

NAD⁺ and NADH in cellular functions and cell death.

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Source

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Abstract

Increasing evidence has indicated that NAD⁺ and NADH play critical roles not only in energy metabolism, but also in cell death and various cellular functions including regulation of calcium homeostasis and gene expression. It has also been indicated that NAD⁺ and NADH are mediators of multiple major biological processes including aging. NAD⁺ and NADH produce the biological effects by regulating numerous NAD⁺/NADH-dependent enzymes, including dehydrogenases, poly(ADP-ribose) polymerases, Sir2 family proteins (sirtuins), mono(ADP-ribosyl)transferases, and ADP-ribosyl cyclases. Of particular interest, NAD⁺-dependent generation of ADP-ribose, cyclic ADP-ribose and O-acetyl-ADP-ribose can mediate calcium homeostasis by affecting TRPM2 receptors and ryanodine receptors; and sirtuins and PARPs appear to play key roles in aging, cell death and a variety of cellular functions. It has also been indicated that NADH and NAD⁺ can be transported across plasma membranes of cells, and that extracellular NAD⁺ may be a new signaling molecule. Our latest studies have shown that intranasal NAD⁺ administration can profoundly decrease ischemic brain damage. These new pieces of information have fundamentally changed our understanding about NAD⁺ and NADH, suggesting novel paradigms about the metabolism and biological activities of NAD⁺ and NADH. Based on this information, it is tempted to hypothesize that NAD⁺ and NADH, together with ATP and Ca²⁺, may be four most fundamental components in life, which can significantly affect nearly all major biological processes. Future studies on NAD⁺ and NADH may not only elucidate some fundamental mysteries in biology, but also provide novel insights for interfering aging and many disease processes.

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NAD⁺ and NADH in brain functions, brain diseases and brain aging.

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Abstract

Numerous studies have suggested that NAD⁺ and NADH mediate multiple major biological processes, including calcium homeostasis, energy metabolism, mitochondrial functions, cell death and aging. In particular, NAD⁺ and NADH have emerged as novel, fundamental regulators of calcium homeostasis. It appears that most of the components in the metabolic pathways of NAD⁺ and NADH, including poly(ADP-ribose), ADP-ribose, cyclic ADP-ribose, O-acetyl-ADP-ribose, nicotinamide and kynurenine, can produce significant biological effects. This exquisiteness of NAD⁺ and NADH metabolism could epitomize the exquisiteness of life, through which we may grasp the intrinsic harmony life has evolved to produce. The exquisiteness also suggests a central regulatory role of NAD⁺ and NADH in life. It is tempted to propose that NAD⁺ and NADH, together with ATP and Ca²⁺, constitute a Central Regulatory Network of life. Increasing evidence has also suggested that NAD⁺ and NADH play important roles in multiple biological processes in brains, such as neurotransmission and learning and memory. NAD⁺ and NADH may also mediate brain aging and the tissue damage in various brain illnesses. Our latest studies have suggested that NADH can be transported across the plasma membranes of astrocytes, and that NAD⁺ administration can markedly decrease ischemic brain injury. Based on this information, it is proposed that NAD⁺ and NADH are fundamental mediators of brain functions, brain senescence and multiple brain diseases. Because numerous properties of NAD⁺ and NADH remain unclear, future studies regarding NAD⁺ and NADH may expose some fundamental mechanisms underlying brain functions, brain pathologies and brain aging.

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NAD⁺/NADH and NADP⁺/NADPH in cellular functions and cell death: regulation and biological consequences.

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Abstract

Accumulating evidence has suggested that NAD (including NAD⁺ and NADH) and NADP (including NADP⁺ and NADPH) could belong to the fundamental common mediators of various biological processes, including energy metabolism, mitochondrial functions, calcium homeostasis, antioxidation/generation of oxidative stress, gene expression, immunological functions, aging, and cell death: First, it is established that NAD mediates energy metabolism and mitochondrial functions; second, NADPH is a key component in cellular antioxidation systems; and NADH-dependent reactive oxygen species (ROS) generation from mitochondria and NADPH oxidase-dependent ROS generation are two critical mechanisms of ROS generation; third, cyclic ADP-ribose and several other molecules that are generated from NAD and NADP could mediate calcium homeostasis; fourth, NAD and NADP modulate multiple key factors in cell death, such as mitochondrial permeability transition, energy state, poly(ADP-ribose) polymerase-1, and apoptosis-inducing factor; and fifth, NAD and NADP profoundly affect aging-influencing factors such as oxidative stress and mitochondrial activities, and NAD-dependent sirtuins also mediate the aging process. Moreover, many recent studies have suggested novel paradigms of NAD and NADP metabolism. Future investigation into the metabolism and biological functions of NAD and NADP may expose fundamental properties of life, and suggest new strategies for treating diseases and slowing the aging process.

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