processes occur. Although mammalian systems exist at around 37 °C, *Aplysia* typically lives at around 15 °C. Therefore, chemical reactions in the *Aplysia* system may progress at about an order of magnitude slower than the analogous chemical reactions in mammals. This is not a minor consideration in the context of molecules capable of triggering a positively reinforcing chain reaction. Controlling such reactions essentially boils down to keeping their forward rates in check. Indeed, it is possible that phosphorylation-dependent regulation of CPEB in mammals may have evolved to circumvent this problem. Overall, much more work will be required to investigate the generality of the findings in *Aplysia*, although this in no way diminishes their impact.

In summary, the papers by Kandel and colleagues[2,3] propose a novel molecular mechanism for the stabilization of long-term memory. The results presented suggest that we pay as careful attention to mRNA residing at the synapse as we have traditionally paid to genes residing in the nucleus. In a world where prions seem to lurk behind every butcher's counter, it is refreshingly ironic to learn that this class of proteins is involved in something as vital as memory formation. □

1. Roberson, E. D. & Sweatt, J. D. *Learn Mem.* **6,** 381–388 (1999).
2. Si, K., Lindquist, S. & Kandel, E. R. *Cell* **115,** 879–891 (2003).
3. Si, K. *et al. Cell* **115,** 893–904 (2003).
4. Liu, J. & Schwartz, J. H. *Brain Res.* **959,** 68–76 (2003).

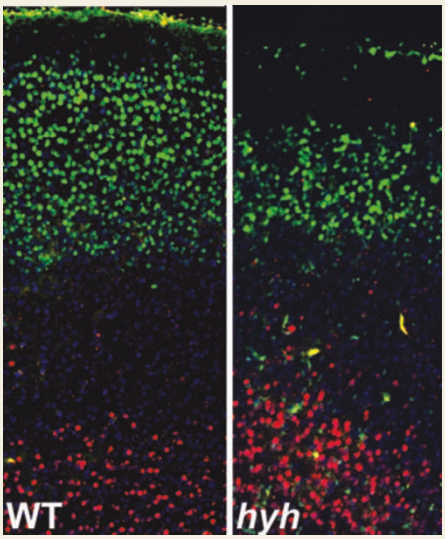
A SNAP decision in neural cell fate

The highly complex, layered structure of the cerebral cortex is fundamental to higher brain functions. However, the underlying genetic factors that regulate its development are poorly understood. In this regard, the *Hyh* mouse represents a potentially useful tool, as it has a remarkably small cerebral cortex. Now, Christopher Walsh and colleagues (*Nature Genet.* DOI: 10.1038/ng1302) characterize the underlying molecular defect of the *hyh* mutant mouse to provide some surprising insights into the development of the cerebral cortex.

The authors first made the surprising observation that *hyh* mice have a mis-sense mutation in the gene encoding α-SNAP, a central component of the SNARE machinery that governs the specificity of vesicle trafficking in a variety of cellular contexts. Levels of α-SNAP protein were markedly reduced in *hyh* mice, resulting from reduced RNA stability rather than inherent instability within the protein. However, the levels of α-SNAP still translated were still important functionally, as an α-SNAP-null allele was lethal.

Next, the authors found that the *αSnap* mutation causes a marked shift in the balance of early- versus late-born neurons — levels of late neurons were decreased, whereas levels of early neurons were increased. The specified programme of early-to-late neuronal differentiation is necessary for the laminar organization of the cortex (see Figure), which is achieved by sequential migration of neurons to each individual layer. Interestingly, loss of late-born neurons seems to be the result of early withdrawal of neural progenitor cells from the cell cycle.

Because asymmetric division of neural precursors is thought to underlie the choice between proliferation and differentiation, the authors hypothesized that α-SNAP would contribute to this decision through the control of polarized vesicular transport. A number of apical markers implicated in neural cell-fate decisions were indeed found to be mis-localized in *hyh* mutant cells. Also, VAMP7, a v-SNARE involved in vesicle transport to apical membranes, was mis-localized from apical membranes in the mutant. Interestingly, partial disruption of α-SNAP in the *hyh* mutant did not seem to affect other more general intracellular transport routes in which α-SNAP is also involved, suggesting that it functions in a dose-dependent manner.



Abnormal cell fates in the cerebral cortex of hyh mutants. Layer-specific markers were used to compare the layer phenotype of wild-type and *hyh* (αSNAP hypomorph) cortexes. Late-born neurons (layers 2–4) are marked in green and early-born neurons (layer 6) are marked in red.

This study is also consistent with earlier observations from the same group (*Nature Genet.* **36,** 69–76 (2004)), showing that disruption of ARF-GEF2 (which blocks transport from the *trans*-Golgi network to the cell surface) also affects the proliferation and migration of neural progenitor cells in the cerebral cortex.

In conclusion, the observations of Walsh and colleagues demonstrate that the defect in cerebral cortex structure is caused by a disruption of α-SNAP-mediated vesicular transport to apical membranes, which is important for controlling the decision of neural progenitor cells to form proliferative versus post-mitotic cells. Now that the identity of the gene mutated in *hyh* mice is known, it should serve as a useful tool to examine wider aspects of neural development.

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