How do proteins in our body achieve muscle movement?

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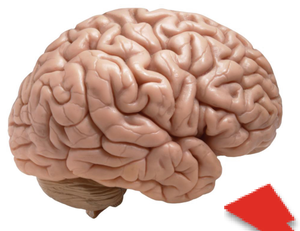
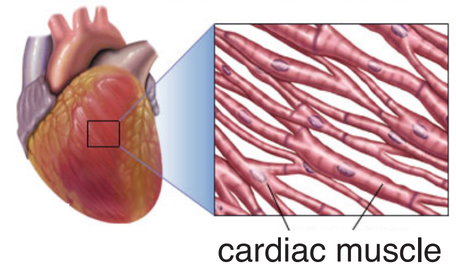
At ANU's John Curtin School of Medical Research, we study proteins involved in muscle movement and contraction. In parcitular, we are trying to establish the crucial molecular interactions between these proteins, with the aim of better understanding of physiological processes that take place in our muscle cells under normal conditions and in disease states. The outcomes of our research might pave the way for the treatment of pathological conditions, associated with skeletal and cardiac muscle disorders.

Muscle contraction

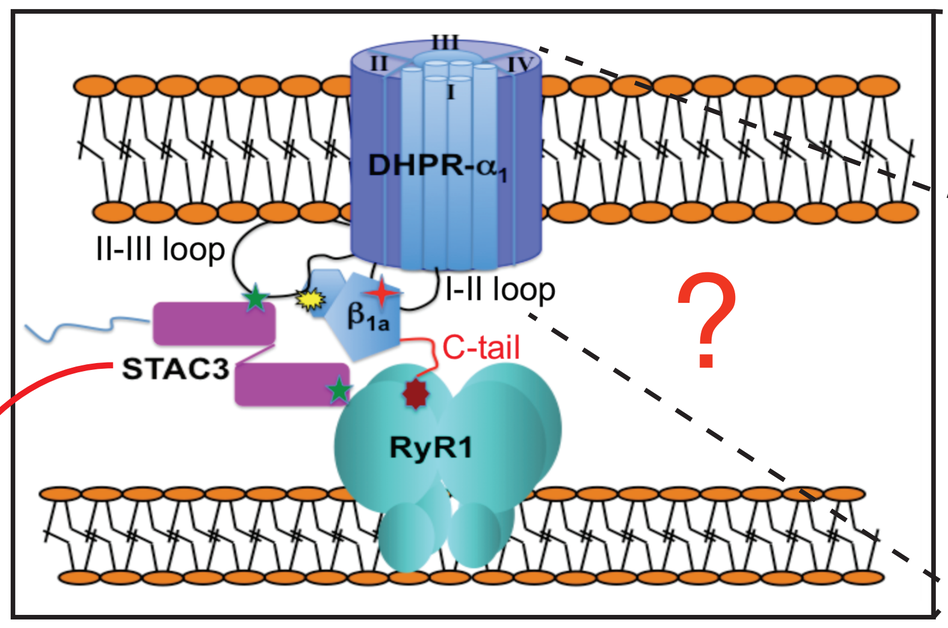


Muscle contraction is initiated by a signal generated in the brain. This stimulus is detected by a voltage-sensing protein called dihydropiridine receptor (DHPR), but it is unknown how the signal is communicated to ryanodine receptor (RyR1), a protein that initiates muscle contraction. This cascade of events is known as the excitation-contraction coupling.

Contraction of cardiac muscle is non-voluntary, but it is realised via a similar mechanism

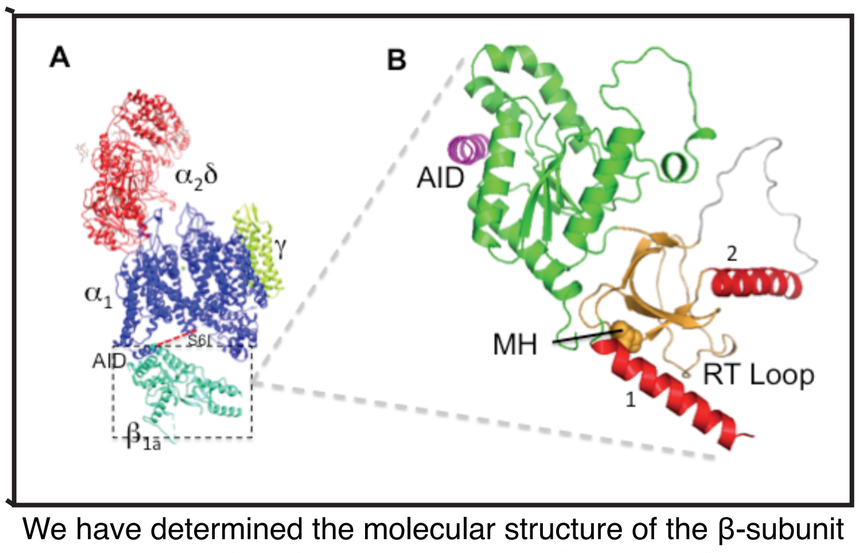


Excitation-contraction coupling



What are the key protein-protein interactions that are involved in the excitation-contraction coupling? The β-subunit of the DHPR and an adaptor protein STAC3 were proposed to play an important role in the signalling, but no molecular details about their interactions are known.

Molecular structures of proteins



We have determined the molecular structure of the β-subunit of the DHPR using X-ray crystallography [2].

[2] Norris, Joseph et al. (2017) doi:10.1074/jbc.M116.763896

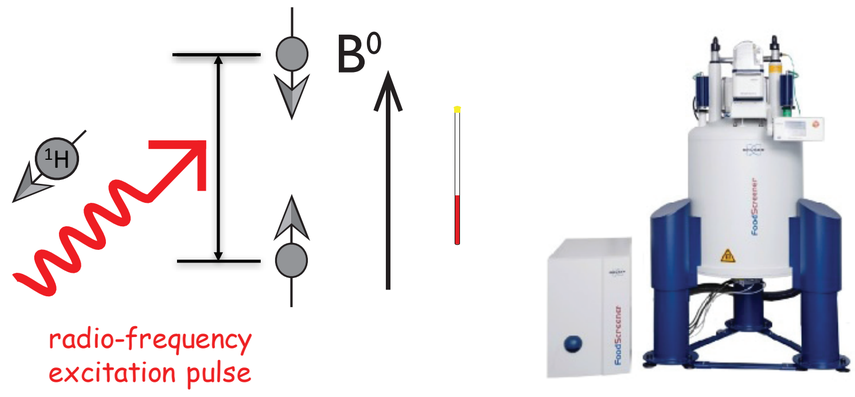
protein mutations might cause diseases

NAM patient	276	VIDDSNEE**S**WRGKIGEKVGF	295
Human	276	VIDDSNEEWWRGKIGEKVGF	295
Chimpanzee	276	VIDDSNEEWWRGKIGEKVGF	295
Dog	278	VIDDSNEEWWRGKIGEKVGF	297
Cattle	274	VIDDSNEEWWRGKIGEKVGF	293
Mouse	272	VIDDSNEEWWRGKIGEKVGF	291
Rat	273	VIDDSNEEWWRGKIGEKVGF	292
Zebrafish	246	VLDDSNEEWWRGKIGEKTGY	265

A mutation of a single amino acid in STAC3 causes Native American Myopathy (NAM) disease [1]. It is impotant to`understand the structural implications of such mutations.

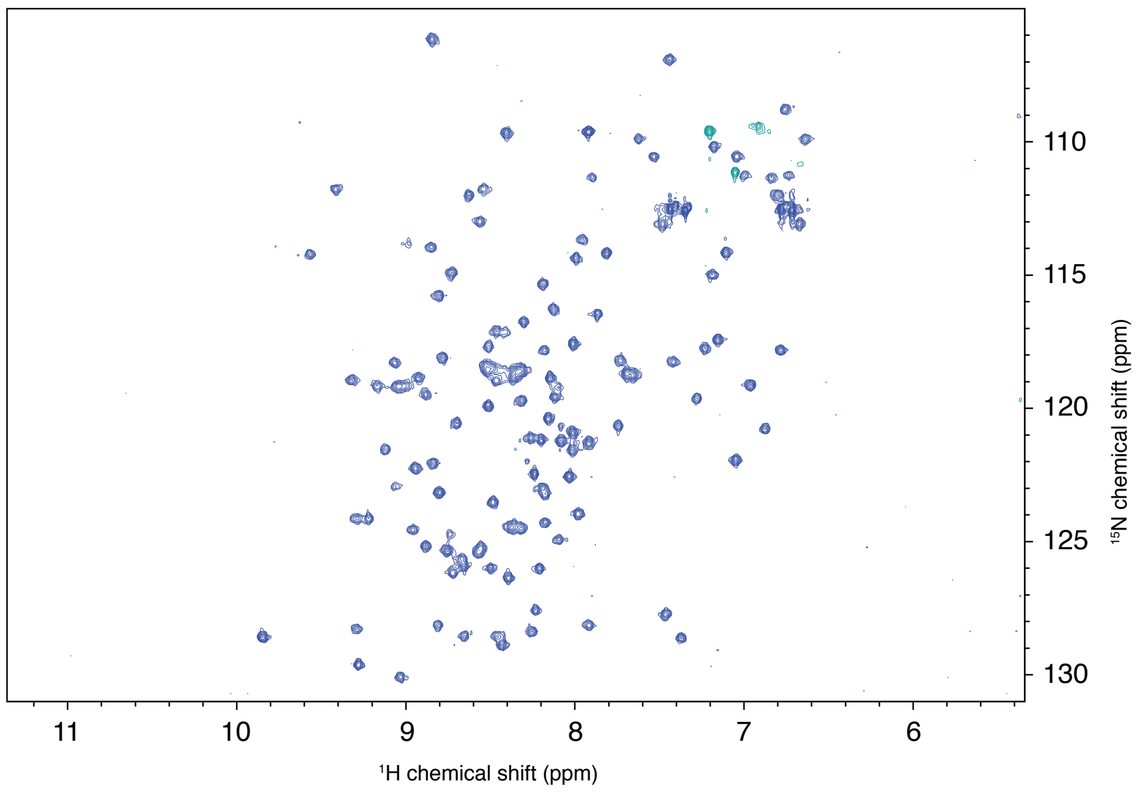
[1] Horstick, Linsey et al. (2013) doi:10.1038/ncomms2952

Nuclear Magnetic Resonance (NMR)



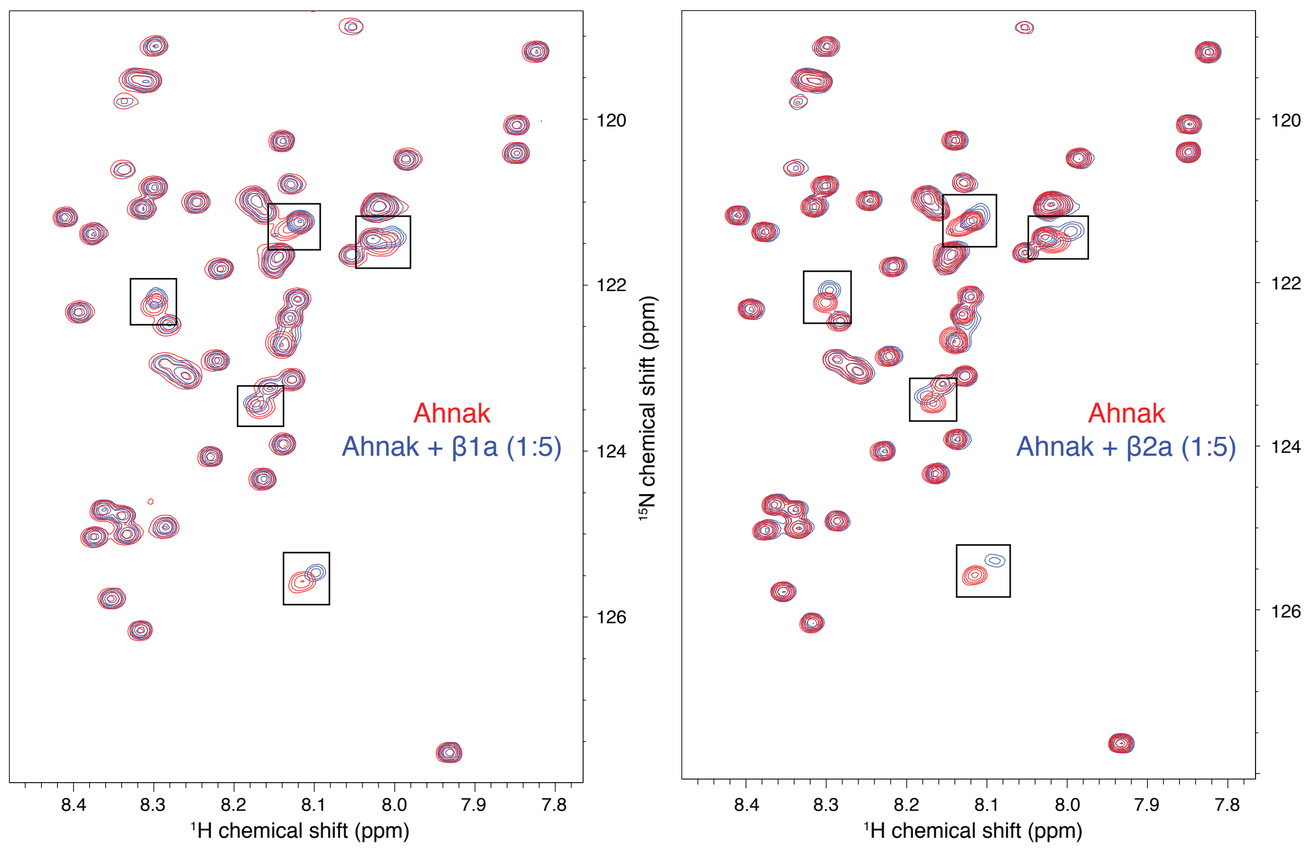
In NMR spectroscopy, a solution of protein is placed in a strong magnetic field, causing atomic nuclei to align with the field and emit signals upon radio-frequency pulse excitation

NMR spectrum of STAC3



NMR spectrum of STAC3, where each 2D peak corresponds to one amino acid. Spectra like this one help us to investigate structure and interactions of proteins.

Interactions of Ahnak and DHPR-β



Perturbations in positions of the peaks in NMR spectra allow to study molecular interactions. These spectra indicate binding of a protein Ahnak with the β-subunit of DHPR.

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