expansions use relatively long noninterrupted repeats already beyond the expansion threshold. What happens at the initial stages, when the so-called 'long-normal' alleles lose their interruption, converting into expansion-prone beasts[27]? These and other questions must be answered before the unified theory for repeat expansions can be complete.

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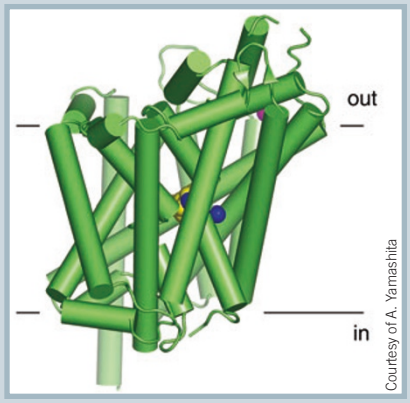
Preventing signal overload



Courtesy of A. Yamashita

Neurotransmitters, such as serotonin, dopamine, and glutamate, relay signals across synapses formed between neurons. After release from a presynaptic cell, these molecules bind to and activate G protein coupled receptors or ligand-gated ion channels located on a postsynaptic cell. Removal of neurotransmitters from synapses is important for effective signal transmission. This is accomplished primarily via re-uptake by integral membrane transporter molecules found in presynaptic termini and glial cells. Transmitter re-uptake accomplishes two things: it restores synaptic transmitter concentrations to basal levels and also replenishes transmitter stores in the presynaptic cell. Members of the Na^+/Cl^--dependent neurotransmitter transporters use the electrochemical potential from the Na^+ and Cl^- gradients to import a variety of molecules, including biogenic amines, like serotonin and dopamine, and amino acids, like γ-aminobutyric acid, glycine and taurine.

The Na^+/Cl^- transporter family is functionally well-studied. Mutations in family members are linked to disorders such as Parkinson disease and epilepsy, and they are the binding targets for antidepressants as well as cocaine and amphetamines. Studies have identified residues involved in substrate specificity, ion binding, and gating. Now, Yamashita *et al.* (*Nature* advance online publication 24 July 2005, doi:10.1038/nature03978) have solved the first crystal structure for this protein family, that of a bacterial leucine transporter from *Aquifex aeolicus* called $LeuT_{Aa}$.

$LeuT_{Aa}$ has 12 transmembrane helices (TM1-12, green rods), confirming the predicted topology for this family, that are arranged to form a 'shallow shot glass' with a very thick base and the opening facing the extracellular space. The structure contains a leucine (yellow CPK), two sodium ions (blue spheres) and a chloride ion (magenta sphere). In this structure, no solvent-exposed channels link the extracellular and intracellular spaces, indicating that the protein is in a closed, or occluded, state. $LeuT_{Aa}$ forms a two-fold crystallographic dimer whose interface is supported by previously performed FRET studies on the serotonin transporter.

The TM1 and TM6 helices, which have the greatest concentration of conserved residues, are interrupted with extended, non-helical conformations roughly at the membrane mid-plane, and it is these regions in the protein core that bind leucine and the sodium ions in a combined dehydrated binding site. The authors propose that discrimination between biogenic amine and amino acid substrates occurs at a residue on TM1, which is a glycine for amino acid transporters like $LeuT_{Aa}$ and an aspartate in biogenic amine transporters. The sodium ions are important for stabilizing the protein core and defining the substrate-binding site. The authors suggest that ion-selectivity is achieved primarily by size, with the sites for sodium coordination simply being too small to accommodate a larger ion, like potassium.

Because the combined leucine and ion binding site in the $LeuT_{Aa}$ structure is closed to both the extra- and intracellular spaces, there must be extra- and intracellular gates. The authors suggest that the unwound regions of TM1 and TM6 act as hinges that exist in different conformational states when substrate is bound and unbound, and that these regions communicate with other areas of the protein to help open and close the two gates. Based upon the structure, the authors put forward a three-step transport cycle: open to outside, occluded, and open to inside. They propose that this mechanism is shared with the glutamate transporter family, despite their differences in protein fold and function. The $LeuT_{Aa}$ structure sheds light on the mechanism of transmitter-ion cotransport as well as ion selectivity and lays the groundwork for future studies on these key players in neurotransmission.

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