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Ablation of B_1- and B_2-kinin receptors causes cardiac dysfunction through redox-nitroso unbalance

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ABSTRACT

Aims: B_1- and B_2-kinin receptors play a major role in several cardiovascular diseases. Therefore, we aimed to evaluate cardiac functional consequences of B_1- and B_2-kinin receptors ablation, focusing on the cardiac ROS and NO generation.

Main methods: Cardiac contractility, ROS, and NO generation, and protein expression were evaluated in male wild-type (WT), B_1- ($B_1^{-/-}$) and B_2-kinin ($B_2^{-/-}$) knockout mice.

Key findings: Impaired contractility in $B_1^{-/-}$ and $B_2^{-/-}$ hearts was associated with oxidative stress through upregulation of NADPH oxidase $p22^{phox}$ subunit. $B_1^{-/-}$ and $B_2^{-/-}$ hearts presented higher NO and peroxynitrite levels than WT. Despite decreased sarcoplasmic reticulum Ca^{2+} ATPase pump (SERCA2) expression, nitration at tyrosine residues of SERCA2 was markedly higher in $B_1^{-/-}$ and $B_2^{-/-}$ hearts.

Significance: B_1- and B_2-kinin receptors govern ROS generation, while disruption of B_1- and B_2-kinin receptors leads to impaired cardiac dysfunction through excessive tyrosine nitration on the SERCA2 structure.

1. Introduction

B_1 and B_2-kinin receptors are G protein-coupled receptors and critical players in a wide range of signaling pathways. Activation of kinins receptors leads to increasing levels of multiple second messengers, such as calcium (Ca^{2+}), inositol 1, 4, 5-trisphosphate, arachidonic acid, and nitric oxide (NO) [1,2]. Indeed, there is compelling evidence showing that both B_1- and B_2-kinin receptors play a major role in the maintenance of cardiac function, as well as mediating cardioprotective actions [3–6]. In a recent study, our group demonstrated that mice lacking B_1- and B_2-kinin receptors display vascular oxidative stress associated with endothelial dysfunction due to uncoupled nNOS activity [7]. However, there is no study evaluating whether kinin receptors modulate cardiac reactive oxygen species (ROS) production.

In this context, NADPH oxidase emerges as a key enzyme responsible for generating ROS, mainly superoxide ($O_2\cdot^-$), in cardiomyocytes. NADPH oxidase is composed of membrane-bound subunits including, $p22^{phox}$ and $gp91^{phox}$ and cytosolic subunits, such as $p47^{phox}$ and $p67^{phox}$ [8]. Undoubtedly, it has been consistently reported the dysfunctional role of oxidative stress on cardiac excitation-contraction coupling [9,10]. Furthermore, abnormality in the antioxidant system further contributes to an inefficient ROS scavenging capacity, leading to oxidative stress [8]. Thus, oxidative stress is intimately implicated in a variety of cardiac diseases, such as mechanical, electrical, and structural remodeling [11,12]. Additionally, excessive levels of ROS and NO may also affect the activity of a variety of proteins involved in cardiac contractile function through redox-nitroso post-translational modifications [10,13]. Therefore, we aimed to evaluate cardiac functional consequences of B_1- and B_2-kinin receptors ablation, focusing on the cardiac ROS and NO generation.

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2. Materials and methods

2.1. Animals

All experimental procedures were approved by the Federal University of Minas Gerais institutional Animal Care and Use Committee. Transgenic *Bdkrb1* and *Bdkrb2* knockout mice were generated as previously described [14,15], and then backcrossed for 10 generations with C57Bl/6 mice (Taconic, Germantown, NY). Isogenic male C57 black/6, C57 black/6 *Bdkrb1*-knockout mice and C57 black/6 *Bdkrb2*-knockout mice, aged 8–12 weeks (WT, $B_1^{-/-}$ and $B_2^{-/-}$, respectively) (23–28 g), were kindly donated by Prof. João Bosco Pesquero (Biophysics Department of the Federal University of São Paulo, UNIFESP, Brazil). Animals were housed under standard conditions and allowed access to food and water ad libitum.

2.2. Isolated heart preparation

After 15 min of heparin administration, the heart was quickly removed and carefully mounted in an aortic perfusion system, as previously described [4]. Heart was perfused with Krebs-Ringer solution (in mM: 118.4 NaCl, 4.7 KCl, 1.2 KH_2PO_4, 1.2 $MgSO_4$·7 H_2O, 2.5 $CaCl_2$, 11.7 glucose, and 26.5 $NaHCO_3$) on a constant flow (2.3–2.6 mL/min), maintained at constant temperature (37 ± 1 °C) and oxygenation (5% CO_2 and 95% O_2). A force transducer was attached to the apex of the heart to record the contractile force. The diastolic tension of 0.2–0.5 g was applied to the heart. Tension and perfusion pressure were continuously recorded on a computer, through a data-acquisition system (Biopac System, Inc., Santa Barbara, CA, USA). Coronary perfusion pressure was recorded via a sidearm connected to a pressure transducer, placed above the tip of the perfusion aortic cannula. Heart rate (HR) was derived from the changes in cardiac tension.

2.3. Quantitative RT-PCR

To assess gene expression, hearts were snap-frozen in liquid nitrogen and total RNA was isolated using TRIzol Reagent (Invitrogen, Carlsbad, CA). First-strand cDNAs were synthesized using Moloney murine leukemia virus (MML-V) reverse transcriptase (Promega, Madison, WI). Real-time PCR was performed using TaqMan® probes for Bdkrb1 (TaqMan® probe Mm04207315_s1), Bdkrb2 (TaqMan® probe Mm00437788_s1), and Gapdh (TaqMan® probe Mm99999915_g) (Applied Biosystems, Foster City, CA). The cycling conditions for TaqMan® were as follows: 10 min at 95 °C, followed by 45 cycles of 30 s at 95 °C, 30 s at 60 °C and 30 s at 72 °C. The relative quantification of mRNA levels was performed as described in detail in User Bulletin 2 (PerkinElmer, Applied Biosystems, Branchburg, NJ, 1997). Briefly, the target gene amount was normalized to the endogenous reference Gapdh and then related to a calibrator (sample with the lowest expression, namely the controls) using the formula $2-DDCt$. Hence, all data that are expressed as an n-fold difference are related to the expression of matched controls. Analyses were performed with the Applied Biosystems® QuantStudio® 5 Real-Time PCR System (Applied Biosystems, Foster City, CA).

2.4. Measurement of intracellular $O_2\cdot^-$ and NO

Fresh left ventricular cardiomyocytes from adult mice were enzymatically isolated as previously described [4]. For measurements of NO and $O_2\cdot^-$, cardiomyocytes were loaded with fluorescent dyes, 4-amino-5 methylamino-2′,7′-difluorofluorescein (DAF-FM diacetate, Molecular Probes) and dihydroethidium (DHE; Calbiochem), respectively [16,17]. Briefly, cells were loaded with 10 μM of DAF or DHE for 30 min at 37 °C. Cells were next washed for 30 min in Tyrode's solution to remove the excess of dye. Confocal images were obtained using excitation/emission wavelengths according to the manufacturer's recommendation. Images were obtained using a Zeiss LSM 510META confocal microscope located at Centro de Aquisição e Processamento de Imagens (UFMG). Mean values of the whole-cell fluorescence were obtained using ImageJ software (NIH).

2.5. Measurement of superoxide dismutase activity

To evaluate superoxide dismutase (SOD) activity, the heart was homogenized in phosphate-buffered saline (pH 7.4) and centrifuged at 12,000 rpm for 30 min. The supernatant, tetrazolium (1.25 mM), and pyrogallol (100 mL/L) were transferred to a microplate and shaken for 5 min. Subsequently, DMSO was added to the mixture, and absorbance measured at 570 nm [18]. SOD activity was expressed as U/mg protein.

2.6. Western blot and immunoprecipitation

Western blots (WB) were performed as previously described, with minor modifications [19]. Hearts were homogenized in ice-cold lysis buffer enriched with protease and phosphatase inhibitors cocktail. Protein content was quantified according to the Lowry assay. Protein samples (40 μg) were denatured and separated using 7.5% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a nitrocellulose membrane. We used anti-gp91^{phox}, anti-p67^{phox}, anti-p47^{phox}, anti-p22^{phox}, anti-Cu/Zn SOD, anti-3-nitrotyrosine, anti-NCX, anti-SERCA2, and anti-GAPDH antibodies (1:1000; Santa Cruz Biotechnology, CA, USA). The immunoprecipitation (IP) was performed as previously described [7]. Briefly, 500 μg of protein extracts were mixed with 10 μL of goat polyclonal anti-SERCA2 antibody (Santa Cruz Biotechnology, CA, USA), and then incubated at 4 °C for 4 h. Prewashed protein A/G magnetic beads (50 μL, Pure-Proteome™ Magnetic Beads, Merck-Millipore, Germany), were added to the samples, and further incubated for 1 h. For detecting the tyrosine nitration (anti-3-nitrotyrosine antibody) on SERCA2, samples were separated by SDS-PAGE (7.5%), as described above. Immunodetection, WB and IP were carried out using enhanced chemiluminescence (Luminata strong™ - Western HRP substrate, Merck-Millipore, Germany). Digitalized images were analyzed by densitometry using ImageJ software (NIH). Protein levels were expressed as ratios of optical densities. GAPDH was used as a control for any variation in protein loading.

2.7. Statistical analysis

All data were expressed as mean ± SEM. Statistical comparisons were performed using GraphPad Prism 6 (San Diego, CA, USA). Normality and equality of variance were tested by Shapiro-Wilk and Levene test, respectively. Significant differences between groups were determined using one-way ANOVA followed by Bonferroni's post hoc test. Values of $p < 0.05$ were considered to be statistically significant. Fluorescence and blots data were presented in arbitrary units.

3. Results

3.1. Impaired contractility in mice lacking B_1- and B_2-kinin receptors

First, we confirmed the genotypes used in the present study. As shown in Fig. 1A and B, we validated the absence cardiac expression of B_1R or B_2R in $B_1^{-/-}$ or $B_2^{-/-}$ mice, respectively. However, a trend toward downregulation in B_1R expression ($p = 0.0521$) was observed in $B_2^{-/-}$ mice (Fig. 1A). In contrast, B_2R expression was upregulated in $B_1^{-/-}$ mice (Fig. 1B). We next evaluate whether B_1- and B_2-kinin receptors modulate cardiac function, we assessed the cardiac contractility through Langendorff-perfused hearts. As shown in the Fig. 1C, the systolic tension was significantly impaired in $B_1^{-/-}$ and $B_2^{-/-}$ hearts compared with WT, whereas no significant changes were observed in the diastolic tension (Fig. 1D) and heart rate (Fig. 1E). Interestingly, the coronary perfusion pressure in $B_1^{-/-}$ and $B_2^{-/-}$ hearts was

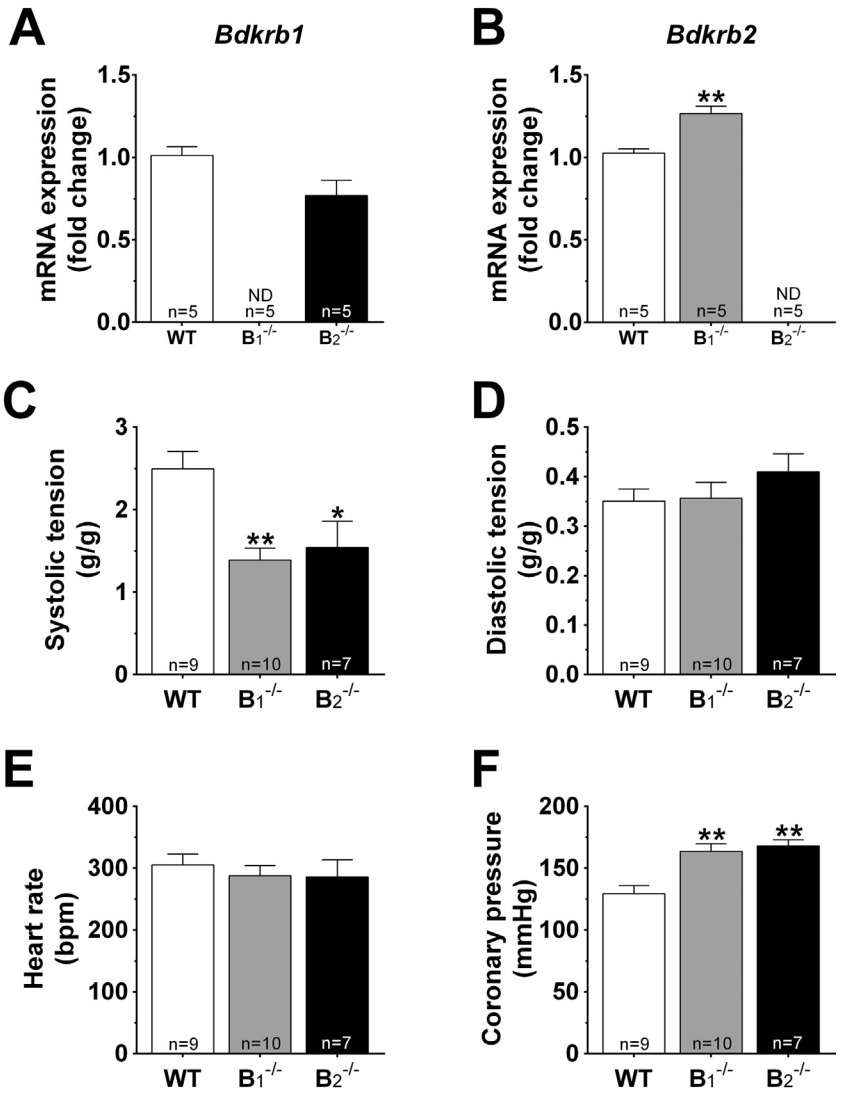

Fig. 1. Impaired contractility in mice lacking B_1- and B_2-kinin receptors. mRNA expression of B_1R (A) and B_1R (B). ND, not detected. C, systolic tension; D, diastolic tension; E, heart rate; F, coronary pressure. n = number of animals. $^*p < 0.05$ and $^{**}p < 0.01$ compared to WT mice.

significantly higher than WT hearts (Fig. 1F).

3.2. B_1- and B_2-kinin receptors modules redox-nitroso balance in the heart

We then investigated whether B_1- and B_2-kinin receptors are involved in the cellular synthesis of ROS. As shown in the Fig. 2A, $B_1^{-/-}$ and $B_2^{-/-}$ mice showed a marked upregulation of $p22^{phox}$ expression compared to WT, while other NADPH oxidase subunits remained unchanged. Accordingly, isolated cardiomyocytes from $B_1^{-/-}$ or $B_2^{-/-}$ mice showed a significant increase in $O_2\cdot^-$ levels (40% and 27%, respectively) compared to WT (Fig. 2B). Furthermore, we found a significant reduction of Cu/Zn SOD protein expression in $B_1^{-/-}$ and $B_2^{-/-}$ hearts compared to WT (Fig. 2C). In accordance, SOD activity was also markedly reduced in $B_1^{-/-}$ (80%) and $B_2^{-/-}$ (70%) hearts compared to WT (Fig. 2D).

Additionally, we demonstrated increased NO levels in cardiomyocytes from $B_1^{-/-}$ and $B_2^{-/-}$ mice (Fig. 3A). To determine whether the augmented $O_2\cdot^-$ and NO production lead to increased peroxynitrite ($ONOO^-$) levels, we assayed the 3-nitrotyrosine levels, an end product formed by NO and $O_2\cdot^-$ reaction. Interestingly, hearts samples obtained from $B_1^{-/-}$ and $B_2^{-/-}$ mice showed higher total 3-nitrotyrosine content in a wide range of molecular weight (from 10 kDa to 250 kDa) than WT (Fig. 3B). Altogether, our results suggest that B_1- and B_2-kinin receptors play a critical role in the cardiac control of redox-nitroso balance.

3.3. Genetic ablation of B_1- or B_2-kinin receptors leads to changes in proteins involved in cardiac contractility and participate in the tyrosine nitration on SERCA2

To assess whether B_1- and B_2-kinin receptors regulate proteins related to the Ca^{2+} handling, we next evaluated whether mice lacking B_1- or B_2-kinin receptors mediate changes in expression of NCX or SERCA2. As shown in the Fig. 4A, hearts from $B_1^{-/-}$ and $B_2^{-/-}$ mice presented a significant upregulation in the NCX expression, associated with a downregulation in SERCA2 levels compared to WT. To determine whether kinin receptors mediate redox-nitroso post-translational modifications in proteins related to the cardiac contractility, we assessed whether SERCA2 is a specific target of $ONOO^-$. We then immunoprecipitated SERCA2 protein using specific antibody and tyrosine nitration assessed using an anti-3-nitrotyrosine antibody. Accordingly, the levels of 3-nitrotyrosine in the structure of SERCA2 were markedly higher in hearts from $B_1^{-/-}$ and $B_2^{-/-}$ mice (3.5 and 2-fold respectively) than WT (Fig. 4B).

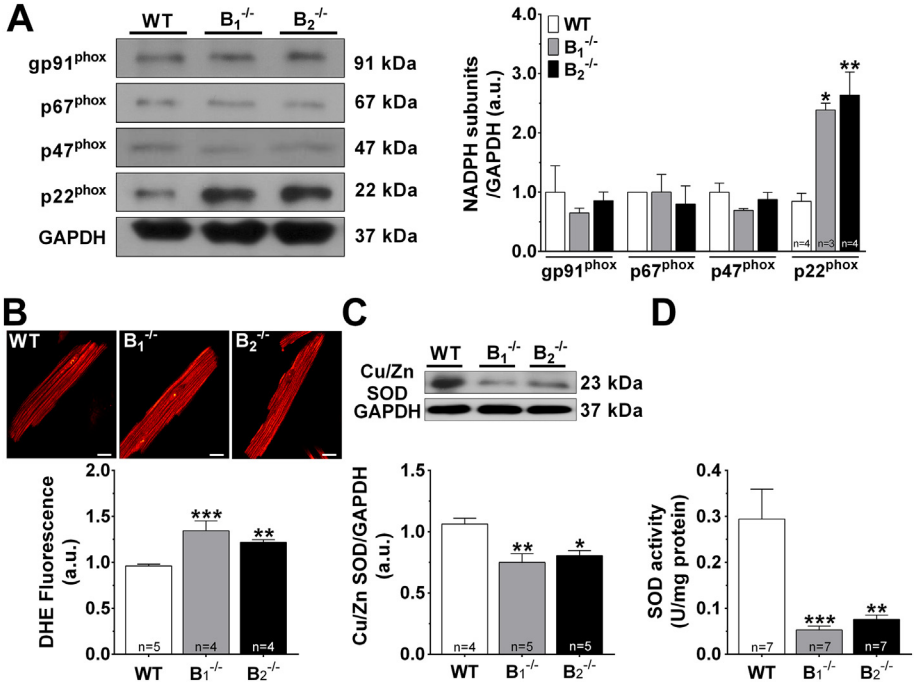

Fig. 2. B_1- and B_2-kinin receptors module ROS generation through NADPH oxidase in the heart. A, Representative western blots of NADPH oxidase subunits (left) and quantitative analysis (right); B, representative DHE images (top, scale bar = 10 μm) and quantitative analysis (bottom); C, representative western blot of Cu/Zn SOD (top) and quantitative analysis (bottom); D, SOD activity. n = number of animals. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ compared to WT mice.

4. Discussion

In the present study, we provide evidence that mice lacking B_1- and B_2-kinin receptors display a remarkable impairment of cardiac contractility associated with downstream changes on SERCA2 through redox-nitroso post-translational modifications. It has been consistently demonstrated that oxidative stress modulates components related to the excitation-contraction coupling in ventricular myocytes [10,13,20]. However, taking into account that exacerbated ROS generation plays a pathological role in the heart, the mechanisms underlying the regulation of ROS production through kinin receptors remained poorly understood until now.

Initially, we confirmed the genetic ablation of the target gene. Indeed, previous studies showed a compensatory upregulation of the remaining kinin receptor in animals with genetic deletion of either B1 or B2 kinin receptor [21–23]. However, we did not find an increase in the expression of B_1R in $B_2^{-/-}$ mice, while B_2R was upregulated in $B_1^{-/-}$ mice. Although unexpected, we hypothesize that the difference in the genetic background used in the present study might be a determining factor in $B_2^{-/-}$ mice. Here, C57BL/6 J strain served as the reference control of genetic background, while previous studies used B6129SvF2 mice [22,23]. Then, we validated previous studies supporting cardiac dysfunction in mice lacking B_1- and B_2-kinin receptors. Recently, our group has demonstrated that B_1- and B_2-kinin receptors form complex heteromers with nNOS and eNOS in vascular cells [7]. Moreover, we showed that $B_1^{-/-}$ and $B_2^{-/-}$ mice display vascular endothelial dysfunction associated with oxidative stress and reduced endothelium-dependent vasodilation through uncoupled nNOS activity [7]. Thus, supporting the high coronary perfusion pressure in $B_1^{-/-}$ and $B_2^{-/-}$ mice.

The present study further showed that B_1- or B_2-kinin receptors govern intracellular mechanisms that control redox homeostasis, here identified by upregulation of the membrane-bound NADPH oxidase $p22^{phox}$ subunit accompanied by increased $O_2^{\cdot -}$ generation. A reasonable explanation for the oxidative stress found in $B_1^{-/-}$ and $B_2^{-/-}$ mice might be a possible unbalance between renin-angiotensin and kallikrein-kinin systems, as previously described [24–26]. Indeed, overactivation of the renin-angiotensin system is commonly associated with a vast number of cardiovascular disorders through NADPH oxidase-dependent mechanisms, such as cardiac hypertrophy and myocardial fibrosis [27–29]. Interestingly, $B_1^{-/-}$ mice do not show cardiac hypertrophy [4,30,31]. Although previous studies have shown that $B_2^{-/-}$ mice display cardiac hypertrophy [31–33], these findings have not been consistently reported [30,34]. These discrepancies may be the result of differences in the gender, age, genetic background or method adopted to evaluate cardiac hypertrophy. Thus, great caution should be taken when interpreting data from this genetic approach, since a large number of off-target genes is profoundly affected by genetic ablation of

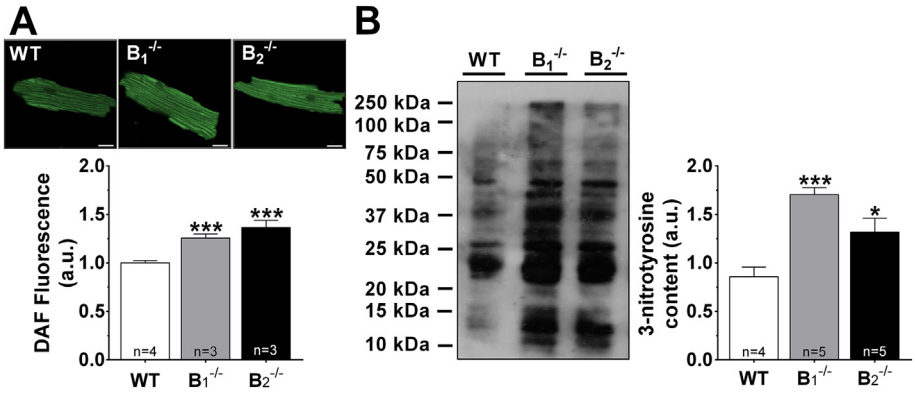

Fig. 3. B_1- and B_2-kinin receptors module redox-nitroso balance in the heart. A, Representative DAF images (top, scale bar = 10 μm) and quantitative analysis (bottom); B, representative western blots of 3-nitrotyrosine (left) and quantitative analysis (right). n = number of animals. $^{*}p < 0.05$ and $^{***}p < 0.001$ compared to WT mice.

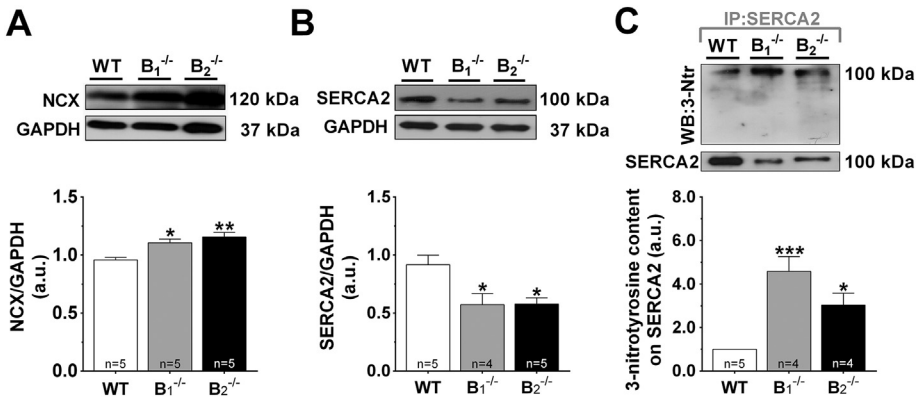

Fig. 4. Genetic ablation of B_1- or B_2-kinin receptors leads to changes in proteins involved in cardiac contractility and participate in tyrosine nitration on SERCA2. A, Representative western blots NCX (top) and quantitative analysis (bottom); B, representative western blots SERCA2 (top) and quantitative analysis (bottom); C, representative immunoprecipitation (IP) of SERCA2 followed by western blot (WB) against 3-nitrotyrosine and SERCA2 (top) and quantitative analysis (bottom). n = number of animals. $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$ compared to WT mice.

kinin receptors, including angiotensin-converting enzyme and angiotensin receptor type 1 [34–36].

We further demonstrated that enhanced NO levels in $B_1^{-/-}$ and $B_2^{-/-}$ ventricular myocytes are associated with higher 3-nitrotyrosine contents than in WT mice, which indicate an unbalance in redox-nitroso status. Downstream, increased $ONOO^-$ generation may lead to specific post-translational modifications on a wide variety of proteins involved in the Ca^{2+} handling and cardiac contractility, such as Ca^{2+} ATPases (including SERCA2), $Na_v1.5$ and $Ca_v1.2$ [13,37]. Along with enhanced NADPH oxidase activity, the lower ROS scavenger property also contributes to ventricular dysfunction due to abnormalities in nitrotyrosine levels on proteins involved in the Ca^{2+} handling. Therefore, we hypothesized that disruption of B_1- and B_2-kinin receptors might affect the cardiac contractility through a redox-nitroso mechanism. Thus, this oxidative environment could favor the appearance of cardiac pathologies, in which abnormalities in the Ca^{2+} signaling and impaired cardiac contractility are recurrent themes [11,38]. Moreover, it is known the dual protective/deleterious role of NO [39,40], while its highly compartmentalized production within cardiomyocytes is related to opposite effects on cardiomyocytes contractility [41,42]. However, whether these micro-nanodomains are also disrupted in $B_1^{-/-}$ and $B_2^{-/-}$ ventricular myocytes further studies are certainly needed.

Indeed, oxidative stress may alter gene expression related to sarcoplasmic Ca^{2+} homeostasis, as shown in failing human hearts and animal models of heart failure [13,43,44]. Here, the molecular remodeling in the protein expression of NCX and SERCA2 in hearts from $B_1^{-/-}$ and $B_2^{-/-}$ mice are strikingly similar as found in humans failing hearts [45–47]. However, although the evidence that cardiomyocyte exposed to a modest oxidative stress leads to activation of NCX by redox modification at cysteine residues [10,48,49], to date, there is no study demonstrating available tyrosine residues on NCX for nitration. On the other hand, SERCA2 contains 18 tyrosine residues and can undergo tyrosine nitration, of which only 2 are highly reactive and essential for its activity [50–52]. Accordingly, our data revealed that disruption of kinins receptors increases oxidative post-translational modifications, leading to nitration of tyrosine residues on the SERCA2 structure. Additionally, increased levels of SERCA2 nitration was previously reported in patients with idiopathic dilated cardiomyopathy [53].

Interestingly, senescent hearts show marked oxidative stress accompanied by nitrotyrosine accumulation and decreased SERCA activity [54,55]. Moreover, a previous study showed changes in the abundance of kinin receptors during aging, presenting an increase in the expression of B_1-kinin receptor, whereas B_2-kinin receptor was significantly reduced in elderly rats [56]. Therefore, the interplay between kinin receptors expression and redox-nitroso balance during the aging process emerge as potential mechanisms in the regulation of cardiac dysfunction during the aging. In line with these findings, old rats present augmented nitration at 294 and 295 tyrosine residues, causing decreased Ca^{2+} reuptake through inhibition of ATPase activity [51,52,57]. Thus, these studies indicate that SERCA2 nitration at tyrosine residues are sub-molecular targets of a redox-nitroso signaling pathway in the heart.

A potential mechanism not explored here is the fact that both kinin receptors are functionally coupled with an array of different key proteins [7,58–61]. Therefore, disruption of these macromolecular protein-protein interactions that are conformationally arranged to play a physiological role might be involved in pathological phenotype shown in $B_1^{-/-}$ and $B_2^{-/-}$ mice.

In summary, we provide mechanistic evidence that B_1- and B_2-kinin receptors govern ROS generation and balance of redox-nitroso signaling pathways. Ultimately, our results suggest that excessive tyrosine nitration on SERCA2 structure might be involved in the impaired cardiac dysfunction found in $B_1^{-/-}$ and $B_2^{-/-}$ mice.

Conflict of interest statement

The authors report no conflict of interest.

Author contributions

TRRM participated in all steps of this study and drafted the manuscript. RMS, ICGJ, GKMA, VAF, LMS, LSAC and AALG data curation. SG, JBP, JLP, AJF, and SLS handled funding, conceived and designed the research. All authors made critical revision of the manuscript.

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