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Bradykinin actions in the central nervous system: historical overview and psychiatric implications

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Review Article

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Abstract

Bradykinin (BK), a well-studied mediator of physiological and pathological processes in the peripheral system, has garnered less attention regarding its function in the central nervous system, particularly in behavioural regulation. This review delves into the historical progression of research focused on the behavioural effects of BK and other drugs that act via similar mechanisms to provide new insights into the pathophysiology and pharmacotherapy of psychiatric disorders. Evidence from experiments with animal models indicates that BK modulates defensive reactions associated with panic symptoms and the response to acute stressors. The mechanisms are not entirely understood but point to complex interactions with other neurotransmitter systems, such as opioids, and intracellular signalling cascades. By addressing the existing research gaps in this field, we present new proposals for future research endeavours to foster a new era of investigation regarding BK's role in emotional regulation. Implications for psychiatry, chiefly for panic and depressive disorders are also discussed.

Significant outcomes

- Bradykinin (BK) plays an important role in emotional regulation
- BK-mediated signalling in the midbrain can modulate defensive reactions, and its dysfunction may be associated with panic attacks
- BK can modulate different neurotransmitters involved in stress response and thereby may be involved in the neurobiology of different psychiatric disorders

Limitations

- The investigation of BK-signalling mechanisms in the forebrain and its functional consequences have been scarcely studied
- A lack of an in-depth understanding of BK-signalling mechanisms in the brain of stressed animals limits the discussion about its involvement in psychiatric disorders

Introduction

In the mid of the last century Maurício Rocha e Silva, Wilson Beraldo and Gastão Rosenfeld (Rocha e Silva *et al.*, 1949), working at the Biological Institute of São Paulo, identified a 'hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and trypsin' that was named *bradykinin* (BK), so far the only relevant bioactive substance discovered in Brazil. The name was a reference to the slow (*bradys*) contraction of the guinea pig isolated ileum produced by a kinin, a word derived from the Greek *kineo*, meaning to move, which encompasses several chemically distinct polypeptide mediators that have potent actions on vascular and extravascular smooth muscles (Hall, 1992).

Following the discovery of BK, intense research in this field led to the characterisation of the complex cascade responsible for its synthesis and degradation in the body, as well as the identification of many important physiological and pathological conditions associated with BK actions (for a detailed review, see Hillmeister and Persson, 2020). It is now well known that the nonapeptide BK (*Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg*) and other mammalian kinins are not naturally stored in their active form, but are part of larger precursor molecules called *kininogens*, which are plasma proteins produced in the liver (Hall, 1992; Kaplan *et al.*, 1998). To unleash their biological activity, kinins must be released from kininogens by limited proteolytic cleavage,

which involves the action of specific serine proteases known as *kininogenases*. These kininogenases, including the *kallikreins*, are found in various tissues and catalyse the precise cleavage of kininogens, resulting in the liberation of active kinin peptides (Hall, 1992; Kaplan *et al.*, 1998). More specifically, BK is a by-product of the initial step of the plasma kinin-forming system, also known as the contact activation cascade, where Factor XIIa converts prekallikrein to kallikrein, leading to the breakdown of high-molecular-weight kininogen (HK) and the subsequent release of BK (Hall, 1992; Kaplan *et al.*, 1998), as depicted in Fig. 1.

The inactivation of BK is carried out by many different kininases, the most important being kininase II, which is also known as angiotensin-converting enzyme (ACE), because it converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. Inhibitors of this enzyme increase BK as well as decrease angiotensin II concentration in the blood and in other tissues. The first ACE inhibitor was the bradykinin-potentiating factor (BPF), a component *of Bothrops jararaca* venom that was isolated by Brazilian pharmacologist Sérgio Henrique Ferreira, while working at the Department of Pharmacology of the Medical School of Ribeirão Preto-USP (Ferreira, 1965). The analogue of BPF, captopril was synthesised in 1975 and approved for medical use in 1980, becoming widely used for treatments of arterial hypertension (Ondetti *et al.*, 1977).

Once released, kinins interact with their target cells by binding to two main membrane-associated receptors (B1 and B2). These are G-protein-coupled receptors (GPCRs), identified based on the affinity to different peptide and nonpeptide receptor antagonists, radioligand binding studies and receptor cloning and expression studies (Hall, 1997; Fortin and Marceau, 2006; Marceau *et al.*, 2020) (Fig. 2 and Table 1). B1 and B2 receptors are differentially expressed throughout the body and mediate a wide range of biological phenomena (Marceau and Regoli, 2004; Fortin and Marceau, 2006). Both receptors are GPCRs and can trigger a variety of intracellular signalling mechanisms through Gαq, including activation of phospholipase C, MAPK and PLA2 (Lau *et al.*, 2020). While B1 has low expression under basal conditions, it is highly upregulated during inflammatory processes and has been associated with the sustained action of BK and other kinins during pathological conditions. Conversely, B2 is constitutively expressed in various tissues and is thought to mediate most of the physiological actions of kinins in healthy conditions (Marceau and Regoli, 2004; Fortin and Marceau, 2006). The functions mediated by B1 or B2 activation depend on the cell type and tissue condition, as they can compensate for one another for signalling (Lau *et al.*, 2020).

Although BK actions in the periphery have been extensively studied over many decades, its role in the central nervous system (CNS) is far less explored and needs to be better understood. Therefore, it is timely to recapitulate the research history on BK's central actions and discuss the present and future implications of this knowledge for psychiatry. The research work on the central actions of BK occurred in two main phases, primarily led by Brazilian scientists working at the University of São Paulo (USP): an earlier period, starting in the late 1960s and continuing along the following decade, and a recent one, from the late 1990s to the present day, separated by a silent period of nearly 20 years.

The historical landscape of BK actions in the brain

The early period

The earlier phase of exploration of BK action in the CNS was motivated by Mauricio Rocha e Silva, while working at the Department of Pharmacology of the Medical School of Ribeirão Preto (FMRP-USP). Although several peripheral actions of BK were already known, bearing significant pathophysiological implications, central actions were ignored due to the assumption that BK could not cross the blood–brain barrier (BBB). As a result, injections of BK into the lateral ventricles of the brain or directly into the cerebral tissue were used in the initial studies aimed at investigating the physiological and behavioural effects of the polypeptide.

In the first study on the central effects of BK, cats bearing electrodes for electrocorticogram recording were injected with BK into the brain's lateral ventricle through an indwelling cannula. The main effects recorded were behavioural sedation and synchronisation of the cortical electrical activity. In addition, spectrofluorometric assays showed that intraventricular BK reduced the brain concentration of noradrenaline, whereas the brain levels of 5-hydroxytryptamine (5-HT) were unchanged (Graeff *et al.*, 1967). The sedative effect observed after intraventricular injection of BK in the cat agreed with results previously reported by Corrado and co-workers (Corrado *et al*, 1960).

A subsequent study was performed in unanaesthetised rabbits. The obtained results showed that intraventricular injection of BK caused a short-lasting behavioural excitation with vocalisation, followed by a long-lasting phase of sedation Graeff *et al.*, 1969). Behavioural excitation was associated with electrocorticogram desynchronisation and respiratory rate increase. Sedation was accompanied by cataleptic immobility and synchronisation of the electrocorticogram. Marked miosis occurred during both phases, and hypotension/bradycardia, followed by hypertension/tachycardia, was also observed. With repeated injections, excitation, miosis and respiratory and cardiovascular changes gradually subsided and eventually disappeared, whereas the sedative effect remained unchanged.

As in the former study, in cats (Graeff *et al.*, 1967), intraventricular BK caused a reduction of the brain stem concentration of noradrenaline, but levels of 5-HT and dopamine did not significantly change (Graeff *et al.*, 1969).

Another behavioural change, catatonia, was also reported following the injection of BK into the cerebral ventricles or into the cisterna magna of rabbits, which was potentiated by morphine (da Silva and Rocha e Silva, 1971).

In parallel, a neurochemical study was carried out aimed at investigating whether the nervous tissue metabolises BK. Initially, anaesthetised rabbits had a cannula implanted into a lateral ventricle for perfusion and a catheter inserted into the cisterna magna to collect the perfusate. BK activity was measured through a biological assay, namely the guinea pig ileum contraction. It was verified that BK added to the perfusion fluid lost its activity along the way, indicating that degrading enzymes were present in the brain tissue, and to characterise this enzymatic activity, homogenised rabbit brains were analysed. Successive centrifugations of the homogenate gave nuclear, mitochondrial, microsomal and supernatant fractions, respectively. BK inactivation was measured, and the results showed that kininase activity was mainly found in the supernatant fraction. This activity was completely inhibited by the ions Cu^{+} and Zn^{+}, as well as by BPF. Diisopropylfluorophosphate, an acetylcholinesterase inhibitor, also caused complete kininase inhibition, whereas partial inhibition was verified with aprotinin, a drug that inhibits trypsin and related proteolytic enzymes (Camargo and Graeff, 1969).

This knowledge was utilised in the subsequent behavioural experiments, which looked at the effect of intraventricular BK on

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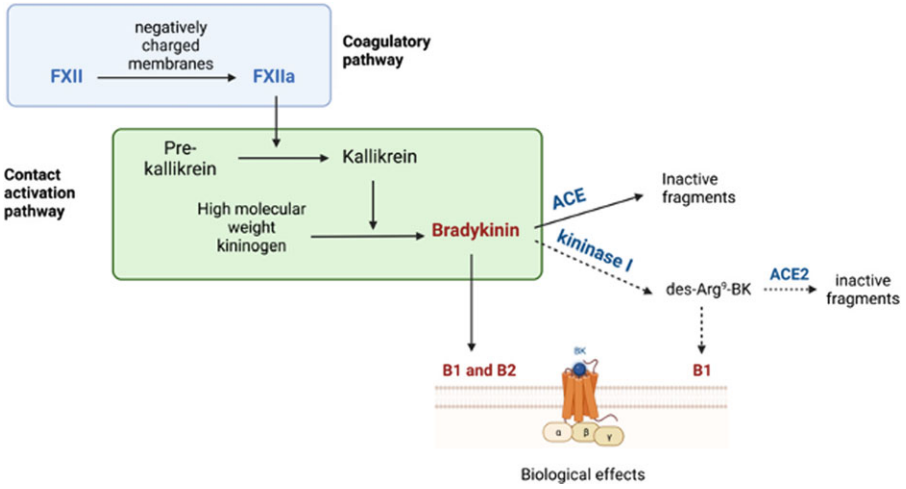

Figure 1. The kallikrein-kinin cascade. Also known as the 'contact activation pathway', this cascade is responsible for releasing active peptides called kinins into body fluids and tissues. Factor XII, or the Hageman factor, initiates this pathway and becomes auto-activated to factor XIIa in small amounts by interacting with negatively charged tissues, endothelial surfaces, or damaged tissues. Factor XIIa is further cleaved to form factor XIIf, an active molecule. The activation of factor XII to factors XIIa and XIIf creates a positive feedback loop. Factor XIIa cleaves prekallikrein to generate an active enzyme called kallikrein, which then cleaves high-molecular-weight kininogens to produce bradykinin (BK). Endothelial cells rapidly inactivate bradykinin through angiotensin-converting enzyme (ACE). Sources: (Sugawara *et al*., 2021; jayasinghe *et al*., 2022).

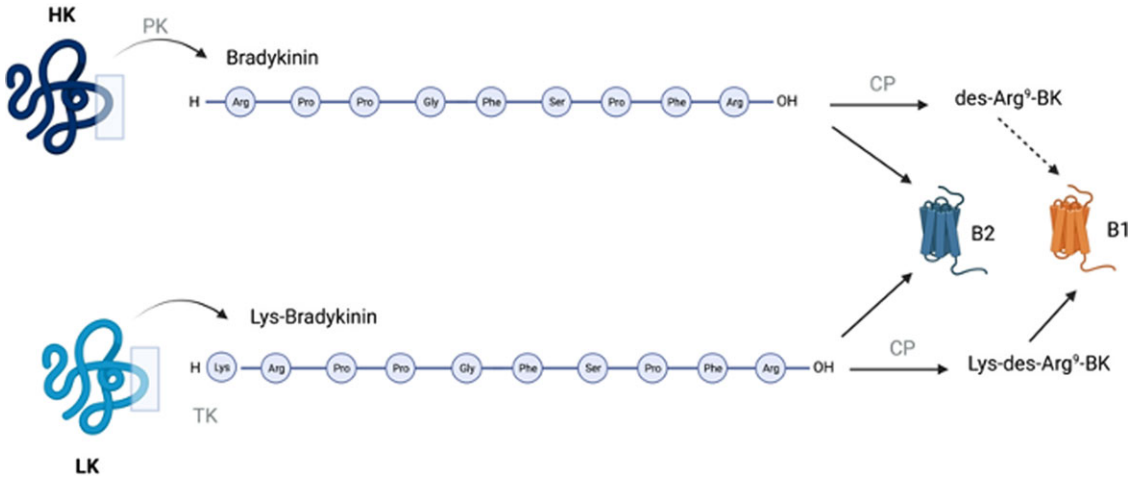

Figure 2. Schematic representation of the kallikrein-kinin system and its interaction with B1 and the B2 receptors. The cleavage of high-molecular-mass kininogen (HK) and low-molecular-mass kininogen by plasma kallikrein and tissue kallikrein, respectively, produces bradykinin and lys-bradykinin, which are active in B1 and B2 receptors. Other enzymes (ACE also known as kininase II), neutral endopeptidase and aminopeptidase cleave kinins at different sites, resulting in their complete pharmacological inactivation. ACE, angiotensin-converting enzyme; CP, carboxypeptidases N and M (= kininase I).

nociception, assessed through the detection of the pain threshold of electric stimuli applied to the tooth pulp of the rabbit. It was verified that intraventricular BK caused a dose-dependent increase in the lowest voltage that determined a reflex response to tooth pulp stimulation, considered as the nociceptive threshold. This antinociceptive effect was potentiated by administering the brain kininase inhibitors aprotinin and BPF. Furthermore, either aprotinin or BPF caused threshold increases following their intraventricular injection, an effect likely to be mediated by endogenous BK. Intracisternal injection of BK was ineffective, indicating regional differences in BK-induced effects due to varying concentrations of BK reaching different brain areas (Ribeiro *et al*., 1971).

These results indicate that BK may play functional roles in the CNS. In this regard, summing up the scant evidence then available, it was suggested that BK might be a neurotransmitter in the CNS (Graeff, 1971), then a quite speculative hypothesis, since the first demonstration of peptide neurotransmission occurred six years later (Hökfelt *et al*., 2001). Nevertheless, this working hypothesis stimulated further research, including the demonstration of BK-like immunoreactive neurons in the CNS (see below), which turned it into a plausible idea.

Among the functions that BK could exert in the brain, the regulation of cardiovascular function has been the most systematically explored. The first study showed that the injection of BK into the lateral ventricle of awake rats increased the mean arterial blood pressure. Similar effects were caused by a related peptide kallidin, given through the same route of administration. The hypertensive effect of BK was blocked by previous intraventricular injection of phentolamine and mimicked by noradrenaline administration, indicating that BK effects involve the regulation of noradrenergic mechanisms and the activation of central alpha-adrenergic mechanisms (Correa and Graeff, 1974).

The following study, performed in urethane anaesthetised rats, showed that the intraventricular injection of BK increased mean arterial blood pressure without affecting heart rate. A similar effect followed its microinjection into the pars ventralis of the lateral septal area, whereas applying the same dose of the peptide at other brain regions involved in cardiovascular regulation was ineffective. As complementary evidence, a bilateral electrolytic lesion of the lateral septal area markedly reduced or completely blocked the hypertensive effect of intraventricular BK. These results suggest that the pars ventralis of the lateral septal area is the main central site of the hypertensive action of BK (Correa and Graeff, 1975).

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Table 1. Summary of bradykinin receptor pharmacology

Receptor	B1	B2
Signalling	GPCR (Gq/11) PLC activation, IP3, DAG, ↑Ca^{2+}	GPCR (Gq/11) PLC activation, IP3, DAG, ↑Ca^{2+} β-arrestins and MAPK, ERK PI3K-Akt
Agonist	des-Arg^9-BK Lys-des-Arg^9-BK	BK Lys-BK Maximakinin Labradimil
	Peptide resistant: Sar-Lys[D-Phe^8]des-Arg^9-BK	Peptide resistant: lobradimil, B-9972
Antagonist	B-9958 Lys-(Leu^8)des-Arg^9-BK	Icatibant B-9430
	MK-0686	Anatibant
Localisation	Generally absent in healthy tissues, and its expression is induced by injury and inflammation	Constitutive in a large number of cells (endothelial, smooth muscle, sensory neurons, epithelium)
Function	Inflammation, pain perception, tissue remodelling	Vasodilation, osmoregulation, smooth muscle contraction, nociception, immunoregulation

Studies such as the aforementioned with the cardiovascular system gave rise to several others aimed at exploring yet unknown biological functions mediated by BK in the brain. For instance, an attempt was made to quantify the behavioural effects of BK and other related peptides. For this purpose, rabbits were trained to lift a bar with their incisor teeth, a response maintained by different schedules of sweetened water reinforcement. Overall, the obtained results showed that BK, angiotensin II and substance P cause selective effects on operant behaviour following intraventricular injection, indicating that these peptides may participate in behavioural regulation (Melo and Graeff, 1975; Graeff and Arisawa, 1978).

Since it cannot cross the BBB, BK must be present in the central nervous system to exert physiological functions. The first study exploring this issue was conducted by Correa and colleagues at Salomon Snyder´s laboratory, USA, using immunofluorescence techniques to localise BK-like immunoreactive structures in the rat brain (Correa *et al.*, 1979). The only brain structure where immunoreactive neuronal cells were observed was the hypothalamus, with particularly dense clusters in the dorsomedial and periventricular nuclei. In addition, nerve fibres and varicose processes were localised in several brain structures, such as the periaqueductal grey matter (PAG), hypothalamus, ventral portion of caudate-putamen, lateral septal area, as well as in the cingulate and perirhinal cortices.

These results point to the existence of kininergic neurotransmission in the brain. Indeed, later studies demonstrated that all components of the kallikrein-kinin system are expressed in the brain, including B1 and B2 receptors (Raidoo and Bhoola, 1998; Gröger *et al.*, 2005). As mentioned before, B1 is scarce under normal healthy conditions but can be expressed in several brain regions in response to various insults, particularly inflammatory ones, where they can be found in microglia cells. B2, on the other hand, is constitutively expressed in neurons, microglia and astrocytes of different brain regions, such as the olfactory bulb, cerebral cortex, hippocampus, basal forebrain, basal ganglia, thalamus, hypothalamus, cerebellum and brainstem nuclei (Chen *et al.*, 2000; Gröger *et al.*, 2005). The activation of such receptors can release glutamate from neurons, and in astrocytes, it can release PGE2, IL-6 and glutamate. For more information on the functioning and distribution of these two BK receptors, see also Marceau *et al.*, 2020 and Othman *et al.*, 2021).

The late period

The question about the behavioural functions regulated by BK has been explored more recently with intracerebral injections applied to the dorsal periaqueductal grey (DPAG). The neurons of this brain region are known to integrate defensive reactions against proximal threats, such as fight, flight or tense immobility (freezing), which have been related to clinical panic attacks (for reviews see Del-Ben and Graeff, 2009; Graeff, 2017).

The first study in this line of inquiry was carried out by Burdin and colleagues (Burdin *et al.*, 1992), in Irene R. Pelá's laboratory, at the Faculty of Pharmaceutical Sciences of Ribeirão Preto, USP. The obtained results showed that intra-DPAG injection of BK increased in a dose-dependent way the threshold to evoke escape behaviour, suggesting an anti-aversive effect. Because previously reported results had shown that intra-DPAG injection of morphine had a similar effect that was antagonised by pre-treatment with naloxone injected intraperitoneally, Burdin and co-workers used the same pre-treatment. They found that the anti-aversive action of intra-DPAG BK was similarly antagonised by naloxone, indicating that BK mobilises opioid mechanisms in the DPAG that decrease aversion.

Escape elicited by electrical stimulation of the rat DPAG is a validated animal model of panic attack (Moreira *et al.*, 2013). Another widely used animal model for such condition is evaluating the escape response performed by rats in the elevated T-maze (ETM). The ETM is an apparatus comprising one arm enclosed by walls perpendicular to two open arms of the same dimensions, all elevated from the ground floor. The ETM is an animal model of both anxiety and panic since the same rat performs two successive tasks inside the maze. The first consists of withdrawal from the enclosed arm to explore the open arm, repeated three times in succession. The open and elevated arms are aversive to rats, which causes gradual increases in the withdrawal latency over repeated attempts, characterising avoidance learning. This task is supposed to reflect anxiety. In addition, the same rat is placed at the end of one open arm, and the time taken to withdraw from this arm to seek refuge in the enclosed arm is measured three times in succession. This escape response is thought to represent panic-like attacks (for a review, see Zangrossi and Graeff, 2014).

The majority of the studies using the ETM were aimed at the exploration of the 5-HT neurotransmission, which is the primary target of the presently used anti-panic medication, namely several antidepressants that inhibit 5-HT uptake and high-potency benzodiazepines, such as alprazolam and clonazepam. In short, the results indicate that 5-HT inhibits escape by activating 5-HT1A receptors localised in the DPAG. These receptors are sensitised by chronic, but not acute, administration of the above anti-panic drugs, modelling their therapeutic regimen. Moreover, they evidenced that the 5-HT1A receptor interacts cooperatively with the mu type of opioid receptor (MOR), leading to a synergistic

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interaction between antidepressants and opiates (for reviews and original references, see Zangrossi and Graeff, 2014; Graeff, 2017).

Summing up the above evidence, it may be concluded that both 5-HT and BK seem to interact with opioids to inhibit escape in the DPAG. To further investigate the BK anti-aversive action, a study was carried out using electrical stimulation of the DPAG, which can trigger panic attacks in humans (Nashold *et al*., 1969). The reported results showed that intra-DPAG injection of BK dose-dependently increased the aversive threshold. This panicolytic-like effect was antagonised by HOE-140, a drug that blocks B2, and by the selective MOR antagonist CTOP. Conversely, the panicolytic-like effect of intra-DPAG injection of the selective MOR agonist DAMGO was hindered by local pre-treatment with either HOE-140 or CTOP, indicating a reciprocal antagonism between the B2 kinin receptor and the MOR. Finally, intra-dPAG injection of the kininase inhibitor captopril was shown to impair electrically induced escape in a dose-dependent way, a panicolytic-like effect blocked by pre-treatment with HOE-140. The last result suggests a mediation of the anti-aversive effect of captopril by B2, which is likely to be intermediated by BK that is present in the nervous tissue of the DPAG (Sestile *et al*., 2017). Therefore, endogenous BK seems to regulate aversion (panic) in the DPAG by activating B2.

The anti-panic action of MOR agonists, as evidenced in animal models of panic, indicates that these drugs may be clinically useful as alternative or adjunctive treatment to currently used antidepressants. However, chronic administration of opioids leads to severe drug dependence. Consequently, drugs that act indirectly on MOR by enhancing the action of endogenous opioids are worth investigating. One such agent is the pentapeptide opiorphin, which inhibits oligopeptidases that degrade brain neuropeptides (Wisner *et al*., 2006). Reported results showed that opiorphin has analgesic and antidepressant effects in experimental animals without inducing either tolerance or dependence after chronic administration (Javelot *et al*., 2010; Popik *et al*., 2010). Using the electrical stimulation of the DPAG and the ETM panic models, it was shown that opiorphin has a panicolytic-like effect mediated by MOR (Maraschin *et al*., 2020).

Because opiorphin may also inhibit the enzyme that degrades BK, its anti-aversive action could be mediated by endogenous BK. To explore this possibility, a study using DPAG electrical stimulation showed that the previous injection of the selective 5-HT1A receptor blocker WAY-100635 into the DPAG did not change the panicolytic-like effect of locally administered opiorphin. As complementary evidence, combined injection of sub-effective doses of the 5-HT1A-agonist 8-OH-DPAT and opiorphin did not have a significant anti-escape effect. These results indicate that opiorphin does not activate the MOR, since it interacts cooperatively with the 5-HT1A receptor to inhibit aversion in the DPAG. In contrast, the B2 blocker HOE-140 reduced the anti-escape effect of opiorphin, and the combination of sub-effective doses of BK and opiorphin had a significant anti-escape effect. Furthermore, the panicolytic-like effect of BK was not affected by pre-treatment with the 5-HT1A agonist WAY-100635. Therefore, the panicolytic-like effect of opiorphin in the DPAG seems to be mediated by endogenous BK, acting on the B2-MOR complex in the DPAG, without modulating local serotonergic mechanisms (Sestile *et al*., 2017).

Summary

Summing up the reviewed evidence, it may be suggested that the neuronal network that integrates panic-related behavioural reactions to proximal threat in the DPAG is modulated by serotonergic, opioidergic and kininergic systems. These defensive behaviours are inhibited by 5-HT through activating the 5-HT1A receptor, which interacts cooperatively with the MOR type of opioid receptor. In addition, BK exerts a similar anti-panic action by activating the B2 receptor, which also interacts with a different MOR, through a yet unknown mechanism. This hypothetical construct is illustrated in Fig. 3.

Psychiatric implications

Panic disorder is characterised by the recurrence of spontaneously evoked panic attacks. A panic attack is a period of intense fear accompanied by at least four of the following symptoms: trembling, shortness of breath, choking, chest pain, palpitation, sweating, dizziness, nausea or abdominal distress, diarrhoea, numbness or tingling sensations, chills or hot ashes, cold hands, headache, insomnia, fatigue, intrusive thoughts and ruminations, derealisation or depersonalisation, fear of losing control or of going crazy and fear of dying. Many patients feel an urge to flee and a sense of impending death from suffocation or a heart attack. Panic attacks occur in several psychiatric disorders and even in normal individuals. To be diagnosed with panic disorder, panic attack events should be accompanied by persistent worry about having another attack and its consequences. Patients usually avoid places or situations where having a panic attack is humiliating or an easy escape route is unavailable. When the avoidance of places is generalised, the condition is named agoraphobia (American Psychiatric Association, 2013).

Anxiety seems to inhibit panic attacks, since panic attacks may happen during sleep. Also, relaxation therapy is ineffective in treating panic disorders and often triggers panic attacks. Clinical observation testifies that panic disorder patients tend to be in a state of persistent tension, which may be a strategy to refrain from panic attacks (Deakin and Graeff, 1991). The concept that anxiety inhibits panic is illustrated in Fig. 3 by the dashed line from the amygdala to the DPAG.

The pharmacological treatment of panic disorder is mainly made with antidepressant agents that primarily affect the 5-HT neurotransmission. The therapeutic effect of these drugs takes about three weeks of daily administration to appear, and during the initial phase, anxiety is often worsened (Baldwin *et al*., 2014; Sartori and Singewald, 2019).

Using animal models of panic, a series of studies carried out at Hélio Zangrossi's laboratory showed that chronic administration of antidepressants sensitises 5-HT1A receptors that inhibit aversion in the DPAG, their acute administration being ineffective. Conversely, reported evidence shows that the same drug treatment gradually down-regulates 5-HT2C receptors in the amygdala, the activation of which enhances anxiety. Because antidepressants are also first-choice medication for treating generalised anxiety disorder, these results may be viewed as a clue to understanding the mechanisms of the therapeutic action of antidepressants. Thus, it has been suggested that the anti-panic action of these drugs is due to enhanced inhibition of DPAG neurons that engender defensive reactions to proximal danger by activating hypersensitive 5-HT1A receptors. In turn, the antianxiety action would result from lessened stimulation by downregulated 5-HT2C receptors of neurons in the amygdala that enhance anxiety (Graeff and Zangrossi, 2010; Vicente and Zangrossi, 2014; Vilela-Costa *et al*., 2021).

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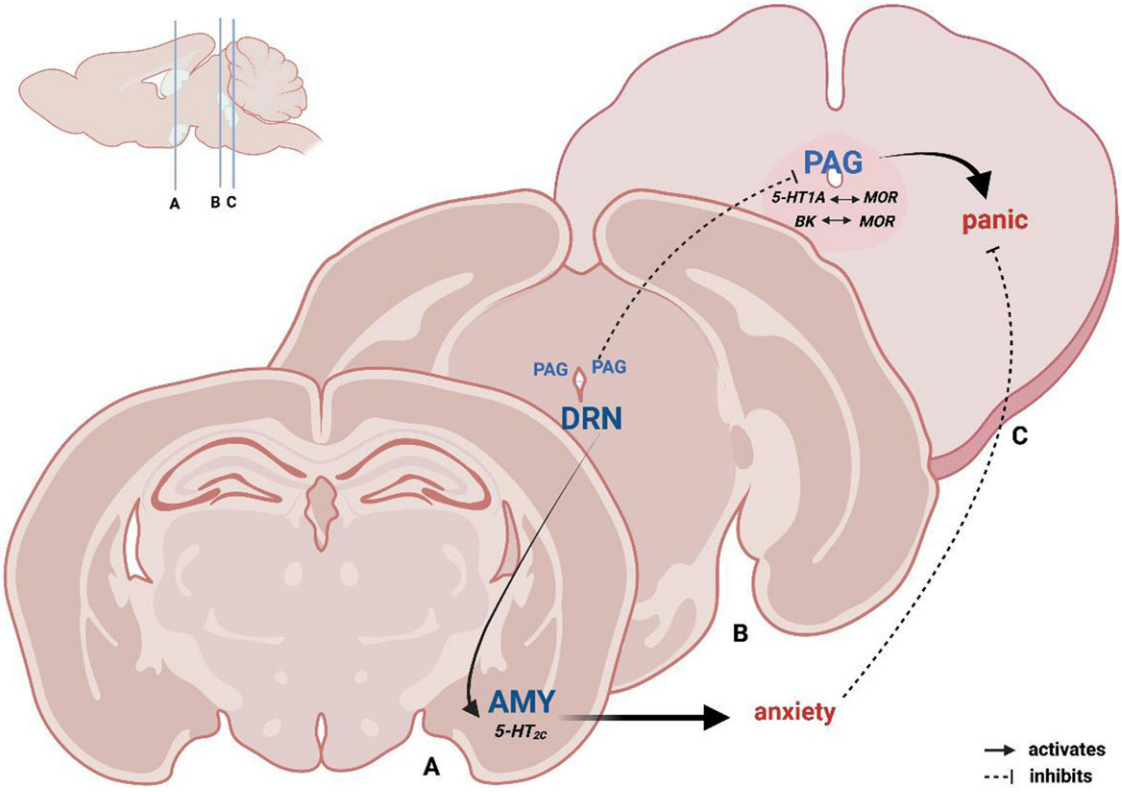

Figure 3. Bradykinin, mu-opioid receptor (MOR) and 5-HT1A receptor interplay in the midbrain and its possible influence on defensive behaviour. 5-HT enhances anxiety by activating 2C receptors in the amygdala and inhibits panic in the dorsal PAG by activating 1A receptors. BK interacts cooperatively with MOR to inhibit panic. The latter is different from the MOR that interacts with 1A. Anxiety generated in the amygdala inhibits panic integrated in the PAG. PAG: periaqueductal grey; DRN: dorsal raphe nucleus; 2C and 1A: 5-HT receptors; MOR: mu-opioid receptor; BKR: B2 kinin receptor.

These findings may also have implications for the understanding of panic disorder pathophysiology. As thoroughly analysed elsewhere (Graeff, 2017), the above-discussed synergistic interaction between 5-HT and endogenous opioids in the DPAG to inhibit proximal defence and, supposedly, panic attacks allow reconciliation of the two main hypotheses on panic disorder pathophysiology. The first proposes that panic disorder patients have a deficient serotonergic inhibition of neurons localised in the DPAG that organise defensive reactions to proximal threats, as well as of sympathomotor control areas of the rostral ventrolateral medulla that generate neurovegetative symptoms of the panic attack. The second proposes that endogenous opioids buffer panic attacks in healthy individuals, their deficit in panic disorder patients resulting in hypersensitivity to suffocation and separation anxiety (Preter and Klein, 2008). Within this perspective, it was further suggested that endogenous opioids are likely to participate in the anti-panic action of antidepressants and that exogenous opioids could be useful for treating panic disorder patients who are resistant to antidepressants (Graeff, 2017).

Following the same reasoning, it may be added that the above-described results show that BK restrains panic-like responses in the DPAG through the activation of B2 that may interact cooperatively with the MOR introducing a new element in regulating panic. Because the anti-panic-like effect of opiorphin is likely to be mediated by the B2-MOR complex (Sestile *et al.*, 2017), and opiorphin has been shown to enhance the panicolytic-like effect of chronic antidepressants following combined injection into the DPAG (Maraschin *et al.*, 2020), it may be suggested that BK is potentially involved in the mechanism of the therapeutic action of antidepressants as well as in the pathophysiology of panic disorder.

Depressive disorders are not only more prevalent than panic disorder but also represent a far greater personal, social and economic burden (Wittchen *et al.*, 2011; Malhi and Mann, 2018). Because depression responds to the same drugs that treat panic disorder (Shankman *et al.*, 2017), it is possible that the above mechanisms of action unveiled by the animal models of panic also participate in mood regulation. As a consequence, exploration of this matter in animal models of depression, as well as in clinical assays seems to be a pathway worth pursuing.

It is well known that a sizable portion of depressed patients are resistant to antidepressants (Kverno and Mangano, 2021). Consequently, other drugs aimed at enhancing their action or acting through different mechanisms are being investigated. A successful example of such an endeavour is ketamine (Bahji *et al.*, 2021), but other options should be considered. As mentioned above, enhancing the action of endogenous opioids by administering opiorphin could be an exciting alternative. However, opiorphin does not cross the BBB. Still, orally active enkephalinase inhibitors are being developed (Poras *et al.*, 2014) and are already undergoing clinical tests for pain management (Southerland *et al.*, 2021). Furthermore, recent evidence indicates that the combined administration of buprenorphine (partial agonist at MOR) and samidorphan (MOR antagonist and κ/δ-opioid receptor partial agonist in vitro) might be an effective treatment in patients that fail to respond to monoaminergic drugs (Fava *et al.*, 2020). Because the above evidence indicates that the panicolytic-like effect of

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opiorphin is mediated by endogenous BK, a question to be explored by future research is whether the same processes apply to the analgesic, antidepressant and other therapeutically relevant effects of enkephalinase inhibitors.

Since the time taken to introduce a new pharmacological agent into clinical practice amounts to several years, a valid alternative is to look for drugs already used for different purposes, a strategy known as repositioning. In the particular case of BK, drugs that inhibit the kininase 2 enzyme that inactivates BK are widely used in treating hypertensive diseases, namely the class of angiotensin conversion enzyme (ACE) inhibitors. In fact, ACE and kininase 2 are different names for the same enzyme (Costerousse *et al*., 1992). Therefore, ACE inhibitors not only block the conversion of angiotensin I to the vasoconstrictor derivative angiotensin II but also enhance the vasodilation caused by BK. It is worth reminding that the last action is not shared by drugs that block the angiotensin AT1 receptor type, which is also generally used to treat hypertensive diseases (Contreras *et al*., 2003).

Reported results show that ACE occurs in the CNS and its inhibitors exert central actions of potential therapeutic interest (Strittmatter *et al*., 1984; Farag *et al*., 2017). Among other applications, ACE inhibitors are being considered for treating anxiety and depressive disorders (Melo and Almeida-Santos, 2020). Because angiotensin is considered to be a neurotransmitter in the CNS, the therapeutic action of ACE inhibitors has been attributed exclusively to their interference with angiotensin (Rocha *et al*., 2018; Sanches and Teixeira, 2021). In this regard, the presently discussed evidence on the central action of BK raises the critical question of to what extent the central actions of ACE inhibitors are mediated by BK, alone or in addition to angiotensin. Interestingly, we have a simple pharmacological tool to investigate this possibility, represented by the AT1 receptor blockers. Whenever the effects of the latter and the ACE inhibitors match, the exclusive mediation by angiotensin will be the likely explanation. Otherwise, the contribution of BK should be investigated. For example, the results of a reported study on the association between suicide and exposure to either ACE inhibitors or AT1 receptor blockers showed that the latter was associated with a higher risk of death by suicide, implying that endogenous BK may lower the same risk (Mamdani *et al*., 2019).

Furthermore, in animal models of depression, BK is likely to mediate the antidepressant-like effect of ACE inhibitors since new results showed that the intraperitoneal injection of captopril rapidly reduced the behavioural readouts associated with depression in mice exposed to the chronic unpredictable stress and the chronic social defeat stress (Luo *et al*., 2020), both well-validated models of depression (Gururajan *et al*., 2019). In addition, lisinopril, another ACE inhibitor that crosses the BBB better than captopril, exerted a faster and longer-lasting effect at the same molar equivalent dose. More relevant to the present argument, this antidepressant-like action seemed to be mediated by the BK system rather than by the renin-angiotensin system since the decreased levels of BK detected in the stressed mice was reversed by captopril through activation of the mammalian target of rapamycin complex 1 (mTORC1) (Luo *et al*., 2020). These findings indicate that the BK-dependent activation of mTORC1 may represent a promising antidepressant mechanism of action, underlining the potential use of ACE inhibitors as fast-acting agents for treating depressive disorders (Luo *et al*., 2020).

Actually, in the late 1980s, several case reports described the antidepressant action of captopril (Zubenko and Nixon, 1984; Deicken, 1986; Cohen and Zubenko, 1988; Germain and Chouinard, 1988; Germain and Chouinard, 1989). Soon after, an open trial has also been carried out (Vuckovic *et al*., 1991). Clearly, double-blind controlled studies using a larger number of patients are necessary to establish the antidepressant action of ACE inhibitors. The perspectives of such studies have been recently boosted by results reported in mice showing that ACE gates brain circuit-specific plasticity via an endogenous opioid in the nucleus accumbens, with important implications for depression and drug addiction (Trieu *et al*., 2022).

More recent evidence from patients also reinforces the association between BK-regulated mechanisms and the pathophysiology of depression. A proteomic analysis showed that in depressed patients the protein K2C1, which is associated with the kallikrein-kinin system activation in the brain and thereby BK synthesis, was downregulated (Choi *et al*., 2021). In line with that, decreased levels of BK have been detected in the plasma of depressed patients in another proteomic study (Kang *et al*., 2019). This evidence supports the perspective that increasing BK levels in the brain can alleviate depressive symptoms and provide an interesting pharmacological tool to develop new treatment options.

Accumulating evidence indicates a link between dysregulation of the immune system and depression (Pape *et al*., 2019; Troubat *et al*., 2021) and interference with inflammatory response may underlie some of BK actions in this pathology as well in other neurological and psychiatric diseases (Levant *et al*., 2006; Talbot and Couture, 2012; Naaldijk *et al*., 2016; Barić and Dobrivojević Radmilović, 2021). In the CNS, microglia are the resident macrophages and primary immune cells, highly reactive to microenvironmental changes caused by different stressors, such as infection, tissue damage or disease (Borst *et al*., 2021). These glial cells can express both BK receptors. In resting microglia, B2 receptors, but not B1 receptors are expressed. When microglia are activated by BK, B1 receptors are upregulated, while B2 are downregulated (Noda *et al*., 2003, 2004). Although the exact role played by each of these microglial receptors in regulating inflammation in the CNS remains unclear (for recent reviews, see Wang *et al*., 2019; Barić and Dobrivojević Radmilović, 2021), pioneering studies by Noda *et al*. (2007a, b) showed that in vitro activation of B1 receptors in the microglia suppresses the release of inflammatory cytokines (TFN-α and IL1-β) induced by the bacterial toxin lipopolysaccharide (LPS), exerting an anti-inflammatory effect.

Later on, using primary microglial rodent culture, Levant *et al*. (2006) reported that the activation of B2 receptors enhanced both basal and LPS-induced prostaglandin E2 synthesis, a proinflammatory response, whereas the administration of Lys-des-Arg(9)-bradykinin, a BK metabolite that acts as a selective B1 receptor agonist, caused the opposite effect. These results suggest a feedback regulatory mechanism of BK on glial cells, in which prostaglandin synthesis is initially enhanced by B2 and eventually blocked by the effect of a BK breakdown product, acting on B1 receptors.

However, the neuroprotective effect of B1 receptor stimulation has been questioned by studies conducted in experimental animals. For instance, injection of LPS in mice increased depression-like behaviour that was reduced by pre-treatment with the selective B1 receptor antagonists R-715 and SSR240612. Moreover, pre-treatment with SSR240612 prevented the increase in number of activated microglial cells in the mouse hippocampus. In addition, the increased immobility time observed in the forced swimming test following LPS treatment was preceded by an enhancement of hippocampal and cortical B1 receptor mRNA expression, and a

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marked production of TNF-α in serum, brain and cerebrospinal fluid. Furthermore, the depression-like behaviour determined by LPS was absent in TNF-α p55 receptor-knockout mice, which also did not show an increased B1 receptor mRNA expression (Viana *et al.*, 2010).

Overall, these findings suggest a complex interplay between B1 and B2 in regulating inflammatory microglial reactivity. The functional consequences of that in the context of depression remain unexplored.

Finally, chronic pain and depression are often interconnected (Bair *et al.*, 2003), and modulation of kinin receptors interferes with pain signalling and the associated inflammatory processing (for a review see Brusco *et al.*, 2023). For instance, B2 receptor activation in a variety of tissues, including postganglionic sympathetic fibres, stimulates the production of several proinflammatory mediators, including prostanoids and cytokines, which contribute to inflammation and hyperalgesia (Walker *et al.*, 1995; Dray, 1997). Although the role of B1 receptors has received less attention, it has been shown that whereas stimulation of this ligand site exacerbates hyperalgesia, its blockade produces analgesia (Dray, 1997). It has been suggested that while B2 receptors play a key role in the acute phase of the inflammatory and pain response, B1 receptors are implicated in the chronic phase of the response (Couture *et al.*, 2001).

Altogether, the evidence mentioned above indicates that the central regulation of pain and inflammation by BK has key consequences to emotional processes associated with psychiatric disorders, which are very often comorbid conditions. Unravelling such intricate mechanisms and their temporal and regional characteristics may be of therapeutical relevance and requires further investigation.

Conclusion and perspectives

The role of BK in the CNS has been studied since the late 1960s. In the early phase, along the 1970s, behavioural and cardiovascular effects of BK injected into experimental animals' lateral ventricles of the brain have been described. Following a 20-year silent interval, a new approach focused on panic models and the DPAG, unveiling a likely role of BK as a modulator of proximal defence reactions, supposedly related to panic disorder. This development points to important implications of this fundamental knowledge to psychiatric disorders, including panic disorder and depression, as indicated by recently reported results. Both the understanding of pathophysiology and effectiveness of pharmacotherapy of these conditions may be improved by further basic as clinical research on the role of BK in the CNS.

To further advance in that direction, it is crucial to understand BK's involvement in regulating cell signalling in different brain regions involved in behavioural regulation. For instance, which receptors and cell types (neurons, astrocytes, microglia) are involved in BK-mediated effects under normal and chronic stress conditions? Moreover, an in-depth understanding of BK effects and its receptors in the effect of antidepressant drugs is needed.

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