OSMOTIC FORCES, GAP JUNCTIONS, AND SPREADING DEPRESSION: A COMPUTATIONAL MODEL.

Bruce E. Shapiro, Department of Biomathematics, UCLA School of Medicine, Los Angeles, CA 90095.

128.6

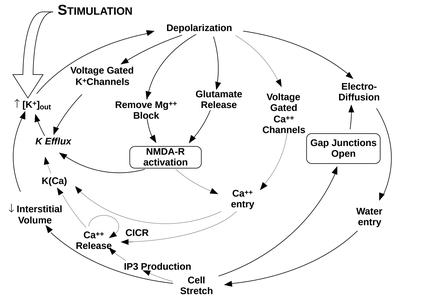
Society for Neuroscience
29th Annual Meeting
October 23-28, 1999
Miami Beach, Florida

INTRODUCTION

Spreading Depression (SD) consists of a slowly moving wave of membrane depolarization and a prolonged depression of EEG activity. It is accompanied by ionic concentration changes lasting for up to two minutes, and typically travels at ≈3 to ≈12 mm/min. Wave passage may be accompanied by increased blood flow and is followed by a prolonged vasodilation. SD is widely believed to cause migraine-with-aura, has been observed during cerebral ischemia, hypoxia, and concussion, and may even induce subsequent ischemic tolerance. There is no generally accepted theory of SD. Previous mathematical models are based on interstitial K+ diffusion, and have treated cytosolic concentrations as purely local. As such, they do not explain why gap junction poisons prevent SD. It seems unlikely that these gap junctions are glial since glial poisons do not prevent SD. The nearly 50% reduction in interstitial volume that occurs during SD has also not been previously modeled.

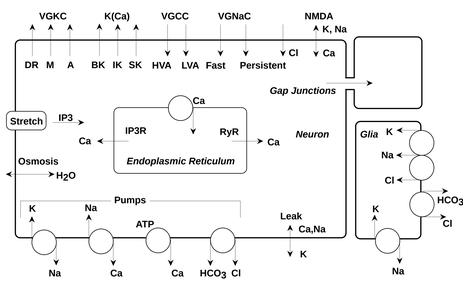
METHOD

A novel model of spreading depression has been developed that differs from previous ones in that it incorporates the effects of (a) gap junctions, (b) intracellular voltage gradients, and (c) osmotically induced volume changes. Ions are allowed to propagate in a neuronal syncytium of gap-junction connected cells. Because large ionic shifts and dendritic voltage gradients occur during SD, standard compartmental, cable-based, or reaction-diffusion models are inappropriate. Thus a full electrodiffusion model is used. Electrodiffusion pushes cytoplasmic K+ away from the stimulation. This movement, along with depolarization-induced Na+ and Cl- fluxes, leads to an osmotic imbalance. This is countered by the flow of water into or out of cells, causing the cells to expand or contract. These cellular volume changes are spatially limited by the surrounding parenchyma (expansion) and intracellular organelles (contraction).



MEMBRANE CURRENTS

The neuronal membrane has three voltage gated K+ currents (VGKC), three Ca^{++} dependent K^+ currents (K(Ca)), two voltage gated Ca^{++} currents (VGCC), two voltage gated Na^+ currents (VGNaC), a passive Cl^- flux, three independent NMDA fluxes (K^+, Ca^{++}, Na^+), three leak currents and four ion pumps. The glial model has three ion pumps. The ER is treated as a large Ca^{++} buffer with IP3-sensitive Ca^{++} channels (IP3R), ryanodine-sensitive Ca^{++} channels (RyR) and a Ca^{++} pump. IP3 is produced from PIP2 by membrane stretch. Ion channels are described by Hodgkin-Huxley models.



MATHEMATICAL MODEL

ELECTRODIFFUSION EQUATION

Continuity Equation: $\nabla \bullet \mathbf{J} + \frac{\partial c}{\partial t} = S$ (S = Source Terms)

Nernst-Plank Equation: $\mathbf{J} = -D\left(\nabla c + \frac{zF}{RT} c \nabla E\right)$

Electrodiffusion Equation: $\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \frac{zF}{RT} \nabla \cdot (Dc \nabla E) + S$

One Dimensional Reduction: $\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D \frac{\partial c}{\partial x}\right) + \frac{zF}{RT} \frac{\partial}{\partial x}\left(Dc \frac{\partial E}{\partial x}\right) - \frac{A}{V} J_m + S$

CYTOSOLIC CONCENTRATIONS: ELECTRODIFFUSION EQUATION

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D \frac{\partial c}{\partial x}\right) + \frac{zF}{RT} \frac{\partial}{\partial x}\left(Dc \frac{\partial E}{\partial x}\right) - \frac{A}{V} J_m + f$$

$$\frac{\partial [K^+]_{in}}{\partial t} = \frac{\partial}{\partial x}\left(D_{K,in} \frac{\partial [K^+]_{in}}{\partial x}\right) + \frac{F}{RT} \frac{\partial}{\partial x}\left([K^+]_{in} D_{K,in} \frac{\partial E}{\partial x}\right) - \frac{A}{V}\left(j_A + j_M + j_{DR} + j_{BK} + j_{IK} + j_{SK} + j_{K,NMDA} + j_{K,leak} - j_{Na/K}\right)$$

$$\frac{\partial [Ca^{++}]_{in}}{\partial t} = \frac{\partial}{\partial x}\left(D_{Ca,in} \frac{\partial [Ca^{++}]_{in}}{\partial x}\right) + \frac{2F}{RT} \frac{\partial}{\partial x}\left([Ca^{++}]_{in} D_{Ca,in} \frac{\partial E}{\partial x}\right) - \frac{A}{V}\left(j_{LVA} + j_{HVA} + j_{Leak} + j_{Ca,NMDA} + j_{Na/Ca} + j_{ATP}\right) + j_{IP3} + j_{Ryanodine} - j_{Pump}$$

$$\frac{\partial [Na^+]_{in}}{\partial t} = \frac{\partial}{\partial x}\left(D_{Na,in} \frac{\partial [Na^+]_{in}}{\partial x}\right) + \frac{F}{RT} \frac{\partial}{\partial x}\left([Na^+]_{in} D_{Na,in} \frac{\partial E}{\partial x}\right) - \frac{A}{V}\left(j_F + j_P - \frac{3}{2} j_{Na,K} - j_{Na,Ca} + j_{Na,NMDA}\right)$$

$$\frac{\partial [Cl^-]_{in}}{\partial t} = \frac{\partial}{\partial x}\left(D_{Cl,in} \frac{\partial [Cl^-]_{in}}{\partial x}\right) - \frac{F}{RT} \frac{\partial}{\partial x}\left([Cl^-]_{in} D_{Cl,in} \frac{\partial E}{\partial x}\right) - \frac{A}{V}\left(J_{Cl,bicarb} + J_{K,m} + J_{Na,m}\right)$$

INTERSTITIAL CONCENTRATIONS: REACTION/DIFFUSION EQUATION

$$\frac{\partial c_{out}}{\partial t} = D_{c,out} \frac{\partial^2 c_{out}}{\partial x^2} + \frac{(A/V) f}{1-f} J_{c,m} - J_{c,glia}$$

$$\frac{\partial [K^+]_{out}}{\partial t} = D_{K,out} \frac{\partial^2 [K^+]_{out}}{\partial x^2} - J_{K,glia}\Big) + \frac{(A/V) f}{1-f}\left(j_A + j_M + j_{DR} + j_{BK} + j_{IK} + j_{SK} + j_{K,NMDA} + j_{K,leak} - j_{Na/K}\right)$$

$$\frac{\partial [Ca^{++}]_{out}}{\partial t} = D_{Ca,out} \frac{\partial^2 [Ca^{++}]_{out}}{\partial x^2} + \frac{(A/V) f}{1-f}\left(j_{LVA} + j_{HVA} + j_{Leak} + j_{Ca,Na/Ca} + j_{ATP} + j_{Ca,NMDA}\right)$$

$$\frac{\partial [Na^+]_{out}}{\partial t} = D_{Na,out} \frac{\partial^2 [Na^+]_{out}}{\partial x^2} + \frac{(A/V) f}{1-f}\left(j_F + j_P - \frac{3}{2} j_{Na,K} - j_{Na,Ca} + j_{Na,NMDA}\right)$$

$$\frac{\partial [Cl^-]_{out}}{\partial t} = D_{Cl,out} \frac{\partial^2 [Cl^-]_{out}}{\partial x^2} + \frac{(A/V) f}{1-f}\left(J_{Cl,bicarb} + J_{K,m} + J_{Na,m}\right)$$

OSMOTIC FORCES

By electroneutrality the number of impermeant cytosolic anions in dV is

$$N_A = V_{rest}\left([Na^+]_{in,rest} + [K^+]_{in,rest} - [Cl^-]_{in,rest}\right)$$

By isotonicity the total external solute concentration $[S]_{out}$ is

$$[S]_{tot} = [Na^+]_{in} + [K^+]_{in} + [Cl^-]_{in} + \frac{N_A}{f\, dV_T}$$

Water flow across the membrane maintains isotonicity

$$\Delta dV / dV = \Delta N_S / N_S$$

where N_S is the total number of interstitial solute ions. Hence

$$\frac{dV}{dt} = \begin{cases} \frac{1}{[S]_{tot}} \sum \frac{d}{dt}([c]_{in} V), & V \le V_{max} \\ 0, & V > V_{max} \end{cases}$$

RESULTS

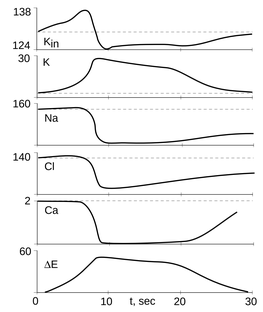
KEY PREDICTIONS

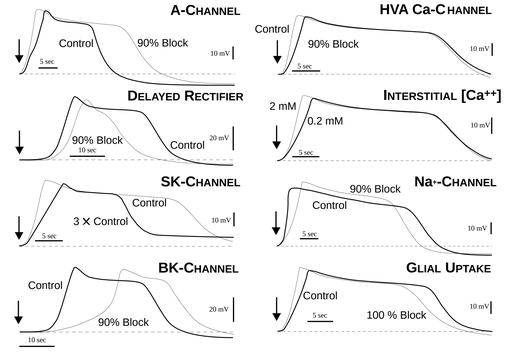
An increase in these parameters ↓	Causes a change in these →	Magnitude	Speed	Slope	Duration	
Cytosolic diffusion constant		↑	↑	↑	↓	
NMDA conductance		↓	↑	×	×	threshold
BK conductance		↑	↑	↑	↑	threshold
SK conductance		×	×	↓	↓	cutoff
IK conductance		×	×	×	×	
DR conductance		↑	↑	↑	↑	threshold
A-channel conductance		×	×	↓	↓	cutoff
Na-channel conductance		↓	↑	↑	↑	
HVA-channel conductance		↑	↑	↑	↑	
LVA-channel conductance		×	×	×	↑	
Interstitial Ca++ conc.		↑	↑	↑	↑	
Diameter		↓	↓	↓	↑	
Glial pumping rate		↓	↓	↓	×	

PREDICTED CONCENTRATION (mM) AND DC-VOLTAGE SHIFT AS A FUNTION OF TIME

Spreading depression was induced by raising $[K^+]_{out}$ to 50 mM at the origin. The waveforms to the right are from a typical simulation with a predicted wave speed of 3.6 mm/min. The curves show the ionic concentrations (interstitial except $[K^+]_{in}$) and DC-Voltage shift at a point 0.5 mm distant from the stimulation, as a function of time. Resting values are indicated by dashed lines.

The two columns on the far right show the effect of various parameters on the shape of the predicted waveform. Each figure corresponds to a different pair of simulations, in which only a single parameter value was varied. The predicted DC-Voltage shift, as observed at a fixed point (either 0.5 or 1.0 mm from the stimulation), is plotted as a function of time. Arrows give the time of stimulation and resting values are indicated by dashed lines. Other parameters vary from figure to figure. Note that the scales are different.





PREDICTED DEPENDENCE ON VARIOUS BIOPHYSICAL PARAMETERS

The figures to the right show the dependence of predicted wave speed and magnitude (max $[K^+]_{out}$) on various parameters. Each figure summarizes a large set of simulations in which only a single parameter was varied.

For $g_{K,NMDA}$ (A) and g_{BK} (B) a parametric set of curves is shown. Each curve corresponds to a different g_{DR}. Wave speed and magnitude are both increasing functions of g_{DR} (C). Above a threshold value of g_{DR} wave speed increases with $g_{K,NMDA}$ and g_{BK}; wave magnitude increases with g_{BK} but decreases with $g_{K,NMDA}$. The insets show the threshold values of g_{DR} for the parameters used in these simulations.

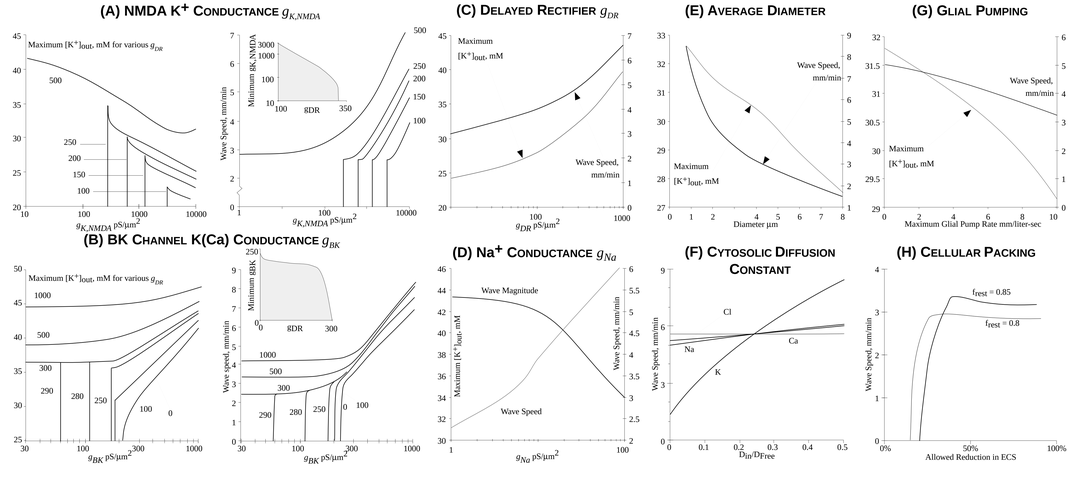
Predicted wave speed is an increasing function of g_{Na} (D) while wave magnitude decreases with g_{Na}. This suggests that that Na^+ currents facilitate SD at low levels and inhibit it at higher levels.

Both the predicted wave speed and wave magnitude decrease with average dendritic diameter (E). This suggests that waves may propagate more strongly in thinner processes.

The predicted wave speed is strongly dependent on the cytosolic diffusion constant of K^+ but is only weakly dependent on the diffusion of other species (F). Reducing D_k to zero is equivalent to blocking gap junctions in this model. This prediction suggests that K^+ movement through gap junctions between neurons is required for SD. Wave propagation is predicted to be only weakly dependent on interstitial diffusion (results not shown).

Both wave speed and wave magnitude decrease with maximum glial pump rate (G). This suggests that glia protect tissue against SD, and that glial failure may facilitate SD.

The simulations predict that SD can not be induced in tissue composed entirely of rigid cells (H). For the range of parameters tested, no waves could be induced unless cells were allowed to expand to fill at least ≈25% to ≈50% of interstitial space. The two curves in (H) correspond to different resting cytosolic volume fractions (the fraction of space occupied by cells).



CONCLUSIONS

GOALS

To model and predict the importance of:

- Ø Volume changes
- Ø Interneuronal gap junctions

in the propagation of spreading depression

ASSUMPTIONS

- Ø Osmotic forces cause water entry/efflux
- Ø Cytoplasmic voltage gradients may be of significance
- Ø Ions propagate through interneuronal gap junctions

PREDICTIONS

- Ø SD will not propagate unless cells can expand
- Ø Propagation is driven by cytoplasmic and not by interstitial diffusion
- Ø Blocking gap junctions prevents SD
- Ø Glial poisons will not prevent SD
- Ø Neuronal Ca^{++} waves propagate with SD (results not shown)
- Ø NMDA, BK (K(Ca)), DR-K^+, HVA-Ca^{++} and Na^+currents facilitate SD
- Ø SK and KA currents and glial pumping protect against (inhibit) SD

SELECTED BIBLIOGRAPHY

Original Report of Spreading Depression

Leão AAP (1944) Spreading depression of activity in the cerebral cortex. J Neurophysiol 7:359-390.

General References on Spreading Depression

Bures J, Buresová O, and Krivánek J (1974) The Mechanism and Applications of Leao's Spreading Depression of Electroencephalographic Activity. New York: Academic Press.

Somjen GG, Aitken PG, Czeh GL, Herreras O, Jing J, Young JN (1992) Mechanism of spreading depression: a review of recent findings and a hypothesis. Can J Physiol Pharmacol 70:S248-54.

Volumetric and Ionic Changes During Spreading Depression

Kraig RP, Nicholson C (1978) Extracellular ionic variations during spreading depression. Neuroscience 3:1045-1059.

Jing J, Aitken PG, Somjen GG (1994) Interstitial volume changes during spreading depression in rat hippocampal slices. Brain Res 604:251-9.

Glia and Spreading Depression

Largo C, Ibarz JM, Herreras O (1997) Effects of the gliotoxin fluorocitrate on spreading depression and glial membrane potential in rat brain in situ. J Neurophysiol 78: 295-307.

Largo C, Tombaugh GC, Aitken PG, Herreras O, Somjen GG (1997) Heptanol but not fluoroacetate prevents the propagation of spreading depression in rat hippocampal slices. J Neurophysiol 77:9-16.

Gap Junctions and Spreading Depression

Martins-Ferreira H, Ribeiro LJ (1995) Biphasic effects of gap junctional uncoupling agents on the propagation of retinal spreading depression. Braz J Med Biol Res 28:991-4.

Nedergaard M, Cooper AJ, Goldman SA (1995) Gap junctions are required for the propagation of spreading depression. J Neurobiol 28:433-444.

Largo C, Tombaugh GC, Aitken PG, Herreras O, Somjen GG (1997) Heptanol but not fluoroacetate prevents the propagation of spreading depression in rat hippocampal slices. J Neurophysiol 77:9-16.

Electrodiffusion Equation

Qian N, Sejnowski TJ (1989) An electro-diffusion model for computing membrane potentials and ionic concentrations in branching dendrites, spines and axons. Biol Cybern 62: 1-15.

Mathematical Models of Spreading Depression

Bures J, Buresová O, and Krivánek J (1974) op. cit.

Reggia JA, Montgomery D (1994) Modeling cortical spreading depression. Proc Annu Symp Comput Appl Med Care, 873-877.

Reggia JA, Montgomery D (1996) A computational model of visual hallucinations in migraine. Comput Biol Med 26:133-41.

Tuckwell HC (1980) Predictions and properties of a model of potassium and calcium ion movements during spreading cortical depression. Int J Neurosci 10:145-164.

Tuckwell HC (1981) Simplified reaction-diffusion equations for potassium and calcium ion concentrations during spreading cortical depression. Int J Neurosci 12:95-107.

Tuckwell HC, Hermansen CL (1981) Ion and transmitter movements during spreading cortical depression. Int J Neurosci 12:109-135.

Tuckwell HC, Miura RM (1978) A Mathematical Model for Spreading Depression. Biophys J 23:257-276.

Revett K, Ruppin E, Goodall S, Reggia JA (1998) Spreading depression in focal ischemia: a computational study. J Cereb Blood Flow Metab 18: 998-1007.

ACKNOWLEDGEMENT

The author was supported by a Systems and Integrative Biology Training Grant from the National Institute of General Medical Sciences of the National Institutes of Health.

FOR MORE INFORMATION

Bruce E. Shapiro
Department of Biomathematics
UCLA School of Medicine
AV-617 CHS
10833 Le Conte Ave
Los Angeles, CA 90095-1766

bshapiro@ucla.edu

http://www.bol.ucla.edu/~bshapiro/

818-393-0980