Cortical Spreading Depression (CSD)

**Electrophysiology:**
- Originally described by Leão (1944)
- Intense and steady depolarization of neuronal and glial membranes with total loss of membrane resistance
- Cessation of spontaneous or evoked synaptic activity after a brief initial excitation
- Massive Ca\(^{2+}\) and Na\(^{+}\) influx
- Massive K\(^{+}\) efflux causing \([K^{+}]_e > 50\) mM, which is a strong depolarizing stimulus essential for the spread of depolarization
- Large unregulated release of glutamate facilitates the spread.
- Evoked by simultaneous depolarization of a critical minimum volume of tissue, such as by trauma, ischemia, or application of excitatory amino acids or high \([K^{+}]_e\)
- Spreads into contiguous areas of cortex at a rate of 2-5 mm/min irrespective of functional divisions or arterial territories

**Impact on cerebral blood flow (CBF) and vascular physiology:**
- Biphasic/triphasic species-dependent CBF changes
- In most species, an initial, small and brief reduction in CBF (<1 min) is followed by a profound hyperemia (200% of baseline for few min), and a longer lasting oligemia (60-90% of baseline, for up to an hour)
- Alters second messenger cascades, immediate early genes, growth factors, neurotransmitter and neuromodulator systems, inflammatory mediators (interleukin-1\(\beta\) or tumor necrosis factor-\(\alpha\)) in vascular wall structures

Despite the multitude of parenchymal as well as vascular molecular effects, CSD is not injurious in normal brain.

**CSD and Migraine: the evidence**

**Migraine aura:**
- Occurs in about 20% of migraine patients
- Classical visual disturbances such as scintillating lines and scotomas, less commonly sensorimotor dysfunction
- Lasts \(\geq 20\) min, precedes the headache by 20-30 min
- Positive aura symptoms often transform into negative phenomena (scintillating wave front transforming into scotoma; paresthesias followed by diminished sensation), resembling the initial excitation followed by depression of all electrical activity during CSD
- Symptoms spread (scintillating scotomas expand, sensorimotor symptoms march) suggesting a propagating cortical electrophysiological phenomenon akin to CSD
- The speed of spread based on functional topography of cortex is \(\sim 3\) mm/min, consistent with experimental CSD

**Neuroimaging provides indirect evidence linking CSD and migraine:**
• Focal increase in fMRI BOLD signal spreading into occipital cortex at 3.5 mm/min retinotopically congruent with patient’s visual experience, followed by a decrease, suggesting an initial increase and then a decrease in cerebral blood flow

**Potential mechanisms triggering CSD in seemingly normal cortex in migraineurs:**

• CSD is evoked by simultaneous depolarization of a critical volume of tissue increasing $[K^+]_e$ above a certain threshold exceeding the ability of buffering systems
• Increased $[K^+]_e$ depolarizes adjacent tissue to initiate the self-sustaining spread
• Do migraineurs have increased cortical excitability & CSD susceptibility?
  ✓ Visual cortex in migraineurs exhibits reduced threshold to evoke phosphenes by transcranial magnetic stimulation
  ✓ Patients with episodic migraine or probable chronic migraine show increased excitability correlated with the frequency of migraine attacks
  ✓ There is a link between migraine and epilepsy
  ✓ Migraine prophylactic agents (many are antiepileptics) decrease CSD susceptibility after chronic, but not acute, treatment

**Ca$^{2+}$ channels and the link between CSD and migraine**

**Ca$^{2+}$ voltage-gated Ca$^{2+}$ channels (P/Q-type) are important modulators of SD:**

• Pharmacological inhibitors of Ca$^{2+}$-2.1 suppress CSD susceptibility
• Tottering and leaner loss-of-function mutations in Ca$^{2+}$-2.1 channels suppress CSD susceptibility

**Familial Hemiplegic Migraine (FHM):**

• Autosomal dominant
• Episodes of prolonged and severe but reversible unilateral neurological deficits (motor, visual, somatosensory and aphasic) lasting minutes to hours accompanying migraine headache
• Also attacks of migraine without aura
• FHM mutations:
  ✓ CACNA1A gene (the pore-forming and voltage sensing $\alpha_{1A}$-subunit of Ca$^{2+}$-2.1 channel, gain-of-function)
  ✓ ATP1A2 gene (Na$^+$/K$^+$ pump $\alpha_2$ subunit, loss-of-function)
  ✓ SCN1A (critical protein for fast inactivation of the neuronal voltage-gated sodium channel, gain-of-function).
• FHM1 (Ca$^{2+}$-2.1 Ca$^{2+}$ channel):
  ✓ Predominantly presynaptic: major role in excitatory neurotransmitter release
  ✓ 18 mutations identified so far shift channel opening towards more negative membrane potentials and delay channel inactivation
  ✓ Channels open with smaller depolarization and stay open longer, more Ca$^{2+}$ enters presynaptic terminals
  ✓ Higher presynaptic Ca$^{2+}$-influx augments acetylcholine release in neuromuscular junction, and depolarization-induced glutamate release in cultured neurons

**FHM1 knockin mouse models:**
**FHM1 mouse models exhibit increased CSD susceptibility and clinical hallmarks of FHM:**

- Knockin mice expressing human R192Q or S218L missense mutations
- Phenotype in cultured neurons:
  - Single channel gain of function: S218L >> R192Q
  - More negative opening voltages and a greater increase in the single channel opening probability in S218L mutation
- Phenotype in patients:
  - R192Q: pure FHM
  - S218L: severe FHM phenotype plus excessive and often fatal cerebral edema
- Phenotype in knockin mice
  - Reduced electrical stimulation threshold for CSD
  - Increased CSD frequency in response to topical KCl
  - Increased CSD propagation speed
  - Enhanced subcortical SD propagation
  - More severe and prolonged neurological deficits after SD resembling the clinical phenotype

**FHM1 mice shed light on genetic and hormonal modulation of migraine susceptibility:**

- Enhanced SD susceptibility and speed, subcortical propagation, and subsequent neurological deficits are modulated by:
  - The strength of single channel gain-of-function caused by allelic mutations (S218L > R192Q)
  - Allele-dosage (phenotype severity homozygous > heterozygous knockin)
  - Gonadal hormones (female knockin > male knockin)
- Therefore, factors modulating susceptibility to migraine also modulate SD susceptibility
- Gonadal hormones modulate genetically-enhanced SD susceptibility (i.e., in knockin mice only)
- Lack of gonadal hormone modulation of SD in wild type mice argues against a simple additive effect between genetic and hormonal factors
- Hormones, not sex chromosome-related differences, were implicated as gender differences were abrogated by gonadectomy or cessation of estrus cycling in senescent mice

Data from FHM1 knockin mouse models of migraine strengthen the link between SD and migraine aura, and underscore the complex synergistic interactions between genetic and hormonal factors determining migraine susceptibility.