it has been already mentioned, ACEIs are commonly used to treat patients with arterial hypertension, ischaemic heart disease, circulatory failure, metabolic syndrome, diabetes, diabetic and hypertension nephropathy. Consequently, the number of patients is enormous, therefore studies on the properties of bradykinin were at the beginning focused on its involvement in the pathomechanisms of adverse drug reactions associated with ACEIs.

Bradykinin (9 amino acids) and kallidin (10 amino acids) are peptides formed locally as a result of a protease activity (trypsins and kallikreins) affecting kininogens present in the alpha-2 globulin fraction in blood. Bradykininogen is a bradykinin precursor. It is converted by proteases mentioned earlier into lysyl-bradykinin that is subsequently converted into bradykinin by a converting enzyme (also called kininase II). Kallikrein – a key enzyme for the production of bradykinin – is converted from prekallikrein by factor XII of the coagulation cascade (1).

Bradykinin and kallidin released locally are thought to be responsible for pain, vasodilation and increased vascular permeability and for locally increased synthesis of prostaglandins. Bradykinin is degraded by kininases, and kininase II, associated with the vascular endothelium, is identical to the angiotensin-converting enzyme. Therefore substances inhibiting a converting enzyme also inhibit kininase II, namely they inhibit bradykinin degradation. In specific situations it may result in increased levels of bradykinin if it is produced or released without degradation at a given site. A physiological role of bradykinin is poorly known, and with regard to pathology its role in the pathomechanisms of inflammation and allergic reactions is emphasised the most.

Regarding clinical practice the most known symptom associated with locally increased bradykinin levels in the respiratory mucous membrane is dry, tiresome cough observed in patients receiving medicinal products that inhibit the angiotensin-converting enzyme. Physicians monitoring patients who have developed this adverse drug reaction should especially focus on how to find a common denominator for other complaints that are apparently not associated and that are presented below.

Bradykinin increases blood vessel permeability resulting in oedema, increased warmth and reddening of tissues. These inflammation symptoms are kinin-dependent and kinins increase endothelial permeability as well as production of interleukin 1 and TNF-α. Swelling of the nasal mucous membrane, runny nose present during cold or rhinovirus infections or pain during rheumatoid arthritis or gout also depend on kinins, including bradykinin that is thought to irritate nerve endings. Bradykinin promotes contraction of smooth muscles, for example in the bronchi or uterus, and relaxation of myocytes in the blood vessels, resulting in vasodilation. Stimulation of B1 and B2 receptors activates osteoclasts and increases bone resorption observed during chronic inflammation.

Bradykinin has been shown to act via the B1 bradykinin receptor the expression of which increases in cells undergoing inflammation, and via the B2 constitutive receptor (2). With regard to a signal transduction cascade the following substances are secondary messengers: substance P, neurokinin A and CGRP – calcitonin gene related peptide (3). It is also worth emphasising that these substances are considered to be components of so called neurogenic inflammation. B1 receptors are involved in pain associated with chronic inflammation, whereas B2 receptors are involved in acute pain. Additionally, bradykinin is thought to promote release of prostacyclin and NO via endothelial B2 receptors (4), and it has extremely beneficial clinical effects on the anticoagulant properties of converting enzyme inhibitors.

Results of many studies have expanded our knowledge and forced us to look at bradykinin not only as a substance responsible for adverse reactions but also as one with potentially beneficial properties.

Inhibition of the ACE activity increases the bradykinin levels and it affects homeostasis of mutual interactions between other mediators. Due to these complex interactions that have not been fully understood angiotensin-converting enzyme inhibitors have antiproliferative, nephroprotective and anticoagulant properties, among others. Some properties of ACEIs are a result of effects on the renin-angiotensin-aldosterone system, and some depend on interactions with numerous substances, including such that have not been fully described or explained.

Cough, a typical effect of ACEIs, is present in more than 10% of patients (typical values are 10-25%), but

in as many as 44% of the Chinese population in Hong Kong (5); this is a proof that presence of adverse reactions during treatment depends on the genetic background of subjects, among others.

Sato and Fukuda evaluated outcomes of treatment and the incidence of adverse drug reactions in 176 patients (90 males and 86 females at the age of 67 ± 11 years) treated with ACEIs due to arterial hypertension for 18 months. Cough was observed in 20% of patients, more frequently in women. In 26 subjects cough cleared spontaneously with continued treatment, but in 5% of patients it was so burdensome that treatment had to be changed. It is interesting to observe that cough was present more rarely in patients receiving concomitant treatment with ACEIs and calcium channel blockers or diuretics compared to those receiving ACEIs alone. It was also observed that cough was present more rarely in patients who took ACEIs before going to bed and not in the morning (6). A potential relationship between bradykinin and a daily rhythm is presented below.

In the respiratory system there is a large amount of bradykinin receptors, therefore cough is the most common adverse effect of ACEI treatment. "Bradykinin" cough is also present in those who do not take ACEIs but who have acute and chronic respiratory diseases such as bronchial asthma. "Bradykinin" cough is thought to be promoted by stimulation of B2 receptors present on C-fibres in the respiratory tract, irrespective of a mechanism that has led to such stimulation. In guinea pigs inhalation with bradykinin results in potent cough and bronchospasm that can be reduced by earlier administration of a B2 bradykinin receptor antagonist (HOE 140 – icatibant). The fact that bronchial mucosa is also a shock organ in guinea pigs might suggest involvement of other mechanisms in the aetiology of cough. However, as bradykinin-induced cough is intensified by ACEIs, and blockade of cholinergic receptors or elimination of the activity of thromboxane, cyclooxygenases and NO synthase does not affect the intensity of this cough it suggests that it is bradykinin that plays an important role in the pathomechanism of this symptom, and not other substances (7).

Researchers are increasingly interested in the role of bradykinin in the pathogenesis of angioedema as it has an acute and sometimes dramatic clinical course. Assuming that an excess of bradykinin present during treatment with ACEIs is responsible for cough or angioedema, in clinical practice it is recommended to use angiotensin receptor antagonists (ARBs) in patients who are at the risk of such symptoms. However, this is not a simple matter as there have been reported cases of angioedema after administration of ARBs. On the other hand, one has to remember that the angiotensin levels are increased when its receptors are blocked. What happens to an excess of angiotensin when its receptors are blocked? There is hardly information in this matter.

It is assumed that these symptoms are also due to abnormal bradykinin metabolism but a mechanism of this phenomenon is still unknown (8). It is known that local angioedema may be present in patients who are not treated with ACEIs and without a history of allergies. There was a case of a 66-year-old male patient, receiving regular treatment with metformin, rosuvastatin, carvedilol, candesartan and saxagliptin due to arterial hypertension, type 2 diabetes, stable angina pectoris, nephrolithiasis and benign prostate hypertrophy who developed a foreign body sensation in his throat and a voice change within 30 minutes. A physical examination showed mild oedema of the soft palate and lingula, without any other signs of allergic reactions or inflammation. With regard to a medical history, the patient denied any tendencies for allergies, also in his family, did not report any known allergies to medicinal products; however, he used to develop cough when treated with ramipril (9).

It is known that various organs may play a role of shock organs in case of allergies. With regard to urticaria or contact eczema skin is such an organ, regarding bronchial asthma – respiratory mucous membrane, and regarding allergic rhinitis – nasal mucous membrane. Despite the fact that antibodies may bind to mast cells present in various tissues, the organ showing the highest levels of such cells exhibits the strongest reaction as it binds the most allergen. In humans, a shock organ may change with age. It means that in the same patient allergy to the same allergen may vary and may change with age.

A similar situation cannot be excluded with regard to bradykinin-related reactions, but differences may regard both the amount of bradykinin and the number and density of bradykinin receptors. It would explain many current ambiguities regarding bradykinin.

Pain control is one of the greatest achievements but also one of the further challenges of modern pharmacotherapy. Understanding the role of bradykinin in the pathomechanism of pain might expand our therapeutic possibilities, especially in cases of pain where currently used medicinal products are hardly effective and in cases which are hardly manageable. The control of neuropathic pain is one of such unsolved clinical problems.

Studies on male Wistar rats have shown that administration of bradykinin into gonads results in pain via stimulation of B2 receptors, and the administration of acetic acid increases intratesticular synthesis of bradykinin that promotes pain. In such cases a bradykinin receptor antagonist (FK 3657) reduced both these effects. It suggests a possible role of bradykinin receptor antagonists in the treatment of pain associated with bradykinin (10).

Inflammatory reactions are almost always accompanied by pain, and bradykinin plays a role in both these processes. Excitability of sensory nerves, including pain-transmitting ones, depends on the activity of T-type calcium ion channels, among others, and their activity increases during inflammation and damage to the peripheral nerves. Bradykinin and ATP have been

shown to increase expression of T-type Ca-dependent channels in neurons of dorsal root ganglia (11).

As it has already been mentioned, neuropathic pain is an unsolved but increasing problem of contemporary medicine. Blockade of B1 receptors reduces neuropathic pain in experimentally induced autoimmune encephalitis and meningitis in mice. Blockade of B1 receptors reduces the production of: mRNA for IL-17, INF-gamma, IL-6, COX-2, NOS 2 (12).

A hypothesis that bradykinin plays a role of a mediator in the development or sensation of neurogenic pain has been verified with regard to migraine headache or burning mouth syndrome (13).

Burning mouth syndrome (BMS) manifests with pain in the oral cavity, combined with visible or not visible signs of inflammation on its mucous membrane. In general, three symptoms are observed: pain in the oral cavity, taste disturbances and saliva production disturbances with lack of any morphological lesions on the oral mucous membranes. These symptoms are usually stable with regard to their intensity, although sometimes they increase in the afternoon and at night. Their etiopathogenesis has not been explained. Patients suffering from such symptoms initially consult internal medicine specialists or general practitioners, are subject to expanded and expensive diagnostic tests, then receive empiric treatment, that is usually a failure.

As a common cause of such symptoms has been searched for, a new medical condition has been formed – BMS combining signs of stomatodynia, glossodynia, burning tongue, intraoral dysaesthesia and others. A diagnosis is usually made when other causes of such symptoms have been excluded, usually after initial treatment. In case of a treatment failure subsequent, difficult and hardly effective treatment is started, as in all cases of neuropathic pain. It is worth mentioning that each out of three typical symptoms of BMS (pain, taste disturbances, saliva production disturbances) may be caused by bradykinin (14). Additionally, neurogenic inflammation is thought to be a cause of taste disturbances (15). In this context there has been a hypothesis that BMS symptoms develop in the central nervous system as a disturbance resulting from the activity associated with an excess of bradykinin (16, 17).

However, involvement of bradykinin is more complex as it is a mediator in signal transduction between various cells, for example between glioblastoma multiforme (GBM) cells and mesenchymal stem cells. It suggests that bradykinin may accelerate development and formation of metastases, and inhibition of its activity in this case might have beneficial effects (18). Cancer cells and other cells present in their microenvironment release substances that irritate nerve fibre endings such as: ATP, formaldehyde, proteases, endothelins, TNF or bradykinin mentioned earlier (19).

Bradykinin is also known to increase inflammatory processes, for example in the CNS, via phosphorylation of such proteins as c-Src, Pyk2, and PKC(α/δ). In subjects with inflammatory process in the CNS the serum activity of metalloproteinase 9 (MMP-9) that is thought to be an inflammatory marker is increased. The extract from *Helminthostachys zeylanica* rhizome used in traditional medicine as an anti-inflammatory agent reduces the MMP-9 levels that have been already increased by bradykinin. This extract inhibits phosphorylation of such proteins as c-Src, Pyk2, and PKC(α/δ) that is stimulated by bradykinin, and also reduces the levels of free oxygen radicals due to increased activity of NADPH oxidase (20).

The role of bradykinin in the processes of consolidation of short-term and long-term memory has been studied. It has been demonstrated that when administered directly into the hippocampus area bradykinin disturbs processes of consolidation of short-term but not long-term memory. This effect may be blocked by earlier administration of a B1 receptor antagonist (des-Arg-10-HOE 140), but not by a B2 receptor antagonist (HOE 140, icatibant). It proves that via B1 receptors bradykinin may disturb memory, for example in the course of post-traumatic, inflammatory and neurodegenerative lesions (21).

Contrary to common opinions bradykinin does not always exert pro-inflammatory properties. Changes in the bradykinin conformation and oligomerisation caused by a metal (copper and zinc) imbalance result in the loss of pro-inflammatory properties of bradykinin. An excess of copper ions, more than zinc ions, affects signal transduction via B1 and B2 receptors (22). These observations regard the nervous tissue affected by Alzheimer's pathology, and it is commonly known that imbalance of these metals are studied as possible reasons for this disease. With regard to Alzheimer's disease it is now necessary to explain whether changes in the ion levels are a result or a cause of disturbances, and how they affect the activity of bradykinin and its receptors.

Proteases and neuropeptides are of vital importance to maintain a correct sleep-wake rhythm. In animals, lack of sleep reduces ACE expression and activity of proteases in the hypothalamus (23). The activity of ACE in the CNS normalises as late as after 96-hour relaxation. Changes in the ACE activity affect the bradykinin levels and metabolism of opioid peptides in the CNS, and it may explain changes observed during lack of sleep such as water and electrolyte imbalance, cognitive disturbances, disturbances related to stress. However, melatonin, a hormone that regulates a daily sleep-wake cycle, has not been shown to affect the activity of calcium channels associated with bradykinin (24).

It is worth emphasising that pruritus, neuropathic pain or poorly healing wounds are unsolved medical problems that are currently associated with bradykinin.

A B1 bradykinin receptor belongs to G-protein coupled receptors and its expression – as it has already been mentioned – is significantly increased during inflammation, but its role in pruritus observed during allergic dermatitis is not clear. However, experimental studies have shown that a B1 receptor antagonist (R 892)

reduces sensation of pruritus, but it has not observed for a B2 receptor antagonist (25).

The effects of a B1 agonist on wound healing in mice or on migration and secretion of metalloproteinases 2 and 9 in human keratinocytes have been studied. It has been demonstrated that B1 receptor stimulation results in small and mild migration of keratinocytes (*in vitro*) and accelerates wound healing in the mice skin. B1 receptor stimulation increases the synthesis and secretion of metalloproteases (2 and 9). A B1 receptor agonist also stimulates EGFR (epithelial growth factor receptor), and Src and ADAM17 kinases are involved in this process. All these factors participate in the migration and differentiation of keratinocytes. It suggests that B1 receptor agonists, similarly to bradykinin, may accelerate wound healing (26).

ACEIs are also responsible for adverse drug reactions associated with the skin and its structures that may account for almost half of all adverse reactions. They include the following: excessive sweating, urticaria, pemphigus, excessive hair loss, hypersensitivity to light (27). The role of bradykinin in their formation cannot be excluded and this is presented below.

The involvement of bradykinin in the pathomechanism of pruritus and wound healing processes is poorly known, but B1 receptors are present in the skin and some effects of their stimulation depend on the activation of the epidermal growth factor receptor (EGFR). Animal studies suggest that B2 receptor agonists accelerate wound healing, even poorly healing wounds observed in the course of diabetes (28).

Bradykinin is a probable cause or one of causes of numerous pathophysiological phenomena, also observed locally, that currently are not treated or treated unsuccessfully, but considered to be not important unspecific ailments that are sometimes described as "idiopathic". Apart from recurrent angioedema such ailments include recurrent swelling of the parotid glands, stomatodynia, xerostomia, taste disturbances and allergic rhinitis (29).

There have been reported numerous cases where local angioedema of the head and neck, potentially life-threatening, observed during treatment, was diagnosed by dentists or physicians on call as part of routine medical care (30-32). Such physicians, ENT specialists and dentists report a great number of local, unspecific complications that probably depend on bradykinin. Although ACEIs and ARBs do not belong to routine agents used in their practice, these physicians should especially watch out for the presence of angioedema or local swelling of tissues in the oral cavity, and should carefully check whether they may be associated with treatment with agents that increase the bradykinin levels (33). Risk factors of angioedema also include the following: black race, status post transplantation, treatment with gliptins or immunosuppressive therapy. It is assumed that symptoms of angioedema that is probably associated with bradykinin metabolism disorders may develop in approximately 10% of patients treated with ARBs (34). The background of these disorders includes lack of or abnormal functioning of C1-esterase inhibitor (C1-INH), a complement component. Esterase affects many transmitter pathways such as a coagulation cascade and kinin system, and it promotes bradykinin synthesis and secretion. In case of abnormal C1-INH functioning the XIIa factor and kallikrein increase bradykinin production as a result of positive feedback (35).

Treatment of bradykinin-induced angioedema, namely a life-threatening condition, is difficult as standard therapeutic methods are hardly effective. In this case inhibition of bradykinin receptors might be successful. Icatibant is the only substance with such properties that is used in treatment – it is a selective, competitive antagonist of B2 receptors, consisting of 5 non-protein amino acids. Hereditary angioedema (HAE) is an indication for its use (36). There was a case of a 75-year-old female patient treated with ACEIs who developed tongue swelling and speech disturbances, but without any signs of anaphylaxia or urticaria. During 6-hour therapy including antihistamine agents, glucocorticosteroids and epinephrine inhalation symptoms progressed and the patient required further treatment at the intensive care unit. 30 minutes after the administration of icatibant the patient's condition improved and 2 hours later tongue swelling regressed (37).

Hereditary angioedema (HAE) is a rare disease with genetic background. Its incidence rate is estimated to be 1:50,000. A C1-esterase inhibitor deficiency is an underlying cause of HAE. Esterase inhibits the production of bradykinin and complement activation. Patients with a genetically conditioned C1-esterase inhibitor deficiency show symptoms due to elevated levels of bradykinin. So far, there have not been any medications that would affect bradykinin metabolism, and research combined with new evidence aimed to prove the role of bradykinin in the pathomechanism of various conditions resulted in a suddenly increased interest of pharmaceutical companies. Treatment was supplemented with a bradykinin synthesis inhibitor (ecallantide), there have been ongoing studies on a recombinant C1-esterase inhibitor derived from rabbit's milk called conestat alpha (Ruconest) and on two C1-esterase inhibitors derived from serum (Berinert, Cinryze) (38).

Damage and loss of podocytes is observed in diabetic nephropathy. Nephrin has the greatest significance with regard to maintaining normal membranes of podocytes. A mutation in the nephrin gene resulting in reduced levels of this protein is responsible for abnormal functioning of podocyte membranes. Effects of bradykinin on rat podocytes have been studied and it has been demonstrated that bradykinin increases the activity of NADPH oxidase (NOX1) and NOX4 protein, and increases phosphorylation of ERK1/2 and Akt factors. Bradykinin increases the levels of the connective tissue growth factor (CTGF), and the nephrin levels (39). Results of these studies suggest that bradykinin has nephroprotective properties.

Vasodilating properties of bradykinin that manifest as tissue hyperaemia may be beneficial if such tissues are exposed to ischaemia.

A protective mechanism called ischaemic preconditioning increases myocardial tolerance to short-lasting episodes of ischaemia. Bradykinin is one of endogenous mediators with vasodilating properties that may exert protective activity in ischaemic tissues, similarly to adenosine. A probable mechanism of such an action could include activation of a pathway with PI3K/Akt/eNOS mediators followed by secretion of NO. This activity would be associated with stimulation of B2 bradykinin receptors (40).

Bradykinin is only an element of the kinin system that currently is a subject of scientific research for scientists who study pathogenesis of various phenomena and who search possibilities how to expand therapeutic options. As it has been already mentioned, the interest in bradykinin was initially associated with its significance in the development of cough observed during treatment with angiotensin-converting enzyme inhibitors. As the bradykinin levels have been shown to be elevated in various disorders it is reasonable to conduct further studies regarding its role in processes present in tissues and organs that are remote in terms of their functions. The involvement of bradykinin is more and more often seen in symptoms the background of which has not been earlier explained. However, these observations, and their conclusions above all, are relatively difficult, as sometimes there are local symptoms such as swelling of the tongue or lingula alone, sometimes – organ symptoms such as urticaria or angioedema that sometimes are thought to be systemic symptoms but in reality they concerns one organ, for example the skin. An additional problem with interpretation of studies is associated with the fact that symptoms depend on the daily rhythm and they may change with age. Possible effects of bradykinin in the central nervous system are more and more often emphasised. Nonetheless, local effects limited to the CNS cannot be excluded. These observations are interesting as they allow to see some medical conditions in a different light than in the past, and it regards burning mouth syndrome, for example. Results of studies on the location, expression, activation and inhibition of bradykinin receptors may allow for more effective treatment of numerous conditions where bradykinin is involved.

BIBLIOGRAPHY

1. Yarovaya GA, Neshkova EA: Kallikrein-Kinin System. Long History and Present. To 90th Anniversary of Discovery of the System. Bioorg Khim 2015; 41(3): 275-291.
2. Charest-Morin X, Marceau F: Beyond the Brady-kinin B1 Receptor: Protein Ligands for a Peptide Receptor. PLoS One 2016; 11(2): e0148246.
3. Lupala CS, Gomez-Gutierrez P, Perez JJ: New insights into the stereochemical requirements of the bradykinin B2 receptor antagonists binding. J Comput Aided Mol Des 2016; 30(1): 85-101.
4. Vanhoutte PM, Zhao Y, Xu A, Leung SW: Thirty Years of Saying NO: Sources, Fate, Actions, and Misfortunes of the Endothelium-Derived Vasodilator Mediator. Circ Res 2016; 119(2): 375-396.
5. Woo KS, Nicholls MG: High prevalence of persistent cough with angiotensin converting enzyme inhibitors in Chinese. Br J Clin Pharmacol 1995; 40(2): 141-144.
6. Sato A, Fukuda S: A prospective study of frequency and characteristics of cough during ACE inhibitor treatment. Clin Exp Hypertens 2015; 37(7): 563-568.
7. Hewitt MM, Adams G Jr, Mazzone SB et al.: Pharmacology of Bradykinin--Evoked Coughing in Guinea Pigs. J Pharmacol Exp Ther 2016; 357(3): 620-628.
8. Strassen U, Bas M, Hoffmann TK et al.: Treatment of angiotensin receptor blocker-induced angioedema: A case series. Laryngoscope 2015; 125(7): 1619-1623.
9. Gabb G, Andrew N: Lump in the throat – a case study. Aust Fam Physician 2013; 42(12): 863-866.
10. Fujimoto K, Yoshino T, Yoshioka K et al.: Intratesticular Bradykinin Involvement in Rat Testicular Pain Models. Low Urin Tract Symptoms 2016; 11. DOI: 10.1111/luts.12133.
11. Huang D, Liang C, Zhang F et al.: Inflammatory mediator bradykinin increases population of sensory neurons expressing functional T-type Ca(2+) channels. Biochem Biophys Res Commun 2016; 473(2): 396-402.
12. Dutra RC, Bento AF, Leite DF et al.: The role of kinin B1 and B2 receptors in the persistent pain induced by experimental autoimmune encephalomyelitis (EAE) in mice: evidence for the involvement of astrocytes. Neurobiol Dis 2013; 54: 82-93.
13. Malhotra R: Understanding migraine: Potential role of neurogenic inflammation. Ann Indian Acad Neurol 2016; 19(2): 175-182.
14. Vellappally S: Burning Mouth Syndrome: A Review of the Etiopathologic Factors and Management. J Contemp Dent Pract 2016; 17(2): 171-176.
15. Ackerman BH, Kasbekar N: Disturbances of taste and smell induced by drugs. Pharmacotherapy 1997; 17(3): 482-496.
16. Mendak-Ziółko M, Konopka T, Bogucki ZA: Evaluation of select neurophysiological, clinical and psychological tests for burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 114(3): 325-332.
17. Sinding C, Gransjøen AM, Schlumberger G et al.: Grey matter changes of the pain matrix in patients with burning mouth syndrome. Eur J Neurosci 2016; 43(8): 997-1005.
18. Pillat MM, Oliveira MN, Motaln H et al.: Glioblastoma-mesenchymal stem cell communication modulates expression patterns of kinin receptors: Possible involvement of bradykinin in information flow. Cytometry A 2016; 89(4): 365-375.
19. Lam DK: Emerging factors in the progression of cancer-related pain. Pain Manag 2016; 6(5): 487-496.
20. Hsieh HL, Yang SH, Lee TH et al.: Evaluation of Anti-Inflammatory Effects of Helminthostachys zeylanica Extracts via Inhibiting Bradykinin-Induced MMP-9 Expression in Brain Astrocytes. Mol Neurobiol 2016; 53(9): 5995-6005.
21. Dong-Creste KE, Baraldi-Tornisielo T, Caetano AL et al.: Kinin B1 receptor mediates memory impairment in the rat hippocampus. Biol Chem 2016; 397(4): 353-364.
22. Naletova I, Nicoletti VG, Milardi D et al.: Copper, differently from zinc, affects the conformation, oligomerization state and activity of bradykinin. Metallomics 2016; 8(8): 750-761.
23. Visniauskas B, Oliveira V, Carmona AK et al.: Angiotensin I-converting enzyme (ACE) activity and expression in rat central nervous system after sleep deprivation. Biol Chem 2011; 392(6): 547-553.
24. Choi TY, Kwon JE, Durrance ES et al.: Melatonin inhibits voltage-sensitive Ca(2+) channel-mediated neurotransmitter release. Brain Res 2014; 1557: 34-42.
25. Liu Y, Liu J, Li M et al.: The effect of kinin B1 receptor on chronic itching sensitization. Mol Pain 2015; 11: 70.
26. Matus CE, Ehrenfeld P, Pavicic F et al.: Activation of the human keratinocyte B1 bradykinin receptor induces expression and secretion of metalloproteases 2 and 9 by transactivation of EGFR. Exp Dermatol 2016; 25(9): 694-700.
27. Wojtaszek B, Korzeniowska K, Jabłecka A: Działania niepożądane leków hipotensyjnych zarejestrowane przez regionalny ośrodek monitorowania działań niepożądanych w Poznaniu. Farm Współ 2009; 2: 10-23.
28. Desposito D, Chollet C, Taveau C et al.: Improvement of skin wound healing in diabetic mice by kinin B2 receptor blockade. Clin Sci (Lond) 2016; 130(1): 45-56.
29. Shirasaki H, Saikawa E, Seki N et al.: Nasal Mucosal Expression of the Receptors for Inflammatory Chemical Mediators. Adv Otorhinolaryngol 2016; 77: 52-58.

30. Baričević M, Mravak Stipetić M, Situm M et al.: Oral bullous eruption after taking lisinopril--case report and literature review. Wien Klin Wochenschr 2013; 125(13-14): 408-411.
31. Lehane RJ: Lisinopril-induced angioedema of the lip. N Y State Dent J 2013; 79(3): 25-27.
32. Raval P: A case report looking at ACE inhibitors as the cause of angioedema during dental treatment. Br Dent J 2014; 216(2): 73-75.
33. Shino M, Takahashi K, Murata T et al.: Angiotensin II receptor blocker-induced angioedema in the oral floor and epiglottis. Am J Otolaryngol 2011; 32(6): 624-626.
34. Fain O, Mekinian A, Gobert D et al.: Drug induced angioedema (ACE-inhibitors and other). Presse Med 2015; 44(1): 43-47.
35. Bouckaert M, Bouckaert M, Wood NH e al.: Oral medicine case book 64: Some aspects of the pathophysiology of angioedema with special reference to the upper aerodigestive tract. SADJ 2014; 69(9): 420-423.
36. Angeletti C, Angeletti PM, Mastrobuono F et al.: Bradykinin B2 receptor antagonist off label use in short-term prophylaxis in hereditary angioedema. Int J Immunopathol Pharmacol 2014; 27(4): 653-659.
37. Ostenfeld S, Bygum A, Rasmussen ER: Life-threatening ACE inhibitor-induced angio-oedema successfully treated with icatibant: a bradykinin receptor antagonist. BMJ Case Rep 2015; pii: bcr2015212891.
38. Cancian M: Diagnostic and therapeutic management of hereditary angioedema due to C1-inhibitor deficiency: the Italian experience. Curr Opin Allergy Clin Immunol 2015; 15(4): 383-391.
39. Abou Msallem J, Chalhoub H, Al-Hariri M et al.: Mechanisms of bradykinin-induced expression of connective tissue growth factor and nephrin in podocytes. Am J Physiol Renal Physiol 2015; 309(11): F980-990.
40. Sharma R, Randhawa PK, Singh N, Jaggi AS: Bradykinin in ischemic conditioning-induced tissue protection: Evidences and possible mechanisms. Eur J Pharmacol 2015; 768: 58-70.

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