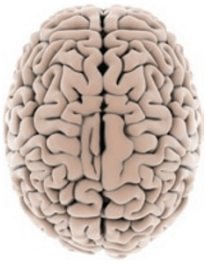
A synaptotoxic form of Aβ



In Alzheimer's disease, there is progressive loss of neurons and synapses in some regions of the brain, resulting in atrophy that can be observed in patients by noninvasive techniques. Histopathological analysis of brain samples from deceased patients show an accumulation of amyloid fibers, composed of the Aβ peptide, forming insoluble deposits that are visible as plaques in between neurons. Whether the Aβ plaques are themselves responsible for Alzheimer's pathology is not clear, and recent lines of evidence suggest otherwise. To identify the pathogenic species of human Aβ, Selkoe and colleagues looked directly at its source: brains from deceased Alzheimer's patients, with brains from healthy individuals as controls. The authors used a traditional biochemical approach to isolate different Aβ forms, as insoluble and soluble fractions with monomers and Aβ oligomers (dimers, trimers and high molecular weight forms). The soluble oligomeric fraction had potent inhibitory effects on synaptic function in mouse hippocampal slices and on a memory test on rats. These toxic effects could be attributed principally to soluble dimers, and this was reproduced using synthetic Aβ dimers, arguing against a contribution from other potential toxic agents in the material from the Alzheimer's brains. Insoluble amyloid fractions containing plaque cores were not synaptotoxic, but toxic dimers were released upon treatment with formic acid, suggesting that *in vivo* the plaques are relatively inert deposits of Aβ, from which dimers and other oligomers might be released and diffuse locally to cause synaptic loss. (*Nat. Med.* advance online publication 22 June 2008, doi:10.1038/nm1782). *IC*

Ribosomal gymnastics

Bacteria contain 61 sense codons, recognized by 45 amino acid–charged tRNAs (aa-tRNAs). These aa-tRNAs have different sequences, lengths and cellular concentrations, possess different post-transcriptional modifications and carry various amino acids. Nevertheless, the ribosome must accommodate every aa-tRNA in the same series of sites. Given their diversity, it has been debated whether aa-tRNAs might affect the kinetics of decoding. To address this issue, Ledoux and Uhlenbeck characterized three decoding substeps using ten representative aa-tRNAs. The first assay examined the equilibrium binding of each aa-tRNA; this step involves changes in the L7/L12 ribosomal proteins, the small ribosomal subunit, and the GTPase activation center. The affinity varied twofold, which was not significantly more than the error of the measurements. The next step, the GTPase activity of EF-Tu, reflects a conformational change in the entire ribosome; again, the variation in the rate of GTP hydrolysis was approximately twofold. Peptide-bond formation, which involves a conformational change in the tRNA's acceptor arm, varied among the aa-tRNAs by 2.5-fold. These experiments were performed with an initiator tRNA in the P site and thus indicate that, at least in the formation of the initial peptide bond, differences in the incoming aa-tRNA do not affect decoding. What is unclear, however, is whether in subsequent elongation steps, when a noninitiator tRNA is present in the P site and interactions that stabilize the Shine-Dalgarno sequence are absent, such uniformity is maintained. As the reactivity of different aa-tRNAs does not affect decoding, the rate of protein synthesis seems to depend just on formation of the active ternary complex, highlighting the substantial flexibility of the macromolecular ribosome structure. (*Mol. Cell* **31**, 114–123, 2008) *AKE*

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Sleepless in *Drosophila*

Sleep is widely conserved and, although its deprivation can have severe effects, the molecular mechanisms underlying its regulation are unclear. Circadian oscillations regulate sleep timing, but a second homeostatic mechanism regulates sleep drive and 'rebound' after sleep deprivation. Sehgal and colleagues have now used *Drosophila melanogaster* genetics to identify a factor specifically involved in homeostatic sleep regulation called Sleepless (SSS). *sss* mutant flies have a reduced number and length of sleep bouts. Furthermore, SSS protein levels in different alleles correlate with phenotypic severity. In the strongest *sss* allele, 9% of flies never sleep, though all show normal activity while awake. Although these flies have other phenotypes, including shaking legs in ether and reduced longevity, their circadian rhythms seem unperturbed. While further work will elucidate the mechanism of its action, SSS seems to be a glycosylphosphatidylinositol (GPI)-anchored protein expressed in the fly brain. The shaking-legs phenotype mentioned above is reminiscent of a previous mutation called *quiver*, and further analysis now indicates that *quiver* is caused by disrupted *sss* splicing. As *quiver* flies are known to have defective Shaker-dependent potassium currents, the authors checked Shaker expression and found it to be diminished in the *sss* mutant. The authors suggest that SSS is a signaling molecule involved in regulating the need for sleep through alterations in Shaker channel activity, a model that awaits further investigation. (*Science* **321**, 372–376, 2008) *SL*

Accessible transport

The transport of sugars, amino acids and neurotransmitters across cell membranes is believed to occur via an alternating-access mechanism, where the transporter protein undergoes conformational changes that alternately expose a central binding cavity to either side of the membrane. With the notable exception of lactose permease, little is known about the structural changes that occur in ATP-independent, carrier-type transporters. The structure of LeuT, a bacterial homolog of the neurotransmitter sodium symporter (NSS) family, is known in a conformation that has its binding cavity near the extracellular space. LeuT is composed of two structural repeats formed by transmembrane helices (TMs) 1–5 and 6–10, which are pseudosymmetrical with respect to the membrane plane. Rudnick, Honig and colleagues have now investigated what the alternate conformation for LeuT, and hence related NSS family members, would be. In the LeuT structure, regions of TMs 1b, 3, 6a and 10 form part of the extracellular vestibule leading toward the substrate binding site. The authors reasoned that, given the intramolecular pseudosymmetry, the cytoplasm-accessible vestibule would be formed by a conformational exchange between repeats and would include regions of TMs 6b, 8, 1a and 5. Cysteine scanning mutagenesis of these regions of the serotonin transporter, a homologous NSS, revealed that these indeed contribute to a solvent-exposed vestibule under conditions that would open the cytoplasmic gate. Modeling studies on LeuT suggest that rocking of a four-helix bundle formed by TMs 1, 2, 6 and 7 would be sufficient to close the extracellular vestibule and open the cytoplasmic one. Although additional studies are needed to flesh out the details, the work here describes a possible permeation pathway for a large and important class of transporters. (*Proc. Natl. Acad. Sci.* published online 22 July 2008, doi:10.1073/pnas.0804659105) *MM*