This Week in The Journal

Amyloid Production Slows APP Transport after Stretch Injury

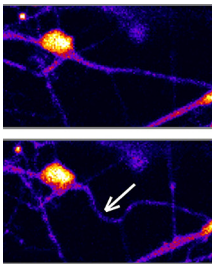
Rodrigo S. Chaves, My Tran, Andrew R. Holder, Alexandra M. Balcer, Andrea M. Dickey, et al.

(see pages 10034–10053)

A blow to the head can deform brain tissue, stretching axons and damaging cytoskeletons. The resulting disruption of microtubule-based transport leads to the accumulation of proteins in axonal swellings. This, along with associated inflammation, mitochondrial dysfunction, and oxidative stress, can cause cognitive deficits and promote axon degeneration. Although cognitive function often returns to normal within days, it sometimes persists for months. Moreover, traumatic brain injury (TBI) may increase the risk of developing a neurodegenerative disease. Much remains to be learned about the molecular mechanisms linking acute trauma to neurodegeneration, however. One challenge is to disentangle the effects of different components of the initial injury, such as axon stretching and glial activation. Chaves et al. did this using a new microfluidics device to rapidly stretch axons of cultured neurons.

Neurons derived from a human induced pluripotent stem cell line were grown on a film that could be rapidly, but mildly, stretched by applying a vacuum. Axons growing parallel to the direction of stretch were themselves stretched by ~12%; when the vacuum force was released, the axons exhibited a wavy appearance indicative of relaxed tension. Importantly, however, axons did not break, microtubules appeared to remain intact, and axons returned to their original morphology within a few minutes. Other signs of severe trauma, including axonal swellings, disruption of neurofilaments, calcium elevation, and activation of stress signaling pathways, were also absent. Nevertheless, mild stretch reproduced some pathological features of mild TBI. Specifically, it slowed the transport of amyloid precursor protein (APP), leading to accumulation of this protein in axons. It also increased levels of β-amyloid peptide ($A\beta$), a cleavage product of APP, in the culture medium. Remarkably, inhibiting secretases that cleave APP to form $A\beta$ not only reduced $A\beta$ secretion, but also rescued axonal transport and accumulation of APP.

Accumulation of APP and $A\beta$ is often detected in models of TBI, leading to the proposal that APP accumulation increases amyloidogenic cleavage to form $A\beta$, which in turn promotes degeneration. But Chaves et al. suggest a different causality: amyloidogenic cleavage impairs axonal transport, causing APP to accumulate. Future work will need to determine how stretch triggers amyloidogenic processing of APP and whether this contributes to cognitive impairment and neurodegeneration.



Stretching neurons caused axons to become wavy (arrow), but did not increase calcium levels (pseudocolored violet, low; yellow, high). See Chaves et al. for details.

SCN2A Variant L1342P Increases Excitability of Human Neurons

Zhefu Que, Maria I. Olivero-Acosta, Jingliang Zhang, Muriel Eaton, Anke M. Tukker, et al.

(see pages 10194–10208)

Epileptic seizures result from excessive, synchronous spiking in large populations of forebrain excitatory neurons. This abnormal activity can stem from hyperexcitability of excitatory neurons and/or insufficient inhibition of these neurons by GABAergic interneurons, both of which can result from mutations in voltage-sensitive sodium or potassium channels. Notably, the effects of these mutations are sometimes counterintuitive. For example, one would predict that seizure-linked variants of *SCN2A*, which encodes sodium channels expressed predominantly in excitatory neurons, enhance channel function and thus increase neuronal activity. But some seizure-linked variants of *SCN2A* reduce channel function. Consequently, antiseizure medications that block these channels may unintentionally increase seizure frequency. Determining how specific seizure-linked mutations affect the activity of human neurons is therefore essential. Que, Olivero-Acosta, et al. did this for *SCN2A* variant L1342P by introducing the mutation into cortical neurons derived from human induced pluripotent stem cells (hiPSCs).

When expressed in HEK cells, L1342P *SCN2A* had both current-enhancing and current-suppressing effects compared to typical *SCN2A*. Specifically, L1342P caused hyperpolarizing shifts in both the activation and fast-inactivation curves of the encoded $Na_V1.2$ channels. These effects appeared to cancel each other out, because there was no significant difference in the window current—the inward current during partial activation and partial inactivation—between L1342P channels and controls. When L1342P was introduced into *SCN2A* in hiPSC-derived neurons, however, the hyperpolarizing shift in the activation curve was accompanied by an increase in sodium current density, a lower spike threshold, and a reduction in the amount of current needed to induce spiking. Consequently, the overall activity of the neuronal population was higher in cultures of L1342P-expressing neurons than in controls. Furthermore, the frequency and intensity of bursting activity were greater and there was more synchronous spiking in L1342P cultures than in controls. Notably, a $Na_V1.2$-selective antagonist reduced spike frequency and synchrony in L1342P–expressing cultures more effectively than a less selective sodium channel blocker commonly used to treat seizures.

These results indicate that the L1342P variant of *SCN2A* causes hyperexcitability of cortical excitatory neurons and thus increases burst generation and synchronous spiking. This explains why the variant is linked to seizure susceptibility. Selective antagonists of $Na_V1.2$ may reduce seizures in people with this variant.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.41.49.2021