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Suppressed Fluctuation in The GABAergic Signaling: Mathematical Modelling of The Neurotransmitter

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ABSTRACT

The chemistry of the gamma aminobutyric acid (GABA) had been established. However, the explanation on the interplay between GABA receptors antagonize fundamental concept of the GABAergic Signaling. For example, glutamate spillover from excitatory afferent terminals leads to the modulation of GABAergic signals. However, this result is true with respect to GABAB receptors only. The physics of its interplay between the GABA receptors was theoretically investigated using the magnetic resonance imaging (MRI) because the proton gradient controls the intermediate energy storage for heat production and flagellar rotation. The MRI investigation of the GABAergic Signaling is not a new concept in medicine. Molecular potential in the receptors increases the peak radiofrequency (*RF*) field (B_1) amplitude and the holding potential of the GABA receptors. The suppressed fluctuation of the GABAergic Signaling was noticed where the receptors are all actively involved in the GABAergic network. Hence, a dual technique was suggested to detect the suppressed GABAergic state in the human body.

Keywords: GABA, receptors, Signal, Magnetic Resonance Imaging

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INTRODUCTION

GABA (γ-aminobutyric acid) is a principal inhibitory neurotransmitter that modulates neuronal excitability (Farrant & Nusser, 2005). Glutamic acid initiates the GABA due to glutamate flow in the Human brain. Glutamate flow in the brain is controlled only when necessary by a system of dam-like structures. The surge of glutamate leads to the chain reaction of neuro-breakdown originating from the damaged neurons. The chemistry of the GABA had been explained (Ortells & Lunt, 1995; Wadiche, Amara, & Kavanaugh, 1995) even though there are still much arguments on the interplay of the GABA receptors. The $GABA_A$ receptors are ligand-gated ion channels made up of a pentameric mixture of protein subunits (Chebib & Johnston, 2000). $GABA_B$ receptors are heterodimeric G-protein coupled receptors (Bowery & Enna, 2000) and $GABA_C$ receptors are ligand-gated ion channels made up of imidazole-4-acteic acid (Johnston, 2002). Most neurons in the central nervous system contain GABA receptors. GABA is loaded into synaptic vesicles by a vesicular neurotransmitter transporter. Vesicular transporter depends on a proton gradient created by the hydrolysis of adenosine triphosphate (ATP). The proton gradient controls the intermediate energy storage for heat production and flagellar rotation. Much has been discussed on the modulation of the GABAergic signals (Semyanov & Kullmann, 2000; Somogyl, 1995) i.e. mechanism that leads to modulation of GABAergic transmission among interneuron. Synapses between hippocampal interneurons are important in the modulation of GABAergic network, though such concept is now faulted by recent discoveries on the receptors. For example, it has been reported that the L(1)-2-amino-4-phosphonobutyric acid depresses GABAergic transmission (Semyanov & Kullmann, 2000).Therefore in this paper we propose a suppression of fluctuated GABAergic signal by the synapses between hippocampal interneurons. The physics of its interplay between GABA receptors was theoretically investigated using the magnetic resonance imaging (MRI). The C NMR was first used to measure the rate of glutamate labeling (Gruetter et al., 1994). This inspired an in-depth experimental investigation-which is the major objective of this paper.

METHODOLOGY: MATHEMATICAL MODELING OF THE GABAERGIC FLOW

The MRI-neuroimaging (Fig1) requires salient technical input to adequately capture the suppressed GABAergic signaling. Earlier, we had discussed the relevance of the intermolecular potential for effective MRI process (Emetere, 2013, 2014; Emetere, Awojoyogbe, Uno, Isah, & Dada, 2014).

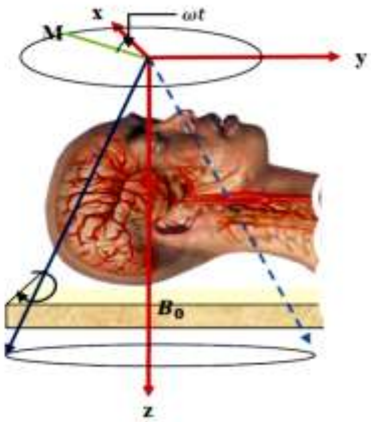

Fig 1. MRI process

The relevance of the possibility of the neuron/spin velocity was captured under the intermolecular potential. The mathematical representation of the discovery is written as,

$$v = \frac{(1+\gamma^2 {B_1}^2 T_1 T_2)\sum_i^N V(x_i)}{\mu.\omega_1 \gamma B_1 M_o T_1 T_2} \quad (1)$$

if $\gamma^2 {B_1}^2 T_1 T_2 \gg 1$,

$$v = \frac{\gamma B_1 \sum_i^N V(x_i)}{\mu.\omega_1 M_o} \quad (2)$$

Therefore the flow velocity of the spin in the laboratory frame which is synonymous to the signaling between GABAergic receptors can be written as

$$v_{xo} = \frac{-\sin(\omega t)\gamma B_1 \sum_i^N V(x_i)}{\mu.\omega_1 M_o} \quad (3)$$

$$v_{yo} = \frac{\cos(\omega t)\gamma B_1 \sum_i^N V(y_i)}{\mu.\omega_1 M_o} \quad (4)$$

Recall if the membrane potential is considered as $V(x_i)$ in Eq (3) and Eq (4), then the membrane potential is defined as

$$v_{xo}(x,t) = \frac{-\sin(\omega t)\gamma}{\mu.\omega_1 M_o} B_1 \sum_i^N V(x_i) \quad (5)$$

$$v_{yo}(y,t) = \frac{\cos(\omega t)\gamma}{\mu.\omega_1 M_o} B_1 \sum_i^N V(x_i) \quad (6)$$

The interplay of the GABA receptors as shown in Fig(3) is driven by the resultant GABAergic flow.

$$v_r = \frac{\gamma}{\mu.\omega_1 M_o} B_1 \sum_i^N V(x_i) \quad (7)$$

Since the membrane potential *V(x)* (measured in mV) develops in time (measured in ms), we differentiate both sides with respect to time

$$\frac{\partial v_r(x,t)}{\partial t} = \frac{\gamma}{\mu.\omega_1 M_o} B_1 \sum_i^N \frac{\partial V(x_i)}{\partial t} \quad (8)$$

The differential rate of GABAergic flow do not negotiate a linear form (Fig2).

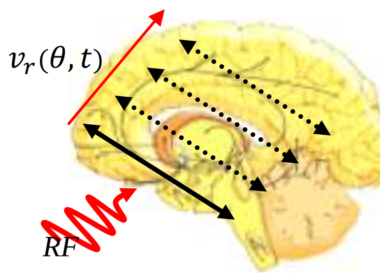

Fig 2. *RF* pulse sequence on the brain

We assumed a spherical geometry i.e. considering the brain structures-shown in Fig (1). Therefore the diffusion equation in the spherical geometry takes the form

$$\frac{\partial v_r}{\partial t} = \frac{a^2}{r^2}\left(\frac{1}{sin\theta}\frac{\partial}{\partial\theta}\left(sin\theta\frac{\partial v_r}{\partial\theta}\right)\right) \quad (9)$$

Here $v_r(x,t) \sim v_r(\theta,t)$, and here a is a positive constant. Eq (8) transforms via spherical geometries to

$$\frac{a^2}{r^2}\left(\frac{1}{sin\theta}\frac{\partial}{\partial\theta}\left(sin\theta\frac{\partial v_r}{\partial\theta}\right)\right) = \frac{\gamma}{\mu.\omega_1 M_o} B_1 \sum_i^N \frac{\partial V(x_i)}{\partial t} \quad (10)$$

Since the B_1 field is applied to a changing geometry (see Fig 3), the GABAergic flow experiences a significant rate of change with time. Hence, $B_1 = \frac{1}{\gamma\lambda}\frac{\partial v}{\partial t}$

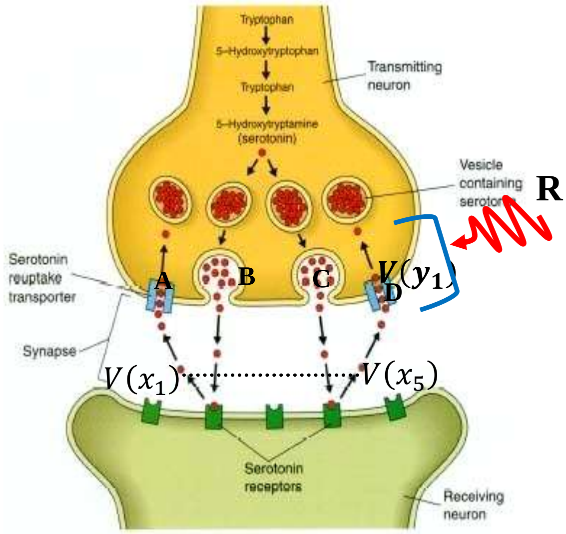

Fig 3. RF pulse influence on Neuro-transport. Image sourced from http://www.medicalterms.info.

Expanding Eq (10) yields

$$\frac{\partial^2 v_r}{\partial \theta^2} = \frac{r^2}{\mu.\lambda\omega_1 M_o}\frac{\partial v}{\partial \theta}\sum_i^N \frac{\partial V(x_i)}{\partial t} \qquad (11)$$

Here $v_r \sim v$ and $a = 1$. If $\frac{1}{k^2} = \frac{r^2}{\mu.\lambda\omega_1 M_o}\sum_i^N \frac{\partial V(x_i)}{\partial t}$, then

$$k^2 \frac{\partial^2 v}{\partial \theta^2} = \frac{\partial v}{\partial t} \qquad (12)$$

Before solving for Eq(12), it is important to discuss the mathematical significance of $\frac{1}{k^2} = \frac{r^2}{\mu.\lambda\omega_1 M_o}\sum_i^N \frac{\partial V(x_i)}{\partial t}$. $\frac{\partial V(x_i)}{\partial t}$ had been discussed by (Riz, Braun, & Pedersen, 2014) as the membrane potential which accounted for the current (measured in pA/pF) in different β-cell channels. Since we are using the MRI approach, the glutamate-known as the neurotransmitter becomes our only focus. In recent study, glutamte chemical exchange saturation transfer effect (GluCEST) was reported to be effective in mapping relative changes in glutamate concentration under the application of the nuclear magnetic resonance (Cai et al., 2012).

Also, past literatures had supported the possibility of the Proton magnetic resonance spectroscopy (1H MRS) to detect several neurotransmitter signature groups using a variety of techniques (Gottschalk, Lamalle, & Segebarth, 2008; Ryner, Sorenson, & Thomas, 1995). Hence, under the influence of the theoretical principles of the proton magnetic resonance spectroscopy, $\frac{1}{\mu.\lambda\omega_1 M_o}$ restricts the membrane potential to only the receptor mediated current of $GABA_A$, $GABA_B$ and $GABA_C$ as shown in the receiving neuron in Fig (3).

We assume that there are no leak currents in the channel. Therefore, the mathematical representation of the membrane potential is written as

$$\frac{\partial V(x_i)}{\partial t} = I_{GA} + I_{GB} + I_{GC} \qquad (13)$$

Where here $I_{GA} = g_{GA}(V - V_{GA})$, $I_{GB} = g_{GB}(V - V_{GB})$, and $I_{GC} = g_{GC}(V - V_{GC})$ and g_{GA} is the $GABA_A$ receptor conductance, g_{GB} is the $GABA_B$ receptor conductance, g_{GC} is the $GABA_C$ receptor conductance, V_{GA} is the reversal potential for the pentameric mixture of protein subunits, V_{GB} is the reversal potential for the heterodimeric G-protein, V_{GC} is the reversal potential for the imidazole-4-acteic acid. (Rorsman & Braun, 2013) calculated the current in the $GABA_A$ receptor as 9.4pA/pF at a holding potential of -70mV. Braun et al. (2010) gave the V_{GA} as -70mV.

However, in Riz et al. (2014) simulations, the range of the g_{GA} is within 0.02 to 0.10 ns/pF to simulate GABA concentration of 100μM. Resolving Eq (12) is paramount to the objective of this research. The trivial solution of Eq (12) is given

$$v(\theta, t) = \sum_{n=1}^{\infty} L_n \sin(2n\theta) \exp(-2n^2k^2\pi t)$$

Here, we applied the boundary conditions

$$\left.\begin{array}{ll} v(0,t) = 0 & t \geq 0 \\ v(\theta,0) = v(\theta) & 0 < \theta < \frac{\pi}{2} \\ v(\theta,0) = 0 & \theta \geq \frac{\pi}{2} \end{array}\right\}$$

$$v(\theta) = \sum_{n=1}^{\infty} L_n \sin(2n\theta)$$

Here $L_n = \frac{4}{\pi}\int_0^t v(\theta)\sin(2n\theta)\, d\theta$. Therefore, the solution is given as

$$v(\theta, t) = \sum_{n=1}^{\infty} \sin(2n\theta)\exp(-2n^2k^2\pi t)\left[\frac{4}{\pi}\int_0^t v(\theta)\sin(2n\theta)\, d\theta\right]$$

Equation (14) is further analyzed – using the separation of variable technique which reduce the equation to

$$v(\theta, t) = A.B.C \qquad (15)$$

Where

$$\left.\begin{array}{l} A = \sum_{n=1}^{\infty} \sin(2n\theta) \\ B = \sum_{n=1}^{\infty} \exp(-2n^2k^2\pi t) \\ C = \frac{4}{\pi}\int_0^t v(\theta).A\, d\theta \end{array}\right\} \qquad (16)$$

Here A represents the angular displacements of protons during spectroscopy which is expected to analyze the glutamate concentrations, B represents the receptor signal response and C represents the GABAergic signaling patterns. In this research, we restricted the research to the A and B factors. The C-factor was neglected because it is out of the research scope.

RESULTS AND DISCUSSION

We analyze the demo of the angular displacements of protons excitation during spectroscopy. This idea expresses a pattern-showing the distribution of protons and by extension the detection of several neuro-transmitter signature groups (see Figure 4 & 5). This process has effect on the Torque of protons at the receptors. Recall that the torque effect is written $\tau = \mu \times B = \mu B sin\theta$. Hence, $A = \frac{\tau}{\mu B cos(n\theta)}$.

In Fig(4), the maximum efficiency of the spectroscopy is between 1^o to 8.05^o, beyond which, the output of the spectroscopy reduces as the angular displacement of the protons increases. Aside the slight MRI abnormality (Scheffler, 1999; Tannús & Garwood, 1997), the increased membrane potential affects the GABA receptor response to the GABAergic signals. Figure (4) shows an orderly kind of spectroscopy while Fig (5) represents the disorderly spectroscopy. The orderly spectroscopy signifies the less neural activity while the disorderly spectroscopy signifies a high neural activity and hormone secretions to initiate the GABAergic flow.

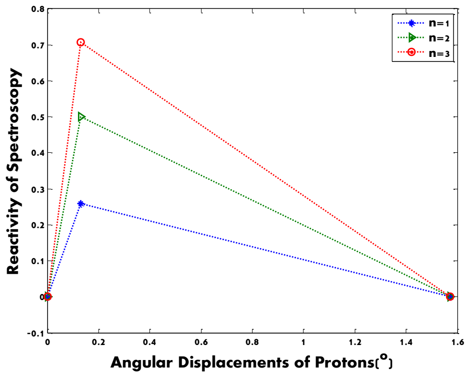

Fig 4. Angular displacements of protons in a orderly spectroscopy

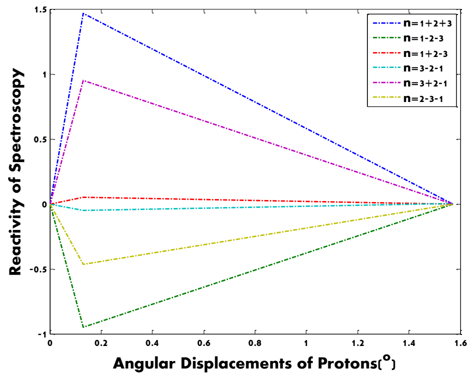

Fig 5. Angular displacements of protons in a disorderly spectroscopy

Figure 5 gives the three likely occurrences expected from the GABA receptors ($GABA_A$, $GABA_B$ and $GABA_C$) during the GABAergic transmission via the hippocampal interneuron. Here we propose the following

i. Three GABA receptors are the vesicular neurotransmitter transporter.
ii. Only one GABA receptor is the vesicular neurotransmitter transporter while the other two receptors are opposed to it in transmission.
iii. Two GABA receptors are the vesicular neurotransmitter transporter while the other receptor is opposed to both in transmission.

The first proposition is the general perception of the expected behavior of the receptors. However, in practicality, the second and third propositions are obtainable experimentally when analyzing neurotransmitter signature groups using the Proton magnetic resonance spectroscopy. This is the first evidence of a suppressed in the GABAergic signaling. Therefore, the rest of our calculation shall be based on proposition 1. Figure 6 is an expression showing the direct relationship between the receptors peak current and the receptors conductance. Neither the receptors peak current nor the receptors conductance has relationship with the nuclear magnetic resonance (NMR) parameter i.e. proton angular displacement. Hence, the second evidence of a suppressed GABAergic signaling is presented.

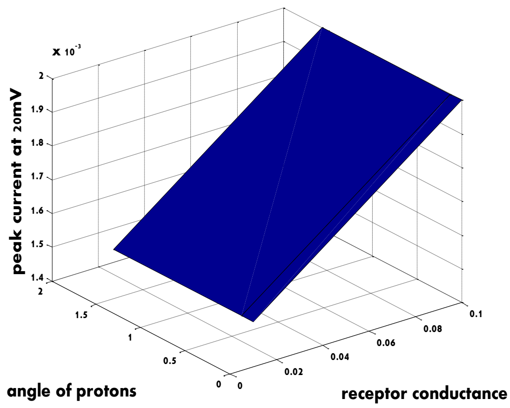

Fig 6. Effect of receptors Peak Current on NMR

The fluctuating nature of the suppressed GABAergic signals is evident in Figures (7, 10, 11) but not in Figures (8,9). The almost linear relation between the molecular and holding potential (see Fig(7)) corresponds with the experimental results of Cai et al. (2012) where the linear dependence of GluCEST and glutamate concentration was illustrated.

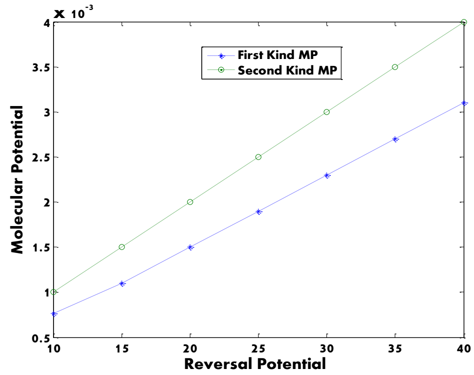

Fig 7. Molecular Vs Holding Potential

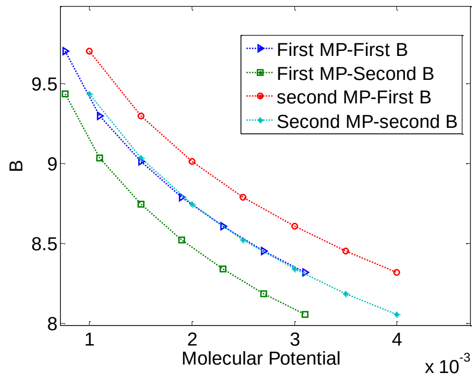

Fig 8. *B* Vs Molecular Potential

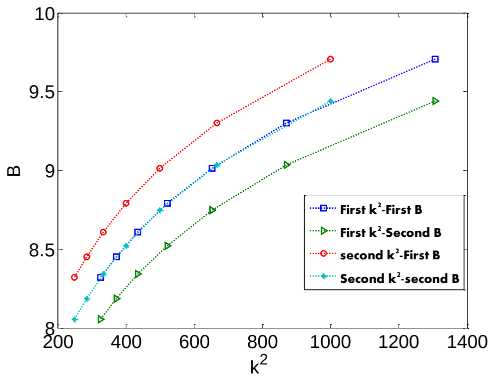

Fig 9. *B* Vs K^2

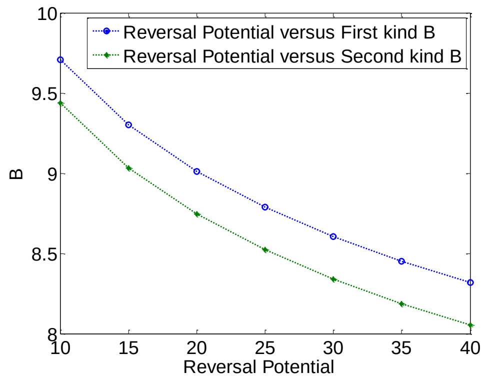

Fig 10. *B* Vs holding potential

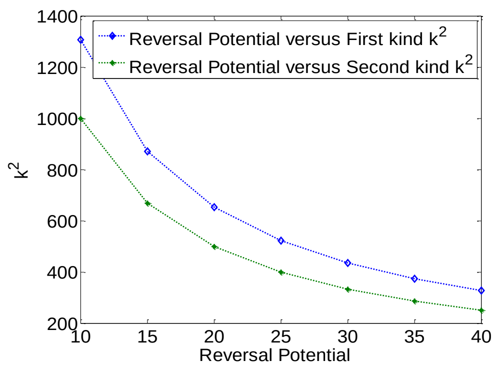

Fig 11. *B* Vs holding potential

Hence, the molecular potential in the receptors increases the peak radiofrequency (*RF*) field (B_1) amplitude and the holding potential. The possibility of using dual technique in the suppressed state i.e. the proton MRI and charge distribution to ascertain the neurotransmitter signature groups has been established. Also, the challenges of modulation of GABAergic network maybe overcome by estimating the fluctuating nature of the suppressed state. Fluctuation was not noticed in the parabolic connection between the B-factor (Eq(16)) and the Molecular potential (Fig 8). Also, fluctuation was not noticed in the parabolic connection (see Fig 9) between the B-factor (Eq(16)) and k^2-factor (Eq (12)). The extension of the fluctuating suppressed GABAergic signals surfaced in Fig (10) and Fig (11).

CONCLUSION

The concept of the fluctuating suppressed GABAergic signaling or transmission has been established. This concept solved the challenges of GABAergic transmission initiated by glutamate spillover from excitatory afferent or other unknown sources. Neither the receptors peak current nor the receptors conductance has relationship with the nuclear magnetic resonance (NMR) parameter i.e. proton angular displacement. However, molecular potential in the receptors increases the peak radiofrequency (*RF*) field (B_1) amplitude and the holding potential. Hence, the need for the use of dual technique (i.e. the proton MRI and charge distribution) to detect neuro-ailments at suppressed state of patients. The maximum efficiency of the Proton magnetic resonance spectroscopy is when the angular displacement of the protons is between 1^o to 8.05^o.

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