Abstract

The heme component of myoglobin plays a crucial role in the pathogenesis of rhabdomyolysis-associated acute kidney injury (RM-AKI). Heme oxiganenase-1 (HO-1) is the rate-limiting enzyme of heme catabolism, and its metabolites, iron, biliverdin, and carbon monoxide, have antioxidant properties. Tin chloride ($SnCl_2$) is a kidney specific HO-1 inducer. In this study, we examined whether the induction of HO-1 in the kidney by $SnCl_2$ pretreatment ameliorates RM-AKI in rats and if the effect is due to the degradation of excess renal free heme. We developed an RM-AKI rat (male Sprague-Dawley rats) model by injecting glycerol (Gly) in the hind limbs. RM-AKI rats were pretreated with saline or $SnCl_2$ or additional SnMP (tin mesoporphyrin, a specific HO inhibitor) followed by Gly treatment. Serum blood urea nitrogen (BUN) and creatinine (Crea) were measured as indicators of renal function. Renal free heme level was assessed based on the levels of δ-aminolevulinate synthase (ALAS1), a heme biosynthetic enzyme, and nuclear BTB and CNC homology 1 (Bach1), an inhibitory transcription factor of HO-1. Elevated free heme levels lead to decreases in ALAS1 and nuclear Bach1. After 24 h of Gly injection, serum BUN and Crea levels in saline-pretreated rats were significantly higher than those in untreated control rats. In contrast, $SnCl_2$-pretreated rats showed no significant increase in the indices. However, additional treatment of SnMP abolished the beneficial effect of $SnCl_2$. Renal ALAS1 mRNA levels and renal nuclear Bach1 protein levels in the saline pretreated rats were significantly lower than those in control rats 3 h after Gly injection. In contrast, the levels in $SnCl_2$-pretreated rats were not altered. The findings indicate that $SnCl_2$ pretreatment confers protection against RM-AKI by virtue of HO-1 induction in the renal system, at least in part through excess free heme degradation.