

The Use of CDME in Cystinosis Research

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Sirs,

With interest we have read the article entitled “Antioxidant effect of cysteamine in brain cortex of young rats” by Kessler et al. [1]. In their study, they showed that cysteamine reduces the oxidative stress caused by administration of cystine dimethyl ester (CDME) in Wistar rats.

In contrast to the antioxidant effects of cysteamine via increased production of glutathion, Jeitner and Lawrence showed that a higher dose of cysteamine induced cytotoxicity by enhanced H₂O₂ production [2]. In addition, the proposed antioxidant effects of cysteamine observed in rats with CDME administration can be different in patients with cystinosis, as Kessler et al. mentioned in their recent paper.

Because research to the pathogenesis of cystinosis was hampered by the lack of a proper in vitro model, many studies have used CDME for its ability to artificially load lysosomes with cystine, mimicking lysosomal cystine accumulation in cystinosis. This technique has been developed in the 70s by Goldman and Reeves [3, 4]. Using CDME loading, alterations in ATP metabolism and increased apoptosis have been demonstrated [5, 6]. More recent studies in human cystinotic tissues indicated the involvement of oxidative stress, possibly via alterations in glutathion metabolism [7–9].

Our group has recently shown that loading of cultured fibroblasts and human proximal tubular cells with CDME

has a direct impact on the viability of the cells by irreversible inhibition of the mitochondrial ATP production and burst of superoxide in the cells [10]. These major effects were not observed in cystinotic cells with comparable cystine levels due to mutations in the *CTNS* gene. This indicates a direct toxic effect of CDME, independent of cystine accumulation.

Based on these data we recommend that the use of CDME should be limited for studying the pathogenesis of cystinosis and conclusions drawn using this model need re-evaluation. Instead, more appropriate cell and animal models with defective *CTNS*, which already have been developed by several groups, can be used for this purpose [11–13].

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