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Non-classical target organs of calcimimetics - The cardiovascular system and the growth plate

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Type II calcimimetic compounds effectively and transiently suppress parathyroid hormone (PTH) secretion by allosterically modulating calcium-sensing receptor (CaR) on parathyroid and increasing the receptor's sensitivity to extracellular ionized calcium, its physiological ligand. They represent a breakthrough for the treatment of primary and uremic secondary hyperparathyroidism.

CaRs are ubiquitously expressed throughout the body tissues, including growth plate hypertrophic chondrocytes and vascular system.

CaR activation by calcimimetic R568 *in vitro* has been shown to promote chondrocyte proliferation and improved longitudinal growth. Moreover, serum testosterone levels, which affect the linear growth, have been shown to be reduced by calcimimetics in uremic patients by about 30 %.

Recently, a study using tail-cuff plethysmography suggested that intermittent administration of the calcimimetic R568 lowers systolic blood pressure in subtotally nephrectomised rats.

Therefore, CaRs may have further functions beyond calcium homeostasis. In the present study, the effects of calcimimetic agents cinacalcet and R568 on longitudinal growth and blood pressure (BP), respectively, were studied in *in vivo* uremic rat model.

In this study, it is shown that cinacalcet does not impact on the growth plate chondrocyte function and the longitudinal growth in growing healthy and uremic male rats, but exerts anabolic action on uremic rats which deserves further study to elucidate the underlying molecular mechanisms.

Long-term calcimimetic R568 administration transiently reduces BP in healthy rats and has a strong persistent antihypertensive action in uremic rats, which is at least in part due to peripheral vasodilation. Injection of daily doses of R568 causes an initial BP increase in sham-operated and uremic rats, which in uremic rats is followed by a marked and sustained antihypertensive effect.

Randomized controlled trials are still required to exclude specific pediatric side effects before routine administration in growing children with chronic kidney disease.

On the basis of these experimental observations, it will be of interest to investigate whether similar BP lowering occurs in uremic patients as well.