Synaptic Input Alteration of Neuron Network interacted with functional GABAergic cell type derived from human epileptic iPSCs

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Abstract: Although iPSCs and neuronal differentiation have provided a new method to study genetic epilepsy caused by *SCN1A* mutations, this technology still has some inherent limitationsthathave limited our understanding of obtained data related to epilepsise. In the present project, we reported a work combining the technology of CRISPR Cas9- and TALEN-mediated gene editing with neuronal differentiation of patient iPSCs to make study of epilepsy can be conducted at the level of not only neuronal subtype but also neuronal networks based on the comparison between patient neurons and its isogenic controls. Using this approach, wefor the first time performed patch clamp recording on a Nav1.1-expressing neuronal subtype and monitored postsynaptic activity of both inhibitory and excitatory types in a system composed of GABAergic and glutamatergic neurons. We found the mutation c.A5768G, which led to no current of Nav1.1 in exogenously transfected system, influenced the properties of not only Nav current density, but also Nav activation in patient-derived Nav1.1-expressing GABAergic neurons. And alterations in Nav further influenced the AP firing ability in patient-derived GABAergic neurons and led to a weakened spontaneous inhibitory postsynaptic currents (sIPSCs), as well as the shift of spontaneous postsynaptic input from the inhibition to excitation dominated state in patient-derived neuron network. These results suggested that although the spontaneous excitatory postsynaptic currents (sEPSCs) did not alter obviously, changes in the sIPSCs alone was sufficient to significantly affect the whole condition of spontaneous postsynaptic currents and increase the risk of occurrence of epileptic seizure.Our findingsfill the gap of our knowledge regarding the relationship between *SCN1A*mutation effect recorded on exogenously transfected cells and on Nav1.1-expressing neurons, and reveals the physiologicalbasis underlying epileptogenesis that is caused by *SCN1A* loss-of-function mutation.These findings providepractical instructions for clinical drug administration.