Supplementary Appendix

This appendix has been provided by the author to give readers additional information about his work.

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Supplementary Appendix

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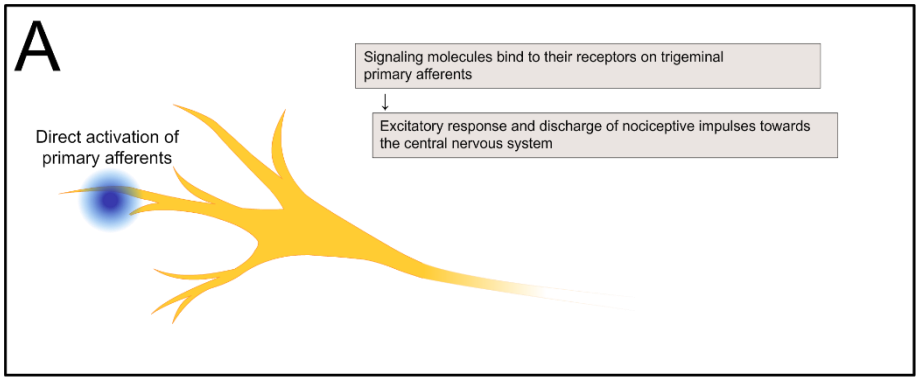
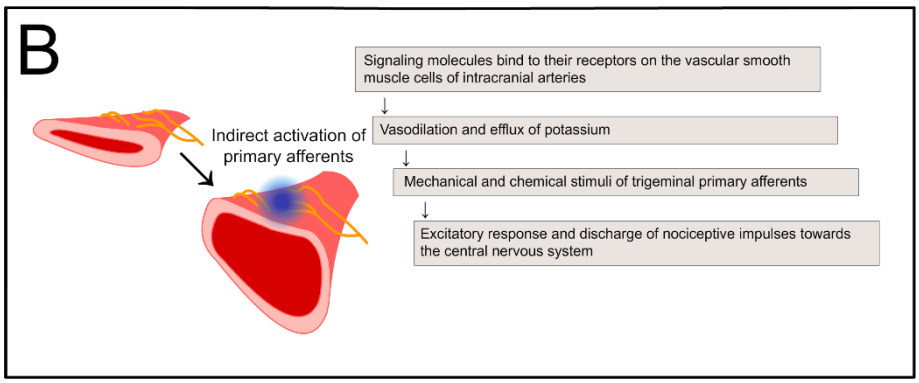
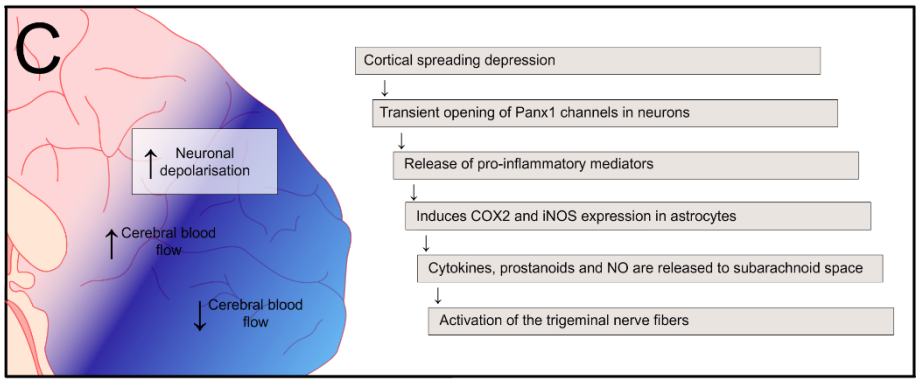
Figure S1: Possible Sites of Origin of Migraine Attacks.



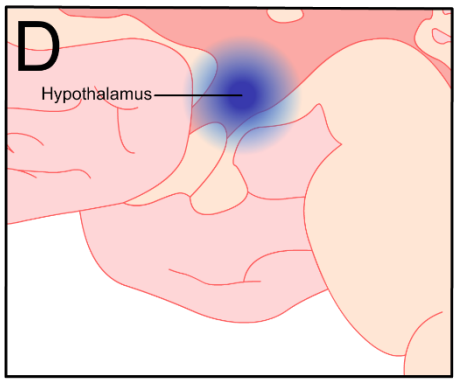
Direct activation and sensitization of trigeminal primary afferents



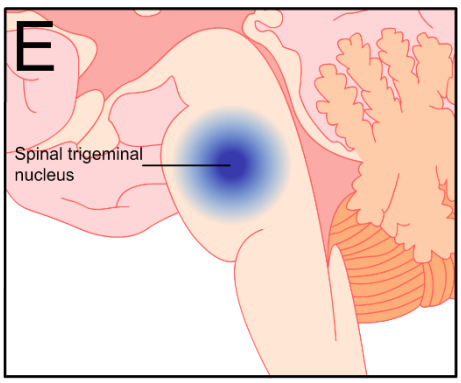
Indirect activation and sensitization of trigeminal primary afferents



Cortical spreading depression



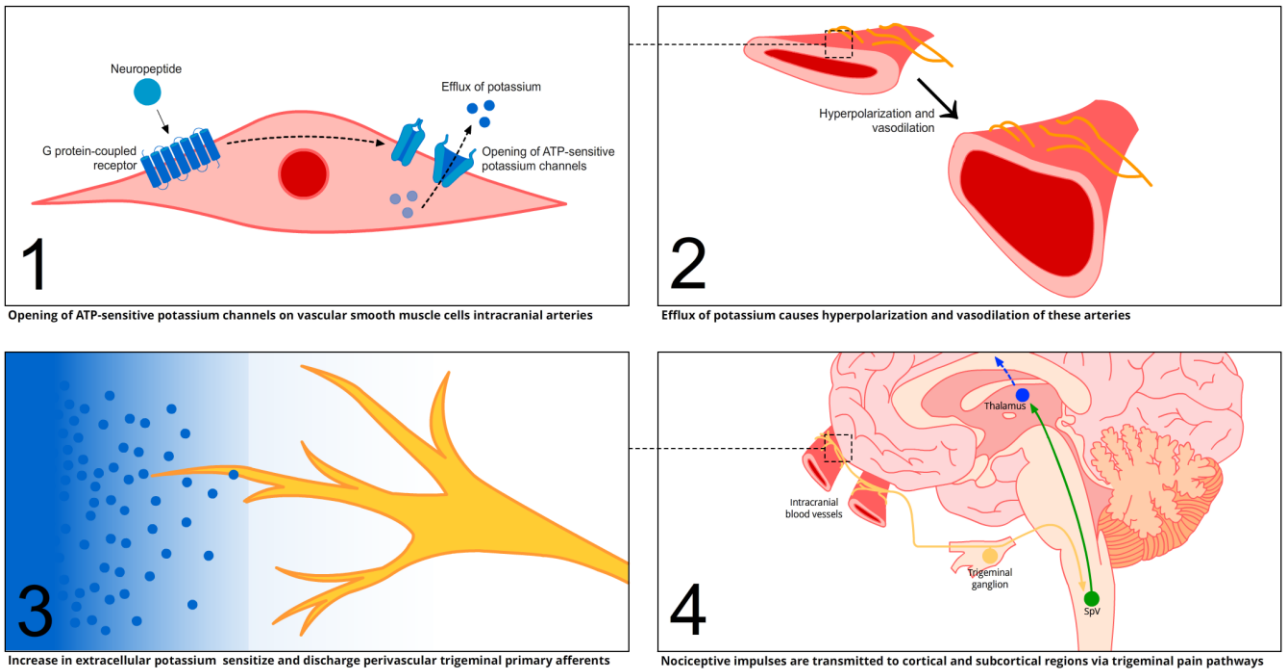
Hypothalamic activation



Brainstem activation

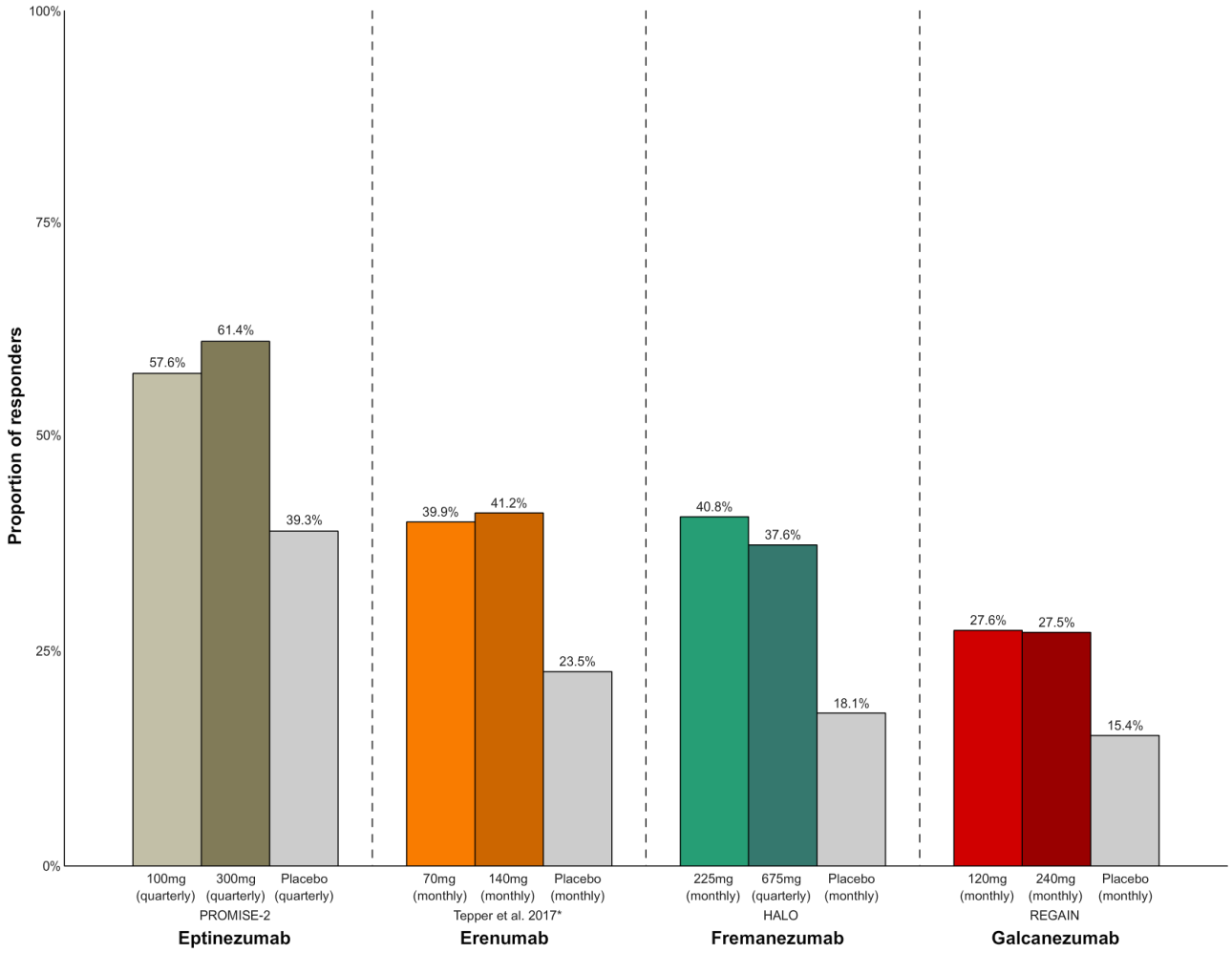
Peripheral Origin. A peripheral origin of migraine attacks is believed to involve direct or indirect activation and sensitization of first order trigeminovascular neurons (**A**-**B**).[1-10] Indirect effects are likely mediated by dilation of intracranial arteries and corresponding efflux of potassium, which yields mechanical and chemical stimulation that activates and sensitizes the perivascular trigeminal nerve endings (**B**).[1-10] **Central Origin**. A central origin of migraine attacks is hypothesized to involve cortical spreading depression (**C**), hypothalamic activation (**D**), and/or brain stem activation (**E**). CSD is widely regarded as the physiological substrate underlying migraine aura.[11,12] CSD is characterized by a self-propagating wave of extensive depolarization across the cerebral cortex which disrupts ionic gradients and is followed by cerebral hypoperfusion.[11] Preclinical data have found that CSD activates peripheral and central trigeminovascular neurons,[13,14] which may be a result of CSD-mediated opening of neuronal Pannexin1 channels.[15] Activation of the hypothalamus and brain stem is believed to be of importance for migraine pathogenesis by proponents of a central origin of migraine attacks.[16,17]

Figure S2: A Proposed Trigeminovascular Ion Channel Hypothesis of Migraine Pathogenesis.



A plausible explanation of migraine pathogenesis suggests the following sequence of events within the framework of the trigeminovascular system: 1) various signaling molecules (e.g. nitric oxide, calcitonin gene-related peptide, pituitary adenylate cyclase-activating peptide) initiate a cascade of intracellular processes that result in opening of ATP-sensitive potassium channels on vascular smooth muscle cells within the intracranial arteries,[4-10,18,19] 2) efflux of potassium causes hyperpolarization and vasodilation of these arteries,[20-22] 3) increase in extracellular potassium provides the requisite electrochemical gradient to sensitize and discharge perivascular trigeminal primary afferents in the walls of intracranial arteries, 4) nociceptive impulses are transmitted to and processed by cortical and subcortical regions via ascending trigeminal pain pathways, ultimately resulting in the perception of migraine pain.[1] Of note, this line of reasoning emphasizes that elevations in extracellular levels of positively charged ions, not potassium exclusively, may be the principal drivers needed to activate and sensitize trigeminal primary afferents in the walls of intracranial arteries.

Figure S3: Responder Rates in Phase III Randomized Clinical Trials of Monoclonal Antibodies against Calcitonin Gene-Related Peptide or Its Receptor for Prevention of Chronic Migraine.



Responder rates are defined as proportion of patients with ≥50% reduction in number of monthly migraine days from baseline to the time of assessment. Of note, REGAIN reported mean proportion of patients with ≥50% reduction in number of monthly migraine days per 30-day assessment period.[23] *Reported erenumab data is from a phase II trial for prevention of chronic migraine, as phase III trial data is not available.[24] PROMISE-2[25]: ≥50% reduction in mean number of monthly migraine days from baseline to week 1 through week 12. Tepper et al.[24]: ≥50% reduction in monthly migraine days from baseline to week 9 through week 12. HALO[26]: ≥50% reduction in mean number of monthly migraine days from baseline to week 1 through week 12. REGAIN[23]: Mean proportion of patients with ≥50% reduction in number of monthly migraine days per 30-day period in month 1 through month 3 compared to baseline.

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