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NEURON–GLIA INTERACTIONS

Parting the waves

Glia are no longer regarded as mere supportive bystanders to the activities of neurons, but much remains to be learnt about the extent and mechanisms of their involvement in different neurological processes. New findings from Robitaille and colleagues indicate a subtle role for glia as both decoders and modulators of synaptic activity.

Using the mouse neuromuscular junction (NMJ) as a general synaptic model, the authors first studied the effects of two physiologically relevant patterns of motor neuron stimulation, one bursting and one continuous. The former induced postsynaptic depression, whereas the latter induced postsynaptic potentiation. More importantly, fluorescent imaging ascertained that the Ca^{2+} responses in the perisynaptic Schwann cells (PSCs) — the glia of the NMJ — also differed: the bursting stimulation provoked several small, oscillating Ca^{2+} responses, whereas the continuous stimulation provoked just one or two responses that were larger and more sustained. Ca^{2+} chelation in the PSCs prior to stimulation reversed the resultant synaptic plasticity, whereas light-activated uncaging of Ca^{2+} in the PSCs that mimicked the two Ca^{2+} responses reproduced the pattern of plasticity observed with direct motor stimulation. Thus, the PSCs responded differently to different types of motor neuron activity, and the nature of the response was an important determinant of the resultant postsynaptic plasticity.

Next, the authors sought to identify the receptors through which the PSCs exerted their effects. An ectonucleotidase inhibitor that prevents the breakdown of ATP reversed the effect of an oscillatory release of caged Ca^{2+} on plasticity and blocked the effect of a more sustained Ca^{2+} release, indicating that the mechanism is purinergic. Indeed, application of an A_1 adenosine receptor antagonist prior to oscillatory Ca^{2+} uncaging resulted in postsynaptic potentiation rather than postsynaptic depression, and application of an A_2 receptor antagonist prior to sustained Ca^{2+} uncaging blocked potentiation. Follow-up experiments using A_1- and A_2-receptor-knockout mice or adenosine receptor agonists supported these findings, and similar results were also obtained for direct motor stimulation of the NMJs.

This study therefore shows that glia can discriminate patterns of synaptic activity and thereby differentially modulate plasticity, and indicates that their effects are probably dependent on A_1 and A_2 adenosine receptors. This could help to guide treatments for conditions in which plasticity mechanisms are disrupted, such as some muscular diseases and certain forms of addiction.

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ORIGINAL RESEARCH PAPER Todd, K. J., Darabid, H. & Robitaille, R. Perisynaptic glia discriminate patterns of motor nerve activity and influence plasticity at the neuromuscular junction. *J. Neurosci.* **30**, 11870–11882 (2010)