The Treatment of Bipolar Disorder: Modeling Lithium’s Effect on Neuronal Bursting

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Bipolar Disorder

- Mental illness characterized by “unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks” (NIMH)
- Extreme mood “episodes” tend to be between two extreme mood-states: mania and depression (NIMH)
- The transition between extreme moods is **not** cyclical; both internal and environmental stressors can trigger a mood swing
Lithium as a Mood Stabilizer

- Lithium is the most commonly prescribed drug for bipolar disorder, the only widely used mood-stabilizer
- Newer mood stabilizers are not typically as effective (Thies-Flechtner, 1996)
- Competing hypotheses about biological mechanism of bipolar and how lithium corrects it
- Lithium treatment tailored to individual
Gene mutation associated with high risk of bipolar disorder causes elevated $Ca^{2+}$ levels (Psychiatric Genomics Consortium, 2011)

Proposed Lithium Mechanism

Lithium $\rightarrow$ Inhibits $IP_3 R$ action $\rightarrow$ Lowers $Ca^{2+}$ $\rightarrow$ Decrease NT
Neurons and Neurotransmitters (NT)

Neurons:
- Type of cell in the nervous system
- Carries information throughout the nervous system by chemical and electrical signals (NINDS)
- Electrical impulse to chemical signal to electrical impulse

Neurotransmitters:
- Chemical messengers that transmit information to a neuron
- Norepinephrine implicated in euphoria/grandiosity, defining characteristics of mania (Goodwin, 1974)
Action Potentials (AP)

- APs are electrical impulses caused by membrane depolarization (Bear, 84)
- Arrival of AP in terminal triggers release of NT (Bear, 122)
Model Hypothesis

- Burst-frequency determines amount of NT released (Wilkins, 232)

Assume high NT release causes mania. And lithium treatment works by lowering intracellular calcium which lowers burst frequency. This decreases NT release which stabilizes mood.
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Morris-Lecar Model

\[
\frac{dV}{dt} = \frac{1}{C} \left[ (I - g_{ca}M_{\infty}(V - V_{ca}) - g_k W(V - V_k) - g_l(V - V_l)) \right]
\]

\[
\frac{dW}{dt} = \frac{\phi(W_{\infty} - W)}{\tau_W}
\]

\[
M_{\infty}(V) = \frac{1}{2} \left[ 1 + \tanh \left( \frac{V - V_1}{V_2} \right) \right]
\]

\[
W_{\infty}(V) = \frac{1}{2} \left[ 1 + \tanh \left( \frac{V - V_3}{V_4} \right) \right]
\]
Bursting in 2-D ML Model

What is a “burst”?

- “a rapid cluster of action potentials followed by a brief pause” (Bear, 106)
- 2-D model, every action potential represents a burst (Williams, 2013)

1 Hayashi, 2016. Orange by Rosa
Nernst Equation for Calcium

\[ I_{Ca} = g_{Ca} M_{\infty} (V - V_{Ca}) \]

**Reversal potential** is the membrane voltage at electrochemical equilibrium (Bear, 68)

\[ V_{Ca} = \frac{RT}{2F} \ln \left( \frac{[Ca^{2+}]_{out}}{[Ca^{2+}]_{in}} \right) \]

So, if intracellular \(Ca^{2+}\) concentration, \([Ca^{2+}]_{in}\), increases, the \(V_{Ca}\) would decrease.
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Lithium Addition to Morris-Lecar Model

How does the addition of lithium change the model?

Lithium $\rightarrow$ Lowers $Ca^{2+}$ $\rightarrow$ Decrease burst freq. $\rightarrow$ Decrease NT

If bipolar disorder is caused by abnormal intracellular levels of calcium, where intracellular calcium is elevated, we would expect the reversal potential of calcium, $V_{Ca}$, to be lower than the average value.
Lithium Addition to Morris-Lecar Model

How does the addition of lithium change the model?

If bipolar disorder is caused by abnormal intracellular levels of calcium, where intracellular calcium is elevated, we would expect the reversal potential of calcium, $V_{Ca}$, to be lower than the average value.
Bifurcations

Using $V_{ca}$ as the bifurcation parameter
Bifurcations

Emergence of Limit Cycles, $V_{Ca} = 85.6$

$T \approx 73.85; f \approx .0135$, for stable LC
Frequency of Limit Cycle
Response Function for Lithium to V_{ca}

\[ V_{ca} = \alpha \tanh(.003(L(t) - 1000)) + \beta; \]

\( \alpha \) and \( \beta \) are scaling factors to account for physiological differences.
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Lithium Concentration in Bloodstream

Differential equation for exponential decay:

\[
\frac{dL}{dt} = -\alpha L
\]

\[L(0) = L_0\]

\[\alpha = \frac{\ln(2)}{36}\]

Solution Flow:

\[\phi_t(L_0) = L_0 e^{-\alpha t}\]

\[L_n = \phi_T(L_{n-1}) + \kappa\]
Equilibrium for Lithium Concentration

FDA has the standard lithium dosage at 300 mg every 8 hours ($\tau = 8, \kappa = 300$):

Where ($L^*$) and when ($t^*$) does $L$ stabilize?
Equilibrium for Lithium Concentration

FDA has the standard lithium dosage at 300 mg every 8 hours ($\tau = 8$, $\kappa = 300$):

\[ L^* \approx 2097.1 \text{ mg} \]

\[ t^* \approx 13 \text{ days} \]
Numerical Simulations

First 36 hours of Lithium, 5 doses

Blood Concentration of Lithium

0 2 4 6 8 10 12 14 16 18

200 400 600 800 1000 1200 1400

L

t

$\times 10^7$
Numerical Simulations

Times Series for Beginning Lithium
Numerical Simulations
Numerical Simulations

Times Series for Beginning Lithium
Numerical Simulations

Blood Concentration of Lithium

![Graph showing the blood concentration of lithium over time. The x-axis represents time in units of 10^7, while the y-axis represents concentration in arbitrary units. The graph shows multiple peaks and troughs, indicating periodic fluctuations in lithium levels.]
Numerical Simulations

Times Series for Beginning Lithium

Phase Portrait for Beginning Lithium
Numerical Simulations

16 days of Lithium treatment

Blood Concentration of Lithium for 16 days
Numerical Simulations

Phase Portrait Long-Term Lithium

Time Series Long-Term Lithium
Frequency Plots

Frequency Plot Beginning Lithium

Frequency Plot Long-Term Lithium
Mood Quantification

Mania

Lithium equilibrium
Conclusion

- Model lithium decreases the burst frequency in the physiological ‘typical’ range by increasing the calcium reversal potential.
- This decreases the amount of neurotransmitter released by the neuron, reducing symptoms of mania.
Future Work

- Sensitivity analysis of parameters
- Determining an ‘optimal’ dosage for stability
References

References


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