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Short-term high-fat diet intake aggravates cisplatin-induced acute kidney injury via increased oxidative stress and mitochondrial damage

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Objectives: Long-term high fat diet (HFD) intake affects kidney physiology and pathogenesis. However, the effect of short-term HFD intake on the acute kidney injury (AKI) is still undefined. Here, we investigated the effect of short-term high-fat diet intake on cisplatin-nephrotoxicity.

Methods: Mice were fed either a HFD or a low-fat diet (LFD) for 11 days or were not fed for 2 days, before cisplatin administration. Cisplatin (20 mg/kg BW) or vehicle was administered to the mice on the 11th day after the change in diet. Some mice were administered either a Mito-TEMPO, mitochondria-specific antioxidant, or vehicle every day beginning 4 days after HFD or LFD feeding until sacrifice.

Results: Cisplatin administration induced functional and structural damages to kidneys in both HFD- and LFD-fed mice, with greater damages in HFD-fed mice than LFD-fed mice. HFD increased cholesterol levels in the plasma and the kidneys, whereas HFD decreased mitochondrial total glutathione (tGSH) level. Cisplatin caused increased oxidative stress and cholesterol levels in the kidneys, along with decreased mitochondrial total GSH and the ratio of reduced GSH to tGSH. In addition, cisplatin increased Fis1 (mitochondria fission 1 protein) expression, and decreased Opa1 (mitochondria fusion 1 protein) expression, with mitochondrial damage and apoptosis of tubular cells of the kidneys in both HFD- and LFD-fed mice. These cisplatin effects were greater in HFD-fed mice than in LFD-fed mice. Administration of Mito-TEMPO significantly inhibited these cisplatin-induced changes in both HFD- and LFD-fed mice, with greater inhibitions in HFD- than in LFD-fed mice.

Conclusions: These data demonstrate that short-term HFD intake impairs the cellular redox system due to depletion of mitochondrial tGSH and increased lipid accumulation, and these changes aggravates cisplatin- nephrotoxicity. These data newly suggest that the control of calorie intake, even for a short period, could be a useful strategy for cisplatin cancer therapies.