Role of high concentrations of mannitol on the stability of hyaluronan in an oxidative stress model induced by xanthine/xanthine oxidase

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Osteoarthritis (OA) is a degenerative joint disease associated with harmful action of reactive oxygen species (ROS). ROS are involved in the degradation of both aggrecan and high-molecular-weight hyaluronan (HMW-HA). The latter plays a key role in the joint lubrication and the visco-elastic and shock absorbing properties of the synovial fluid (SF).

Viscosupplementation consists in injecting intra-articularly exogenous HMW-HA to restore the SF rheological properties, that are dramatically decreased in OA. However the injected HA is also rapidly degraded by ROS, decreasing its effectiveness and duration of action.

Background

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Objective

To evaluate the ability of Mannitol, a powerful oxygen free radical scavenger, to reduce exogenous HMW-HA degradation using a model of oxidative stress induced by xanthine (X) + xanthine oxidase (XOD).

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Methods

Hyaluronan (MW# 0.8mDa) was submitted to an oxidative stress generated by the addition of X + XOD.

Then solution of the same HA + 35g/L of Mannitol in PBS buffer was studied.

Different enzyme concentrations (XOD 109 mUI/mL and 218 mUI/mL) were used and the HA properties were studied after 24 hours of contact at ambient temperature.

Changes of the viscosity of the solution were assessed by rheometry (using a rheometer at 25°C with a cone and plate geometry, steady-state viscosity was determined in Pa.s, as a function of the shear rate).

HA MW was determined by steric exclusion chromatography before and after oxidative stress.

Results

The presence of X/XOD degraded HA in the conditions tested:

- HA viscosity decreased as a function of XOD concentration,
- HA MW decreased dramatically by 36.6%.

On the opposite, in presence of high concentration of Mannitol:

- HA viscosity was stable,
- HA MW decreased only slightly (-11.9%).

Conclusion

High concentrations (3.5%) of mannitol protect HA from ROS-mediated degradation.

These in vitro data suggest that mannitol may increase the intra-articular residence time of HA and consequently may improve clinical efficacy of viscosupplementation.