SA1

What is human ageing?

T. Kirkwood

Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Ageing is a particularly demanding process to study, since its mechanisms are multiple, complex, highly interactive, and often stochastic in nature. Indeed, a barrier to progress has been the coexistence of multiple, seemingly competing hypotheses. The challenge is therefore to identify how to create the necessary joined-up understanding of the complex mechanisms of ageing in ways that will expose targets that might help to postpone age-related ill health and support healthy ageing. The intrinsic malleability of the ageing process, as revealed by current work, suggests that this goal is certainly attainable although it will require a major expansion in research volume if we are to reach it. Since age is the single biggest risk factor for a very wide spectrum of diseases, which individually attract major research effort, the prize of identifying exactly why aged cells are more vulnerable to pathology, and thereby how such pathology might be delayed or prevented, seems eminently worthwhile.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA2

Sarcopenia; Effects of diet and physical activity

W.J. Evans

Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Sarcopenia is defined as the age-associated decline in skeletal muscle mass (1). It is associated with weakness and poor functional capacity in older people (2). The etiology of sarcopenia is multifactorial and potential causes of loss of muscle include decreased physical activity, decreases in anabolic hormone level, decreased protein intake, poor nutritional status, and inflammation that may be secondary to increases in body fatness. In addition, hospitalization and bed rest may contribute to accelerated sarcopenia. Increased body fatness in older people has strong influence on functional capacity and may be a more powerful predictor of late-life disability than sarcopenia. If obesity results in reduced functional capacity in older people, voluntary weight loss by energy restriction is associated with increased mortality. This increased in risk may be caused by losses in skeletal muscle and bone mineral contents when weight loss is accomplished without exercise. We have demonstrated that consumption of the current Recommended Dietary Allowance for protein of 0.8 g/kg/d by older people results in a loss of muscle mass (3). Decreased energy intake to lose weight may result in an inadequate dietary protein intake and an accelerated loss of muscle. While it is now well known that resistance exercise training can increase muscle mass, strength and functional capacity even in very old people, the effects of bed rest in elderly people are less well understood. Our laboratory has explored the effects of 10 days of complete bed rest in healthy older people (mean age 67 years). We have reported (4) that even though these subjects consumed the recommended dietary allowance for protein during the 10 days of bed rest they experienced a decrease in nitrogen balance that was accompanied by a large loss of muscle mass and function. The fractional synthetic rate (FSR) of skeletal muscle protein was measured using a 24-hour infusion of 15N-phenyalanine and muscle biopsies. The 10 days of bed rest resulted in a loss of almost 1 kg of muscle from the legs and substantial decreases in VO2peak (-15.1%), strength (-19%), and a 30% reduction in FSR. This loss of muscle mass and function resulted in an overall decrease in physical activity after the bed rest period (5). This 10-day period of bed rest also results in a substantial increase in insulin resistance as measured by a euglycemic glucose clamp that may the cause of the decrease in skeletal muscle protein synthetic rate. Incorporating 15 minutes of walking each substantially attenuates the losses of muscle mass and function. Episodic period of inactivity in elderly people due to illness, depression, or hospitalization may result in losses in muscle mass and function that may be so large that recovery without aggressive rehabilitation becomes problematic.

Evans W. What is sarcopenia? J. Gerontol. 1995;50A(special issue):5-8.

Evans W. Functional and metabolic consequences of sarcopenia. Journal of Nutrition 1997;127:998S-1003S.

Campbell WW, Trappe TA, Jozsi AC, Kruskall LJ, Wolfe RR, Evans WJ. Dietary protein adequacy and lower body versus whole body resistive training in older humans. J Physiol 2002;542:631-42.

Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 2007;297:1772-4.

Kortebein P, Symons TB, Ferrando A, et al. Functional impact of 10 days of bed rest in healthy older adults. J Gerontol A Biol Sci Med Sci 2008;63:1076-81.

Work performed was partially funded by a National Institutes of Health grant PO1AG023591

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA3

Mechanisms underlying age associated muscle wasting in human beings

M. Rennie

School of Graduate Entry Medicine and Health, University of Nottingham, Derby, UK

Rodent models of muscle wasting rarely display the underlying processes observed in human muscle wasting to be of much use heuristically. This is probably because of a greater metabolic stability of the human body than that observed in rodents. Thus the proper study of human age related muscle wasting has to be made in human beings. When this is done it is apparent that in the basal state, in healthy active persons between 50 and 80 y, there are few signs of derangements of muscle protein synthesis or breakdown or of increased markers of catabolic processes, possibly with the exception of increased signs of increased sub clinical inflammation in muscle. However there do appear to be major deficits in the ability of muscles from

older persons to efficiently regulate the maintenance of their muscle during feeding. Dose response studies show that the hyperbolic relationship between myofibrillar protein synthesis and availability of essential amino acids amino acids is shifted down and to the right and that giving large amounts of amino acids is unable to overcome this anabolic resistance. Oddly post-menopausal women have a greater anabolic resistance than do older men. The anabolic resistance is also shown by the decreased phosphorylation of molecules in the PKB-mTOR-eIF4BP1 pathway in response to amino acid availability. The muscle synthetic system is refractory to amino acid provision irrespective of the availability of insulin, IGF-1 and growth hormone. On the other hand insulin is a major regulator of muscle protein breakdown in human muscle and we now have good evidence that there is blunting of the ability of older muscle to decrease proteolysis in response to low concentrations of insulin, such as those observed after light meals. The anabolic resistance of both arms of protein turnover is probably causally important in the slow development of sarcopenia. Simply providing more amino acids is not in my view a solution to the problem, and the most up to date nitrogen–balance data confirms the idea that the dietary protein requirements of older persons are not increased. What is needed is a way of retuning the muscles response to dietary protein. One way might be via exercise. Our recent work has shown that the sigmoidal dose response between muscle protein synthesis and resistance exercise intensity is shifted down wards and to the right in older men. Decreased physical activity itself, even in young subjects, can produce anabolic resistance of muscle protein synthesis, which cannot be acutely overcome by increasing amino acid availability. Long tem bed rest also produces anabolic resistance of the whole body which cannot be overcome by feeding more protein. There is substantial interest in the proposition that a feature of anabolic resistance, including that of ageing is due to decrements in nutritive blood to human muscle. We have evidence that the blood flow responses to feeding and resistance exercise are less in the muscles of older persons and that they improve with resistance training. These improvements seem to be associated with better responses of muscle protein metabolism to food. However our understanding of the regulation of the size of the muscle mass with ageing and physical activity remains poor and a great deal more work is required to improve it.

Supported by BBSRC, US NIH, EXEGENESIS program of the EC, and Unilever pls.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA4

Lifelong increases in HSP content of skeletal muscle results in preservation of mass, function and regeneration in old mice

A. Kayani, G. Close, M. Jackson and A. McArdle

School of Clinical Sciences, University of Liverpool, Liverpool, UK

Frailty is the major contributor to health care problems and poor quality of life in older people. Although frailty is recognised to be multifactorial, the major contributor is thought to be skeletal muscle weakness. By the age of 70, the average human has lost approximately 30% of skeletal muscle and 40% of maximum force generation (1). This decline in neuromuscular function and strength and lack of functional reserve increases the risk of falls, hypothermia, incontinence and contributes to increasing lack of independence. The mechanism(s) by which the development of this age related loss of muscle

mass and function occurs are poorly understood although a failure in the ability to activate the stress or Heat shock response has been implicated. The Heat shock protein (HSP) content of skeletal muscle of adult mammals is increased following both short and long-term exercise protocols. In contrast the HSP content and the ability to activate a stress response are modified in skeletal muscle with age (2). Transgenic studies have demonstrated that this blunted response plays a key role in development of age-related functional deficits. Lifelong overexpression of the cytosolic HSP, HSP70 in skeletal muscle of mice prevented the age-related loss of specific force (force/cross sectional area(CSA)) generation but not the age-related loss of maximum tetanic force generation observed in muscles of old wild type mice (3). In addition, and unlike muscles of old wild type mice, HSP70 overexpression facilitated the complete recovery of force generation in EDL muscles of old transgenic mice at 28 days following a severe protocol of damaging lengthening contractions. Further studies have demonstrated that lifelong overexpression of the mitochondrial chaperone, HSP10 in skeletal muscle of mice prevented the age-related loss of force and CSA observed in quiescent muscles of old wild type mice and furthermore, protected muscles of both adult and old mice from damage following contraction-induced injury. These data demonstrate that the development of all aspects of age-related muscle weakness and atrophy are not inevitable. The protective effect of overexpression of HSP10 in the mitochondria of skeletal muscle strengthens the hypothesis of the involvement of mitochondrial dysfunction in the development of these deficits and the differential effects of different HSPs highlight the specific functions of individual HSPs in skeletal muscle. The mechanism responsible for the inability to activate a stress response in old muscle is unclear although modified signalling by Reactive Oxygen Species is thought to play a role. Data suggest that the defect occurs prior to dissociation of the Heat Shock transcription factor, HSF1 from an inactive to an active form in the cytosol since data from mice treated with the HSP90 inhibitor and HSF1 activator, 17-AAG, demonstrate an increased HSP70 content of skeletal muscles of adult and old mice (4).

Skelton DA, Greig CA, Davies JM, Young A.1994. Strength, power and related functional ability of healthy people aged 65-89 years. Age Ageing.23:371-7

2. Adaptive responses of mouse skeletal muscle to contractile activity: The effect of age.2006. Vasilaki A, McArdle F, Iwanejko LM, McArdle A. Mech Ageing Dev. 127:830-9

3. McArdle A, Dillmann WH, Mestril R, Faulkner JA, Jackson MJ. 2004. Overexpression of HSP70 in mouse skeletal muscle protects against muscle damage and age-related muscle dysfunction. FASEB J. 18:355-7

4. Kayani AC, Close GL, Broome CS, Jackson MJ, McArdle A.2008. Enhanced recovery from contraction-induced damage in skeletal muscles of old mice following treatment with the heat shock protein inducer 17-(allylamino)-17-demethoxygeldanamycin. Rejuvenation Res. 11:1021-30

This work was funded by Research into Ageing, BBSRC, MRC, National Institutes of Health (USA) and the Wellcome Trust.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA5

Satellite cells, muscle hypertrophy and the aged environment

S.D. Harridge

Division of Applied Biomedical Research, King's College London, London, UK

Twenty years ago Carlson and Faulkner (1989) made the interesting observation that if a muscle from an aged rat was transplanted into a young host the recovery potential of that muscle, in terms of mass and force production, was similar to that of a transplanted young muscle. Conversely, both young and old muscles recovered less well if they were transplanted into an aged as opposed to young host. This study provided the first evidence of a negative age-related effect of the systemic environment on skeletal muscle. More recently these observations have been supported by work on parobiotic mice, animals which share a conjoined circulation. Using this model, recovery to a damaged older muscle was markedly improved if the aged animal shared its circulation with a younger animal (Conboy et al. 2005). Recent studies (Carlson et al. 2008) suggest that this age-related impairment to recovery from damage relates to changes in a number of signalling pathways (Notch, TGF-beta, pSmad3). These pathways regulate the proliferation and the myogenic commitment of satellite cells. Satellite cells are the muscle's stem cells, which are juxtaposed to muscle fibres and are required not only for repair, but also for adaptation and hypertrophy. Whilst age-related impairments in the recovery of muscle from damage have been demonstrated in rodent studies, human exercise studies have shown that even the muscles of very elderly people are very able to increase satellite cell number and hypertrophy in response to overload. We have recently used a primary cell / serum model to study the effects of the age of systemic environment on the behaviour of human cells extracted from muscle biopsies in culture. We have shown that committed myoblasts show similar abilities to both proliferate and differentiate when cultured in either a young or old serum (George et al. 2008). Furthermore, the cell itself (i.e. whether it originates from a young or elderly donor) shows no age-dependent behaviour. These findings would therefore suggest that a sufficient number of satellite cells are able to successfully progress through the myogenic lineage and can contribute to adaptation, even in an apparently hostile aged milieu.

Carlson BM & Faulkner JA. (1989) Muscle transplantation between young and old rats: age of host determines recovery. Am J Physiol. 256:C1262-6.

Carlson ME, Hsu M & Conboy IM. (2008) Imbalance between pSmad3 and Notch induces CDK inhibitors in old muscle stem cells. Nature 454:528-32

Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL & Rando TA. (2005) Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature.433:760-4.

George TE, Velloso C & Harridge, S. (2008) Aged human serum does not determine myogenicity in human primary muscle cells. Proc Physiol Soc 11, C54.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA6

A review of how specific muscle force changes with age and other factors

R.C. Woledge

Division of Applied Biomedical Reseach, Kings College London, London, UK

Larger muscles are stronger than smaller muscles; but not all variations in muscle strength are due to variations in muscle size. Ageing causes both muscle size and muscle strength to fall; but the fall in strength is greater than the fall in size (Newman et al. 2003). Decline in muscle quality is reflected in the ratio of force to CSA, termed 'specific muscle force', although shortening speed and power output may also decline. The evidence for age related decline in specific muscle force comes both from relatively small studies with individual muscles or muscle groups (e.g. Phillips et al. 1993) and also from larger studies in which muscle mass is measured for the whole body or lower extremity (e.g. Newman et al. 2003). The decline in specific force is not due to loss of actomyosin from the muscles, because the ability to resist stretch is not lost (Phillips et al. 1991). This also suggests that activation failure is unlikely to be the cause of the reduced specific force.Permeabilised ('skinned') muscle fibres can in principle be used to test whether changes in the intracellular milieu is responsible for force loss. Most published results do show a decline with age in the specific force of skinned muscle fibres (e.g. Yu et al. 2007), but there are some exceptions (e.g. Trappe et al. 2003), which leaves open the possibility that the responsible factors may be removed by skinning in some conditions. In humans the loss of specific muscle force has a different time course in men and women (Phillips et al. 1993). In women there is a relatively abrupt force loss at the menopause, which can be reversed by hormone replacement therapy (Skelton et al. 1999). In men the force loss occurs more gradually. Other factors which can change specific force are inorganic phosphate and temperature. Sudden changes in these variables alter force on a timescale short compared to the lifetime of crossbridges. (Crossbridges are the structures within muscle which develop force between the actin and myosin filaments.) At least with temperature change, force can be altered without changing the stiffness of the muscle. This shows that attached crossbridges in muscle exist in a mixture of states exerting different forces. Recently Ochala et al. (2007) showed that the specific force loss in skinned muscle fibres is not accompanied by any change in stiffness, suggesting that the ageing effect also is altering the proportions of these different force producing crossbridge states. If this is so there might be an interaction between temperature change and the process that reduces specific force with age. It is hoped to communicate some new experimental results on this point.

Newman, AB, Haggerty, CL, Goodpaster, B, Harris, T, Kritchevsky, S, Nevitt, M, Miles, TP, & Visser, M Strength and Muscle Quality in a Well-Functioning Cohort of

Older Adults: The Health, Aging and Body Composition Study J Am Geriatr Soc 51:323–330, 2003.

Ochala, J, Frontera, WR Dorer DJ, Van Hoecke J, & Krivickas LS Single Skeletal Muscle Fiber Elastic and Contractile Characteristics in Young and Older Men Journal of Gerontology: Biol Sci 2007, Vol. 62A, 375–381

Phillips S.K., Bruce S.A. & Woledge R.C. In mice, the muscle weakness due to age is absent during stretching. Journal of Physiology (London) 1991; 437: 63-70

Phillips S.K., Rook K.M., Siddle N.C., Bruce S.A., Woledge R.C. Muscle weakness in women occurs at an earlier age than in men but strength is maintained by hormone replacement therapy. Clinical Science 1993; 84: 95 98

Skelton D.A., Phillips S.K., Bruce S.A., Naylor C.H. & Woledge R.C. Hormone replacement therapy increases muscle strength of adductor pollicis in postmenopausal women. Clinical Science 1999; 96: 357-364

Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J & Trappe T 2003: Single muscle fibre contractile properties in young and old men and women. J Physiol. 2003 47-58

Yu F., Hedstrom M., Cristea A., Dale N. & Larsson L. Effects of ageing and gender on contractile properties in human skeletal muscle and single fibres. Acta Physiol 2007, 190, 229–241.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA8

Generating a robust molecular perspective of ageing-related changes in human skeletal muscle phenotype

J. Timmons

Stockholm University, Stockholm, Sweden

Profiling of global RNA abundance, using gene-chip technology, is a powerful systems biology tool for determining the molecular alterations in human skeletal muscle. The present research strategy was designed to move beyond the large number of small studies carried out in the human muscle physiology field, by providing data that could be more easily compared across physiological or pathophysiology states. In many cases the data is directly associated with skeletal muscle function or exercise capacity, to yield a more physiological interpretation of molecular phenotype. Data will be presented on a range of age related muscle conditions, under a variety of physiological states from > 300 subjects. This will include the largest analysis of human muscle phenotype in Type II diabetes, and the first global molecular analysis of cancer cachexia, intensive-care and exercise responses in human skeletal muscle. The dangers of drawing conclusions from small, poorly matched, cohorts will be exemplified using several examples, while I will show how global transcript profiling highlights the limitations of muscle protein synthesis approaches to study muscle physiology. Contrast will made across these studies, to exemplify how physiological context can facilitate interpretation of data and why systems biology extends beyond, yet benefits from the physiological sciences. Finally, current limitations of gene-chip strategies and studies will be discussed and future directions suggested.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA10

Regulation of bone mass and architecture by mechanical and biochemical interactions

T. Skerry

Human Metabolism, Univesity of Sheffield, Sheffield, UK

The strength of the skeleton is dependent on its mass, architecture and material properties. As we all differ in the demands we place on our skeletons, it is reasonable that we each tune our bone strength to our individual requirements. This provides the lightest structure to incur minimal costs of growth, maintenance and use with an adequate safety factor. At first impression, it seems that a relatively simple mechansm could account for the influence of mechanical forces on bone. However this is not so. The way that the skeleton responds to different forms of exercise/loading, and the different responses in different skeletal sites, and with age and sex show that this is a very complex system. Further complexity is added by the interactions of mechanical and other biochemical influences which are regulated by competing physiological demands.

The effects of these interactions are to regulate dynamically the mass and architecture of each bone. In general the material properties do not appear to be regulated by adaptive mechanisms but are specified for each skeletal site during development. The alteration of bone strength therefore depends upon orchestration of the actions of populations of bone forming osteoblasts and bone resorbing osteoclasts, in order to form or remove bone in a way that is appropriate for function.

The regulation of bone formation and resorption by those effector cells is likely to involve osteocytes, which are in an ideal position to sense and signal onwards the mechanical requirements of a region of bone.

In recent years, interest in osteocyte biology has grown considerably. However while the specific signalling events induced in osteocytic cells after loading have increased knowledge in the area, there is still a gap in understanding of how complex physiological loading (as opposed to simple modelled stretching) influences cells differently, and how these effects interact with other osteotropic influences. The ability of the skeleton to retain information on the effect of previous loading, and to modify the response to subsequent events is particularly poorly understood, yet may represent an important part of the way that age related changes occur in bone. Our studies suggest that a signalling system involving the excitatory amino acid glutamate and utilising synapse-like communications betweeen cells could provide this memory-like function in bone.

Improved understanding in these areas is likely to have pervasive implications in our ailiity to prevent or treat bone loss in the elderly.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA11

Does tendon tissue change when we get older?

M. Kjaer[1,2], K. Heinemeier[1,2], S. Dossing[1,2], M. Kongsgaard[1,2], M. Hansen[1,2] and S.P. Magnusson[1,2]

[1]University of Copenhagen, Copenhagen, Denmark and [2]Institute of Sports Medicine, Bispebjerg Hospital, Copenhagen, Denmark

Embryonic and neonatal animal tendons have a large potential to form fibrils and tendon structures. In adult humans the tendon collagen fractional synthesis rate is around 1% per day but it is unclear to what extent this ends up in structural fibrillar collagen structures of the tendon. Exercise results in increased synthesis and turnover of matrix proteins, with special emphasis on collagen. The stimulation of collagen synthesis by other growth factors can be shown in both animal and human models where insulin like growth factor 1 (IGF-1) and transforming growth factor beta1 (TGF-b1) expression increases accompanying or preceding a rise in procollagen expression and collagen synthesis. As IGF-I decreases with age, it is likely that collagen synthesis will decrease with ageing. The adaptation time to chronic loading is longer in tendon tissue compared to contractile elements of skeletal muscle or heart, and only with very prolonged loading, significant changes in gross dimensions of the tendon are observed. Interestingly, the tendon dimensions do also enlarge with ageing despite a decrease in physical activity. The exact changes in properties of tendons with ageing are not fully determined, but stiffness increases and recent evaluation of the content of cross links reveal that non-enzymatic advanced glycation end products (AGEs) are accumulated in elderly tendons. Interestingly, already in younger age a correlation between AGE content of tendon and age is found. Increased cross-linking may contribute to age related changes in tendon properties.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA12

Ageing, exercise and immune function

J.M. Lord

Immunology, Birmingham University, Birmingham, UK

Average life expectancy in the developed world is increasing at a rate of 2 years per decade and, if this continues, by the year 2020 one in five of the population will be aged 65 years and over. Despite the increase in average lifespan, the period of good health enjoyed during a lifetime (healthspan) has not kept pace and there is evidence that the time spent in ill health in old age is increasing (1). Susceptibility to infectious disease increases with age and infection related mortality accounts for almost 15% of deaths amongst those aged over 85 years (1). These data suggest a decline in the functioning of the immune system with age, a process termed immunesenescence. In addition, there are age-related alterations to the Hypothalamic-Pituitary-Adrenal (HPA) axis, a key effector of the response to

stress. The reduced ability to produce the immune enhancing hormone dehydroepiandrosterone (DHEA) results may contribute to immunesenescence and leave older adults more susceptible to infections following physical trauma such as hip-fracture (2,3).

It is proposed that the age-related changes to both the immune system and the HPA axis result in increased vulnerability to stress in older adults, and factors that can modify the impact of the stress response upon immunity should be sought. One potential intervention is exercise. It is well known that physical activity declines with age in humans and that physically active older adults have fewer infections (4) and evidence will be presented that this is achieved via positive effects on immune system components.

1. Ageing: Scientific Aspects. House of Lords Science and Technology Committee report. Vol 1, 19-65. 2005. The Stationery Office, Norwich, UK.

2. Bauer ME (2005). Stress. 8(1):69-83.

3. Butcher SK & Lord JM (2004). Aging Cell. 3(4):151-160.

4. Leveille SG, et al (2000). J. Am.Ger.Soc. 48(12):1582-1588.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA13

What have we learnt from master athletes?

H. Degens

Institute for Biomedical Research into Human Movement and Health, Manchester Metropolitan University, Manchester, UK

Ageing is associated with a progressive decrease in exercise capacity. This decrease can be attributed to loss of power generating capacity of the muscles and maximal aerobic capacity (VO_{2max}) as a consequence of muscle wasting, alterations in muscle contractile properties and cardiac function. It is to be expected that reduced activity levels at old age contribute to the age-related decrement in cardiovascular and muscle function. Master athletes are a unique population to study to what extent these changes are related to ageing per se, as they maintain a high level of physical activity and suffer less from co-morbidities than the normal ageing population (1). The importance of physical activity is readily seen in the higher power generating capacity of the muscle and VO_{2max} in master weight lifters (2) and endurance (3) athletes, respectively, than that in age-matched sedentary people. The elevated VO_{2max} in endurance trained master athletes is attributable to a larger stroke volume and maximal cardiac output (3). Nevertheless, master athletes show a similar age-related decline in muscle power and VO_{2max} as sedentary people (2,3). Part of this might be related to a diminished training stimulus to the heart and/or muscles as a consequence of the reduced training intensity at old age (3). Despite this age-related decline in performance, the VO_{2max} and muscle power of master athletes is similar to that of sedentary people up to 20 years younger. Hence, their quality of life is significantly better than that of other people of their age, which is further enhanced by diminished arterial stiffness and peripheral vasoconstriction (3), an improved glucose tolerance and lipid profiles similar to younger people (4). It is encouraging to note that at advanced age improvements in cardiovascular and muscle function can also be realised by short term training programmes (5,6). Similar to the decline in VO_{2max} and muscle power of master athletes, the response to training programmes may be attenuated at old age (7). In conclusion, the study of master athletes has taught us that life-long, or only recently started, exercise training in old age is an adequate means on improving the quality of life and to delay the decline in exercise performance in old age. It has also shown us that high activity levels do not entirely prevent the age-related reduction in muscle power and VO_{2max}. Thus the question remains as to the cause of the inherent loss of exercise capacity as a result, it appears, of the ageing process per se. Some of the factors associated with ageing are changes in circulating substances, such as hormones and cytokines, and the ongoing denervation-reinnervation process (7).

Rittweger J, Kwiet A, Felsenberg D. Physical performance in aging elite athletes—challenging the limits of physiology. J Musculoskelet Neuronal Interact 2004: 4: 159-160.

Pearson SJ, Young A, Macaluso A, Devito G, Nimmo MA, Cobbold M, Harridge SD. Muscle function in elite master weightlifters. Med Sci Sports Exerc 2002: 34: 1199-1206.

Tanaka H, Seals DR. Endurance exercise performance in Masters athletes: age-associated changes and underlying physiological mechanisms. J Physiol 2008: 586: 55-63.

Rosenbloom C, Bahns M. What can we learn about diet and physical activity from master athletes? Holist Nurs Pract. 2006: 20:161-168.

Morse CI, Thom JM, Mian OS, Muirhead A, Birch KM, Narici MV. Muscle strength, volume and activation following 12-month resistance training in 70-year-old males. Eur J Appl Physiol 2005: 95: 197-204.

Seals DR, Desouza CA, Donato AJ, Tanaka H. Habitual exercise and arterial aging. J Appl Physiol 2008:105:1323-1332.

Degens H. Age-related skeletal muscle dysfunction: causes and mechanisms. J Musculoskelet Neuronal Interact 2007: 7: 246-252.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA14

Neuromuscular adaptations to strength training in the elderly

P. Aagaard

University of Southern Denmark, Odense, Denmark

Aging is characterized by loss of spinal motor neurons (MNs) due to apoptosis, elevated amounts of circulating cytokines and increased cell oxidative stress. The age-related loss of spinal MNs leads to a reduction in muscle fiber number and size (sarcopenia), resulting in impaired mechanical muscle performance that in turn leads to a reduced functional capacity during everyday tasks. At the same time, however, aging involves substantial reorganization in the neuromuscular system and the CNS, which includes partial reinnervation of deinnervated muscle fibers. Experimental findings comprise the presence of very large motor units with aging, fiber type grouping, compressed rate coding during graded muscle contraction, reduced resting H-reflex excitability, and reduced TMS-evoked motor potentials suggesting decreased excitability in corticospinal pathways. Maximum muscle strength and power are markedly

decreased with aging, even in highly trained strength athletes. Strength training leads to increased muscle strength and power in the elderly, including very old individuals (80 yrs). Notably, maximum power increased more after strength training using heavy loads (80% 1RM) than less heavy loads (50% 1RM). While rapid muscle force production (rate of force development, RFD = $\Delta F/\Delta t$) is reduced with aging, increases in RFD and contractile impulse ($\int Fdt$) can be observed following strength training concurrently with signs of elevated neuromuscular activity (increased surface EMG amplitude). Maximum RFD is influenced by maximal MN firing frequency and the presence of MN discharge doublets. Maximum firing frequency during isometric or dynamic MVC is reduced with aging, along with a reduced incidence of MN doublet firing. Importantly, maximum MN firing frequency is increased in the elderly with strength training. Frail elderly may show reduced central muscle activation (CA) assessed by electrical muscle stimulation superimposed during MVC. CA may increase with strength training in the elderly, where individual changes in CA and maximal muscle strength (MVC) were related in very old individuals (+80). Unilateral long-term limb disuse is accompanied by a selective reduction in CA for the affected limb. Short-term (2 wks) limb immobilization led to reduced CA in old but not young subjects, indicating that the neuromuscular system of old individuals may be affected more severely by short-term unloading. Subsequent re-training by means of resistance exercise (4 wks) appeared to fully restore CA in old individuals, while young subjects increased CA above pre training levels.Old individuals may show increased antagonist muscle coactivation during MVC, although not a universal finding. If elevated prior to training, antagonist coactivation typically decreases following strength training in the elderly, although increased antagonist coactivation may also occur. Nevertheless, elderly typically show elevated muscle coactivation during daily movement tasks such as stair climbing and step descent, which seems to be unaffected by strength training. Force steadiness is impaired with aging, as reflected by elevated SD during isometric and dynamic force tracking tasks. Notably, strength training leads to improved force steadiness. In conclusion, elderly individuals demonstrate substantial adaptive plasticity in the neuromuscular system in response to strength training (resistance exercise), which may effectively compensate for the age-related decline in muscle size and neuronal function.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA15

Myotendinous adaptations to ageing, disuse and training

M.V. Narici

Institute for Biomedical Research into Human Movement, Manchester Metropolitan University, Manchester, UK

Muscles and tendons show a remarkable plasticity in response to chronic loading, unloading and ageing. In a recent unloading study we showed a significant decrease (-8%) in human vastus lateralis (VL) muscle fibre fascicle length after 23 days of unilateral lower limb suspension (ULLS) (1). Concomitantly, patellar tendon (PT) stiffness decreased by 29% after 23 days ULLS (1). These changes are similar to those found in ageing since lower limb fibre fascicle length and tendon stiffness are respectively reduced by 10% and 36%, in older humans (2). These changes are expected to have an impact on the VL length-force relation (L-F), since a decrease in tendon stiffness would cause a left shift in the VL fascicles L-F relation, away from the force plateau region (3). However, since in both disuse and ageing, fascicle length was shorter, lesser sarcomere shortening would be expected upon contraction, thus shifting the L-F relation to the right, closer to the optimum region (3). Thus a compensation between the fascicular and tendon changes seems to occur. However, this effect may only partly mitigate the force loss, since it cannot compensate the decline in force due to the loss of motor units (MUs) with ageing (4) or to the decrease in single fibre specific tension occuring with ageing and disuse (5). Loading, instead, produces the opposite effects: after 14 weeks of resistance training in older men, VL fascicle length increased by 8-10% (3), while PT tendon stiffness increased by 65%. The rapid muscle remodeling produced by these experimental paradigms, seems regulated by changes in the mechano-sensitive costameric protein focal adhesion kinase (FAK), believed to be an up-stream regulator of protein synthesis. Overloading of avian muscle causes a massive increase in FAK content (+112% after 1 day and 611% after 8 days) and activity (+370% after 1.5 and 13 days) (6). Instead, unloading produces opposite effects, since FAK content and activity decrease by 20 and 30%, respectively, within 10 days of ULLS in humans (7).

Thus the loss of muscle force observed with ageing and unloading likely reflects the combined effect of muscular and tendinous adaptations and, limited to old age, also of neuropathic processes responsible of the loss of MUs. In both ageing and unloading these myotendinous alterations may be largely reversed with loading, though muscle weakness due to MUs loss with age, cannot be prevented. The structural remodeling of skeletal muscle, detectable within few days of loading or unloading, seems mediated by changes in costameric proteins involved in mechanotransduction.

de Boer MD, Maganaris CN, Seynnes OR, Rennie MJ & Narici MV. (2007). Time course of muscular, neural and tendinous adaptations to 23 day unilateral lower-limb suspension in young men. J Physiol 583, 1079-1091.

Narici MV & Maganaris CN. (2007). Plasticity of the muscle-tendon complex with disuse and aging. Exerc Sport Sci Rev 35, 126-134.

Reeves ND, Narici MV & Maganaris CN (2006). Myotendinous plasticity to ageing and resistance exercise in humans. Exp Physiol 91, 483-498.

Lexell J, Henriksson-Larsen K, Winblad B & Sjostrom M. (1983). Distribution of different fiber types in human skeletal muscles: effects of aging studied in whole muscle cross sections. Muscle Nerve 6, 588-595.

D'Antona G, Pellegrino MA, Adami R, Rossi R, Carlizzi CN, Canepari M, Saltin B & Bottinelli R. (2003). The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. J Physiol 552, 499-511.

Fluck M, Carson JA, Gordon SE, Ziemiecki A & Booth FW. (1999). Focal adhesion proteins FAK and paxillin increase in hypertrophied skeletal muscle. Am J Physiol 277, C152-162.

de Boer MD, Selby A, Atherton P, Smith K, Seynnes OR, Maganaris CN, Maffulli N, Movin T, Narici MV & Rennie MJ. (2007). The temporal responses of protein synthesis, gene expression and cell signalling in human quadriceps muscle and patellar tendon to disuse. J Physiol 585, 241-251.

Professor Michael Rennie of the University of Nottingham, School of Graduate Entry Medicine and Health, Derby City Hospital, had an instrumental role in the investigations into the myogenic responses with ULLS. His work, and that of his collaborators, is fully acknowledged.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA16

Ageing and neuromuscular control of movement

R. Enoka

Integrative Physiology, University of Colorado, Boulder, CO, USA

Declines in the control of movement experienced by older adults are mediated by adaptations in motor unit activity. It has been proposed, for example, that the reduced ability of older adults to perform steady contractions at low forces is attributable to a greater variability in the discharge of action potentials by motor neurons. To evaluate this hypothesis, the discharge characteristics of motor units in a hand muscle of young and old adults were determined during brief isometric contractions over a range of contraction intensities. The experimental measurements were imported into a computational model of motor unit recruitment and rate coding to examine the association between discharge variability and force steadiness. The results indicated a strong association between population levels of motor unit discharge variability and steadiness, but there were no differences in discharge variability between young and old adults. Nonetheless, old adults are often less steady than young adults, especially when exerting low forces and after being exposed to a stressor that increases physiological arousal. Furthermore, there are moderate levels of association across the lifespan between measures of steadiness during weak contractions with hand muscles and performance on tests of hand function. Collectively, these findings underscore the significant influence of task specificity when comparing the performance capabilities of young and old adults. As the task requirements change, so does the synaptic input received by the motor neurons. A striking example of a difference between young and old adults is the discharge characteristics of motor units recruited during sustained, submaximal contractions. Discharge variability can be much greater for young adults when they sustain isometric contractions at different target forces compared with old adults, which suggests that some combination of the synaptic input and the intrinsic properties of the motor neurons differ for these groups of individuals. Furthermore, similar improvements in the accuracy of a rapid isometric contraction to a target force were accomplished by different adaptations in the agonist and antagonist muscles by young and old adults. These comparisons indicate that understanding the declines in the control of movement by older adults requires studies that focus on the relevant adaptations that influence the control of the involved muscles.

The work was supported by the National Institute on Aging in the USA.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA17

Mobility limitation in old age

T. Rantanen

Finnish Center for Interdisciplinary Gerontology, University of Jyväskylä, Jyväskylä, Finland

Safe mobility is important for quality of life of older people while mobility limitation may lead to loss of autonomy and further deterioration of health. Mobility is typically assessed first of all with tests on maximal or customary walking speed over shorter distances or walking endurance over longer distances. Self-reports of perceived difficulty walking particular distances are commonly used in epidemiological studies. Using data of the Finnish Twin Study on aging, we found that 20-50 % of individual differences in walking speed and walking endurance are explained by genetic factors among older women. Other factors underlying poor mobility which we have analyzed in our data include poor strength and balance, overweight and obesity, sensory deficits such as poor vision and hearing, falls, pain, fear of moving outdoors, sedentary behavior and negative environmental features. People with mobility limitation often suffer from unmet need for physical activity manifested as perceiving no opportunity to participate in exercise even though would want to do so. We carried out a randomized controlled trial on physical activity counseling among 632 community living people aged 75-81 years who were at most moderately active, had no apparent memory problems and who at baseline were able to walk at least minimally. The experimental group received a single face-to-ace counseling session followed up with supportive telephone contacts every for months for two years. Data on perceived difficulty walking 500 m and 2 km were collected every six months for the two year study period as well as one and half year follow-up after the end of the intervention. Intervention group developed statistically significantly less difficulties in 2 km walk than control group. Results for 500 m walk parallel but remained non-significant. Behavioral interventions may be useful in preventing development of mobility limitation in old age. More research is needed on sustainable ways to promote mobility in old age.

Rantanen T, Guralnik JM, Ferrucci L, Penninx BWJH, Leveille SG, Sipilä S, Fried LP. Coimpairments as predictors of severe walking disability in older women. Journal of the American Geriatrics Society 2001; 49: 21-27

Ortega-Alonso A. Pedersen NL, Kujala UM, Sipilä S, Törmäkangas T, Kaprio J, Koskenvuo M, Rantanen T. A Twin study on the heritability of walking ability among older women. J Gerontol Med Sci 2006; 61A:1082-1085

Stenholm S, Rantanen T, Heliövaara M, Koskinen S. The Mediating Role of C-reactive Protein and Muscle Strength between Obesity and Walking Limitation. J Am Geriatr Soc 2008;56:462-469

Ortega-Alonso A, Sipilä S, Kujala UM, Kaprio J, Rantanen T. Body fat and mobility are explained by common genetic and environmental influences in older women. Obesity 2008;16:1616-21.

Viljanen A, Kaprio J, Pyykkö I, Sorri M, Pajala S, Kauppinen M, Koskenvuo M, Rantanen T. Hearing as a predictor of falls and postural balance in older female twins. J Gerontol Med Sci, in press.

Rantakokko M, Mänty M, Iwarsson S,Törmäkangas T, Leinonen R, Heikkinen E, Rantanen T.Fear of moving outdoors and development of outdoor walking difficulty among older people. J Am Geriatr Soc, in press.

Mänty M, Heinonen A, Leinonen R, Törmäkangas T, Hirvensalo M, Kallinen M, Sakari-Rantanen R, von Bonsdorff M, Heikkinen E, Rantanen T. Long-Term Effect of Physical Activity Counseling on the Development of Mobility Limitation Among Older People: A Randomized Controlled Study. J Gerontol Med Sci, in press

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.

SA18

The science behind falls prevention programmes

D.A. Skelton

HealthQWest, School of Health and Social Care, Glasgow Caledonian University, Glasgow, UK

This session will consider the evidence for exercise as an important factor within a multifactorial fall prevention programme and exercise alone as both a preventative and a rehabilitative tool. It will also consider the need for balance specificity, tailoring, adequate duration and intensity, sufficient progression, education and telephone support. Epidemiological evidence suggests that, compared with a sedentary lifestyle, spending over three hours targeted exercise each week can halve the risk of osteoporosis, falls-related injuries and hip fracture 1. But the relationship between physical activity and falls is actually U-shaped, where those who are most sedentary and those who are most active (increased exposure to potential risk) are at increased risk 1. Robust RCTs of tailored, targeted exercise training over one year reduce the risk of falls and fractures in community dwelling older adults exercising in their own home (Otago Home Exercise Programme)2. Group exercise programmes for fallers have the added benefit of social inclusion, improving self-efficacy and reducing fear of falls when people have the chance to share experiences and solutions. Falls Management Exercise (FaME), delivered once a week for 9 months with a home exercise programme twice a week, halved the risk of falls compared to that in controls and reduced the likelihood of death or admission to institutional care 3. To date, FaME is the only programme to integrate retraining the ability to get down to and up from the floor and to include floor coping skills such as crawling and rolling to ensure avoidance of a long-lie after a fall. Targeted training can also improve balance and strength, and reduce pain and the incidence of fractures in elderly women with established osteoporosis. Although consensus and guidelines still favour a multi-factorial approach 4, a recent review 5, showed that exercise offers many other benefits wider than just preventing falls, so perhaps is the best "single" intervention that we could offer on a population basis. The science behind delivering effective falls prevention exercise involves ensuring tailoring and progression of exercise, highly challenging balance, a dose of at least 50 hours and avoidance of a walking programme 5. Our next challenge is to increase uptake and adherence to strength and balance training. When should we advise people to start strength and balance re-training? Studies suggest that certain activities, such as Tai Chi, if started when people have only mild deficits of strength and balance, can reduce the chance of falls. Most research, however, suggests that starting strength and balance training appears most effective when the participants are just at that critical threshold where daily home tasks are at the limits of the person's stability. Small gains in balance and strength benefit by enabling the person to cope more safely with the activities of daily living.

1. Gregg EW, Pereira MA, Caspersen CJ. Physical activity, falls, and fractures among older adults: a review of the epidemiologic evidence. J Am Geriatr Soc 2000; 48:883-93.

2. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM Randomized controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. Brit Med J 1997; 315:1065-69.

3. Skelton D, Dinan S, Campbell M, Rutherford O. Tailored group exercise (Falls Management Exercise — FaME) reduces falls in community-dwelling older frequent fallers (an RCT). Age Ageing 2005; 34: 636-9

NICE Guideline 21. Falls: the assessment and prevention of falls in older people. 2004. National Institute of Clinical Evidence, London.

5. Sherrington C, Whitney J, Lord S, Herbert R, Cumming R, Close JCT. Effective Exercise for the Prevention of Falls: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2008; 56: 2234-2243.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.