Effects of spaceflight on the musculoskeletal system: NIH and NASA future directions

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"The Effects of Space Travel on the Musculoskeletal System," a workshop held at the National Institutes of Health on October 3 and 4, 1990, was sponsored jointly by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Aeronautics and Space Administration (NASA). Attended by 80 invitees, it was chaired by Michael F. Holick, Boston University School of Medicine, and Kenneth M. Baldwin, University of California at Irvine. Participants reviewed the normal function and structure of bone and muscle, as well as independent and interactive responses of these tissues to activity and disuse on Earth and in the microgravity environment of space. They then focused on those future directions of research, summarized in this report, that are relevant to the missions and interests of both agencies. A comprehensive review of the presentations is available from NIAMS.[2]

BONE AND MUSCLE RESEARCH

NIAMS and NASA share interest in the underlying mechanisms of the effects of use and disuse of bone and muscle, and in the prevention and treatment of bone and muscle diseases. Expected benefits of research supporting these interests are the maintenance of integrity of the musculoskeletal system throughout life and while on extended space travel.

Workshop participants identified topics of interest to both agencies in bone (1) and in muscle (2) research. A brief description of each is followed by specific questions generated by discussions of the participants.

Evaluating Three-Dimensional Structure and Integrity of Bone

Recent improvements in noninvasive imaging procedures (ultrasound, single and dual photon absorptiometry, dual energy x-ray absorptiometry, quantitative computed tomography) may substantially improve the assessment of fracture risk. Measurements using these techniques can be related to measurements of in vitro fracture loads. They may be applicable also to the evaluation of the biomechanical consequences of given levels of osteopenia and bone loss induced in microgravity and the effectiveness of countermeasures for spaceflight crews. Through noninvasive procedures, can fracture risk and 3-dimensional architecture of bone be more accurately determined in the elderly and in candidates for prolonged spaceflight? How can these procedures be used most effectively to assess skeletal remodeling after spaceflight and to monitor the effects of exercise regimes in the elderly?

Ground-based Models of Response of Bone to Changes in Gravitationally Induced Stress and to Therapeutic Intervention

Examples of ground-based models include the Lanyon-Rubin turkey wing experimental model (3), which has been used to study effects of unloading and adaptive bone remodeling from strain induced by load-related variables; the unloading of the hindlimbs of rats (2b, 4); and bed-rest studies of disuse osteoporosis in human volunteers (5). These are valuable models for the microgravity environment because of the limited data on humans in weightlessness, and because they can be used to guide future research applicable to mechanisms of bone loss and to physiological effects in the space environment. Discussants called for further development of these and other models, and for their more aggressive application to areas insufficiently researched. What minimal dynamic loads and forms of load delivery will maintain the structural integrity of bone? How can the effects of gravity and hypergravic forces on bone be distinguished? How does the dose response of loading differ during bone development and after maturation? What additional models can be developed to observe osteonal or internal bone remodeling? Do any aspects of bone metabolism correlate with differences in blood flow observed in microgravity? Can bed-rest studies of disuse osteopenia be enhanced to isolate the effects of hormonal changes, determine alterations in local bone metabolism, and assess the effectiveness of therapeutic agents (6) to prevent bone loss?

Bone Mineral and Matrix; Regulatory Activities at Cellular and Molecular Levels

Development of the composite microstructure of bone is a highly complex, multistep, genetically con-

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trolled process with cell-mediated activities operating at the molecular level (7). In the unique environment of space, the considerable difference in the behavior of biophysical processes in fluids from that in 1g offers an unmatched opportunity to study the crystal formation and structure of bone. Among the hormones or factors that regulate (or influence regulation of) the development and integrity of bone structure are vitamin D_3, parathyroid hormone, estrogen, glucocorticoids, and calcitonin. Various polypeptide growth factors or cytokines, believed to regulate bone at the cellular level, have been discovered or suggested relatively recently. Cytokines may be systemic or hematological in origin, or locally synthesized by skeletal cells in bone matrix or by cells from adjoining tissues. How they function in vivo is still obscure; most current information is derived from cell cultures in 1g (8). Similarly, the messengers (or signals) of applied load, and the cellular receptors, whether operating directly on the cell and its membrane, or indirectly on the associated extracellular matrix proteins and mineral, are not understood. What is the effect of microgravity on the formation and structure of bone crystal salts and on the behavior of bone matrix proteins? Does cortisol bind to bone cell receptors; does it influence receptor binding of local growth factors? What are other effects or influences of hormones on calcium metabolism and bone remodeling at the molecular, cellular, and higher organizational levels in 1g and microgravity? What is the effect of reduced gravity on the expression of growth factors from skeletal and endocrine cells? Do these cells show an altered number of receptors and receptor affinities to growth factors derived from other cells, such as monocytes? Can transduced load signals be studied in cell and tissue culture in 1g and in microgravity to elucidate relationships between applied load and response of bone cells?

Muscle-bone Relationships; Countermeasures to Muscle Atrophy

Much of the force on bone is exerted by muscle. The two tissues are highly interdependent and interactive. A relatively constant level of strain is normally present in most bones throughout the body, but the intermediate physiological signals that control these interactions are not defined. In addition, it is not clear which features of bone loss can be attributed independently to compromised muscle function. Whether due to spaceflight or immobilization, disuse muscle atrophy can be countered by load bearing exercises or, less effectively, by exercise that involves isometric, concentric, and eccentric muscle activity. Hormone therapy and electrostimulation might augment exercise, but not replace it.

The relationship of musculoskeletal activity to the nervous system is evident in astronauts re-entering 1g (9) and in newly ambulant patients previously immobilized for long periods; both must coordinate muscular movements with exertion of large forces. Responses of rats flown in space compared with those using hindlimb suspension in 1g support the view that this experimental method can be a useful and valid ground-based model for studying neuromuscular adaptations to spaceflight (10). What are the inherent loads applied to the seemingly unloaded bones of astronauts, and bed rest subjects and patients? What combination of exercise programs and other countermeasures can best maintain muscle strength, size, and functions in spaceflight? What is the influence of these programs on bone mass and fracture resistance? To what degree are the chemical factors that modulate muscle metabolism and growth in response to use or disuse patterns communicated to bone? To what degree do these factors modulate the response of bone cells? By what physiological mechanisms does the neuromuscular system respond to different force environments? What measurements are best used to determine the extent and rates of neuromuscular adaptation and readaptation?

Regulatory Activities in Muscle at Cellular and Molecular Levels

Research on the formation of vertebrate skeletal muscle and muscle fibers has accelerated, but many details of myosin expression and myogenesis are still unknown (11, 12). The response of skeletal muscle to load-bearing and unloading also involves poorly understood cellular and molecular mechanisms that modulate synthetic and degradative processes in slow fibers (13). Relatively little is known about the regulation of the synthesis of myosin isoforms and the up- and down-regulation of calcium transporters in the sarcoplasmic reticulum which have different transport rates. In contrast, the chemistry of control of muscle contraction and the molecular structures responsible for force development are well known. As in bone, hormones are active regulators. As examples, hypothyroidism blunts the up-regulation of the fast myosin isoform and the degree of atrophy during unloading; hyperthyroidism inhibits fast-to-slow transformation; glucocorticoids are thought to modulate the balance between protein synthesis and degradation as demonstrated in the unweighted rat soleus muscle (2b); growth hormone increases mass in atrophied muscles or in subjects lacking insulin-like growth factor-1, but has little effect on musculature of normal subjects. Changes in the biophysical behavior of cells in low gravity may stimulate endocrine adaptations. For example, growth hormone secretion is markedly reduced in rats flown in space (14), which may indirectly affect muscle function. What causes the rapid degradation of slow fibers during unloading; what causes them to be synthesized as load is applied? How are skeletal muscle fibers signaled that they are unloaded or load-bearing? How are myosin isoforms synthesized? How are calcium transporter replacements regulated? What is the role of hormonal regulation in the transformations of skeletal muscle to load-bearing and unloading? What can human disease conditions (involving compromised muscle strength and regulatory function) reveal about the mechanisms of transporter up- and down-regulation, the modulation of myosin isoform synthesis, and the regulation of muscle protein synthesis in general?

The Extracellular Environment of Muscle

Innervation and the neuromuscular junction augment programmed development of muscle (15). Each of three possible programs—preprogrammed, neuronal-dependent, and

activity-dependent—results in a different combination of troponin T, alpha-actinin, and tropomyosin isoforms. Single fibers are thought to coexpress the programs in different ratios. In addition, myonuclei near neuromuscular junctions synthesize mRNA for acetylcholine receptors. Recently, the regulatory role of the myotendinous junction (16) has received considerable attention. It is at this site that the muscle fiber terminates and attaches to collagen fibers of the tendon, allowing force to be transmitted to the tendon. Dystrophin, the protein product of the Duchenne muscular dystrophy locus (17), is enriched (18) at the myotendinous junction and participates where the myofibrils attach to basement membrane tendons. With disuse and in Duchenne muscular dystrophy, myofibrillar membrane folding is aberrant and attachment is weaker. How are muscle development processes initiated and regulated? What signals between neurons and myofibrils lead to neuronal-dependent development? What is the influence of modified muscle use on the concentration and distribution of myotendinous junction proteins?

SUMMARY

Prolonged bed rest, undertaken by volunteers or resulting from injury and disease, can impair bone and muscle function and structure; extended travel in space also induces these effects. Fluid shifts and disrupted fluid balance may also contribute to observed musculoskeletal aberrations in the weightless environment. Some molecular and cellular events involved in the loading and unloading of the musculoskeletal system are under neural and endocrine influence or control, whereas other events are influenced by local growth factors. Studies are in progress to develop interventions that preserve or improve musculoskeletal integrity in 1g. The NIAMS and NASA are interested in basic and clinical studies of the influence of microgravity on the musculoskeletal system. The interagency workshop results form the basis for new collaborative and cooperative research emphases for the biomedical community under a broad agreement between the National Institutes of Health and NASA.

REFERENCE NOTES

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