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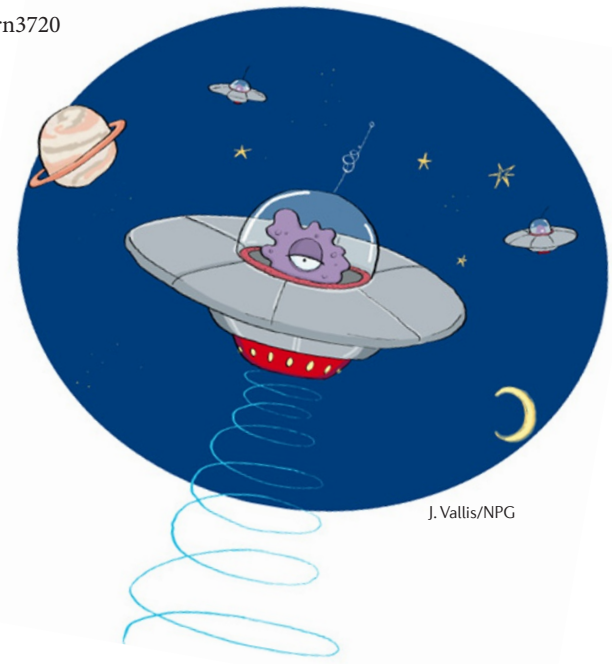

J. Vallis/NPG

SYNAPTIC TRANSMISSION

Invasion of the astrocytes!

The gap junction protein connexin 30 (CX30) is expressed on astrocytes, but little is known about its role in astrocyte function. Rouach and colleagues now show that CX30 regulates synaptic transmission by controlling the extension of astrocytic processes into the synaptic cleft.

The authors used mice lacking *Cx30* (*Cx30*$^{-/-}$ mice) to investigate the role of this connexin in synaptic transmission, focusing on Schaffer collateral–CA1 synapses in the hippocampus. Excitatory synaptic transmission, but not inhibitory transmission, was reduced in hippocampal slices from *Cx30*$^{-/-}$ mice compared with control slices, and this was due to a decrease in synaptic glutamate levels. This reduction in excitatory transmission had functional consequences: *Cx30*$^{-/-}$ mice showed reduced hippocampal long-term potentiation (LTP) induced by brief tetanic stimulation and impaired contextual fear conditioning compared with control mice.

Astrocytes express glutamate transporters (GLTs), which clear glutamate from the synapse. The authors therefore hypothesized that increased glutamate clearance underlies the change in glutamate transmission in *Cx30*$^{-/-}$ slices. Indeed, Schaffer collateral stimulation induced a greater amplitude of GLT currents in *Cx30*$^{-/-}$ slices than in wild-type slices (as well as smaller neuronal responses), which is suggestive of increased glutamate transport in *Cx30*$^{-/-}$ slices. Reducing the amplitude of GLT currents, through pharmacological inhibition of GLT1, normalized synaptic glutamate levels and neuronal responses in *Cx30*$^{-/-}$ slices and restored LTP in *Cx30*$^{-/-}$ mice. Thus, an absence of CX30 is associated with increased glutamate clearance and, consequently, reduced glutamate transmission.

The authors established that the increase in glutamate clearance was not mediated by alterations in astrocytic GLT expression or the channel function (gap junctions or hemichannels) of CX30. However, connexins also have non-channel functions, which can be mediated by their intracellular carboxy-terminal domain. Re-expression of full-length CX30 but not re-expression of a C-terminally truncated form of CX30 (CX30ΔCter) in CA1 astrocytes of *Cx30*$^{-/-}$ mice restored glutamate transmission, suggesting that CX30 regulates glutamate clearance through a non-channel function.

What might this function be? Glutamate clearance levels are partially determined by the extent to which glial cells cover neurons, so the authors assessed whether CX30 regulates astrocyte morphology. Electron microscopy revealed morphological changes in astrocytes of *Cx30*$^{-/-}$ mice that suggested a greater area of neurons was covered by astrocytic processes in these animals. These changes disappeared when full-length CX30 was re-expressed in *Cx30*$^{-/-}$ mice but not when CX30ΔCter was re-expressed, indicating that the regulation of astrocyte morphology is dependent on the C-terminal domain of CX30. The authors further showed that CX30 also suppressed cell migration and cell adhesion to the extracellular matrix.

Detailed analysis revealed that *Cx30*$^{-/-}$ mice had a fivefold increase in the number of astrocytic processes in close proximity to postsynaptic densities as well as a higher number of synaptic clefts that were contacted by astrocytes. Moreover, in a computational synapse model, an astroglial process invading a synapse by 150 nm reduced AMPA receptor currents by 50% and doubled GLT currents (compared with a synapse without astroglial invasion), suggesting that extension of astroglial processes into synapses indeed reduces excitatory transmission.

This study has shown that astroglial CX30 controls the efficacy of glutamate clearance, and thereby glutamate transmission, through a non-channel role — namely, by regulating astroglial invasion of synapses.

Leonie Welberg

> “CX30 regulates glutamate clearance through a non-channel function”

ORIGINAL RESEARCH PAPER Pannasch, U. *et al.* Connexin 30 sets synaptic strength by controlling astroglial synapse invasion. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3662 (2014)

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