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Role of Insulin / Insulin Receptor in Learning and Memory from the View Point of Protein Vibration

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Abstract Exploring the impact of insulin/insulin receptor on learning and memory formation from the view point of protein vibration constitutes the main objective of the paper .Protein vibration due to external stimuli in the form of EEG rhythms and its consequences on learning and memory traces particularly with respect to diabetic patients may be considered as exemplary objective of the paper. It has been pointed out by the author that learning and memory formation depend on molecular weights of protein. These proteins vibrate in different forms due to external stimuli in accordance with their molecular weights. .However, a number of experiments had been conducted by different authors on mechanism of functioning of insulin/insulin receptor in brain. Hence, it has been proposed by the author differently that diabetic patient suffer from loss of memory due to the presence of insulin of light molecular weights in their brain. The theoretical results of the author are found compatible with those obtained from the field survey conducted by the author.

Keywords CNS insulin, Lesions, Ischaemia, Apo E-4 allele, GLUT, Protein Vibration, Signaling pathway etc

1. Introduction

The brain is registered as a target organ for insulin and insulin receptor (IR). It has now been established that insulin in the central nervous system (CNS) exhibits more diverse actions while the primary function of insulin is to regulate glucose homeostasis in some classical peripheral insulin target tissues like adipocyte, muscle and liver. In addition, a direct role of CNS insulin / insulin receptor (IR) in learning as well as insulin receptor (IR) deterioration with brain degenerative dementia (e.g Alzheimer's disease etc) have raised increasing interest. These attracted the scholars to unfold the cellular and molecular basis for CNS insulin / insulin receptor (IR) action on learning and memory in the context of behavioral, electrophysiological and biochemical studies. It has been pointed out by the scholars of the day that at molecular level, insulin / insulin receptor (IR) participate in regulation of learning and memory through specific signaling pathways. One of these pathways is found to be associated with the formation of long-term memory.

It was observed by Park et al. (1) that administration of insulin into the 3rd cerebral ventricles of rats which undergone passive avoidance training experiences resulted in higher memory retention levels compared to those rats which were injected saline and heat-inactivated insulin. In this respect some reverse effects were also observed by different scholars. Kopf and Baratti (2) showed that "intraperitoneal (i.p.) injection of insulin without simultaneous administration of glucose which is necessary for maintaining normal glucose levels impaired retention in mice, trained for either habituation learning task or inhibitory avoidance.'' On the other hand, Kern et al. (3) observed that systemic infusion of insulin under proper maintenance of glucose clamp exhibited significant memory improvement particularly in verbal memory and selective attention.''

Diversified results are observed in case of administration of insulin to human subjects. A cognitive task responding to an auditory stimulus, as observed by Kern et al (4) showed negative shift in auditory-evoked potential in specific cortical areas. These are practically thought to be associated with working memory processes. However, Pelosi and Blumhardt (5) held the view that ''aged population with impaired memory showed increased latencies and amplitudes in components of auditory-evoked potentials after administration of insulin / insulin receptor.'' All these suggest that the insulin / insulin receptor (IR) signaling is activated in the early stage of memory formation and this may play role in memory sorting for long-term storage.

2. Insulin or Insulin Receptor and Signalling Pathway

A good number of scholars conducted experiments on the mechanism of functioning of insulin or insulin receptor (IR). The CNS insulin receptor does function differently from

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those in classical insulin target tissues.

The experimental evidences along with the results of brain specific deletion of insulin receptor clearly indicate that insulin / insulin receptor (IR) contributes significantly to glucose homeostasis. It was also noted by Stochhorst et al. (6) and Woods et al. (7) that 'CNS administered insulin showed a Pavlovain conditioning effect on peripheral glucose levels in both humans and animals.' From all these findings it can obviously be held that the ''action of insulin / insulin receptor in the brain is predominantly mediated by its role in neuron-modulations,'' which is expected to take part in learning and memory formation.

With respect to modulation of memory associated neuronal activities Wei-Qin Zhao (8) held the view that during learning insulin first binds to the subunit of insulin receptor which in turn causes the activation of tyrosine kinase of the beta-subunit.'' This activated insulin receptor is expected to be involved in learning and memory formation.

Thus it can be held that receptors are excited only at the very outset of stimulation (on receptors) and the others remain non excited when stimulation cease (off-receptors). Still others are excited both at the beginning and at the end of stimulation (on and off receptors). These receptors, however, constitute as sources of constant flow of impulses. These can react with increase or decrease of the frequency of imputes under the action of external stimuli.

Henceforth, the signals (impulses) pass on to respective insulin which in turn is engaged in different purposes concerning the necessity of the individuals.

Recent studies on the role of insulin / insulin receptor (IR) in the functions of central nervous system including learning and memory at synaptic and molecular levels have significantly advanced our knowledge. In spite of these, many substrates of insulin and its interactions with insulin receptor (IR) and other receptors along with kinase molecules directly associated with learning experience are yet to be explored. Scholars are conducting in-depth studies at cellular and molecular levels with respect to specific deletions of insulin and insulin receptor (IR) in the brain.

3. Methodology

In view of the above discussion, the author attempts to examine the problem from the view point of one of the author's suggestion (9) of ''protein vibration'', responsible for recalling the learnt events. Here protein vibration is caused by external stimuli. However, protein also vibrates due to electrostatic force generated in it. The suggestion of protein vibration lies in the fact that when an impulse gets to a neuron, the structural change of the membrane lipid occurs and during this phase of structural change, vibrations occurring in protein as expected to be responsible for memory measure. The more stable the protein is, more is the memory. The corresponding author in a recent paper (9) shows that recalling the learnt event depends on the number of frequencies of vibration in protein.

The present paper attempts to focus on the underline mechanism of protein vibration with the application of four basic types of EEG rhythms of amplitudes 20 to 100 and 150 to 350 microvolt's and frequencies in the range of 0.5 to 30 cycles per second.

It is hypothesized that by measuring the difference energy between the initial (External stimuli in the form of EEG rhythms) and the final level, it would be possible to correlate the happenings related to learning events and memory traces in the brain.

The problem of protein vibration responsible for memory was considered in the light of the solution of the standard form of Schrodinger Equation. Inserting the potential energy function $v=1/2\ kr^2$ in one dimensional Schrodinger Education

$$\frac{-h^2}{8\pi^2 m}\ \frac{d^2\psi}{dr^2} + v(r)\psi = €\psi \qquad (1)$$

turns to

$$\frac{-h^2}{8\pi^2 m}\ \frac{d^2\psi}{dr^2} + \frac{1}{2}\ kr^2\psi = €\psi \qquad (2)$$

The energies of the allowed vibration states derived from the solutions of the Schrodinger's Equation are

$$Evib = \left(v + \frac{1}{2}\right)\frac{h}{2\pi}\sqrt{\frac{k}{m}} \qquad v = 0, 1, 2 \qquad (3)$$

While the expression for vibration frequency stands as

$$Vvib = \frac{1}{2}\sqrt{\frac{k}{m}} \qquad (4)$$

Vibration occurring in protein depends on molecular weight of the concerning proteins available in particular portions of the brain. Thus, frequent vibrations, as the author (9) held, are created in light proteins of small molecular weight while slow vibrations are created in proteins of comparatively large molecular weight. The memories emerged due to frequent vibrations may be termed as instant or subconscious memory while those due to slow vibrations are termed as long-term memories.

Basing on this, it was established by one of the author (9) that retentively depends on the magnitudes of frequencies of vibration generated in protein due to external stimuli, while magnitudes of vibration depend on the molecular weight of protein.

For the sake of the present study, the molecular weights of insulin and its derivates are tabled in Table-1. Insulin and their derivatives have been identified with the name of the inventors as.

Table 1.

Sl.No	Name of the inventor	Name of the insulins	Molecular weights of insulins in KD
1	Sjogren and Svedberg	$Insulin_{SS}$	35.100KD
2	Svedberg and Pedersen	$Insulin_{SP}$	40.900KD
3	Experimental Data	$Insulin_{ED}$	46.000KD
4	Jole Meyer	$Insulin_{JM}$	5.808 KD

Vibration frequencies of these insulin's are evaluated by using Equation (4) and these are tabled in Table-2.

Table 2. Vibration frequencies (m^{-1}) of some insulin's with different molecular weights (KD)

External Electrical Stimuli (EEG) microvolts	m=5.8	m=35.10	m=40.90	m=46
E=20	.93	.49	.46	.43
E=25	1.33	.56	.52	.48
E=50	1.95	.76	.73	.68
E=100	2.77	1.12	1.04	.98
E=150	3.52	1.40	1.29	1.22
E=250	4.46	1.80	1.67	1.58
E=350	5.27	2.14	1.98	1.87

This means Vibration frequencies of insulin (s) are inversely proportional to the molecular masses.

Using Equation $E_{vib} = h\vartheta$ and after necessary conversion in S.I units, Vibration energies of the concerned insulin's have been evaluated. These are tabled in Table No.3

Statistical Approach:

In view of the above observations of Insulin/Insulin receptor vibration frequencies and the speculation for retention of learnt events, the author has conducted field studies for correlating the observations with hypothetical result. The observations of the field studies were analyzed from the view point of statistical approach.

The Study consists of 50(fifty) populations of which 13 belong to type II diabetes and are treated with insulin and medicines (tablets) of different doses, the rest belong the type I diabetes that are treated with normal medicines (tablets). Field survey was conducted through a questionnaire designed by the author for collecting the relevant data of the individual patient and memory testing was conducted by engaging investigators. The questionnaire with respect to memory testing was prepared keeping in view the following principal of memory testing.

Table 3. Vibration energy of insulin with different molecular weights KD

	Initial energy due to applied microvolt	Final energy $x10^{-22}$ j			
E	Equaling to Joules	m=5.8	m=35.10	m=40.90	m=46
20	11.0 X 10^{-22} j	.022	.010	.010	.009
25	13.75 X 10^{-22} j	.029	.012	.011	.010
50	27.50 X 10^{-22} j	.042	.016	.016	.014
100	55.00 X 10^{-22} j	.060	.024	.022	.021
150	82.50 X 10^{-22} j	.077	.030	.028	.026
250	137.50 X 10^{-22} j	.098	.039	.036	.034
350	192.50 X 10^{-22} j	1.201	.047	.043	.041

i) Retrospective memory---------- information about incident remembered.
ii) Prospective memory ---------- information to be remembered (recitation)
iii) Short term memory ---------- incident to be remembered.
iv) Long term memory ---------- telling description
v) Self cued ---------- something about self.
vi) Environmental cued ---------- something about environment.

Our study was mainly concerned with 1st four components of memory testing process.
The findings of the study are briefly shown in Table No.4

Table 4.

Responses of the patients to memory measure after1/2/3 hours of administration of insulin

Memory measure in percent of scores	Patients of different age group					
	(25-40) Years	(41-50) Years	(51-60) Years	(61-70) Years	(71-80) Years	Total
41-50	1	3	4	2	--	10
51-60	--	7	6	1	--	14
61-70	1	7	3	1	--	12
71-80	--	4	5	1	--	10
81-90	--	--	2	1	1	4
						50

Responses of the patients to memory measure after 6/7/8 hours of administration of insulin

Memory measure in percent of scores	Patients of different age group					
	(25-40) Years	(41-50) Years	(51-60) Years	(61-70) Years	(71-80) Years	Total
41-50	4	7	6	2	--	19
51-60	--	6	4	--	--	10
61-70	1	6	4	--	--	11
71-80	--	2	2	--	--	4
81-90	--	3	--	--	1	4
						48

Measure of different statistical factors incorporated with the survey data

Item	S.D	Co-efficient of Variances (c.v)	t-value	IZI value
Measure of memory w.r to meaningful incidents after 1/2/3 hour of taking insulin	14.1	107($C.V_A$)	3.5	4.6
Measure of memory with r.to meaningful incidents after 6/7/8 hours of taking insulin.	12.7	127 ($C. V_B$)		

4. Results and Discussion

i) $C.V_A$ for 1 hour < $C.V_B$ for 6 hours. This means $C.V_A$ for 1 hour is more consistent than $C.V_B$ for 6 hours.

ii) Tabulated t_{05} to = 1.96 and t_{01} = 2.58
Since calculated value of t=3.5 is much greater than t=0.05 and to.01, it is highly significant and it is concluded that there is significant differences in measure of memory between two conditions (memory measured after 1/2/3 hours of taking insulin and 6/7/8 hours of taking insulin).

iii) Tabulated value of Z due to two tailed test are 1z1 = 2.58 at 1% and 1z1 =1.96 at 5% level of significance. The calculated value of 1z1 = 4.6 is much higher than the above two values. It is highly significant at both levels of significances. Hence, we conclude that there is significant difference in two levels of memory measure.

Other findings of the statistical approach

The study was conducted with 50 diabetes patients of age group 32-73. Among these 25 were male and 25 were female.

(i) From educational point of view, the patients are of Class VIII standard to graduate level. They belong to various professions like govt. job, teacher, house wives etc.

(ii) Before attacking of diabetes, the memories of the patients are as follows:
Below average = 6 persons securing below 40% scores.
Average = 28 persons securing (40-50%) scores.
Out standing = 16 persons securing above 60% scores.

(iii) From the view point of Physical fitness of the patients after attack of diabetes, 30 patients responded that they feel physically weak, while 20 patients kept silence in this respect.

(iv) In respect of taking exercise 15 patients replied that they walk regularly for 45 minutes to 1 hour, 5 patients replied that they undertake yoga regularly. On the other hand, the rest 30 do not undertake any sort of exercise.

(v) Out of 50 patients of age group (32-73) years, 13 may be categorized as patients of type-II diabetes. The memory score as revealed from the study lie within (41-50)% for 10 (ten) patients, (51-60)% for 2 patients even after 6 hour of taking insulin. One patient of age group (71-80) years attained memory score in the (61-70)% after 1 hour of taking medicine. However, it comes down to the range (41-50)% after 6 hours of taking insulin. This proves that type II diabetic patients are more depended on taking insulin (protein) for their surveillance and their memory level does not improve except for few exceptional cases where it shows memory rises after taking insulin. However, in case of other patients, the memory comes down after 6/7/8 hours of taking insulin.

Thus it can be held that injection of insulin which is basically a protein may increase the memory in case of human beings too who are suffering from diabetes. This is found to be in parity with findings of Louis and Josefa Flexner (10) in 1963 with injections of protein inhibitor puromycin in mice. They found that learning was effective from day 1 to 3 in blocking long-term memory in mice. The author also verified these findings with his theoretical approach of ‘’Protein Vibration’’ in measuring memory level (11). The nature of memory level in both the cases is found of to be compatible.

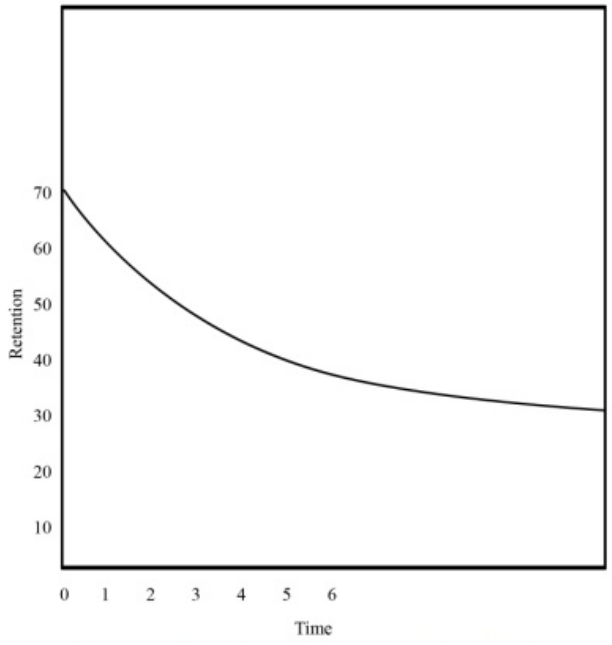

Figure 1. Loss of memory of diabetic patient having insulin of light molecular weight

The findings, however, predict that diabetic patients administered with insulin (proteins) can retain the learnt events at first three hours of administration not more than 60% of the learnt events and gradually the memory level comes down. It may also be held from the findings of Banks and Kastin (12) that the brain insulin receptor has smaller molecular weights, both in alpha and beta subunits. On the other hand, these are also in parity with the findings of Frolich et al (13) that insulin and insulin receptors are found in reduced form in the brain of Alzheimer's patients. All these findings support our theoretical approach of protein vibration where it is shown that persons having light insulin (5.38 KD) are not able to retain learnt events as much those with insulin of large molecular weights.

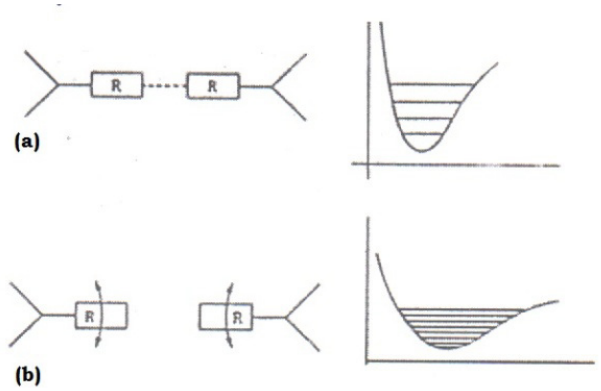

Figure 2. Vibration energy spacing of protein molecules

It is found from Table No. 2 that more the molecular weight of protein molecule is, the less would be the magnitude of vibration frequency and more the frequency of vibration is, less would be the molecular weight of protein. This means there is frequent vibration in case of protein of less molecular weight, while reverse may be found in case of proteins of higher molecular weight. These are shown diagrammatically in Fig.2.

It is also found on the figures that more apart and depart energy levels are, the stronger the amino acid residue bonds are. And hence the probability of conformational change of protein with large molecular weights are less, the consequences of which are stable memory.

On the other hand it has also been established that more the oscillation, the more and closely spaced are the energy levels as shown in Fig. 2.(b). And this results in loose binding of amino acid residues, this may result in short term memory in patients particularly of type II diabetes.

5. Conclusions

From the above discussion of biophysical approaches, it may now be held that insulin / insulin (IR) participates in regulation of learning and memory. From the field study it is found that interruption of insulin production and IR activity causes deficits in learning and memory formation. This is found to be happened in our field study concerning type II diabetic patients. Thus frequent vibrations as shown in Fig. 2 (b) may occur in type II diabetic patients having light insulin of approximately 5.38 KD molecular weights. However, this study does not constitute any Alzheimer's patient, from which the role of abnormal insulin / insulin receptor (IR) levels and their activities could also be verified with other studies. Future in-depth study with administration of insulin at cellular and molecular level by using modern technique like EEG, MIR etc may open vista of knowledge to the scholars concerning the role of insulin / insulin receptor in the brain.

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