Seminar/Talk

SCN2A in neurodevelopmental disorders

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Host: Peter Jonas

De novo mutations in the gene SCN2A are strongly associated with autism spectrum disorder (ASD) and intellectual disability. The majority of ASD-associated SCN2A mutations are protein truncating variants, resulting in loss-of-function conditions where individuals have only one functional copy of SCN2A instead of the normal two. These conditions are also known as haploinsufficient cases, as the single functional allele cannot compensate for the loss of the truncated allele. SCN2A encodes the protein NaV1.2, a voltage-gated sodium channel that is expressed throughout the brain, including neocortical excitatory neurons. Using a mouse model heterozygous for Scn2a, we have explored how Scn2a haploinsufficiency affects neocortical circuits. We found that NaV1.2 loss resulted in developmentally distinct deficits in neocortical excitatory neurons. Scn2a haploinsufficiency impaired action potential initiation early in development, whereas a deficit in dendritic excitability persistsed throughout life. These excitability deficits were associated with impaired excitatory synapses, even when Scn2a is disrupted late in development. These findings suggest that NaV1.2 function is critical throughout life, raising the possibility that restoring normal NaV1.2 function, even later in development, may result in a therapeutic benefit for individuals with ASD-associated SCN2A mutations. Work ongoing in the lab is exploring if and when rescue of Scn2a must occur to achieve therapeutic benefits.

Thursday, September 19, 2019 11:30am - 12:30pm
Mondi Seminar Room 1, Central Building

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