IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 19, Issue 2 Ser. 1 (Mar. – Apr. 2024), PP 38-43
www.Iosrjournals.Org

F-INSULIN-$^{[51-M]}$-ADIABATIC CELL [FI$^{[51-M]}$AC]

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Date of Submission: 14-03-2024 Date of Acceptance: 27-03-2024

A Brief Introductory Note

Strictly speaking, I, myself is not eligible to discuss about anything related to biochemistry because, I am ‟zero" as far as such subject is concerned though I used to teach a very few concepts under ‟biomolecules" that includes carbohydrates. As a person of immense interest in engineering, medical, physics and applied-chemistry I always so eager to learn, read and listen to these marvelous concepts and in fact, I wrote a few articles on viruses, secret of nature, etc., and put forward many of my hypotheses. Of course, truly accepting that, I am not eligible to discuss about such wonderful concepts, especially related to bio-technology. Right from 2019 (especially during covid-19 pandemic), I got incredible level of interest in biochemistry/physiology, especially in viruses, amino-acids, proteins and my dream is to synthesize a universal protein which I expect to cure/control all types of viral infections. By nature′s gift, I got a minute level of creativity which enabled me in thinking differently from most of my fellowmen/associates. This present hypothesis by name F-Insulin[51-M] [Future—Insulin[51-Modified]] is my new hypothesis in which I focused on various parameters that affect or changes that would be brought due to change in one or more α-amino acid moieties of α- chain or/and β-chain of human Insulin. Of course, I never say, I am the first person to think like this or hypothesize.

In this F-Insulin$^{[51-M]}$, my main focus is on what changes likely to occur when:
[i] one α-amino acid in α-chain (21 AA) or β-chain (30 AA) is changed its position
[ii] such α-chain or β-chain is made Cysteine rich
[iii] when α-AA preceding or succeeding Cysteine is changed by other α-AA
[iv] when α-AA moieties preceding and succeeding Cysteine are interchanged
[v] each chain (α and β) is started with each possible α-AA [eg: Alanine]
[vi] each chain is made hydrophobic α-AA rich and many more……

Target-1: Insulin-Basic Traits

I think, there is no need to remind anyone about the crucial role played by this *peptide based hormone*. I here by doing an infinite number of salutes to one of the versatile Nobel laureate, Mr.Sanger.F, who won Nobel prize, twice, a rarest event in the scientific history. Mr.Sanger.F, who discovered the α-AA sequence of insulin (α, β-chains) along with S-S linkages and I am here with furnishing the basic α-AA sequence of two long polypeptide chains [α and β].

Chain-[α]

[i] Begins with Glycine [Gly], [ii] Ends with Asparagine [Asn], [iii] has 21 α-AA
[iv] has one internal S–S linkage $(Cys\text{-}Cys)_{[6\text{-}11]}$,
[v] has two external S-S links with β-chain $(Cys\text{-}Cys)_{[\alpha\text{-}7\text{-}\beta\text{-}7]}$
Sequence [1 letter code]: G-I-V-E-Q-C-C-A-S-V-C-S-L-Y-Q-L-E-N-Y-C-N [21]
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Codes: [p = preceding, s = succeeding, n = number of, P = position]

S.No	Name (α-AA)	[n]	[P]	%(by mol)	Linked to
[1]	Alanine, [A]	1	8	4.76	$^{[p]}C,S^{[s]}$
[2]	Asparagine, [N]	2	18,21	4.76	$^{[p]}E,^{[s]}Y,^{[p]}C$
[3]	Cysteine, [C]	4	6,7,11,20	19.04	$^{[p]}Q,^{[s]}C,^{[s]}C^{[s]}A,^{[p]}V,^{[s]}S$
[4]	Glutamic acid, [E]	2	4,17	9.52	$^{[p]}V,^{[s]}Q,^{[p]}L,^{[s]}N$
[5]	Glutamine, [Q]	2	5,15	9.52	$^{[p]}E,^{[s]}C,^{[p]}Y,^{[s]}L$
[6]	Glycine, [G]	1	1	4.76	1st member
[7]	Isoleucine, [I]	1	2	4.76	$^{[p]}G,^{[s]}V$
[8]	Leucine, [L]	2	13,16	4.76	$^{[p]}S,^{[s]}Y,^{[p]}Q,^{[s]}E$

[9]	Serine, [S]	2	8,12	9.52	$^{[p]}$A,$^{[s]}$V,$^{[p]}$C,$^{[s]}$L
[7]	Tyrosine, [Y]	2	14,19	9.52	$^{[p]}$L,$^{[s]}$Q,$^{[p]}$N,$^{[s]}$C
[8]	Valine, [V]	2	3,10	9.52	$^{[p]}$I,$^{[s]}$E,$^{[p]}$S,$^{[s]}$C
	Total	[21]	----	----	-------

Contribution to chain: C, E = Q = S = Y = V, A = N = G = I = L [decreasing]

Chain-[β]

[i] Begins with: Phenyl alanine [Phe];
[ii] Ends with: Alanine [Ala]
[iii] has 30 α-AA moieties;
[iv] has no internal S-S linkage but two S-S linkages with
α-chain [$Cys_{[8,\alpha]}$-$Cys_{[7,\beta]}$; $Cys_{[20,\alpha]}$-$Cys_{[17,\beta]}$] as external linkages.
[v] Sequence (1 letter code):
F-V-N-Q-H-L-C-G-S-H-L-V-E-A-L-Y-L-V-C-G-E-R-G-F-F-Y-T-P-K-A [30]
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Codes: [p = preceding, s = succeeding, n = number of, P = position, % by mol*]

S.No	Name (α-AA)	[n]	[P]	%	Linked to
[1]	Alanine, [A]	2	14,30	6.67	$^{[p]}$E,L$^{[s]}$,$^{[p]}$K
[2]	Arginine, [R]	1	22	3.33	$^{[p]}$E,$^{[s]}$G
[3]	Asparagine, [N]	1	3	3.33	$^{[p]}$V,
[4]	Cysteine, [C]	2	7,19	6.67	$^{[p]}$L,$^{[p]}$G,$^{[s]}$V,$^{[p]}$G
[5]	Glutamic acid, [E]	2	13,21	6.67	$^{[p]}$V,$^{[p]}$A,$^{[s]}$G,$^{[p]}$R
[6]	Glutamine, [Q]	1	4	3.33	$^{[p]}$N,$^{[s]}$H
[7]	Glycine, [G]	3	8,20,23	10.0	$^{[p]}$C,$^{[s]}$S,$^{[p]}$C,$^{[s]}$E,$^{[p]}$R,$^{[s]}$F
[8]	Histidine, [H]	2	5,10	6.67	$^{[p]}$Q,$^{[s]}$L,$^{[p]}$S,$^{[s]}$L
[9]	Leucine, [L]	4	6,11,15,17	13.33	$^{[p]}$H,$^{[s]}$C,$^{[p]}$H,$^{[s]}$V,$^{[p]}$A,$^{[s]}$Y,$^{[p]}$,$^{[s]}$V
[10]	Lysine, [K]	1	29	3.33	$^{[p]}$P,$^{[s]}$A
[11]	Phenyl alanine, [F]	3	1,24,25	10.0	1st member, $^{[p]}$G,$^{[s]}$F,$^{[p]}$F,$^{[s]}$Y
[12]	Proline, [P]	1	28	3.33	$^{[p]}$T,$^{[s]}$K
[13]	Serine, [S]	1	9	3.33	$^{[p]}$G,$^{[s]}$H
[14]	Threonine, [T]	1	27	3.33	$^{[p]}$Y,$^{[s]}$P
[15]	Tyrosine, [Y]	2	16,26	6.67	$^{[p]}$L,$^{[s]}$L,$^{[p]}$F,$^{[s]}$T
[16]	Valine, [V]	3	2,12,18	10.0	$^{[p]}$F,$^{[s]}$N,$^{[p]}$L,$^{[s]}$E,$^{[p]}$L,$^{[s]}$C
	Total	30			

Contribution to chain: L, G = F = V, A = C = E = H = Y, R = N = Q = K = P = S = T [decreasing]

Target-2: Analysis-(α, β-chains)-Hypothesis-My Views

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[1] α-chain begins with Glycine but the same moiety is absent at any other place

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[2] β-chain begins with Phenyl alanine and the same also found at the specific position (24 and 25 as successive members) respectively.

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[3] Number of distinct α-AA in β-chain = 2 x number of distinct α-AA in α-chain.
[4] Of 20 types, a total of 4 types missing among 51-(α)-AA moieties.

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[5] α-chain is richest in Cysteine but β-chain, Leucine. Why?

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[6] α-chain is found to have greater stability because of internal S–S apart from external S–S linkages.

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[7] Though Insulin belongs to globular type, the Proline moiety in β-chain may not fit exactly to the expected helical conformation, so might be protruded out of the plane along with other two [Lysine and Alanine]. However, these three α-AA may be stabilized by strong ionic forces/dipole-dipole interactions.

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[8] As a general rule, each chain must be read as N-terminal → C-terminal, it

may be assumed that, NH_2 part of glycine might be as H_3N^+ and COOH part of Asparagine, as $O=C-O^{[-]}$. A similar argument is valid in case of β-chain.

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[9] As many α-AAs are coded by more than one codon, I assume, the specific codon that has coded specific α-AA need not be the same in every human or a family member. This may be the reason behind why every member need not get diabetes (type-1 or 2) from ancestors. If my assumption were true, one must analyze which specific codon was utilized in coding specific α-AA and analysis has to be made on various blood samples belonging to different members of the given family. If my argument is to be tested, one must make specific codon to code specific α-AA of a diabetic [say P] compared to an adiabatic [say Q] but P and Q from same family [preferably from the same parents*]. Has such a mode of selecting specific codon to code specific α-AA achieved anywhere else? However, one must get a doubt that, why natural selection was not made such a way in all cases? I assume ability of codon, say UGU ≠ UGC w.r.t Cysteine.

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[10] What would be the effect if the sequence of α-AA is changed in both chains? Does it affect its hypoglycemic ability? or not? For example, taking α-21 (α-AA) chain, if one synthesizes a new polypeptide taking 2^{nd} α-AA as 1^{st} and keeping the 21^{st} as 1^{st}, we get: New Polypeptide [α_1-chain]

I-V-E-Q-C-C-A-S-V-C-S-L-Y-Q-L-E-N-Y-C-N-G [21]

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Like this, we may consider 21 possibilities for α-chain (21 amino acids). Like this β-chain too, we get 30 possible polypeptides. Here, one may consider about even interchange of any two randomly. Does such a new polypeptide has same sort of ability as naturally occurring one?

New Polypeptide [eg: β_1-chain]

V-N-Q-H-L-C-G-S-H-L-V-E-A-L-Y-L-V-C-G-E-R-G-F-F-Y-T-P-K-A-F [30]

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

[11] I have a wild imagination that, this small part of m-RNA sequence (used to synthesize this peptide hormone) in fact originated from DNA-segment, so, does an extremely small region of very long DNA strand (billion BP) that synthesizes m-RNA (by transcription) occur only at one specific horizon or several horizons occur at different parts of DNA part is my doubt? As each cell requires energy (as ATP) and each cell has DNA, I opine that, this specific region is present at regular intervals (as far as distance is concerned) so that, a continuous supply of insulin is possible to regulate blood glucose level. (*DNA = helical based)

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[12] As every biochemist knew about anomeric pair of D-glucose (α, β-forms) whose equilibrium mixture has specific rotation of $+52.7^0$, does insulin affect both anomeric forms to same extent or not? It is so important that, β-form is more abundant (64% by mol) so, the <u>amount of insulin utilized per 1.0 mol</u> of β-anomer eventually be higher than other. If so, does a person having type-1 diabetes and the one having type-2, I believe that, this anomeric content may play a crucial role to make person to become type-1 or 2. Insulin dependent person needs more insulin so, he/she must have excess of β-form in cell. This means the perfect equilibrium often fails to exist in the cells of such persons. (note: α-form⇔β-form coexist in equilibrium at pH = 7, but inside the cell, the pH need not always be 7 or in blood plasma, it varies 7.26-7.32)

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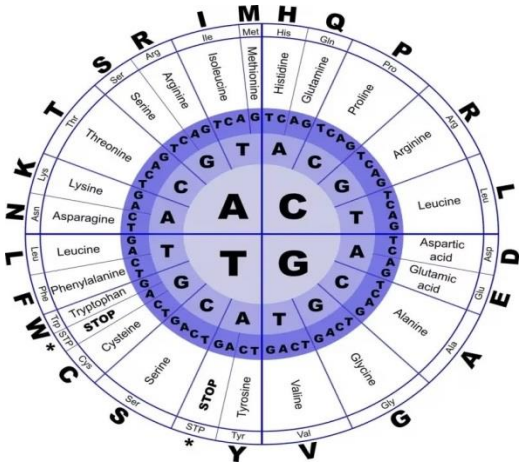
[13] Observe the DNA-codon circle: [read U in place of T to get m-RNA-codon]



[Courtesy: google.com]

Check the m-RNA sequence corresponding to each possible α-chain (21 α-AA):
[*I have put different possible but permissible codon to represent α-AA if it has two/more codons] [α-chain = natural*] [13 such α-chains are shown]

[*α chain to α_6 chain]

S.No	[α]	RNA	[α_1]	RNA	[α_2]	RNA	[α_3]	RNA	[α_4]	RNA	[α_5]	RNA	[α_6]	RNA
1	G	GGU	I	AUU	V	GUU	E	GAG	Q	CAG	C	UGU	C	UGC
2	I	AUU	V	GUU	E	GAG	Q	CAG	C	UGU	C	UGC	A	GCC
3	V	GUU	E	GAG	Q	CAG	C	UGU	C	UGC	A	GCC	S	UCC
4	E	GAG	Q	CAG	C	UGU	C	UGC	A	GCC	S	UCC	V	GUC
5	Q	CAG	C	UGU	C	UGC	A	GCC	S	UCC	V	GUC	C	UGC
6	C	UGU	C	UGC	A	GCC	S	UCC	V	GUC	C	UGC	S	UCG
7	C	UGC	A	GCC	S	UCC	V	GUC	C	UGC	S	UCG	L	CUG
8	A	GCC	S	UCC	V	GUC	C	UGC	S	UCG	L	CUG	Y	UAU
9	S	UCC	V	GUC	C	UGC	S	UCG	L	CUG	Y	UAU	Q	CAA
10	V	GUC	C	UGC	S	UCG	L	CUG	Y	UAU	Q	CAA	L	CUA
11	C	UGC	S	UCG	L	CUG	Y	UAU	Q	CAA	L	CUA	E	GAA
12	S	UCG	L	CUG	Y	UAU	Q	CAA	L	CUA	E	GAA	N	AAC
13	L	CUG	Y	UAU	Q	CAA	L	CUA	E	GAA	N	AAC	Y	UAC
14	Y	UAU	Q	CAA	L	CUA	E	GAA	N	AAC	Y	UAC	C	UGC
15	Q	CAA	L	CUA	E	GAA	N	AAC	Y	UAC	C	UGC	N	AAC
16	L	CUA	E	GAA	N	AAC	Y	UAC	C	UGC	N	AAC	G	GGU
17	E	GAA	N	AAC	Y	UAC	C	UGC	N	AAC	G	GGU	I	AUU
18	N	AAC	Y	UAC	C	UGC	N	AAC	G	GGU	I	AUU	V	GUU
19	Y	UAC	C	UGC	N	AAC	G	GGU	I	AUU	V	GUU	E	GAG
20	C	UGC	N	AAC	G	GGG	I	AUU	V	GUU	E	GAG	Q	CAG
21	N	AAC	G	GGC	I	AUG	V	GUU	E	GAG	Q	CAG	C	UGU

[α_7 chain to α_{13} chain]

S.No	[α_7]	RNA	[α_8]	RNA	[α_9]	RNA	[α_{10}]	RNA	[α_{11}]	RNA	[α_{12}]	RNA	[α_{13}]	RNA
1	A	GCC	S	UCC	V	GUC	C	UGC	S	UCG	L	CUG	Y	UAU
2	S	UCC	V	GUC	C	UGC	S	UCG	L	CUG	Y	UAU	Q	CAA
3	V	GUC	C	UGC	S	UCG	L	CUG	Y	UAU	Q	CAA	L	CUA
4	C	UGC	S	UCG	L	CUG	Y	UAU	Q	CAA	L	CUA	E	GAA
5	S	UCG	L	CUG	Y	UAU	Q	CAA	L	CUA	E	GAA	N	AAC
6	L	CUG	Y	UAU	Q	CAA	L	CUA	E	GAA	N	AAC	Y	UAC
7	Y	UAU	Q	CAA	L	CUA	E	GAA	N	AAC	Y	UAC	C	UGC
8	Q	CAA	L	CUA	E	GAA	N	AAC	Y	UAC	C	UGC	N	AAC
9	L	CUA	E	GAA	N	AAC	Y	UAC	C	UGC	N	AAC	G	GGU
10	E	GAA	N	AAC	Y	UAC	C	UGC	N	AAC	G	GGU	I	AUU
11	N	AAC	Y	UAC	C	UGC	N	AAC	G	GGU	I	AUU	V	GUU
12	Y	UAC	C	UGC	N	AAC	G	GGU	I	AUU	V	GUU	E	GAG
13	C	UGC	N	AAC	G	GGU	I	AUU	V	GUU	E	GAG	Q	CAG
14	N	AAC	G	GGU	I	AUU	V	GUU	E	GAG	Q	CAG	C	UGU
15	G	GGU	I	AUU	V	GUU	E	GAG	Q	CAG	C	UGU	C	UGC

16	I	AUU	V	GUU	E	GAG	Q	CAG	C	UGU	C	UGC	A	GCC
17	V	GUU	E	GAG	Q	CAG	C	UGU	C	UGC	A	GCC	S	UCC
18	E	GAG	Q	CAG	C	UGU	C	UGC	A	GCC	S	UCC	V	GUC
19	Q	CAG	C	UGU	C	UGC	A	GCC	S	UCC	V	GUC	C	UGC
20	C	UGU	C	UGC	A	GCC	S	UCC	V	GUC	C	UGC	S	UCG
21	C	UGC	A	GCC	S	UCC	V	GUC	C	UGC	S	UCG	L	CUG

β-chain [30 α-AA, only 7 possibilities shown*]

S.No	[β]	RNA	[β_1]	RNA	[β_2]	RNA	[β_3	RNA	[β_5	RNA	[β_6	RNA	[β_7	RNA
1	F	UUU	V	GUU	N	AAU	Q	CAG	H	CAC	L	CUC	C	UGC
2	V	GUU	N	AAU	Q	CAG	H	CAC	L	CUC	C	UGC	G	GGC
3	N	AAU	Q	CAG	H	CAC	L	CUC	C	UGC	G	GGC	S	UCC
4	Q	CAG	H	CAC	L	CUC	C	UGC	G	GGC	S	UCC	H	CAU
5	H	CAC	L	CUC	C	UGC	G	GGC	S	UCC	H	CAU	L	CUG
6	L	CUC	C	UGC	G	GGC	S	UCC	H	CAU	L	CUG	V	GUG
7	C	UGC	G	GGC	S	UCC	H	CAU	L	CUG	V	GUG	E	GAA
8	G	GGC	S	UCC	H	CAU	L	CUG	V	GUG	E	GAA	A	GCA
9	S	UCC	H	CAU	L	CUG	V	GUG	E	GAA	A	GCA	L	CUA
10	H	CAU	L	CUG	V	GUG	E	GAA	A	GCA	L	CUA	Y	UAC
11	L	CUG	V	GUG	E	GAA	A	GCA	L	CUA	Y	UAC	L	CUC
12	V	GUG	E	GAA	A	GCA	L	CUA	Y	UAC	L	CUC	V	GUA
13	E	GAA	A	GCA	L	CUA	Y	UAC	L	CUC	V	GUA	C	UGC
14	A	GCA	L	CUA	Y	UAC	L	CUC	V	GUA	C	UGC	G	GGG
15	L	CUA	Y	UAC	L	CUC	V	GUA	C	UGC	G	GGG	E	GAG
16	Y	UAC	L	CUC	V	GUA	C	UGC	G	GGG	E	GAG	R	AGG
17	L	CUC	V	GUA	C	UGC	G	GGG	E	GAG	R	AGG	G	GGA
18	V	GUA	C	UGC	G	GGG	E	GAG	R	AGG	G	GGA	F	UUC
19	C	UGC	G	GGG	E	GAG	R	AGG	G	GGA	F	UUC	F	UUU
20	G	GGG	E	GAG	R	AGG	G	GGA	F	UUC	F	UUU	Y	UAU
21	E	GAG	R	AGG	G	GGA	F	UUC	F	UUU	Y	UAU	T	ACG
22	R	AGG	G	GGA	F	UUC	F	UUU	Y	UAU	T	ACG	P	CCG
23	G	GGA	F	UUC	F	UUU	Y	UAU	T	ACG	P	CCG	L	CUG
24	F	UUC	F	UUU	Y	UAU	T	ACG	P	CCG	L	CUG	A	GCG
25	F	UUU	Y	UAU	T	ACG	P	CCG	L	CUG	A	GCG	F	UUU
26	Y	UAU	T	ACG	P	CCG	L	CUG	A	GCG	F	UUU	V	GUU
27	T	ACG	P	CCG	L	CUG	A	GCG	F	UUU	V	GUU	N	AAU
28	P	CCG	L	CUG	A	GCG	F	UUU	V	GUU	N	AAU	Q	CAG
29	L	CUG	A	GCG	F	UUU	V	GUU	N	AAU	Q	CAG	H	CAC
30	A	GCG	F	UUU	V	GUU	N	AAU	Q	CAG	H	CAC	L	CUC

Target-3: Stereo-chemical interaction-Codon versus α-Amino acid

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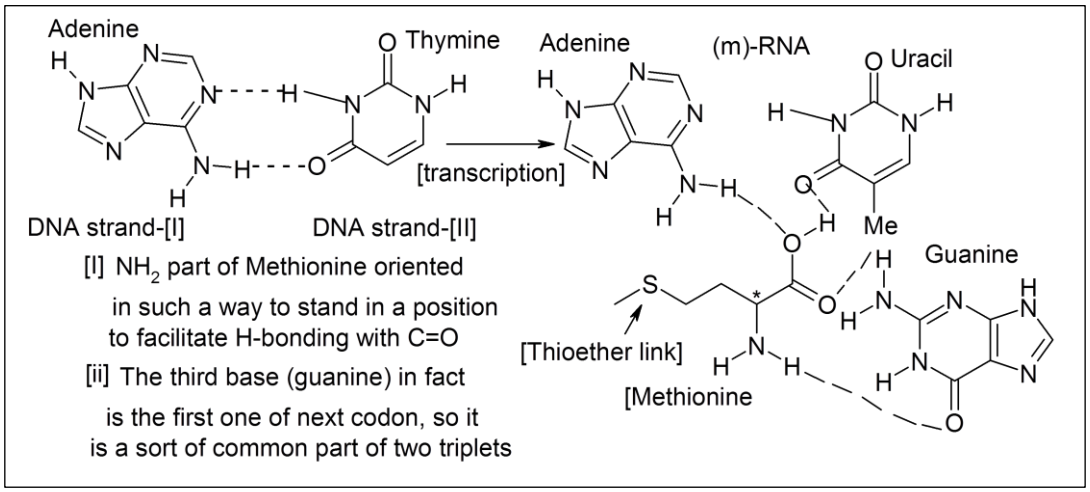
[1] I need not introduce the term "codon" which brings specific α-AA in the synthesis of a protein to occupy specific position based on sequence. Out of 64 codons, 3 are stop type (UAA, UAG and UGA) and other 61, code for 20 α-AA.

[2] The start codon AUG that codes Methionine (*ethyl methyl Thioether derivative of glycine) in bacteria has its complimentary triplet ATG in one of 2 strands of DNA must have TAC on its opposite strand obeying pairing rule. Now why does AUG code the only α-AA i.e methionine, why cannot other one or more than one α-AA? [A hypothetical interaction between Methionine-AUG shown]



[3] A similar but so complex mechanism might be expected to explain codon-AA relationship.
[4] When 21 (from α-chain) and 30 (from β-chain) are concerned, a total of 51 types (see tables) of Insulin may be possible. However, the S-S link changes its position and whether this change brings any dramatic change in hypoglycemic ability or not is a big debate or experiment.
[5] Why we need to synthesize at least 51 types of Insulin anomalies?
Reason: If we synthesize the native Insulin with same sequence (natural), it may not show same sort of efficiency in every Insulin-dependent diabetic patient. So if 51 types are available, it is possible to analyze which is the best one that suits a given body (*by analyzing blood sample-synthetic Insulin sample)

Disclaimer

This article is purely hypothetical and is originated from my sub-conscious state. Except the diagram (page: 4), which I used here, no other information stated in this small article was copied from any magazine/article/thesis/else. The natural sequence of Insulin however selected from google.com. This article never intended to criticize any scientist/pharmaceutical Inc./biochemist/virologist/else and I always hope that, any top R&D platform may show interest in this article/my views to bring my thoughts to practical platform.

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