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## **$\beta$ -Hydroxybutyrate attenuates cisplatin-induced acute kidney injury through the regulation of cellular senescence**

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**Objectives:**  $\beta$ -Hydroxybutyrate ( $\beta$ OHB), the main circulating ketone body, is metabolic fuel and endogenous signaling molecule with multi-systemic benefits. Recent studies have demonstrated an exogenous  $\beta$ OHB therapy has a reno-protective effect in various animal models of kidney disease. Cellular senescence involves proliferation arrest in response to stress, which can damage neighboring cells. In the present study, we investigated whether the exogenous  $\beta$ OHB affects kidney damage via the regulation of cellular senescence in the murine model of cisplatin-induced acute kidney injury (AKI).

**Methods:** Cisplatin-induced AKI was induced by intraperitoneal injection of cisplatin into C57BL/6 male mice.  $\beta$ OHB was administered intraperitoneally before cisplatin injection. The mice were divided into four groups: Control,  $\beta$ OHB, cisplatin, and  $\beta$ OHB + cisplatin. Renal function, histologic findings, senescence marker, and senescence-associated secretory phenotype (SASP) marker were investigated.

**Results:** The histologic damage score and serum creatinine levels were significantly lower in the  $\beta$ OHB + cisplatin group than in the cisplatin group. Protein expression of the senescence marker, p21, was increased in the cisplatin group compared to the  $\beta$ OHB + cisplatin group. Gene expression of Cdkn1a and Cdkn2a, which translates p21 and p16 respectively, was markedly increased in the cisplatin group but attenuated in the  $\beta$ OHB + cisplatin group. Gene expression of SASP markers (tumor necrosis factor- $\alpha$ /interleukin-6/interleukin-1) was also upregulated in the cisplatin group compared to the  $\beta$ OHB + cisplatin group.

**Conclusions:** The present study shows that  $\beta$ OHB attenuates cisplatin-induced AKI, which is associated with the suppression of cellular senescence. Further studies are needed to determine the role of the ketone body in cellular senescence occurring in AKI.