DO WE KNOW ENOUGH ABOUT THE MECHANISM OF DIETHYLENE GLYCOL TOXICITY TO PROPOSE NEW THERAPIES?

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Objectives: Diethylene glycol (DEG) ingestion, mostly through adulterated pharmaceuticals, has produced numerous mass poisonings recently in the developing world. DEG poisoning is difficult to diagnose in most settings and the only effective treatment has been the use of hemodialysis, which also lacks wide availability. Our goal has been to better understand the mechanisms of DEG toxicity in order to develop pharmacologic agents that might be useful, particularly in suspected poisonings world-wide. DEG poisoning is characterized by acute kidney injury, hepatotoxicity and peripheral neuropathy. To better understand the mechanism of toxicity, we have shown in human, animal, and cellular studies that diglycolic acid (DGA) is the primary metabolite that accumulates and produces a specific necrotic toxicity in the kidney proximal tubule. The detailed mechanisms for the toxic effects of DGA are not understood.

Methods: Studies in human proximal tubule (HPT) cells have suggested that DGA induces mitochondrial dysfunction. To localize this mitochondrial inhibition, we have conducted studies in isolated rat kidney mitochondria and in HPT cells.

Results: These studies have discovered the novel finding that DGA acted as a calcium chelator with a potency as strong as the classic calcium chelator, EGTA. DGA also inhibited mitochondrial respiration using glutamate/malate as substrate in concentrations less than that observed in rat kidneys after DEG treatment. This effect was related to its ability to chelate calcium. Independent of this, DGA also reduced succinate-supported respiration, likely due to its ability to inhibit succinate dehydrogenase. Hence, DGA has multiple anti-mitochondrial effects - directly inhibiting succinate dehydrogenase and indirectly reducing Complex I respiration (glutamate/malate) by decreasing the supply of reducing equivalents (NADH) and likely acting as a calcium chelator.

Conclusions: These results explain how DGA inhibits oxidative phosphorylation in kidney cells, thereby leading to necrotic cell death and eventually to the acute kidney injury displayed by DEG. Studies are ongoing to determine why DGA accumulates in kidney tissue after DEG ingestion in order to design ways to reduce this accumulation and hence DGA toxicity. Such knowledge could lead to new therapies.