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Store-operated calcium entry induced by activation of Gq-coupled alpha1B adrenergic receptor in human osteoblast

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ABSTRACT

Recent studies have revealed that the sympathetic nervous system is involved in bone metabolism. We previously reported that noradrenaline (NA) suppressed K^+ currents via Gi/o protein-coupled alpha$_{1B}$-adrenergic receptor (α_{1B}-AR) in human osteoblast SaM-1 cells. Additionally, it has been demonstrated that the intracellular Ca^{2+} level ($[Ca^{2+}]_i$) was increased by NA via α_{1B}-AR. In this study, we investigated the signal pathway of NA-induced $[Ca^{2+}]_i$ elevation by using Ca^{2+} fluorescence imaging in SaM-1 cells. NA-induced $[Ca^{2+}]_i$ elevation was suppressed by pretreatment with a PLC inhibitor, U73122. This suggested that the $[Ca^{2+}]_i$ elevation was mediated by Gq protein-coupled α_{1B}-AR. On the other hand, NA-induced $[Ca^{2+}]_i$ elevation was completely abolished in Ca^{2+}-free solution, which suggested that Ca^{2+} influx is the predominant pathway of NA-induced $[Ca^{2+}]_i$ elevation. Although the inhibition of K^+ channel by NA caused membrane depolarization, the $[Ca^{2+}]_i$ elevation was not affected by voltage-dependent Ca^{2+} channel blockers, nifedipine and mibefradil. Meanwhile, NA-induced $[Ca^{2+}]_i$ elevation was abolished following activation of store-operated Ca^{2+} channel by thapsigargin. Additionally, the $[Ca^{2+}]_i$ elevation was suppressed by store-operated channel inhibitors, 2-APB, flufenamate, $GdCl_3$ and $LaCl_3$. These results suggest that Ca^{2+} influx through store-operated Ca^{2+} channels plays a critical role in the signal transduction pathway of Gq protein-coupled α_{1B}-AR in human osteoblasts.

1. Introduction

Bones are constantly remodeled throughout life. Bone homeostasis is maintained by a balance between the activities of bone-forming osteoblasts and bone-resorbing osteoclasts. In recent years, many studies have demonstrated that the sympathetic nervous system is involved in bone metabolism [1–5]. Osteoporosis can be induced by continuously high sympathetic tone, which is recovered from by using β-adrenergic receptor (β-AR) blocker [6,7]. Previous studies, including ours, showed that mRNAs of α- and β-ARs were expressed in human osteoblasts [1,8,9]. Although a number of studies have suggested that up-regulation of osteoclastogenesis and osteoclastic activity via β-AR caused enhancement of bone resorption [3,10,11], the physiological role of α-ARs in bone metabolism has been less well studied.

We previously reported that noradrenaline (NA) increased cell proliferation by suppressing K^+ channels via Gi/o-coupled α_{1B}-AR in human osteoblast SaM-1 cells. On the other hand, application of NA also increased the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) via Gq protein-coupled α_{1B}-AR [12]. In general, NA-induced $[Ca^{2+}]_i$ elevation is mediated by Ca^{2+} release from endoplasmic reticulum via the Gq/phosphoinositide-phospholipase C (Gq/PI-PLC) pathway. However, recent studies have demonstrated that Ca^{2+} influx through Ca^{2+}-permeable channels and Na^+/Ca^{2+} exchanger is involved in α_1-AR-mediated $[Ca^{2+}]_i$ elevation in several tissues [13–19]. The molecular component of Ca^{2+} influx and its importance in Ca^{2+} signaling differ among tissues.

In this study, we investigated the signal transduction pathway of NA-induced $[Ca^{2+}]_i$ elevation in human osteoblast SaM-1 cells. We observed that α_1-AR-mediated $[Ca^{2+}]_i$ elevation was suppressed not only by a PLC inhibitor, U73122, but also by removing extracellular Ca^{2+}. Interestingly, the response to NA was completely abolished in Ca^{2+}-free extracellular solution. This suggested that Ca^{2+} influx plays a predominant role in α_1-AR-mediated Ca^{2+} signaling. Additionally, NA-induced $[Ca^{2+}]_i$ elevation was inhibited by pretreatment with either thapsigargin or store-operated Ca^{2+} channel inhibitors. These results suggested that activation of Gq

Abbreviations: 2-APB, 2-aminoethyl diphenylborate; AR, adrenergic receptor; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; MG-63, human osteosarcoma-derived osteoblast-like cell line; NA, noradrenaline; PDL, population doubling level; PI-PLC, phosphoinositide-phospholipase C; PLC, phospholipase C; SaM-1, human periosteum-derived osteoblastic cells.

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protein-coupled-α_1-AR induces $[Ca^{2+}]_i$ elevation mainly via store-operated Ca^{2+} channels in human osteoblasts.

2. Materials and methods

2.1. Cell culture

The human osteoblasts used in this study, SaM-1 cells, were provided by Dr. Koshihara, who prepared them with informed consent from an explant of ulnar periosteum tissue from a 20-year-old male patient who underwent curative surgery [20]. These cells have a mitotic lifespan of 34 population doubling levels (PDLs), and we used them at a PDL of 22–24 for our experiments. We confirmed that the cells were capable of calcifying at this level [21]. The cells were cultured in alpha-modified minimum essential medium (Invitrogen, Carlsbad, CA, USA) containing 10% fetal bovine serum (Moregate Biotech, Bulimba, Australia) and 60 μg/ml kanamycin at 37 °C in 95% humidified air containing 5% CO_2. The growth media were renewed every 2 days. For optical measurements of $[Ca^{2+}]_i$, they were seeded on a glass cover slip 1–2 days before the experiments.

2.2. Optical measurements of $[Ca^{2+}]_i$

We used Cal-520 AM, a highly sensitive Ca^{2+} fluorescent dye, for optical measurements of $[Ca^{2+}]_i$. SaM-1 cells were loaded with Cal-520 AM (2.5 μM) for 30 min and washed three times with extracellular solution, which contained 124 mM NaCl, 3 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 14 mM D-glucose and 10 mM HEPES (pH adjusted to 7.4 with NaOH), just before use. Then, the glass cover slip was transferred to a superfusion chamber on the stage of a confocal laser scanning microscope (LSM710, Carl Zeiss, Hallbergmoos, Germany). Cells were superfused with extracellular solution at a rate of 2 ml/min. The fluorescence was recorded every 2 s at room temperature at an excitation wavelength of 488 nm and the data were analyzed using ZEN 2009 software (Carl Zeiss). Stock solutions of drugs were prepared and diluted 1000-fold into extracellular solution just before use. Unless otherwise noted, drugs were bath-applied and fluorescence was recorded from the cells that showed a response to repeated application of NA.

2.3. Chemicals

L-Noradrenaline, prazosin, an α_1-AR selective antagonist, U73122, a PLC inhibitor, nifedipine, an L-type voltage-dependent Ca^{2+} channel blocker, mibefradil, a T-type voltage-dependent Ca^{2+} channel blocker, 2-aminoethyl diphenylborate (2-APB), flufenamate, $GdCl_3$ and $LaCl_3$ were purchased from Sigma Aldrich (St. Louis, MO, USA). KB-R-7943, a Na^+/Ca^{2+} exchanger reverse mode inhibitor, was purchased from Tocris Biosciences (Bristol, UK). Thapsigargin was purchased from Wako (Osaka, Japan). Cal-520 AM was purchased from COSMO BIO (Tokyo, Japan). Cal-520 AM, U73122, nifedipine, KB-R-7943, thapsigargin, 2-APB and flufenamate were dissolved in dimethyl sulfoxide. All other chemicals used were of reagent grade.

2.4. Statistical analysis

All data are expressed as mean ± SEM. In the optical measurements of $[Ca^{2+}]_i$, fluorescence intensity recorded from each cell was used for analysis. The data were recorded from more than 3 independent experiments. The comparison of NA-induced $[Ca^{2+}]_i$ elevation before and after drug treatment was carried out with the paired *t*-test. For multiple comparisons, the two-tailed *t*-test combined with Bonferroni's correction following one-way analysis of variance was used. Differences with p values <0.05 were considered significant.

3. Results

3.1. Involvement of Ca^{2+} influx in NA-induced $[Ca^{2+}]_i$ elevation

Consistent with previous studies, bath application of NA dose-dependently increased $[Ca^{2+}]_i$ and the response was significantly inhibited by prazosin and a PLC inhibitor, U73122 (Fig. 1A–C). To examine whether Ca^{2+} influx was involved in the NA-induced $[Ca^{2+}]_i$ elevation, we used Ca^{2+}-free extracellular solution, which contained 5 mM EGTA instead of 2 mM $CaCl_2$. In the Ca^{2+}-free extracellular solution, NA had no effect on Ca^{2+} fluorescence (Fig. 1D). Additionally, we examined the effects of NA on $[Ca^{2+}]_i$ elevation induced by switching perfusate from Ca^{2+}-free solution to normal solution. Pretreatment with NA significantly increased the Ca^{2+} influx from extracellular fluid (Fig. 1E).

3.2. Elucidation of Ca^{2+}-influx pathway

Previous studies have demonstrated that activation of α_1-AR can induce Ca^{2+} influx via several kinds of pathway, including voltage-dependent Ca^{2+} channel, reverse mode of Na^+/Ca^{2+} exchanger, store-operated Ca^{2+} channel and receptor-operated Ca^{2+} channel in several tissues [13–19].

First, we examined the involvement of voltage-dependent Ca^{2+} channels. The expression of L-type and T-type voltage-dependent Ca^{2+} channel families was previously reported in osteoblasts [22,23]. However, neither nifedipine, an L-type voltage-dependent Ca^{2+} channel blocker, nor mibefradil, a T-type voltage-dependent Ca^{2+} channel blocker, inhibited NA-induced $[Ca^{2+}]_i$ elevation (Fig. 2A, B and D).

In general, Na^+/Ca^{2+} exchanger plays an important role in Ca^{2+} homeostasis by pumping Ca^{2+} out of the cytosol. On the other hand, it was suggested that local accumulation of Na^+ drove Na^+/Ca^{2+} exchanger in reverse mode, and the mechanism was involved in α_1-AR-mediated $[Ca^{2+}]_i$ elevation [16]. However, Na^+/Ca^{2+} exchanger inhibitor, KB-R-7943, did not suppress, but rather enhanced NA-induced $[Ca^{2+}]_i$ elevation in SaM-1 cells (Fig. 2C and D).

Next, we examined the involvement of store-operated and receptor-operated Ca^{2+} channels. Passive depletion of endoplasmic reticulum Ca^{2+} store by a sarco/endoplasmic reticulum Ca^{2+}-ATPase inhibitor, thapsigargin, activated store-operated Ca^{2+} channels. Bath application of NA had no effect on Ca^{2+} fluorescence following treatment with thapsigargin (Fig. 3A). This result suggested that NA-induced Ca^{2+} influx was mediated through store-operated Ca^{2+} channels, but not through receptor-operated Ca^{2+} channels. Additionally, we examined the effects of store-operated channel inhibitors, 2-APB, flufenamate, $GdCl_3$ and $LaCl_3$, on NA-induced $[Ca^{2+}]_i$ elevation. In the presence of any of these inhibitors, NA-induced $[Ca^{2+}]_i$ elevation was significantly suppressed (Fig. 3B–E).

4. Discussion

Our previous study suggested that α_{1B}-AR can be coupled to both Gq-protein and Gi/o-protein, and NA increased $[Ca^{2+}]_i$ via the Gq/PI-PLC pathway and also inhibited K^+ current via the Gi/o/Gβγ pathway in human osteoblast SaM-1 cells [12,24]. In this study, NA-induced $[Ca^{2+}]_i$ elevation was significantly suppressed by a PLC inhibitor, U73122. This result is in agreement with our conventional understanding. On the other hand, NA-induced $[Ca^{2+}]_i$ elevation was completely abolished in Ca^{2+}-free extracellular fluid. Additionally, pretreatment with NA significantly

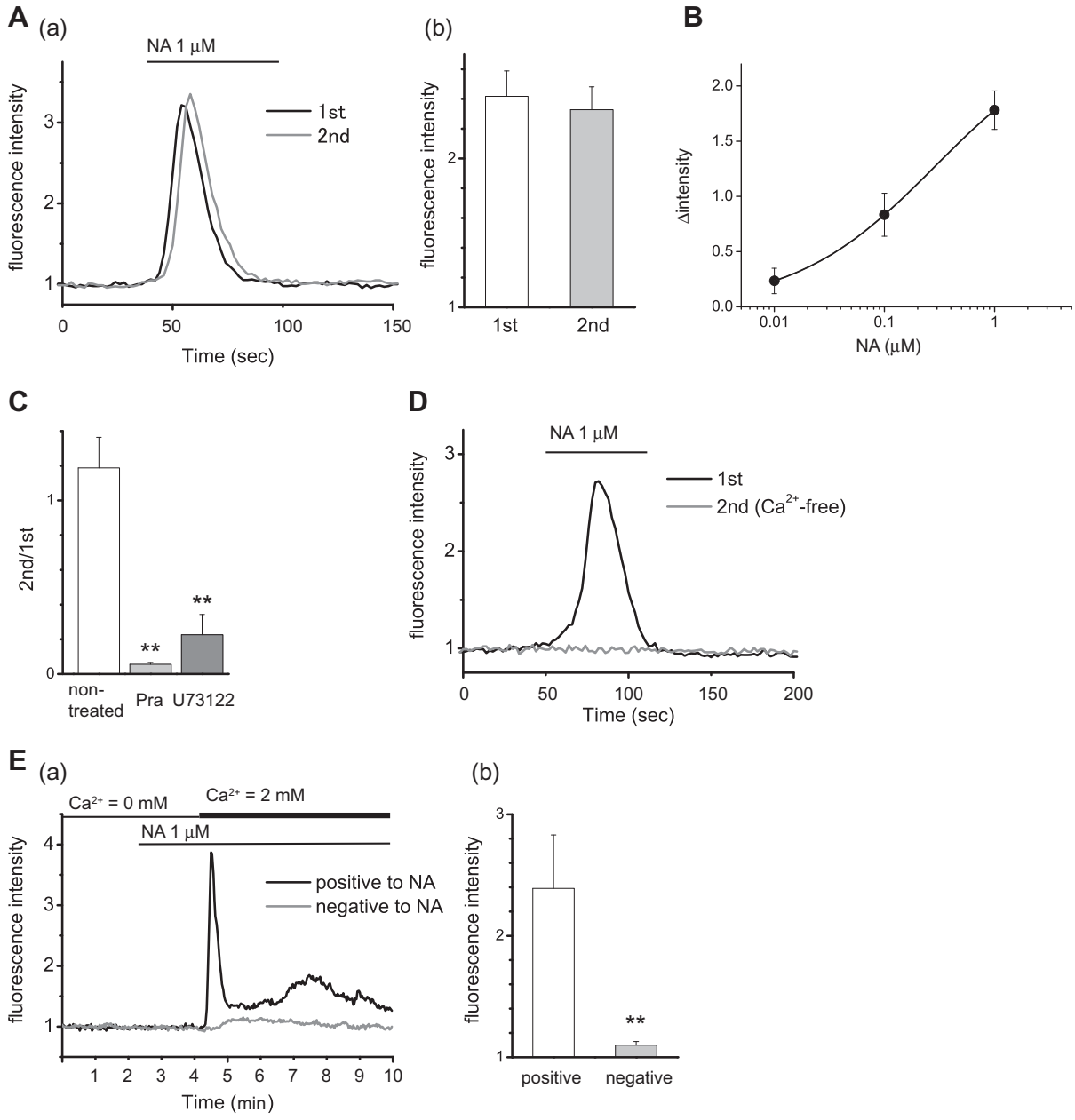

Fig. 1. Involvement of Ca^{2+} influx in NA-induced $[Ca^{2+}]_i$ elevation. (A) NA-induced $[Ca^{2+}]_i$ elevation. (a) Representative traces of $[Ca^{2+}]_i$ elevation induced by repeated application of NA in SaM-1 cells. (b) The average peak intensity in 1st and 2nd treatments ($n = 21$). (B) The dose–response relationship of the effect of NA. (C) The effect of NA in the presence of an α_1-AR blocker, prazosin, and that in the presence of a PLC inhibitor, U73122 ($n = 13$ and 12, respectively). (D) Representative traces of the response to NA in the presence of extracellular Ca^{2+} (1st treatment) and in the absence of extracellular Ca^{2+} (2nd treatment) in the extracellular fluid. (E) The Ca^{2+} influx from extracellular fluid induced by switching the perfusate from Ca^{2+}-free to normal (Ca^{2+}-containing). (a) Representative traces recorded from cells that showed positive (black line) and negative (gray line) responses in preliminary treatment with NA. (b) Summary of the effects of NA on the response to the addition of Ca^{2+} into extracellular fluid (positive to NA, $n = 5$; negative to NA, $n = 13$). Values are shown as the mean ± SEM. $^{**}p < 0.01$ compared with the control.

increased Ca^{2+} influx induced by switching the perfusate from Ca^{2+}-free solution to Ca^{2+}-containing solution. These results indicate that Ca^{2+} influx from extracellular fluid is the predominant pathway of NA-induced $[Ca^{2+}]_i$ elevation.

Recent studies have demonstrated that Ca^{2+} influx is involved in α_1-AR-mediated $[Ca^{2+}]_i$ elevation in several tissues, and L-type and T-type voltage-dependent Ca^{2+} channels, Na^+/Ca^{2+} exchanger, store-operated Ca^{2+} channel and receptor-operated Ca^{2+} channel are thought to be the relevant pathways [13–19]. In our previous study, Gi/o protein-coupled α_{1B}-AR-mediated K^+ channel inhibition was shown to cause membrane depolarization [24], which was thought to activate voltage-dependent Ca^{2+} channels. However, in the present study, both an L-type voltage-dependent Ca^{2+} channel inhibitor, nifedipine, and a T-type voltage-dependent Ca^{2+} channel inhibitor, mibefradil, had no effect on NA-induced $[Ca^{2+}]_i$ elevation. Therefore, Gi/o protein-coupled α_{1B}-AR-mediated K^+ channel inhibition and voltage-dependent Ca^{2+} channels did not seem to be involved in NA-induced $[Ca^{2+}]_i$ elevation. Additionally, the effect of NA was significantly increased by KB-R-7943, a Na^+/Ca^{2+} exchanger inhibitor. It is reported that KB-R-7943 inhibited not only reverse mode but also forward mode of Na^+/Ca^{2+} exchanger at the concentration used here [25]. Therefore, it is suggested that Na^+/Ca^{2+} exchange operated predominantly in forward mode to return $[Ca^{2+}]_i$ elevated by NA to its resting state. On the other

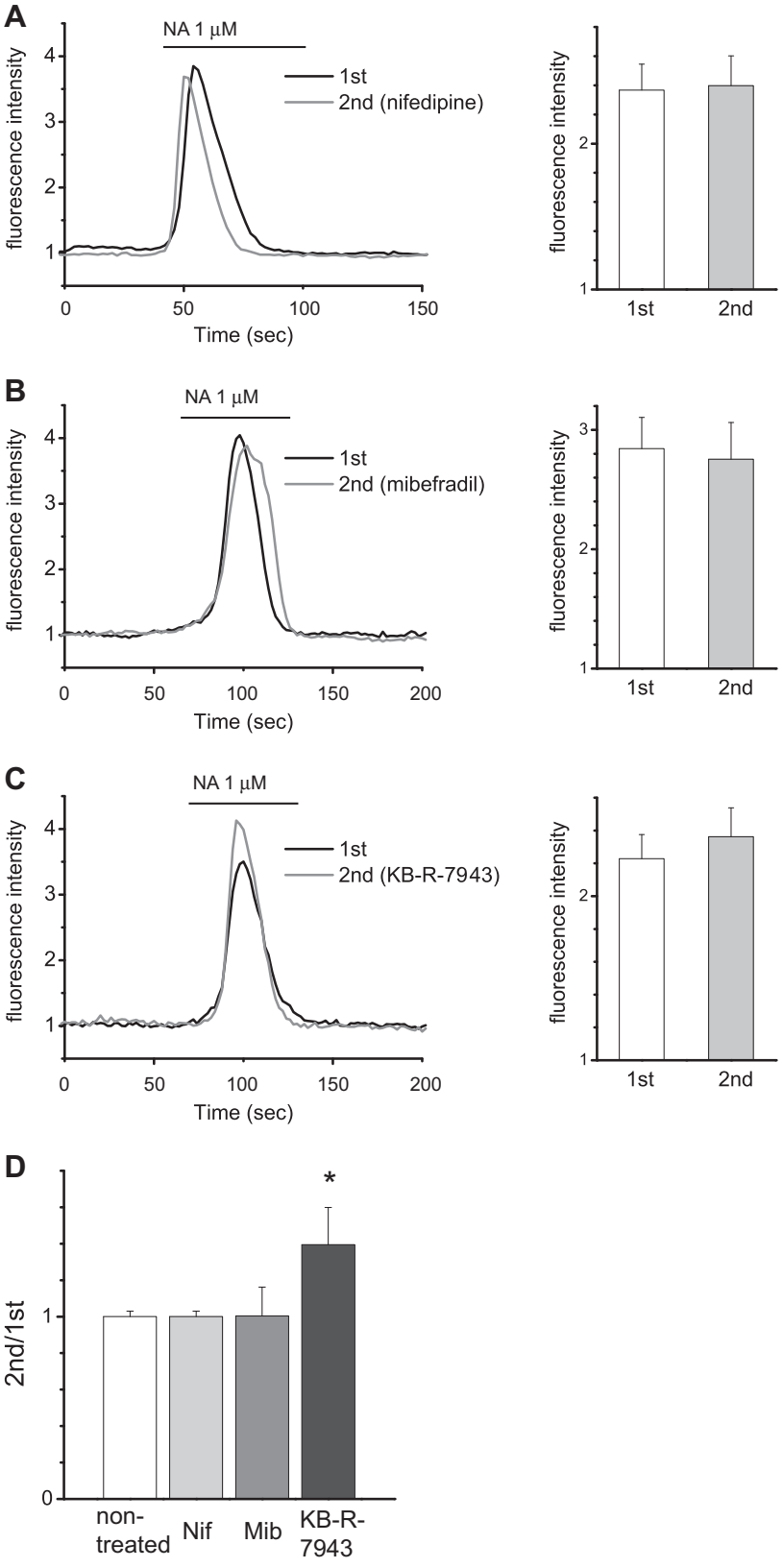

Fig. 2. The effects of voltage-dependent Ca^{2+}-channel inhibitors and Na^{+}/Ca^{2+} exchanger reverse mode inhibitor on NA-induced $[Ca^{2+}]_i$ elevation. (A–C) Representative traces of NA-induced $[Ca^{2+}]_i$ elevation in the presence of 10 μM nifedipine (A, $n = 18$), 10 μM mibefradil (B, $n = 14$) and 10 mM KB-R-7943 (C, $n = 20$). (D) Summary of the effects of these inhibitors on NA-induced $[Ca^{2+}]_i$ elevation (non-treated, $n = 22$). Values are shown as the mean ± SEM. $^{*}p < 0.05$ compared with the control.

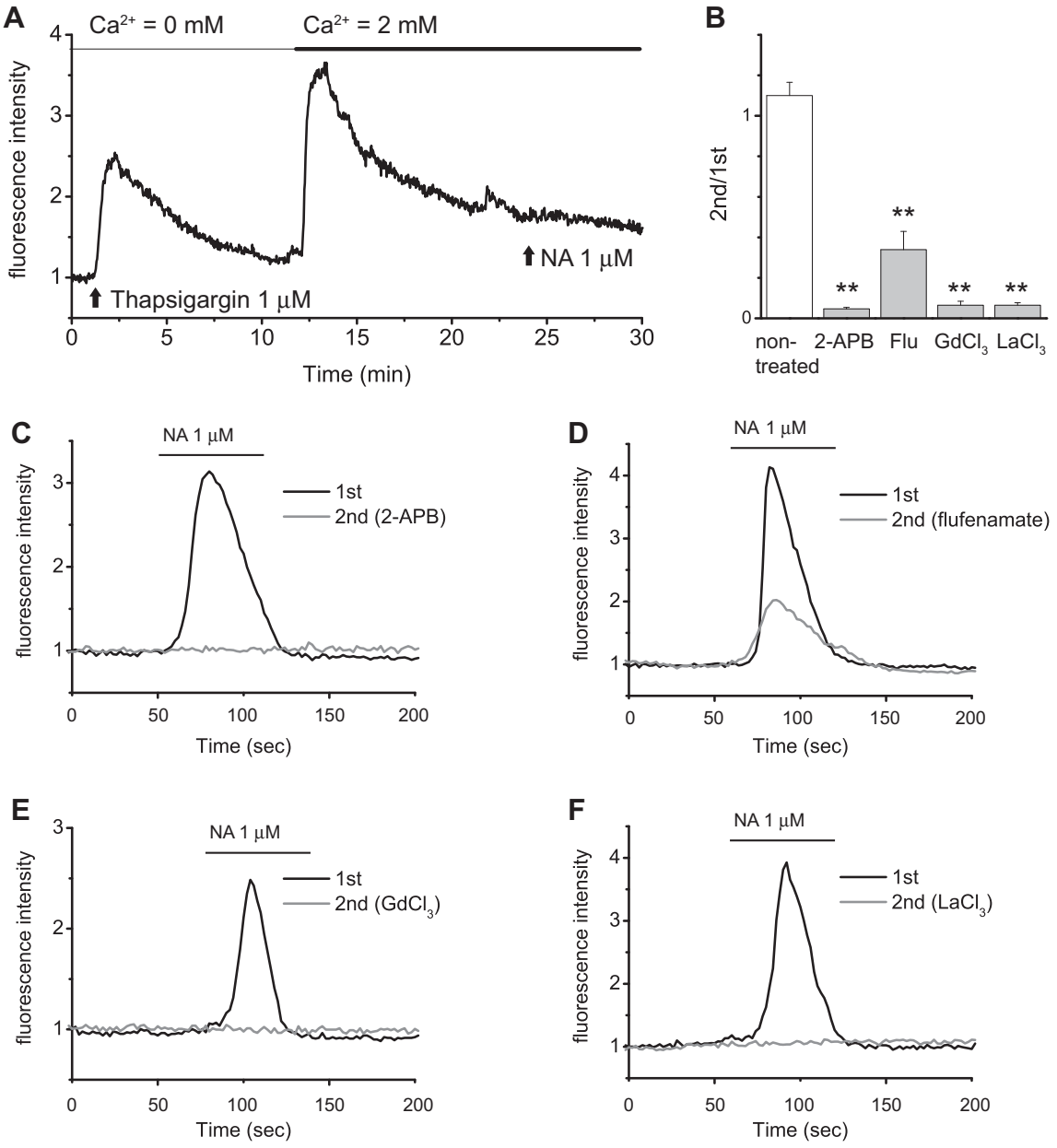

Fig. 3. Involvement of store-operated Ca^{2+} channel in NA-induced $[Ca^{2+}]_i$ elevation. (A) Representative trace of the effect of NA following treatment with thapsigargin. (B–F) The effects of store-operated Ca^{2+} channel inhibitors, 2-APB, flufenamate, $GdCl_3$ and $LaCl_3$, on NA-induced $[Ca^{2+}]_i$ elevation ($n = 22$, 26, 22, 23 and 19, respectively). (B) Summary of the effects of store-operated Ca^{2+} channel inhibitors. (C–F) Representative traces of NA-induced $[Ca^{2+}]_i$ elevation in the presence of 100 μM 2-APB (C), 100 μM flufenamate (D), 10 μM $GdCl_3$ (E) and 10 μM $LaCl_3$ (F). Values are shown as the mean ± SEM. $^{**}p < 0.01$ compared with the control.

hand, in the state of store-operated Ca^{2+} channel activation by pretreatment with thapsigargin, NA had no effect on Ca^{2+} fluorescence. Additionally, in the presence of reagents reported to inhibit store-operated Ca^{2+} entry, 2-APB, flufenamate, $GdCl_3$ and $LaCl_3$, the effect of NA was also inhibited [26–29]. These results suggest that NA activates store-operated Ca^{2+} channel via the Gq/PI-PLC pathway.

In our previous studies, bradykinin, a mediator of pain and inflammation, increased $[Ca^{2+}]_i$ via B_2 receptor and the Gq/PI-PLC pathway in SaM-1 cells. Bradykinin-induced $[Ca^{2+}]_i$ elevation was also inhibited by pretreatment with thapsigargin. However, the removal of extracellular Ca^{2+} significantly decreased the peak amplitude and duration of B_2-receptor-mediated $[Ca^{2+}]_i$ elevation, but did not abolish it [28]. These results indicate that the store-operated Ca^{2+} channel is involved in both α_{1B}-AR- and B_2 receptor-mediated Ca^{2+} signaling; however, it may play different roles in these types of signaling. In general, the store-operated Ca^{2+} channel is activated by endoplasmic reticulum Ca^{2+} depletion, which is thought to contribute to refilling the Ca^{2+} store. On the other hand, a number of studies have demonstrated that store-operated Ca^{2+} entry can also directly regulate Ca^{2+} signal transduction [30]. Additionally, Zeng et al. [29] reported that there is a store-independent pathway for the regulation of store-operated Ca^{2+} influx. Therefore, the result that NA-induced $[Ca^{2+}]_i$ elevation disappeared upon the removal of Ca^{2+} from extracellular fluid suggested the possibility that store-operated Ca^{2+} channel plays a critical role in α_1-AR-mediated Ca^{2+} signal transduction.

Recent studies suggested that the Orai channel family and the TRPC channel family are candidates for molecular components of the store-operated Ca^{2+} channels [27,31–34]. Previous reports,

including that on our study, demonstrated the mRNA expression of the TRPC channel family in osteoblasts [28,35,36]. Although, to our knowledge, the expression of the Orai channel family has never been reported in osteoblasts, gene disruption of Orai1 results in the inhibition of osteoblast differentiation [37,38]. In MG63 cells, human osteoblast-like cells, platelet-derived growth factor-induced proliferation was inhibited by treatment with store-operated Ca^{2+} channel blockers [35]. Determination of the molecular component and the physiological role of store-operated Ca^{2+} channel in human osteoblasts should be addressed in future study.

In conclusion, our results presented here suggest that Ca^{2+} influx through store-operated Ca^{2+} channel plays a predominant role in α_{1B}-AR-mediated $[Ca^{2+}]_i$ elevation in human osteoblasts, SaM-1 cells. They also suggest the possibility that store-operated Ca^{2+} channels have a critical role in the regulation of bone remodeling via the sympathetic nervous system.

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