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Review Article

The Role of Lithium on the Excitability of Neurons

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Abstract

Role of cations such as sodium, potassium, calcium and lithium in bipolar disorder has been studied extensively in the past. Ionic gradients exert significant influence on the neurons by affecting the resting membrane potentials, action potentials, neurotransmitter release, signaling and signal transduction. Clinical measurements show that the membrane potentials of leucocytes in bipolar patients are significantly hyperpolarized whereas they are slightly depolarized in euthymic patients on lithium. Calculations using Goldman-Hodgkin-Katz equation show that lithium would depolarize the membrane potential. Hodgkin's circuit representing the neuronal membrane potentials and the ionic gradients confirms these calculations. Experimental data supporting these calculations are also reviewed. Action potentials in neurons are generally analyzed with the help of equivalent electric circuits. These circuits belong to a class of antiresonant parallel circuits. The specific circuits used by Hodgkin-Huxley and Cole are analyzed along with the basic circuit in this class. Comparison of these results with currently available electroencephalographic measurements shows that the basic circuit is the most suitable circuit for human neurons. This analysis leads to a non-dimensional parameter called excitability. Excitability is very useful in comparing epilepsy, mania and depression. It also helps in understanding the role of anticonvulsants in both epilepsy and in mania. Available experimental evidence in support of these theoretical results is also presented. It is further shown that the rate of neurotransmitter release is related to excitability. According to this analysis lithium reduces the excitability by reducing the membrane resistance.

Keywords: Bipolar Disorder; Excitability; Lithium; Anti-convulsants; Neurotransmitter Release

Introduction

Ever since John Cade discovered the efficacy of lithium as a mood stabilizer, a great deal of interest was devoted to the role of cations in Bipolar Disorder (BD) [1-3]. Detailed measurements of sodium and potassium gradients across the cell membranes from bipolar patients were made. Cation gradients play a significant role in the resting membrane potentials, action potentials, signaling and transduction in neurons. An understanding of this role is of great interest in Bipolar Disorder (BD). The first systematic measurements of membrane potentials in leukocytes from bipolar patients, normal controls and euthymic patients on lithium were made by El-Mallakh et al [4] in 1996. Thiruvengadam [5] calculated the effect of lithium on membrane potentials using Goldman-Hodgkin-Katz equations showing that lithium would depolarize the membrane potentials. The experimental results of El-Mallakh et al [4] confirmed this result. The direct current circuit used by Hodgkin and Huxley [6] was also used to further confirm this result. Graf et al [7], Adam-Vizi et al [8] and Yonemura and Sato [9] conducted various experiments confirming that lithium would depolarize the membrane potentials.

The effect of lithium on action potentials has also been the subject of study by various investigators including Graf et al [7] and Ulrich et al [10]. Hodgkin and Huxley [6] and Cole [11] used alternating current circuits to analyze their action potential measurements in squid giant axons. These circuits belong to a class

of circuits called antiresonant parallel circuits. Thiruvengadam [12] used these circuits as well as a circuit which is basic to this class of circuits and called it the basic circuit. This analysis led to a non-dimensional parameter called excitability (See Appendix at the end of the paper). The excitability consists of three basic electrical properties of the membrane namely the resistance, the conductance and the inductance. It is shown that lithium reduces the resistance of the membrane thereby reducing the excitability which in turn reduces the action potentials. The earlier measurements by Graf et al [7] and Ulrich et al [10] confirm this result. Furthermore this analysis explains how anticonvulsants are effective mood stabilizers since epilepsy and mania are connected by excitability. Katz [13] showed that the probability of the release of vesicles containing the neurotransmitters is related to the action potentials. Since excitability controls the action potentials, the release rate is dependent on excitability. Thus lithium plays a role on the release of neurotransmitters by altering the excitability.

Lithium and Membrane potential

The voltage difference across the cell membrane is called the membrane potential. This potential difference is caused by the ionic gradients across the membrane. The primary contribution for this potential comes from sodium and potassium gradients. The cell maintains the homeostasis of this potential by controlling these gradients by means of an enzyme called Na+, K+ -ATPase which is also known by other names including Na+ K + pump and simply Na pump. This enzyme transports three ions of Na to the exterior of the cell and two ions of potassium to the interior of the cell. Since this transport takes place against the higher concentration of the ions, this enzyme is known as a pump. The cell membrane is generally negatively charged and hence it is said to be polarized. When it is excessively polarized it is called hyperpolarized. When it is less polarized it is said to be depolarized.

Earliest attempt to study the effect of lithium on membrane potential was made by Yonemura and Sato [9] in 1967 using frog muscle fibers immersed in Li Ringer solution. They found that lithium would depolarize the membrane after a few hours ranging from two to four hours. The next study was performed by Graf et al [7] in 1983 using the membrane of the frog spinal cord motor neurons. They found that 15 mmol Li would depolarize the membrane within 10 minutes. They also found that the intra cellular potassium would decrease during that time. Adam-Vizi et al [8] confirmed this result in 1987 using rat cortex slices. In 1996, El-Mallakh et al [4] reported the results of their investigations on hospitalized manic patients, matched normals and euthymic patients on lithium. The membrane potentials of leukocytes from hospitalized manic patients were significantly hyperpolarized while those of euthymic patients were slightly depolarized when compared with that of controls. Thiruvengadam [5] calculated the membrane potential of mammalian neurons using the Goldman-Hodgkin-Katz (G-H-K) equation and found that the addition of lithium would depolarize the membranes. The modified G-H-K equation with the addition of lithium is given by (see ref.7 for its derivation)

$$V = 62\log_{10}\frac{4.7 + \frac{P_{Li}}{P_{Na}}\frac{Li_0^+}{Na_0^+}}{100} \quad \text{---------- [1]}$$

Where V = the membrane potential
P_{Li} =Permeability of lithium
P_{Na}=Permeability of sodium
Li_0 = extra cellular concentration of lithium
Na_0 = extra cellular concentration of sodium.
From this equation it follows that the membrane potential would depolarize with the addition of lithium [7].

Lithium and membrane resistance

Hodgkin and Huxley [6] showed that the total conductance of the membrane is the algebraic sum of the contributions from the conductance of potassium ions, sodium ions and chlorine ions (Koester, [14]). If we add lithium as another conductor in the Direct Current (DC) circuit as shown in figure 1, the total conductance will increase because the algebraic sum of the conductance will increase. Since the resistance is the inverse of conductance, the resistance will decrease by the addition of lithium. Cole [15], as early as 1941, measured the electrical resistance of squid giant axon membrane in seawater environment. Following Cole, Guttmann [16] found that the resistance of membranes in nerve and muscle fibers of frogs decreased during the action of narcotics and other chemicals such as $MgCl_2$, $CaCl_2$, and $BaCl_2$. In spite of the large literature on lithium, there is no direct measurement of the resistance of excitable membranes with lithium. It would be useful to collect such data in the future. Again, figure 1 demonstrates that an increase in resistance will hyperpolarize the membrane potential and a decrease will depolarize it according to Ohm's law. This confirms the prediction of G-H-K equation. Furthermore the significant result of this analysis is that lithium would decrease the resistance of the membrane.

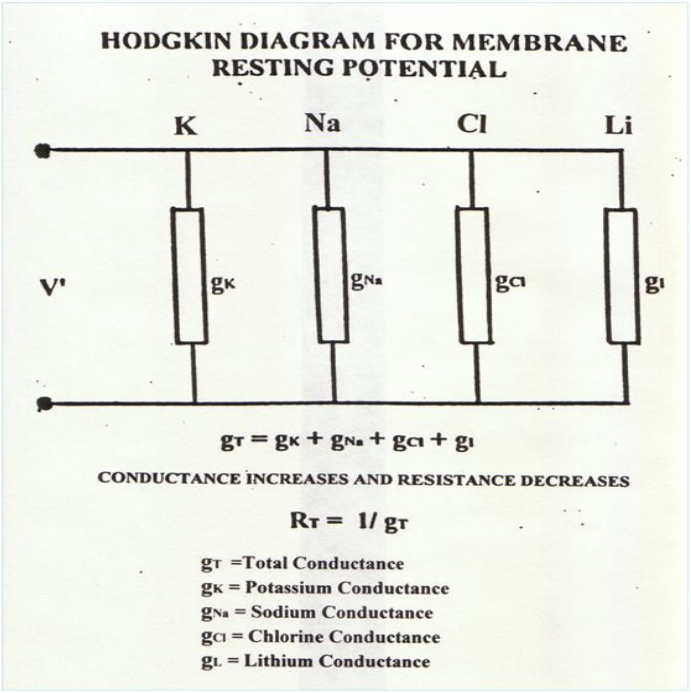

Figure 1: A direct current circuit is generally used to represent the membrane conductance. K+, Na+, Cl- are the normal ions that give rise to the membrane resting potential. The total conductance is given by the algebraic sum of these three conductances. However, if lithium is added as an additional cation, then the total conductance will increase as shown in this figure. Since resistance is the reciprocal of conductance, the resistance will decrease by the addition of lithium.

Membrane resistance and excitability of neurons

What role does the resistance of membranes play in bipolar disorder? In order to answer this question, let us analyze the electrical response of membranes. It is common practice in neuroscience to use equivalent electrical circuits for studying the currents in the membrane [17]. When the current and the voltage vary with time, as is the case with action potentials in excitable membranes, only Alternating Current (AC) circuits must be used. Hodgkin and Huxley [6] used the Alternating Current (AC) circuit shown in figure 2(a) in which the resistance and the capacitance are parallel to each other. Cole [11] used the AC circuit shown in figure 2(b) in which an inductance is added in series with the resistance. The capacitance is parallel to both of them. The reason for adding the inductance was that Cole consistently measured the inductance in all of his measurements and he could not ignore it. The above two AC circuits are special cases of a class of circuits known as parallel antiresonant AC circuits [18,19]. The basic circuit among this class of circuits is shown in figure 2(c) in which the resistance, the inductance and the capacitance are all parallel to each other.

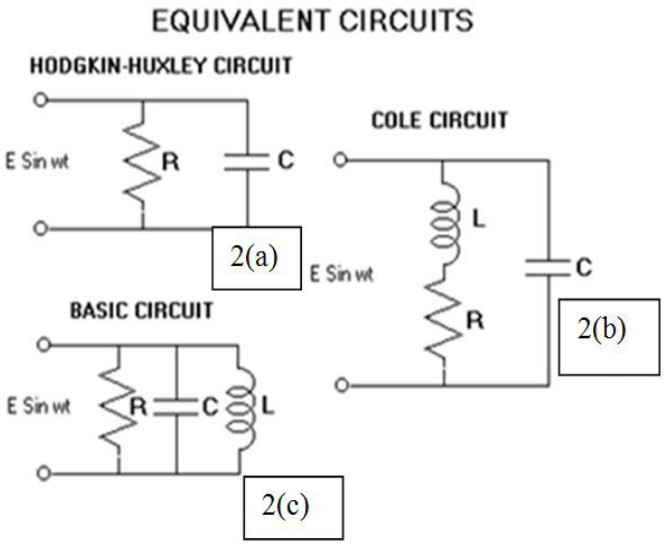

Figure 2: The Alternating Current (AC) circuits used in the analysis of the role of membrane resistance in the amplification of action potentials are shown in this figure. These circuits have been used by early pioneers in neuroscience such as Cole, Hodgkin and Huxley. 2(a) shows the AC circuit used by Hodgkin-Huxley to analyze their data obtained from giant axons of squids. The circuit in 2(b) was used by Kenneth Cole to calculate the inductance of the membranes of giant axons of squids. The basic parallel circuit, 2(c), is the fundamental circuit in this class of circuits known as antiresonant parallel circuits.

The response of these circuits to a train of input signals generated in the neuron can be analyzed using the electrical circuit theory as shown in the Appendix. From this analysis it can be shown that the excitability of the membrane is given by the following equation:

$$E_x = \frac{R^2 C}{L}$$

Where Ex = Excitability
R = Resistance
C = Capacitance
And L = Inductance.

As shown in the Appendix, the available clinical data suggest that the basic circuit represents the human neurons.

Electrical signals produced in the cell body of neurons are amplified as action potentials and transmitted through the axon to its terminal called the synapse. These action potentials trigger the biochemical reactions responsible for the release of vesicles containing the neurotransmitters. An understanding of this process comes from the analysis of electrical circuits such as the basic circuit. The response of this circuit is shown in figure 3. According to this figure, the relative action potentials (y-axis) decrease

with increasing relative frequencies (x-axis) up to a value of one and then increase with increasing relative frequencies. The relative action potential is a measure of how much the input signal is amplified. The relative frequency is the ratio between the frequency at which that particular action potential is transmitted and the resonant frequency of the neuron. Analyses of published clinical EEG data show that the resonant frequency is about 15 cycles per second in humans [20]. Most observed frequencies are less than this frequency. Frequencies above 30 cps are rare. Hence only the relative frequencies less than one are of interest in this study. The relationship between the relative action potentials and the relative frequency depend upon the excitability of the neuron. The higher the excitability the higher is the relative action potential at a given relative frequency. This ability to magnify the action potentials decreases as the excitability decreases at the same frequency. For example the action potential may be amplified as much as 50 times at a relative frequency of 0.2 corresponding to an excitability of 100. On the other hand it would amplify only by an actor of three at the same relative frequency corresponding to an excitability of one. This figure demonstrates how the relative action potentials depend significantly on the excitability which in turn is governed by the electrical properties of the membrane.

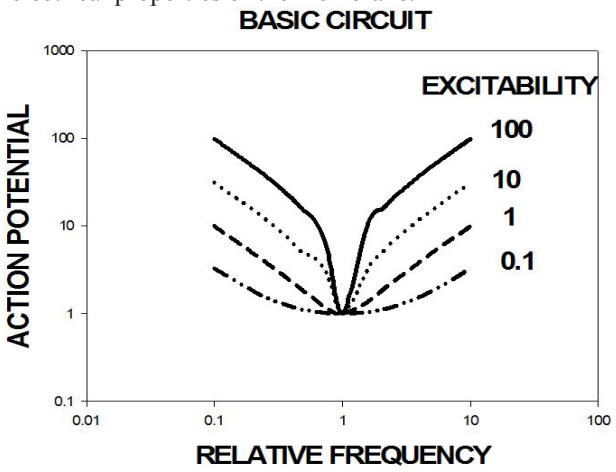

Figure 3: The relationship between the relative action potential and the relative frequency at various excitabilities is shown in this figure. (Refer the Appendix for the derivation). At a given excitability the relative action potentials decrease with increasing relative frequencies and then increase with increasing relative frequencies. This is the classic case of antiresonant response of this class of circuits. The excitability is the second parameter that controls the relative action potentials. As the excitability increases the relative action potentials also increase at a given relative frequency. The higher values of excitability represent epilepsy as evidenced by clinical EEG data. Excitabilities around one indicate normal controls. Mania and depression are on either side of normal controls. (Refer the Appendix for further discussion). Since resistance plays a large role in excitability, lithium also exerts a significant influence on the excitability through its effect on resistance. The efficacy of anticonvulsants in mood stabilization and epilepsy is also relevant to this figure.

The clinical EEG data from epileptic patients (Figure 8) show that the excitabilities can be as high as 1000 in epileptic patients. The excitability would be in the range of one in babies (Figure 9 and [21]). It is most likely that the excitability for normal adults would be in the same range. The evidence for mania comes from the fact that the addition of lithium decreases the membrane resistance as shown in figure 1. The decrease in resistance would decrease the excitability thereby decreasing the action potentials. Graf et al [7] found that the action potentials in frog spinal cord neurons were reduced during lithium treatment. Ulrich et al [10] noticed that the EEG amplitudes in normal volunteers decreased after ten days of lithium treatment. This is perhaps the mechanism by which lithium mediates the mania and stabilizes the mood. Goodwin and Jamison [1] as well as several articles in [2] summarize the vast majority of knowledge accumulated so far on the role of lithium in bipolar disorder. The additional evidence comes from the fact that some effective mood stabilizers are also anticonvulsants. Although these data indirectly support the present analysis, it would be useful to collect direct experimental evidence connecting excitability and lithium effects. The data that directly support the concept of excitability come from the Electro Encephalographic (EEG) data from epileptic patients as discussed in the appendix. The electrodes used in vagus nerve stimulation technique offer an opportunity to collect such data [22]. The relative action potentials are less than one at lower excitabilities less than one. This suggests that the reported efficacy of vagus nerve stimulation is due to the resetting of the excitabilities in depressive patients. It is also suggested that this is the mechanism of action of electro convulsive therapy in depressive patients. The next task is to show how the rate of release of vesicles containing the neurotransmitters is related to the excitability.

Excitability and the rate of release of vesicles

Katz [13] showed that the voltage pulses (action potentials) arriving at the axon terminal trigger the release of vesicles containing neurotransmitters. He used several statistical methods to calculate the probability of release of these vesicles (see also 23). Let us use a simple Poisson distribution to demonstrate how excitability is related to the rate of release of vesicles. Since the excitability controls the action potentials at a given frequency (Figure 3), let us use the excitability in the Poisson distribution as shown below:

$$N = N_{\max} e^{-1/E_x} \quad \text{---------- [2]}$$

Where N = Number of vesicles released per unit time,

N_{max} = Maximum possible number released per unit time

And E_x = Excitability.

A plot of the relative rate of release as a function of the ex-

citability is shown in figure 4. The relative rate decreases slowly with decreasing excitability and then decreases rapidly at excitabilities less than 10. This figure supports the prevailing view that the excessive release of neurotransmitters leads to seizures and the lack of sufficient release rates leads to depression. The threshold seizure values can be assigned either as threshold excitability or as threshold release rate. Clinical research is needed to determine these thresholds.

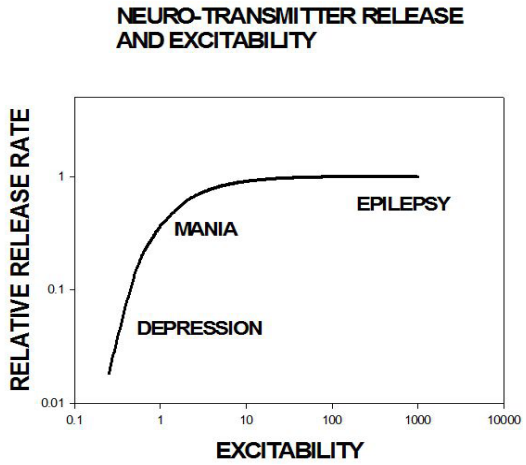

Figure 4: The relative rate release of vesicles as a function of excitability is shown in this figure. At higher excitabilities the relative rate of release is close to 100 percent. This would explain the seizures. At excitabilities less than ten, the release rate decreases rapidly. At excitabilities less than one, the release rates approach ten percent. Further clinical research is needed to determine the threshold excitabilities for seizures, mania and depression.

Concluding Remarks

Calculations using the Goldman-Hodgkin-Katz equation indicate that the membrane potential would be depolarized by the addition of lithium. Similarly, an analysis of the direct current circuit for the membrane resting potential shows that the addition of lithium would reduce the electrical resistance of the membrane thereby depolarizes the membrane if lithium acts as a cation in addition to potassium and sodium. A non-dimensional parameter called the excitability is derived from the study of the alternating current circuits that are generally used as equivalent circuits representing the action potentials of the membranes. The excitability is given by the square of the resistance times the capacitance divided by the inductance of the membrane. The excitability governs the amplification of the potentials in the membrane at a given frequency. Since the addition of lithium would reduce the resistance, it would also reduce the excitability of the membrane thereby reducing the potentials. It is also shown that the rate of release of vesicles containing the neurotransmitters is related to the excitability. These results offer a possible explanation of how lithium mediates mania.

An attempt has been made to apply some of the basic neuroscience ideas to understand a complex illness such as bipolar disorder. Further research is needed to relate the effects of anticonvulsants such as sodium valproate, carbamazepine, lamotrigine, topiramate and gabapentin with the excitability of neurons. Direct measurement of membrane potentials and resistance with different levels of lithium would be useful using the methods of Ward et al [24]. Direct measurement of excitability using vagus nerve stimulation electrodes would provide data from humans with the illness at different levels of mood stabilizers [22].

Appendix

A. Analysis of the equivalent electrical circuits: The pioneers in neuroscience used equivalent electrical circuits to understand their measurements of membrane potentials and action potentials. The voltage response of the three AC circuits shown in figure 2 may be analyzed as follows. Since the Hodgkin-Huxley circuit and Cole circuit are special cases of the basic circuit we will start with the basic circuit. The equation for impedance is given by [See (18 and 19)]:

$$Z = \frac{1}{\sqrt{\frac{1}{R^2} + \left[\frac{1}{X_L} - \frac{1}{X_C}\right]^2}} \quad \text{---------- [1]}$$

$$V = V_0 Sin\omega t \quad \text{---------- [2]}$$

Where R = the membrane resistance,
Z = the membrane impedance
$X_L = \omega L$ = the inductive reactance,
ω = the angular frequency of voltage and current,
L = the inductance of the membrane,
C = the capacitance of the membrane,
$X_C = 1/\omega C$ = the capacitive reactance of the membrane,
V_0 = the maximum voltage at t=0 in $V=V_0 \sin\omega t$ and t = time

The natural frequency of the circuit is given by:

$$\omega_n = \frac{1}{\sqrt{LC}} \quad \text{---------- [3]}$$

Using equation [3] in [1] and rearranging, we get

$$Z = \frac{1}{\sqrt{\frac{1}{R^2} + \frac{1}{X_C{}^2}}} \quad \text{---------- [4]}$$

Where

$$E_x = \frac{R^2 C}{L} \quad \text{---------- [5]}$$

Let us call R/Z ratio as M. Then

$$M = \sqrt{1 + E_x\left(\frac{\omega_n}{\omega} - \frac{\omega}{\omega_n}\right)^2}$$

Ex is called the excitability of the membrane since it gives the combination of the electrical properties of the membrane indicating how excitable the membrane is. The amplification of the current is larger at higher excitabilities at a given frequency. Cole [11] called the inverse of excitability as "Damping". M is the factor by which the input currents are magnified as a result of the impedance of the anti-resonant parallel circuits. Since the current is directly proportional to the voltage as per Ohm's law, M also represents the amplification of action potentials and therefore it is called the Relative Action Potential. The relationship between the relative action potentials and the relative frequency □/□n is plotted in figure 3 for various values of the excitability for the basic parallel circuit.

The Hodgkin-Huxley circuit (figure 2a) is a special case of the basic circuit in which there is no inductance. For this circuit, the impedance is given by (see ref.18):

$$Z = \frac{1}{\sqrt{\frac{1}{R^2} + \frac{1}{X_C{}^2}}} \quad \text{---------- [6]}$$

$$= \frac{R}{\sqrt{1 + \left(\frac{R}{X_C}\right)^2}} \quad \text{---------- [7]}$$

For this case:

$$M = \sqrt{1 + (\omega RC)^2} \quad \text{---------- [8]}$$

Figure 5 shows a plot of this equation [8].

The equation for the impedance, Z, for the Cole circuit shown in figure 2b is given by (see ref.19):

$$Z = \frac{\sqrt{R^2 + (\omega L)^2}}{\sqrt{(1 - \omega^2 LC)^2 + (\omega RC)^2}} \quad \text{------- [9]}$$

Substituting equation [3] in [9], we get:

$$Z = \frac{R\sqrt{1 + \frac{1}{E_x}\left(\frac{\omega}{\omega_n}\right)^2}}{\sqrt{\left[1 - \left(\frac{\omega}{\omega_n}\right)^2\right]^2 + E_x\left(\frac{\omega}{\omega_n}\right)^2}} \quad \text{---------- [10]}$$

Again

$$M = \sqrt{\frac{\left[1 - \left(\frac{\omega}{\omega_n}\right)^2\right]^2 + E_x\left(\frac{\omega}{\omega_n}\right)^2}{1 + \frac{1}{E_x}\left(\frac{\omega}{\omega_n}\right)^2}} \quad \text{------ [11]}$$

Figure 6 shows a plot of this equation [11].

B. Discussion of the equations: Equations [6], [8] and [11] are shown plotted in figures 3, 5, and 6 respectively. They show that the Relative Action Potential decreases with decreasing excitabilities at a given relative frequency. It was shown in figure 1 that the addition of lithium would decrease the membrane resistance. From equation [5], a decrease in resistance would decrease the excitability. For example, if the resistance decreases by a factor of two, the excitability would decrease by a factor of four. Such a decrease in excitability would have a profound effect on the membrane potentials. In order to verify which circuit represents the human neurons, available clinical data from Electroencephalographic (EEG) measurements were used as discussed below.

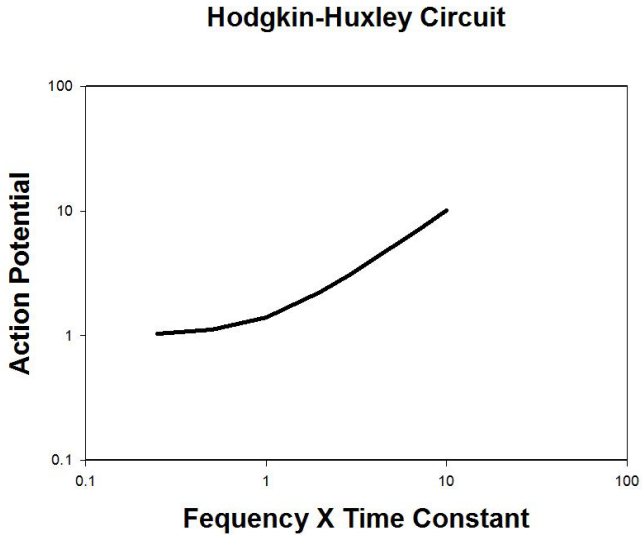

Figure 5: This figure shows the relative action potentials as a function of the relative frequency for the Hodgkin-Huxley circuit. The available clinical EEG data for humans do not agree with the response of this circuit. The clinical data show a decrease in relative voltages with increasing relative frequencies at relative frequencies below one whereas this circuit predicts an increase with relative frequencies.

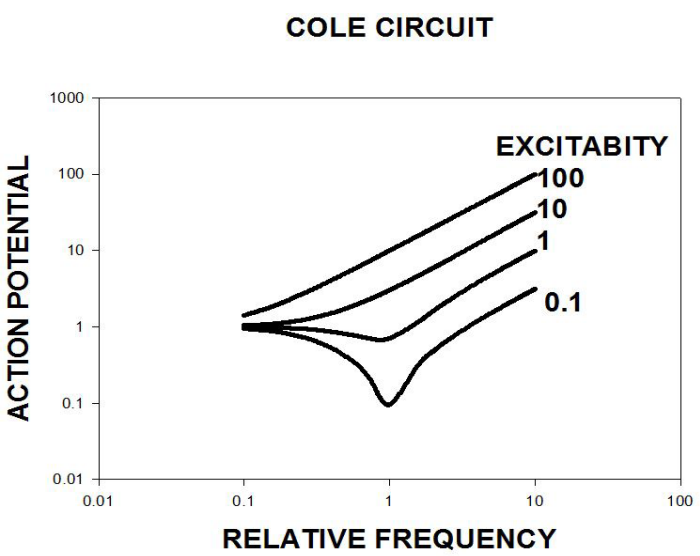

Figure 6: This figure shows the response of Cole circuit. Again the clinical EEG data from epileptic patients do not support the predictions of this circuit.

C. Comparison with clinical results: Barlow [20] analyzed the epileptic EEG data from Gottingen Library of Clinical EEG data. He plotted the amplitudes of the voltages in decibel scale as a function of frequency for a large set of data. Figure 7 shows the re-plot of the data from figure 7-13 of Barlow's book [20]. The resonant frequency was assumed to occur at zero decibels (since log 1 = 0) and was determined to be about 15 cycles per second by extrapolation of the curve. The solid lines represent the equation [6] for excitabilities of 100 and 1000. The relative action potentials are presented in decibel scale to match the clinical data. The data points represented by squares, circles, +s, and xs are for different sets of EEGs smoothed out by Barlow over a range of frequencies. For a complete discussion of each set of data, reference [20] may be consulted. The data presented in figure 7 lend credence to the basic parallel circuit shown in figure 2c and the analysis shown in figure 3. The results of Hodgkin-Huxley circuit shown in figure 5 and of Cole circuit shown in figure 6 would not agree with these clinical data.

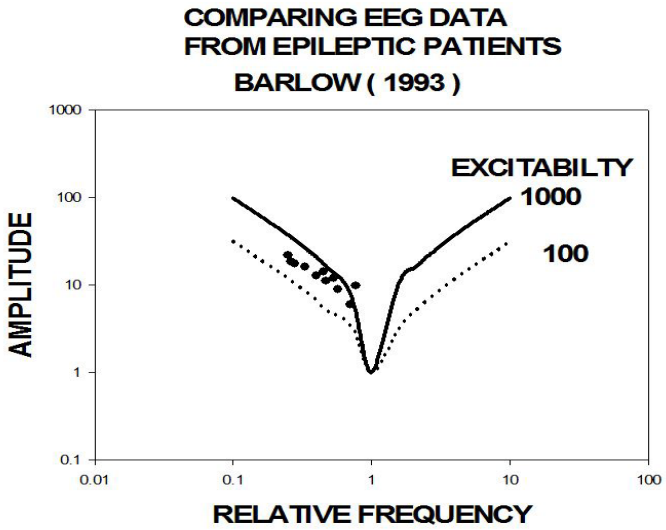

Figure 7: This figure compares the clinical EEG data from epileptic patients with the predictions of basic circuit. The squares, circles, +s and xs shown in this figure are taken from Barlow (26). The voltages are shown in decibel scales for comparison. Only the basic circuit predicts the right relationship between the voltages and the frequencies. It is interesting to note that the excitabilities are in the range 100 to 1000 in epileptic patients. Refer the text for further discussion of this figure.

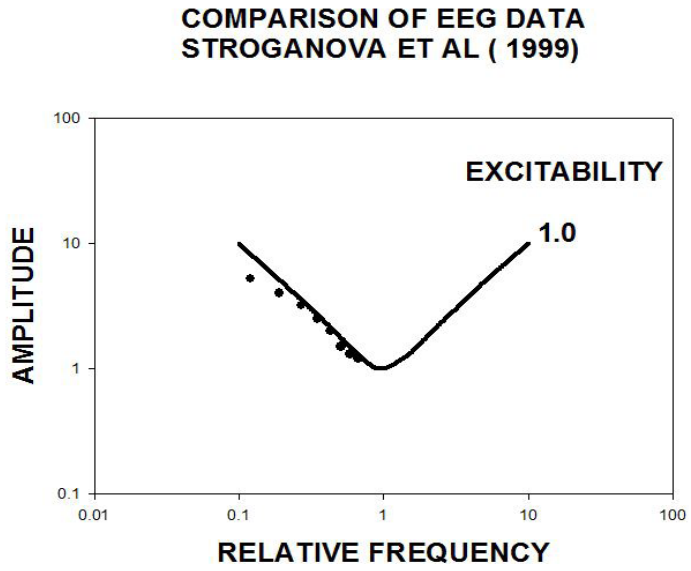

Figure 8: This figure shows a comparison of the relative action potentials predicted by the basic circuit with the clinical EEG data from eight months old infants and eleven months old infants by Stroganova et al [27]. The filled circles and squares are for the eight months old infants and the open circles and squares are for the eleven months old infants at two scalp locations during visual attention. The excitabilities are in the range of 0.5 to 1.0.

Figure 8 shows a similar comparison of the data collected by Stroganova et al [21] with the predictions of the basic circuit. Two sets of data (one for eight months old infant and the other for 11 months old infant) during visual attention at two electrode locations (AF3 and O1) are plotted against relative frequency. The solid line represents the predictions of the basic circuit for an excitability of one. Figure 9 shows the classification of EEG frequency ranges and their corresponding amplitude ranges in EEG technology. For example, the lowest frequency delta waves have the highest amplitudes whereas the highest frequency beta waves have the lowest amplitudes. Theta and alpha waves have the middle ranges of frequencies and amplitudes. The figures 8 and 9 again lend support to the basic circuit.

The main purpose of the analysis is to understand the role of lithium in bipolar disorder. However, one cannot ignore the way the excitabilities line up in a sequence indicating epilepsy at higher excitabilities and "normal" at excitabilities around one. According to this analysis, excitabilities for mania fall in between the values for epilepsy and "normal" values and the values for depression would be below normal values. Clinical data from vagus nerve electrodes (22) would be useful in verifying these predictions. It is also interesting to note that several anticonvulsants are also effective in bipolar disorder.

References

1. Goodwin FK, Jamison KR (1990) Manic depressive illness, Oxford university press.
2. Soares, JC, Gershon, S, (Eds.) (2000) Bipolar disorders, Basic mechanisms and therapeutic implications, Marcel Dekker, Inc.
3. Manji HK, Bowden CL, Belmaker RH (Eds.) (2000) Bipolar medications: Mechanisms of action, American Psychiatric Press, Inc.
4. El-Mallakh RS, Li R, Worth CA, Peiper SC (1996) Leukocyte transmembrane potential in bipolar illness, J. Affective Disorders 41: 33-3
5. Thiruvengadam A (2001) Effect of lithium and sodium valproate ions on resting membrane potentials in neurons: an Hypothesis J Affective Disorders 65: 95-99
6. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerveJ. Physiology (London) 117: 500-544
7. Grafe P, Reddy MM, Emmert H, Tenbruggencate G (1983) Effects of lithium on electrical activity and potassium ion distribution in the vertebrate central nervous system, Brain Research 279: 65-76.
8. Adam-Vizi V, Banay-Schwartz M, Wajda I,Lajtha A (1987) Depolarization of brain cortex slices and synaptosomes by lithium. Determination of K^+ equilibrium potential in cortex slices, Brain Research 410: 257-63.
9. Yonemura K and Sato M (1967) The resting membrane potential and cation movement in frog muscle fibers after exposure to lithium ions, The Japanese Journal of Physiology 17: 678-97.
10. Ulrich G, Herrmann WM, Hegerl U, Mueller-Oerlinghausen, B (1990) Effect of lithium on the dynamics of encephalographic vigilance in healthy subjects. J Affect Disord 20; 19-25
11. Cole KS (1928) Equivalent electric circuits J Gen Physiology 12: 29
12. Thiruvengadam A (2001) Electro-biochemical coupling, excitability of neurons and bipolar disorder, Fourth International Symposium on Bipolar Disorder, Bipolar Disorder Supplement 1: 3.
13. Katz B (1969) The release of neural transmitter substances, Thomas, Springfield, IL.
14. Koester J, Membrane potential, Ch.6, in Principles of neuroscience, 3rd ed. (Eds. Kandel, ER, Schwartz, J, and Jessel, TM,), New York, Elsevier, 1991; p.90 and p.1036.
15. Cole KS (1941) Rectification and inductance in the squid giant axon J Gen Physiology 25: 29-51.
16. Guttmann R (1939) The electrical impedance of muscle during the action of narcotics and other agents. J Gen Physiology 40: 567-591
17. Shepherd G (1999) Electronic properties of axons and dendrites, Ch. 5, Fundamental neuroscience, (Zigmond, M, et al.) Academic Press.
18. Dawes CL (1947) A course in electrical engineering, Vol. II, Alternating current, McGraw-Hill, New York.
19. Kerchner R, Corcoran G (1962) Alternating current circuits, John Wiley & Sons, Inc. New York.
20. Barlow, JS (1993) The electroencephalogram - its patterns and origins, A Bradford book, MIT Press, Cambridge, MA. p.100.
21. Stroganova TA, Orekova E, Posikera (1999) EEG alpha rhythm in infants, Clinical Neurophysiology 110: 997-1012.
22. George MS, Sackeim HA, Rush JA, Marangell LB, Nahas Z, et al. (2000)Vagus nerve stimulation: A new tool for brain research and therapy, Biological Psychiatry 47: 287-295.
23. KANDEL, ER, CH.13, TRANSMITTER RELEASE, PRINCIPLES OF NEURAL SCIENCE, (EDS. KANDEL ET AL). ELSEVIER, NEW YORK, 1991.
24. Ward MW, Rego AC, Frenguelli BG, Nicholls DG (2000) Mitochondrial membrane potential and glutamate excitotoxicity in cultured cerebellar granule cells, Journal of Neuroscience 20: 7208-7219.