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BIOINFORMATICS AND MOLECULAR MODELING OF THE CAMEL INSULIN RECEPTOR

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ABSTRACT

Camels are well known for their high blood glucose content and marked glucose tolerance. In order to understand the glycemic control in camels the role of insulin receptor was investigated. The camel insulin receptor sequence, structure model, and domain content were compared with those of humans and other vertebrates. The results indicated 100% identity rate in old world camels, 99.7% identity rate with new world camels and 96% with humans. There was a high identity rate among insulin receptors in domestic animals (82.3–100%). Despite the conserved features of the insulin 1 binding site (the main functional insulin molecules), the second insulin-binding site in camel insulin receptors showed interesting differences. Most of the sequence differences between human and camel insulin receptors were concentrated in the insertion domains (ID), particularly the ID-β loop. ID-α′~αCT′~ID-β, which is important for insulin receptor signal transduction, showed a greater positive electrostatic potential in camels. Such differences might be associated with the noticed hyperglycemia and insulin resistance in camels by affecting the movement of the α-CT helix which lies between the IDs and significantly affects the main insulin molecules, lowering the affinity at insulin site 1 and by affecting the transmission of the insulin signal to the intracellular domain.

Key words: Camel, dynamics, glucose, insulin receptor, insulin resistance, simulation

Camels have physiological, anatomical and behavioral adaptation mechanisms for survival in desert environment (Gebreyohanes and Assen, 2017). Badryyah *et al* (2005) found that plasma glucose level in camels was significantly higher than that of goats. Food deprivation decreases plasma glucose levels in both monogastric mammals and ruminants of similar size as the camel (Evans, 1971; Rule *et al,* 1985). However, serum glucose level of camels was maintained during fasting and was increased after feeding had commenced (Wensvoort *et al,* 2004). The glycemia increases from 20 to 80% without glucosuria after 10 days of water deprivation. The hypo-insulinemia would allow the camel to maintain a low basal metabolism by decreasing glucose use (Ouajd and Kamel, 2005). Guo *et al* (2021) found that fasting in Bactrian camels is accompanied by changes in the activation of insulin pathways in various camel tissues, normal insulin levels, and increased lipolysis and insulin resistance, which returns to normal after eating. Díaz-Medina *et al* (2017) found in suckling dromedaries, a natural state of hyperglycemia and an increase in insulin resistance with age, while decreasing their tolerance to glucose, insulin secretion and insulin sensitivity, with reduced signs of use of free fatty acids (NEFA) from fat mobilisation.

Glycemic control is managed by insulin in both ruminants and monogastric animals (Sasaki, 2002). Insulin and insulin-like growth factors (IGFs) constitute a fundamental family of hormone polypeptides that play definite physiological roles in mammals and other species. Insulin is the key regulator of the homeostasis of carbohydrates and influences the metabolism of lipids and proteins (Frampton *et al,* 2020; Saltiel and Kahn, 2001). Specific cell surface receptors are needed for the physiological functions of insulin, and subtle differences in the structure and function of the receptors may account for significant variations in the biological activity of hormones. Compared with human and bovine insulin, the camel insulin showed attracting thermostability

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that might modulates the camel insulin function (Ismail, 2021). Furthermore, camel milk has been utilised in the treatment of diabetics due to its camel insulin content (Ashraf *et al,* 2021; Zheng *et al,* 2021). In this context, camel insulin showed marked structural differences and stability due to several amino acids replacements (Kandeel *et al,* 2022).

Although many insulin-like peptides exist in invertebrates, yet only one insulin receptor has been identified (Ruvkun and Hobert, 1998). The structure of insulin receptors comprises covalently-linked homodimers composed of several structural domains (Rentería *et al,* 2008). The insulin receptor is related to the superfamily Tyrosine Kinase (RTK) subclass II (White, 2017), which is a class of transmembrane receptors where the extracellular domain bears the ligand-binding site and exerts its intracellular signaling through the activation of intracellular tyrosine kinase.

In camel, the levels of glucose vary widely and are higher than in other ruminants (Nazifi *et al,* 1998). The high blood glucose levels in camels were hypothesised to be related to a higher glucagon level in camels than in humans and other ruminants (Abdel-Fattah *et al,* 1999) or camels bearing a natural insulin resistance. Insulin resistance is characterised as a condition in which the sensitivity of the target cells to react to ordinary insulin levels is reduced (Boura-Halfon and Zick, 2009); hence, the ordinary insulin levels fail to trigger metabolic actions. Camel adaptations to dry weather include maintaining a high glucose level in the blood of up to 1300 mg/dL with a loss of water in the urine. In this way, the camel can hold plasma water in order to resist water deprivation (Yagil, 1985). Camel tissues have a poor insulin response and low insulin sensitivity (Kaske *et al,* 2001).

There is an information gap regarding the camel insulin receptor and its contribution to the observed higher blood glucose and apparent insulin resistance in camels. Present study is aimed to identify camel insulin receptor sequence, structure model, and biological aspects. This study will compare camel insulin receptors with human and vertebrate insulin receptors as well.

Materials and Methods

Retrieval of insulin receptor sequences

The sequences used in this study were retrieved from the available GenBank and protein database (https://www.ncbi.nlm.nih.gov/). The retrieved sequences and their database accession numbers were Human XP_011526290, *Camelus dromedarius* XP_031292936, *Camelus bactrianus* XP_010965094, *Camelus ferus* XP_032322128, Canine XP_005633279, Ovine XP_004008598, Mouse NP_034698, Swine XP_020939599, Bovine XP_027403423, Rabbit XP_008247399, and Equine XP_023500375. In addition to the old world camelids, new world camelid insulin receptors were also retrieved. The new world camelids insulin receptor sequence was retrieved for Alpaca (*Vicugna pacos*) XP_031545692.

Searching homologs and orthologues

The search for identical sequences was based on the non-redundant (nr) database at NCBI. The basic local alignment search tool was used to investigate potential similar hits (Madden, 2013).

Comparison of human and camel insulin receptor putative domains and motifs

The putative domain content was analysed using the domain prediction tool available at NCBI (http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml) (Marchler-Bauer *et al,* 2005). The requests for motif searches were submitted to the motif search tool at the Kyoto Encyclopedia of Genes and Genomes (https://www.genome.jp/tools/motif/).

Multiple sequence alignment

The sequences of domestic animals and human insulin receptors were aligned using the sequence alignment tool with the CLC genomic software (Qiagen software, Denmark).

Phylogenetic tree

The phylogenetic relations were constructed and viewed with the CLC genomics workbench by using the sequences of insulin receptors from domestic animals.

Proteomic and genomic tools

The bioinformatics resource portal tools (ExPASy) (Artimo *et al,* 2012; Gasteiger *et al,* 2003) and tools at EBI (Cook *et al,* 2018; Labarga *et al,* 2007) were used for the analysis of protein sequences.

Construction of molecular models

Requests for molecular models were submitted to the Swiss model server. The retrieved structure models were inspected for the correct outliers using the Molprobity server. The structure models were energy minimised and compared with human insulin receptors by using a variety of software, including

ICM Molsoft, Molegro virtual docker, and the CLC drug discovery workbench.

Results

Comparison of human and camel insulin receptors

The human and camel insulin receptor sequences were aligned, and the alignment statistics were retrieved. The sequence comparison of human and serum camel receptors is provided in Fig 1. Camel and human receptors shared high homology with the identity% at 96% and the number of different amino acids at 54 residues. Most of the residue differences were in the range of 750–800 (human sequence numbers).

Insulin receptor in camelids

The sequence of insulin receptors was compared in the old world camel species *C. dromedaries, C. ferus* and *C. bactrianus* (Fig 2A). There were no differences in the insulin receptors protein sequence in the old world camel species, and there was a 100% identity rate. In comparing the differences between insulin receptors in the old world and new world camels, a sequence alignment was performed, and the results of the alignment summary are provided in Fig 2B. There was a very high identity per cent of 99.7% between the *Vacugna pacos* insulin receptor and the old world camels. There were only four amino acid differences in the insulin receptor sequences.

Insulin receptor in humans, dromedary camels, and other animals

Multiple sequence alignments were generated for the insulin receptor sequences from humans, camelids, and several animal species (Fig 3). There were no great differences among the examined sequences. The identity% was from 82.3 to 100%. The lowest identity% was with the chicken insulin receptor (82.3%) followed by the mouse and rabbit receptors. In contrast, the identity% was not lower than 97% between human, camelid, bovine, ovine, swine, canine, feline, and equine insulin receptors.

Motif and domain content of camel insulin receptor

The domains and motif contents of human and camel insulin receptors were compared (Fig 4-7). All studies revealed the lack of any differences in the domain constituents or motif contents between the human and camel insulin receptors. The conserved domain contents in the human and camel insulin receptors included a tyrosine kinase catalytic domain, receptor L domain, insulin receptor transmembrane segment, fibronectin type III domain, and furin-like cysteine-rich region.

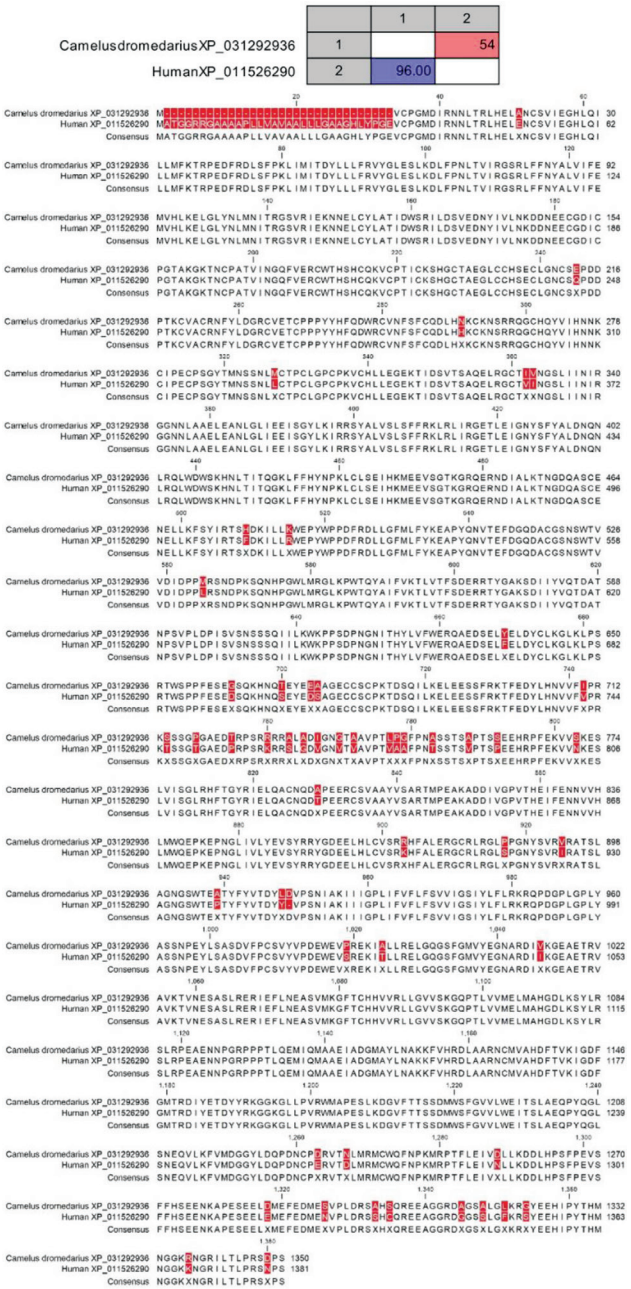


Fig 1. Pairwise alignment of human and camel insulin receptors. The upper panel shows the comparison statistics. The number of residue differences are highlighted in red and the identity% is highlighted in blue. The lower panel shows the sequence alignment. The different residues are in white and highlighted in pink.

Molecular models and insulin receptor structure

We constructed a molecular model of camel insulin based on the recently resolved human insulin receptor bond with insulin (PDB ID 6pxv). The

A

		1	2	3
CamelusdromedariusXP_031292936	1		0	0
CamelusferusXP_032322128	2	100.00		0
CamelusbactrianusXP_010965094	3	100.00	100.00	

B

		1	2	3	4
CamelusferusXP_032322128	1		4	0	0
VicugnapacosXP_031545692	2	99.70		4	4
CamelusdromedariusXP_031292936	3	100.00	99.70		0
CamelusbactrianusXP_010965094	4	100.00	99.70	100.00	

Fig 2. Summary of the multiple alignment statistics for the insulin receptor sequences. A) Comparison of old world camelids (*C. dromedaries, C. ferus*, and *C. bactrianus* insulin receptor). B) Comparison of the old world and new world camelid insulin receptor sequences. The upper right diagonal panel shows the number of residue differences. The lower left diagonal panel shows the identity.

		1	2	3	4	5	6	7	8	9	10	11	12	13
BovneXP_027403423	1		11	23	30	40	36	36	36	46	64	35	85	238
OvneXP_004008598	2	99.18		27	33	43	39	39	39	49	66	38	88	239
SwineXP_020939599	3	98.29	97.99		29	39	32	32	32	47	63	33	88	236
EquineXP_023500375	4	97.77	97.55	97.84		33	33	33	33	39	57	28	82	234
CatXP_023100560	5	97.03	96.80	97.10	97.55		45	45	45	51	63	29	91	237
CamelusdromedariusXP_031292936	6	97.32	97.10	97.62	97.55	96.65		0	0	54	69	38	93	238
CamelusferusXP_032322128	7	97.32	97.10	97.62	97.55	96.65	100.00		0	54	69	38	93	238
CamelusbactrianusXP_010965094	8	97.32	97.10	97.62	97.55	96.65	100.00	100.00		54	69	38	93	238
HumanXP_011526290	9	96.58	96.36	96.51	97.10	96.21	95.99	95.99	95.99		49	47	69	236
RabbitXP_008247399	10	95.24	95.09	95.32	95.76	95.32	94.87	94.87	94.87	96.36		61	85	247
CanineXP_005633279	11	97.40	97.17	97.55	97.92	97.84	97.17	97.17	97.17	96.51	95.46		87	239
MouseNP_034698	12	93.69	93.47	93.47	93.91	93.24	93.10	93.10	93.10	94.88	93.69	93.54		233
ChickenXP_001233399	13	82.33	82.26	82.48	82.63	82.41	82.33	82.33	82.33	82.48	81.66	82.26	82.56	

Fig 3. A summary of the multiple alignment statistics for the insulin receptors in humans and domestic animals. The upper right diagonal panel shows the number of residue differences. The lower left diagonal panel shows the identity. The cells are highlighted according to a color scale from red to blue, where red is the lowest and blue is the highest.

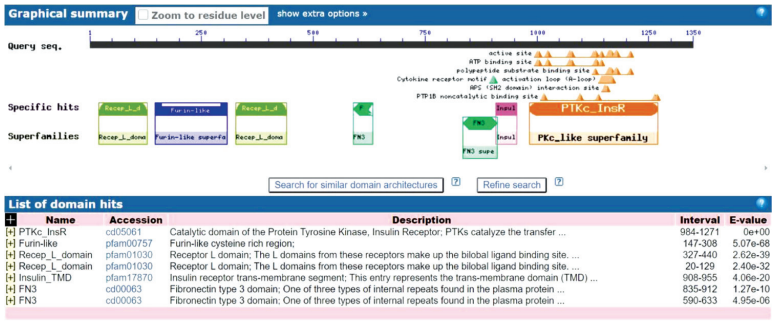


Fig 4. The human insulin receptor domain content. The results were generated using the NCBI domain search tool. The figure was generated using the NCBI domain server.

coverage rate was 99% of the input sequences with a sequence identity of 95.81%.

The domain composition of the insulin receptor included the leucine-rich domains L1 (52–163) and L2 (359-469), a furin-like cysteine-rich region (179-340), fibronectin type III domains (FNIII-1 629-663, FNIII-2 795-829, FNIII-3 863-936), an insulin receptor transmembrane segment (940-986), protein kinase domain or PK (1024-1287), RNA binding domain B2 (1052-1106), and kinase-like domain (1146-1277) (Fig 8).

The insulin S1 and S1`-binding site

The structure is composed of a dimer containing two insulin molecules per monomer. The first insulin in the first monomer was termed S1, and its corresponding insulin molecule on the second monomer was termed S1`. Similarly, the second insulins were termed S2 and S2` for the first and second monomers, respectively. The first insulin S1 molecule is placed between the L1 domain of one monomer, the FnIII-1` domain, and the α-CT` helix of the other monomer. There were no significant differences in the amino acid composition at the insulin-binding site of the insulin receptor between human and camel insulin receptors. In the L domain, there were three amino acid differences: E51A in the L1 domain and V363I and I364V. This indicates minor amino acid differences in the L domain. No other significant differences were found in the α-CT helix.

The insulin second S2-binding site

A potential second S2 insulin-binding site is proposed near the junction of the FnIII-1 and FnIII-2 fibronectin domains (McKern *et al,* 2006; Scapin *et al,* 2018). Insulin S2 interacts directly with the FNIII-1 domain and the loop connecting the FNIII-1 and FNIII-2 domains.

The differences between human and camel insulin receptors

Little differences were observed between the human and camel insulin receptor sequences. However, a large number of amino acid replacements were observed at the residue range of 746-803, which corresponded to the insertion domain beta (ID-β).

A common structure linking insulin S1 and S2 molecules

The ID-β loop was a common structure linking the binding of the insulin receptor with the two insulin S1 and S2 molecules. This loop was found to have most of the sequence differences

between human and camel insulin receptors.

In comparing the camel and human ID-β domain sequence, about 16 amino acid replacements were observed (Table 1.). In human ID-β, the different residues comprise four polar uncharged R-group, 10 nonpolar aliphatic R-group, and two charged residues. The camel ID-β lacks the charged residues, which are replaced by two nonpolar residues.

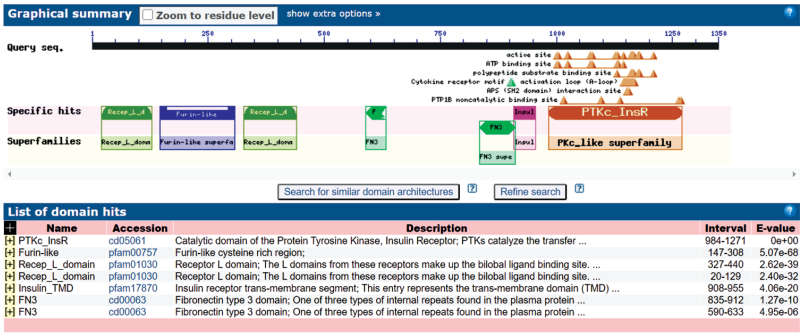
The surface electrostatic potential of human and camel ID-α~αCT~ID-β

Based on the observed differences in the composition of ID-α′~αCT′~ID-β between human and camel insulin receptors, the surface electrostatic maps were compared (Fig 9). The results indicated that the human ID-α′~αCT′~ID-β bears a higher negative electrostatic potential, which is replaced by a positive charge in camel ID-α′~αCT′~ID-β.

Discussion

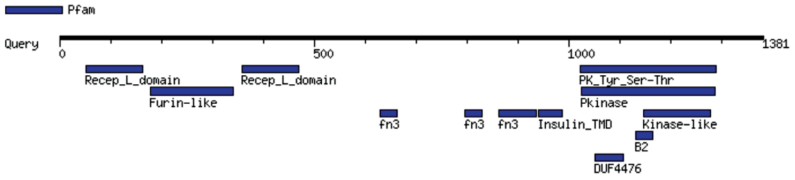
In this study, a trial was adopted to understand the potential contributing factors for the resistance of camels to high glucose contents by analysing the potential differences between camel, human, and other vertebrate insulin receptors.

The L1 subdomain and the α-CT helix are essential for insulin binding (De Meyts and Whittaker, 2002). More recently, the α-CT helix and CR domain are important in binding insulin-galgrine (González-Beltrán and Gómez-Alegría, 2021). As there were no amino acid differences in the L1 domain, the FnIII-1 domain, and the α-CT helix between human and camel insulin receptors, the binding mode of the insulin-1 molecule with the insulin receptor appeared to be conserved between humans and camels. However, recent studies have revealed the importance of structural rearrangements in the formation of insulin binding sites (Gutmann *et al*, 2020).



Name	Accession	Description	Interval	E-value
[+] PTKc_InsR	cd05061	Catalytic domain of the Protein Tyrosine Kinase, Insulin Receptor; PTKs catalyze the transfer ...	984-1271	0e+00
[+] Furin-like	pfam00757	Furin-like cysteine rich region;	147-308	5.07e-68
[+] Recep_L_domain	pfam01030	Receptor L domain; The L domains from these receptors make up the bilobal ligand binding site. ...	327-440	2.62e-39
[+] Recep_L_domain	pfam01030	Receptor L domain; The L domains from these receptors make up the bilobal ligand binding site. ...	20-129	2.40e-32
[+] Insulin_TMD	pfam17870	Insulin receptor trans-membrane segment; This entry represents the trans-membrane domain (TMD) ...	908-955	4.06e-20
[+] FN3	cd00063	Fibronectin type 3 domain; One of three types of internal repeats found in the plasma protein ...	835-912	1.27e-10
[+] FN3	cd00063	Fibronectin type 3 domain; One of three types of internal repeats found in the plasma protein ...	590-633	4.95e-06

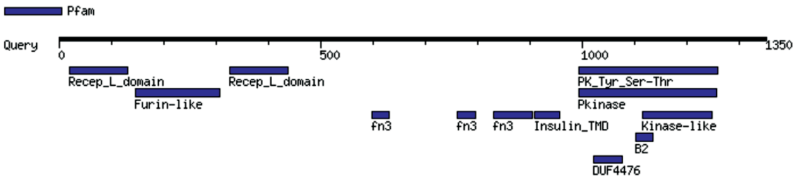
Fig 5. The camel insulin receptor domain content. The results were generated using the NCBI domain search tool. The figure was generated using the NCBI domain server.



Pfam (9 motifs)

Pfam	Position(Independent E-value)		Description
PK_Tyr_Ser-Thr	1023..1289(9.8e-95)	Detail	PF07714, Protein tyrosine and serine/threonine kinase
Recep_L_domain	52..163(2.9e-25) 359..469(6e-29)	Detail	PF01030, Receptor L domain
Pkinase	1024..1287(6.2e-41)	Detail	PF00069, Protein kinase domain
Furin-like	179..340(3.6e-36)	Detail	PF00757, Furin-like cysteine rich region
Insulin_TMD	940..986(2.2e-21)	Detail	PF17870, Insulin receptor trans-membrane segment
fn3	629..663(0.00044) 795..829(0.56) 863..936(3e-05)	Detail	PF00041, Fibronectin type III domain
Kinase-like	1146..1277(0.0045)	Detail	PF14531, Kinase-like
B2	1132..1165(0.33)	Detail	PF11473, RNA binding protein B2
DUF4476	1052..1106(0.32)	Detail	PF14771, Domain of unknown function (DUF4476)

Fig 6. The human insulin receptor motifs content. The results were generated using the KEGG motifs search tool. The figure was generated using the KEGG motif search server.



Pfam (9 motifs)

Pfam	Position(Independent E-value)		Description
PK_Tyr_Ser-Thr	992..1257(1.4e-94)	Detail	PF07714, Protein tyrosine and serine/threonine kinase
Recep_L_domain	20..131(2.8e-25) 327..437(1.7e-28)	Detail	PF01030, Receptor L domain
Pkinase	994..1255(4.1e-40)	Detail	PF00069, Protein kinase domain
Furin-like	147..308(2.5e-36)	Detail	PF00757, Furin-like cysteine rich region
Insulin_TMD	908..955(1.7e-20)	Detail	PF17870, Insulin receptor trans-membrane segment
fn3	597..631(0.00045) 760..796(0.75) 831..904(2.1e-05)	Detail	PF00041, Fibronectin type III domain
Kinase-like	1115..1246(0.0032)	Detail	PF14531, Kinase-like
B2	1101..1134(0.32)	Detail	PF11473, RNA binding protein B2
DUF4476	1021..1075(0.31)	Detail	PF14771, Domain of unknown function (DUF4476)

Fig 7. The camel insulin receptor motifs content. The results were generated using the KEGG motifs search tool. The figure was generated using the KEGG motif search server.

Table 1. The different residues between human and camel insulin receptor at the ID-β domain. Position number is according to the human insulin receptor sequence.

Position	Residue in human	Nature of residue in human	Residue in camel	Nature of residue in camel
746	Threonine	Polar uncharged R-group	Serine	Polar uncharged R-group
750	Threonine	Polar uncharged R-group	Proline	Nonpolar, aliphatic R-group
755	Proline	Nonpolar, aliphatic R-group	Threonine	Polar uncharged R-group
760	Lysine	Basic charged (positive charge)	Proline	Nonpolar, aliphatic R-group
763	Serine	Polar uncharged R-group	Alanine	Nonpolar, aliphatic R-group
765	Glycine	Nonpolar, aliphatic R-group	Alanine	Nonpolar, aliphatic R-group
767	Valine	Nonpolar, aliphatic R-group	Isoleucine	Nonpolar, aliphatic R-group
770	Valine	Nonpolar, aliphatic R-group	Glycine	Nonpolar, aliphatic R-group
772	Valine	Nonpolar, aliphatic R-group	Alanine	Nonpolar, aliphatic R-group
777	Valine	Nonpolar, aliphatic R-group	Leucine	Nonpolar, aliphatic R-group
778	Alanine	Nonpolar, aliphatic R-group	Proline	Nonpolar, aliphatic R-group
779	Alanine	Nonpolar, aliphatic R-group	Glycine	Nonpolar, aliphatic R-group
783	Threonine	Polar uncharged R-group	Alanine	Nonpolar, aliphatic R-group
788	Valine	Nonpolar, aliphatic R-group	Alanine	Nonpolar, aliphatic R-group
792	Proline	Nonpolar, aliphatic R-group	Serine	Polar uncharged R-group
803	Asparagine	Acidic charged (negative charge)	Serine	Polar uncharged R-group

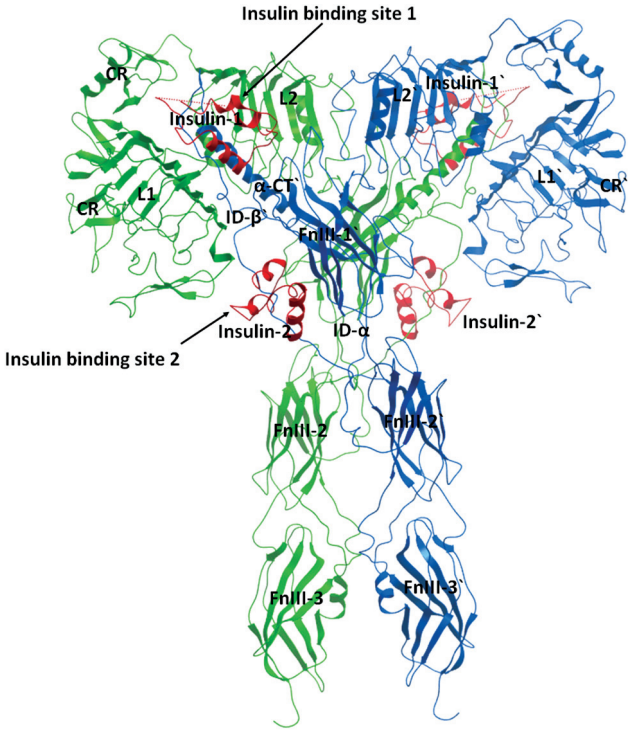


Fig 8. A structure model of the camel insulin receptor ectodomain showing different domains.

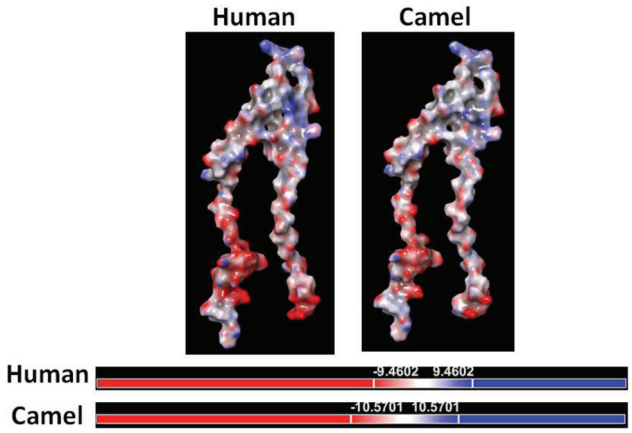


Fig 9. The surface electrostatic potential of ID-α′~αCT′~ID-β in humans and camels. The negative charge is displayed in red. The positive charge is displayed in blue. The neutral residues are in white.

The molecular dynamics of full-length insulin receptors revealed important structural changes of insulin receptors. Interestingly, the ID-α′~αCT′~ID-β′ domains form a long loop around the binding sites of insulin. Structure rearrangements involving the ID-α′~αCT′~ID-β′ are essential to allow the formation and access of insulin to its first binding site (Yang *et al,* 2020).

The concept of the binding of four insulin molecules to insulin receptors was proven on a structural basis (Gutmann *et al,* 2020). However, the exact interactions of these four insulin molecules as well as the insulin receptor structural changes and signal transduction are still not understood. Several assumptions were made to implement the contribution of the four insulin molecules to the insulin receptor function. In association with these speculations, the binding of insulin at site 2 is weaker than at site 1; therefore, insulin dissociates from

site 2 upon formation of the strong binding site 1. As site 2 is very close to site 1 and comprises the binding of insulin 2 with the L1′ domain and the αCT helix, the second site might be essential for favorable conformational changes in site 1 to achieve the proper binding of insulin 1 by enhancing favorable structural changes (Gutmann *et al,* 2020; Yang *et al,* 2020).

There was also an important difference between the conformation of the bound insulin at sites 1 and 2. The insulin at site 1 was in open or receptor-bound conformation, while insulin at site 2 was in closed form, similar to insulin in solution or not bound to the insulin receptor (Gutmann *et al,* 2020). The additional interaction of insulin 2 with ID loops was observed. There was an asymmetric binding of insulin 2 with IDs loops and their αCT/αCT` helices, which are critical for high-affinity binding. The conformational changes from the L1~CR~L2~Fnш-1 and ID-α~αCT~ID-β domains are transmitted through the transmembrane domain and induce structural and functional changes in the intracellular domain of the insulin receptor.

Previous studies on the hagfish (*Myxine glutinosa*) insulin receptor indicated a conserved insulin site 1 residue composition. However, insulin binding showed slow kinetics and a low binding affinity (De Meyts, 2004). This was attributed to differences in two site 2 residues. Similarly, the camel insulin receptor bears several differences in the site 2 composition that might contribute to the observed low insulin sensitivity in camels.

In ruminants, the mechanism of action of insulin on the glucose metabolism is similar to monogastric animals. Glucose transport controls the rate of glucose utilisation. In skeletal muscles and adipose tissues, there are three glucose transporters: Glucose transporter 1, 3, and 4 (GLUT1, GLUT3, and GLUT4) (Sasaki 2002). The insulin-sensitive glucose transporter GLUT4 (as with monogastric animals) is believed to be the key protein in the regulation of the glucose uptake and metabolism in ruminants. By inducing the translocation of GLUT 4 from an intracellular membrane pool to the plasma membrane in adipocytes and muscles, insulin controls the glucose transport.

In addition, insulin-induced GLUT4 translocation is triggered via the typical intracellular signaling pathway of the signaling pathway of insulin. The process of the translocation of GLUT4 mRNA and protein and insulin-induced GLUT4 on adipocytes and muscles in ruminants is slower than in rodents and human subjects. Despite a normal status, the resistance of insulin to the stimulatory action of the glucose metabolism in ruminants in comparison with monogastric animals could be attributed to the lower GLUT4 content and lower insulin signal transduction ability, which lead to decreased glucose transport operations (Sasaki, 2002). The translocation of signal and the observed changes in GLUT4 activity might be attributed to the observed camel receptor structure differences.

Combined together, the camel insulin binding receptor bears several indicators of low insulin activity comprising conserved insulin 1 site composition, the presence of several mutations in the insulin site 2 composition, a different electrostatic potential of ID-α′~αCT′~ID-β, and a low homology of ID loops—in particular ID-β. The changes in insulin site 2 and the ID loops might extend their effects to the αCT helix and decrease the insulin binding affinity. The ID-α~αCT~ID-β in the camel structure appears to be domain with the most influence. The different ID loop compositions might affect the signal transduction to the signaling bridge and modulate the intracellular insulin signaling.

In conclusion, there was a high identity rate among insulin receptors in domestic animals (82.3–100%), while human and camel insulin receptors shared 96% identity. Despite the conserved features of the insulin 1 binding site (the main functional insulin molecules), the second insulin-binding site in camel insulin receptors showed interesting differences. Most of the sequence differences between human and camel insulin receptors were concentrated in the insertion domains, particularly the ID-β loop. Such differences might be associated with the noticed hyperglycemia and insulin resistance in camels by 1) affecting the movement of the α-CT helix, which lies between the IDs and significantly affects the main insulin molecules, 2) lowering the affinity at insulin site 1, and 3) affecting the transmission of the insulin signal to the intracellular domain. These findings contribute to our knowledge regarding glycemic control and the function of the insulin receptors in camels.

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Human and animal rights

No animals / humans were used for the studies that are basis of this research.

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Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

MK designed and performed this study. MG, MB, SA and SI analysed data, and MK wrote the manuscript. MG, MB, SA and SI revised the manuscript. All authors approved the final version of the manuscript.

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