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Review

Ca^{2+} microdomains, NAADP and type 1 ryanodine receptor in cell activation☆

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ABSTRACT

Nicotinic acid adenine dinucleotide phosphate (NAADP) is a Ca^{2+} mobilizing second messenger that belongs to the superfamily of regulatory adenine nucleotides. Though NAADP has been known since 20 years, several aspects of its metabolism and molecular mode of action are still under discussion. Though the importance of the type 1 ryanodine receptor was discovered and published already in 2002 Hohenegger et al. (2002 Oct 15) , recent data re-emphasize these original findings in pancreatic acinar cells and in T-lymphocytes.
Here we review recent developments in NAADP formation and metabolism, putative target Ca^{2+} channels for NAADP with special emphasis on the type 1 ryanodine receptor, and NAADP binding proteins. The latter are basis for a unifying hypothesis for NAADP action. Finally, the role of NAADP in T cell Ca^{2+} signaling and activation is discussed. This article is part of a Special Issue entitled: Calcium and Cell Fate edited by Jacques Haiech, Claus Heizmann and Joachim Krebs.

1. Regulatory adenine nucleotides and NAADP

NAADP belongs to a superfamily of signaling molecules, the regulatory adenine nucleotides. These comprise the long known intracellular co-substrates adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD) and their metabolites (Fig. 1). Although the intracellular functions of ATP and NAD in energy metabolism have been known for decades, it only became evident in the past couple of years that ATP and NAD can be released from cells. ATP and its metabolites adenosine diphosphate, adenosine monophosphate and adenosine, generated by ectoenzymes CD39 and CD73, fulfill important paracrine signaling functions, especially regulating local inflammatory responses (Fig. 1; reviewed in [2]). In a similar manner, NAD, when released from cells, may serve on the one hand as substrate for ADP-ribosylation of target proteins (Fig. 1), e.g. the P2X7 purinergic receptor (reviewed in [2]). On the other hand NAD can be converted by CD38 in type II conformation to generate extracellular cyclic adenosine diphosphoribose (cADPR) and adenosine diphosphoribose (ADPR) (Fig. 1). The former acts as paracrine signaling molecule in several cell systems (reviewed in [3]).

In addition, ATP and NAD can also be converted inside cells to second messenger molecules involved in the transmission of extracellular signals into the intracellular machinery to generate appropriate cellular responses. ATP can be converted to the second messenger 3′,5′-cyclic adenosine monophosphate (Fig. 1), while NAD serves as precursor of cADPR and ADPR. The intracellular conversion of NAD to ADPR and cADPR likely proceeds via CD38 in type III conformation, meaning that the N-terminus of CD38 is located within the cytosol (Fig. 1). ADPR may also be produced by degradation of poly-ADP-ribosylated proteins (reviewed in [4]). The synthetic pathway to NAADP is less clear and will be discussed below. In addition to these well studied messenger molecules, additional signaling metabolites of NAD have been described, e.g. 2′-phospho-cyclic adenosine diphosphoribose [5,6] and diadenosine homodinucleotide compounds P18 and P24 [7,8].

While 3′,5′-cyclic adenosine monophosphate activates protein kinase A, the NAD metabolites cADPR, ADPR and NAADP are all regulators of the free cytosolic Ca^{2+} concentration. ADPR, the main product of CD38, binds to the NudT9 homology domain to open the non-specific cation channel transient receptor potential, subtype melastatin 2 (TRPM2; [9]). cADPR evokes release of Ca^{2+} from the endoplasmic reticulum (ER) by opening of ryanodine receptors (RyR), likely via a specific binding protein [10,11].

In this review we will concentrate on NAADP (Figs. 1, 2), the most potent endogenous Ca^{2+} releasing molecule known to date. It is confirmed that NAADP is rapidly produced upon cell stimulation [12–15] and releases Ca^{2+} from endogenous Ca^{2+} stores. As will be specified

Abbreviations: ATP, adenosine triphosphate; ADPR, adenosine diphosphoribose; cADPR, cyclic adenosine diphosphoribose; ER, endoplasmic reticulum; IP_3, D-*myo*-inositol 1,4,5-trisphosphate; IP_3R, D-*myo*-inositol 1,4,5-trisphosphate receptor; NAADP, nicotinic acid adenine dinucleotide phosphate; NAADP-BP, NAADP binding protein; NAD(P), nicotinamide adenine dinucleotide (phosphate); NFAT, nuclear factor of T cells; RyR, ryanodine receptors; RyR1 (or 2, or 3), type 1 (or 2, or 3) ryanodine receptor; TRP-ML1, transient receptor potential cation channel, subtype mucolipin 1; TRPM2, transient receptor potential cation channel, subtype melastatin 2.

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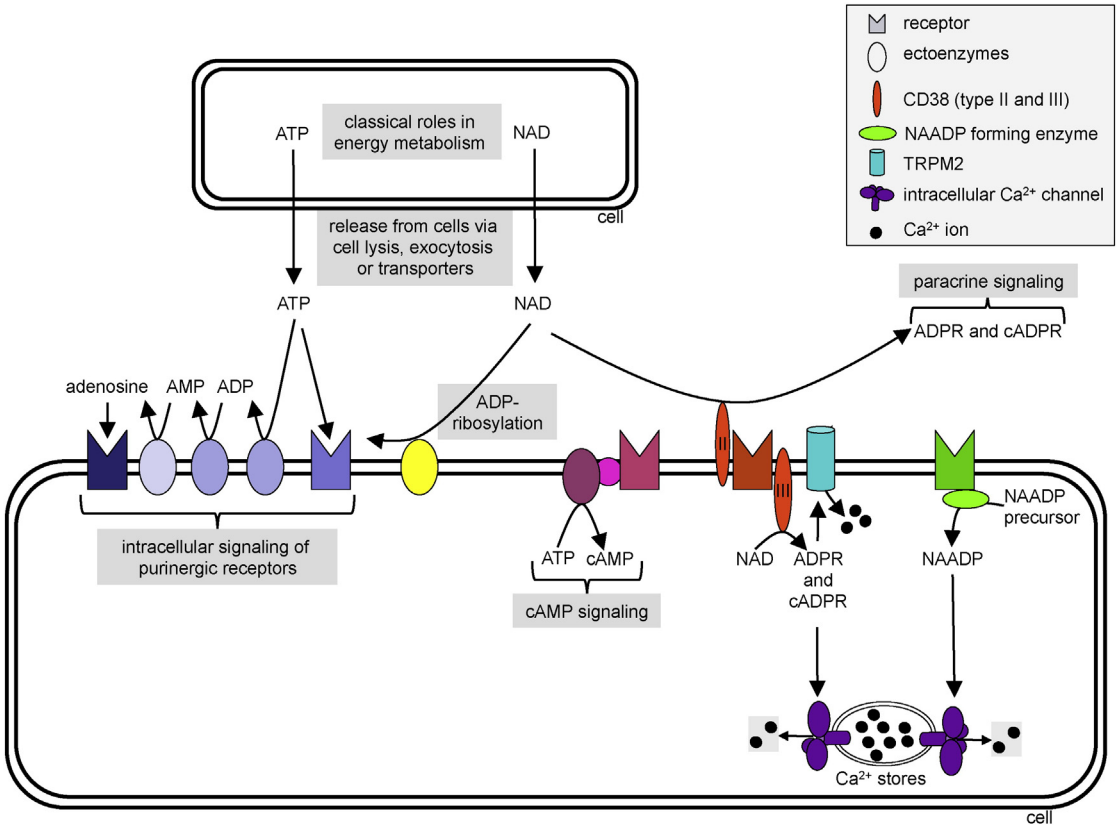

Fig. 1. Overview of extra- and intracellular regulatory adenine nucleotides. While ATP and NAD fulfill their classical roles in energy metabolism inside cells, they may be released from cells, e.g. at sites of inflammation. ATP may act on purinergic receptors and/or is converted by ecto-enzymes CD39 and CD73 via ADP and AMP to adenosine. Purinoceptors and adenosine receptors activate specific intracellular signaling that is not discussed in detail here. Extracellular NAD either serves as substrate for ADP-ribosylation (reviewed in [2]) or may be converted by ecto-enzyme CD38 (in type II conformation) to cADPR and ADPR. Work mainly carried out by De Flora and co-workers (reviewed in [3]) showed extracellular (paracrine) effects of cADPR and ADPR. Here, cADPR is taken up by certain cell types via nucleoside transporters and acts intracellularly on RyR, while ADPR appears to act via purinergic receptors. cAMP signaling, the canonical 2nd messenger pathway, is briefly displayed, too. The adenine nucleotide 2nd messengers cADPR and NAADP both release Ca^{2+} from intracellular stores; while ER/SR is accepted as target store for cADPR, different types of intracellular membrane compartments have been postulated as target store for NAADP, e.g. ER, nuclear membrane, acidic stores, or exocrine granules. Thus, the target store for Ca^{2+} releasing 2nd messengers is termed 'Ca^{2+} stores' here. The part dealing with NAADP is intended to highlight facts generally accepted: NAADP is rapidly formed inside the cell, but the precursor is still under debate. Further, it is accepted that NAADP likely does not bind to any channel directly, but rather acts via binding proteins. These NAADP-BP then may activate different ion channels located on 'Ca^{2+} stores'.

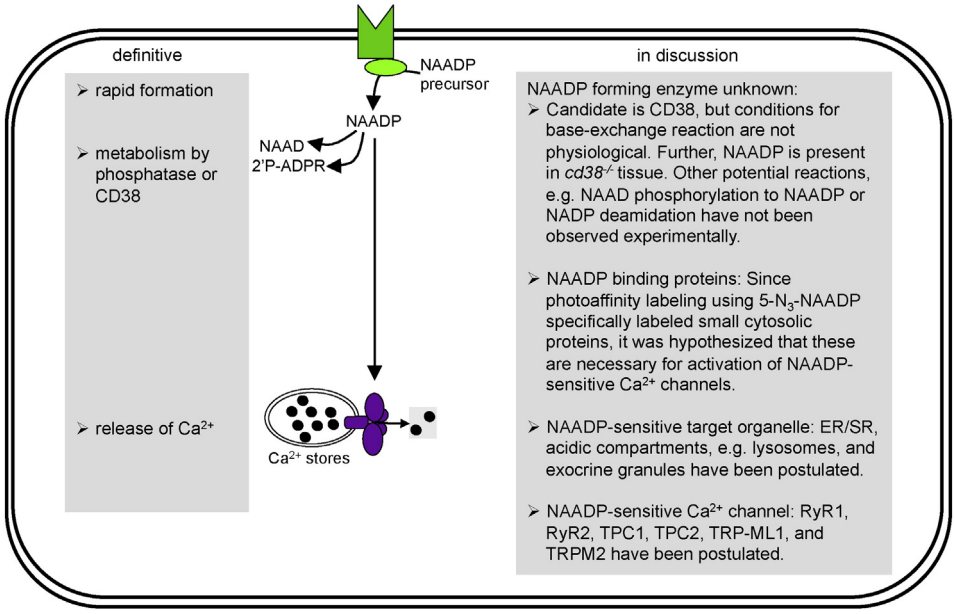

Fig. 2. Definitive vs speculative aspects of NAADP signaling. The figure displays aspects of NAADP signaling that are generally accepted ('definitive'; left side) vs aspects that are controversially discussed ('in discussion'; right side). In summary, rapid formation of NAADP, its metabolism to 2′-phospho-ADPR or to NAAD, and its strong Ca^{2+} releasing activity are well acknowledged. In contrast, enzymes, organelles and channels involved in this process are less clear; the main controversial points are summarized in the box below 'in discussion'.

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