This Week in The Journal

Slow-Wave Sleep Rhythms May Induce LTD

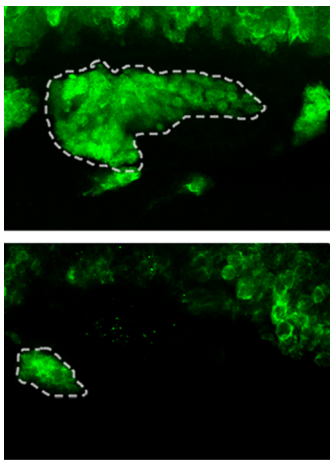
Romain Pigeat, Patrick Chausson, Fanny M. Dreyfus, Nathalie Leresche, and Régis C. Lambert

(see pages 64–73)

As we sleep, our brains progress through stereotypical patterns of activity that define different sleep stages. The functions of these activity patterns are not fully understood, but they might contribute to memory consolidation. Indeed, different types of memory appear to be consolidated during different sleep stages. Evidence suggests, for example, that slow-wave sleep (SWS) is particularly important for consolidating declarative memories, and it has been hypothesized that newly acquired memories are transferred to long-term storage and integrated with older memories during this stage.

SWS is characterized by widespread synchronous oscillations between hyperpolarized down-states and depolarized up-states that include high-frequency firing. The oscillations are generated primarily by reciprocally connected excitatory thalamocortical (TC) neurons and inhibitory neurons in the thalamic reticular nucleus (NRT). High-frequency spiking in NRT neurons causes hyperpolarization of TC neurons, thus de-inactivating low-threshold T-type calcium channels. These channels open when IPSPs subside, resulting in calcium elevation, depolarization, and rebound spiking in TC neurons. Feedback from TC neurons to NRT neurons evokes subsequent rounds of inhibition.

Note that the pattern of activity that occurs in NRT–TC pairs during SWS is similar to that underlying synaptic plasticity throughout the CNS: presynaptic action potentials lead to postsynaptic calcium elevation. In fact, Pigeat et al. report that stimulating NRT fibers in rat brain slices while depolarizing postsynaptic TC neurons from −80 to −30 mV—a protocol meant to mimic the NRT bursts and TC depolarization during SWS—resulted in long-term depression of IPSCs (I-LTD). Buffering calcium or blocking T channels prevented the induction of I-LTD, but blocking other calcium channels types did not, indicating that T channels were necessary and sufficient for I-LTD induction. Blocking metabotropic glutamate receptors blocked I-LTD, suggesting there was a heterosynaptic component (activation of glutamatergic synapses was required to alter GABAergic synapses), but stimulating a subset of GABAergic inputs to a cell produced I-LTD selectively at those synapses, indicating there was also a homosynaptic component. Finally, I-LTD required activation of $GABA_A$ receptors and the Ca^{2+}/calmodulin-dependent phosphatase calcineurin, which has been previously shown to mediate LTD through interactions with $GABA_A$ receptor subunits.



When dominant-negative *Fgfr1* was expressed in developing zebrafish (bottom), SAG area (defined by neuronal marker expression, green) was reduced compared to controls (top) in the neurogenic region (dashed lines) of the otic placode. See the article by Wang et al. for details.

FGF Drives Neurogenic Fate in the Otic Placode

Jialiang Wang, Ying Wu, Feng Zhao, Yuting Wu, Wei Dong, et al.

(see pages 234–244)

During development, peripheral sensory neurons and their associated structures arise from the neural crest and cranial placodes—specialized ectodermal regions that border the neural plate that forms the CNS. The otic placode forms neural (VIIIth ganglion neurons), sensory (hair cells), and nonneural structures of the inner ear, including both auditory and vestibular components. As in all tissues, this development proceeds through a sequential process of fate restriction, proliferation, and differentiation controlled by numerous genes and signaling pathways.

Fibroblast growth factors (FGFs) are required to specify neurogenic fate early in otic development, and they also appear to contribute to specification of some hair cell types. In zebrafish, knocking down Fgf8a or Fgf3 greatly reduces the size of the statoacoustic ganglia (SAG), and knocking down both proteins prevents ear formation altogether. To further elucidate the role of FGF signaling at different stages of otic development, Wang et al. used heat-activated mutants and inhibitors of various signaling pathways.

Expressing a dominant-negative form of the FGF receptor (*Fgfr1*) 10–12 hours post fertilization (hpf) greatly reduced SAG area, whereas overexpressing *Fgf8* at this stage modestly increased SAG area. Importantly, neither manipulation affected overall ear development and neither affected SAG area when applied after 14 hpf, suggesting that FGF signaling selectively affects otic neurogenesis at 10–14 hpf. But applying an FGFR antagonist at 10–14 hpf reduced the number of ultricular hair cells as well as reducing SAG area, confirming that FGF signaling is required to specify at least some hair cell fates.

Interestingly, FGF appeared to affect neurogenesis and hair cell development through different downstream effectors: inhibiting phosphoinositide 3-kinases (PI3Ks) reduced SAG area without affecting hair cell number, whereas disrupting ERK1/2 signaling reduced hair cell numbers without affecting SAG area. Given this divergence, it is somewhat surprising that Atoh1a, a transcription factor involved in hair cell determination, was found to contribute to SAG neurogenesis and to be regulated by FGFR–PI3K signaling. As expected from previous research, the transcription factor Sox9a also contributed to SAG neurogenesis downstream of FGFR–PI3K signaling. By investigating the shared targets of these transcription factors, Wang et al. identified two previously unrecognized contributors to otic neurogenesis: *tlx2* and *eya2*.