Literature Review

The Research Leading to MHB3™ Hyaluronan

ABSTRACT

Numerous studies show that exogenous hyaluronan (also known as hyaluronic acid, sodium hyaluronate, or hyaluronate sodium) can interrupt inflammatory processes and modify the course of disease progression in osteoarthritis and other causes of Chronic Joint Pain. The fundamental basis for these findings lies in the normal role of endogenous hyaluronan in the healthy body. This role can be enhanced by supplying hyaluronan, for example, through viscosupplementation (intra-articular) injection. However, it has recently been demonstrated that an orally administered hyaluronan biopolymer (MHB3™ Hyaluronan, Cogent Solutions Group, LLC) can attenuate inflammatory processes, with favorable safety and effectiveness profiles compared to those of injectable formulations. Oral hyaluronan, in particular the highly bioavailable formulation of MHB3™ Hyaluronan, is therefore recommended for long-term maintenance of critical joint structures and for ongoing anti-inflammatory prophylaxis.

INTRODUCTION

Treatment of Chronic Joint Pain typically involves the administration of non-steroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroids. However, it is increasingly recognized that the risk profile of such medications does not warrant their use in many circumstances. For this reason, there has been gradual but widespread acceptance of the use of drugs and supplements based on hyaluronan, a natural constituent of joints, having a favorable safety profile. This review highlights basic and clinical research revealing the physiological role of hyaluronan in the maintenance of joint health and the therapeutic role of hyaluronan in the treatment of inflammation, concluding with a summary of the state of current understanding concerning the absorption and distribution of MHB3™ Hyaluronan.

HYALURONAN

A ubiquitous constituent of mammalian tissues, hyaluronan, a linear alternating copolymer of D-glucuronic acid β-1,3-D-*N*-acetylglucosamine-β1,4, is particularly abundant in connective tissue. A single hyaluronan molecule can have a molecular weight as great as 8-10 million Daltons (Tammi et al. 2002). **About one-fourth of the hyaluronan in the body is found in the skeleton and joints. Certain specialized tissues and structures, such as synovial fluid, have particularly high concentrations of hyaluronan.** Considerable hyaluronan is carried in lymphatic vessels. Its persistence in plasma is quite limited, with a turnover of between 15 and 35% every minute, since it is removed efficiently and degraded by hepatic endothelial cells (Fraser at al. 1997).

HYALURONAN IN THE HEALTHY JOINT

Hyaluronan, while critical to the function of synovial fluid, is important to other joint structures as well. Articular (hyaline) cartilage in joints contains a large volume of interfibrillar material, including a high concentration of hyaluronan. Hyaluronan serves as the scaffolding to which interfibrillar proteoglycans, especially aggrecan, bind, conferring structural stability to the cartilage. In general, the osmotic pressure created by hydration of the interfibrillar material is opposed by tension in the collagen network (Cohen et al. 1998). Compression forces interfibrillar material out of hyaline cartilage. Osmotic pressure causes the exuded interfibrillar material to move back into hyaline cartilage once the load is removed. **Since hyaline cartilage lacks a blood supply (Suh et al. 1995), hyaluronan-facilitated re-entry is the sole means by which nutrients are carried into hyaline cartilage.**

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CHANGES IN HYALURONAN WITH AGING, INJURY OR DISEASE STATES

With aging or osteoarthritis, the superficial collagen network of articular cartilage loses its structural integrity. The interfibrillar component swells as the osmotic pressure created by its hydration is less efficiently opposed by the structurally unsound collagen network. Each cycle of load-bearing thus involves less transfer of fluid out of the cartilage and back in, as the pressure gradient which permits the transfer cycle is diminished (Poole et al. 2002). Concomitant with the changes in the collagen network are changes in hyaluronan. With aging, injury or osteoarthritis, the molecular weight of hyaluronan is decreased. The smaller hyaluronan molecules diffuse more easily in and out of hyaline cartilage and form a less extensive scaffolding to which proteoglycans can bind. As a practical matter, a diminution in the abundance of high molecular weight hyaluronan molecules means that each cycle of load-bearing will involve less fluid turnover and hence less nutrition of the cartilage (Moreland 2003). High molecular weight hyaluronan at joint interfaces normally impedes the flow of fluid, in a phenomenon known as outflow buffering, from the joint cavity into the subsynovial lymphatics. **In osteoarthritis the concentration and the molecular weight of hyaluronan in joints are decreased.** As a result, the hyaluronan less effectively impedes the outflow of fluid from the joint cavity into the subsynovial lymphatic system (Sabaratnam et al. 2005). **This greatly increases the requirement that hyaluronan be replaced.**

HYALURONAN AND THE CONTROL OF JOINT INFLAMMATION

Non-steroidal anti-inflammatory drugs (**NSAIDs**) have been used to control joint pain and improve function but **are associated with gastrointestinal, cardiovascular and renal adverse events, and are not believed to ameliorate the mechanical and metabolic causes of osteoarthritis** (Sarzi-

Puttini et al. 2005). However, an abundance of hyaluronan maintains the long-term structural integrity of the joint cavity. Because these large molecules diffuse only slowly, yet bind large volumes of water, they effectively resist the tendency of compression to force fluid out of the joint and into the general circulation (Coleman et al. 1999). Persistence of hyaluronan in the joint is comparable for endogenous and exogenous hyaluronan (Brown et al. 1991), consistent with favorable results observed in cases of hyaluronan supplementation. Hyaluronan is also directly involved in regulation of the inflammatory response. At sites of inflammation, deposition of hyaluronan, and its complexation with other macromolecules, promotes adhesion of leukocytes rather than their further migration, effectively preventing the leukocytes from receiving more proinflammatory signals in the underlying tissue. The hyaluronan also physically sequesters the proinflammatory mediators, effectively attenuating the inflammatory response (Day and de la Motte 2005). Clinical and experimental work is consistent with the efficacy of hyaluronan in the treatment of certain joint conditions. For example, a recent prospective, randomized, double-blind placebo controlled study evaluated the efficacy of intraarticular hyaluronan for osteoarthritis of the knee. Three weeks post-treatment outcomes were significantly more favorable for the treatment than the control group. However, by weeks 6 and 12 there were no longer any significant differences between the groups (Petrella and Petrella 2006). Recent clinical data are consistent with the notion that **provision of exogenous hyaluronan promotes endogenous hyaluronan production** (Bagga et al. 2006). Exogenous hyaluronan's stimulation of endogenous hyaluronan synthesis stands in contrast to the well-established observation that corticosteroid administration leads to diminished hyaluronan biosynthesis. An abundance of data indicates that **corticosteroids such as hydrocortisone can suppress production of hyaluronan**. In particular, it has been shown that hydrocortisone decreases the expression of *HAS2*, which encodes one of the isoforms of hyaluronan synthase, in response to cytokine stimulation, leading to decreased synthesis of hyaluronan (Jacobson et al. 2000; Wilkinson et al. 2004). It has also been demonstrated that hydrocortisone inhibits the activation of HAS1, another of the hyaluronan synthase isoforms, by interfering with signaling via the p38 mitogen-activated protein kinase pathway (Stuhlmaier and Pollaschek 2004). In addition, methylprednisolone has been shown to cause a decrease in proteoglycan synthesis and an increase in degradation of newly synthesized proteoglycans in cartilage explants (Doyle et al. 2005).

HYALURONAN ABSORPTION AND DISTRIBUTION

MHB3™ Hyaluronan is absorbed and distributed to joints. Considerable hyaluronan transport appears to take place via the lymphatics (Liu 2003). A specific receptor for hyaluronan, LYVE-1, was identified on lymph vessel walls (Banerji et al. 1999). Since joint cavities are avascular, all hyaluronan within the joint either is produced locally or arrives by diffusion. Hyaluronan flux from the intestine is stimulated by free fatty acids and bile acids (Reed et al. 1992). Importantly, it has been shown that the molecular weight of hyaluronan found in serum following intravenous administration of a 400,000 dalton formulation is less than that found in serum following oral administration. Vascular inflammatory response was attenuated less effectively by intravenous hyaluronan of 400,000 daltons than by orally administered hyaluronan (Turley and Asculai 2003). MHB3™ Hyaluronan **has been shown to be absorbed and effective against important pathophysiological processes, such as inflammation** (Turley 2008). Recent observational clinical studies are consistent with these laboratory findings (Lukens 2005; Kiburz 2006). It has been reported that in racing Quarter Horses intravenous hyaluronan delayed, but only at a statistically insignificant level, the onset of symptoms typically treated by intraarticular injection (McIlwraith et al. 1998). A comparison of intravenous and oral hyaluronan of identical molecular weight range shows that higher molecular weight fragments persist for a longer duration in plasma following oral administration, consistent with the greater observed efficacy of orally administered hyaluronan in decreasing the hallmarks of inflammation (Turley and Asculai 2003). MHB3 Hyaluronan **improves the molecular weight range of circulating hyaluronan by increasing the high molecular weight portion (anti-inflammatory) and decreasing the low molecular weight portion (pro-inflammatory)** (Turley 2008).

SUMMARY

MHB3™ Hyaluronan has been shown to be absorbed and bioactive. It can confer a greater and more persistent anti-inflammatory effect than injected hyaluronan. Where occasional injections yield a therapeutic benefit of limited duration, or suppress endogenous hyaluronan production, daily oral hyaluronan supplementation is indicated.

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