

**Investigations of
Insulin-Like Growth Factor I Cell Surface Binding:
Regulation by Insulin-Like Growth Factor
Binding Protein-3 and Heparan Sulfate Proteoglycan**

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ABSTRACT:

The primary aim of this text is to gain insight on how cellular activation by a insulin-like growth factor (IGF-I), in the presence of insulin-like growth factor binding protein-3 (IGFBP-3), is influenced by heparan sulfate proteoglycans (HSPG). Initial research will be presented, assumptions and hypotheses that were included in the development of mathematical models will be discussed, and the future enhancements of the models will be explored. There are many potential scenarios for how each component might influence the others. Mathematical modeling techniques will highlight the contributions made by numerous extracellular parameters on IGF-I cell surface binding. Tentative assumptions can be applied to modeling techniques and predictions may aid in the direction of future experiments.

Experimentally, it was found that IGFBP-3 inhibited IGF-I Bovine Aortic Endothelial (BAE) cell surface binding while p9 HS slightly increased IGF-I BAE cell surface binding. IGFBP-3 has a higher binding affinity for IGF-I (3×10^{-9} M) than p9 HS has for IGF-I (1.5×10^{-8} M) as determined with cell-free binding assays. The presence of p9 HS countered the inhibiting effect of IGFBP-3 on IGF-I BAE cell surface binding.

Although preliminary experiments with labeled p9 HS and IGFBP-3 indicated little to no cell surface binding, later experiments indicated that both IGFBP-3 and p9 HS do bind to the BAE cell surface. Pre-incubation of BAE cells with either IGFBP-3 or p9 HS resulted in an increase of IGF-I BAE cell surface binding. There was a more substantial increase of IGF-I surface binding when cells were pre-incubated with IGFBP-3 than p9 HS. There was a larger increase of IGF-I BAE cell surface binding when cells were pre-incubated with p9 HS than when p9 HS and IGF-I were added simultaneously. This suggests that IGFBP-3 and p9 HS surface binding plays key role in IGF-I surface binding, however, p9 HS surface binding does not alter IGF-I surface binding as much as IGFBP-3 surface binding seems to.

Experimental work helps further the understanding of IGF-I cellular activation as regulated by IGFBP-3 and p9 HS. Developing mathematical models allows the researcher to focus on individual elements in a complex systems and gain insight on how the real system will respond to individual changes. Discrepancies between the model results and the experimental data presented indicate that soluble receptor inhibition is not sufficient to account for experimental results.

The alliance of engineering analysis and molecular biology helps to clarify significant principles relevant to the conveyance of growth factors into tissue. Awareness of the effects of individual parameters in the delivery system, made possible with mathematical models, will provide guidance and save time in the design of future therapeutics involving growth factors.