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A computational model for investigating the effects of changes in bioavailability of insulin-like growth factor-1 on the homeostasis of the intervertebral disc

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ABSTRACT

Insulin-like growth factor-1 (IGF-1) is well-known for upregulating cell proliferation and biosynthesis of the extracellular matrix in the intervertebral disc (IVD). Pathological conditions, such as obesity or chronic kidney disease cause IGF-1 deficiency in plasma. How this deficiency impacts disc homeostasis remains unknown. Pro-anabolic approaches for the treatment of disc degeneration based on enhancing IGF-1 bioavailability to tissue-cells are considered, but knowledge of their effectiveness in enhancing cellular anabolism of a degenerated disc is limited.

In this study, we developed a computational model for disc homeostasis specifically addressing the role of IGF-1 in modulating both extracellular matrix biosynthesis and cellularity in the IVD. This model was applied to investigate how changes in IGF-1 bioavailability, namely deficiency or enhancement of growth factor, affect disc health.

In this study, it was found that IGF-1 deficiency mainly affects the biosynthesis of ECM components, especially in the most external regions of the IVD such as the cartilage endplates and the outer portion of annulus fibrosus. Also, a total of three approaches for increasing IGF-1 bioavailability as a therapy for degenerated IVDs were investigated. It was found that all these strategies are only beneficial to those disc regions receiving sufficient nutritional supply (i.e., the outmost IVD regions), while they exacerbate tissue degradation in malnourished regions (i.e., inner portion of the disc). This suggests that pro-anabolic growth factor-based therapies are limited in that their success strongly depends on an adequate nutritional supply to the IVD tissue, which is not guaranteed in degenerated discs.

1. Introduction

The integrity of the intervertebral disc (IVD) is regulated by a delicate homeostatic equilibrium between production (anabolism) and destruction (catabolism) of extracellular matrix (ECM) components operated by disc cells. The insulin-like growth factor-1 (IGF-1) is a naturally-occurring polypeptide protein hormone which plays an important role in stimulating growth during childhood and helps build and repair tissues in adults [1]. In particular, the IGF-1 is a key player in IVD homeostasis by upregulating both cell proliferation and biosynthesis of ECM components in a dose-dependent fashion [2,3]. The IGF-1 is either endogenously produced by disc cells [4] or exogenously delivered via plasma from the liver [5]. Once in the IVD, IGF-1 binds to IGF-1 cell surface receptors (R1), initiating the signaling cascade that leads to cell division and production of new ECM [6].

The bioavailability of IGF-1 to its receptor on disc cells is regulated by several concurring chemical reactions in the tissue. For instance, insulin and IGF-2, delivered to the IVD via plasma, can also bind to either R1 or their own receptors (IR and R2, respectively) [7]. Binding of insulin with R1 has no known downstream effects, while its interaction with IR regulates cell metabolic functions [8]. Binding of IGF-2 with either R1 or R2 also has no known downstream effects either. It has been proposed that the competitive interaction of this growth factor with R1 represents a mechanism for regulating the IGF-1 signaling pathway. Instead, the primary role of the complex IGF-2-R2 is the regulation of IGF-2 levels in the tissue: bound IGF-2 is sequestrated and removed from the tissue via lysosomal degradation [9], making R2 a 'clearance receptor' [10]. Moreover, both IGF-1 and IGF-2 can bind to IGF-binding proteins (IGFBPs). The results of these

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reversible reactions are bound complexes that prevent IGF-1 and IGF-2 from interacting with cell receptors. It has been proposed that the role of IGFBPs is to extend the half-life of IGFs in the IVD [10–12].

Under several circumstances, the availability of IGF-1 to disc cells may be altered. For instance, low plasma levels of IGF-1 have been reported in the obese population and in subjects affected by chronic kidney diseases [13,14]. Although a correlation between obesity and disc degeneration has been reported [15,16], it is not clear whether this may be attributed to the reduced bioavailability of IGF-1 in the obese population. Also, impaired solute delivery to the disc has been individuated as a possible cause for IVD degeneration: insufficient nutrient supply causes disc cell-death [17–22]. How critical to disc degeneration is an impaired IGF-1 supply is yet to be determined. Furthermore, for more than a decade, scientists have been testing pro-anabolic treatments for IVD degeneration based on exogenous administration of growth factors [23–27]. In particular, the exogenous delivery of IGF-1 to degenerated IVD via intradiscal injections has been investigated theoretically and experimentally. However, the outcomes of these studies indicate that the benefits of this type of treatment to enhance the bioavailability of IGF-1 to IVD cells are limited [27,28]. In principle, alternative drug delivery strategies might be considered as well: antibodies targeting IGF-2 have been developed [29], and they may be used to reduce the levels of active IGF-2 in the disc, thus facilitating the interaction between IGF-1 and its receptor; also, levels of IGFBPs in the tissue could be altered to promote IGF-1-R1 formation. The effectiveness of these potential strategies for enhancing cellular anabolism in the extracellular matrix of a degenerated intervertebral disc has never been investigated.

Computational modeling in biology and medicine is playing an ever increasing role in the advancement of science (e.g., mechanisms of respiration [30,31], IVD [32], bioengineering [33], etc.). Models can be deployed in several ways, including hypothesis testing, providing mechanistic interpretation of phenomena observed in experiments, and testing the viability of new approaches. The first objective of this study was to develop a computational model for IVD homeostasis able to describe the role of IGF-1 on the regulation of IVD homeostasis. The other objectives were to apply the model to: (1) understand the implications of reduced bioavailability of IGF-1 in disc cells on the health of the tissue, and (2) investigate the effectiveness of strategies enhancing IGF-1 bioavailability in disc cells as therapies for IVD repair.

2. Methods

A theoretical framework for describing IVD homeostasis was developed. It was based on previously reported diffusive-reactive models describing the role of IGF-1 in upregulating the biosynthesis of ECM components and cellularity in the disc [12,34], The nomenclature adopted for all the chemical species contemplated in the model is summarized in Table 1. Briefly, in the ECM of IVD, the reversible binding of IGF-1 to IGF-1 cell receptor (R1) initiates a signaling cascade culminating in increased cell proliferation and biosynthesis of proteoglycans [2,3,6]. IGF-1 is either endogenously secreted by disc cells, or exogenously delivered to the disc via the vascular network surrounding the tissue. The bioavailability of IGF-1 to its cell receptor is regulated by several competitive binding reactions due to the presence of insulin and IGF-2 (which competitively bind to R1), and IGF binding proteins (which sequestrate IGF-1, preventing it from interacting with its cell receptor). There are many IGF binding proteins, each of them having different affinities for IGF molecules. Hereby, we adopt a previously proposed simplification which individuates two groups of IGF binding proteins [10]: IGFBP-(1-5), having the same affinity for either IGF-1 or IGF2, and IGFBP-6, exclusively binding to IGF-2 [35–37]. Since both IGF-mediated PG synthesis and cell proliferation increase the nutritional demand of disc cells [28], transport and metabolism of nutrients (i.e., oxygen, glucose, and lactate) are considered, and it is assumed that cellularity decreases when glucose levels fall below a critical threshold [19,21,38,39]. A schematic representation of the adopted theoretical framework is shown in Fig. 1. A detailed description of the model is presented in the following sections..

Table 1
Nomenclature for the chemical species contemplated in the model.

Symbol	Description
IGF-1	Insulin-like growth factor-1
IGF-2	Insulin-like growth factor-1
Insulin	Insulin
R1	IGF-1 cell surface receptor
R2	IGF-2 cell surface receptor
IR	Insulin cell surface receptor
IGF-1-R1	Bound complex of IGF-1 and IGF-1 cell surface receptor
IGF-2-R1	Bound complex of IGF-2 and IGF-1 cell surface receptor
Insulin-R1	Bound complex of Insulin and IGF-1 cell surface receptor
IGF-2-R2	Bound complex of IGF-2 and IGF-2 cell surface receptor
Insulin-IR	Bound complex of Insulin and Insulin cell surface receptor
IGF-1-IR	Bound complex of IGF-1 and Insulin cell surface receptor
IGFBP-(1-5)	Insulin-like growth factor binding proteins (1-5)
IGFBP-6	Insulin-like growth factor binding protein 6
BC1	Bound complex of IGF-1 and IGFBP-(1-5)
BC2	Bound complex of IGF-2 and IGFBP-(1-5)
BC3	Bound complex of IGF-2 and IGFBP-6
O^2	Oxygen
Glucose	Glucose
Lactate	Lactate
ρ^{cell}	Cell density

2.1. IGF-1, IGF-2, Insulin and their receptors

The competitive reactions of IGF-1, IGF-2, and insulin with cell surface receptors are hereby modeled as previously described [10]. More specifically, both IGF-1 and IGF-2 bind to the R1 receptor, but only IGF-2 can bind to the IGF-2 cell receptor R2 [7]. In addition, Insulin binds to its own specific receptor (IR). However, binding reactions between Insulin and R1, and IGF-1 and IR may also occur [6,40]. The molecular interaction of each protein with the cell surface receptor is modeled as a first order reversible reaction, and the formation of the bound complex can be followed by a process of internalization which eliminates the ligand and frees the receptor [41]. All the possible ligand-receptor interactions contemplated in the model are summarized below:

$$IGF-1+R1 \underset{k_{-1R1}}{\overset{k_{+1R1}}{\rightleftharpoons}} \text{IGF}-1-\text{R1} \overset{k_{-i}}{\Longrightarrow} R1, \tag{1}$$

$$IGF-2+R1 \underset{k_{-2R1}}{\overset{k_{+2R1}}{\rightleftharpoons}} \text{IGF}-2-\text{R1} \overset{k_{-i}}{\Longrightarrow} R1, \tag{2}$$

$$Insulin+R1 \underset{k_{-3R1}}{\overset{k_{+3R1}}{\rightleftharpoons}} \text{Insulin}-\text{R1} \overset{k_{-i}}{\Longrightarrow} R1, \tag{3}$$

$$IGF-2+R2 \underset{k_{-2R2}}{\overset{k_{+2R2}}{\rightleftharpoons}} \text{IGF}-2-\text{R2} \overset{k_{-i}}{\Longrightarrow} R2, \tag{4}$$

$$IGF-1+IR \underset{k_{-1IR}}{\overset{k_{+1IR}}{\rightleftharpoons}} \text{IGF}-1-\text{IR} \overset{k_{-i}}{\Longrightarrow} IR, \tag{5}$$

$$Insulin+IR \underset{k_{-3IR}}{\overset{k_{+3IR}}{\rightleftharpoons}} \text{Insulin}-\text{IR} \overset{k_{-i}}{\Longrightarrow} IR. \tag{6}$$