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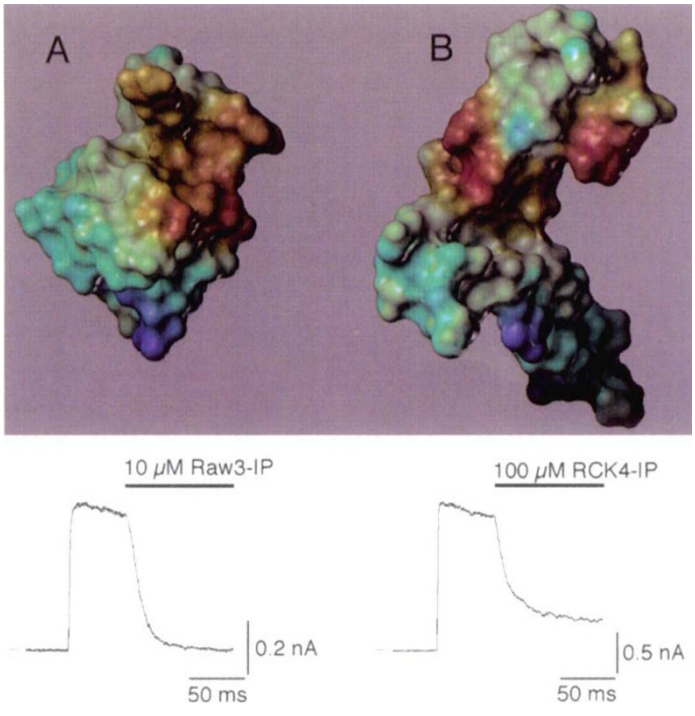
Take away this ball and chain

One could argue that without intention, there is no meaningful action. But without neuronal activity, there would be neither, at least for most of us. The nearly miraculous properties of neurons are explainable by the regulated flow of ions through specific transmembrane channels. In the propagation of an action potential, the gating of these ions by their respective channels is regulated by the voltage across the membrane, so that a change in the potential due to sodium entering the cell is quickly followed by potassium's exit upon the activation of its channel.



The inactivation of voltage gated potassium (K_v) channels is beginning to be understood at a structural level, and is thought to occur when an N-terminal 'ball' domain, attached to the cytoplasmic side of the channel by a 'chain', physically blocks the channel. One can remove this ball and chain by cleaving it from the rest of the channel, abolishing inactivation, which can then be restored by adding ball domains—synthesized as peptides—back to the experimental mix. This can be seen in electrophysiological recordings from membrane patches containing K_v channels (bottom of figure; the bar indicates addition of the peptides). To take full advantage of this system, Christof Antz and co-workers (C. Antz *et al. Nature*, **in the press**) have determined the structures of the ball domains (top left and right in the figure) from two mammalian K_v channels, Raw3 and RCK4, by NMR. The Raw3 peptide (top left), consistent with its conception as a ball, is compact and well-ordered. Positive charges are grouped at one side of the molecule, while negatively charged and hydrophobic patches are near the 'bottom' of the molecule. The action of the Raw3 ball is inhibited by phosphorylation at two serine residues exposed on the surface of the structure, one within the hydrophobic patches and one in the positively charged cluster. Regulation may also occur through the formation of an intramolecular disulphide.

The inactivation peptide from the RCK4 channel (top right) has a rather different structure from that of the Raw3 ball, being less compact and well-ordered. Perhaps as a consequence RCK4 is not nearly as potent an inactivator of K_v channels (bottom of figure), but still inactivates despite the significant structural differences. The explanation of how two such structurally different peptides can have similar roles may lie in the similar distribution of hydrophobic and charged domains between the two molecules. The dipole moments of these peptides are also similar. Together, these common factors may serve to orient these inactivation peptides within the channel vestibule in a similar way. **AF**