In vitro and in vivo studies using non-traditional bisphosphonates

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Abstract

Non-traditional bisphosphonates, that is, bisphosphonates that do not inhibit osteoclast viability or function, were initially reported in the 1990s by Socrates Papapoulos' group. Originally designed to study the role of the R1 residue of aminobisphosphonates on bisphosphonate affinity for hydroxyapatite, these modified bisphosphonates retained similar affinity for mineralized bone as their parent compounds, but they lacked the potential to inhibit the mevalonate pathway or bone resorption. We found that, similar to classical bisphosphonates, these non-traditional compounds prevented osteoblast and osteocyte apoptosis in vitro through a pathway that requires the expression of the gap junction protein connexin 43, and the activation of the Src/MEK/ERK signaling pathway. Furthermore, one of those compounds named IG9402 (also known as amino-olpadronate or lidadronate), was able to inhibit osteoblast and osteocyte apoptosis, without affecting osteoclast number or bone resorption in vivo in a model of glucocorticoid-induced osteoporosis. IG9402 administration also ameliorated the decrease in bone mass and in bone mechanical properties induced by glucocorticoids. Similarly, IG9402 prevented apoptosis of osteoblastic cells in a model of immobilization due to hindlimb unloading. However, in this case, the bisphosphonate was not able to preserve the bone mass, and only partially prevented the decrease in bone mechanical properties induced by immobilization. The effect of IG9402 administration was also tested in a mouse model of masticatory hypofunction through the induction of masseter muscle atrophy by unilateral injection of botulinum toxin type A (BoNTA). IG9402 partially inhibited the loss of trabecular bone microstructure in the mandibular condyle, but not the decrease in masseter muscle mass induced by BoNTA administration. In summary, these non-traditional bisphosphonates that lack anti-resorptive activity but are able to preserve osteoblast and osteocyte viability could constitute useful tools to study the consequences of preventing apoptosis of osteoblastic cells in animal models. Furthermore, they could be used to treat conditions associated with reduced bone mass and increased bone fragility in which a reduction of bone remodeling is not desirable.

Keywords

KeyWords Plus:OSTEOCYTE APOPTOSIS; BOTULINUM TOXIN; MASTICATORY MUSCLES; BONE; CONNEXIN-43; DISSOCIATION; OSTEOCLASTS; OSTEOBLAST; OSTEONECROSIS; INHIBITION

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