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)

http://semana.mct.gov.br/index.php/content/view/4411/Aristides_Leao_1914_1993.html

Leão, A.P., 1944a.
SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX.
J. Neurophysiol. 3, 359-390.

Leão, A.P., 1944b. PIAL CIRCULATION AND SPREADING DEPRESSION OF ACTIVITY IN THE CEREBAL CORTEX.
J. Neurophysiol. 7, 391-396.

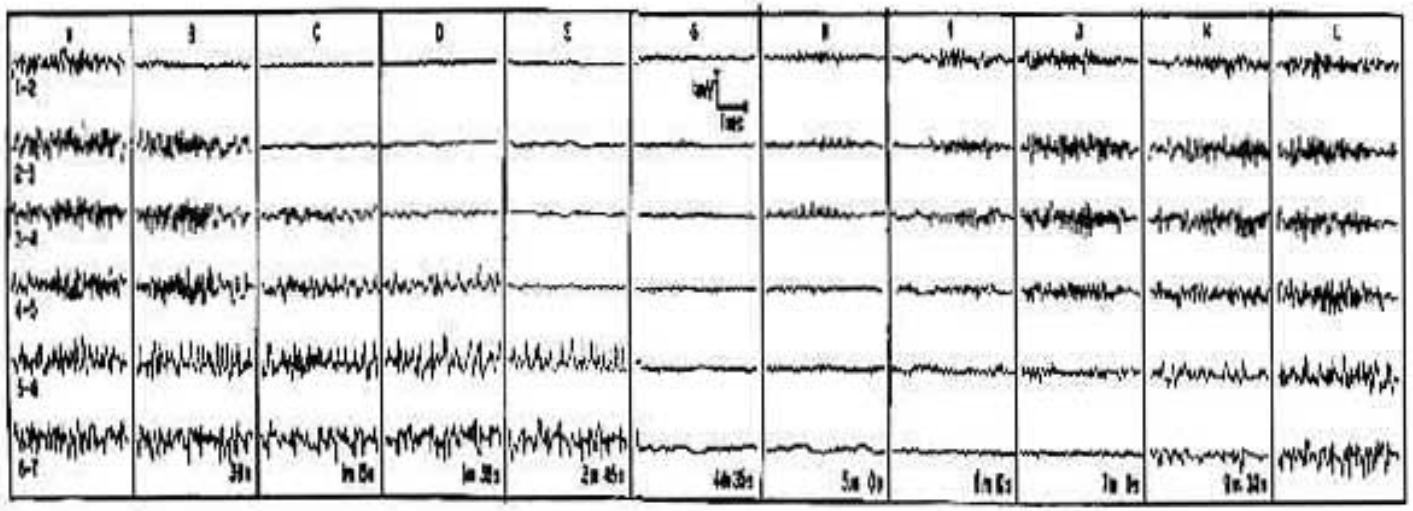
Leão, A.P., 1947.
FURTHER OBSERVATIONS ON THE SPREADING OF DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX.
J. Neurophysiol. 7, 409-414.

Leão, A.P., 1951.
THE SLOW VOLTAGE VARIATION OF CORTICAL SPREADING DEPRESSION OF ACTIVITY.
EEG Clin. Neurophyiol. 3: 315-321.

Leão, A.P., Morison, R.A., 1945.
PROPAGATION OF SPREADING CORTICAL DEPRESSION.
J. Neurophysiol. 8, 33-45.

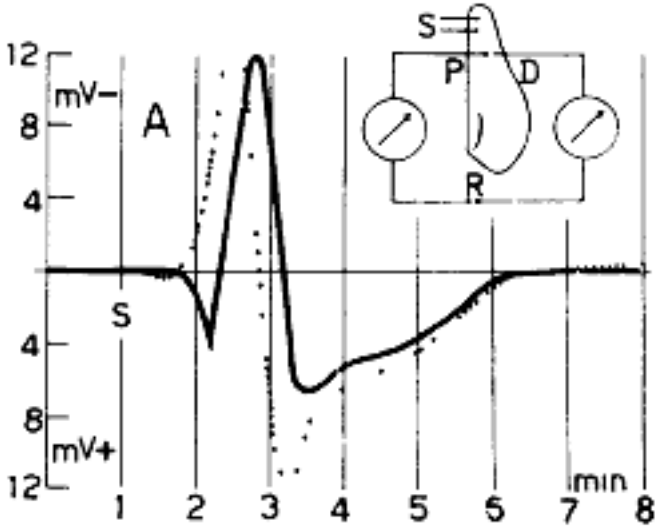
Characteristics of spreading cortical depression

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



Modified from Leão, 1944

Slow surface depolarization



From Leño, 1951

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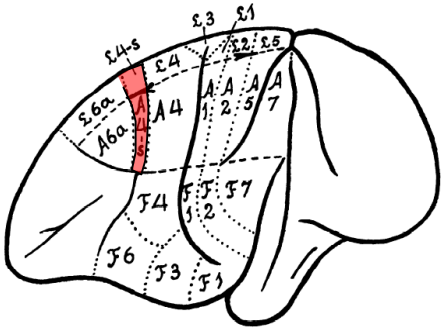
SD invalidates the concept of the "suppressor strip"

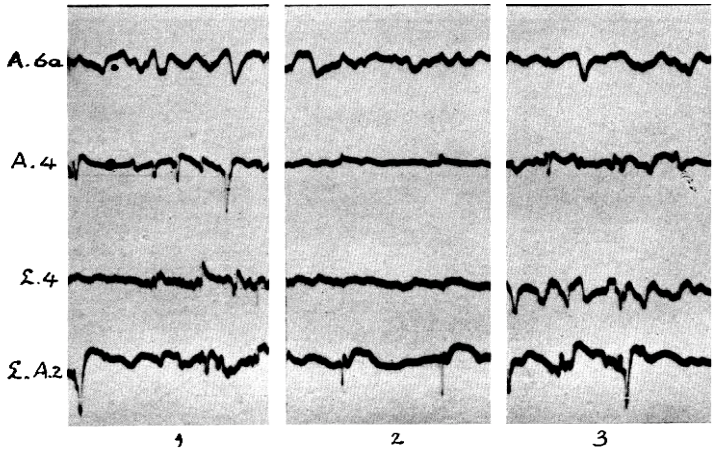
J.G. **Dusser** de Barenne

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

Warren S. McCulloch

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





BEFORE STRYCHNINE | **7 min. AFTER** | **11.5 min. AFTER**

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)

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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

Characteristics of spreading cortical depression (cont.)

Bernice Grafstein

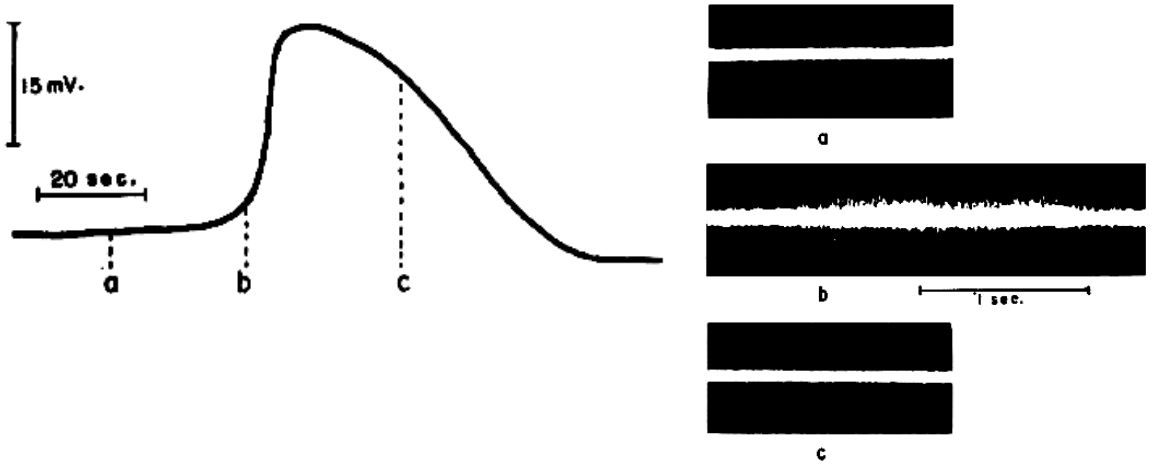
Benedict Delisle Burns

MECHANISM OF SPREADING CORTICAL DEPRESSION

B. Grafstein

J. Neurophysiol. 19: 154-171 (1956)

Onset of slow surface depolarization is accompanied by neuronal excitation



Modified from Grafstein, 1956

The hypothesis

MECHANISM OF SPREADING CORTICAL DEPRESSION

B. GRAFSTEIN

J. Neurophysiol. 19: 154-171 (1956)

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:

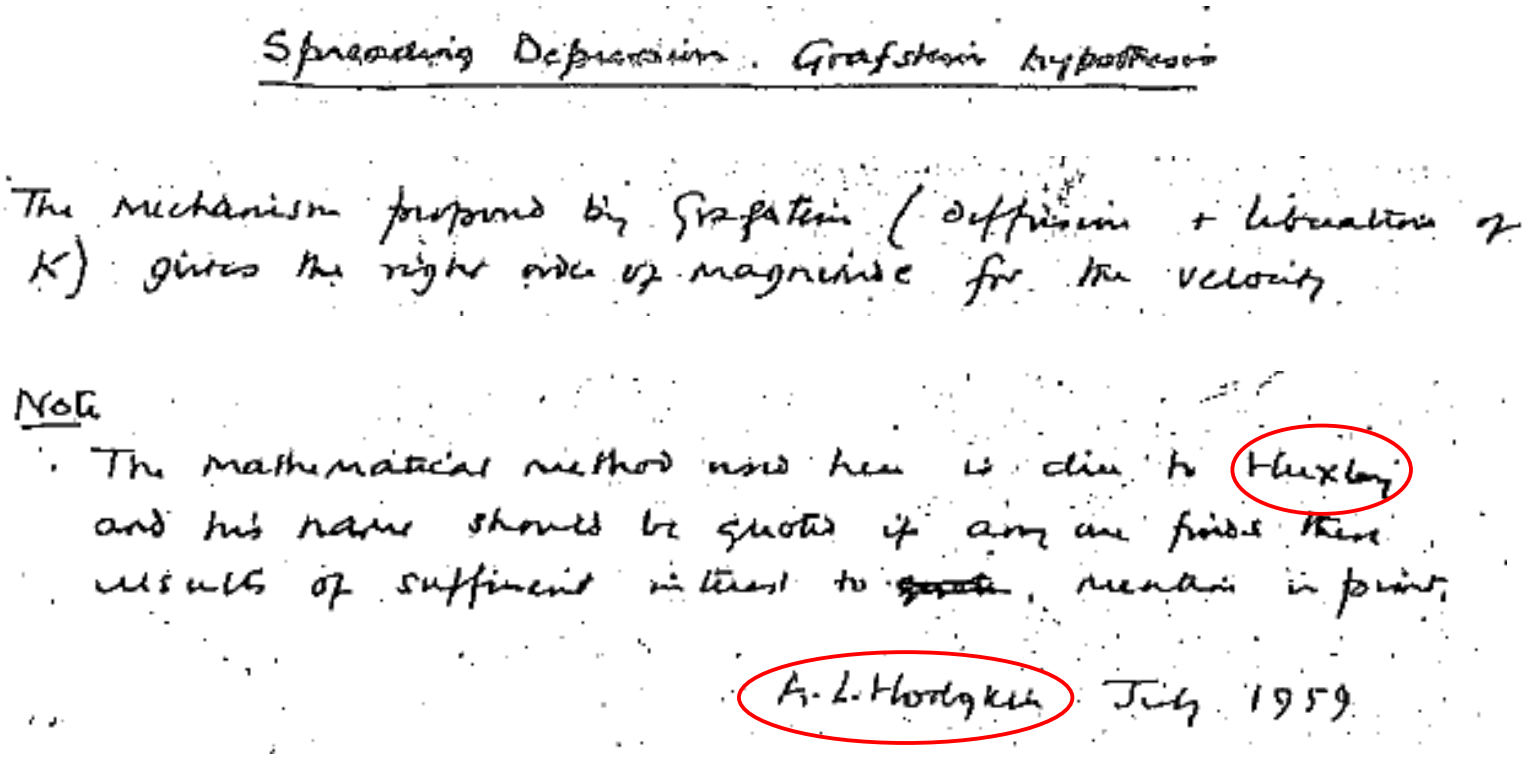
Your paper, "The mechanism of spreading cortical depression," has now been the rounds of the Editorial Board, and has been accepted for publication. There were rather sharp differences of opinion concerning your interpretations, although none of the readers questioned the validity of your data.

Very sincerely yours,

John F. Fulton

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~~, mention in print.

A. L. Hodgkin July 1959

Some vindication

POTASSIUM OUTFLUX FROM RABBIT CORTEX DURING SPREADING DEPRESSION

F. J. Brinley, Jr., E. R. Kandel, and Wade H. Marshall

J. Neurophysiol. 23:246-256 (1960)

50 years later -- still grumbling!

Electrical prodromals of spreading depression void Grafstein's potassium hypothesis

Oscar Herreras

J Neurophysiol 94:3656-3657, 2005. doi:10.1152/jn.00709.2005

White knights to the rescue

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
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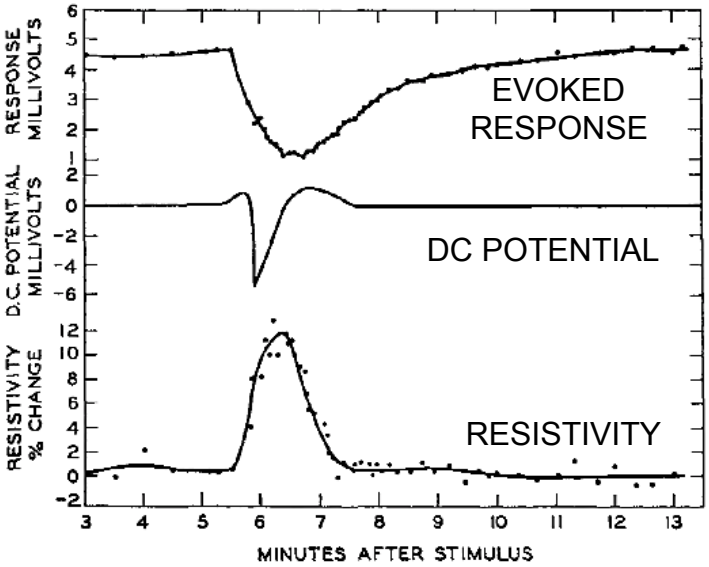
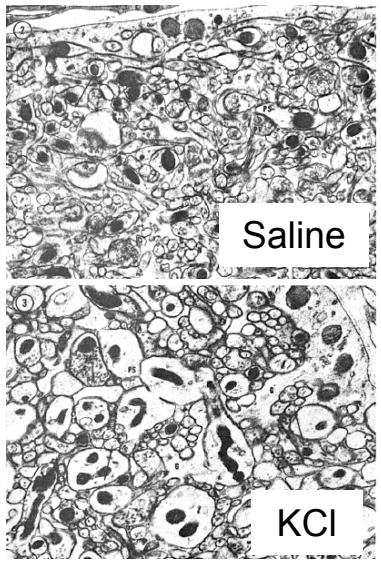
Duke University Medical Center
Durham, North Carolina
E-mail: g.somjen@cellbio.duke.edu

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[1]

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[1]

A. VAN HARREVELD AND F. I. KHATTAB

J. Neurophysiol. 30: 911-929 (1967)

* LEÃO, A. A. P. AND FERREIRA, H. M. Altração da impedância elétrica no decurso da depressão alastrante de atividade do córtex cerebral. *Anais Acad. Brasil. Cienc.* 25: 259–266, 1953.

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

H. Martins-Ferreira

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

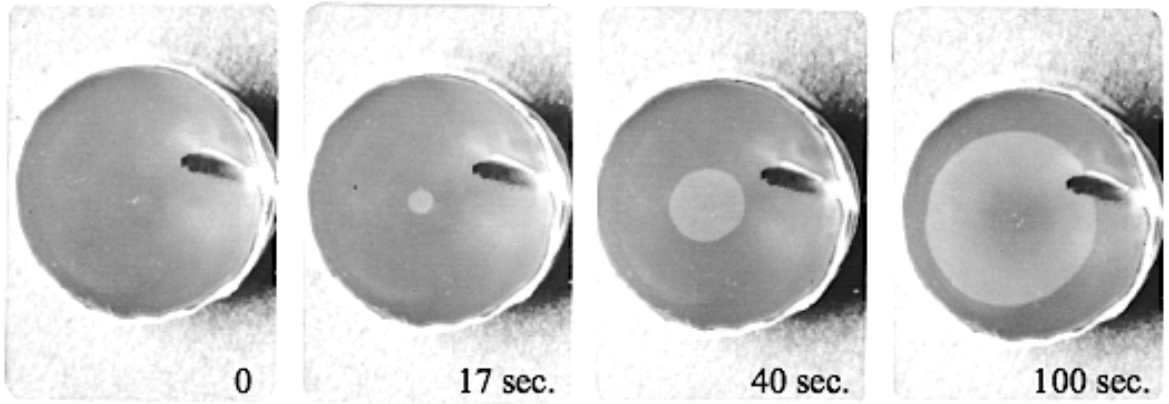


Figure modified from Martins-Ferreira et al., 2000

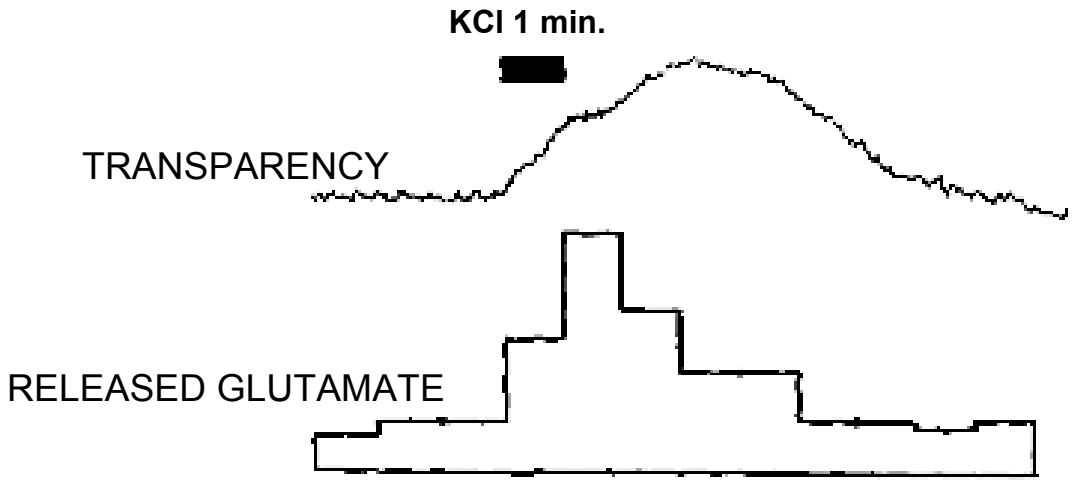
LIGHT-SCATTERING CHANGES ACCOMPANYING SPREADING DEPRESSION IN ISOLATED RETINA

H. MARTINS-FERREIRA AND G. DE OLIVEIRA CASTRO

J. Neurophysiol. 29: 715-726 (1966)

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

J. Neurobiol. 2: 13-29 (1970)

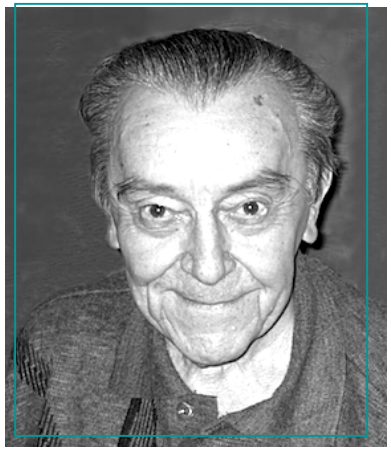
COMPOUNDS IN BRAIN EXTRACTS CAUSING SPREADING DEPRESSION OF CEREBRAL CORTICAL ACTIVITY AND CONTRACTION OF CRUSTACEAN MUSCLE

A. VAN HARREVELD

J. Neurochemistry 3: 300-315 (1959)

Spreading depression as a tool to study brain function

Jan Bures



http://www.biomed.cas.cz/fgu/en/index.php?skript=prezentace.php

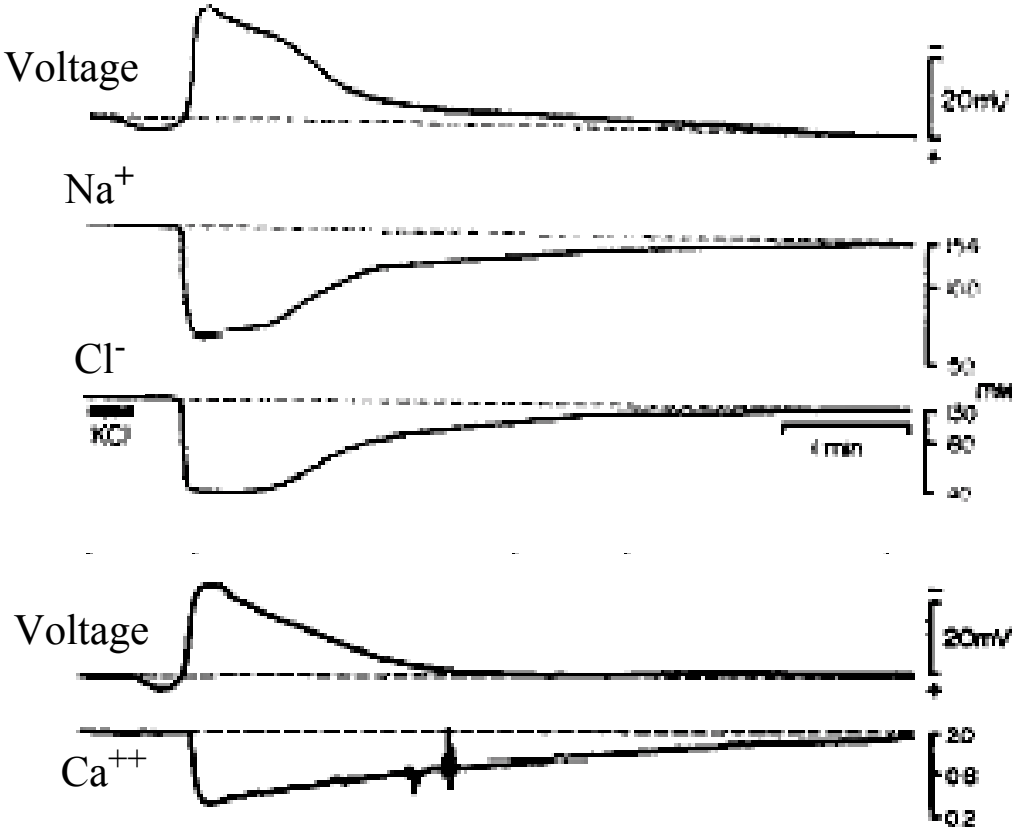
Bures, J., & Buresova, O. The use of Leao's spreading cortical depression in research on conditioned reflexes. *Electroencephalography and Clinical Neurophysiology, Supplement*, 1960, *13*, 359–376.

Bures, J., & Buresova, O. Cortical spreading depression as a memory disturbing factor. *Journal of Comparative and Physiological Psychology*, 1963, *56*, 268–272. (a)

SD involves ionic changes in addition to K^+

Richard P. Kraig

Charles Nicholson



EXTRACELLULAR IONIC VARIATIONS DURING SPREADING DEPRESSION

R. P. KRAIG and C. NICHOLSON

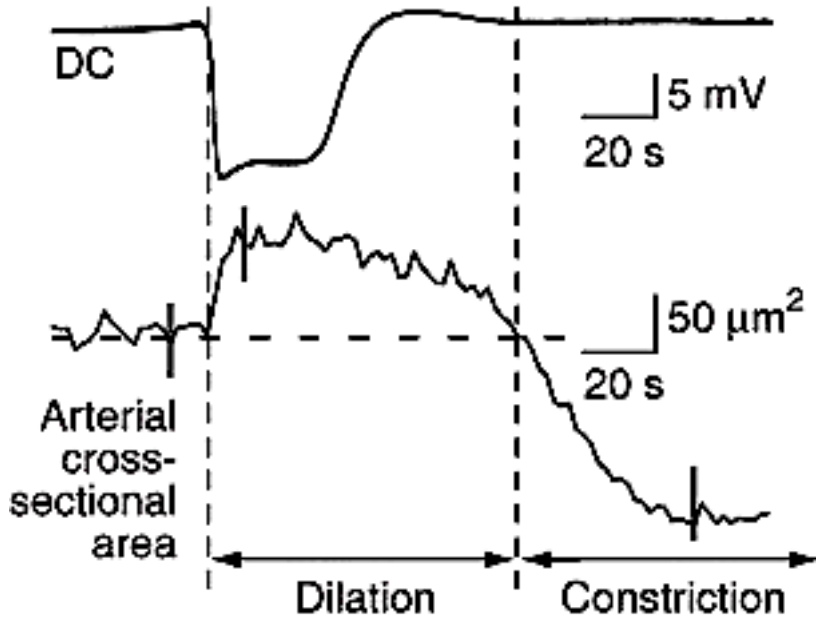
Neuroscience 3: 1045-1059 (1978)

Vascular changes

Vascular changes during SD in mouse cortex

Takahiro Takano

Maiken Nedergaard

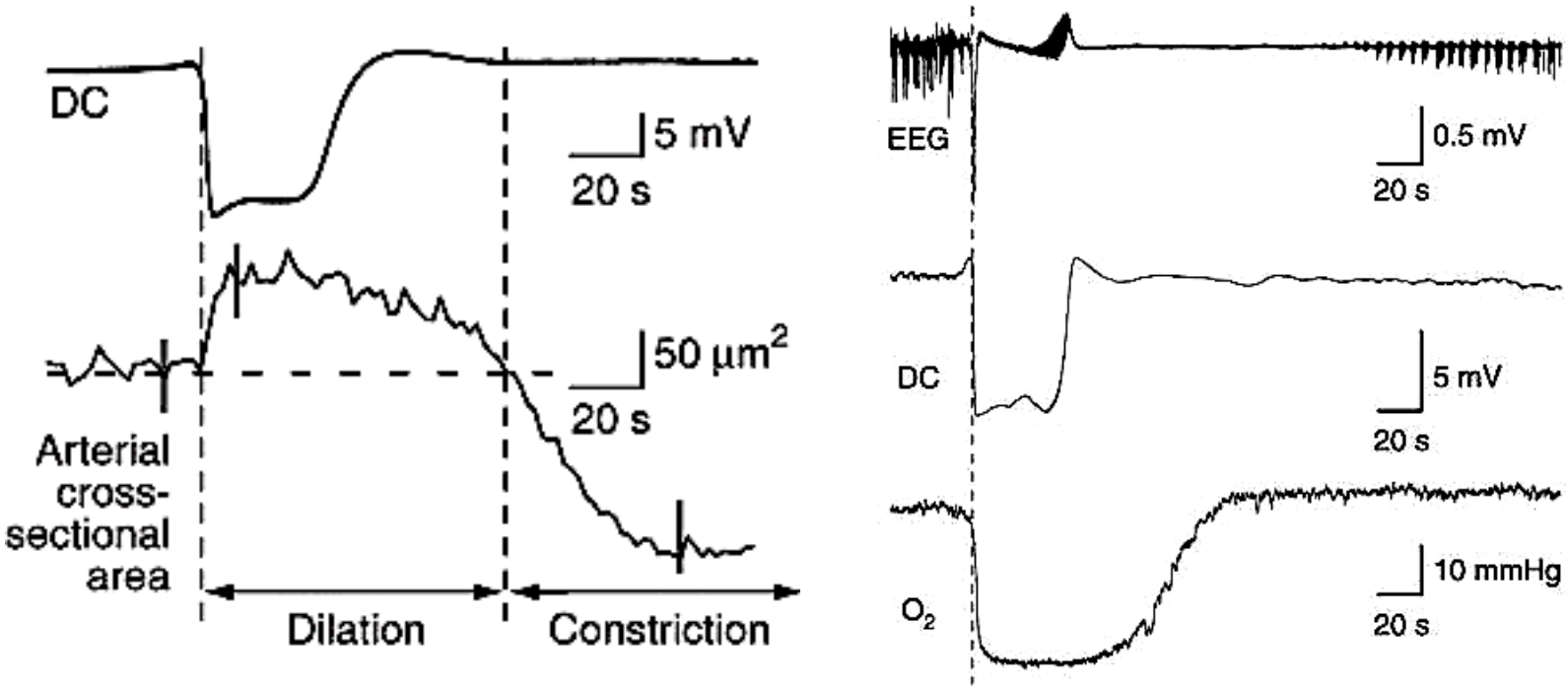


CORTICAL SPREADING DEPRESSION CAUSES AND COINCIDES WITH TISSUE HYPOXIA

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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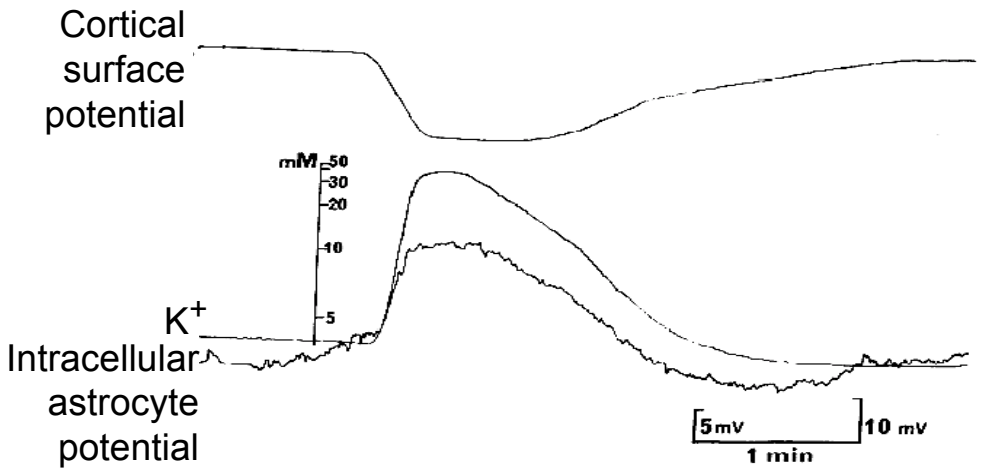
Nature Neuroscience 10, 754 - 762 (2007)

The role of astrocytes

Astrocytes depolarize during SD



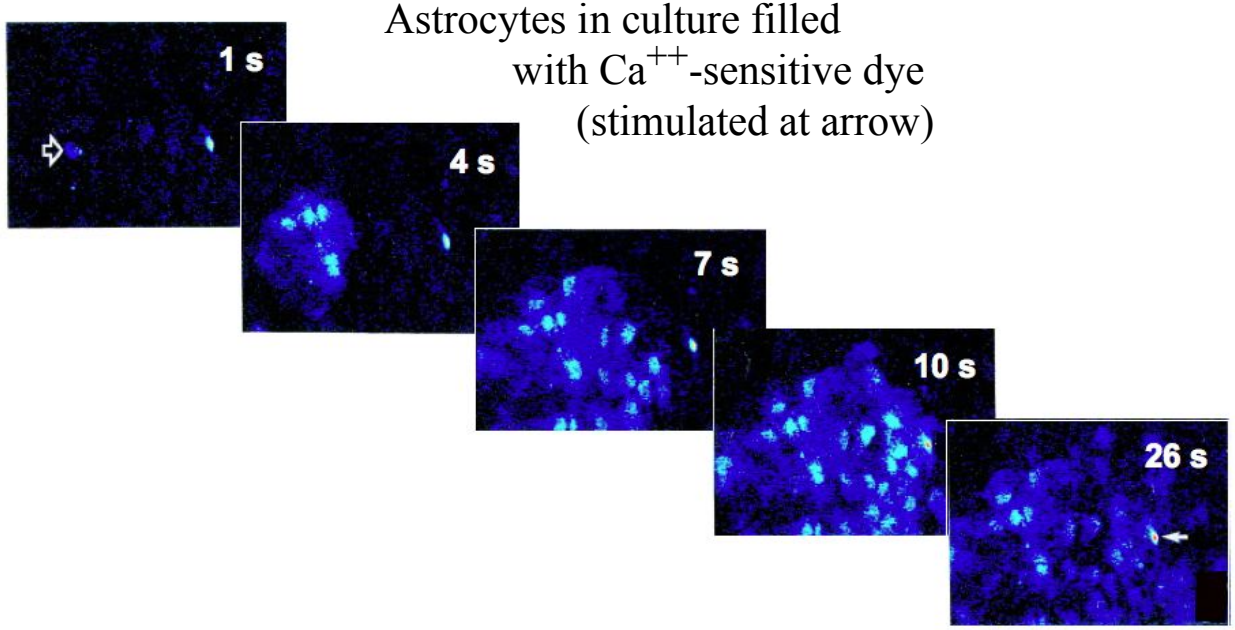
Modified from Sugaya et al., 1974

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

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

J. NeurophysioI. 38:822-841 (1974)

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

Do astrocyte Ca^{2+} waves contribute to SD?

YES

GAP JUNCTIONS ARE REQUIRED FOR THE PROPAGATION OF SPREADING DEPRESSION

M. Nedergaard, A.J.L.Cooper and S.A. Goldman

J. Neurobiol. 28: 433-444 (1995)

NO

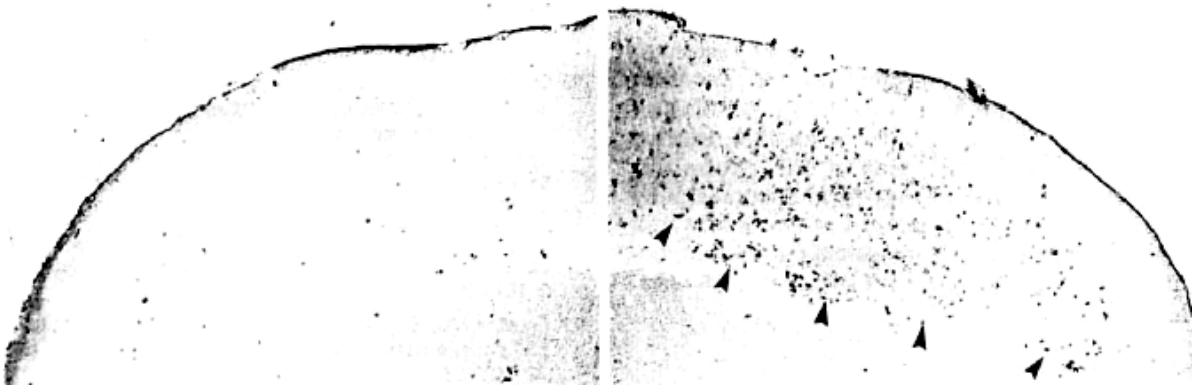
DIFFERENT MECHANISMS PROMOTE ASTROCYTE Ca^{2+} WAVES AND SPREADING DEPRESSION IN THE MOUSE NEOCORTE X

O. Peters, C. G. Schipke, Y. Hashimoto, and H. Kettenmann

J. Neurosci. 23: 9888–9896 (2003)

The role of microglia

SD activates microglia in cerebral cortex



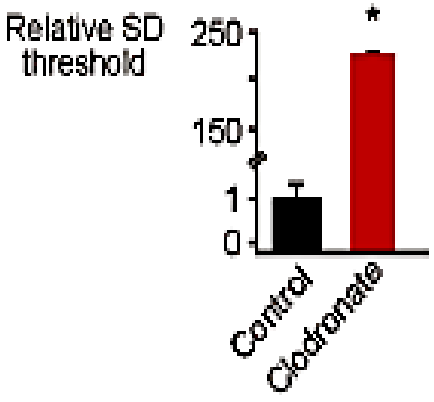
Normal 24 hr after SD

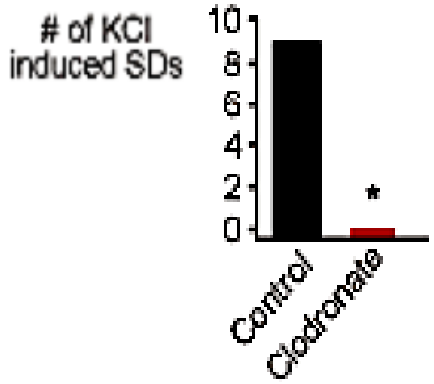
MICROGLIAL REACTION IN THE RAT CEREBRAL CORTEX INDUCED
BY CORTICAL SPREADING DEPRESSION

J. Gehrmann, G. Mies, P. Bonnekoh, R. Banati, T. lijima, G.W. Kreutzberg and K.-A. Hossmann

Brain Pathology 3: 11-17 (1 993)

Initiation of spreading depression requires microglia





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

K.M. Pusic, A.D. Pusic, J. Kemme and R.P. Kraig.
Glia 62:1176–1194 (2014)

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The migraine connection

Spread of SD = spread of visual aura activity on the cortex

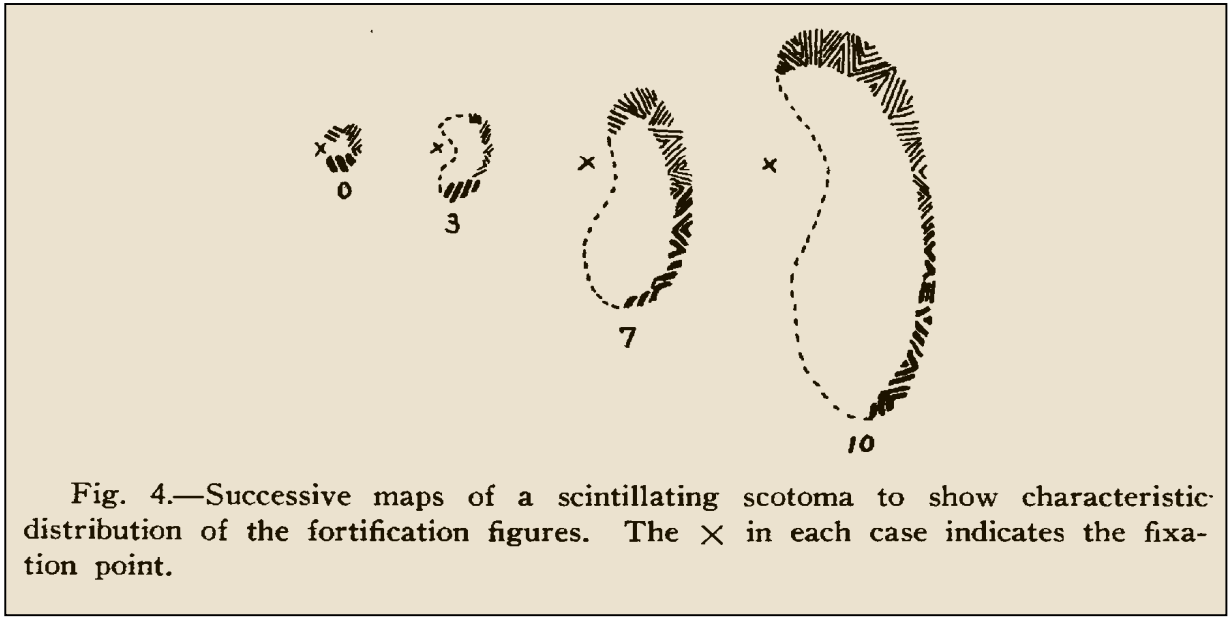


Fig. 4.—Successive maps of a scintillating scotoma to show characteristic distribution of the fortification figures. The × in each case indicates the fixation point.

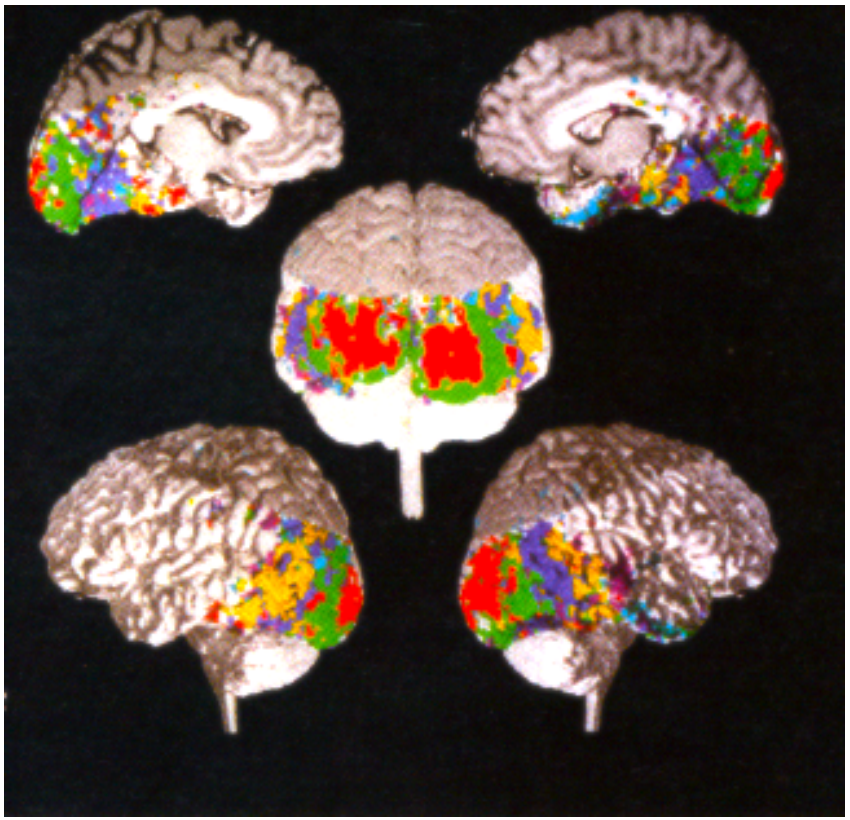
From Lashley, 1947

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

P.M. Milner, Ph.D.

EEG Clin. Neurophysiol. 10: 705 (1958)

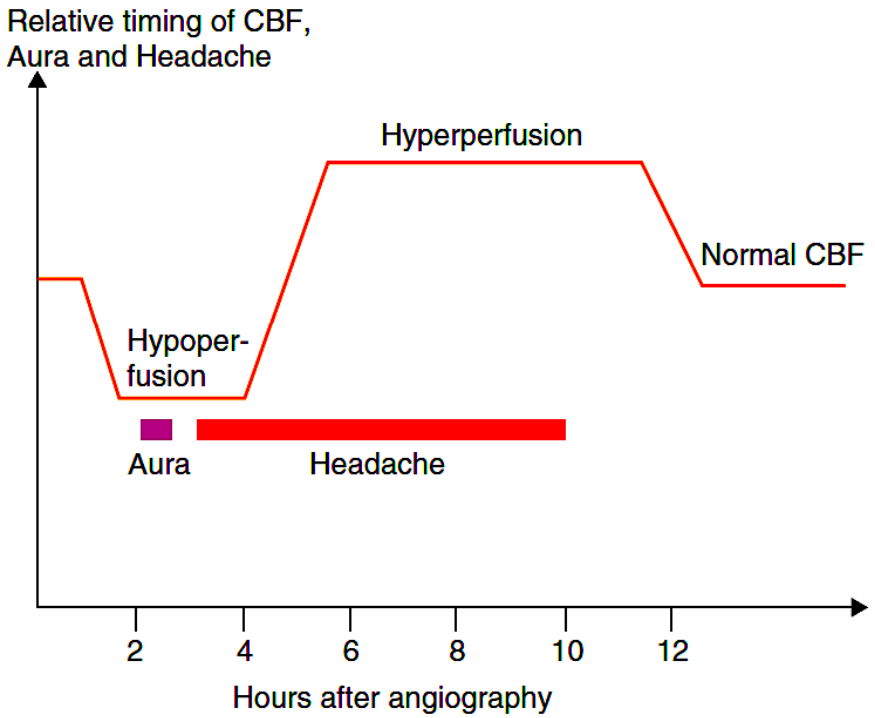
First demonstration of spreading depression during migraine using PET



BILATERAL SPREADING HYPOPERFUSION DURING SPONTANEOUS MIGRAINE HEADACHE

R.P. Woods, M. Iacoboni and J.C. Mazziotta
New Eng. J. Med. 331: 1689-1692 (1994)

Typical course of cerebral blood flow changes in migraine



Modified from Tfelt-Hansen, 2010, after original from Olesen et al., 1990

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

J. Olesen, L. Friberg, T. Skyhøj Olsen, H.K. Iversen, N.A. Lassen, A.R. Andersen and A.Karle

Ann. Neurol. 28: 791–798 (1990)

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

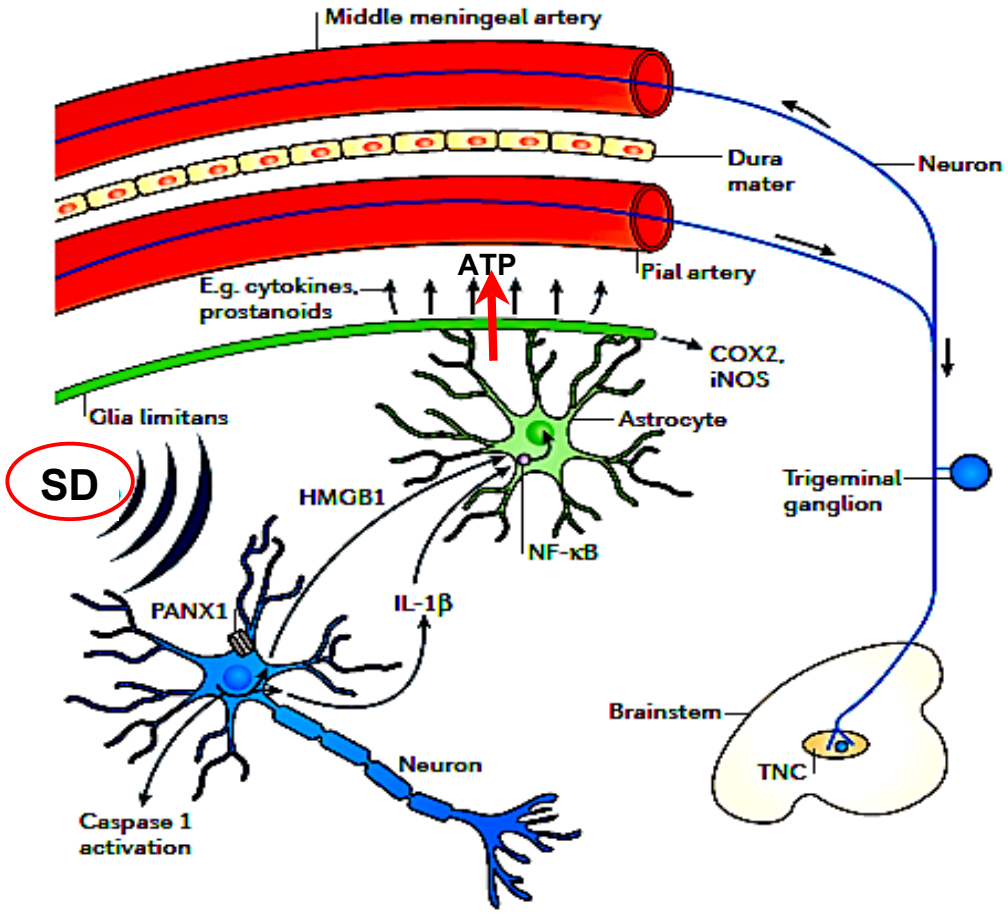
Svatopluk Adámek , František Vyskočil

Brain Research 1370: 215-219 (2011)

8.0 +/- 0.6 mM K^+
vs.
14.4 +/- 0.4 mM K^+

How do SD events cause headache?

Trigeminovascular hypothesis of migraine headache



Modified from Pietrobon & Moskowitz, 2014

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

D. Pietrobon and M. Moskowitz

Nature Rev. Neurosci. 15: 379-393 (2014)

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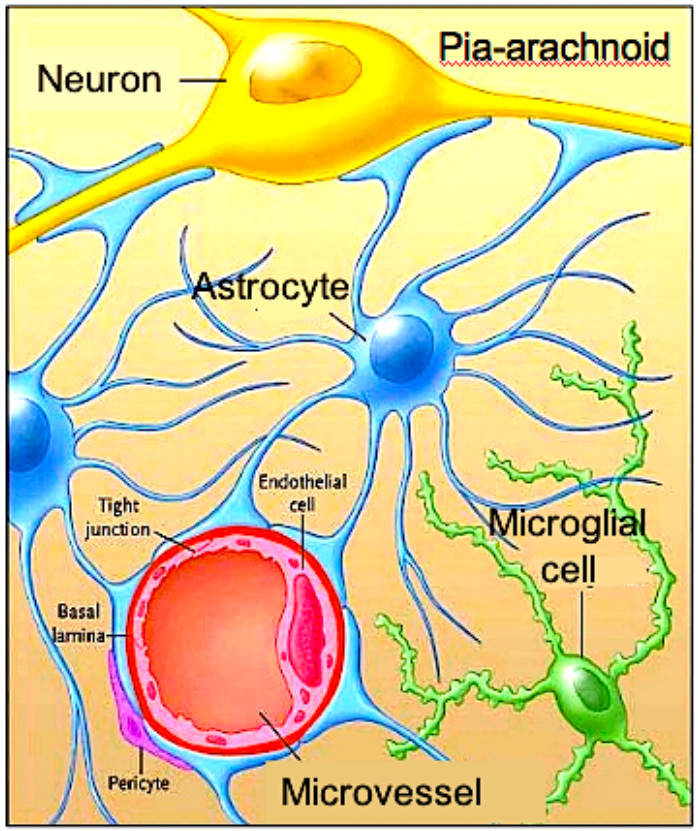
The message

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