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Intracellular NAADP increase induced by extracellular NAADP via the P2Y11-like receptor

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ABSTRACT

The aim of the study was to identify a signalling pathway allowing NAADP-induced intracellular NAADP increase and involving the P2Y11-like receptor. P2Y11-like and β-adrenergic receptors may play important regulatory roles within the cardiovascular system. Both receptors have been shown to be involved in triggering myocardial preconditioning. Using a Langendorff model we report a positive inotropic response induced by extracellular NAADP via P2Y11-like receptor stimulation. In cardiomyocyte cultures, P2Y11-like receptor stimulation by extracellular NAADP ([NAADP]e) increased intracellular cADP-ribose and NAADP concentration as evidenced by direct measurements. NF546, a new selective P2Y11 receptor agonist, increased intracellular cAMP, cADP-ribose and NAADP concentration confirming the involvement of the P2Y11-like receptor in this signalling pathway. NF157, a P2Y11 receptor antagonist, suppressed the increase in intracellular cADPr, NAADP and NAAD induced by either [NAADP]e or NF546. The response profile for intracellular cADP-ribose and NAADP concentration following P2Y11-like stimulation with NF546 was similar to reported data relating β-adrenergic stimulation with isoprenaline. This response represents the signature of the Gs/ADP-ribosyl cyclase activity. Moreover, this study provides a signalling pathway: intracellular NAADP increase induced by extracellular NAADP via metabotropic activity of P2Y11-like receptor. This pathway implying P2Y11-like could take part in the intracellular calcium rise reported for extracellular NAADP.

1. Introduction

Beta-nicotinamide adenine dinucleotide (β-NAD+) is present in mammalian serum at around 100 nM [1], and can be released extracellularly from cells by lytic and nonlytic mechanisms [2–6]. It can be metabolized to cyclic adenosine diphosphate-ribose (cADP-ribose) and to nicotinic acid adenine dinucleotide phosphate (NAADP) by ADP-ribosyl cyclase [7]. Mutafova-Yambolieva et al. (2007) and Moreschi et al. (2006) showed that β-NAD+ was an agonist of the human P2Y1 and P2Y11 receptors [8,9].

Several works have studied the intracellular increase of calcium induced by extracellular NAADP [10–13]. The results suggest that NAADP either enters the cell to induce intracellular effects or trigger a metabotropic response via P2Y receptor leading to cAMP, IP3 and cyclic ADP-ribose (cADPr) production. No studies considered the possibility that intracellular NAADP increase could be induced by extracellular NAADP via the P2Y11-like receptor.

Singaravelu et al. (2006) confirmed that 10 μM extracellular NAADP were able to partly activate P2Y receptors in mammalian astrocytes and to induce intracellular calcium increase [11]. Moreschi et al. (2008), using a model of hP2Y(11)-transfected 1321N1 astrocytoma cells, reported evidence that extracellular NAADP was a full P2Y11 receptor agonist and that 1 μM NAADP, the lowest tested concentration, already showed significant metabotropic activation which induces intracellular cyclic AMP (cAMP), inositol triphosphate (IP3) and cADPr increase [12]. Heidemann et al. [12] suggested that the calcium transients triggered by extracellular NAADP occurred following intracellular entry of NAADP via connexin hemichannels. As reported by Moreschi et al. [10], extracellular NAADP, also, triggered a concentration-dependent elevation of calcium in 1321N1-hP2Y11 cells, secondary to the intracellular production of IP3, cAMP and cyclic ADP-ribose (cADPR). Kim et al., [13] reported that 0.1 μM NAADP was able to induce intracellular cADPr accumulation in hepatic stellate cells [13].

Ectocellular localization of the active site of ADP-ribosyl cyclase [10] and [4] suggests the presence of extracellular NAADP. We recently reported that NAADP was present in myocardial interstitial medium and that its concentrations sharply increased during heart ischemia [6].

Abbreviations: cADPr, cyclic ADP-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate.

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Among cAMP, IP3 and cADPr, NAADP has been reported as the most potent intracellular messenger of calcium mobilizing mediator. β-Adrenergic receptor signalling induces, via Gs/cAMP/ADP ribose cyclase, a positive inotropic response involving not only cAMP and IP3 but also NAADP and cADPr [14]. As β-Adrenergic receptor, P2Y11 receptor is also coupled to Gs subunit. P2Y11 receptor stimulation with a stable analog of ATP induces a positive inotropic response [15], and it has been reported that extracellular ATP induces intracellular calcium signalling involving intracellular NAADP [16]. Extracellular ATP is a well-known P2 agonist and notably a full agonist of the P2Y11 receptor [17]. Therefore P2Y11 receptor stimulation which is able to trigger a positive inotropic response might induce an intracellular NAADP concentration increase. Extracellular NAADP, as a full agonist of the P2Y11 receptor [10], might also induce intracellular NAADP increase via P2Y11-like receptor stimulation.

The aim of the study was to identify a signalling pathway allowing NAADP-induced intracellular NAADP increase and involving the P2Y11-like receptor. Firstly, using a Langendorff model we studied the positive inotropic response induced by extracellular NAADP via P2Y11-like receptor stimulation and confirmed previously reported data [15]. Secondly, cADPr and NAADP intracellular concentrations were determined following extracellular application of NAADP involving P2Y11-like stimulation. To confirm the involvement of the P2Y11-like receptor in this signalling pathway, we used NF546 as a new selective P2Y11 receptor agonist [18] and determined intracellular cAMP, cADPr and NAADP accumulation.

2. Materials and methods

2.1. Compounds and chemical reagents

NAADP, 8,8′-[Carbonylbis[imino-3,1-phenylencecarbonylimino(4-fluoro-3,1-phenylene)carbonylimino]]bis-1,3,5-naphthalenetrisulfonic acid hexasodium salt (NF157) and 4,4′-(Carbonylbis (imino-3,1-phenylen-e-carbonylimino-3,1-(4-methyl phenylene) carbonylim-ino))-bis(1,3-xylene-alpha,alpha′-diphosphonic acid tetrasodium salt (NF546) were purchased from Tocris® Bioscience (France R&D Systems Europe, Lille, France). Acetonitrile, methanol and formic acid were purchased from Biosolve (DIEUZE, France). Other chemical compounds were purchased from Sigma® (Saint Quentin Fallavier, France).

2.2. Isolated heart preparation

Experiments were approved and conducted in conformity with laws and regulations controlling experiments and procedures for animal research in France and the European Convention for the Protection of Vertebrate Animals used in Experimental and Other Scientific Purposes. The study was approved by the local ethics committee. Wistar rat (Two-month-old male) hearts were prepared according to the non-working Langendorff mode using retrograde perfusion system at constant pressure as previously described [6,19].

2.3. Experiments

All experiments lasted a total of 35 min: t0 to 20-min of stabilization, t20 to t35-min of treatment. Randomized rat hearts were assigned to 5 groups to receive treatment as follows. The control group was perfused with KHB (t20, 35-min). The groups 2 and 3 were perfused with 0.1 or 1 μM NAADP (t25, 35-min) respectively. The group 4 was perfused with 1 μM NF157 (t20, 35-min). The group 5, called 1 μM (NAADP + NF157), was perfused with 1 μM NAADP (between t25, 35-min) bracketed with 1 μM NF157 (t20, 35-min), a P2Y11 receptor antagonist. In order to ovoid significant rheological alteration, treatment perfusion flow was fixed to 1% of the mean coronary flow.

2.4. Measurements

Evaluation of measurements was done in a randomized blinded manner for all experiments.

2.5. Contractile parameters

The contractile parameters were measured during the whole perfusion period. The difference between systolic pressure (mm Hg) and the left ventricular end-diastolic pressure (LVEDP, mm Hg) represented the left ventricular developed pressure (LVDP, mm Hg). The heart rate (HR, beats min^{-1}) was measured at the same time. Maximal (dP/dt_{max}) and minimal (dP/dt_{min}) values of the first derivative of left ventricular developed pressure (mm Hg s^{-1}) were measured at the same times.

2.6. Cell culture

Cardiomyocyte cultures were performed as previously described [6,19].

2.7. Intracellular cAMP, cADPr, NAADP and NAAD accumulation Assay

Neonatal rat cardiomyocytes in culture were stimulated for 30-min, in 6-well plates for cAMP accumulation assay, or 10-min, in 6-well plates for cADPr, NAADP and NAAD assay, at 37 °C with extracellularly applied concentrations of NAADP in the absence or presence of 10 μM NF157, added 15-min before NAADP. In order to confirm the involvement of P2Y11-like receptor in the signalling pathway triggered by extracellular NAADP, we used NF546 as a new selective P2Y11 receptor agonist. Neonatal rat cardiomyocytes in culture were stimulated for 30-min, in 6-well plates for cAMP accumulation assay, or 10-min, in 6-well plates for cADPr, NAADP assay, at 37 °C with extracellularly applied concentrations of NF546 in the absence or presence of 10 μM NF157, added 15-min before NF546. The time course for cADPr, NAADP and NAAD changes in response to P2Y11-like receptor stimulation induced by NF546 was also studied in 6-well plates. Intracellular cAMP accumulation was determined as previously described [20]. For cADPr, NAADP and NAAD intracellular quantification, the stimulation medium was aspirated, washing the cell with buffer phosphate, then 1 ml of glacial (−80 °C) methanol containing 0.1 M of formic acid was added. cADPr, NAADP and NAAD were extracted after submitting cardiomyocytes to 5 cycles of ultra-sonication (1 min/and 1 min free). The organic supernatant was collected and evaporated to dryness under nitrogen. The extracts were reconstituted with 30 μl of solution containing 60% of acetonitrile, 40% of methanol. They were injected into an ultra-performance liquid chromatography coupled to tandem mass spectrometry detection system (Xevo-TQ MS; Waters corporation) and quantified as described [6]. Concentrations were calculated, based on calibration curve of spiked blank reconstitution solution, using the peak area ratio of the compound to the internal standard (8-Bromoadenosine 3′,5′-cyclic monophosphate). Total protein content was determined using Bradford assay in 1 control well/plate.

2.8. Statistical analysis

Statistical analyses were performed using Prism 4.00; GraphPad Software, San Diego, CA. All values are expressed as mean ± sem of experiments. $p < 0.05$ was considered to be statistically significant. Differences between groups were evaluated using one-way

analysis of variance (ANOVA). If the F ratio was significant, Tukey's Multiple Comparison (post hoc) test was applied to assess significance ($p < 0.05$). In the experimentations of just two groups, the differences were assessed using unpaired t test. EC_{50} values for agonists were derived from data of pooled and normalized log concentration–effect curves fitted according to the nonlinear four-parameter logistic equation (Prism 4.00; GraphPad Software, San Diego, CA). $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Extracellular NAADP induces myocardial contractility

Baseline functional data did not differ between groups. At the end of treatment, only the 1 μM NAADP group exhibited higher values of LVDP compared to 1 μM (NAADP + NF157) group ($p < 0.05$) (Table 1). The 1 μM NAADP group also exhibited higher values of dP/dt_{max} (%) and dP/dt_{min} (%) compared to all other groups ($p < 0.05$), without significant differences in heart rate which is in agreement with the suggested inotropic effect [15] induced by P2Y11-like receptor stimulation (Table 1). 1 μM NF157 completely suppressed the increase in LVDP, dP/dt_{max} and dP/dt_{min} induced by 1 μM NAADP (Table 1).

3.2. Extracellular NAADP induces intracellular cADPr, NAADP and NAAD accumulation

Extracellular NAADP induced a concentration-dependent increase in cADPr and NAAD intracellular concentrations (Fig. 1). NAAD is a NAADP metabolite [21]. EC_{50} was 6.39 μM for cADPr production and 6.96 μM for NAAD production (Fig. 1). 10 μM NF157 were able to inhibit intracellular cADPr, NAADP and NAAD production induced by application of 100 μM extracellular NAADP for 10 min (Fig. 1). 10 μM NF157 concentration was chosen to ensure 90% inhibition of P2Y11 receptor activity [6,22].

3.3. Extracellular NF546 induces intracellular cAMP, cADPr, NAADP and NAAD accumulation

We used NF546 in order to confirm the involvement of P2Y11-like receptor in the signalling pathway triggered by extracellular NAADP. Extracellular NF546 induced a concentration-dependent increase in cAMP and NAADP intracellular concentrations (Fig. 2). The approximated EC_{50} relating cAMP accumulation (Fig. 2) was in the same order of magnitude compared to previously published data [18]. 10 μM NF157 were able to inhibit intracellular cAMP, cADPr, NAADP and NAAD production induced by application of 1 μM NF546 for 10 min (Fig. 2). Regarding cAMP accumulation and previous published data [6,10,18], NF546 is approximately 10 times ($EC_{50\text{-NAADP}}/EC_{50\text{-NF546}}$) more potent than extracellular NAADP.

3.4. Time course of intracellular cADPr, NAADP and NAAD changes in response to P2Y11-like receptor stimulation induced by NF546

NF546 induced a biphasic increase in intracellular NAADP concentration (Fig. 3). We observed a transient increase in NAADP levels with a peak at 15 s, then a return to baseline values by about 2 min, followed by a delayed and sustained increase for at least 10-min (Fig. 3). The relative transient increase in NAADP after stimulation was about 1.6-fold (Fig. 3). These results are in accordance with recently published data following isoprenaline stimulation in isolated perfused rat heart [14]. NF546 induced an increase in intracellular cADPr (3.87-fold) and NAAD (2.38-fold) concentrations with maximum accumulation at about 5-min (Fig. 3). The NAAD and cADPr concentrations were in the same range. Intracellular cADPr level before stimulation is within reported data in heart tissue [23]. Basal values of intracellular NAADP are an accordance with the more recently reported data in heart [14,24].

4. Discussion

Using an isolated rat heart model, 1 μM extracellular NAADP was able to increase contractility via the P2Y11-like receptor. Extracellular NAADP via P2Y11-like receptor induced intracellular NAADP and cADPr increases. The involvement of the P2Y11-like receptor in this signalling pathway, was confirmed by using NF546, a selective P2Y11 receptor agonist [18]. Extracellular NAADP and NF546 were able to induce intracellular cAMP [6], cADPr and NAADP accumulation in cardiomyocyte cultures. One μM NF157, a suramin-derived P2Y11 receptor antagonist [22], suppressed the response induced by extracellular NAADP and NF546.

Like β-adrenergic stimulation induced by isoprenaline [14], extracellular NAADP, and NF546, were able to induce intracellular increase of cADPr and NAADP via P2Y11-like stimulation. Like isoprenaline, 1 μM NAADP was also able to induce a positive inotropic response in Langendroff model. A similar inotropic response of β-adrenergic and P2Y11-like receptors has also been reported by Balogh et al. [15] in cardiomyocyte cultures.

It has been reported that P2Y receptor subtypes evoke different calcium signals in cultured aortic smooth muscle cells [25]. This calcium signal evoked by P2Y1, 2, 4, 6 receptor subtypes stimulation was unaffected by inhibition of ryanodine or intracellular NAADP receptors [25]. This implies that this response could be independent of cADPr, NAADP and ADP-ribosyl cyclase. Contrarily to the P2Y11-like receptor, P2Y1, 2, 4, 6 are not linked to the Gs protein subunit. ADP-ribosyl cyclase has been reported to be coupled to cAMP signalling in cardiomyocytes [26]. ADP-ribosyl cyclase mediates production of both cADPr and NAADP [21,27]. Contrarily to P2Y1, 2, 4, 6 receptors, P2Y11-like receptor is coupled to Gs subunit which is able to induce cAMP production [6,28]. P2Y11-like stimulation was able to induce, like β-adrenergic stimulation via Gs/ADP-ribosyl cyclase pathway, intracellular cAMP, cADPr and NAADP production. The response profile for cADPr and NAADP following P2Y11-like stimulation with NF546 (Fig. 3)

Table 1
dP/dt_{max} and dP/dt_{min} and LVDP at the end of treatment.

Groups	dP/dt_{max} % of baseline values	dP/dt_{min} % of baseline values	LVDP (%) of baseline values
Control ($n = 6$)	101.8 ± 1.5	101.9 ± 1.9	95.7 ± 1.6
0.1 μM NAADP ($n = 6$)	102.38 ± 2.0	103.6 ± 2.6	104.6 ± 1.6
1 μM NAADP ($n = 6$)	$129.9 \pm 8.8^{*,£,\&,\#}$	$126.6 \pm 6.1^{*,£,\&,\#}$	$110.1 \pm 2.3^{*,\#}$
1 μM NF157 ($n = 6$)	98.7 ± 3.9	101.2 ± 6.6	101.7 ± 2.5
1 μM (NAADP + NF157) ($n = 6$)	96.5 ± 3.7	97.3 ± 0.8	96.2 ± 2.1

Maximal (dP/dt_{max}) and minimal (dP/dt_{min}) values of the first derivative of left ventricular pressure (mm Hg s^{-1}). LVDP: left ventricular developed pressure; Data are means ± sem. Data at the end of treatment was expressed as percentage of the basal mean value (before treatment). $^{*}p < 0.05$ compared to control rat hearts; $^{\&}p < 0.05$ compared to rat hearts treated with 1 μM NF157; $^{\#}p < 0.05$ compared to rat hearts treated with 1 μM (NAADP + NF157); $^{£}p < 0.001$ compared to rat hearts treated with 0.1 μM NAADP.

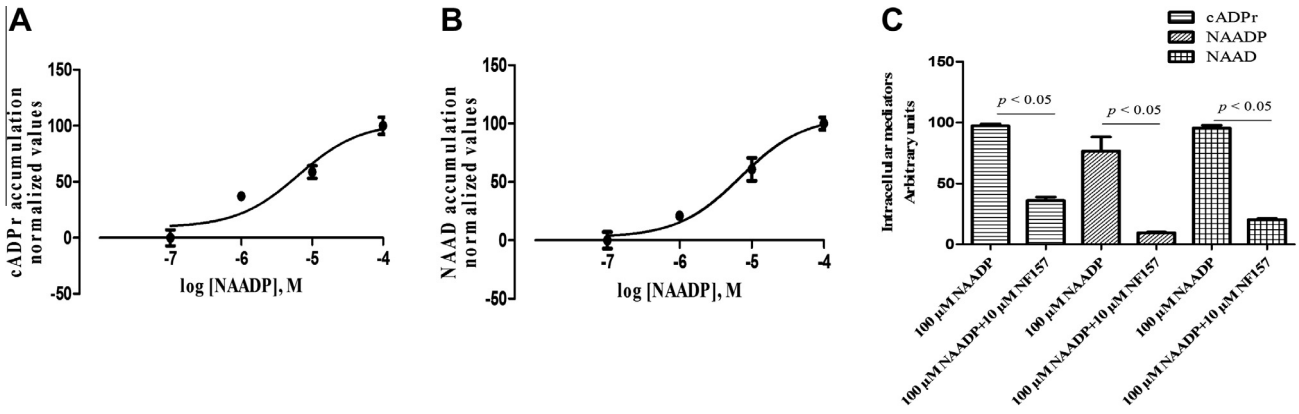

Fig. 1. Increases of intracellular cyclic ADP-ribose, NAADP and NAAD induced by extracellular NAADP. Extracellular NAADP concentration-response curves for cADPr (A) and NAAD (B) accumulation in rat cardiomyocytes. The effect of 10 µM NF157, a P2Y11 receptor antagonist, on cADPr, NAADP and NAAD accumulation induced by 100 µM extracellular NAADP (C). Data are means ± sem (n = 4). pEC50 [NAADP] = 5.194, CI95 [5.704–4.684], for cADPr accumulation. pEC50 [NAADP] = 5.157, CI95 [5.538–4.777], for NAAD accumulation.

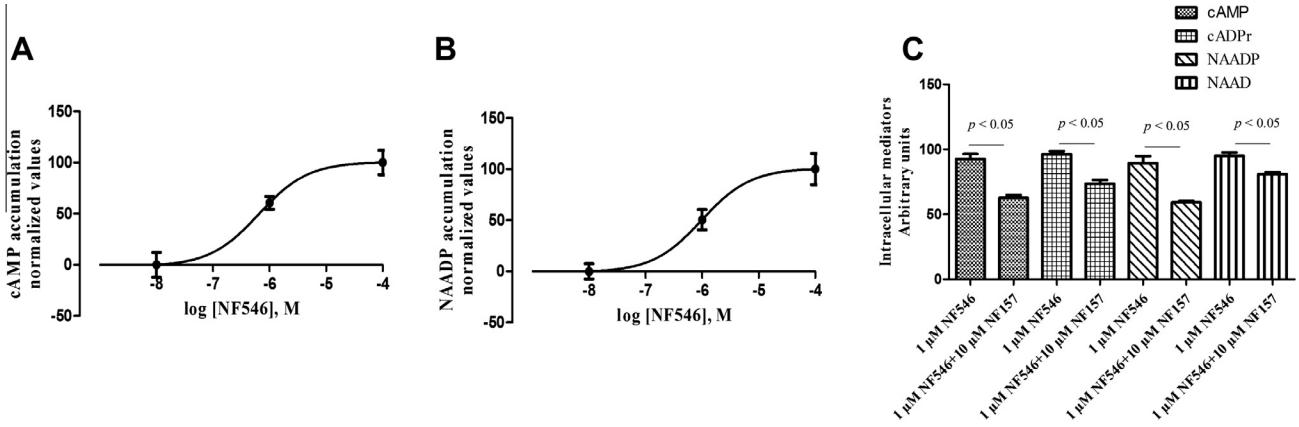

Fig. 2. Increases of intracellular cAMP, cADPr, NAAD and NAADP induced by NF546. Extracellular NF546 concentration-response curves for cAMP (A) and NAADP (B) accumulation in rat cardiomyocytes. The effect of 10 µM NF157, a P2Y11 receptor antagonist, on cAMP, cADPr, NAADP and NAAD accumulation induced by 100 µM extracellular NAADP (C). Data are means ± sem (n = 4).

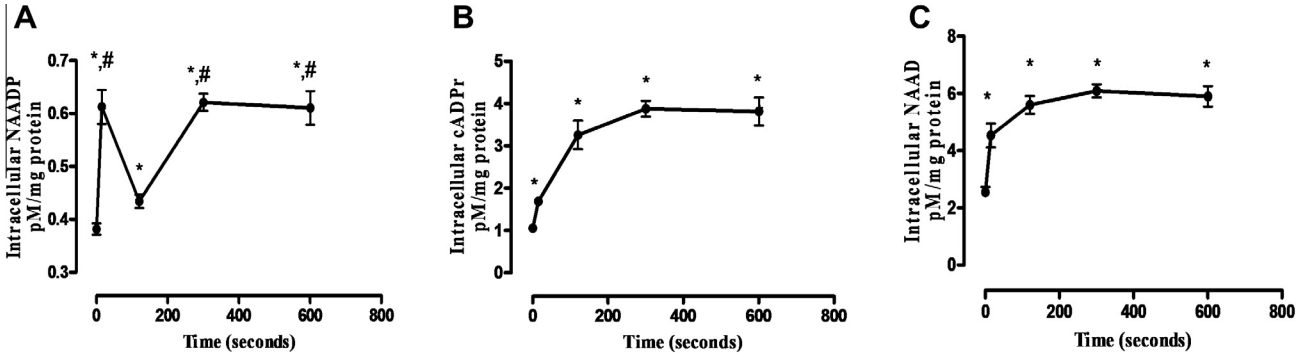

Fig. 3. The time course for NAADP, cADPr and NAAD changes in response to P2Y11-like receptor stimulation induced by NF546. The time course for NAADP (A), cADPr (B) and NAAD (C) concentration changes in response to P2Y11-like stimulation induced by 1 µM NF546. Data are means ± sem (n = 4). $^{*}p < 0.05$, compared to concentrations corresponding to time 0-s; $^{\#}p < 0.05$ compared to concentrations corresponding to time 120-s.

was similar to β-adrenergic stimulation with isoprenaline [14]. As previously published, this response represents the signature of the Gs/ADP-ribosyl cyclase activity [14,26,29].

Like β-adrenergic response, P2Y11-like receptor stimulation caused an increase in the contractile force. Other similarities between P2Y11 and adrenergic receptor response have also reported. Both receptors have been shown to be able to trigger myocardial preconditioning and to afford cardioprotective effects against ischemia/reperfusion injury [6,19,30,31].

In conclusion, extracellular NAADP triggered a positive inotropic response via P2Y11-like stimulation. P2Y11-like receptor stimulation induced temporal profiles for intracellular cADPR and NAADP similar to β-adrenergic receptor stimulation. The intracellular increases of these calcium mediators likely explain, beside

cAMP and IP3 increase [15], the inotropic response following P2Y11-like stimulation. Moreover, this study provides a signalling pathway: intracellular NAADP increase induced by extracellular NAADP via metabotropic activity of P2Y11-like receptor. This pathway implying P2Y11-like stimulation could explain, at least partly, the reported calcium rise induced by extracellular NAADP [10–13].

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