Contribution of High Concentrations of PTH(1-34) to Muscle Weakness in Uremia by Suppression of Guanidinoacetic Acid Synthesis

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Dear Sir,

Baczynski et al. [1] demonstrated that intraperitoneal administration of high doses – 200 or 300 U/day for 4 days – of PTH (1–34) impaired the production, transfer-ance and/or utilization of energy in skeletal muscle in rats. We have carried out this study to clarify whether a high concentration of PTH (1–34) as a uremic toxin contributes to the muscle weakness in uremia caused by the suppression of guanidinoacetic acid (GAA) synthesis. GAA, a precursor of creatine, is an essential substrate for muscle energy metabolism [2]. GAA is formed from arginine and glycine by glycine-amidinotransferase (trans-amidinase) mainly in the kidney [2]. Magri et al. [3] and McGuire et al. [2] demonstrated that transamidinase was located only in the proximal segment of the nephron, especially in the inner mitochondrial membranes. Takeda [4] also demonstrated that GAA synthetic activity was detected in rat tubular suspensions [4]. On the other hand, muscular creatine deficiency might induce muscle weakness in uremic rats [5]. 1×10^{-6} to 1×10^{10} M of PTH (1–34) (Toyojozo Co. Ltd., Tokyo, Japan) was added to the tubular suspension, and then incubated with 1 mM arginine and 1 mM glycine at 37 °C for 60 min. 1×10^{-6} M of PTH (1–34) significantly suppressed the synthesis of GAA, as shown in figure 1, although the concentration was higher than that in uremic serum.

Baczynski et al. [1] reported that administration of high doses of PTH (1–34) impaired the mitochondrial oxygen consumption in skeletal muscles. Thus, we speculated

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PTH (1–34), M

Fig. 1. Effect of various concentrations of PTH (1–34) on GAA synthesis in rat tubular suspension. Values are mean $\pm$ SE. Statistical analyses were performed by the Mann-Whitney rank-sum test (* $p < 0.01$).

that a high concentration of PTH (1–34) might suppress GAA synthesis by direct impairment of mitochondrial activity in the proximal tubules.

It is indicated that high concentrations of PTH (1–34) suppress GAA synthesis and enhance creatine deficiency. These findings suggest that a high concentration of PTH (1–34) might contribute to muscle weakness in uremia.

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