SPREADING DEPRESSION AS A HOLISTIC PROCESS:
A HISTORICAL PERSPECTIVE

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I do not have a financial interest in commercial products or services related to the subject of this lecture.
Why we are here

Aristides A.P. Leão
(1914-1993)


Characteristics of spreading cortical depression

Sequential disappearance of electrical activity, advancing over cortex several mm/min

Modified from Leão, 1944

Slow surface depolarization

From Leño, 1951
SD invalidates the concept of the “suppressor strip”

J.G. Dusser de Barenne

http://www.uic.edu/depts/mcne/founders/page0027.html

Warren S. McCulloch

http://www.nesfa.org/boskone/b05/photos.html

**FUNCTIONAL ORGANIZATION IN THE SENSORY CORTEX OF THE MONKEY (MACACA MULATTA)**

J. G. DUSSER DE BARENNE AND W. S. McCULLOCH

J. Neurophysiol. 1: 369-85 (1938)
Significance of spreading depression/depolarization

Initiating conditions:
- strong electrical stimulation/activity
- depolarization
- KCl
- mechanical impact
- trauma
- anoxia/ischemia
- hypoglycemia

Relevant clinical conditions:
- migraine aura
- epilepsy/postictal symptoms
- head injury/concussion/chronic traumatic encephalopathy
- stroke
- subarachnoid hemorrhage
Onset of slow surface depolarization is accompanied by neuronal excitation

Modified from Grafstein, 1956
The hypothesis

MECHANISM OF SPREADING CORTICAL DEPRESSION

B. GRAFSTEIN


The intense neuronal activity preceding depression results in the liberation of $K^+$ into the interstitial spaces in sufficient quantity to depolarize adjacent cells. These are in turn thrown into intense activity, and liberate more $K^+$. 
Some uneasiness?

JOURNAL OF NEUROPHYSIOLOGY

333 CEDAR STREET
NEW HAVEN 11, CONNECTICUT

6 July 1955

My dear Dr. Grafstein:

Your paper, "The mechanism of spreading cortical depression," has now been the rounds of the Editorial Board, and has been accepted for publication. There were rather sharp differences of opinion concerning your interpretations, although none of the readers questioned the validity of your data.

Very sincerely yours,

John F. Fulton, M.D.
Some high-quality support

Spreading Depression, Grafstein hypothesis

The mechanism proposed by Grafstein (diffusion + liberation of K) gives the right order of magnitude for the velocity.

Note
The mathematical method used here is due to Huxley, and his name should be quoted if any one finds these results of sufficient interest to quote meantime in print.

A. L. Hodgkin, July 1959
Some vindication

POTASSIUM OUTFLUX FROM RABBIT CORTEX DURING SPREADING DEPRESSION


50 years later -- still grumbling!

**Electrical prodromals of spreading depression void Grafstein's potassium hypothesis**

*J Neurophysiol* 94:3656-3657, 2005. doi:10.1152/jn.00709.2005
REPLY (condensed):

The release of K⁺ is an essential factor giving SD its all-or-none characteristic ... It was Grafstein (1956) who first suggested a critical role for K⁺.

George Somjen  
Departments of Cell Biology and Neurobiology  
Duke University Medical Center  
Durham, North Carolina  
E-mail: g.somjen@cellbio.duke.edu

Anthony Strong  
Departments of Cell Biology and Neurobiology  
Department of Clinical Neuroscience  
King’s College  
London, United Kingdom  
E-mail: anthony.strong@kcl.ac.uk
More features of SD
In SD there is increased tissue resistance, cell swelling and decreased extracellular space.

Some relations between resistivity and electrical activity in the cerebral cortex of the cat.

W. H. Freygang, Jr. and W. M. Landau
J. Cell Comp. Physiol. 45: 377-392 (1955)

Changes in cortical extracellular space during spreading depression investigated with the electron microscope.

A. Van Harreveld and F. I. Khattab
J. Neurophysiol. 30: 911-929 (1967)

Spreading depression can be visualized in retina by change in light scattering

H. Martins-Ferreira

http://www.abc.org.br/resultado.php3?codigo=hiss

Figure modified from Martins-Ferreira et al., 2000

LIGHT-SCATTERING CHANGES ACCOMPANYING SPREADING DEPRESSION IN ISOLATED RETINA

H. MARTINS-FERREIRA AND G. DE OLIVEIRA CASTRO

SD is accompanied by glutamate release and can be initiated by glutamate

Antonie van Harreveld

GLUTAMATE RELEASE FROM THE RETINA DURING SPREADING DEPRESSION

A. VAN HARREVELD and EVA FIFKOVÁ

COMPounds in brain extracts causing spreading depression of cerebral cortical activity and contraction of crustacean muscle

A. VAN HARREVELD
J. Neurochemistry 3: 300-315 (1959)
Spreading depression as a tool to study brain function

Jan Bures


SD involves ionic changes in addition to K⁺
Vascular changes
Vascular changes during SD in mouse cortex

CORTICAL SPREADING DEPRESSION CAUSES AND COINCIDES WITH TISSUE HYPOXIA

T. Takano, G.-F. Tian., W. Peng, N. Lou1, D. Lovatt, A.J. Hansen, K.A. Kasischke1 and M. Nedergaard

Nature Neuroscience 10, 754 - 762 (2007)
Hypoxia during SD, even during vasodilation phase

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Nature Neuroscience 10, 754 - 762 (2007)
The role of astrocytes
Astrocytes depolarize during SD

Modified from Sugaya et al., 1974

NEURONAL AND GLIAL ACTIVITY DURING SPREADING DEPRESSION IN CEREBRAL CORTEX OF CAT

Sugaya, E., Takato, M., and Noda, Y.

Calcium waves in astrocytes (mediated by gap junctions and ATP diffusion) spread at the same rate as SD.

Astrocytes in culture filled with Ca\(^{++}\)-sensitive dye (stimulated at arrow)

Modified from Martins-Ferreira et al., 2000
<table>
<thead>
<tr>
<th>YES</th>
<th>GAP JUNCTIONS ARE REQUIRED FOR THE PROPAGATION OF SPREADING DEPRESSION</th>
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<td>M. Nedergaard, A.J.L. Cooper and S.A. Goldman</td>
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<th>NO</th>
<th>DIFFERENT MECHANISMS PROMOTE ASTROCYTE Ca^{2+} WAVES AND SPREADING DEPRESSION IN THE MOUSE NEOCORTEX X</th>
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<td>O. Peters, C. G. Schipke, Y. Hashimoto, and H. Kettenmann</td>
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The role of microglia
MICROGLIAL REACTION IN THE RAT CEREBRAL CORTEX INDUCED BY CORTICAL SPREADING DEPRESSION


Brain Pathology 3: 11-17 (1993)
Initiation of spreading depression requires microglia

![Graph showing relative SD threshold and number of KCl induced SDs for control and clodronate treated samples.](image)

Drug (clodronate) that depletes microglia blocks initiation of SD by K⁺ in hippocampal slice cultures.

Adapted from Pusic et al., 2014

**SPREADING DEPRESSION REQUIRES MICROGLIA AND IS DECREASED BY THEIR M2A POLARIZATION FROM ENVIRONMENTAL ENRICHMENT**


The migraine connection
Spread of SD = spread of visual aura activity on the cortex

Fig. 4.—Successive maps of a scintillating scotoma to show characteristic distribution of the fortification figures. The X in each case indicates the fixation point.

From Lashley, 1947

NOTE ON A POSSIBLE CORRESPONDENCE BETWEEN THE SCOTOMAS OF MIGRAINE AND SPREADING DEPRESSION OF LEÃO

P.M. Milner, Ph.D.

First demonstration of spreading depression during migraine using PET

BILATERAL SPREADING HYPOPERFUSION DURING SPONTANEOUS MIGRAINE HEADACHE

R.P. Woods, M. Iacoboni and J.C. Mazziotta
Typical course of cerebral blood flow changes in migraine

TIMING AND TOPOGRAPHY OF CEREBRAL BLOOD FLOW, AURA, AND HEADACHE DURING MIGRAINE ATTACKS


Why women are more susceptible to migraine?

Potassium-selective microelectrode revealed difference in threshold potassium concentration for cortical spreading depression in female and male rat brain.

Svatopluk Adámek, František Vyskočil

8.0 +/- 0.6 mM K+ vs. 14.4 +/- 0.4 mM K+
How do SD events cause headache?
Trigeminovascular hypothesis of migraine headache

CHAOS AND COMMOTION IN THE WAKE OF CORTICAL SPREADING
DEPRESSION AND SPREADING DEPOLARIZATIONS

D. Pietrobon and M. Moskowitz
The message
Mechanisms participating in spreading depression

- K$^+$ release by neuronal activity and depolarization
- Internalization of Na$^+$, Cl$^-$ and Ca$^{2+}$ and cell swelling
- Glutamate release from neurons and astrocytes
- Astrocytic Ca$^{++}$ waves via gap junctions and ATP release
- Vasodilation/vasoconstriction
- Microglial activation (inflammation)
- Anoxia
- NO generation
- Blood-brain barrier disruption
The neurovascular unit: multiple participants in spreading depression

Modified from Del Zoppo, 2006