Chondroitin sulfate possesses novel mechanisms of action

By Patrick du Souich, MD, PhD

Structure of chondroitin sulfate influences its absorption, according to a number of studies.

In healthy cartilage, a superb equilibrium exists between the functions of the chondrocyte and elements of the matrix. In the presence of an aggression, this equilibrium is destabilized, and the de novo synthesis of the matrix is reduced and degradation is increased. The net result is necrosis or apoptosis of the cartilage cells.

Chondroitin sulfate reduces inflammatory signs and symptoms and delays the progression of cartilage destruction in patients with osteoarthritis. According to animal and in vitro studies, this response results from the combination of numerous effects (Table).

Chondroitin sulfate increases the synthesis of cartilage matrix components such as hyaluronic acid and proteoglycans and reduces the degradation of cartilage matrix components, specifically collagen II, glycosaminoglycans (GAG) and proteoglycans (PG), and reduces necrosis and apoptosis of chondrocytes.

On the other hand, chondroitin sulfate reduces the activity of collagenase, N-acetylg glucosaminidase, aggrecanase 1 and 2, matrix metalloproteinase (MMP) 3, MMP-9, MMP-13, MMP-14, cathepsin B and elastase. Chondroitin sulfate elicits an anti-inflammatory effect probably through diverse mechanisms such as decreasing nuclear factor κB (NF-κB) nuclear translocation, diminishing the expression of cyclo-oxygenase-2 (COX-2) and phospholipase A2, and reducing the concentrations of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), prostaglandin E2 (PGE2), nitric oxide and reactive oxygen species (ROS).

The structure and properties of polysaccharides strongly influence their absorption and bioavailability if taken orally.

Proof of action

A recent study analyzed the histology of left ankle joints in rats fed dietary bars containing placebo, chondroitin sulfate or a combination of chondroitin sulfate and glucosamine sulfate. The rats also received saline or an injection of Freund’s complete adjuvant.

In absence of chondroitin sulfate or the combination of chondroitin sulfate and glucosamine, the injection of Freund’s adjuvant produced a clear deterioration of the cartilage, e.g. cartilage thickness decreased. In rats fed chondroitin sulfate or the combination of chondroitin sulfate and glucosamine sulfate, the structures of the cartilage resembled those of healthy animals. In addition, the decrease in thickness was less pronounced in rats fed chondroitin sulfate and absent in rats receiving the chondroitin sulfate/glucosamine combination. This study clearly proves that chondroitin sulfate and glucosamine protect the cartilage.

Another study examined the effect of glucosamine and chondroitin sulfate concentrations on inducible nitric oxide synthase (iNOS), COX-2 messenger RNAs (mRNA), and PGE2. IL-1β increased iNOS and COX-2 mRNAs and PGE2 concentrations, an effect that was almost completely abrogated by both chondroitin sulfate and glucosamine. These results provide an explanation for some of the drugs’ anti-inflammatory properties.

Another study documented the effect of glucose, glucuronic acid, N-acetylg glucosamine, N-acetylgalactosamine, N-acetylmannosamine and glucosamine on levels of nitric oxide in human articular chondrocytes stimulated with IL-1β. Researchers reported that N-acetylgalactosamine, glucosamine and N-acetylg glucosamine prevented the increase in nitric oxide. Glucose, glucuronic acid and N-acetylmannosamine did not modify the production of nitric oxide. This study confirms the results of

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others showing that chondroitin sulfate reduces iNOS mRNA. It is noteworthy that chondroitin sulfate is a long chain of disaccharides of glucuronic acid and N-acetylgalactosamine with sulfates in positions 4 and 6. These studies shed light on the mechanisms underlying the anti-inflammatory and anti-apoptotic effects of chondroitin sulfate.

Chondroitin sulfate reduces the concentrations of reactive species and diminishes the translocation of NF-κB (unpublished results). These findings could factor into the reduction of MMPs, COX-2, IL-1β and TNF-α, thereby decreasing the progression of osteoarthritis. Chondroitin sulfate also elicits an effect on the nucleus by activating the formation of proteoglycans and hyaluronic acid.

**Remaining questions**

We still do not understand the full mechanism of action of chondroitin sulfate underlying the clinical response of osteoarthritis. One of the most intriguing phenomenon is how chondroitin sulfate can elicit an intracellular effect and whether chondroitin sulfate degradation products (shorter chains of disaccharides) contribute to this effect. One of the potential gates used by chondroitin sulfate to gain access into the cell could be the CD44 receptor, which is also responsible for proteoglycan degradation. Finally, taking into account that IL-1β, TNF-α and fibronectin proteolytic fragments (FN-f) elicit identical effects in the chondrocyte, e.g. activation of the Erk1/2, p38MAPK, NF-κB, MMP-13, MMP-3 and aggrecanases, we may hypothesize that the mechanism of action of chondroitin sulfate could involve extracellular blockade of FN-f receptors, the receptor for advanced glycation end products RAGE, the Toll-like receptor 2 TLR-2, and the α5β1 fibronectin receptor.

**References**


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