The 63rd Symposium of the Society of General Physiologists: "muscles" instead of squid at Woods Hole

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On Cape Cod, a discussion of "mussels" usually conjures up images of tasty bivalves served with lemon and melted butter. However, the "muscles" of interest at this year's 63rd Symposium of the Society of General Physiologists (SGP) in Woods Hole, MA during the second week (9–13th) of September were of the cardiac, skeletal, and smooth varieties. The SGP Symposium, entitled "Muscle in Health and Disease," marked the first time that the meeting was held in conjunction with the Physiological Society of the UK, bringing together muscle researchers from both sides of the Atlantic for the annual gathering of physiologists at the Marine Biological Laboratory (MBL).

Meeting coorganizers H. Lee Sweeney (University of Pennsylvania) and David Eisner (University of Manchester) assembled and coordinated a diverse program comprised of lectures and posters from many of the world's leaders in muscle structure, function, and (patho)physiology. Research presented during the five-day meeting reflected several recurring themes, or cross-cutting trends, in physiological investigation, including: (1) the utility of molecular studies in elucidating fundamental muscle protein/cell function and the pathophysiology of muscle disease, (2) the increasing use of high-resolution, optical methods (quantum dot technology, x-ray diffraction, and fluorescence resonance energy transfer), (3) the incredible promise of new animal models of disease and stem cell–based studies in basic research and the development of novel therapies, and (4) the impact of translational urgency on basic research investigation. These underlying themes emerged to various degrees during each of the different sessions of research focus, which included motor proteins, the contractile apparatus, Ca^{2+} signaling and regulation, and mechanisms of muscle disease and repair.

After a few opening remarks from MBL Director Gary Borisy and outgoing President of the Society of General Physiologists Kathleen Dunlap (Tufts University), the first evening of the meeting kicked off with a session chaired by David Eisner that focused on motor proteins. Co-organizer H. Lee Sweeney opened the session by describing progress from his team regarding the molecular structures of myosin transition states during the cross-bridge cycle and how mistuning of myosin kinetics during muscle contraction can lead to motor dysfunction and disease. By showing data visualizing the interactions of actin filaments and purified myosin VI with quantum dot technology, David Warshaw (University of Vermont) presented compelling evidence for myosin heads stepping "foot over foot" along actin filaments during contraction. To the amusement of all, while walking across the stage Dr. Warshaw demonstrated with "Gumby-like" precision how myosin can quickly change directions along two intersecting actin tracks. Malcolm Irving (King's College London) closed the first session by describing recent work using x-ray diffraction to probe changes in sarcomere structure at rest and during tetanus.

On the next morning, the program's focus shifted to the contractile apparatus in a session chaired by H. Lee Sweeney. Mathias Gautel (King's College London) described mechanisms linking the sarcomere to signaling pathways that regulate gene expression and protein turnover, while John Solaro (University of Illinois at Chicago) discussed how the contractile apparatus is modulated by a wide array of kinases (e.g., PKA, PKCε, and PAK1) and phosphatases (e.g., PP2A). Samantha Harris (University of California, Davis) introduced the group to cardiac myosin binding protein C (cMyBP-C), a sarcomeric protein that limits the rate of cross-bridge cycling and for which cMyBP-C mutations are linked to hypertrophic cardiomyopathy (HCM) in humans. In the initial portion of Harris's presentation, she reviewed her work demonstrating that the unique amino-terminal m-domain of cMyBP-C binds to either F-actin or thin filaments, and that these interactions are inhibited by phosphorylation of the m-domain. In the latter part of her talk, Harris presented preliminary work using a feline model of HCM.

After breaking for the afternoon, the discussion of contractile proteins continued in an evening session chaired by John Solaro. Rick Moss (University of Wisconsin) began by sharing his laboratory's findings

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of the role of cMyBP-C dysfunction in HCM. Work from Moss's team showed that genetic disruption of the cMyBP-C gene in mice results in accelerated cross-bridge cycling in the myocardium, ventricular hypertrophy, and cardiac dysfunction similar to that observed in patients afflicted with HCM. Elizabeth McNally (University of Chicago) presented provocative results involving the identification of genetic modifiers that influence the phenotypic variability of muscle function in mouse models of muscular dystrophy. Hugh Watkins (Oxford University) brought the discussion back to HCM with a focus on the development of potential therapies, including both gene replacement and pharmacological strategies. During this session, the group was also treated to a short talk by Hugh Huxley (Brandeis University), whose elegant studies over the last 50+ years has provided the basis for much of the work presented during the first three sessions. Dr. Huxley first touched on some of his early groundbreaking work, and then discussed his more recent x-ray diffraction studies with a focus on cMyBP-C.

Regulation of Ca^{2+} signaling in both cardiac and skeletal muscle was the topic of discussion during the morning of the third day in a session chaired by Samantha Harris. Susan Hamilton (Baylor College of Medicine) presented her group's findings regarding the disruption of proper Ca^{2+} and reactive oxygen/nitrogen species signaling in skeletal muscle of mice carrying a mutation in the type 1 ryanodine receptor gene that is linked to malignant hyperthermia and central core disease in humans. Using a variety of genetically modified mice, Clara Franzini-Armstrong (University of Pennsylvania) presented an elegant description of how correct targeting of calsequestrin 2 at the junctional apex of the terminal cisternae of the sarcoplasmic reticulum is critical for proper formation of the Ca^{2+} release unit in cardiac muscle. Moreover, Franzini-Armstrong showed that two other junctional proteins, triadin and junctin, synergistically support Ca^{2+} release unit formation by ensuring proper calsequestrin localization. Kurt Beam (University of Colorado Denver) assessed current knowledge of the basic molecular interactions that support excitation–contraction coupling in skeletal muscle. Beam's group used a complementary combination of electrophysiological, optical, and ultrastructural approaches to provide new insights into the spatial relationship and potential sites of interaction between the skeletal L-type Ca^{2+} channel and the ryanodine receptor. He also touched briefly on how the coupling between the L-type channel and the ryanodine receptor may be altered in a mouse model of malignant hyperthermia. In the last talk of the session, meeting co-organizer David Eisner described how inherited catecholamine-induced arrhythmias arise from disruptions in the delicate balance between the activities of the cardiac L-type Ca^{2+} channel, type 2 ryanodine receptor, Na^+/Ca^{2+} exchanger (NCX1), and the sarco-endoplasmic reticulum Ca^{2+}-ATPase pump.

Clearly, much of the research described in the Ca^{2+} signaling session was based on work made possible by engineered mouse models. However, the session also included a short talk from Rachael Ashworth (Queen Mary, University of London), who detailed how her laboratory has used the nonmammalian zebrafish model system to investigate the relationship between contractile activity and muscle development. Ashworth's graduate student, Houdini Ho-Tin Wu, was awarded first prize in the student poster competition for his work describing the developmental regulation of the five different zebrafish ryanodine receptor isoforms.

After breaking for the afternoon, the program continued after dinner in the first of two sessions on muscle disease and repair. In the first talk of this session chaired by Michael Walsh (University of Calgary), Tejvir Khurana (University of Pennsylvania) discussed the transcriptional/posttranslational regulation of utrophin and the therapeutic potential of interventions designed to increase cell-wide utrophin expression in Duchenne muscular dystrophy. David Allen (University of Sydney) offered an alternative view for the increased susceptibility of dystrophic (*mdx*) mice to stretch-dependent muscle damage. Specifically, Allen presented results from his group suggesting that stretch-induced damage of *mdx* muscle fibers is mediated by ROS-induced activation of src kinase and subsequent enhancement of Ca^{2+} entry via stretch-activated TRPC channels. Susan Wray (University of Liverpool) concluded the session with a sometimes shocking talk that described a correlation between obesity and difficult labors and an increased incidence of Caesarean section. Although Wray's talk started with somewhat of an epidemiological slant, she proceeded to discuss the molecular physiology of this connection. Wray proposed that decreased uterine contractility in obese women is, at least in part, a consequence of elevated levels of cholesterol causing an increase in K^+ current density via large conductance, Ca^{2+}-sensitive K^+ (BK) channels that reduce uterine myometrial smooth muscle excitability.

The final day of the symposium continued with the second session on muscle disease and repair chaired by Susan Wray. The first two talks of the session detailed new insights into the signaling mechanisms involved in the regulation of vascular smooth muscle contraction. Michael Walsh commenced the session by presenting his team's work on the myogenic response in rat cerebral arteries. Specifically, Walsh's group found that transmural pressure-induced vasoconstriction arises in part from rho kinase–mediated inhibition of myosin light chain phosphatase and a subsequent increase in myosin light chain phosphorylation. Mark Nelson (University of Vermont) then described a novel mechanism of neurovascular coupling by which neural activity

rapidly triggers a change in local blood flow through small cerebral arterioles in the brain. This coupling mechanism results from glutamate release causing an increase in Ca^{2+} levels in nearby astrocytes, which in turn activates astrocytic BK channel activity. Nelson went on to show that this enhancement of K^+ efflux via activated astrocytic BK channels elicits local smooth muscle relaxation by stimulating inward-rectifying potassium channels of adjacent vascular smooth muscle cells. After a coffee break, cardiac physiology again became the area of interest with Richard Vaughn-Jones (University of Oxford) describing the influence of subcellular pH gradients on connexin-mediated ion diffusion between neighboring ventricular myocytes. In a fascinating talk, Christine Mummery (University of Leiden) reported provocative new findings regarding the promise that cardiovascular stem cells hold for regenerative medicine and also highlighted the need for the participation of additional physiologists in this rapidly growing field.

The morning session of the final day concluded with two short talks from the recipients of the 2009 SGP Cranefield Awards. In addition to the traditional Paul F. Cranefield Award (for which there was no recipient this year), in 2005 the SGP instituted two new Cranefield Awards, one each to be given annually to a postdoctoral fellow and a graduate student, respectively, who are the first authors of significant manuscripts published in the *JGP*. The Graduate Student Cranefield Award was presented to Andrés Jara-Oseguera (Universidad Nacional Autónoma de México) for his work using quaternary ammonium ions to map the pore of TRPV1 channels (Jara-Oseguera et al., 2008) in the laboratory of Dr. León Islas. Dr. Giovanni Ziffarelli (Institute of Biophysics, CNR Genova), a senior postdoctoral fellow in the laboratory of Dr. Michael Pusch, won the Postdoctoral Fellow Cranefield Award for his study exploring the dependence of fast ClC-0 channel gating on intracellular pH (Zifarelli et al., 2008). However, in his talk, Ziffarelli discussed his more recent (and equally interesting) work on the adenine nucleotide and pH dependence of ClC-5 H^+/Cl^- antiporter activity.

The muscle symposium culminated with a keynote address given by Kevin Campbell (University of Iowa, HHMI) on Sunday evening. To start, Dr. Campbell escorted the audience through a nostalgic "photographic retrospective" highlighting his personal journey from studying EC coupling as graduate student at the University of Rochester through his early days as an independent investigator at the University of Iowa. Members of the audience, who impacted Campbell's career during these formative times, in particular Clara Franzini-Armstrong and Kurt Beam, were pointed out and their influences fondly recalled. From there, Campbell described how careful and detailed biochemical experimentation (i.e., biochemical purification of dystrophin) led him from the EC coupling field to the discovery and characterization of the dystroglycan complex and its integral role in skeletal muscle disease. He then went on to describe more recent work from his group regarding the essential role of dysferlin in muscle repair. Throughout his address, Campbell highlighted the importance of communication between his laboratory and clinicians in the progress that he has made in our current understanding of the molecular underpinnings of muscular dystrophy.

After Campbell's keynote address, a short reception ensued, followed immediately by a closing seafood feast and award session. The meal featured plentiful lobster, clams, and mussels; you know, the ones that go so well with lemon and melted butter.

Upcoming *JGP* Perspectives in Muscle in Health and Disease

The overwhelming success of the Muscle in Health and Disease Symposium has inspired a future *JGP* Perspectives series that will broadly address many of the major themes of the 2009 SGP Symposium. For this upcoming Perspectives, a subgroup of symposium speakers selected and recruited by representatives from the SGP council and the *JGP* editorial board will address current controversies and breakthroughs in their respective fields.

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