The glutamate receptor interacting protein Shisa-9 alters hippocampal neuronal network synchronization

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Background:
The function of neuronal networks in the brain and the synchronization of neuronal activity rely on fast synaptic transmission via glutamate receptors, in particular, AMPA receptors. The properties of AMPARs are modulated by protein-protein interactions in the postsynaptic terminal. How these interactions affect synchronization of the neuronal network is unknown. In this study, we assessed how the AMPAR-interacting protein Shisa-9 affects hippocampal oscillations via its EVTV protein-interaction domain.

Methods:
Using multielectrode arrays, extracellular field potentials were measured at 30º±0.5ºC in 400-µm thick acute hippocampal slices that were isolated from 2-week-old mice. Oscillations were chemically induced by the addition of either the muscarinic cholinergic agonist carbachol (25 µM) or the metabotropic glutamate receptor agonist DHPG (10 µM). Prior to recording, the brain slices were incubated for 1 hour with a peptide containing the intracellular segment of the Shisa-9 protein either containing the interacting EVTV site (Shisa 9+evtv) to disrupt endogenous interactions between Shisa-9 and other postsynaptic proteins or with the EVTV site removed (Shisa 9-evtv).

Results:
Shisa 9+evtv treatment, which interfered with protein-protein interactions, decreased the frequency of cholinergic-induced oscillations from 20.0±1.6 to 18.7±1.7 Hz (n=10, $p< 0.05$). The inactive form (Shisa 9-evtv) was without effect. With respect to DHPG-induced oscillations, Shisa 9+evtv increased the amplitude from 0.4±0.2 to 1.3±1.1 $\mu V^2/Hz$ and decreased the width of the power spectral density from 6.8±0.9 to 4.2±1.6 Hz (n=9, $p< 0.001$) but did not affect oscillation frequency. The Shisa 9-evtv peptide was without effect on DHPG-induced oscillations.

Conclusions:
These results demonstrate that protein-protein interactions with the AMPAR modulatory peptide Shisa 9+evtv affect neuronal network synchronization as revealed by measuring fast network oscillations. Both cholinergic-induced and glutamatergic-induced oscillations were affected, suggesting that these two principal excitatory synaptic pathways are modulated by AMPAR modulatory proteins.

References:
Engelhardt et al. 2010, Mann et al. 2005, Oren et al. 2006, Palhalmi et al. 2004.