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The role of palmitoylation of the insulin receptor in insulin resistance: A hypothesis

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Abstract

Palmitoylation is attachment of a palmitoyl group to the cysteine residues of a protein. The intermediary in this process is Palmitoyl CoA, which is formed during the activation of fatty acids in the beta oxidationn of the palmitic acid, consequent to the shift of the energy metabolism to beta oxidation from glycolysis, in DM2.The insulin receptor has cysteine rich domains in the cytosolic portion of the beta sub unit connected by disulfide bonds. It is hypothesized that the palmitoylation forms a thio-ester bond with cystein residues of the beta sub units of the insulin receptor. Depalmitoylation results in substitution of thiol (-SH) in place of the disulfide (S-S) bonds (S-S), due to the hydrolysis by the thio-esterase enzyme. The disulfide bonds are responsible for formation of the functional tettameric form of the insulin receptor. Consequent to the substitution of the SH group in place of S-S group, during depalmitoylation, the functional specificity of the insulin receptor is lost. This leads to the failure of conformational changes and auto-phoshorylation of the beta sub units when insulin binds to the extra cellular insulin binding receptor domain. Also failure of the cascade of phosphorylation of other signalling proteins occurs. Consequently, the failure of the intra-cellular transduction of the signals results in failure of the translocation of the GLUT 4 transporter to the cell membrane. This results in the hyperglycaemia in spite of hyper insulinemia and mo glucose enters into the cell- a state called insulin resistance in DM 2.

Keywords: Palmitoylation; Insulin receptor; Insulin resistance; Beta oxidation of fats Acetyl CoA; GLUT 4.

1. Introduction

To understand the proposed hypothesys; it is essential to refresh the basic tenets of what is known about the structure of the insulin receptor; the role of disulfide bonds in the maintaining of the structural and functional integrity of the insulin receptor; the post receptor intra cellular insulin signal transduction; the circumstances under which the palmitoylation of the insulin receptor occurs; the initial steps of beta oxidation of fats and about mechanism of the palmitoylation.

1.1. The insulin receptor

The insulin receptor; a membrane glycoprotein, has two alfa and two beta sub units connected by disulfide bonds.The two alfa sub units are extracellular and bear a insulin binding site. The beta sub units are trans- membrane with membrane and cytosol parts. later has cysteine rich domain; ATP binding site and has intrinsic tyrosinase activity [1]

1.2. Disulfide bonds

The disulfide bonds give the ininsulin receptor; the functional tetrameric form. They are situated one intra (CysA6 and CysA11) and two inter-chain (CysA7-CysB7 and CysA20-CysB 19) positions [2;3].The disulfide bond (Dsb) enzymes are responsible for the formation and isomerization of disulfide bonds. Dsb A and Dsb B are responsible for thiol oxidation

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and Dsb C; Dsb G; are responsible for disulfide isomerization [4].The role of these disulfide bonds in making the insulin receptor functional cannot be over emphasized; as the sub units existing as mono and dimers have no functional activity. This author hypothesized; that disruption of the formation of the disulfide bond formation might be responsible for insulin resistance [5].

1.3. Post receptor intra cellular insulin signal transduction:

Extensive coverage of this topic is out of scope of this article. the aspects relevant to this topic are only considered here..

When insulin binds to it's extracrllular binding site; conformational changes and autophosphorylation of the tyrosine residues of the beta sub units occurs. Other signalling proteins are also phosphorylated subsequently. This activates PIP3 / AKT pathway that help to translocate the intracellular GLUT 4 transporter to the cell membrane. (exocytosis) Then GLUT 4 transports glucose; across the cell membrane into the cytosol. It is important to note that GLUT 4 translocation doesn't occur in the absence of insuli.

1.4. Palmitoylation

Palmitoylation involves the addition of a 16-carbon fatty acid, the palmitic acid to a cysteine residue of a protein via a labile acyl-thioester linkage. S- palmitoylation is reversible where as N -Palmitoylation is irreversible.It is proposed that the cysteine residues of the Cytotosolic part of the beta sub unit; are S- palmitoylized. The S- palmitoylation involves the intermediary palmitoyol CoA which incidentally is formed in the activation stage of Beta oxidation of palmitic acid[6;7].

1.5. The circumstances under which the the proposed palmitoylation occurs

There is shift in energy metabolism in DM 2; from aerobic glycolysis to beta oxidation of fats. How the shift in energy metabolism occurs in DM2; is explained by the Randle's cycle"(8). Obviously the lack of sufficient secretion of the insulin triggers this shift in the energy metabolism. Under physiological conditions, beta-oxidation is a significant source of metabolic energy during interprandial periods and high energy demand states, such as exercise [9]. These metabolic conditions induce the release of fatty acids from adipose tissue due to the secretion of circulating hormones, such as epinephrine and glucagon, which increase the rate of lipolysis [10].

1.6. The initial steps in the beta oxidation of fats:

The 'activation' of Palmatic acid to palmitoyl CoA,occurs by combining with CoA enzyme, a reaction catalyzed by palmtitoyl CoA transferase. Activation of fatty acids requires the formation of a thioester bond with Coenzyme A, an ATP-dependent process carried out by acyl-CoA synthetasese [11] Equation (1) below depicts the reaction

Palmitate + CoA-SH + ATP → Palmitoyl-CoA + AMP + Pyrophosphate.---- (1)

This activation reaction occurs in cytosol and beta oxidation of fats occur inside the Mitochondria. Since palimitoyl CoA can not pass through the outer membrane of the mitochondria, to facilitate the same, it is combined with Carnitine, in a rate limiting step, catalyzed by the enzyme Carnityl acyl transferase 1(CPT 1). The complex passes through the outer mitochondrial membrane. The carnitine is released from the complex, by the enzyme, Carnityl acyl transferase 2 (CPT 2) at the inner mitochondrial membrane. The acyl group is subjected to beta oxidation. The end products of the beta oxidation are shown below in equation 2.

Acetyl CoA, FADH2, NADH and H+ ----- (2)

The overall reaction, using palmitoyl CoA as a model substrate is shown in equation 3.

7 FAD + 7 NAD+ + 7 CoASH + 7 H2O +

H(CH2CH2)7CH2CO-SCoA -->

8 CH3CO-SCoA + 7 FADH2 + 7 NADH + 7 H+. --------- (3)

The acetyl CoA enters the citric acid cycle and then is oxidized in the electron transport system, generating ATP. Each mole of palmatic acid finally yields 129 ATP molecules.

2. The proposed hypothesis

Palmatic acid is available to the body by dietary source; de novo synthesis in the liver and y endogenous synthesis from medium and short chain Fatty acids. (F A). The FA that enters the beta oxidation cycle of fats is also the 16 C palmitic acid. The palmatic acid before entering beta oxidation cycle is combined with Co A to form Palmotoyl CoA in a process called 'activation'; as already stated above. Palmitoyl CoA is the intermediary in the palmitoylation of the cysteine residues in the cytosolic portion of the beta sub unit of the insulin receptor. As the first step of beta oxidation ie the formation of Carnitine palmatoyl CoA is a rate limiting step; the Palmatoyl COA formed in excess than the enzyme Carnitine palmotoyl transferase could handle; remains free in the cytosol. The cyytosolic beta sub units of the insulin receptor have cysteine rich domains. Palmitoylation occurs at the cysteine domains. Further; the S- Palmitoylation is a cytosolic process.The situation is thus congenial for palmitoylation of the cysteine residues on the beta sub unit with palmitoyl CoA. THIS Is S- palmitolyation; which is reversible. The forward reaction is catalyzed by the palmitoyl transferase enzyme which attaches a thioester moity to the cysteins of the beta sub unit to which disulfide bond is attached.The reverse reaction is catalyzed by palmitoyl thioesterase enzyme. This is a hydrlrolase which hydrolyses the the thioester to thiols, according to the reaction below.

$$RC(O)SR + H2O \rightarrow RCO2H + RSH. \text{ ----- } (4)$$

This removes the acyl group and leaves the thiol moity attached to the the cysteine. This changes the redox status of the disulfide bonds in the insulin receptor; as the thiol is the reduced form (-SH) of the disulfide bond (–S–S–). The formation of a disulfide bond between two cysteine residues stabilizes a protein tertiary structure, by ensuing it's proper folding,vmainly by decreasing the conformational entropy. (Conformational entropy (ΔSconform) of a protein is defined by the degree of flexibility and the number of different conformations that can be sampled). But with the above mentioned substitution of thiol, the insulin receptor, loses it's functional specificity of the tetrameric form The insulin receptor; consequently loses it's functional specificity of the tetrameric form. This prevents conformational changes and auto- phosphorylation of the tyrosine residues of the beta sub unit and subsequent phosphorylation of the other signalling proteins. This disrupts the post receptor signalling ;through PIP 3/ AKT/ and PKCzeta path ways; with consequent failure to translocate the glucose transporter molecule; GLUT 4; to the cell membrane; a step that is necessary for the glucose uptake by the cell. Hence no glucose could be transported into the cell , and hyperglycaemia persists in the blood inspite of the presence of hyper insulinemia; resulting in a state that is called Insulin resistance.

3. Conclusion

The palmitoylation of the insulin receptor contributing to the insulin resistance in DM 2; has been proposed and substantiated. The precise mechanism of how palmitoylation and depalmitoylation cycles are regulated awaits further studies [12].

Compliance with ethical standard

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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