Tissue non-specific alkaline phosphatase inhibition: a novel strategy to prevent the development of vascular calcification?

Background and Aim

Vascular calcification is a major clinical problem, particularly in elderly and in patients suffering from chronic kidney disease (CKD), diabetes and osteoporosis. Pyrophosphate (PPi) is a well-known calcification inhibitor that binds to nascent hydroxyapatite crystals and further prevents the incorporation of inorganic phosphate (Pi) into these crystals. However, the enzyme tissue non-specific alkaline phosphatase (TNAP), which is highly expressed in calcified arteries, degrades extracellular PPi into Pi ions, by which PPi loses its ability to block vascular calcification. Here, we aimed to evaluate whether a TNAP inhibitor is able to prevent the development of arterial calcification in a rat model of warfarin-induced vascular calcification.

Study Design and Methods

- Induction of vascular calcification by a warfarin containing diet
- Daily administration of vehicle versus TNAP inhibitor via i.p. catheter
- Biochemical analysis
  - Serum phosphorus and calcium levels
  - Serum alkaline phosphatase (ALP) activity
  - Serum aspartate transaminase (AST) and alanine transaminase (ALT) to exclude possible liver toxicity
- Evaluation of vascular calcification in the aorta, femoral or carotid arteries
- Evaluation of osteo-chondrogenic reprogramming of vascular smooth muscle cells (VSMCs) in the aorta

Results

1. Inhibition of vascular calcification in the aorta and peripheral arteries by daily TNAP inhibitor treatment

Daily treatment with a TNAP inhibitor significantly reduced vascular calcification as indicated by a significant decrease in calcium content in the aorta and peripheral arteries and a distinct reduction in area % calcification on Von Kossa stained aortic sections as compared to vehicle condition.

2. Effect of a TNAP inhibitor treatment on the osteo-chondrogenic switch of VSMCs

TNAP inhibitor treatment did not alter the mRNA expression of osteo/chondrogenic marker genes TNAP, Cbfa-1, SOX9, collagen 1 and 2. mRNA expression of osteo/chondrogenic marker genes (A) TNAP, (B) Cbfa-1, (C) Collagen 1, (D) Collagen 2 and (E) SOX9.

3. Calcium and phosphorus balance

No differences in serum calcium and phosphorus levels between vehicle and TNAP inhibitor treated rats were observed.

4. Serum liver enzymes

After 7 weeks of treatment with a TNAP inhibitor, no changes in serum ALT and AST activity were found, suggesting that TNAP inhibitor treatment did not induce liver toxicity.

5. Serum ALP activity

Serum alkaline phosphatase activity levels were not altered between vehicle and TNAP inhibitor treated rats.

Conclusion

Treatment with a TNAP inhibitor significantly reduced the development of vascular calcification in the aorta and peripheral vessels of a rat model with warfarin-induced vascular calcification.

References


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