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Kinin B1 receptor mediates memory impairment in the rat hippocampus

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Abstract: The bradykinin (BK) receptors B1R and B2R are involved in inflammatory responses and their activation can enhance tissue damage. The B2R is constitutively expressed and mediates the physiologic effects of BK, whereas B1R expression is induced after tissue damage. Recently, they have been involved with Alzheimer's disease, ischemic stroke and traumatic brain injury (TBI). In this study, we investigated the role of bradykinin in short and long-term memory consolidation (STM and LTM). It was observed that bilateral injection of BK (300 pmol/μl) disrupted the STM consolidation but not LTM, both evaluated by inhibitory avoidance test. The STM disruption due to BK injection was blocked by the previous injection of the B1R antagonist des-Arg[10]-HOE140 but not by the B2R antagonist HOE140. Additionally, the injection of the B1 agonist desArg[9]-BK disrupted STM and LTM consolidation at doses close to physiological concentration of the peptide (2.3 and 37.5 pmol, respectively) which could be reached during tissue injury. The presence of B1R located on glial cells around the implanted guide cannula used for peptide injection was confirmed by immunofluorescence. These data imply in a possible participation of B1R in the STM impairment observed in TBI, neuroinflammation and neurodegeneration.

Keywords: bradykinin; B1R; B2R; cognitive processes; memory impairment.

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Introduction

The kinins bradykinin (BK) and kallidin (Lys-BK) are classical proinflammatory peptides released during tissue injury. Their actions lead to cell migration, vasodilation, increased vascular permeability, pain and hyperalgesia (Marceau and Bachvarov, 1998). Kinin effects are mediated by two transmembrane G protein coupled receptors (GPCR), namely B1 (B1R) and B2 (B2R), expressed centrally and peripherally (Regoli et al., 2001). The B2R is a constitutive receptor, its stimulation leading to fast desensitization (Bascands et al., 1993; Mathis et al., 1996). It mediates most of the kinin actions and has high affinity for BK and high sensitivity to low concentrations of the synthetic antagonist Hoe 140 (Regoli et al., 1998). Conversely, B1R has higher affinity to des-Arg[9]BK and Lys-des-Arg[9]-BK (Regoli and Barabe, 1980). B1R is resistant to desensitization and is barely distributed in tissues under physiological conditions (Leeb-Lunderberg et al., 2005), but shows increased densities under pathological conditions, such as chronic neurological diseases (Marceau and Bachvarov, 1998; Prat et al., 1999, 2000).

Likewise the peripheral systems, kallikrein-kinin system and all their components have been described in central nervous system (CNS) (Hori, 1968; Correa et al., 1979; Kariya et al., 1981; Perry and Snyder, 1984). Exogenous administration of BK peptide into CNS leads to alterations in animal behavior (Okada et al., 1977), arterial blood pressure (Pearson et al., 1969; Unger et al., 1981; Buccafusco and Serra, 1985; Lindsey et al., 1997), and body temperature (Almeida e Silva and Pela, 1978). The

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estimated concentration of BK in whole rat brain samples is 0.6 pmol/g (Elrod et al., 1986).

Kinin B2 receptor has a ubiquitous distribution in the CNS of several species, such as rats (Ongali et al., 2003; Cloutier et al., 2004; Viel et al., 2008; Caetano et al., 2010), mice (Ma et al., 1994b; Caetano et al., 2015), guinea-pigs (Sharif and Whiting, 1991; Fujiwara et al., 1998), bovines (Kozlowski et al., 1988) and humans (Bhoola et al., 1992; Ma et al., 1994a; Raidoo et al., 1996; Raidoo and Bhoola, 1997; De Sousa Buck et al., 2002) being observed in cortical astrocytes (Cholewinski et al., 1991), pons, medulla, spinal cord, cortex, hippocampus (Sharif and Whiting, 1991; Fujiwara et al., 1998), cerebellum (Ma et al., 1994a), pituitary gland (Ma et al., 1994b), hypothalamus, thalamus, caudate putamen, cerebral cortex and brain stem (Raidoo et al., 1996).

The B1R was also observed in many tissues such as cerebral cortex, cerebellum, hippocampus, pituitary gland, hypothalamus (Chai et al., 1996), spinal cord dorsal horn (Wotherspoon and Winter, 2000), thalamus, caudate putamen, spinal cord (Raidoo and Bhoola, 1997; Campos et al., 2005; Viel et al., 2008) and in the inferior olivar nucleus (De Sousa Buck et al., 2002). Induction and increase in densities of this receptor can be observed during inflammation, tissue lesion, cancer, experimental treatment with bacterial endotoxins, some cytokines and growth factors or in the presence of its own agonist (Marceau and Bachvarov, 1998; Yang et al., 2001).

Our group showed that infusion of human 1–40 Aβ peptide in rats leads to an increase in kinin concentration in the cerebrospinal fluid (Iores-Marçal et al., 2006), increase in B1R densities in memory related areas suggesting an enhanced activation of the kallilkrein-kinin system (KKS) (Iores-Marçal et al., 2006; Viel et al., 2008). These alterations of the KKS were accompanied by neuronal loss and disruption in memory consolidation. Additionally, a single dose of BK administered in the rat hippocampus promoted hyperphosphorylation of Tau protein, leading to impairment of learning and memory consolidation (Wang and Wang, 2002). In this way, this study aimed at evaluating the involvement of BK in short- and long-term memory formation of Wistar rats and at characterizing the type of receptor, B1 or B2, involved in this process.

Results

BK impairs short-term memory consolidation through B1R activation

To evaluate the influence of BK on short-term memory consolidation, 300 pmol of the peptide was administered bilaterally over the CA1 hippocampal area immediately after the acquisition session (AS) in the inhibitory avoidance apparatus. In this paradigm, an increase in the latency to enter the dark side of the box, in the test session (TS), indicates memory consolidation. The short-term-memory consolidation was assessed 90 min later. Animals injected with BK showed no significant increase in latency [AS=10.5 s (6.17 s/19.65 s) and TS=21.3 s (11.18 s/62.03 s); $p>0.05$] when compared to animals injected with artificial cerebrospinal fluid (aCSF) [AS=23.6 s (13.6 s/58.0 s) and TS=32.5 s (20.3 s/298.0 s); $p<0.05$] (Figure 1) indicating that BK caused short-term memory impairment.

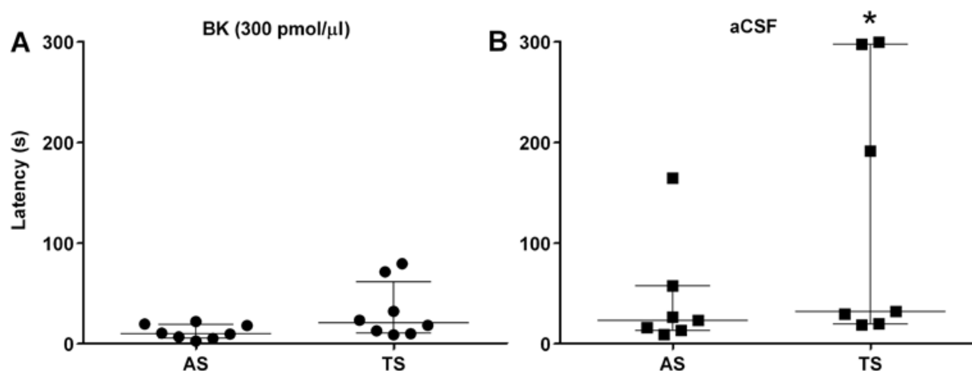

Figure 1: Effect of BK on short-term memory formation.
Bilateral injection of BK (300 pmol/µl, n=8, 'A') or aCSF (n=7, 'B') over the CA1 hippocampal area immediately after the acquisition session (AS), in the inhibitory avoidance apparatus (footshock intensity, 0.5 mA; interval between sessions, 90 min), impaired short-term memory formation. Data are expressed as median (interquartile range) in seconds and were significant when $*p<0.05$ (Wilcoxon test for paired and non-parametric data). AS, Acquisition session; TS, test session.

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In order to verify which receptor is involved with this memory impairment, the pharmacological blockade of B1R or B2R was performed through bilateral injection of the B1 antagonist des-Arg[10]-HOE140 or the B2 antagonist HOE140 followed by BK, at isomolar concentration. The increase of latency of animals injected with the B1 antagonist indicates that B1R blockade disrupted the memory impairment caused by the BK injection [AS=26.8 s (15.2 s/39.5 s) and TS=298.0 s (56.5 s/298.0 s); $p<0.05$, Figure 2A]. Otherwise, injection of the B2 antagonist did not block the memory impairment caused by the BK injection [AS=28.40 s (16.0 s/138.6 s) and TS=56.0 s (22.6 s/90.9 s); $p>0.05$, Figure 2C]. Injection of the B1 or B2 antagonist followed by aCSF did not alter short-term memory consolidation [B1R antagonist+CSF: AS=17.8s (7.6s/32.2s) and TS=83.8 s (37.7 s/298.0 s); $p<0.05$ – B2R antagonist+CSF: AS=17.8 s (13.1 s/70.9 s) and TS=203.8 s (48.0 s/298.0 s); $p<0.05$, Figure 2B and D].

To confirm the data obtained with the pharmacological blockade of B1R, 300 pmol/μl of the biostable B2R agonist NG291 was administered bilaterally over the CA1 hippocampal area immediately after the AS [29.3 s (29.3 s/49.2 s)] in the inhibitory avoidance apparatus. No short-term memory impairment was observed as the latency in TS [233.5 s (52.5 s/298.0 s)] was significantly greater from the latency in AS (Figure 3).

BK does not impair long-term memory but desArg⁹-BK does

To evaluate the influence of BK on long-term memory consolidation, BK (300 pmol) was administered bilaterally over the CA1 hippocampal area, immediately after the AS and the long-term memory formation was tested 24 h later. BK injection showed no impairment of long-term memory formation [AS=14.6 s (11.1 s/20.6 s) and TS=36.7 s (14.3 s/270.0 s); $p<0.05$], as well as the aCSF injection [AS=22.6 s (4.2 s/83.8 s) and TS=182.0 s (14.3 s/298.0 s); $p<0.05$, Figure 4A and C]. Considering that the effect of BK on short-term memory was mediated by B1R action, the effect of des-Arg⁹-BK on long-term memory formation was

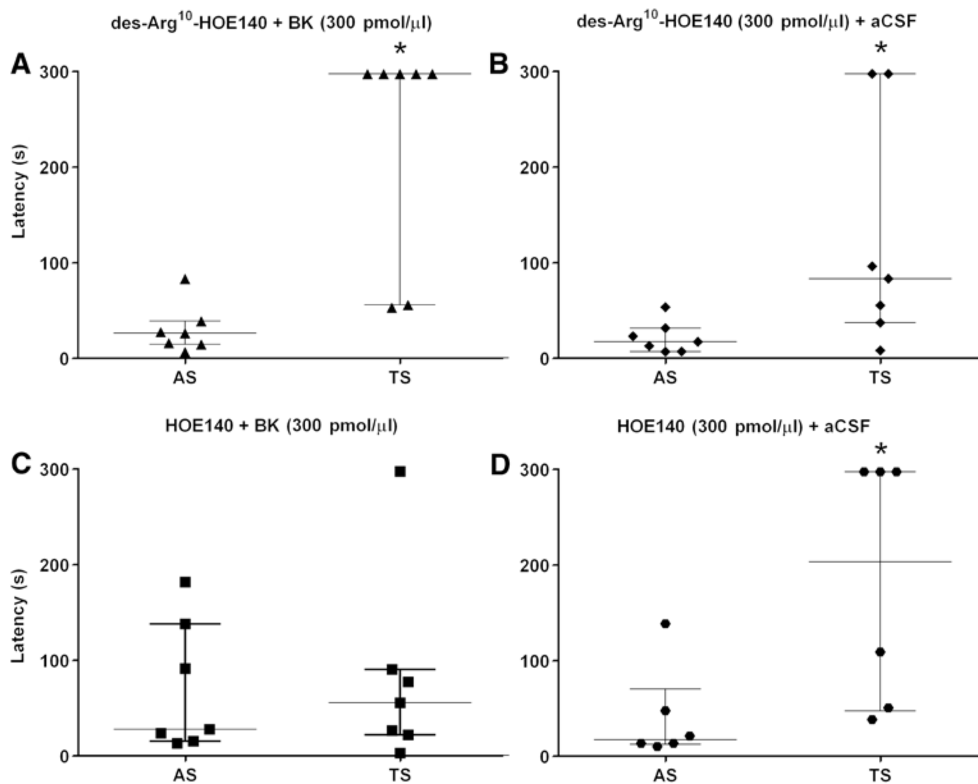

Figure 2: Kinin B1R mediates the effect of BK in the hippocampus.
B1R blockade disrupted the memory impairment caused by the BK injection (n=7, 'A') but not the blockade of the B2R (n=7, 'C'). The injection of B1 (n=7,'B') or B2 (n=6, 'D') antagonists showed no alteration on memory consolidation. Peptides were injected in a concentration of 300 pmol/μl. Data are expressed as median (interquartile range) in seconds and were significant when *$p<0.05$ (Wilcoxon test for paired and non-parametric data). AS, Acquisition session; TS, test session.

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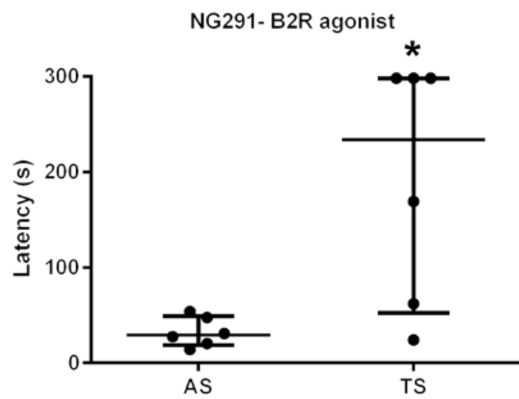

Figure 3: NG291 B2R agonist do not disrupt short-term memory formation.
Bilateral injection of NG291, a biostable B2R agonist (300 pmol/μl, n=6) over the CA1 hippocampal area immediately after the acquisition session (AS), does not disrupt the short-term memory formation. Data are expressed as median (interquartile range) in seconds and were significant when *p<0.05 (Wilcoxon test for paired and non-parametric data). AS, Acquisition session; TS, test session.

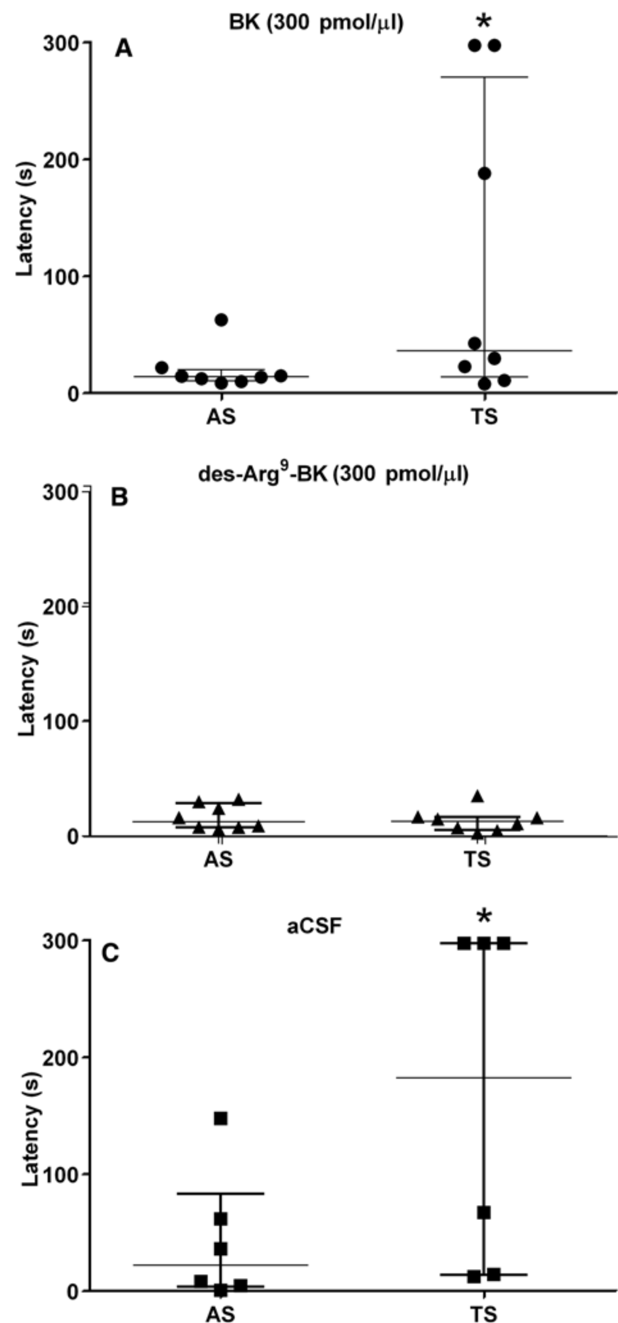

Figure 4: Effect of BK on long-term memory formation.
Bilateral injection of BK (300 pmol/μl, n=8, 'A') or aCSF (n=6, 'C') did not disrupt the long-term memory formation but injection of des-Arg^9-BK did (300 pmol/μl, n=8, 'B'). Long-term memory formation was assessed on an inhibitory avoidance task (footshock intensity, 0.5 mA; interval between sessions, 24 h). Data are expressed as median (interquartile range) in seconds and were significant when *p<0.05 (Wilcoxon test for paired and non-parametric data). AS, Acquisition session; TS, test session.

tested. The bilateral injection of des-Arg^9-BK (300 pmol) was able to significantly block the long-term memory formation [AS=12.6 s (7.8 s/28.8 s) and TS=13.0 s (5.5 s/16.8 s), p>0.05, Figure 4B).

The B1R agonist des-Arg^9-BK leads to short- and long-term memory formation impairment in doses close to physiological concentration

In order to verify if doses close to physiological concentration are able to impair memory formation, decreasing concentrations of des-Arg^9-BK were tested until no memory impairment was observed. Doses ranging from 75 to 0.6 pmol and 37.5 to 4.68 pmol were applied in short and long-term memory evaluation, respectively (Table 1). The lowest doses that caused memory impairment were 2.3 pmol for short-term memory [AS=22.5 s (16.6 s/33.0 s) and TS=27.3 s (8.4 s/60.3 s), p>0.05, Figure 5A and B] and 37.5 pmol for long-term memory [AS=16.3s (13.1 s/50.7 s) and TS=37.4 s (35.3 s/54.3 s), p>0.05, Figure 5C and D].

B1R immunolabelings in the injection site

In order to confirm the presence or not of B1R in the surrounding area of the injection site (CA1 area of the hippocampus) and identify in which cell type the B1R is located, qualitative double immunolabelings against B1R and NeuN (neuronal marker), or GFAP (astrocyte marker), or Iba1 (microglia marker) were performed in brain tissue sections of the antero- posterior level of the implanted

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Table 1: Effect of des-Arg⁹-BK in different concentrations (median with interquartile ranges) on short- and long-term memory.

[ ] pmol	Short-term memory		Long-term memory	
	AS (s)	TS (s)	AS (s)	TS (s)
300	–	–	12.7 (7.8/28.9)	13.1 (5.3/16.8)
75	68.2 (11.6/96.5)	81.7 (12.7/298.0)	–	–
37.5	11.5 (5.2/23.4)	38.1 (7.7/63.1)	16.3 (13.2/50.8)	37.4 (35.4/54.3)
18.7	16.7 (11.1/100.6)	89.0 (21.2/298.0)	12.2 (8.5/23.9)	74.4 (36.9/280.5)[a]
9.3	9.9 (7.0/28.2)	26.1 (14.2/250.0)	18.2 (9.4/34.3)	67.2 (29.8/298.0)[a]
4.6	17.3 (12.5/30.6)	74.5 (20.2/108.0)	17.9 (13.5/25.3)	55.5 (37.1/136.4)[a]
2.3	22.6 (16.6/32.9)	27.3 (8.4/60.3)	–	–
1.17	18.1 (11.1/38.5)	298.0 (53.1/298.0)[a]	–	–
0.58	25.2 (11.1/26.4)	105.4 (31.7/166.7)[a]	–	–

Data were considered significant where [a]$p<0.05$. AS, Acquisition session; TS, test session.

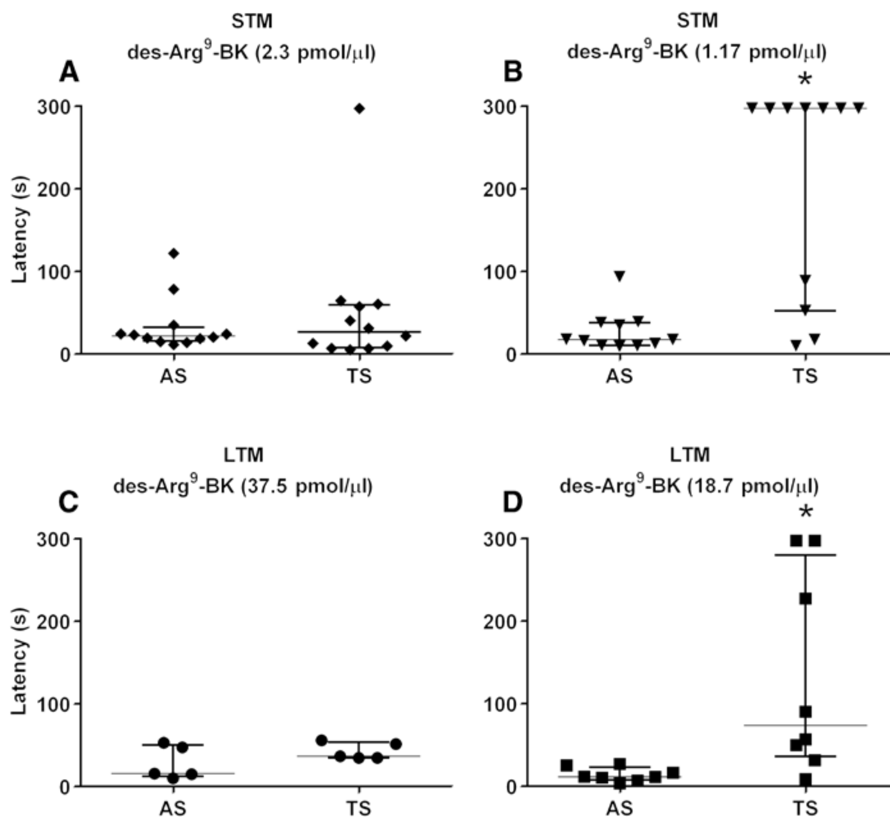

Figure 5: Determination of the lowest doses capable of causing short and long-term memory formation impairment.
The lowest doses of des-Arg⁹-BK leading to memory impairment were 2.3 pmol (n=12) for short-term memory (STM, 'A') and 37.5 pmol (n=5) for long-term memory (LTM, 'C'). Bilateral injection of des-Arg⁹-BK at 1.17 pmol (n=11, 'B') and 18.7 pmol (n=8, 'D') did not disrupt short- or long-term memory formation, respectively. Data are expressed as median (interquartile range) in seconds and were significant when $*p<0.05$ (Wilcoxon test for paired and non-parametric data). AS, Acquisition session; TS, test session.

guide cannula. The contralateral side, with no cannula implantation, of the same slice served as a control. Specific labeling for B1R was observed only in the tissue surrounding the guide cannula (Figure 6) with no labeling in the equivalent position of the contralateral side (Figure 7J–L). Very scarcely NeuN labeling was observed in the region labeled for B1R with no colocalization for these two proteins (Figures 6 and 7A–C). Immunolabeling colocalizing B1R with astrocytes (GFAP) and microglia (Iba1) was prevailing (Figure 7D–I). This data let us suggest that the tissue lesion promoted by the guide cannula induced the expression of B1R prevailing in astrocytes and microglia.

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Discussion

Our data show that the activation of B1R by the BK metabolite des-Arg[9]-BK leads to the impairment of short- and long-term memory consolidation. Most importantly, the B1 agonist dose necessary to impair the short and long-memory consolidation (2.3 and 37.5 pmol, respectively) could be considered close to physiological concentration of the peptide and be reached during tissue injury. Elrod and co-workers (1986) have found 0.6 pmol/g as the concentration of bradykinin in the whole brain, an increase of this concentration being possible after tissue injury or undetectable disease conditions (Elrod et al., 1986). Additionally, in human plasma, values of 170 and 22 pmol/ml of BK and des-Arg[9]-BK, respectively, were found (Simões et al., 2013). The same work describes an increase of about 80% in desArg[9]-BK 45 min after exercise training with no changes in BK concentration. It is important to remark that the dose necessary to impair the long-term memory is 16 times higher than that necessary to impair the short-term memory. Considering that the agonist des-Arg[9]-BK is a BK metabolite, probably the amount of B1 agonist

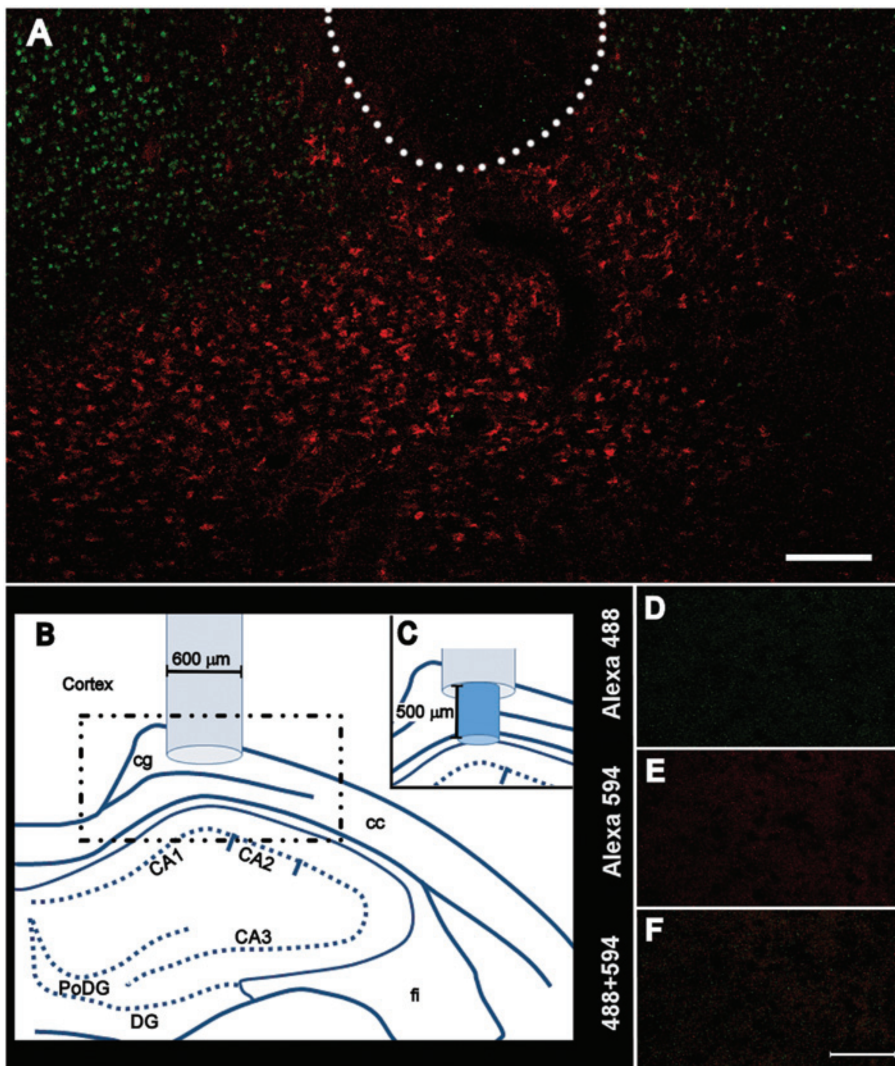

Figure 6: Kinin B1R immunolabeling.
Panel (A) depicts a composition of several images acquired at lower magnification (10×) representing the localization of kinin B1R labeling (red) surrounding the tissue disruption caused by the guide cannula (dotted line) and neurons labeled in green. Panel (B) shows a line draw representing the region pictured in panel (A) (dashed square) and the position of the guide cannula. Panel (C) shows a line draw showing the calculated placement of the needle. Panels (D)–(F) show images from the region below the guide cannula (injured tissue), incubated only with the secondary antibodies and represent the background fluorescence of the analyzed region. cc, Corpus callosum; cg, cingulum; CA1, field CA1 of hippocampus; CA2, field CA2 of hippocampus; CA3, field CA3 of hippocampus; PoDG, polymorphic layer of the dentate gyrus; DG, dentate gyrus; fi, fimbria. Scale bar in panel (A) is 200 µm and scale bar in panel (F) is 50 µm and is applied to panels (D)–(F).

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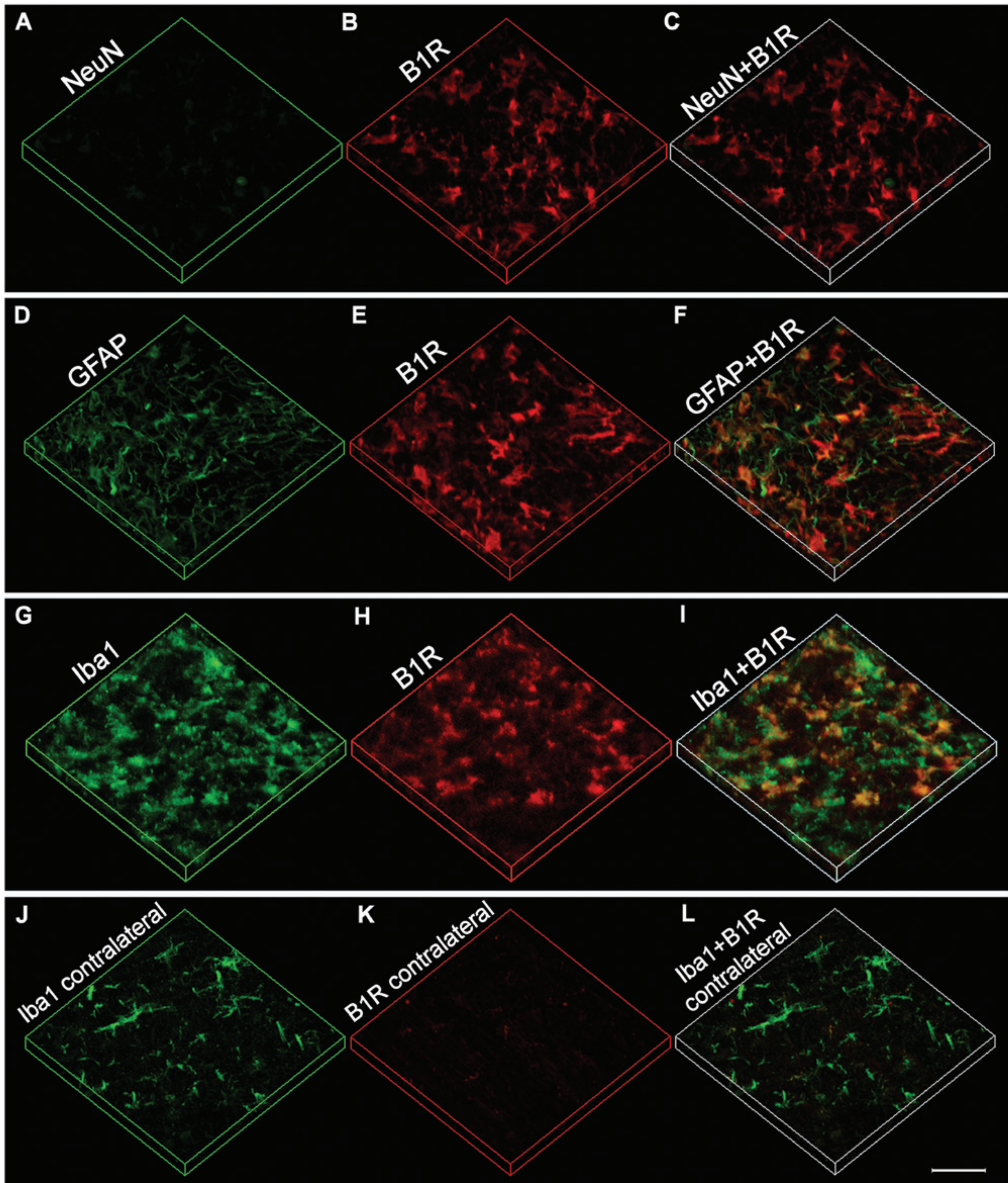

Figure 7: Kinin B1R colocalization.
Representative images showing the double immunofluorescence labeling for B1R (red) and NeuN (A–C), or GFAP (D–F), or Iba1 (G–I). The Figure shows B1R labeling localized in astrocytes (GFAP) and microglia (Iba1) but not in neurons (NeuN). Panels (J)–(L) show the absence of B1R labeling in the equivalent contralateral region, in the same slice, from the image shown on panels (G)–(I). Scale bar in panel (I) is 50 µm.

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generated from the metabolism of the injected amount of BK was sufficient to impair the short-term memory but not the long-term memory.

Regardless of the well-established role of kinins in the peripheral systems, their participation in central nervous system diseases is still unclear (Amaral et al., 2010; Viel and Buck, 2011; Naffah-Mazzacoratti et al., 2014; Caetano et al., 2015). In this way, in an Alzheimer's disease model in rats, our group reported significant increase in kinin concentration in the cerebrospinal fluid, suggesting an enhanced activation of the kallikrein-kinin-system (Iores-Marçal et al., 2006) and disruption in memory consolidation accompanied by an increase in B1R densities in memory related areas, including the CA1 and CA3 hippocampal areas (Viel et al., 2008). Other works concerning autoimmune CNS diseases also suggested a role for B1R, but the literature is not consensual about its exact role. Despite the numerous previous studies showing that targeted interruption of kinin receptor-mediated pathways predominantly exerts anti-inflammatory effects (Dutra et al., 2011; Göbel et al., 2011) one group suggests that activation of kinin B1R limits encephalitogenic T lymphocyte recruitment to the central nervous system (Schulze-Topphoff et al., 2009). It is very important to consider that CNS autoimmune diseases as well as neurodegenerative diseases are chronic inflammatory conditions and our model is more closely related to an acute inflammatory response. In this way, the memory disruption due to B1R activation observed in this work could be more associated to mild traumatic brain injury.

The kallikrein-kinin system has been frequently associated to mild traumatic brain injury (Unterberg et al., 1986; Schilling and Wahl, 1999; Plesnila et al., 2001; Austinat et al., 2009; Albert-Weissenberger et al., 2012). Mild traumatic brain injury (TBI) is one of the major public health issues and is characterized by a traumatically induced physiological disruption of the brain. Many symptoms could be associated with this condition including loss of memory for events immediately before or after the incident, being associated with the disruption of working and short-term memory (Liu et al., 2013; Levin and Diaz-Arrastia, 2015). In relation to time duration, memories are similar in terms of content, but consolidation mechanisms are independently, separated processes (Izquierdo, 2002). Short-term memory lasts <6 h and does not require synthesis of new proteins (Izquierdo et al., 1998; Izquierdo, 2002). Long-term memory takes about 6 h to be consolidated into a more or less stable form (Izquierdo and Medina, 1997) requiring synthesis of new proteins, making memory last for days, months or years (Izquierdo et al., 1998; Izquierdo, 2002; Vianna et al., 2000).

It has already been shown that TBI could lead to an increase of B1R and a decrease of B2R (10–50%) in several brain regions (Ongali et al., 2006), an increase in brain tissue bradykinin, significant up-regulation of B1R mRNA, and enhanced expression of kinin receptor in cells of the traumatic penumbra (Trabold et al., 2010). The same authors show that only B2R are involved in the development of secondary brain damage, brain edema formation, and functional recovery after experimental TBI (Trabold et al., 2010). In an experimental protocol with longer observation of animals submitted to experimental TBI (3 and 7 d), a central participation of B1R was observed. In that work mice lacking B1R showed improved functional outcome after focal closed head injury and the protective effect persisted at later stages after trauma. Similar conditions were obtained when using a pharmacological blocker of B1R, the antagonist R-715, in wild-type animals even when the antagonist was applied 1 h after trauma (Albert-Weissenberger et al., 2012). The blocking of B2R had no effect. Functionally, the inhibition of B1R mitigated axonal damage, apoptosis of neurons, and astrocyte activation, while the impact on post-traumatic inflammation was small (Albert-Weissenberger et al., 2012).

Another important finding of this work is the presence of B1R in astrocyte and microglia, around the guide cannula. No B1R immunolabeling was observed in the equivalent region of the contralateral side of the brain, where no injury occurred. The localization of B1R in astrocytes and microglia, which are related to neuroinflammatory response, allows us to suggest a possible signaling pathway involved in the observed responses to des-Arg^9-BK.

When activated, B1R and B2R couple to G-protein Gαq, Gαi2 and Gαi3 subunits leading to an increase in cytosolic calcium. However, the cell signaling that induces the increase in calcium is different. Whereas B2R utilizes calcium from the endoplasmic reticulum, B1R utilizes extracellular calcium (revised by Prado et al., 2002). Calcium is extremely important for postsynaptic events necessary for activity-dependent neuronal gene expression and synaptic plasticity, events that are essential for learning and memory (Lynch, 2004; Ataei et al., 2015) and, consequently, important for long-term structural and functional stabilization of synaptic connections. However, potentiation or depression of the synapse after synaptic activity depends upon the quantity and the duration of calcium influx (Lee et al., 2009). Situations where increases of calcium go beyond physiological limits can

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be similar to loss of neurons as happens during aging or certain neurodegenerative states (Hidalgo and Núñez, 2007). We showed that the implantation of the cannulas induced a great expression of B1R that were co-localized with microglial cells. It was already shown that in injured tissues microglial migration is dependent on B1R and calcium influx (Ifuku et al., 2007). Microglial activation and neuroinflammation are implicated in cognitive dysfunction as a consequence of different causes like trauma, post-operative situations and drug abuse (Perez-Polo et al., 2015, Wang et al., 2015; Zamberletti et al., 2015). Besides, in injured tissues, activation of B1R leads to increases of neuroinflammatory responses mediated by TNFα, IL-1β and other pro-inflammatory mediators, which also cause cognitive dysfunction (Viel and Buck, 2011).

For this reason, we believe that during tissue injury, the increase in the expression of B1R can greatly increase the entrance of calcium and raises intracellular calcium concentration, microglial migration and neuroinflammation, leading to memory impairment or even neuronal cell death.

Conclusions

The tissue lesion due to the guide cannula led to the increase of B1R and this damage could be considered a type of traumatic brain injury. This data implies a possible participation of B1R in the short-term memory impairment observed in TBI (Yang et al., 2013) as well as in the inflammation, edema and neurodegeneration (Ongali et al., 2006; Trabold et al., 2010; Liu et al., 2013). Our data corroborate recent findings considering B1R an important pharmacological target for the treatment of TBI.

Materials and methods

Animals

A total of 170 male Wistar rats (3–4 months old; FCMSCSP, São Paulo, Brazil) were used. They were housed in groups of five per cage in a temperature-controlled room (21±1°C) subjected to a 12 h light/dark cycle, with food and water *ad libitum*.

All efforts were done to reduce the number of animals and their suffering. The experimental proceedings were performed according to the 'ethics principles for the use of laboratory animals' described by the Brazilian Society of Laboratory Animal Science (SBCAL, Brazil). The experimental protocols were approved by the Animal Ethics Committee from Santa Casa de São Paulo School of Medical Sciences, under the number 009/14.

Stereotaxic brain surgery

The animals were anesthetized (equithesin, 4 ml/kg) and submitted to a stereotaxic brain surgery for implantation of two guide-cannulas placed 0.5 mm above each side of the CA1 area of the hippocampus (coordinates: anterior -2.5 mm; lateral 2.0 mm and vertical 2.5 mm, related to bregma) (Paxinos and Watson, 2007). Five days after the surgery the animals were submitted to the evaluation of cognitive processes.

Evaluation of aversive-related memory

To evaluate this type of memory, an inhibitory avoidance shuttle box was used (Ugo Basile, Varese, Italy). The box has two chambers, a dark and a light one, separated by a guillotine-door. The method is based on the animal's aversion for lighted places and its preference for closed and dark places. On the acquisition session, the animal was placed in the light chamber. After 2 s, the door was opened and the animal was left to explore the box. When the animal entered the dark chamber, the door was closed and the animal received an electrical stimulus of 0.5 mA on the paws, for 2 s. Time spent to get in the dark chamber was recorded. After that, animals were returned to their home cage. Maximum time for animals staying in the box was 5 min. On the test session, 90 min or 24 h later, for short- and long-term memories respectively, the animals were placed in the lighted side of the box again and the time spent to enter the dark chamber was recorded. The greater the avoidance latency, the more efficacious the memory process. In the test sessions, no electric shock was used. Animals were used only once in each test session.

Evaluation of the effect of kinin analogs over memory consolidation

To evaluate the effect of kinin analogs over memory consolidation, bilateral injection of the desired concentration of the peptides started 30 s after the acquisition session in the inhibitory avoidance shuttle box and the animal tested (test session) 90 min or 24 h after de acquisition session. Peptide injections were done using gingival needle (30G) connected to a 10 µl syringe (Hamilton Co., Bonaduz, Switzerland) by a polyethylene catheter (PE10). The gingival needle was 0.5 mm longer than the guide cannula. The syringe was placed in an automated infusion pump adjusted to inject the desired volume in 90 s. When using des-Arg^{10}-HOE140 (B1 antagonist) or HOE140 (B2 antagonist), these antagonists were injected before BK at isomolar concentration (300 pmol/µl). Concentrations of des-Arg^{9}-BK are described in Table 1. To confirm the data obtained with the pharmacological blockade of B1R, the biostable B2R agonist NG291 ([Hyp(3),Thi(5),(N)Chg(7),Thi(8)]-bradykinin), a synthetic B2R-selective agonist with greater *in vitro* and *in vivo* potency and duration of action, was used instead of BK (300 pmol/µl; Savard et al., 2013). The time between antagonist and agonist injections was kept the shortest possible (not longer than 20 s). Injection site was histologically confirmed in all the animals. All the peptides used were purchased from Sigma-Aldrich (St. Louis, USA) except for the B2R agonist NG291 which was synthetized in the laboratory of Dr. Fernand Gobeil (Université de Sherbrooke, Sherbrooke, QC, Canada). All the working solutions were prepared in aCSF.

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B1R immunolabeling procedure

In order to confirm the presence or not of B1R in the surrounding area of the CA1 area of the hippocampus and identify in which cell type the B1R is located, double immunolabelings against B1R and NeuN (neuronal marker), or GFAP (astrocyte marker), or Iba1 (microglia marker) were performed. For this experiment a group of 5 animals (n=5) received a unilateral guide cannula and was not injected with any solution to avoid the excessive damage of the tissue. The non-implanted contralateral side of the brain served as a control. Five days after the stereotaxic surgery the animals were anesthetized with isoflurane and the brain tissue fixed via transcardiac perfusion with 4% paraformaldehyde in 0.1 M phosphate buffered saline (PBS), pH 7.5. The brains were removed and post-fixed in the same fixation solution at 4°C for 1 d and incubated in 30% sucrose in the same fixation solution at 4°C for 1 d. The tissues were embedded in OCT compound (Neg 50, Thermo Sci., Waltham, USA) and rapidly frozen with frosting spray (Cytocool II, Thermo Sci., Waltham, USA). Frozen sections (40 µm) were obtained with a cryostat (-20°C, Micron HM525, Zeiss, Jena, Germany) and collected in PBS. The slices were immunohistochemically processed by free-floating for B1R receptor colocalization with neurons, astrocyte or microglia. The background was controlled incubating the tissue only with secondary antibodies. Briefly, the sections were washed three times (5 min) in PBS. Non-specific sites were blocked by incubating with goat serum (normal serum) for 1 h and incubating with primary antibody against B1 receptor (1:50) (ABR-011 Alomone Labs, Jerusalem, Israel) overnight at 4°C. Then slides were washed three times in PBS for 2 min and incubated with secondary antibody (Alexa Fluor 594, A11012 Life Technologies, Thermo Fisher Scientific, Grand Island, USA) for 2 h at room temperature. For the second labeling, the sections were washed three times (5 min) in PBS and incubated for 3 h with primary antibody against one of the following proteins: NeuN (ABN78, Merck Millipore, Darmstadt, Germany), Iba1 (ab108539, Abcam Cambridge, USA), GFAP (ab16997, Abcam Cambridge, USA). The slices were processed as described for B1R immunolabeling using a secondary antibody conjugated with Alexa Fluor 488 (A11008 Life Technologies, Thermo Fisher Scientific, Grand Island, USA). The slices were mounted on Superfrost slides (Fisher Scientific Co., Pittsburgh, USA) and coverslip with ProLong® Diamond Antifade Mountant (P36961, Life Technologies, Thermo Fisher Scientific, Eugene, USA). Specificity of the anti-B1R was confirmed using excess free antigen (antibody control antigen serum) before incubation with the primary antibody as a negative control. Images were acquired and analyzed using a Zeiss Laser Scanning Microscope (LSM 780, Zeiss, Jena, Germany).

Statistical analysis

Data obtained in the inhibitory avoidance shuttle box were expressed as medians and interquartile ranges. Nonparametric statistics was used because of the heteroscedasticity of the data and because a 300 s ceiling was established.

Comparisons were performed between the acquisition session and the test session in each group using Wilcoxon matched-pairs nonparametric test. Due to significant differences between the acquisition session latencies of the different groups and the aCSF group, the test session latencies were not compared between different groups. All analyses were done using GraphPad Prism 6 (GraphPad Software Inc., La Jolla, USA). Values were considered significant when $p<0.05$.

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