PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Bisphosphonates prevent osteocyte apoptosis

ArticleInfo		
ArticleID	:	226
ArticleDOI	:	10.1186/ar-1999-66755
ArticleCitationID	:	66755
ArticleSequenceNumber	:	183
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 1999–11–30 OnlineDate : 1999–11–30
ArticleCopyright	:	Current Science Ltd1999
ArticleGrants	:	
ArticleContext	:	130753311

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Keywords

Apoptosis, bisphosphonate, calcitonin, glucocorticoid, osteoblast, osteocyte

Context

Bone quality is maintained by the concerted action of osteoclasts (bone-resorbing cells), osteoblasts (bone-forming cells), and osteocytes, which appear to have a mechanosensory function and respond to microdamage. Glucocorticoid treatment causes an increase in apoptosis of osteoblasts and osteocytes, which may contribute to increased bone fragility and the higher incidence of fractures in glucocorticoid-treated patients. Bisphosphonates are currently the most important class of antiresorptive drugs used in the treatment of such metabolic bone disorders. As well as inhibiting bone resorption by osteoclasts and decreasing the risk of fractures, long-term treatment with bisphosphonates can modestly increase bone mass, suggesting that these drugs may have effects in addition to their antiresorptive action. To determine whether bisphosphonates and calcitonin could help to reduce fracture risk and increase bone mass *in vivo*by preventing apoptosis of osteocytes and osteoblasts, thereby preserving the osteocytic network in bone and causing a net increase in bone density.

Significant findings

Concentrations of 1 nM-1 ?M bisphosphonates suppressed apoptosis (nuclear degeneration, caspase activation and loss of cell viability) of MLO-Y4 cells and osteoblasts. This protective effect was evident regardless of the apoptosis-inducing agent (etoposide, TNF-a or dexamethasone). Similar effects were observed with 5 ng/ml calcitonin, which was shown to bind specifically to MLO-Y4 cells. Inhibition of apoptosis by bisphosphonates and calcitonin was associated with a rapid but transient increase in phosphorylation of ERKs 1 and 2. ERK activation appeared to be necessary for the antiapoptotic effect, since the ERK inhibitors PD98059 and U0126 prevented the suppression of apoptosis. Finally, alendronate treatment *in vivo* prevented bone loss and decreased the prevalence of osteocyte and osteoblast apoptosis in prednisolone-treated mice.

Comments

This study suggests that pharmacological doses of bisphosphonates and calcitonin, in addition to inhibiting bone resorption, may have the ability to promote the survival of osteocytes and osteoblasts in vivo, thereby maintaining the osteocytic network in bone, reducing bone fragility and hence reducing the risk of fracture. However, bisphosphonates probably affect many metabolic pathways and affect a wide variety of cell types in vitro, and caution should be taken when extrapolating such effects in vitro to more physiological conditions. Also, it remains unknown whether osteoblasts or osteocytes could be exposed to such concentrations of bisphosphonates, since these drugs target to bone mineral and appear to be selectively internalised by osteoclasts. Nevertheless, these interesting observations warrant further study and may have important implications for drug therapy and our understanding of bone physiology.

Methods

The osteocytic cell line MLO-Y4 or calvarial osteoblasts were treated *in vitro*with calcitonin or bisphosphonates (etidronate, pamidronate, alendronate, olpadronate or an amino-derivative of olpadronate) for 1 h. Apoptosis was then induced by the addition of tumour necrosis factor alpha(TNF-a), etoposide or dexamethasone. Apoptosis was quantitated by examination of nuclear morphology, terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) assay, the presence of caspase activity and increased trypan blue uptake. The effects of bisphosphonates and calcitonin on phosphorylation of extracellular signal-regulated kinases (ERKs) was assessed by western blotting. Apoptosis of osteocytes and osteoblasts was also quantitated, using TUNEL assay, on undecalcified sections of vertebral bone from prednisolone-treated mice.

References

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