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Title: Effect of NAD⁺ boosting on kidney ischemia-reperfusion injury

Introduction: Ischemia-reperfusion injury (IRI) is a model for acute kidney insufficiency (AKI), which results in tubular damage, dysfunction of the mitochondria and autophagy, decreased kidney cellular nicotinamide adenine dinucleotide (NAD⁺) with progressing fibrosis and CKD to follow. NAD⁺ is a co-enzyme for several proteins, including the NAD⁺ dependent sirtuins. NAD⁺ augmentation, e.g. by using it’s precursor, nicotinamide riboside (NR), improves mitochondrial homeostasis and organismal metabolism. In the present investigation, the effects of prophylactic administration of NR on post-IRI-induced AKI were studied in the rat.

Methods: Rats were randomly selected for sham or IRI. Sham and IRI were further divided into two subgroups for treatment with 500g NR/ kg rat or vehicle for two weeks before AKI induction. Bilateral ischemia was induced by clamping of both renal arteries for 45 minutes, and the rats were euthanized after 24 hours or 14 days post surgeries. Plasma biochemistry was measured, and kidneys were harvested and used for qPCR, WB, NAD⁺ assays, and histology examination.

Result: Bilateral IRI reduced kidney NAD⁺, resulted in tubular damage, reduced Klotho, and altered autophagy flux. AKI initiated progression to CKD, shown by induced profibrotic Periostin (postn) and Inhibin (Inhba) both 24 hours and 14 days after surgery. NR restored tissue NAD⁺ to that of the sham group, increased autophagy (reduced p62) and Sirtuin1, but didn’t ameliorate renal tubular damage and profibrotic genes in the 24 hours and 14 days IRI models.

Conclusion: AKI induced depletion of NAD⁺ and impaired autophagy, while administration of NR restored tissue NAD⁺ and increased autophagy. Prophylactic administration of NR did however not ameliorate the tubular damage of the IRI rats or rescue the initiation of fibrosis in the long-term AKI to CKD model, which are pivotal events in the pathogenesis CKD.