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.