Journal of Fundamental and Applied Sciences

ISSN 1112-9867

Available online at http://www.jfas.info

Special Issue

In celebrating the 10th anniversary of JFAS

THEORETICAL STUDY OF THE SUBSTITUTION EFFECT ON THE PROTEIN/PROTEIN INTERACTION: APPLICATION ON DIABET DESEASE

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Received: 07 December 2019/ Accepted: 29 December 2019 / Published online: 01 January 2020

ABSTRACT

Diabetes pathology present actualy a real public health problem. In order to highlight the most favored modes of interaction between insulin and its receptor, and thus elucidated the substitution effect of sulfur by other element (selinum) in the receptor bridges on its affinity for the insulin, we elaborate a theoretical study by molecular modeling namely molecular docking (more commonly known as docking) between insulin and the insulin receptor with disulphide bridges and diselenide bridges. Complexes (insulin/receptor) stability was elucidated using molecular dynamics methodes. Our results show that there is a difference between the interaction energies. Indeed, the selinium substitution of sulfur implied good complementarity between isinsulin and its receptor this is in good agreement with several experimental findings.

Keywords: Protein/protein interaction; Sulfur; Docking; Molecular dynamic; Tpe 2 diabetes.

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doi: http://dx.doi.org/10.4314/jfas.v12i1S.20

1. INTRODUCTION

Selenium (Se) has been considered as highly toxic trace element or carcinogen for long time [1]. It is today regarded as a trace element indispensable to man. Epidemiological surveys have been conducted all over the world to determine selenium status in different diseased and non-diseased populations. These studies show that the relationship between the level of Se and different pathologies is ambiguous [2].

Recently, experimental researche shows that a regular selenium status minimise the risk of type 2 diabetes. In particular, the risk is reduced by 24% in people who have a good status in selenium compared to the other pasiants with Se deficiency [3]. In this type of diabetes the problem is linked to insulin resistance, the involvement of Insulin receptor in the mechanisms of insulin resistance has been demonstrated on several cases and the main one is congenital insulin resistance related to a mutation affecting the geometry of the insulin - receptor binding site [4].

The insulin receptor (IRS) is formed of two extracellular α chains linked by disulfide bonds with two β-transmembrane chains. Each α chain has a complete domain of hormone binding. The β subunit consists of a helical transmembrane domain followed by a juxtamembrane domain containing a catalytic tyrosine kinase domain flanked by two regulatory regions, the first involved in the internalization of the receptor and in the binding to (IRS)Substrate. 1-4 and Shc, the second containing two phosphotyrosine binding sites [5], [6].

Our aim in this work is to compare by meanes of theoretical chemistry approaches (molecular doking and molecular dynamics) the sulfur substitution effect on the interaction between insulin and its receptor. Once, in the native state ie: without changing the disulfide bridges. Than, by changing the sulfur atoms of the bridges into selenium. This comparison will allow us to know the difference between interaction energies of insulin receptor with insulin in both cases and conclude the most stable complex which will clarify the substitution effect.

2. MATERIALS AND METHODS

2.1. Material

Insulin (5hpu): Insulin is a hormone naturally secreted by the pancreas, specifically by specialized cells located in the islets of Langerhans [7]. It stimulates the absorption of blood

glucose by so-called insulin-dependent tissues (liver, skeletal muscle and adipose tissue) and its storage in the form of glycogen (glycogenesis). These will use glucose as energy or store it for future use [8].

Insulin is a heterodimed compound of two subunits, A chain and B chain, interconnected by two disulfide bridges and one intrachain disulfide bridge in chain A.

The insulin was downloaded (Fig. 1) from the Book haven Protein Data Bank database (www.rcsb.org/pdb). The physico-chemical properties of insulin are given in Table 1.

Table 1. Chemical and physical properties of insulin

PDB Code	Formula	Molecular weight
5hpu	C257H383N65O77S6	5 807,57 ± 0,299 g/mol

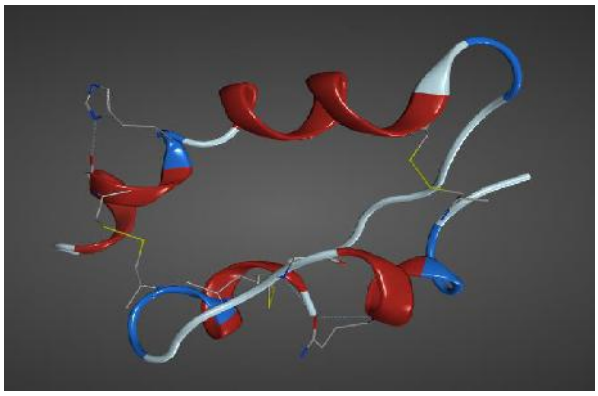

Fig.1. Insulin (5hpu)

Insulin receptor (4zxb): Belongs to the tyrosine kinase receptor family consisting of 4 glycosylated peptides linked by disulfide bridges [9].

They form a glycoprotein of 400 kDa. There are two pairs of subunits: two transmembrane subunits (β) (80 kDa) have an enzymatic activity of protein kinase, and two subunits (120 kDa) are on the surface of the cell membrane and each α chain possesses a complete domain of hormone binding [10]. All 4 subunits have a cylindrical shape [5, 6].

IRS higher resolution structure has been detected by several researchers [10]. It plays a key role in glucose homeostasis and regulates the metabolism of lipids, proteins and carbohydrates [11].

The IRS download (Figure 2) was also performed from the Book haven Protein Data Bank database (www.rcsb.org/pdb) [12].

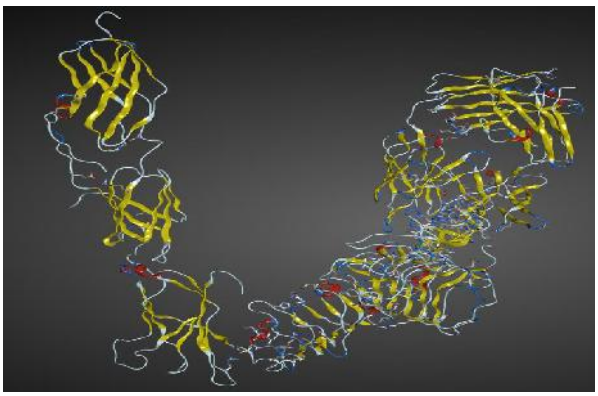

Fig.2. Insulin Receptor (4zxb) with Sulfur

The sulfur substitution by selenium on the bridges and the obtained structure and sequence are given in Figures 3 and 4, we note that the substitution was made using MOE (Molecular Operating Environnement) programme [13].

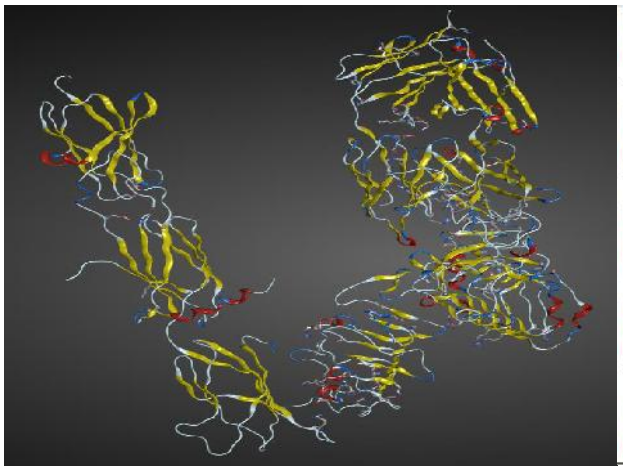

Fig. 3. Insulin Receptor (4zxb) with selenium

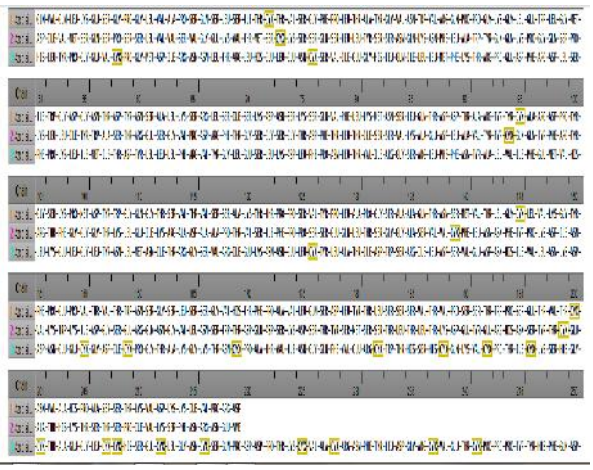

Fig.4. Receiver sequence with disulfide bridges changed to diselenide bridges

2. 2. METHODS

After downloading the insulin we minimized its energy to achieve the most stable conformer on the other hand, the downloaded IRS structure, was simplified by eliminating the water molecules and co-crystallization molecules, and then we optimized it using MOE with the MMFF94X force field molecular dynamics (MD) was also used to minimize its energy aiming to get the best conformation. Docking was performed using Hex software [14] to visualize the interaction of insulin with its receptor following tow steps. First, between insulin and IRS in his native state (with disulfide bridges); Secondly, between insulin and receptor by

changing the disulfide bridges by selenium. Finally we launched the molecular dynamics study using MOE software this step is important to verify the complexes stabilities.

3. RESULTS AND DISCUSSION

3.1. Proteins optimization

The optimised structures of insulin, native insulin receptor with sulfur (IR_S) and IR with sulsuf substituted by selenium (IR_{Se}) was done by MOE software with the MMFF94X force field. The obtained results are presented in **Table 2**.

Table 2. Obtained energy values for insulin, IR_S and IR_{Se}

Protein	Insulin	4zxb (SH)	4zxb (Se)
Energy MM	$3{,}37904\times10^{2}$ Kcal/mol	$-7{,}3223\times10^{2}$ Kcal/mol	$-6{,}95858\times10^{2}$ Kcal/mol

Obtained results given in **Tables 3** show that the IR stability decrease one substituting S by Se. Indeed, the obtained energies values in the native state with (S) are less than the energy values obtained with (Se). Therefore, we conclude that selenium substitution with sulfur at the insulin receptor does not lead to a stabilization of the system from an energy point of view.

3.2. The insulin-receptor complexes

Complex energy optimization of IRs and IRse

The energy optimization of the complexes was done with the MOE software energy values are given in Table 3, and Figure 5,6 show the optimized complexes.

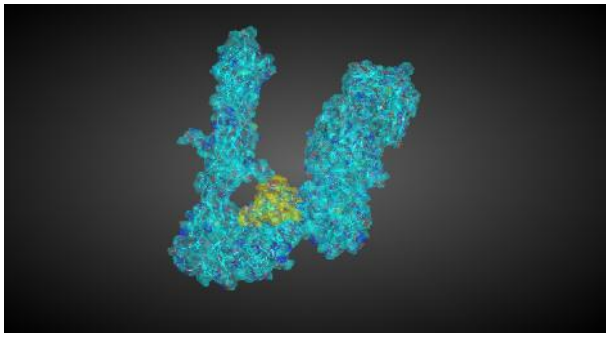

Fig.5. The complex (Insulin/IRs) optimized

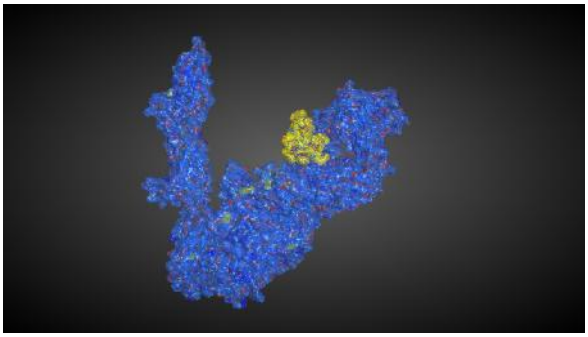

Fig.6. The complex (Insulin/IRse) optimized.

Table 3. Complex energies

Complexe	IRs	IRse
Energy (MM)	-4,62136×10^3 Kcal/mol	-4,53011×10^3 Kcal/mol
Energy (DM)	-4,62804×10^3 Kcal/mol	-4,94119×103 Kcal/mol

It turns out that the systems have become more stables. Indeed, their energy went from a value of -4,62136×10^{3}Kcal/mol to a lower value of -4,62804×10^{3}Kcal/mol for insulin/IRscomplexe and from -4,53011×10^{3}Kcal/mol to -4,94119×103 Kcal/mol for insulin/IRse complexe.

On the other hand the obtained results for the optimization of the insulin / IRS complex with molecular mechanics in the normal state and after the change of the sulfur atoms of the bridges with selenium atoms show that the complex with (S) is energetically more stable than the complex with (Se)E (IRs) (- 4.62804 × 103Kcal / mol <-4.53011 × 103Kcal / mol) this is not the case after MD calculation, indeed, for MD the IRse complexe is more stable than the IRs one and therefore substitution of sulfur by selenium at the level of the complex does not lead to stabilization of the system from an energy point of view. So in the free or complex state the receiver is always more stable with sulfur than selenium by MM but if the system is perturbed (MD) the receptor with selenium atoms present the most stable structure of complexe.

3.3. Interactions energies

In order to find out the Insulin/insulin receptors interaction energies between in the tow studies cases the interaction energies are calculated as folow

E1 interaction = Potential E (insulin/ (IRs) complex) - [Potential E (IRs) + Potential E (Insulin)].

E2 interaction = potential E (insulin /IRse complex) - [potential E (IRse) + potential E (Insulin)].

Obtained results are summarized in Table 4.

Table 4. The interaction energies of the Insulin / insulin receptor complexes

Complxe	**Insulin /IRs**	**4zxb (Se)/insulin**
Interaction energies	$-0{,}89366\times10^{2}$ Kcal /mol	$-0{,}4811016\times10^{3}$Kcal /mol

Table 4 shows that the interaction energy of the complex with IRse / insulin is lower (- 0.4811016 × 10^{3}Kcal / mol) compared to the second (IRs / insulin) which has an energy equal to (-0.89366 × 102Kcal / mol). Our results show that selenium leads to a stability of the complex and consequently to a vaforable effect on the regulation of blood glucose.

4. CONCLUSION

In this work we elucidated theoretically the effect of sulfur substitution by selenium at the level of the IR in order to verify the substation effect on the interaction energy between the insulin receptor and insulin and establish the substitution of sulfur by selenium effect on the onset of diabetes.

In our work we focused on the molecular interactions between insulin and its receptor precisely their potential energies and interactions using molecular modeling methods namely molecular mechanics, molecular dynamics and molecular doking.

The obtained results of the insulin receptor optimization with molecular mechanics in the normal state and after sulfur substitution show that the receptor with (S) is energetically more stable than the receptor with (Se) and therefore the substitution of sulfur by selenium at the insulin receptor level does not lead to system stabilization from an energy point of view, these results are then confirmed by the energy minimization of the receptors.

In the same way, the results of the optimization of the insulin / insulin receptor complex with molecular mechanics in the normal state and after the change of the bridges show that the complex with (S) is energetically more stable than the complex with (Se) and therefore, substitution of selenium for sulfur at the complex level does not lead to system stabilization from an energy point of view. So in the free or complex state the receptor is always more stable with sulfur than selenium.

Finally, we calculated the interaction energy between the two complexes (with sulfur and with selenium) and it was concluded that the interaction energy of the complex with selenium

(insulin) /IRse) is lower by compared to the second (insulin /IRs) .And from these results we can say that the selenium receptor gives a better interaction with insulin than that with sulfur and thus selenium leads to a stability of the complex consequently provides positive effect on the operation of the regulation of blood glucose.

This is in good agreement with several findings and clinical trials that aim to determine the effects of selenium on diabetes mismatch. First of all, the EVA prospective study carried out in France found that the high selenium status in men (between 94 and 155 µg / L) was associated with a decrease in the risk of hyperglycemia [15].

Similarly, in the United States, in a recent study of two different-sex cohorts including 3630 women and 3535 men, the level of selenium in the nails was inversely associated with the risk of type 2 diabetes [3].

A study to evaluate the selenium level in a sample of the diabetic population of the city of Tlemcen in Algeria [16] confirms the first studies cited where it found that the selenium rate in diabetics is lower than that observed in controls (83.58 ± 5.42 66, 13 ± 6.54 µg / L). The difference is significant (P = 0.04).

5. ACKNOWLEDGEMENTS

Autors thanks the Algerian Ministry of Higher Education and Scientific Research for the support under the PRFU project (approval No. **B00L01EP130220190002**). Autors thanks also Mr GHALEM Said the director of the laboratory of Natural and Bioactive Substances Tlemcen University, Algeria.

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How to cite this article:
Ghomri A, Missoum N. Bouchentouf S. Theoretical study of the substitution effect on the protein/protein interaction: application on diabet desease J. Fundam. Appl. Sci., 2020, *12(1S), 278-287.*