Heart of the matter

The molecular switch that controls the beating of the heart does not work in the way scientists previously thought, according to new research from the University of Texas at Houston Medical School, TX, USA and the University of Alberta, Edmonton, Canada [*J. Biol. Chem.* (1997) 27, 18216–18221]. The researchers believe that the discovery could have profound implications for the design of drugs for heart disease.

Pulling the strings...

The switch that pulls the heart strings is a control molecule known as cardiac troponin C (cTnC), which is one of three polypeptide chains in a complex of regulatory proteins found on the thin filament of cardiac muscle. cTnC detects calcium ions released in response to the heartbeat nerve impulse and binds to them. This binding event changes its conformation, causing the heart muscle to contract. The calcium ions are then released and the cTnC reverts to its original shape, relaxing the heart muscle again. "A fundamental feature of the molecular mechanism of muscle regulation is a cyclic change in the three-dimensional conformation of the cTnC as it binds and releases calcium," explains Texas biochemist Dr John Putkey. "Troponin C can be conceptualized as a molecular switch: when calcium is bound, the muscle contracts, when calcium is released, the muscle relaxes," he adds.

cTnC and sTnC

The protein sequence of cTnC is similar to a compound found in skeletal muscle known as sTnC, one of a family of shape-shifting calcium-binding proteins. Dr Brian Sykes and his team at Alberta have previously studied the three-dimensional structure of sTnC in the presence and absence of calcium. The calcium-bound form of sTnC has an exposed hydrophobic region on the surface that is thought to be a site of interaction with other regulatory proteins and with drugs that affect muscle contraction. Researchers had assumed calcium would induce similar changes in both cTnC and sTnC. Recently, Putkey and Sykes used NMR spectroscopy and recombinant DNA techniques to resolve the three-dimensional solution structure of cTnC, with the surprising finding that exposure of the cTnC hydrophobic surface is far less than in sTnC.

Implications for selectivity

The discovery has important implications for the basic mechanism of regulation of skeletal and cardiac muscle, and provides information that may lead to the design of drugs that bind specifically to cTnC and exert selected effects on cardiac muscle contraction, says Putkey. "We found that unlike calcium binding in sTnC, binding did not cause movements of so-called α-helical segments of cTnC and the resultant 'opening' and exposure of the hydrophobic surface of the structure expected", explains Sykes.

The assumption of current therapy for congestive heart failure is that cTnC is very similar to sTnC, but understanding cTnC should help in designing new drugs to increase the sensitivity of cTnC to calcium ions without affecting sTnC. This could lead to more effective treatments with fewer side effects.

Putkey adds, "To fix or modify any machine one must know how it works. If that machine is a protein, then you need to know its three-dimensional structure. The structures of the cardiac and skeletal forms of TnC reveal profound and largely unexpected differences. These three-dimensional views provide valuable clues about how cTnC works and how we may selectively modify its function."

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  1359-6446/97/$17.00. PII: S1359-6446(97)01103-3