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Ca^{2+} RELEASING PROCESS AND NICOTINIC ACID ADENINE DINUCLEOTIDE PHOSPHATE

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The paper is devoted to recognizing of nicotinic acid adenine dinucleotide phosphate (NAADP) as releaser of intracellular calcium from intracellular stores. It was revealed the current concepts of the mechanisms of NAADP synthesis inside the cell resuming involve enzyme CD38. The effect of NAADP was described in several cells and tissue preparation, as well as in sea urchin eggs. Briefly, it was characterized the acidic store of cells, that is sensitive to NAADP as it had been shown by different authors. Assumed mechanisms of Ca^{2+} accumulating in acidic store predict involve proton gradient across membrane of acidic store. The channels structure of acidic store and endoplasmatic reticulum are considered as receptors to NAADP. Potential mechanisms for NAADP-induced calcium release was considered: direct model, trigger Ca^{2+}-induced Ca^{2+}-releasing model, promiscuous coupling model, conformational coupling model and also unifying hypothesis, that explains the differences between other mechanisms. Physiological processes in which NAADP is involved are described.

Keywords: NAADP, acidic store, Ca^{2+}, ryanodine receptor, two-pore channels.

Nicotinic acid adenine dinucleotide phosphate (NAADP) is a naturally occurring nucleotide that has been shown to be involved in the release of calcium from intracellular stores in a wide variety of cell types [32; 45].

NAADP was discovered as a trace contaminant of commercially available NADP [47]. This may not be too surprising since the structure of NAADP is very similar to that of NADP, the only existing difference is the substitution of nicotinic acid as the base instead of nicotinamide (Fig. 1). Besides this small change has enormous biological effects since whilst NADP is inactive, NAADP is very potent at generating Ca^{2+} signals. The latter was discovered by Lee and colleagues whilst studying Ca^{2+} release mechanisms in sea urchin eggs homogenates [22].

The first demonstration that NAADP level increases in response to an extracellular stimulus arose from studying sea urchin fertilization (NAADP changed in both the eggs and sperm upon contact) [19]. The transduction mechanisms that couple cell stimuli to such NAADP increases are elusive. To date, the most favoured hypothesis is the so-called „*base-exchange reaction*" (nicotinic acid + NADP → NAADP + nicotinamide) which is catalyzed by ADP-ribosyl cyclases (a family of enzymes including CD38 and

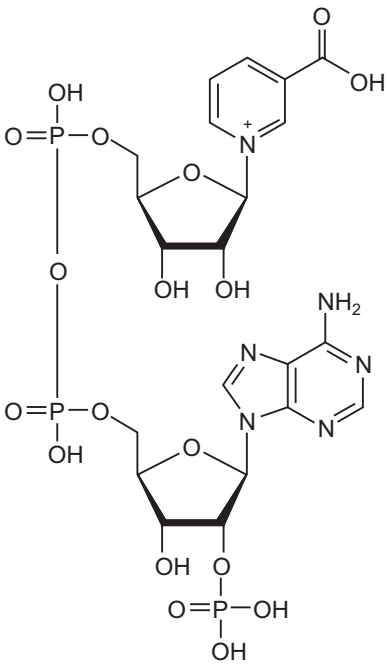

Fig. 1. Nicotinic acid adenine dinucleotide phosphate (NAADP)

Рис. 1. Нікотинацидаденіндинуклеотид фосфат (НААДФ)

CD157 in mammals and orthologs in sea urchin and *Aplysia ovotestis*). The latter were first discovered as the synthetic enzymes for cADPR but later revealed to be multifunctional, promiscuous enzymes that can also produce NAADP. Certainly NAADP production can occur *in vitro* but whether it occurs *in vivo* is following question (because genetic knock-out or knock-down of ADP-ribosyl cyclases has no effect on NAADP production in some cell types), and there may be other routes which might require different substrates and enzymes [58].

A recent study indicates that CD38 is required for cholecystokinin-elicited NAADP generation and suggests that CD38 is an NAADP synthase, which is required for receptor-activated Ca^{2+} release in pancreatic acinar cells [24]. The mechanism of NAADP-induced Ca^{2+} release is of particular interest in pancreatic acinar cells, because cholecystokinin evokes pancreatic enzyme secretion in human acinar cells [56].

NAADP-induced Ca^{2+}-release in different cell's type. The initial studies performed on the stratified sea urchin eggs indicated that NAADP is able to release Ca^{2+} from an internal store that different from the endoplasmic reticulum (ER) [46]. In particular Churchill et al. in 2002 identified this store as the reserve granule of sea urchin eggs, an acidic compartment related to lysosomes [18]. It was also shown that NAADP-induced Ca^{2+} release is also widespread in mammalian systems. However the question arises how and from which intracellular store does NAADP elicit Ca^{2+} release in mammalian cells? In the fact it is still difficult to answer to this because the effects depend on cell's type. In particular the rat brain microsomes were the first mammalian preparation in which NAADP-induced Ca^{2+} release was demonstrated [4]. In this preparation, the NAADP-regulated Ca^{2+} release mechanism (as in sea urchin eggs) was independent of extravesicular Ca^{2+} concentrations, unrelated to inositol-1,4,5-trisphosphate receptor (IP_3R) and ryanodine receptor (RyR) inhibitors, but was inhibited by micromolar concentrations of dihyropyridines or diltiazem [4]. The exocrine pancreatic acinar cell was the first intact mammalian cell type in which NAADP-induced Ca^{2+} release was clearly reported [13]. Studies on isolated nuclei from exocrine pancreatic acinar cells have demonstrated Ca^{2+} liberation elicited by NAADP (and also by cADPR) can be blocked by ryanodine or ruthenium red [36]. This is in contrast to the sea urchin eggs [18; 47]. In human pancreatic beta cells, NAADP mobilizes Ca^{2+} from a pool that is insensitive to either ryanodine or the IP_3R antagonist, xestospongin C, and might mediate the autocrine inhibitory effects of insulin on further release of this hormone [40]. In intact pulmonary arterial myocytes, NAADP mobilizes Ca^{2+} from a pool that is insensitive to either ryanodine or the IP_3R antagonist, xestospongin C, and might mediate the autocrine inhibitory effects of insulin on further release of this hormone in human pancreatic beta cells [40]. In intact pulmonary arterial myocytes, NAADP mobilizes Ca^{2+} from a bafilomycin-

sensitive store. Where as xestospongin C had little effect on NAADP-induced Ca^{2+} release, both ryanodine and thapsigargin reduced but did not abolish NAADP's effects [6; 43]. In rat aortic microsomes, NAADP released Ca^{2+} by a mechanism insensitive to IP_3R or RyR blockers but which was inhibited by dihydropyridines [79]. In striated muscle, NAADP released Ca^{2+} from rat heart microsomes, which was unaffected by ryanodine and divalent cations, but blocked by dihydropyridines [3]; however, it should be noted that direct interactions of NAADP with purified RyRs from both skeletal [39] and cardiac muscle [53] have been reported by some but not others [23].

Characteristics of the acid Ca^{2+} stores. Organelles rich in both H^+ and Ca^{2+}, the so called „acidic Ca^{2+} stores" include acidocalcisomes (best characterized in protists) and vacuoles (present in many organisms including plants and yeast) [61].This is a blanket term that encompasses a spectrum of acidic vesicles that include endosomes, lysosomes, and lysosome-related organelles and secretory vesicles, zymogen granules (ZGs) and acidocalcisomes. The aptly named acidocalcisomes are small acidic organelles that contain high concentrations of Ca^{2+}. They are also rich in phosphorous [61].

All eukaryotic cells contain lysosomes (termed vacuoles in plants and fungi), with the exception of some highly specialized cells such as mammalian erythrocytes, which lack multiple organelles including lysosomes. Lysosomes degrade exogenous and endogenous macromolecules derived from biosynthetic and endocytic pathways, and catabolize cytosolic components that are obtained from the autophagic pathway [50; 70].

Christensen et al. used endocytosed dextran-based Ca^{2+} indicators and performed careful calibration of the indicators with respect to pH, determined a luminal Ca^{2+} concentration of ~ 500 mkM inside lysosome [17]. Endosomes are also likely to contain significant concentrations of Ca^{2+} since they are formed during invagination of the plasma membrane and Ca^{2+} thus will incorporate extracelluar Ca^{2+} which is usually present at ~ 1 mM. Thus, lysosomes and endosomes might be suggesred as significant stores of Ca^{2+} [62]. The zymogen granules (ZGs) have an extraordinarily high total Ca^{2+} concentration (>10 mM) and isolated single ZGs can release Ca^{2+} in response to both $InsP_3$ or cADPR [33] and also to NAADP [35]. The acid stores do not possess thapsigargin-sensitive Ca^{2+}-pumps, but have a Ca^{2+} uptake mechanism that depends on a bafilomycin-sensitive vacuolar H^+-pump [35]. It is therefore likely that Ca^{2+} accumulation into the acid store occurs through a Ca^{2+}/H^+-exchange mechanism [63] (Fig. 2). The major part of acid Ca^{2+} stores in pancreatic acinar cells is undoubtedly localized in the ZGs, but other acid compartments such as, for example, endosomes-including post-exocytotic endocytic vacuoles – and lysosomes also play important roles [64]. It was shown that clamping the cytosolic [Ca^{2+}] at the normal resting level abolishes NAADP-induced, but not IP_3- or cADPR-elicited Ca^{2+}-release from the thapsigargin-insensitive store. This suggests that Ca^{2+}-induced Ca^{2+} release plays a more important role for NAADP-elicited Ca^{2+} release from the acid store than from the ER [64].

Possible mechanisms for NAADP-induced Ca^{2+} release. Early hypotheses explaining NAADP-induced Ca^{2+}-releasing mechanism were reviewed by A. Galion and O.Petersen in 2005 [33].

The ***„direct model"*** assumes that NAADP binds directly to the RyR on Ca^{2+} stores (ER or acidic compartments) increasing channel open probability, also NAADP may bind and directly regulate plasma membrane Ca^{2+} channels [39, 52].

The ***„trigger Ca^{2+}-induced Ca^{2+} release model"*** suggests that there is a specific NAADP receptor/Ca^{2+}-release channel that is located in a discrete Ca^{2+}-storage organ-

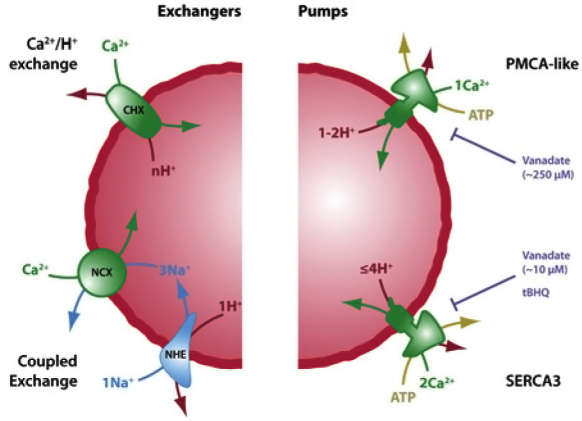

Fig. 2. Ca^{2+} -filling mechanisms of acidic Ca^{2+} stores [54]. Archetypal endolysosomal vesicles. The left-hand hemisphere depicts putative Ca^{2+}-exchange modes, the upper mechanism shows pure Ca^{2+}/H^{+}-exchange and the lower mechanism shows coupled transport, electroneutral NHE (Na^{+}/H^{+}-exchanger) acting with a NCX (Na^{+}/Ca^{2+}-exchanger). Clearly, the NCKX family (Na^{+}/Ca^{2+}-K^{+} exchanger) could substitute for NCX. The right-hand hemisphere shows putative Ca^{2+} pumps (for simplicity, with low or negligible thapsigargin sensitivity): a PMCA-like Ca^{2+}-ATPase (plasma membrane Ca^{2+}-ATPase) that translocates only 1 Ca^{2+} per cycle, with low vanadate sensitivity; and a SERCA3-like Ca^{2+}-ATPase (sarcoendoplasmic reticulum Ca^{2+}-ATPase) that translocates 2 Ca^{2+} per cycle, with high vanadate sensitivity and inhibitable by tBHQ (tert-butylhydroquinone) [54]

Рис 2. Механізми наповнення кальцієм кислотних Ca^{2+} депо [54]. Прототип ендо-лізосомної везикули. Ліва півкуля зображає гіпотетичні Ca^{2+}-обмінні моделі, верхній механізм показує простий Ca^{2+}/H^{+}-обмінник. Механізм, зображений нижче, відображає спряжений транспорт – електронейтральний NHE (Na^{+}/H^{+}-обмінник), який працює узгоджено з NCX (Na^{+}/Ca^{2+}-обмінником). Очевидно, що родина NCKX (Na^{+}/Ca^{2+}-K^{+} обмінників) може замінити NCX. Права півкуля демонструє гіпотетичні Ca^{2+}-помпи (для спрощення, з низькою або незначною чутливістю до тапсигаргіну): PMCA-подібна Ca^{2+}-АТФ-аза (Ca^{2+}-АТФ-аза плазматичної мембрани), яка переносить лише 1 Ca^{2+} за цикл, з низькою чутливістю до ванадату; та SERCA3-подібна Ca^{2+}-АТФ-аза (Ca^{2+}-АТФ-аза сарко-ендоплазматичного ретикулуму), яка транспортує 2 Ca^{2+} на цикл, із високою чутливістю до ванадату та пригнічується tBHQ (терт-бутил-гідрохіноном) [54]

elle (acidic store). Localized Ca^{2+} release from this pool then recruits IP_3Rs and RyRs located in a the ER by Ca^{2+}-induced Ca^{2+} release (CICR) following by globalization of the Ca^{2+} signals [13; 21]. In the most cells type lysosomes and lysosomal-related organelles constitute a much smaller cellular volume than the ER, and consequently mobilization of Ca^{2+} stores in lysosomes might be expected to produce only small and localized cytoplasmic Ca^{2+} transients [30]. Nevertheless, NAADP can initiate regenerative global Ca^{2+} signals (oscillations and waves) and this is because 'trigger' Ca^{2+} provided by NAADP is subsequently amplified by recruitment of IP_3Rs and RyRs that exhibit the characteristic property of CICR [20, 21]. This may occur by two ways: most obviously by trigger Ca^{2+} stimulating ER channels via the CICR, but also by trigger Ca^{2+} being sequestered into and 'priming' the ER (which sensitizes ER channels from the luminal face) [54] (Fig. 3). Such communication between Ca^{2+}-storing organelles demands close appositions as typified by the interactions between SR (sarcoplasmic reticulum)/ER and mitochondria [68] that is cemented physically by mitofusins acting to tether the organelles together [28].

This model suggests existance an analogous juxtaposition of acidic organelles and ER [54]. Lysosome/SR junctions have certainly been observed in vascular smooth muscle cells which are the site of initiation of NAADP and agonist-evoked Ca^{2+} signals [27; 41; 42; 55]. 'Chatter' between TPCs and endoplasmic reticulum Ca^{2+} channels is dis-

rupted when TPCs are directed away from the endolysosomal system [60]. This suggests that intracellular Ca^{2+} release channels may be closely apposed, possibly at specific membrane contact sites between acidic organelles and the endoplasmic reticulum [60]. Whether this „chatter" is ubiquitous and requires specialized tethering proteins still remain to be confirmed. Recentlly, it was indicated by co-immunoprecipitation experiments that endogenously expressed TPC-2 associates STIM1 and Orai1, in MEG01 cells but only upon depleting of intracellular Ca^{2+} stores. These results provide strong evidence for modulation of SOCE by TPC2 involving *de novo* association between TPC2 and STIM1, as well as Orai1, in human cells [49].

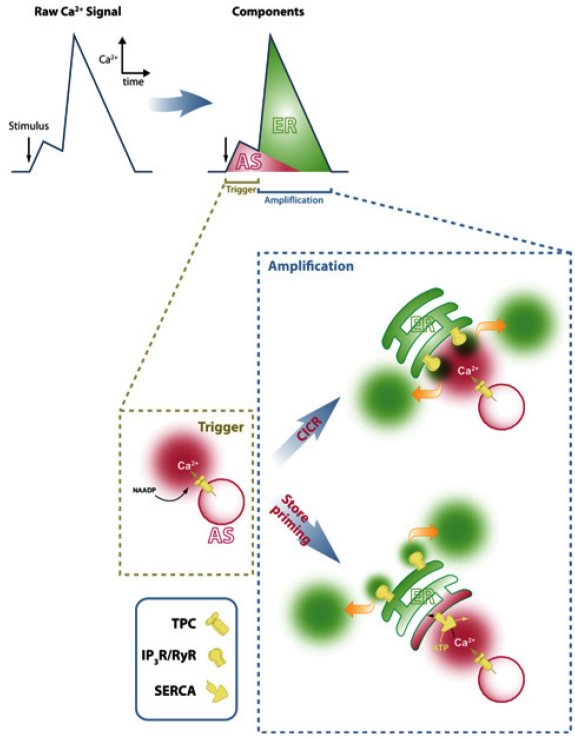

Fig. 3. Trigger hypothesis of NAADP-induced Ca^{2+} release. Schematic diagram of a global Ca^{2+} transient induced by a stimulus depicted in two components: first the small phase [AS (acidic stores); red] followed by the subsequent large regenerative spike (from the ER; green). 'Trigger' Ca^{2+} is released from acidic Ca^{2+} stores by NAADP to gives a globally small (but locally high) [Ca^{2+}] (first phase). There are two modes of recruiting the ER Ca^{2+}-release channels, CICR (upper scheme) and store priming (lower scheme). Trigger Ca^{2+} acts at the cytosolic face of ER channels (IP_3Rs or RyRs) to sensitize them by CICR and evoke a global (green) Ca^{2+} spike. Alternatively, trigger Ca^{2+} is taken up into the ER by SERCA action and acts to luminally sensitize ER channels and thereby evoke a global Ca^{2+} spike (green) [54]

Рис. 3. Тригерна гіпотеза НААДФ-індукованого вивільнення Ca^{2+}. Принципова схема глобального Ca^{2+} транзієнта індукованого стимулами, зображена у двох компонентах: початкова невелика фаза [AS (кислотні депо); червоні] та наступний значний регенеративний спайк (із ЕПР, зелений). 'Тригерний' Ca^{2+}, вивільнений із кислотних Ca^{2+} депо за дії НААДФ, створює глобально невеликі (але локально високі [Ca^{2+}] (перша фаза). Існує дві моделі, що залучають канали вивільнення Ca^{2+} з ЕПР, Ca^{2+}-індуковане вивільнення Ca^{2+} (CICR, верхня схема) і праймінг депо (нижня схема). Тригерний Ca^{2+} впливає на цитозольну поверхню каналів ЕПР ($IФ_3$-чутливих чи ріанодин-чутливих), підвищуючи їхню чутливість до CICR і викликаючи глобальний (зелений) Ca^{2+} спайк. Крім того, тригерний Ca^{2+} захоплюється всередину ЕПР роботою SERCA і впливає люмінально, підвищуючи чутливість каналів ЕПР і у такий спосіб викликає глобальний Ca^{2+} спайк (зелений) [54]

In the ***„model of promiscuous coupling"***, the NAADP-binding protein is not a Ca^{2+} channel *per se*, rather it is an integral membrane protein that can associate and regulate Ca^{2+}-release channels such as RyRs [36], in the ER or acidic stores (including secretory granules), or calcium influx channels in the plasma membrane.

The ***conformational coupling model*** assumes that NAADP directly interacts with a distinct NAADP-regulated Ca^{2+}-release channel in a discrete store. This channel can release Ca^{2+} in response to NAADP, but the channel may also directly interact with other Ca^{2+}-release channels (IP_3Rs or RyRs) or with plasma membrane Ca^{2+}-influx channels. This model provides one explanation for how desensitizing concentrations of NAADP apparently render IP_3Rs or RyRs insensitive to their respective agonists [5] or desensitize Ca^{2+} influx [19], even in the absence of Ca^{2+} release.

Recently Guse A. proposed ***„unifying hypothesis"*** [38] suggesting that NAADP binding protein could also bind to different ion channels.

NAADP receptor is still unrecognized. The fundamental question that remains unanswered is the identity of the NAADP receptor. Transient receptor potential mucolipin (TRPML) and two-pore channels (TPCs) are Ca^{2+}-permeable ion channels revealed within the endolysosomal system. Both structures have been proposed as a potential targets for NAADP [54]. Whereas both metabotropic (P2Y) and ionotropic (P2X) families of purinoceptors are well-studied cell-surface receptors for ATP and other nucleotides, P2X4 has been found to be expressed in lysosomes and targeting motifs identified [67].

However, there are no currently available reports regarding that NAADP can modulate this channel, although high concentrations of NAADP may interact with P2Y receptors at the plasma-membrane-activating phospholipase C-linked signalling pathways [54]. Resently it was shown that the Ca^{2+}-signals evoked by each P2Y receptor subtype required activation of phospholipase C and release of Ca^{2+} from intracellular stores via IP_3Rs, but they were unaffected by inhibition of ryanodine or NAADP [37].

Notably, the TPCs family of endolysosomal proteins was recently has been shown to be regulated by NAADP [7; 12; 34]. Currently it is almost sustain that TPCs works as NAADP-sensitive Ca^{2+} channels, that was confirmed using by multiple approaches such as molecular manipulation of TPCs levels by overexpression [7; 8; 12; 80] or knockdown [7; 12], as well as electrophysiological analyses [10; 65; 71; 77], all support the role of TPCs as NAADP-sensitive Ca^{2+} channels. The physiological importance of TPCs has been confirmed for smooth muscle contraction [74], differentiation [1] and endothelial cell activation [31], consistent with earlier studies implicating NAADP in these processes [6; 10 ;11]. However, whether TPCs directly interact with NAADP still are questionable unresolved issue. Notably, overexpression of mammalian TPC2 modestly increased [^{32}P]NAADP binding activity, but the increase in binding was much lower than the increase in TPC2 mRNA levels (3-fold *versus* ~250-fold) [12]. Although [^{32}P]NAADP binding activity was also found in immunoprecipitation studies using antibodies to sea urchin TPCs [69]. The proteins photolabeled by [^{32}P-5N_3]NAADP have molecular masses smaller than the sea urchin TPCs, and antibodies to TPCs do not detect any immunoreactivity that comigrates with either the 45-kDa or the 40-kDa photolabeled proteins [76]. Interestingly, antibodies to TPC1 and TPC3 were able to immunoprecipitate a small fraction of the 45- and 40-kDa photolabeled proteins, suggesting that these proteins associate with TPCs. These data suggest that high affinity NAADP binding sites are distinct from TPCs [76]. Quite surprising the report recently appealed suggesting that TPCs are not gated by NAADP [14]. It was identified an endolysosomal ATP-sensitive

Na^+ channel ($lysoNa_{ATP}$), which is a complex formed by TPCs1 and TPCs2 and mTOR (mammalian target of rapamycin) [14].

Genetic analysis of the lysosomal storage disease MLIV (mucolipidosis type IV) uniquely identified mutations in a gene encoding a putative ion channel [2], where as other storage diseases are due to defects in enzymes or transporters. The protein encoded by this gene, TRPML1, has homologies with ion channels of the Trp (transient receptor potential) family [73]. Two homologues mucolipin-2 and mucolipin-3 were subsequently identified [16]. TRPML1 was found as expected to localize to lysosomes, and lysosometargeting motifs were identified [66; 75]. TRPML1 is a cation channel with evidence that it is permeant to H^+, Ca^{2+} and Fe^{2+}, among others [15; 29; 44]. As the first ion channel definitively localized to lysosomes, it was an obvious candidate for mediating NAADP-evoked Ca^{2+} release from acidic stores. The results of Zhang A.F. et al. [80] suggest that NAADP increases lysosomal TRP-ML1 channel activity to release Ca^{2+}, which promotes the interaction of endosomes and lysosomes and thereby regulates lipid transport to lysosomes. Failure of NAADP-TRP-ML1 signaling may be one of the important mechanisms resulting in intracellular lipid trafficking disorder and consequent mucolipidosis. Recent studies in controversial established that TRPML1 and TPCs are present in the same complex, they function as two independent organellar ion channels and that TPCs, not TRPMLs, are the targets for NAADP [77].

Although there is substantial evidence that RyRs are the principal effectors of cADPR-induced Ca^{2+}release from the ER, a number of studies have also implicated RyRs in NAADP-evoked Ca^{2+} release [25; 35]. In many cells, NAADP-evoked Ca^{2+} release is certainly sensitive to RyR blockers, and in many cases this may be a manifestation of the trigger hypothesis, where NAADP recruits ER stores via CICR [41; 42]. However, in a number of studies, NAADP has been proposed to directly activate RyRs on the ER [52; 39], their major site of subcellular localization, or RyRs on acidic stores, for which there is some evidences [51]. Study by Dammermann and Guse [25] in Jurkat cells extensivly characterize a robust Ca^{2+}-mobilizing response to microinjection of NAADP, which has the characteristic bell-shaped dose-response curve in mammalian cells. Furthermore, this response is sensitive to RyR inhibition and RNAi (RNA interference)-based knockdown of RyR expression [25]. In addition the latter effects are apparently insensitive to agents that interfere with Ca^{2+} storage by acidic organelles [25]. Similarly, in pancreatic acinar cells, NAADP releases Ca^{2+} from the nuclear envelope, a contiguous Ca^{2+} store with the ER, which again is sensitive to RyR inhibitors, but not by agents affecting acidic store Ca^{2+} store [35]. Direct evidence for NAADP regulation of RyRs has come from studies on purified RyRs incorporated into lipid bilayers, whereby NAADP at nanomolar concentrations was found to activate the skeletal muscle RyR1 isoform with conductances typical for authentic RyRs [39]. Such conclusions are based on the purity of the incorporated protein fractions. However, other bilayer studies of purified RyRs have failed to show their significant activation by NAADP [39; 23]. Besides heterologous expression of RyRs in HEK-293 cells enhances cADPR, but not NAADP evoked Ca^{2+} release [57]. Furthermore, ot was revealed that NAADP mobilizes Ca^{2+} in cells lacking RyRs, but requiring TPC expression [12; 57].

Physiological roles of NAADP-induced Ca^{2+} release. NAADP has been shown to regulate a variety of cellular functions including muscle contraction and differentiation [62]. It is generally believed that NAADP pathway recruits in the same agonists signaling pathways that previously were thought to be couple exclusively to IP_3 production

[32]. The latter include endothelin-1 [42], cholecystokinin [78], and glutamate [59]. Such a multiplicity of Ca^{2+} release channels as well as their modulation by wild variety of extracellular triggers provides a favour explanation for the heterogeneity of the Ca^{2+} signals. The resulting Ca^{2+} signals have been implicated in a variety of cellular events including fertilisation [19; 48], neuronal growth [9] and blood pressure control [11]. Recent study highlighted a selective role for NAADP in stimulating exocytosis in immune cell which is crucial for their function. [26]. It was shown that NAADP activates TPCs to triger exocytosis via a way that is not mimicked by global Ca^{2+} signals induced by IP_3 or ionomycin, suggesting that local Ca^{2+} nanodomains around TPCs. Hence, the NAADP/TPC pathway surves to generate Ca^{2+} signals and consequently to exocytosis of cytolytic granules folloving by cell killing [26].

Furthermore, NAADP signaling pathway is involved in insulin-induced stimulating GLUT4 and GLUT1 translocation and glucose uptake in adipocytes [72].

CONCLUSIONS

Much evidence indicates that NAADP evokes cytosolic Ca^{2+} signals through the concerted mobilization of Ca^{2+} acidic stores and the ER. Spatial localization of intracellular Ca^{2+} channels is therefore likely to be an important determinant of cellular Ca^{2+} signalling. Future studies are needed to evaluate and define the subcellular arrangments through which channels communications are happening. The fundamental question that still remains unanswered is how to identity the NAADP receptor.

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ПРОЦЕС ВИВІЛЬНЕННЯ Ca^{2+} І НІКОТИНАЦИДАДЕНІНДИНУКЛЕОТИД ФОСФАТ

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Стаття присвячена відкриттю нікотинацидаденіндинуклеотид фосфату (НААДФ) як речовини, що здатна вивільнювати Ca^{2+} з внутрішньоклітинних депо. Розкрито сучасні уявлення про механізми синтезу НААДФ у клітині за участі ферменту CD38. Вплив НААДФ описано для різних клітин та тканинних препаратів як ссавців, так і яєць морського їжака. Коротко охарактеризовано кислотне депо клітин, яке, як показано різними дослідниками, є чутливим до НААДФ. Можливі механізми наповнення цих депо кальцієм залучені до створення протонного градієнта на мембранах кислих депо. Перелічені канальні структури кислотних депо і ендоплазматичного ретикулуму, які можуть вважатися рецепторами НААДФ. Розглянуто існуючі на сьогодні гіпотези впливу НААДФ на внутрішньоклітинні кальцієві депо: пряма модель, тригерна, проміжного спряження та конформаційного спряження, а також уніфікована гіпотеза, що пояснює розбіжності між усіма механізмами. Описано фізіологічні процеси, у яких залучений НААДФ.

Ключові слова НААДФ, Ca^{2+}, ацидофільне депо, ріанодинові рецептори, двопорові канали.

ПРОЦЕСС ОСВОБОЖДЕНИЯ Ca^{2+} И НИКОТИНАЦИДАДЕНИНДИНУКЛЕОТИД ФОСФАТ

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Статья посвящена открытию никотинацидадениндинуклеотид фосфата (НААДФ) как вещества, которое способно вызывать освобождение Ca^{2+} из внутриклеточных дэпо. Раскрыто современные представления о механизмах синтеза НААДФ в клетке с участием фермента CD38. Влияние НААДФ описано для различных клеток как млекопитающих, так и яиц морского ежа. Кратко охарактеризировано кислотное депо клеток, которое, как это показано разными исследователями, чувствительное к НААДФ. Предполагаемые механизмы наполнения этих депо кальцием вовлечены к созданию протонного градиента на мембранах кислых депо. Перечислены канальные структуры кислотных дэпо и эндоплазматического ретикулума, которые могут считаться рецепторами НААДФ. Рассмотрены существующие сегодня гипотезы влияния НААДФ на внутриклеточные кальциевые депо: прямая модель, тригерная, промежуточного спряжения и конформационного спряжения, а также унифицированная гипотеза, которая объясняет разногласия между всеми механизмами. Описаны физиологические процессы, в которые вовлечен НААДФ.

Ключевые слова: НААДФ, Ca^{2+}, ацидофильное депо, рианодиновые рецепторы, двухпоровые каналы.

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