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## NAD+ and NADH in cellular functions and cell death.

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#### Abstract

Increasing evidence has indicated that NAD<sup>+</sup> 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<sup>+</sup> and NADH are mediators of multiple major biological processes including aging. NAD<sup>+</sup> and NADH produce the biological effects by regulating numerous NAD<sup>+</sup>/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<sup>+</sup>-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<sup>+</sup> can be transported across plasma membranes of cells, and that extracellular NAD<sup>+</sup> may be a new signaling molecule. Our latest studies have shown that intranasal NAD<sup>+</sup> administration can profoundly decrease ischemic brain damage. These new pieces of information have fundamentally changed our understanding about NAD<sup>+</sup> and NADH, suggesting novel paradigms about the metabolism and biological activities of NAD<sup>+</sup> and NADH. Based on this information, it is tempted to hypothesize that NAD<sup>+</sup> and NADH, together with ATP and Ca<sup>2+</sup>, may be four most fundamental components in life, which can significantly affect nearly all major biological processes. Future studies on NAD<sup>+</sup> 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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