So far, there is no efficient treatment that could stop the pathological process of osteoarthritis (OA), and the management of the disease is mainly based on the alleviation of clinical symptoms by nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics compounds. However, some natural products have been proposed as symptomatic treatments, and named symptomatic slow acting disease modifying drugs (SYSADOA). They include glucosamine sulfate (GS), chondroitin sulfate (CS), hyaluronan (intra-articular injection), diacerein, and avocado/soybean unsaponifiable extracts. GS and CS are sold as nutraceuticals over-the-counter in the United States but they are clinically used as anti-arthritic drugs in some European countries. However, their clinical efficacy has never been clearly demonstrated and the recent large-scale multicenter trial Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) showed no significant effect of CS over placebo (Clegg et al. 2006). Several sulfated polysaccharides were also used to stimulate the tissue repair process (Verbruggen and Veys 1977). Recent data have also been reported which clearly demonstrate that dietary glucosamine could not be directly efficient in stimulating chondroitin sulfate synthesis in articular cartilage (Silbert 2009).

CS is a glycosaminoglycan (GAG) largely present in articular cartilage. It is formed of repeated disaccharide units of glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc). As constituents of proteoglycans (PGs), these anionic components contribute to the hydration of cartilage and its resistance to mechanical compression. The use of CS to improve the clinical symptoms of OA is historically based on the vague assumptions that administration of a cartilage matrix component would help chondrocytes to replace the lost environment (Uebelhart et al. 2006). Several sulfated polysaccharides were also used to stimulate the tissue repair process (Verbruggen and Veys 1977).

The mechanisms of action of CS on cartilage metabolism are not well understood. Several in vitro studies demonstrated that CS has great influence on both cartilage explants and isolated articular chondrocytes. CS stimulates the proteoglycan synthesis of bovine and human chondrocytes (Bassleer et al. 1998; Legendre et al. 2008), whereas it decreases interleukin-1β (IL-1β)-induced expression of matrix metalloproteinase-1, -3, and -13 and aggrecanase-1 and -2 (Chan, Caron, Orth 2005; Montfort et al. 2005; Legendre et al. 2008). Furthermore, some anti-inflammatory properties have been attributed to CS, based on its ability to inhibit human leukocyte chemotaxis and phagocytosis, to protect the plasma membrane from oxygen reactive species (Ronca et al. 1998) and to reduce cyclooxygenase-2 (COX-2) expression and prostaglandin E2 production by chondrocytes (Chan, Caron, Rosa, et al. 2005; Legendre et al. 2008). Recently, CS was also found to counteract IL-1β-depressed expression of transforming growth factor-β (TGF-β) receptors in chondrocytes (Legendre et al. 2008).

However, it is unlikely that these limited chondroprotective and anti-inflammatory properties could be exerted in vivo by CS on articular cartilage following oral administration of the glycosaminoglycan. In fact, polysaccharides are poorly absorbed through the digestive system (Baici et al. 1992), and only 12–13% of ingested CS is absorbed intact into the bloodstream (Sakai et al. 2002). Furthermore, the half-life of CS in the circulatory system is 3–15 min, after intravenous administration (Sakai et al. 2002). When CS was administered orally to patients as a single dose of 1200 mg/day, a time peak was observed at 4 h and a maximum plasma concentration of 3.8 ± 0.6 μg/mL was measured (Ronca et al. 1998). This level is below the concentrations of CS generally used in most of the published in vitro studies. All together, these data indicate that orally administered CS is not systematically distributed to articular cartilage and that the mechanism of the CS effect in oral treatment of OA, if any, might be mediated by other pathways.

On the other hand, we may hypothesize that bringing CS in contact with joint cells could mimic the chondroprotective and anti-inflammatory effects of CS observed in vitro. This view has been recently reinforced by our study showing that CS was also capable of increasing the production of high-molecular-weight hyaluronan by cultured osteoarthritic synovial fibroblasts (Figure 1) (David-Raoudi et al. 2009). Therefore, it is reasonable to suppose that CS injected into the synovial fluid would be in direct contact with both synoviocytes and superficial chondrocytes, and therefore would exert similar effects as those found in vitro. By providing a local source, one would also eliminate the need of large amounts of CS. As such, sufficient CS can be made available and not be lost via absorption into the bloodstream. In support of such approach, intra-articular delivery of CS has been recently shown to be effective for the repair of joint defects in a rabbit model (Hui et al. 2007). Furthermore, it might be interesting to associate CS with the already existing HA intra-articular delivery. By combining these two glycosaminoglycans, which both have moderate anti-inflammatory properties (Morreale et al. 1996; Ronca et al. 1998; Kydd et al. 2007; Yasuda 2007), it may be possible to further improve therapeutic efficacy. Moreover, that CS could upregulate the local hyaluronan synthesis by joint cells would probably provide the supply...
of hyaluronan for a longer period of time than single injection of exogenous hyaluronan, which is known to have a short-life period.

However, the problem of purity and chemical structure of commercial CS samples has to be solved first. In contrast with hyaluronan, CS cannot be prepared by engineering, and animal extracts (bovine, ichthyic, avian) are still the only available sources. More information on the sequential arrangement of the disaccharide units within the chain is also required since this may have an impact on the CS biological function. Today, the requirements for quality manufacturing of nutraceuticals are not as strict as for pharmaceuticals (Adebowale et al. 2000; Saad et al. 2005; Sim et al. 2005; Barnhill et al. 2006; Malawaki et al. 2007; Lamari 2008). Great differences have been found in the composition of commercial CS preparations, particularly in the ratio of 0-, 4-, and 6-sulfated disaccharides, reflecting the great differences in the species or tissue origin (Malawaki et al. 2007).

In conclusion, to improve the efficacy of CS as a therapeutic agent in knee OA treatment, it would be of great interest to deliver solutions of this glycosaminoglycan directly into the synovial cavity, alone or in association with hyaluronan. This new approach will allow CS to exert its chondroprotective and anti-inflammatory effects on joint cells through the mechanisms already described in in vitro systems.

References

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Conflict of interest statement

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Abbreviations

CS, chondroitin sulfate; GAG, glycosaminoglycan; GS, glucosamine sulfate; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGs, proteoglycans; SYSADOA, symptomatic slow acting disease modifying drugs.