intestinal inorganic phosphate (Pi) transport.\textsuperscript{1} PFA competitively inhibits type II Na/Pi cotransporters (intestinal NaPi-IIb, and renal NaPi-IIa and NaPi-IIc).\textsuperscript{1} Conversely, it is not an inhibitor of type III Pi transporters, namely the ubiquitous Pit-1 and Pit-2, as we have shown\textsuperscript{2} and as Professor Giachelli has demonstrated recently in this journal.\textsuperscript{3}

PFA successfully prevents Pi-induced calcification of vascular smooth muscle cells (VSMCs; EC\textsubscript{50} of 60 µM),\textsuperscript{4} but it inhibits Pi transport with very low affinity (K\textsubscript{i} 2.6 mM)\textsuperscript{2} because these cells only express type III Na/Pi cotransporters.\textsuperscript{2} Therefore, the mechanism of vascular prevention by PFA should be different from that of Pi-transport inhibition, as we have described recently (Figure 1).

In a recent study,\textsuperscript{4} we clarified the mechanism whereby PFA prevents VSMC calcification. We showed that PFA inhibits calcium-phosphate deposition in a process that is independent of any cell activity or metabolism and that is inhibits calcium-phosphate deposition in a process that is independent of any cell activity or metabolism and that is

**Figure 1** Effect of phosphonoformic acid (PFA) on inorganic phosphate (Pi) transport and calcium deposition in vascular smooth muscle cells.

Despite the fact that phosphonoformic acid (PFA) is a very weak inhibitor of the type III phosphate transporters present in vascular smooth muscle, its inhibition of calcification in cultured vascular smooth muscle cells (VSMCs) has been used to support a role for phosphate transport in vascular calcification.\textsuperscript{1} However, as pointed out by Villa-Belletso and Sorribas,\textsuperscript{2} PFA is also a non-hydrolyzable analog of pyrophosphate (PPI). PPI is a potent, direct inhibitor of hydroxyapatite crystal formation that inhibits vascular calcification \textit{in vitro} and \textit{in vivo}, a property shared by a number of analogs, including bisphosphonates.\textsuperscript{3} Not surprisingly, Villa-Belletso and Sorribas have shown that this is also the mechanism by which PFA inhibits calcification in VSMCs. This is yet another example of a ‘specific’ inhibitor that, like most ‘specific’ inhibitors, is not specific.

Subsequent studies using antisense RNA directed against Pit-1 have also shown inhibition of calcification in VSMCs,\textsuperscript{4} supporting a role for phosphate transport. However, caution must also be exercised in interpreting these results because VSMCs undergo substantial phenotypic changes in culture and lack the normal elastin matrix, which is the site of medial calcification \textit{in vivo}. Using the whole aorta culture method, we have been unable to duplicate many of the findings in VSMCs related to medial calcification. Thus, the intriguing and potentially important role of phosphate transporters in vascular calcification, although widely cited, remains to be proven in a relevant model.


**Response to ‘On vascular calcification prevention with phosphonoformate and bisphosphonates’**

Kidney International (2009) 75, 1356; doi:10.1038/ki.2009.113

Koba A. Lomashvili\textsuperscript{1} and W. Charles O’Neill\textsuperscript{1}

\textsuperscript{1}Emory University, Renal Division, WMB 338, Atlanta, Georgia, USA

Correspondence: W. Charles O’Neill, Emory University, Renal Division, WMB 338, 1639 Pierce Dr, Atlanta, GA 30322, USA.

E-mail: wonell@emory.edu