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ABSTRACT

Molecular Engines: Conversion of biochemical to mechanical energy in the cardiac muscle

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The cell is the common denominator of all living creatures and life is sustained by the continuous intra-cellular conversion of biochemical energy, by nucleotide hydrolysis, to mechanical energy. Life is maintained and perpetuated by intensive intra-cellular activity involving molecular translocation and sophisticated reversible biochemical reactions by complex protein machines. A wide range of intracellular motoric activity and cellular motility depends on millions of linear and rotary molecular protein motors of nanometer scale, which propel (bacteria, sperms), transport (neural network, ion pumps, membrane build-up, cell division), upgrade biochemical fuel (Adenosine Tri Phosphate [ATP]) and perpetuate motion (muscle shortening contraction).

Nanomedicine is the study of biotechnology, physiology, pharmacy and biosensors at the cellular level, all aimed at manipulating and affecting natural cellular and intracellular phenomena in order to achieve better and longer life. Specific goals are: 1) Maintain and improve human health on the molecular scale by targeted medical procedures, 2) Identify and define diseases by genomic analysis, 3) Diagnosis and therapy, including aging, 4) Discover new drugs.. To achieve these goals we must understand the nature of the nano-scale and pico-second intracellular phenomena and develop some unique capabilities to manipulate this molecular world with precision. This involves the ability to construct objects with 3D positional control of molecular structures, manipulate atoms with atomic scale control, avoid harmful mistakes in pico-second constructions, identify and continuously correct unavoidable errors. This study deals with the most important need to develop theoretical analytical tools for understanding and anticipating the intracellular controlling mechanisms involved in normal and pathological situations, as well as the technical capability to observe molecular events by motility assay techniques, so as to be able to identify, and eventually affect, incipient molecular based pathologies.

METHODOLOGY

Insight into the mechanisms of energy production and its conversion to mechanical energy is essential for any future simulation and/or manipulation of molecular nano-scale motoric devices. Here we focus on the molecular motors activating the beating heart. The human heart is an ingeniously constructed four-chambers organ, that beats some 3 billion times in a normal life span and assures that the cells in the body organs are continuously nourished by blood carrying oxygen and metabolites. The muscle contractions are generated by the sarcomeres, the intracellular contractile elements, which are made up of millions of linear molecular actin-myosin motors. Simultaneous production of ATP by millions of enzymatic rotary motors provide the chemical fuel needed for power generation by the linear myosin motors, which are controlled by intracellular surging fluxes of calcium ions The simultaneous motion of the actin-myosin filaments, which make up the intracellular sarcomeres, determines the functional characteristics of the contracting heart muscle.

It is important to note that the active head of the myosin, which forms the crossbridge (XB) with the actin filament, is 19nm long and 5nm thick, much smaller than any human-made nano-motor. The isolated myosin heads create a unitary force of about 2pN and a stroke step of 5nm. Each cubic mm of muscle tissue contains 40.10^{12} motor units. It is obviously interesting to know how does the muscle regulates these motor units and what are the mechanisms that yield the outstanding high efficiency of the molecular motors in the muscle.

Our earlier studies reveal that the contractile filament function in the sarcomere at the sub-cellular organelle level is modulated by two main feedback mechanisms that regulate XBs recruitment (1) and dictate the linear relationship between the energy consumed (ATP hydrolysis), and the mechanical energy (2,3). The calcium ions binds to the regulatory proteins of the contractile filaments and regulates the number of activated motor units (4) These two intracellular feedback mechanisms, the positive cooperativity one and a negative mechanical one, conveniently and convincingly explain the regulation of energy conversion in the cardiac muscle (5,6,).

The present analysis defines the conversion efficiency and the determinants of the muscle's economy. The intracellular interplay between efficiency and economy determines the adaptability of the heart muscle to he prevailing loading conditions. The experimental system that allows to observe and to measure the molecular linear motor at work is briefly discussed.

RESULTS

The kinetics of the molecular motion of the linear motors in cardiac (and skeletal) muscles was studied by image analysis of the motility assay of isolated actin filaments sliding over the isolated myosin heads. The analysis allowed to study the dynamics of the interactions between the actin molecule and the myosin heads, and to explore the kinetics of the biochemical processes that supply the energy for the molecular motor.

A most significant result pertains to the identification and characterization of two kinds of kinetics involved in myosin-actin Xb dynamics. The analysis of the acquired images suggests that Xb dynamics is determined by two distinctive kinetic mechanisms: A fast physical kinetics which relates to the actin-myosin Xb attachment/detachment cycle and a two orders of magnitude *slower* biochemical kinetics, which relates to the reactions of mucleotide binding and dissociation.

The motor efficiency of energy transduction from ATP to molecular motion is about 70%. Higher efficiencies exist in rotary molecular motors, e.g. the ATPase enzyme, which is instrumental in the ADP+P$\leftrightarrow$ATP reaction and the production of biochemical energy. Obviously, man is challenged in his pursuit of new technical horizons by nature's nanoscale functional design.

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