

# The function of insulin in mammalian cell culture

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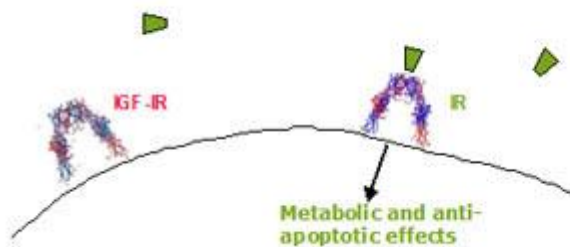
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Insulin is a 5,8kD protein hormone secreted in vivo by the  $\beta$ -cells of the pancreatic islets of Langerhans (1). Insulin and the related insulin-like growth factors IGF-I and IGF-II act on cells through binding to specific receptors, the insulin receptor (IR) (1,2) and the type 1 IGF receptor (IGF-1R) (3,4), two highly homologous dimeric transmembrane glycoproteins that are part of the receptor tyrosine kinase (RTK) family. Insulin and IGF-I have high affinity (0,1-0.2 nM) for their cognate receptor but can bind at high concentration with a 100-500 lesser affinity to the noncognate receptor. Physiologically, the role of insulin is primarily metabolic while the IGFs are primarily growth factors, as evidenced by the phenotypes of mice where either receptor gene has been knocked out (5). The specificity is far from absolute, however (6,7), and in cells where the insulin receptor is absent, the IGF-IR can mediate metabolic effects (8), while in cells without IGF-I receptors, insulin can mediate mitogenic effects (9). Insulin through the IR also inhibits apoptosis induced by serum withdrawal in a variety of cell types (10-16). The signalling pathways of the IR and IGF-IR are largely shared (6-8). In cells with both IRs and IGF-IRs, hybrid receptors are present that behave essentially as IGF-IRs (8) In mammalian cell culture, recombinant insulin is added at approximately 100 times the physiological concentration. Insulin at this high concentration acts as a growth factor, with anti-apoptotic and mitogenic effects. These effects are not only through activation of the IR but also through activation of the IGF-1R. See Fig. 1a and b.

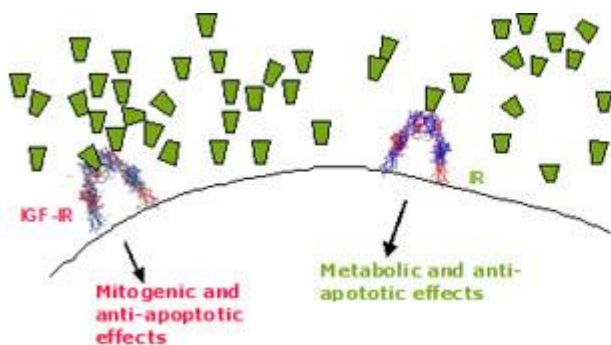
**Figure 1a:** Physiological function of insulin. Both IR and IGF-1R are expressed on the surface of a mammalian cell, but only the IR is activated by insulin at physiological concentration of insulin.

 = insulin

Structure of the receptor extracellular domain from ref. 19, PDB accession code 2DTG.  
Drawn using DSViewerPro.

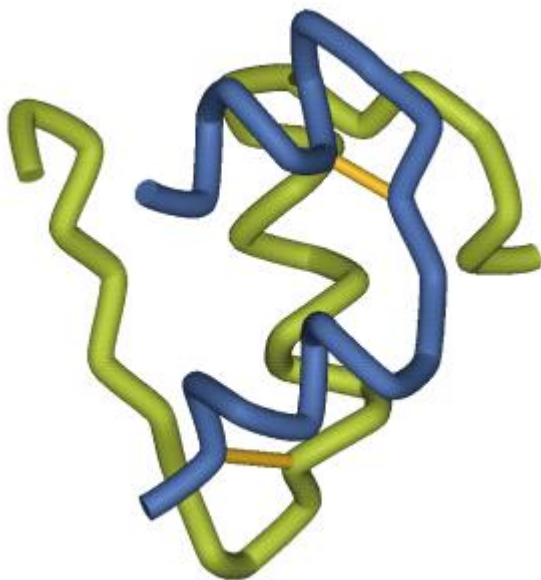
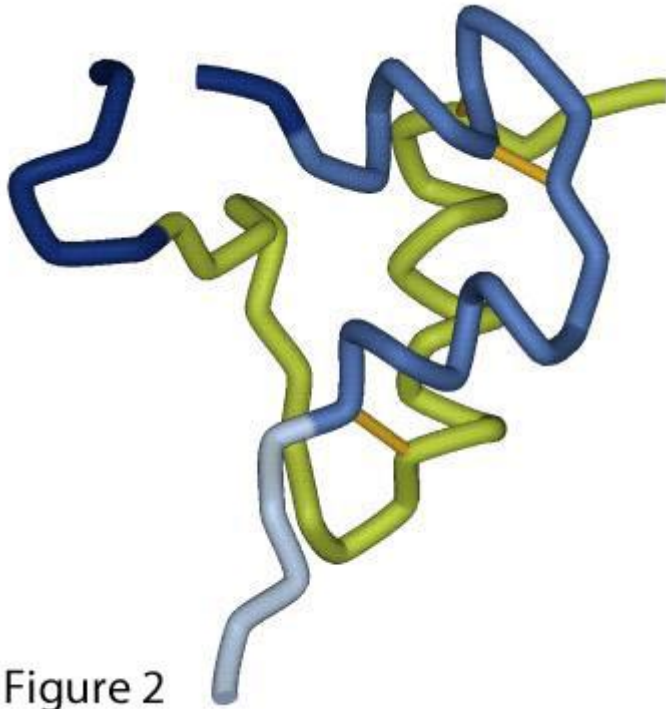


**Figure 1b:** Function of insulin in mammalian cell culture. High concentrations of insulin trigger a mitogenic effect via the IGF-1R, and are resulting in a variety of effects via the native IR.



The insulin and IGF-1 molecules have a high degree of homology as well (1,2). In the folding of the molecule and in the surface areas involved in receptor binding the two molecules are highly alike.

**Figure 2:** Similar folding of insulin (A-chain -blue- 21 aa, B-chain-green- 30 aa) and IGF-1 (70 aa), C-domain in dark blue, D-domain in light blue. From reference 2, PDB accession codes 9INS and 1GZR. Drawn with DSViewerPro.





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