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ENHANCED THALAMOCORTICAL SYNAPTIC TRANSMISSION AND DYSREGULATION OF THE EXCITATORY-INHIBITORY BALANCE AT THE THALAMOCORTICAL FEED-FORWARD INHIBITORY MICROCIRCUIT IN A MOUSE MODEL OF FAMILIAL HEMIPLEGIC MIGRAINE

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Familial hemiplegic migraine (FHM) is a rare monogenic form of migraine with aura, characterized by attacks of severe unilateral headache and aura symptoms (including visual, somatosensory, language disturbances and hemiparesis) which may be long-lasting, as well as by interictal alterations in sensory physiology. The neurobiological mechanisms underlying the onset of migraine attacks and the interictal dysfunction in multisensory information processing in FHM and other migraines remain unknown (Brennan-Pietrobon 2018). FHM type 1 (FHM1) is caused by gain-of-function mutations in the CaV2.1 channel, which plays a dominant role in neurotransmitter release at many brain synapses (Pietrobon, 2013). We have previously shown that excitatory synaptic transmission at several intracortical pyramidal cell synapses is enhanced in knock-in mice carrying FHM1 mutations (FHM1 mice); in striking contrast, inhibitory synaptic transmission at fast-spiking (FS) and other interneuron synapses is unaltered (Tottene et al, 2009; Vecchia et al, 2015). These findings suggested the hypothesis that dysregulation of the excitatory-inhibitory (E/I) balance in specific circuits in the cerebral cortex (and other brain structures) is a key pathogenic mechanism in FHM (Vecchia-Pietrobon, 2012). Here, to test this hypothesis, we investigated thalamocortical (TC) synaptic transmission and the E/I balance set by the TC feed-forward inhibitory (FFI) microcircuit in FHM1 mice. This microcircuit is very interesting to study in the context of migraine because it is critical in gating information flow to the cortex (including trigeminovascular nociceptive information) and in coordinating excitation and inhibition in the initial phases of cortical sensory processing preventing over-excitation (Tremblay et al, 2016). We show that TC synaptic transmission in somatosensory cortex is enhanced in FHM1 mice. Due to similar gain-of-function of TC excitation of layer 4 excitatory and fast-spiking (FS) inhibitory neurons elicited by single thalamic stimulations, neither the E/I balance nor the integration time window set by the TC FFI microcircuit were altered in FHM1 mice. However, during repetitive thalamic stimulation, the typical shift of the E/I balance towards excitation and the widening of the integration time window were both smaller in FHM1 compared to wild-type mice, revealing a dysregulation of the E/I balance, whereby the balance is relatively skewed towards inhibition. This is due to an unexpected differential effect of the FHM1 mutation on short-term synaptic plasticity at TC synapses on cortical excitatory and FS inhibitory neurons. Our findings point to enhanced transmission of sensory, including trigeminovascular nociceptive, signals from thalamic nuclei to cortex and TC E/I imbalance as mechanisms that may contribute to the headache and to increased sensory gain and sensory processing dysfunctions in FHM.

Aumentata trasmissione sinaptica talamo-corticale e disregolazione del bilancio eccitazione-inibizione nel microcircuito talamo-corticale in un modello animale di emicrania emiplegica familiare.
L'obiettivo generale del nostro progetto di ricerca e' quello di capire i meccanismi che causano l'emicrania emiplegica familiare (FHM), una forma rara di emicrania con aura, caratterizzata da attacchi gravi di mal di testa unilaterale e sintomi dell'aura (includenti disturbi visivi, sensitivi, di linguaggio e emiparesi) che possono essere molto prolungati. I meccanismi neurobiologici che causano gli attacchi di emicrania e le disfunzioni interictali nel processamento degli stimoli sensoriali nella FHM e altre emicranie rimangono sconosciuti. Noi studiamo tali meccanismi utilizzando topi

transgenici “knock-in” portanti mutazioni umane come modello animale (topi FHM). La FHM di tipo 1 (FHM1) è causata da mutazioni determinanti guadagno di funzione in un canale del calcio che è essenziale per il controllo del rilascio di neurotrasmettitore alle sinapsi cerebrali. Abbiamo precedentemente dimostrato che nei topi FHM1 la trasmissione sinaptica alle sinapsi eccitatorie intracorticali è aumentata, mentre la trasmissione alle sinapsi inibitorie è inalterata. Questi risultati hanno suggerito l’ipotesi che l’alterata regolazione del bilancio eccitazione-inibizione in specifici circuiti della corteccia cerebrale (e altre aree del cervello) sia un meccanismo chiave nella patogenesi della FHM. Per verificare questa ipotesi abbiamo studiato nei topi FHM1 la trasmissione sinaptica talamo-corticale e il bilancio eccitazione-inibizione del microcircuito talamo-corticale, che media inibizione “feedforward” e svolge un ruolo critico nel trasferimento dell’informazione sensoriale (inclusa quella nocicettiva trigemino-vascolare) alla corteccia cerebrale e nel prevenire la sovra-eccitazione. I nostri dati mostrano una aumentata trasmissione sinaptica talamo-corticale e una disregolazione del bilancio eccitazione-inibizione del microcircuito talamo-corticale nei topi FHM1. Queste alterazioni possono contribuire a generare il mal di testa e le disfunzioni nel processamento degli stimoli sensoriali nella FHM.

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