Glucose Regulation by the Action of Insulin Signaling Pathway

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Abstract
As we all know if we consume much of carbohydrate rich food, it may increase the sugar (glucose) levels in our blood which in turn may cause severe damage to our health. In this case Insulin, a hormone synthesized from beta cells of islets of Langerhans comes into play by regulating the glucose levels in our body through Insulin signaling pathways where Insulin acts as a ligand molecule by binding to its two receptor subunits i.e. alpha & beta respectively where insulin binds to the later subunit by autophosphorylation and as a result of this tyrosine molecules becomes the attachment point for other proteins such as IRS-1 (insulin receptor substrates). Phosphorylation in the IRS1 or IRS2 initiates the PI3K/AKT and Ras-Raf-MEK-MAPK signaling pathway. Our article deals in detail on how insulin regulates the glucose level by various signaling pathway.

Introduction
Begin with insulin signaling the question comes what insulin is and why and when to use this signaling? Insulin is a hormone composed of two polypeptide chain each contain 51 amino acid which is synthesized from beta cells of islets of langerhans. This polypeptide chain are linked by two disulfide bridges. When we just have our food and the food is rich in carbohydrates and carbohydrates are made up of polysaccharides which broken into glucose molecule. Therefore, glucose level increase in blood which can be toxic to our body. Insulin signaling use to maintain the glucose level in our body.

Insulin Signalling Pathway Process
For insulin signaling the main component is insulin receptor (INS-R) which is made up of two alpha and two beta subunits . Two alpha unit of INS-R are found in extracellular side or on the outer face of the plasma membrane, which creates gap where insulin binds. Two beta subunits are transmembrane protein which help in spanning, but also have component which is facing cytoplasmic side of the cell. This region of beta subunit is very important which provide the actual activity to the receptor. This part of beta subunit contains tyrosine kinase which phosphorylates tyrosine molecule on target protein or target enzyme.

Insulin works as a ligand (primary messenger) molecule in this pathway. Insulin bind to the cavity of alpha subunit after that alpha subunit closes so that insulin cannot come out from that point. After insulin binds to the alpha subunit it does the confrontational changes leads to activation of beta subunit by autophosphorylation at the tyrosine residue of carboxy terminal domain of beta subunit in the presence of ATP.

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When the tyrosine molecules phosphorylates it become the attachment point for other proteins. In this the important protein IRS-1 (insulin receptor substrates) which is phosphorylates by tyrosine kinase on tyrosine residues. Phosphorylation in the IRS1 or IRS2 leads to triggers PI3K/AKT and Ras-Raf-MEK-MAPK signalling pathway.

**PI3K/AKT Signalling Pathway**

IRS-1 molecules are known as adaptor protein which does not have catalytic activity but brings other proteins to the receptor. Here it act as docking site for the lipid kinase known as PI-3 kinase (phosphoinositide kinase). This enzyme binds with the IRS-1 at the phosphorylated region.

This leads to the activation or phosphorylation of specific type of molecule which is present in the plasma membrane known as PIP2 (phosphatidylinositol 4,5-diphosphate). PI-3 kinase which takes phosphate group from ATP and convert PIP-2 to PIP-3 (phosphatidylinositol 3,4,5-trisphosphate). Now PIP3 moves along the plasma membrane and activate PIP3 dependent protein kinase (PDK-1) which ultimately activates effector protein PKB (protein kinase B).

PKB is not bound in the membrane, it can move anywhere in the cytoplasm of that cell. PKB it activates the enzyme which are responsible for transforming glucose into glycogen and also triggers the transporters to move into membrane and cause the re-absorption of glucose into the cell.

Once the PKB activated, it phosphorylates Glycogen synthase kinase3 (GSK3) on serine residue which is the inactive form of GSK3. Which help in Glycogen synthase enzyme remain active and leads to synthesis of glycogen from glucose is accelerated.

PKB activate and movement of glucose transporter GLUT4 (Glucose transporter 4) from internal membrane vesicles to the plasma membrane, which improve the uptake of glucose.

**MAP-kinase signalling pathway:** Once insulin bind to the insulin receptor (INS-R) it does the phosphorylation of insulin receptor substrates (IRS) on tyrosine residue which act as a docking site for other protein. When SH2 domain of Grb2 binds to the IRS it leads the activation of another signaling pathway name as MAP-kinase signalling pathway. Now this Grb2 binds with the nucleotide exchange factor SOS which converts GDP to GTP on Ras and activates Ras. Raf is recruited and activated by Ras. Once Ras got activated it phosphorylates the two serine residue of MEK and it is also do the phosphorylation on the threonine and tyrosine residue of ERK to activate it. After it got activated it moves to the nucleus and ERK regulates the transcription factor like ELK1 by activating it. This ELK1 join with the one SRF molecule to trigger the transcription and translation of those genes which are responsible for a particular function in that time.