Effect of Glucosamine and Chondroitin Sulphate on Mediators of Osteoarthritis

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Concentrations of glucosamine that more closely approximate those achieved after oral administration in horses regulate gene expression of some mediators of osteoarthritis in vitro. The influence of chondroitin sulphate on regulation of these selected genes was limited. Authors’ addresses: Department of Large Animal Clinical Sciences, College of Veterinary Medicine (Neil, Caron), and Department of Animal Science, College of Agriculture and Natural Resources (Orth, Coussens, Chan), Michigan State University, East Lansing, MI 48824-1314; e-mail: neilkirsten@hotmail.com (Neil). © 2006 AAEP.

1. Introduction

Joint disease, and in particular osteoarthritis, is an important cause of lameness in horses. The hallmark of osteoarthritis is the degeneration of articular cartilage, in part mediated by cytokine induced gene expression of degradative enzymes and inflammatory mediators. Nutraceuticals containing glucosamine and chondroitin sulphate have gained popularity as a treatment for osteoarthritis in humans and animals. Although clinical trials in horses are sparse, recent human trials support potential chondroprotective effects of these compounds, with both glucosamine and chondroitin sulphate found to protect against radiographic progression of knee and finger joint osteoarthritis, respectively. In these patients, improvement with respect to pain and physical function seems to depend on the severity of osteoarthritis lesions; those with mild to moderate disease seem to respond better than those with advanced osteoarthritis. Whether a similar response would be expected in horses remains to be determined.

Originally, beneficial effects of glucosamine and chondroitin sulphate supplementation were attributed to the provision of raw materials required for assimilation of cartilage components—glucosamine being a structural component of glycosaminoglycans (GAGs) and chondroitin sulphate being an important GAG constituent of proteoglycans, in particular aggrecan, the largest and most predominant proteoglycan in cartilage. However, the effect of these compounds seems to be more widespread. In vitro studies have shown a number of effects on the expression or activity of many mediators of osteoarthritis, including matrix metalloproteinases (MMPs), aggrecanases, nitric oxide (NO), and prostaglandin E₂. Nonetheless, most in vitro research in this area has been performed with concentrations that exceed those achievable after oral administration.

Glucosamine and chondroitin sulphate concentrations as low as 250 μg/ml³,⁴ have been effective in
inhibiting cartilage degradation in vitro. In comparison, measured plasma concentrations after oral administration of glucosamine have been ~1.0–20 μg/ml. In other studies, chondroitin sulphate concentrations have been in the range of 19–208 μg/ml depending on the species studied, molecular weight of chondroitin sulphate, and single versus multiple dose pharmacokinetics.5–8 Thus, the purpose of this study was to determine if glucosamine and chondroitin sulphate, at in vitro doses that more closely approximate those achieved clinically, influence gene expression of selected mediators of osteoarthritis in cytokine-stimulated equine articular chondrocytes.

2. Materials and Methods
Chondrocyte pellet cultures were established using grossly normal articular cartilage obtained from metacarpophalangeal joints of horses. Pellet cultures were incubated with glucosamine (2.5–10.0 μg/ml) or chondroitin sulphate (5.0–50.0 μg/ml) for 1 h before stimulation with a subsaturating dose of recombinant equine interleukin-1β (reIL-1β; 0.5 ng/ml). RNA was isolated after a 12-h incubation period. Effects on gene expression of a number of mediators of cartilage catabolism in osteoarthritis were assessed with quantitative real-time polymerase chain reaction. Genes evaluated included MMPs (MMP-1, -2, -3, -9, -13), aggrecanases (agg-1, -2), inducible NO synthase (iNOS), and cyclo-oxygenase-2 (COX-2).

3. Results
Glucosamine significantly reduced reIL-1β–induced mRNA expression of MMP-13 and aggrecanase-1 at 10.0 μg/ml. A trend for reduction in cytokine-induced expression was also observed for iNOS and COX-2. Chondroitin sulphate had no effect on gene expression at the concentrations tested.

4. Discussion
Glucosamine reduced cytokine-stimulated gene expression of a number of mediators of osteoarthritis pathophysiology, in agreement with previous in vitro studies, albeit at a lower concentration. However, chondroitin sulphate had no effect at the concentrations tested in contrast to recent studies using bovine articular cartilage explants, which showed a regulatory effect on gene expression using 20 μg/ml chondroitin sulphate.9,10 Currently recommended oral dose rates of glucosamine and chondroitin sulphate are 22 and 8.8 mg/kg, respectively.11 In a recent equine pharmacokinetic study using a single dose of glucosamine hydrochloride at a similar dose rate (20 mg/kg through nasogastric tube),12 the maximum serum concentration measured was 5.8 ± 1.7 μM (~1.0 μg/ml), with even lower concentrations measured in synovial fluid. Although the lowest effective concentration used in our study reported here was comparatively higher (10.0 μg/ml), our results show that this compound is capable of regulating gene expression of some mediators of osteoarthritis at doses that are more relevant than those used previously. This is further supported by recent studies using bovine cartilage explants, with gene expression regulated by concentrations as low as 5.0 μg/ml.11,12 These studies have also shown that concentrations of glucosamine and chondroitin sulphate in combination seem to be more effective than either compound alone, with similar findings in equine cartilage explants.13 Further studies are indicated to determine the ideal effective concentration of these compounds in combination, both in vitro and in horses afflicted with osteoarthritis.

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References