Nature Reviews Neuroscience | AOP, published online 14 October 2015; doi:10.1038/nrn4051

INTERNEURONS

Neuronal tuning

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Classes of parvalbumin-expressing (PV^+) fast-spiking (FS) interneurons can be differentiated according to aspects of their firing patterns, including the time to first spiking when such cells are brought close to their threshold potential. Although some PV^+ FS interneurons fire readily under this condition, others exhibit a notable delay until generating their first spike, and how this difference in timing is regulated has been unclear. Now, however, a study shows that protein levels of the transcription factor ER81 may have a key role in such regulation, and that, strikingly, network activity — through dynamically altering ER81 levels — can tune the delay to spiking in PV^+ FS interneurons in layer 2/3 (L2/3) of the adult mouse cortex.

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The authors previously showed that some neurons derived from the medial ganglionic eminence (MGE), the region from which PV^+ interneurons originate, express ER81. Here, they found ER81-expressing ($ER81^+$) PV^+ interneurons throughout the neocortex of postnatal mice. However, only about 60% of L2/3 PV^+ interneurons expressed detectable levels of ER81.

Given these findings, the authors examined whether ER81 expression is associated with the time to first spiking in PV^+ interneurons. In somatosensory cortex slices, L2/3 $ER81^+PV^+$ FS interneurons exhibited delayed spiking, whereas L2/3 PV^+ FS interneurons in which ER81 could not be detected showed a short latency to firing. Following the knockout of *Er81* in the embryonic MGE, most cortical PV^+ FS interneurons in the postnatal brain showed a reduction in firing latency, and a similar phenotype was observed following the conditional knockout of *Er81* in the adult mouse cortex. These findings suggest that ER81 modulates PV^+ FS interneuron excitability.

How does ER81 regulate the excitability of these cells? Kv1.1-containing potassium channels in the axon initial segment are thought to have a role in delaying spiking near the threshold potential in FS interneurons as part of a gating mechanism for inhibition, so the authors examined whether ER81 regulates Kv1.1 expression. They found that cortical FS interneurons from adult conditional *Er81*-knockout mice had lower levels of Kv1.1 than such cells from control mice. Moreover, through chromatin immunoprecipitation experiments, they showed that ER81 could bind to the promoter region of *Kcna1* (which encodes Kv1.1). Thus, these findings suggest that ER81 controls the delay to spiking near the spiking threshold, at least partly, through regulating Kv1.1 levels.

Interestingly, the authors also found that, irrespective of their ER81 levels, nearly all L2/3 FS interneurons in adult mice had similar levels of *Er81* mRNA. It is known that activity-induced intracellular changes in calcium levels can alter ER81 transcription and activity. The authors therefore examined the effects of pharmacologically manipulating network activity in cortical slices on ER81 levels in L2/3 FS interneurons. Strikingly, increasing network activity decreased the proportion of $ER81^+$ FS interneurons and the mean latency to firing of FS interneurons, whereas decreasing network activity had the opposite effects.

These results reveal that neural activity may dynamically tune the properties of a group of FS interneurons in the adult mouse brain through a transcription-mediated mechanism.

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ORIGINAL RESEARCH PAPER Dehorter, N. *et al.* Tuning of fast-spiking interneuron properties by an activity-dependent transcriptional switch. *Science* **349**, 1216–1220 (2015)