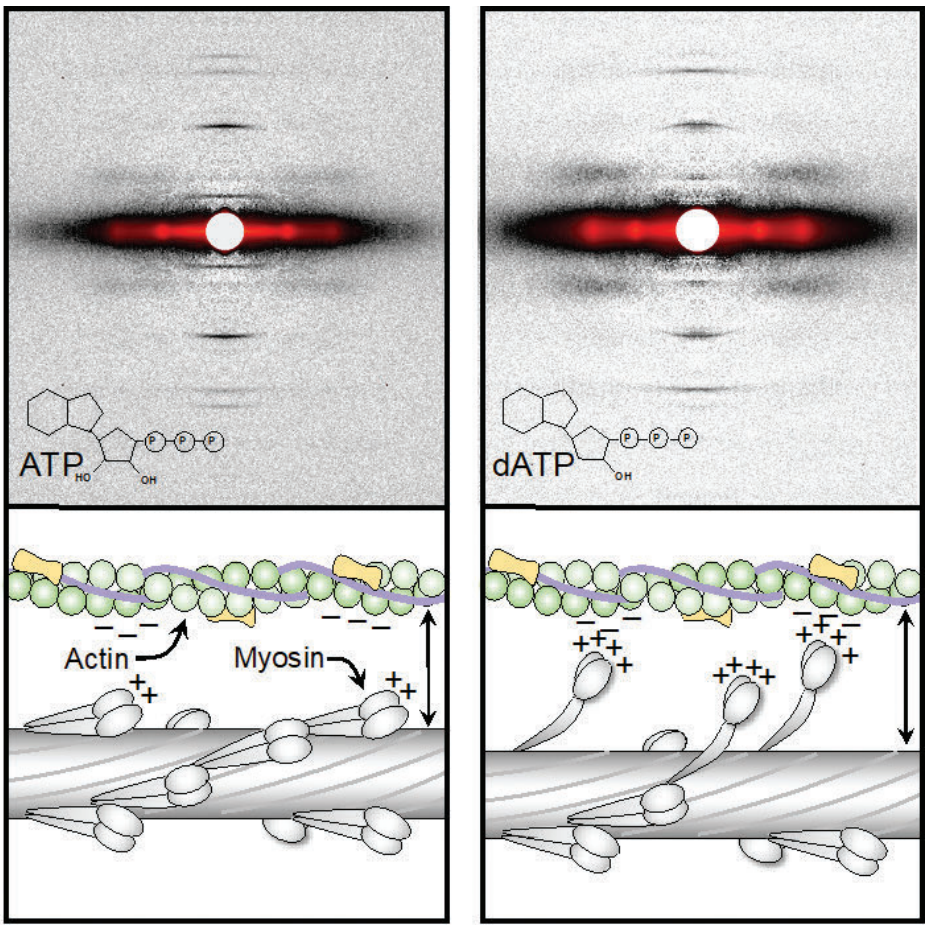
Enhancing the Power Stroke of Cardiac Muscle Could Help Those with Heart Failure

The molecular interactions that drive muscle contraction have been investigated for decades. Basically, force is generated when the thick-filament motor protein, myosin, breaks down adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (Pi) and uses the released energy to move filaments of the thin-filament structural protein, actin. Cardiac muscle can use an alternative form of ATP, 2-deoxy-ATP (dATP), which has been shown to generate even more contractile force than standard ATP. Interestingly, this is true in both healthy heart muscle and in heart muscle with diminished function, such as that seen in people with heart failure. This has led to the intriguing possibility that dATP, or molecules that act in a similar manner, might be used as a therapy to improve cardiac muscle function in people with heart failure. Recently, researchers used data from studies at the APS and other experiments to try to understand the structural basis for dATP's remarkable effect. The work may help in the design of therapeutics that are urgently needed to enhance contraction of failing hearts.



The research team, from the University of Washington, the University of California at San Diego, and the Illinois Institute of Technology had previously shown that dATP could improve contractility in heart muscle and were interested in learning more about why it worked. However, the very fast time frame of the weak interactions between myosin and actin makes it difficult to these study small changes. The first approach they used was a computational structural analysis in which they compared the atomically detailed structures of actin and myosin in the presence of ADP + Pi and dADP + Pi. After analysis of the effects of small changes created by the different molecules, predictions from this analysis suggested that dADP + Pi would increase the number of polar (i.e., charged) interactions between actin and myosin and enhance their affinity. This, they hypothesized, would increase the association kinetics of the actin-myosin interaction. They were able to confirm this using Brownian dynamics simulations that showed that the greater electrostatic interactions between actin and myosin result in faster association kinetics between the two proteins.

Next, these differences were confirmed in an in vitro motility assay in which the fraction of sliding actin filaments is measured on a myosin-coated surface over a range of ionic strengths. Previous work with fast skeletal muscle myosin had shown that the fraction of sliding filaments decreases with increasing ionic strength but that this decrease is slower with dATP than ATP, consistent with the increased electrostatic interactions idea. However, the map of surface charges on cardiac myosin and fast skeletal myosin differ somewhat, so the team felt it was important to demonstrate that cardiac muscle myosin also exhibited this behavior in the motility assay. As they had hypothesized, they observed significantly greater actin sliding with dATP than with ATP over a range of ionic strengths.

To assess effects of dATP on the structure of myosin, the team turned to small-angle x-ray scattering. Using rat cardiac muscle preparations observed under physiological conditions that would maintain the muscle in a resting conformation, the team used the Bio-CAT 18-ID-D beamline at the APS to measure x-ray diffraction patterns from ATP- and dATP-treated muscles. The two-dimensional x-ray diffraction pattern images allowed them to measure the periodicity of myosin along the thick filaments and the orientation of the myosin heads with regard to both thick and thin filaments. The x-ray diffraction data suggested that the myosin heads were shifted away from the thick myosin filaments and leaned more toward the actin filaments with dATP compared to ATP, decreasing the pre-power stroke distance between the myosin head and actin filament (Fig. 1).

A number of myosin-targeted therapies are currently under development and these results provide important clues to how small changes in molecular interactions may translate into therapeutically valuable changes in muscle contraction. — Sandy Field

< Fig. 1. Quantitative image analysis of x-ray diffraction patterns from cardiac muscle treated with ATP (top left panel) and dATP (top right panel) reveals a structural basis for the enhancement of cardiac contraction with dATP. The bottom panels illustrate the difference between resting myosin motors in the presence of ATP (bottom left) and dATP (bottom right) and their interaction with the actin filament. In the presence of dATP, myosin motors have a slightly altered conformation that increases their electrostatic interaction with actin, bringing them closer to the actin filaments and improving the likelihood that they will be available to generate force during cardiac contraction.

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