ACUTE KIDNEY INJURY

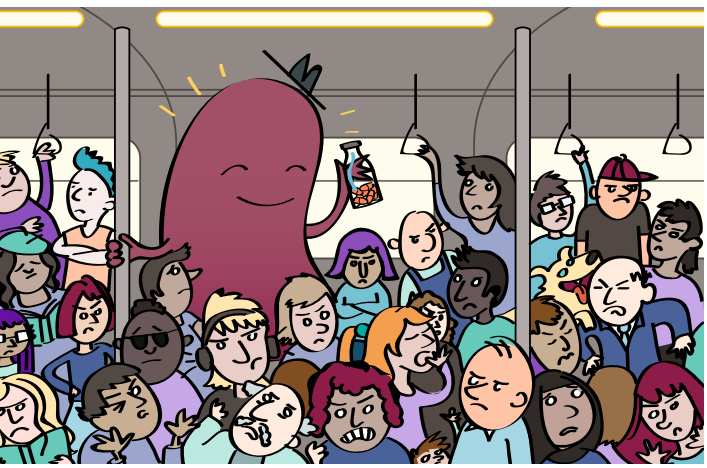
Augmenting NAD$^+$ may combat kidney stress

> impairment in de novo NAD$^+$ biosynthesis characterizes patients at risk of AKI

NAD$^+$ metabolism has been identified as a potential therapeutic target for various diseases that are characterized by substantial metabolic stress. Moreover, NAD$^+$ repletion has been shown to increase lifespan in experimental organisms. Now, new data from Samir Parikh and colleagues suggest that augmenting NAD$^+$ metabolism might improve outcomes in patients at risk of acute kidney injury (AKI).

"Our team is interested in identifying the molecular and physiological basis of resilience — how does the body tolerate severe acute stressors arising from major surgery, severe infection or extensive trauma?" says Parikh. "The kidney is a highly metabolic organ with an extremely important role in this stress response."

To investigate the effects of acute stress on kidney metabolism, the researchers analysed the urinary metabolome of a mouse model of AKI. "This unbiased method not only confirmed a series of metabolic changes that were consistent with tubular injury, but also identified a distinct signal strongly related to de novo NAD$^+$ biosynthesis, namely an elevation in the levels of quinolinate," says Parikh. "The only known role of quinolinate in metabolism is to serve as an intermediate in the conversion of tryptophan to NAD$^+$."



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In further experiments, the researchers identified quinolinate phosphoribosyltransferase (QPRT) as a mediator of resistance to AKI. This enzyme metabolizes quinolinate in one of the final steps of de novo NAD$^+$ biosynthesis. In mice, renal ischaemia led to reductions in the renal expression of QPRT and NAD$^+$ and an increase in urinary quinolinate levels. Knockout of one allele of QPRT recapitulated these effects and increased susceptibility to AKI compared with control mice.

To investigate whether urinary quinolinate concentration could be used as a non-invasive tool to identify impaired de novo NAD$^+$ metabolism in patients at risk of AKI, the researchers used a mass spectrometry approach. They assessed the urinary NAD$^+$ metabolome in a small group of patients undergoing cardiac bypass surgery and confirmed their findings in a separate cohort of >300 patients in the intensive care unit. They report that early elevations in urinary quinolinate levels and in the urinary quinolinate:tryptophan ratio were associated with an increased risk of AKI and adverse outcomes in these populations. "These data suggest that impaired NAD$^+$ metabolism leading up to kidney injury is not solely a laboratory phenomenon, but a robust finding in patients at risk of AKI," comments Parikh.

Finally the researchers assessed whether augmenting NAD$^+$ levels using oral administration of the NAD$^+$ salvage pathway precursor nicotinamide (NAM; an analogue of vitamin B3) could protect the kidneys of patients undergoing cardiac surgery. "Use of NAM to increase NAD$^+$ biosynthesis bypasses the metabolic block at quinolinate," explains Parikh. In this phase I randomized trial, NAM treatment led to an increase in the levels of circulating NAD$^+$ metabolites and was associated with higher estimated glomerular filtration rate, a reduced incidence of AKI and lower circulating levels of troponin T (a marker of cardiac injury) compared with placebo. "This trial was a small pilot in 41 patients so any conclusions are preliminary at best," cautions Parikh. "That being said, the results suggest that high doses of NAM were well tolerated, that oral administration of NAM significantly affected NAD$^+$ metabolism and that this treatment reduced the risk of AKI in the study cohort."

The researchers conclude that impairment in de novo NAD$^+$ biosynthesis characterizes patients at risk of AKI and suggest that novel therapies that augment NAD$^+$ levels could represent an important advance in the management of this population. "NAD$^+$ metabolism may be an intriguing new pathway for developing future clinical tools to predict, stratify and hopefully one day even treat AKI," adds Parikh. "Moreover, given that ageing is a major risk factor for AKI, our new findings move the basic science of NAD$^+$ and longevity into a discrete clinical context. A whole series of questions also arise about how other metabolically active organs such as the heart and brain handle acute and chronic stress, and whether these responses could also involve NAD$^+$."

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