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TRANSPORT OF INSULIN-LIKE GROWTH FACTOR 1 IN INTERVERTEBRAL DISC: EFFECT OF BINDING INTERACTIONS AND INHOMOGENEOUS DISTRIBUTION OF BINDING PROTEINS IN ANNULUS FIBROSUS AND NUCLEUS PULPOSUS

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INTRODUCTION

The intervertebral disc (IVD), being the largest avascular structure in human body, receives nourishment from the vascular network present near its periannular surface and at cartilage endplates (CEPs). It is believed that insufficient nutritional supply is a major cause for disc degeneration [1]. Understanding the mechanisms of solute transport in IVD is crucial for elucidating the etiology of disc degeneration, and to develop strategies for tissue repair (*in vivo*), and tissue engineering (*in vitro*). Transport in IVD is complex and involves a series of electromechanical, chemical, and biological coupled events. This study focused on the implications of solute-tissue reversible binding reactions on transport phenomena in the disc. A two dimensional (2D) finite element model was developed to predict diffusive-reactive transport in IVD. The numerical model was used to simulate transport of insulin-like growth factor 1 (IGF-1) in IVD, in the presence of binding interactions between IGF-1 and IGF-binding proteins (IGFBP-3) located on the extracellular matrix (ECM) of the disc.

THEORETICAL BACKGROUND

A model based on the mixture theory [2-4] was used in this study. The IVD was considered to be a mixture of: (1) an elastic, porous, permeable, negatively charged solid phase characterized by the presence of binding sites (IGFBP-3); (2) an interstitial fluid phase; (3) an electrolyte phase (NaCl); (4) a non-charged solute (IGF-1), able to reversibly bind to the binding sites (IGFBP-3) located in the solid phase, to generate a bound complex. The reversible binding of IGF-1 to IGFBP-3 was described by the Langmuir binding model [5].

METHODS

Human lumbar IVD was schematized as a 2D axisymmetric object consisting of two anatomical regions, the nucleus pulposus (NP) and the annulus fibrosus (AF), with dimensions and properties similar to those reported in the previous study [7]. In this study, it was assumed that the NP was superiorly and inferiorly confined by perfectly permeable CEPs. In contrast, the AF was superiorly and inferiorly confined by perfectly impermeable vertebral bodies. At the CEPs and on the lateral (i.e. periannular) surface, IVD was in contact with a physiological solution containing NaCl and IGF-1, see Figure 1a.

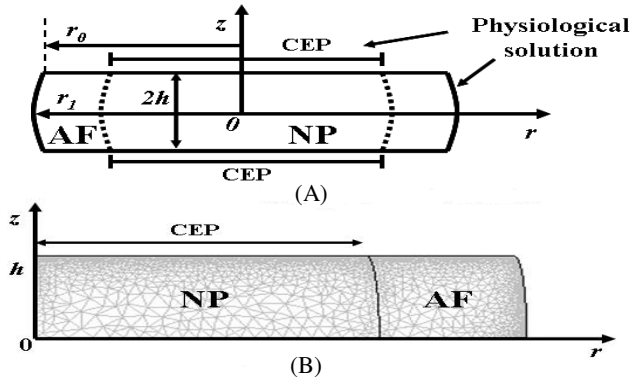

Figure 1: (a) The IVD (h = 5 mm, r_o = 19.5 mm, and r_1 = 20 mm) is shown. Along the lateral surface of AF and at CEP, the disc is in contact with a physiological solution containing 0.15 M NaCl, and IGF-1. (b) Computational domain representing the upper right quadrant of the disc.

Due to the geometrical symmetry of the problem of interest, only the upper right quadrant of the disc was modeled with a mesh consisting of 3284 quadratic Lagrange triangular elements, see Figure 1b. The

implicit solver of COMSOL® (Comsol 3.2, Comsol, Inc., Framingham, MA) was used for the simulations. Due to the lack of experimental data, transport and binding properties of IGF-1 in disc were assumed to be similar to those reported for articular cartilage [6,8]. The concentration of IGFBP-3 in IVD was assumed to be proportional to its cellular density, i.e. higher in AF (32 nM) than in NP (15.3 nM). The absorption of IGF-1 from the physiological solution surrounding the disc was investigated. Simulations were performed at several concentrations of IGF-1 in the physiological solution (IGF-1 concentration varying from 0.01 to 1000 nM).

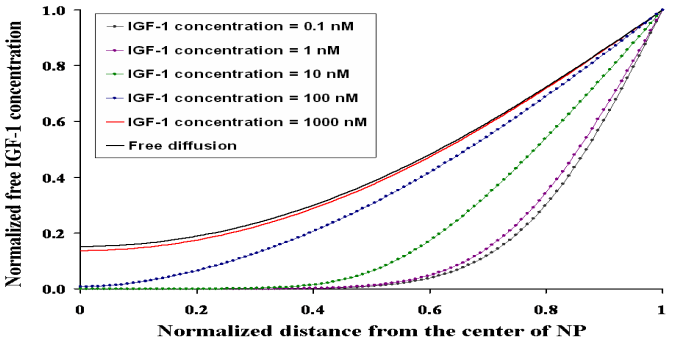

Figure 2: Profiles of concentration of free IGF-1 in NP (along axial direction, *r = 0*) after 48 hours of absorption, parametric with IGF-1 concentration in physiological solution. The concentration profile in the case of free diffusion is also shown (black line).

RESULTS AND DISCUSSION

The uptake and distribution of IGF-1 in IVD were calculated after 48 hours of IGF-1 absorption from the physiological solution in contact with the disc. The profiles of concentration of free IGF-1 in NP along the axial direction of the disc (*r = 0*), at various concentration of IGF-1 in the physiological solution, are reported in Figure 2. Data were normalized with respect to IGF-1 concentration in the physiological solution, and compared to that obtained for the case of free diffusion (i.e. no binding interactions). For low solute concentrations in the physiological solution, IGF-1 interacted with IGFBP-3 forming bound complexes on the ECM of the tissue. In this case, the penetration of free IGF-1 in NP was significantly lower than that obtained for the case of free diffusion (black line). In contrast, when the concentration of IGF-1 in the physiological solution was significantly higher than that of IGFBP-3 (>100 nM), the effect of binding interactions was negligible since all the binding sites present in the disc were saturated. Hence, IGF-1 concentration profiles were similar to that obtained in the case of free diffusion. Similar results were found in AF (data not shown).

Due to binding reactions, the uptake of IGF-1 in IVD (i.e. total mass of solute in tissue) increased when compared to that obtained for the case of free diffusion. The uptakes of free and bound IGF-1 in NP and AF, as a function of IGF-1 concentration in the physiological solution, are reported in Figure 3. Data were normalized with respect to IGF-1 uptake in the case of free diffusion. The lower the solute concentration in the physiological solution was, the higher the relative uptake of bound IGF-1 in the tissue. The opposite trend was found for the uptake of free IGF-1. When compared at the same solute concentration in the physiological solution, the uptake of bound IGF-1 in AF was higher than that in NP. This was due to the fact that IGFBP-3 concentration in AF (32 nM) was higher than that in NP (15.3 nM).

In summary, the objective of this study was to investigate the effect of binding interactions on IGF-1 transport in IVD. A finite element model, based on the mixture theory for charged hydrated soft tissues, was used to describe the coupled diffusive-reactive solute transport and electromechanical behavior of the disc. Numerical results indicated that, although binding increases IGF-1 uptake relatively, solute transport across the disc is slowed by the interactions with the binding proteins present in the ECM of the tissue. These findings are consistent to those reported in previous studies [6,8]. It is concluded that, in modeling IGF-1 transport in IVD, it is crucial to include binding phenomena.

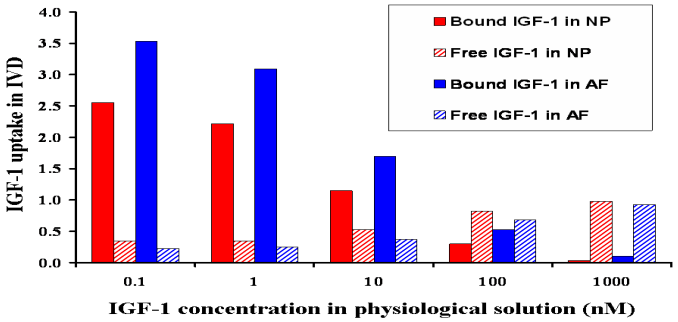

Figure 3: IGF-1 uptake in NP (red) and AF (blue) after 48 hours of absorption, parametric with IGF-1 concentration in physiological solution. Data normalized with respect to solute absorption in the case of free diffusion.

ACKNOWLEDGEMENTS

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