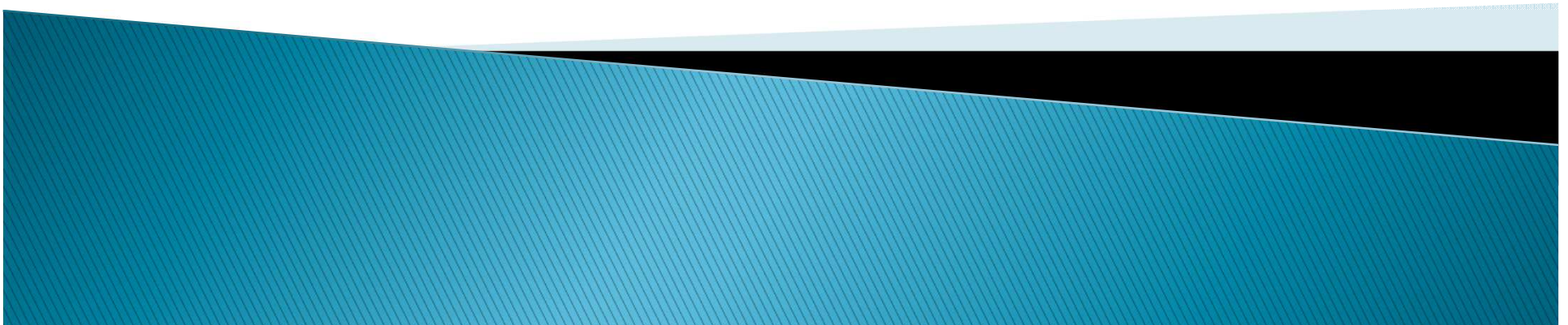


Migraine 100

CSD, Serotonin and Neurogenic inflammation

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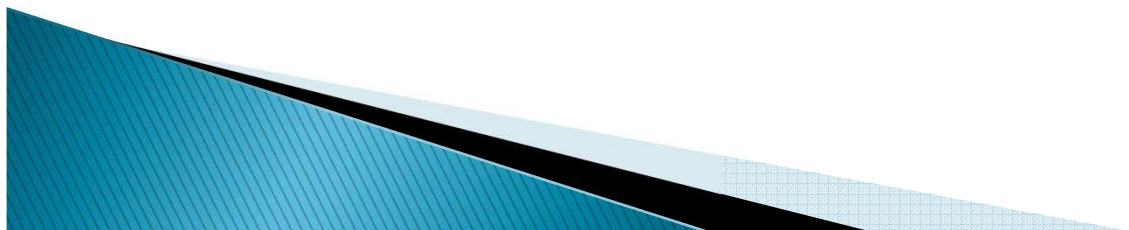
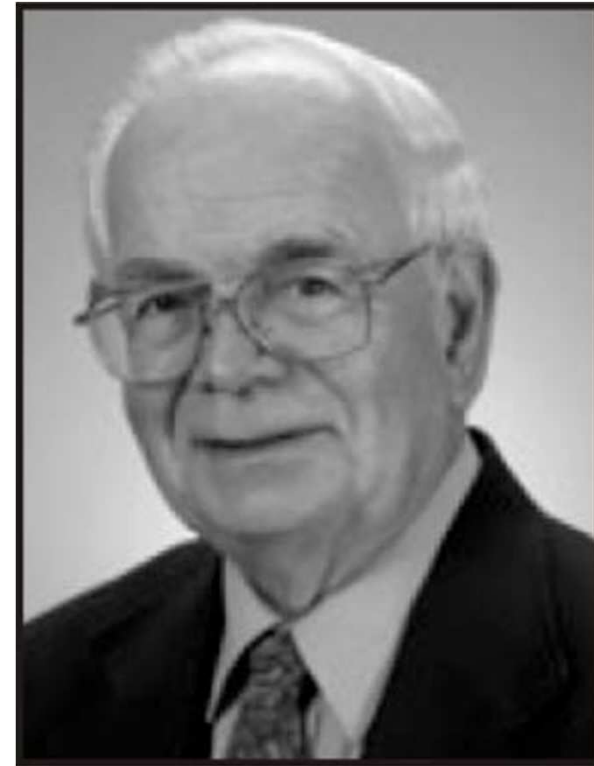
Migraine 100 : 1940–1980

- ▶ Description of visual auras – Karl Lashley
- ▶ Cortical spreading depression – Aristides Leão
- ▶ Serotonin and introduction of methysergide – Wolff
- ▶ Olegemia and CSD
- ▶ Neuro-inflammation



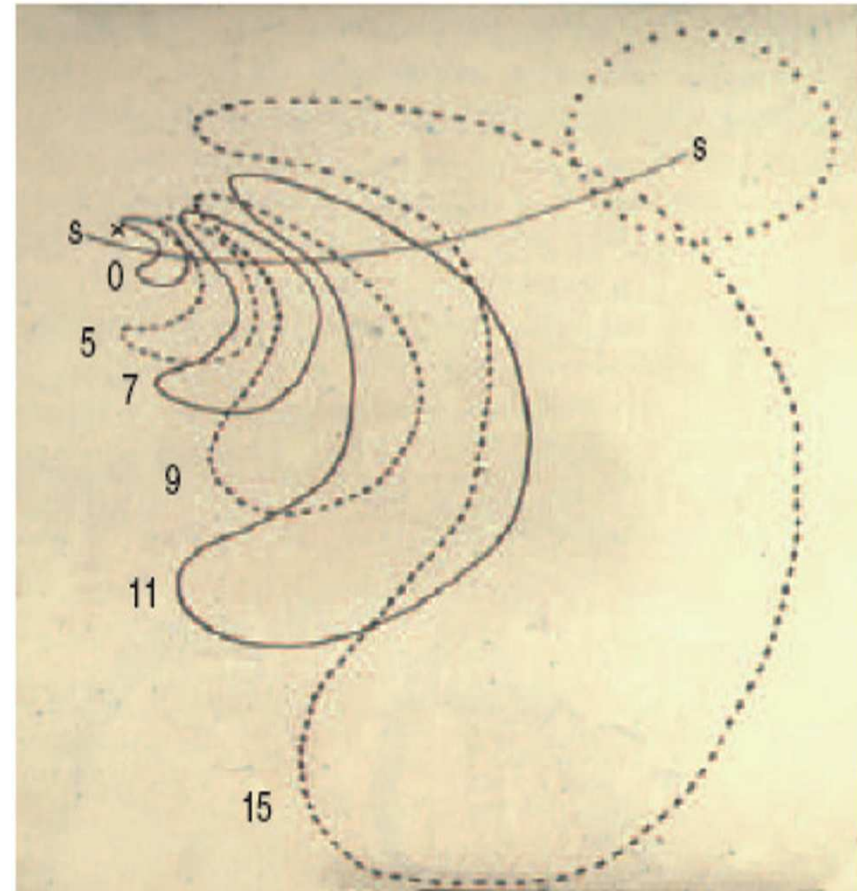
Description of visual auras

- ▶ Karl Spencer Lashley (1890–1958)
- ▶ Prof. of psychology in Harvard
- ▶ American.
- ▶ Zoologist in the early life.
- ▶ Focused in psychology and comparative biology later.



> 100 visual aura

- ▶ The shape of scotoma and fortification figures maintained its shape during the whole process.
- ▶ From macula to blind point



Theory

- ▶ An excitatory process (scintillation) and an inhibitory process is initiated in visual cortex and spread over to neighboring area.
- ▶ During the process, the activities extinguish in the initiative area. And the process of inhibition also spread with the same rate as the excitatory process.
- ▶ The rate is approximately 3 mm/min.
 - Antero–posterior length of visual striae is 67mm.
 - It took 20 mins for the aura to spread.



Cortical depression spreading

- ▶ Aristides Leão (1914–1993)
- ▶ Brazilian
- ▶ Prof. of Harvard

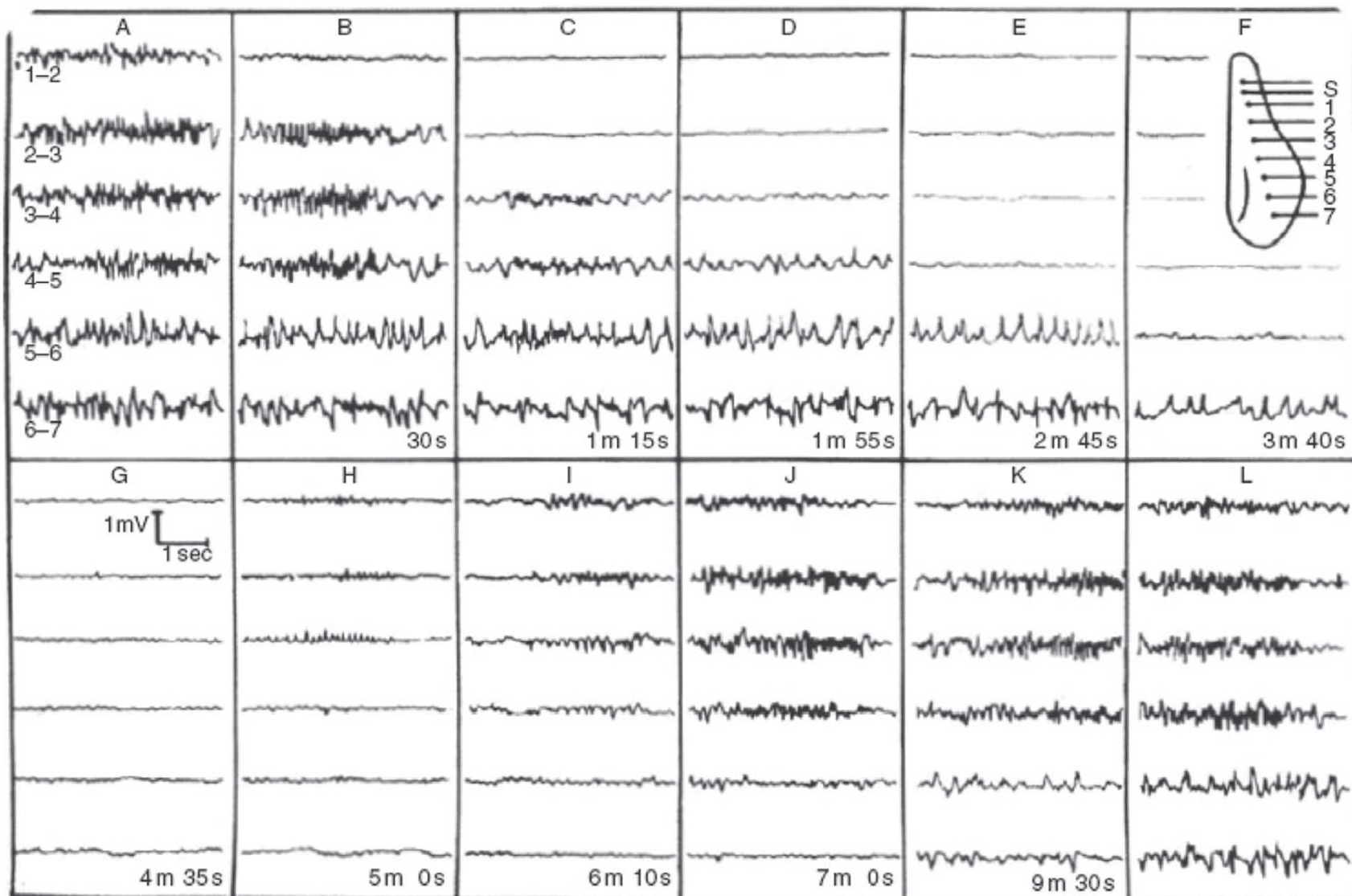


Cortical depression

- ▶ 1944
- ▶ First noticed during stimulation of rabbit cortex.
 - A marked, enduring, reduction of electrical activity, a reduction which appears first at the region that has been stimulated, and spreads out from that location in all directions.
 - Recovery took 5–10 minutes.



CSD is a spreading depression of the EEG



Findings

- ▶ A wave of dilatation of pial vessels accompanied with CSD.
- ▶ The CSD may be related to migraine with aura due to the slow development of scotoma and sensory symptoms.
- ▶ However, he seemed unaware of Lashley's paper and never measured the velocity of CSD.
- ▶ The connection was later discussed in 1980's.



Serotonin and methysergide

- ▶ Synthesized in 1948
 - Sero-tonin – Serum vasoconstricter
- ▶ Wolff et al
 - Peri-vascular injection produced migraine symptoms.
- ▶ Methysergide
 - A derivative of LSD 25. Antagonist of serotonin.



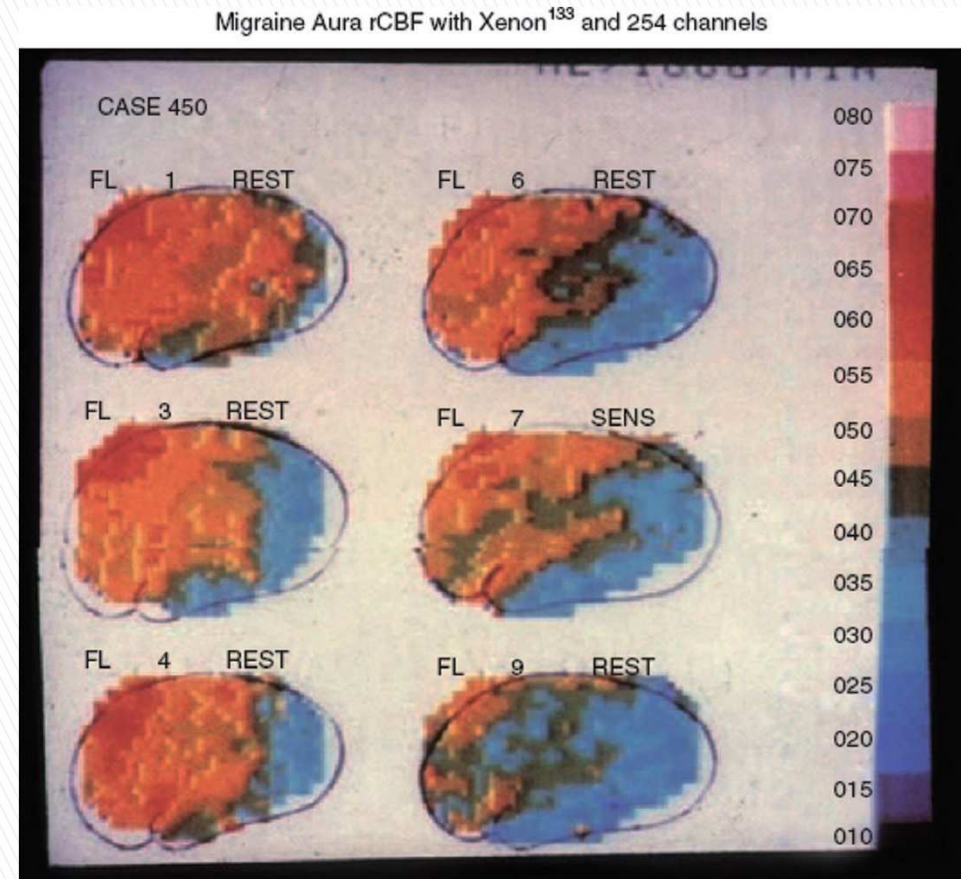
Methysergide

- ▶ Serious side effects were noticed 5 years after marketing.
 - Retroperitoneal fibrosis. – Around 1 / 5000.
 - Later, cardiac and pulmonary fibrosis were also noted.
 - Also, hallucinogenic.
- ▶ Although non-successful, methysergide opened the route to further searching of serotonin antagonist.



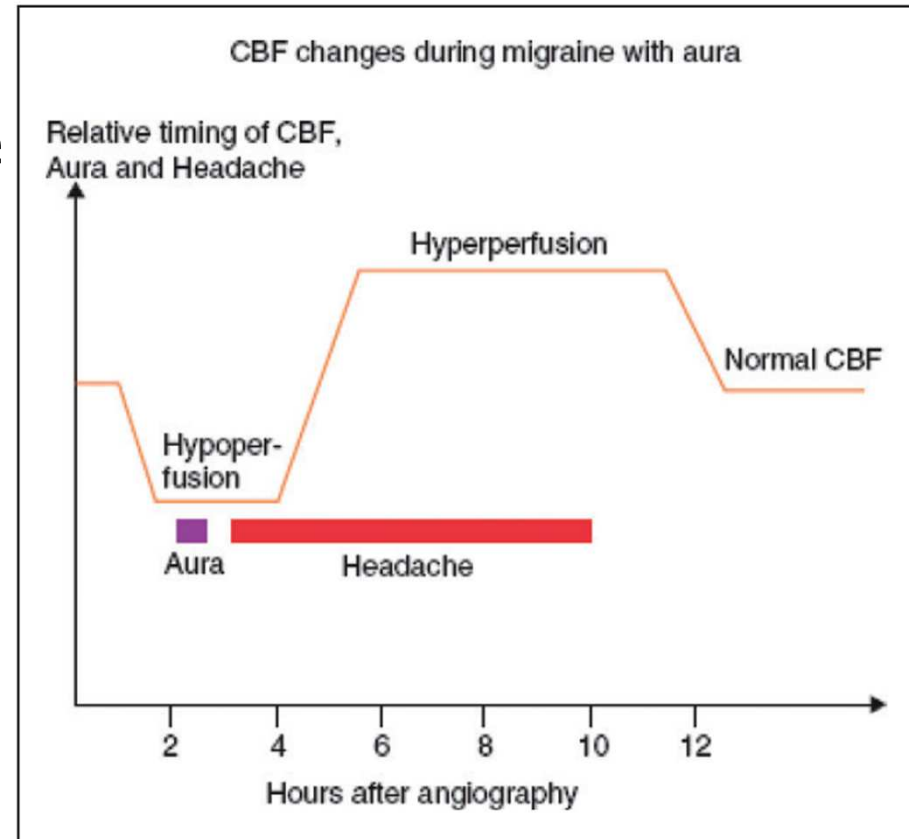
Olegemia and CSD

- ▶ Vascular theory lead to studies of reduced cerebral blood flow (rCBF)
 - 6 examined during aura and 3 into the headache stage
 - All developed rCBF in aura stage.
- ▶ CSD was related to hyperemia then.



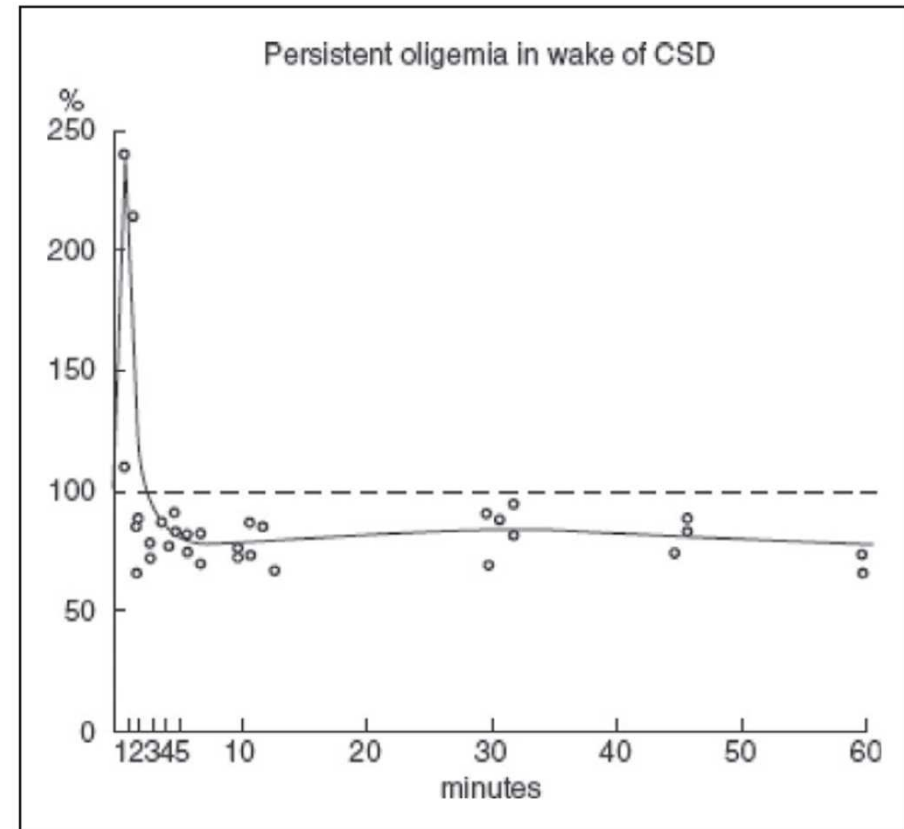
~Olesen et al. 1981

- ▶ Later techniques (SPECT)
 - Hyperemia in headache stage.
 - Linked the relation of CSD.



Olegemia and CSD

- ▶ 1982 Lauritzen et al
 - Hyperemia lasted several minutes after CSD, but was followed by 15–28% of oligemia for >1 hour.
- ▶ First documented oligemia after CSD.



Similarity

- ▶ Reduced rCBF and oligemia after CSD.
 - Similar spreading speed. (2–3 mm/min)
 - Similar reactivity in CO₂ responses.
 - Similarly preserved auto-regulation in BP
- ▶ Also, CSD provoked plasma protein leakage within the dura mater.
 - A “bridging” mechanism between neural activities and blood flow.



Other characters of CSD

- ▶ A common therapeutic target for migraine
 - Topiramate, Valproate, Propranolol, Amitriptyline, Methysergide all decrease CSD frequency by 40–80%.
 - Chronic administration is effective while acute one isn't.
- ▶ Similar activities (depressed EEG activities) were observed in brain infarction and intracranial hemorrhage.



Neurogenic inflammation

- ▶ 1979. – Substance P is proposed to be released by trigeminal nerve and cause vasodilatation in migraine and cluster headache.
- ▶ Substance P is located in pial and subarachnoid vessels in many other species.
- ▶ Substance P may be released during neuronal afferent process and cause sterile inflammation of neighboring vessels.
- ▶ It explained the ipsilateral character of migraine and other vascular headache.



Extension of the model

- ▶ Electric stimulations of trigeminal nerve increased protein tracer in ipsilateral dura.
- ▶ Ergotamine, Dihydroergotamine, Ergot alkaloid all inhibit extravasation.
- ▶ All acute anti-migraine medications have proven to inhibit neurogenic protein extravasation(NPE). But drugs inhibiting NPE don't always cure headache.



Thanks for your attention

