Publications from the MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research

Issue 1
(January to June 2014)
Theme 1
Mechanisms of Ageing in the Musculoskeletal System

This theme is based on researching into 4 key areas:

- Anabolic blunting: Building on our discovery of anabolic resistance in older people.
- Increased adiposity and sarcopenia: exploring the mechanisms of these processes at a molecular and cellular level.
- Effects of ageing on muscle microvascular blood flow.
- Endocrine disruption: Probing the mechanisms underlying changes in the ageing physiology brought on by physical inactivity and an unhealthy weight.

Publications

Narici MV
Knee extensor fatigue resistance of young and older men and women performing sustained and brief intermittent isometric contractions.

McPhee JS1, Maden-Wilkinson TM, Narici MV, Jones DA, Degens H.
Abstract
Introduction: Susceptibility to muscle fatigue during aging could depend on muscle activation patterns.
Methods: Young (mean age 22 yrs) and older (mean age 70 yrs) men and women completed 2 fatigue tests of knee extensor muscles using voluntary and electrically stimulated contractions. Results: Older subjects displayed a shift to the left of the torque-frequency relationship and held a sustained voluntary isometric contraction at 50% maximal strength for significantly longer than young (P<0.001). Young and old showed similar fatigue during electrically-induced, intermittent isometric contractions (1-s on, 1-s off for 2 min), but women fatigued less than men (P=0.001). Stronger muscles fatigued more quickly, and slower contractile properties were associated with longer sustained contractions. Discussion: The slowing and weakness of older muscle was associated with superior fatigue resistance during sustained isometric contractions. Young and old showed similar fatigue following a series of brief, intermittent contractions, but women fatigued less than men. © 2014 Wiley Periodicals, Inc.

Buckley CD
Proresolving lipid mediators and mechanisms in the resolution of acute inflammation.

Buckley CD, Gilroy DW, Serhan CN.
Abstract
Inflammatory responses, like all biological cascades, are shaped by a delicate balance between positive and negative feedback loops. It is now clear that in addition to positive and negative checkpoints, the inflammatory cascade rather unexpectedly boasts an additional checkpoint, a family of chemicals that actively promote resolution and tissue repair without compromising host defense. Indeed, the resolution phase of inflammation is just as actively orchestrated and carefully choreographed as its induction and inhibition. In this review, we explore the immunological consequences of omega-3-derived specialized proresolving mediators (SPMs) and discuss their place within what is currently understood of the role of the arachidonic acid-derived prostaglandins, lipoxins, and their natural C15-epimers. We propose that treatment of inflammation should not be restricted to the use of inhibitors of the acute cascade (antagonism) but broadened to take account of the enormous therapeutic potential of inducers (agonists) of the resolution phase of inflammation.
Murton AJ, Billeter R, Stephens FB, Greenhaff PL


Transient transcriptional events in human skeletal muscle at the outset of concentric resistance exercise training.


Abstract

We sought to ascertain the time course of transcriptional events that occur in human skeletal muscle at the outset of resistance exercise (RE) training in RE naive individuals and determine whether the magnitude of response was associated with exercise-induced muscle damage. Sixteen RE naive men were recruited; eight underwent two sessions of 5 × 30 maximum isokinetic knee extensions (180°/s) separated by 48 h. Muscle biopsies of the vastus lateralis, obtained from different sites, were taken at baseline and 24 h after each exercise bout. Eight individuals acted as nonexercise controls with biopsies obtained at the same time intervals. Transcriptional changes were assessed by microarray and protein levels of heat shock protein (HSP) 27 and αB-crystallin in muscle cross sections by immunohistochemistry as a proxy measure of muscle damage. In control subjects, no probe sets were significantly altered (false discovery rate < 0.05), and HSP27 and αB-crystallin protein remained unchanged throughout the study. In exercised subjects, significant intersubject variability following the initial RE bout was observed in the muscle transcriptome, with greatest changes occurring in subjects with elevated HSP27 and αB-crystallin protein. Following the second bout, the transcriptome response was more consistent, revealing a cohort of probe sets associated with immune activation, the suppression of oxidative metabolism, and ubiquitination, as differentially regulated. The results reveal that the initial transcriptional response to RE is variable in RE naive volunteers, potentially associated with muscle damage and unlikely to reflect longer term adaptations to RE training. These results highlight the importance of considering multiple time points when determining the transcriptional response to RE and associated physiological adaptation.

Narici MV


Diagnostic criteria for sarcopenia and physical performance.


Abstract

Relative and absolute muscle mass and muscle strength are used as diagnostic criteria for sarcopenia. We aimed to assess which diagnostic criteria are most associated with physical performance in 180 young (18-30 years) and 281 healthy old participants (69-81 years) of the European study MYOAGE. Diagnostic criteria included relative muscle mass (total or appendicular lean mass (ALM) as percentage of body mass), absolute muscle mass (ALM/height squared and total lean mass), knee extension torque, and handgrip strength. Physical performance comprised walking speed, Timed Up and Go test (TUG), and in a subgroup physical fitness. Diagnostic criteria for sarcopenia and physical performance were standardized, and the associations were analyzed using linear regression models stratified by age category, with adjustments for age, gender, and country. In old participants, relative muscle mass was associated with faster walking speed, faster TUG, and higher physical fitness (all p < 0.001). Absolute muscle mass was not associated with physical performance. Knee extension torque and handgrip strength were associated with faster walking speed (both p ≤ 0.003). Knee extension torque was associated with TUG (p = 0.001). Knee extension torque and handgrip strength were not associated with physical fitness. In young participants, there were no significant associations between diagnostic criteria for sarcopenia and physical performance, except for a positive association between relative muscle mass and physical fitness (p < 0.001). Relative muscle mass, defined as lean mass or ALM percentage, was most associated with physical performance. Absolute muscle mass including ALM/height squared was not associated with physical performance. This should be accounted for when defining sarcopenia.
Acute dietary protein intake restriction is associated with changes in myostatin expression after a single bout of resistance exercise in healthy young men.


Abstract
Skeletal muscle satellite cells (SCs) play an important role in the myogenic adaptive response to exercise. It remains to be established whether nutrition plays a role in SC activation in response to exercise. In the present study, we assessed whether dietary protein alters the SC response to a single bout of resistance exercise. Twenty healthy young (aged 21 ± 2 y) males were randomly assigned to consume a 4-d controlled diet that provided either 1.2 g protein ⋅ kg body weight(-1) ⋅ d(-1) [normal protein diet (NPD)] or 0.1 g protein ⋅ kg body weight(-1) ⋅ d(-1) [low protein diet (LPD)]. On the second day of the controlled diet, participants performed a single bout of resistance exercise. Muscle biopsies from the vastus lateralis were collected before and after 12, 24, 48, and 72 h of post-exercise recovery. SC content and activation status were determined using immunohistochemistry. Protein and mRNA expression were determined using Western blotting and reverse transcription polymerase chain reaction. The number of myostatin + SCs decreased significantly at 12, 24, and 48 h (range, -14 to -49%; P < 0.05) after exercise cessation, with no differences between groups. Although the number of myostatin + SCs returned to baseline in the type II fibers on the NPD after 72 h of recovery, the number remained low on the LPD. At the 48 and 72 h time points, myostatin protein expression was elevated (86 ± 26% and 88 ± 29%, respectively) on the NPD (P < 0.05), whereas it was reduced at 72 h (-36 ± 12% compared with baseline) in the LPD group (P < 0.05). This study demonstrates that dietary protein intake does not modulate the post-exercise increase in SC content but modifies myostatin expression in skeletal muscle tissue. This trial was registered at clinicaltrials.gov as NCT01220037.

Wilkinson DJ, Franchi MV, Narici MV, Szewczyk NJ, Greenhaff PL, Atherton PJ, Smith K

Abstract
Quantification of muscle protein synthesis (MPS) remains a cornerstone for understanding the control of muscle mass. Traditional [(13)C]amino acid tracer methodologies necessitate sustained bed rest and intravenous cannulation(s), restricting studies to ~12 h, and thus cannot holistically inform on diurnal MPS. This limits insight into the regulation of habitual muscle metabolism in health, aging, and disease while querying the utility of tracer techniques to predict the long-term efficacy of anabolic/anticatabolic interventions. We tested the efficacy of the D2O tracer for quantifying MPS over a period not feasible with (13)C tracers and too short to quantify changes in mass. Eight men (22 ± 3.5 yr) undertook one-legged resistance exercise over an 8-day period (4 × 8-10 repetitions, 80% 1RM every 2nd day, to yield "nonexercised" vs. "exercise" leg comparisons), with vastus lateralis biopsies taken bilaterally at 0, 2, 4, and 8 days. After day 0 biopsies, participants consumed a D2O bolus (150 ml, 70 atom%); saliva was collected daily. Fractional synthetic rates (FSRs) of myofibrillar (MyoPS), sarcoplasmic (SPS), and collagen (CPS) protein fractions were measured by GC-pyrolysis-IRMS and TC/EA-IRMS. Body water initially enriched at 0.16-0.24 APE decayed at ~0.009%/day. In the nonexercised leg, MyoPS was 1.45 ± 0.10, 1.47 ± 0.06, and 1.35 ± 0.07%/day at 0-2, 0-4, and 0-8 days, respectively (~0.05-0.06%/h). MyoPS was greater in the exercised leg (0-2 days: 1.97 ± 0.13%/day; 0-4 days: 1.96 ± 0.15%/day, P < 0.01; 0-8 days: 1.79 ± 0.12%/day, P < 0.05). CPS was slower than MyoPS but followed a similar pattern, with the exercised leg tending to yield greater FSRs (0-2 days: 1.14 ± 0.13 vs. 1.45 ± 0.15%/day; 0-4 days: 1.13 ± 0.07%/day vs. 1.47 ± 0.18%/day; 0-8 days: 1.03 ± 0.09%/day vs. 1.40 ± 0.11%/day). SPS remained unchanged. Therefore, D2O has unrivaled utility to quantify day-to-day MPS in humans and inform on short-term changes in anabolism and presumably catabolism alike.
Wilkinson DJ, Narici MV, Smith K, Atherton PJ


Protein Carbonylation and Heat Shock Proteins in Human Skeletal Muscle: Relationships to Age and Sarcopenia.

Beltran Valls MR, Wilkinson DJ, Narici MV, Smith K, Phillips BE, Caporossi D, Atherton PJ.

Abstract

Aging is associated with a gradual loss of muscle mass termed sarcopenia, which has significant impact on quality-of-life. Because oxidative stress is proposed to negatively impact upon musculoskeletal aging, we investigated links between human aging and markers of oxidative stress, and relationships to muscle mass and strength in young and old nonsarcopenic and sarcopenic adults. Sixteen young and 16 old males (further subdivided into "old" and "old sarcopenic") were studied. The abundance of protein carbonyl adducts within skeletal muscle sarcoplasmic, myofibrillar, and mitochondrial protein subfractions from musculus vastus lateralis biopsies were determined using Oxyblot immunoblotting techniques. In addition, concentrations of recognized cytoprotective proteins (eg, heat shock proteins [HSP], αβ-crystallin) were also assayed. Aging was associated with increased mitochondrial (but not myofibrillar or sarcoplasmic) protein carbonyl adducts, independently of (stage-I) sarcopenia. Correlation analyses of all subjects revealed that mitochondrial protein carbonyl abundance negatively correlated with muscle strength ([1-repetition maximum], p = .02, r² = -.16), but not muscle mass (p = .13, r² = -.08). Abundance of cytoprotective proteins, including various HSPs (HSP 27 and 70), were unaffected by aging/sarcopenia. To conclude, these data reveal that mitochondrial protein carbonylation increases moderately with age, and that this increase may impact upon skeletal muscle function, but is not a hallmark of (stage-I) sarcopenia, per se.

Atherton PJ, Selby A, Narici MV


Architectural, functional and molecular responses to concentric and eccentric loading in human skeletal muscle.

Franchi MV, Atherton PJ, Reeves ND, Flück M, Williams J, Mitchell WK, Selby A, Beltran Valls RM, Narici MV.

Abstract

AIM:

We investigated architectural, functional and molecular responses of human skeletal muscle to concentric (CON) or eccentric (ECC) resistance training (RT).

METHODS:

Twelve young males performed 10 weeks of concentric (CON) or eccentric (ECC) resistance training (RT) (n = 6 CON, 6 ECC). An additional 14 males were recruited to evaluate acute muscle fascicle behaviour and molecular signalling in biopsies collected from vastus lateralis (VL) after 30 min of single bouts of CON or ECC exercise. VL volume was measured by magnetic resonance imaging. Muscle architecture (fascicle length, Lf; pennation angle, PA) was evaluated by ultrasonography. Muscle remodelling signals to CON or ECC loading [MAPK/AKT-mammalian target of rapamycin (mTOR) signalling] and inflammatory pathway (TNFαMurf-1-MAFbx) were evaluated by immunoblotting.

RESULTS:

Despite the ~1.2-fold greater load of the ECC group, similar increases in muscle volume (+8% CON and +6% ECC) and in maximal voluntary isometric contraction (+9% CON and +11% ECC) were found after RT. However, increases in Lf were greater after ECC (+12 vs. +5%) while increases in PA were greater in CON than ECC (+30 vs. +5%). Distinct architectural adaptations were associated with preferential growth in the distal regions of VL for ECC (+ECC +8% vs. +CON +2) and mid belly for CON (+ECC +7 vs. CON +11%). While MAPK activation (p38MAPK, ERK1/2, p90RSK) was specific to ECC, neither mode affected AKT-mTOR or inflammatory signalling 30 min after exercise.

CONCLUSION:

Muscle growth with CON and ECC RT occurs with different morphological adaptations reflecting distinct fibre fascicle behaviour and molecular response.
Bartlett DB, Lord JM

Calcif Tissue Int. 2014 May 25. [Epub ahead of print]

Inflammation, Telomere Length, and Grip Strength: A 10-year Longitudinal Study.

Abstract
Telomere attrition has been associated with age-related diseases, although causality is unclear and controversial; low-grade systemic inflammation (inflammaging) has also been implicated in age-related pathogenesis. Unpicking the relationship between aging, telomere length (TL), and inflammaging is hence essential to the understanding of aging and management of age-related diseases. This longitudinal study explored whether telomere attrition is a cause or consequence of aging and whether inflammaging explains some of the associations between TL and grip strength. We studied 253 Hertfordshire Ageing Study participants at baseline and 10-year follow-up (mean age at baseline 67.1 years). Participants completed a health questionnaire and had blood samples collected for immune-endocrine and telomere analysis at both time points. Physical aging was characterized at follow-up using grip strength. Faster telomere attrition was associated with lower grip strength at follow-up (β = 0.98, p = 0.035). This association was completely attenuated when adjusted for inflammaging burden (p = 0.86) over the same period. Similarly, greater inflammaging burden was associated with lower grip strength at follow-up (e.g., interleukin [IL]-1β: β = -2.18, p = 0.001). However, these associations were maintained when adjusted for telomere attrition (IL-1β, p = 0.006). We present evidence that inflammaging may be driving telomere attrition and in part explains the associations that have previously been reported between TL and grip strength. Thus, biomarkers of physical aging, such as inflammaging, may require greater exploration. Further work is now indicated.

Narici M, Szewczyk NJ

Spaceflight and ageing: reflecting on Caenorhabditis elegans in space.
Honda Y¹, Honda S, Narici M, Szewczyk NJ.

Abstract
The prospect of space travel continues to capture the imagination. Several competing companies are now promising flights for the general population. Previously, it was recognized that many of the physiological changes that occur with spaceflight are similar to those seen with normal ageing. This led to the notion that spaceflight can be used as a model of accelerated ageing and raised concerns about the safety of individuals engaging in space travel. Paradoxically, however, space travel has been recently shown to be beneficial to some aspects of muscle health in the tiny worm Caenorhabditis elegans. C. elegans is a commonly used laboratory animal for studying ageing. C. elegans displays age-related decline of some biological processes observed in ageing humans, and about 35% of C. elegans’ genes have human homologs. Space flown worms were found to have decreased expression of a number of genes that increase lifespan when expressed at lower levels. These changes were accompanied by decreased accumulation of toxic protein aggregates in ageing worms’ muscles. Thus, in addition to spaceflight producing physiological changes that are similar to accelerated ageing, it also appears to produce some changes similar to delayed ageing. Here, we put forward the hypothesis that in addition to the previously well-appreciated mechanotransduction changes, neural and endocrine signals are altered in response to spaceflight and that these may have both negative (e.g. less muscle protein) and some positive consequences (e.g. healthier muscles), at least for invertebrates, with respect to health in space. Given that changes in circulating hormones are well documented with age and in astronauts, our view is that further research into the relationship between metabolic control, ageing, and adaptation to the environment should be productive in advancing our understanding of the physiology of both spaceflight and ageing.
Application of the \([\gamma^{32}P]\) ATP kinase assay to study anabolic signaling in human skeletal muscle.


Abstract

AMPK (AMP-dependant protein kinase)-mTORC1 (mechanistic target of rapamycin in complex 1)-p70S6K1 (ribosomal protein S6 kinase 1 of 70 kDa) signaling plays a crucial role in muscle protein synthesis (MPS). Understanding this pathway has been advanced by the application of the Western blot (WB) technique. However, because many components of the mTORC1 pathway undergo numerous, multisite posttranslational modifications, solely studying the phosphorylation changes of mTORC1 and its substrates may not adequately represent the true metabolic signaling processes. The aim of this study was to develop and apply a quantitative in vitro \([\gamma^{32}P]\) ATP kinase assay (KA) for p70S6K1 to assess kinase activity in human skeletal muscle to resistance exercise (RE) and protein feeding. In an initial series of experiments the assay was validated in tissue culture and in p70S6K1-knockout tissues. Following these experiments, the methodology was applied to assess p70S6K1 signaling responses to a physiologically relevant stimulus. Six men performed unilateral RE followed by the consumption of 20 g of protein. Muscle biopsies were obtained at pre-RE, and 1 and 3 h post-RE. In response to RE and protein consumption, p70S6K1 activity as assessed by the KA was significantly increased from pre-RE at 1 and 3 h post-RE. However, phosphorylated p70S6K1(thr389) was not significantly elevated. AMPK activity was suppressed from pre-RE at 3 h post-RE, whereas phosphorylated ACC(ser79) was unchanged. Total protein kinase B activity also was unchanged after RE from pre-RE levels. Of the other markers we assessed by WB, 4EBP1(thr37/46) phosphorylation was the only significant responder, being elevated at 3 h post-RE from pre-RE. These data highlight the utility of the KA to study skeletal muscle plasticity.

Maintenance of muscle mass and load-induced growth in Muscle RING Finger 1 null mice with age.

Hwee DT, Baehr LM, Philp A, Baar K, Bodine SC.

Abstract

Age-related loss of muscle mass occurs to varying degrees in all individuals and has a detrimental effect on morbidity and mortality. Muscle RING Finger 1 (MuRF1), a muscle-specific E3 ubiquitin ligase, is believed to mediate muscle atrophy through the ubiquitin proteasome system (UPS). Deletion of MuRF1 (KO) in mice attenuates the loss of muscle mass following denervation, disuse, and glucocorticoid treatment; however, its role in age-related muscle loss is unknown. In this study, skeletal muscle from male wild-type (WT) and MuRF1 KO mice was studied up to the age of 24 months. Muscle mass and fiber cross-sectional area decreased significantly with age in WT, but not in KO mice. In aged WT muscle, significant decreases in proteasome activities, especially 20S and 26S β5 (20-40% decrease), were measured and were associated with significant increases in the maladaptive endoplasmic reticulum (ER) stress marker, CHOP. Conversely, in aged MurF1 KO mice, 20S or 26S β5 proteasome activity was maintained or decreased to a lesser extent than in WT mice, and no increase in CHOP expression was measured. Examination of the growth response of older (18 months) mice to functional overload revealed that old WT mice had significantly less growth relative to young mice (1.37- vs. 1.83-fold), whereas old MuRF1 KO mice had a normal growth response (1.74- vs. 1.90-fold). These data collectively suggest that with age, MuRF1 plays an important role in the control of skeletal muscle mass and growth capacity through the regulation of cellular stress.
Hassan-Smith ZK, Tomlinson JW, Lavery GG


11β-HSD1 is the major regulator of the tissue-specific effects of circulating glucocorticoid excess.

Morgan SA, McCabe EL, Gathercole LL, Hassan-Smith ZK, Larner DP, Bujalska IJ, Stewart PM, Tomlinson JW, Lavery GG

Abstract

The adverse metabolic effects of prescribed and endogenous glucocorticoid (GC) excess, Cushing syndrome, create a significant health burden. We found that tissue regeneration of GCs by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), rather than circulating delivery, is critical to developing the phenotype of GC excess; 11β-HSD1 KO mice with circulating GC excess are protected from the glucose intolerance, hyperinsulinemia, hepatic steatosis, adiposity, hypertension, myopathy, and dermal atrophy of Cushing syndrome. Whereas liver-specific 11β-HSD1 KO mice developed a full Cushingoid phenotype, adipose-specific 11β-HSD1 KO mice were protected from hepatic steatosis and circulating fatty acid excess. These data challenge our current view of GC action, demonstrating 11β-HSD1, particularly in adipose tissue, is key to the development of the adverse metabolic profile associated with circulating GC excess, offering 11β-HSD1 inhibition as a previously unidentified approach to treat Cushing syndrome.

Philp A


Molecular brakes regulating mTORC1 activation in skeletal muscle following synergist ablation.


Abstract

The goal of the current work was to profile positive (mTORC1 activation, autocrine/paracrine growth factors) and negative [AMPK, unfolded protein response (UPR)] pathways that might regulate overload-induced mTORC1 activation with the hypothesis that a number of negative regulators of mTORC1 will be engaged during a supra-physiological model of hypertrophy. To achieve this, mTORC1-IRS1/2 signaling, BIP/CHOP/IRE1α, and AMPK activation were determined in rat plantaris muscle following synergist ablation (SA). SA resulted in significant increases in muscle mass of ~4% per day throughout the 21 days of the experiment. The expression of the insulin-like growth factors were high throughout the 21d of overload. However, IGF signaling was limited since IRS1 and 2 were undetectable in the overloaded muscle from day 3 to day 9. The decreases in IRS1/2 protein were paralleled by increases in GRB10\textsuperscript{Thr501/503} and S6K1\textsuperscript{Thr389} phosphorylation, two mTORC1 targets that can destabilize IRS proteins. PKB\textsuperscript{Thr473} phosphorylation was higher from 3-6 days and this was associated with increased TSC2\textsuperscript{Thr1462} phosphorylation. The phosphorylation of TSC2\textsuperscript{Thr1344} (an AMPK site) was also elevated whereas phosphorylation at the other PKB site, Thr\textsuperscript{1462}, was unchanged at 6d. In agreement with the phosphorylation of Thr\textsuperscript{1345}, synergist ablation led to activation of α1-AMPK during the initial growth phase, lasting the first 9 days before returning to baseline by day 12. The UPR markers CHOP and BIP were elevated over the first 12 days following ablation, whereas IRE1α levels decreased. These data suggest that during supra-physiological muscle loading, at least three potential molecular brakes engage to down-regulate mTORC1.
Theme 2
Interventions to Reduce Musculoskeletal Ageing

The interventional strand of our research aims to deliver enormous value for public health, focusing on clinical studies in human populations to ensure that research outcomes can be effectively and efficiently translated into patient benefit as quickly as possible. These are based around exercise strategies, diet and nutrition and pharmacological interventions.

Publications

Sapey E, Lord JM
Phosphoinositide 3-kinase inhibition restores neutrophil accuracy in the elderly: toward targeted treatments for immunosenescence.

Abstract
Immunosenescence is the functional deterioration of the immune system during natural aging. Despite increased susceptibility to bacterial infections in older adults, age-associated changes to neutrophil responses are only partially understood, and neutrophil migration has not been characterized in detail. Here we describe reduced chemotaxis but preserved chemokinesis toward a range of inflammatory stimuli in migrating neutrophils isolated from healthy older subjects. Cross-sectional data indicate that migratory behavior changes in the sixth decade of life. Crucially, aberrant migration may increase "bystander" tissue damage and heighten inflammation as a result of excess protease release during inaccurate chemotaxis, as well as reducing pathogen clearance. We show evidence of increased neutrophil protease activity in older adults, namely, raised levels of neutrophil protease substrate-derived peptides and evidence of primary granule release, associated with increased systemic inflammation. Inaccurate migration was causally associated with increased constitutive phosphoinositide 3-kinase (PI3K) signaling; untreated neutrophils from old donors demonstrated significant PI3K activation compared with cells from young donors. PI3K-blocking strategies, specifically inhibition of PI3Kγ or PI3Kδ, restored neutrophil migratory accuracy, whereas SHIP1 inhibition worsened migratory flaws. Targeting PI3K signaling may therefore offer a new strategy in improving neutrophil functions during infections and reduce inappropriate inflammation in older patients.

Greig CA
Responsiveness of muscle size and strength to physical training in very elderly people: a systematic review.
Stewart VH, Saunders DH, Greig CA.

Abstract
The purpose of this review was to determine whether very elderly muscle (>75 years) hypertrophies in response to physical training. The databases MEDLINE; EMBASE; CINAHL Plus and SPORTDiscus were systematically literature searched with reference lists of all included studies and relevant reviews. Controlled trials (inactive elderly control group) involving healthy elderly participants over 75 years participating in an intervention complying with an established definition of physical training were included. Data extraction and quality assessment were performed using the PEDro scale. Data analysis was performed on muscle size and strength using RevMan (software version 5.1). Four studies were included of which four of four measured changes in gross muscle size. Training induced increases in muscle size from 1.5%-15.6% were reported in three of four studies, and one of four studies reported a decrease in muscle size (3%). The greatest gain in muscle mass was observed in a study of whole body vibration training. Meta-analysis of three studies found an increase of thigh muscle cross-sectional area (mean difference 2.31 cm(2) or 0.2%, 95% confidence interval (CI): 0.62 to 4.00; P = 0.008) and muscle strength (standardized mean difference 1.04, 95% CI: 0.65 to 1.43; P < 0.001). Physical training when delivered as resistance training has the ability to elicit hypertrophy and increase muscle strength in very elderly muscle.
Macdonald IA


Sex differences in the composition of weight gain and loss in overweight and obese adults.

Millward DJ, Truby H, Fox KR, Livingstone MB, Macdonald IA, Tothill P.

Abstract

Sex differences in the ratio of fat mass (FM):fat-free mass (FFM) during weight change should differentially affect the extent of weight change during energy imbalance in men and women. In the present study, we determined FM and FFM contents by dual-energy X-ray absorptiometry and calculated the P-ratios (protein energy/total energy) of excess weight and weight loss during a randomised controlled trial of four commercial weight loss regimens. Overweight and obese women (n 210) and men (n 77) were studied at baseline and at 2 and 6 months during weight loss on four dietary regimens: Dr Atkins’ New Diet Revolution; The Slim-Fast Plan; Weight-Watchers programme; Rosemary Conley’s Diet and Fitness Plan. At baseline, the percentage of FFM (%FFM) and P-ratios of excess weight were 40 % and 0·071 for men and 27 % and 0·039 for women. At 2 months, men had lost twice as much weight as women and three times more FFM than women, indicating higher FFM content and P-ratios of weight loss for men, 0·052, than for women, 0·029, with no dietary effects. Between 2 and 6 months, the rate at which weight was lost decreased and the %FFM of weight loss decreased to similar low levels in men (7 %) and women (5 %): i.e. P-ratios of 0·009 and 0·006, respectively, with no dietary effects. Thus, for men compared with women, there were greater FFM content and P-ratios of weight change, which could partly, but not completely, explain their greater weight loss at 2 months. However, protein-conserving adaptations occur with increasing weight loss and over time, more extensively in men, eventually eliminating any sex difference in the composition of weight loss.

Breen L

Age (Dordr). 2014 Apr 24. [Epub ahead of print]

Influence of exercise intensity on training-induced tendon mechanical properties changes in older individuals.

Grosset JF, Breen L, Stewart CE, Burgess KE, Onambélé GL.

Abstract

This study compared the effects of low vs. high intensity training on tendon properties in an elderly population. Participants were pair-matched (gender, habitual physical activity, anthropometrics, and baseline knee extension strength) and then randomly assigned to low (LowR, i.e., ~40 % 1RM) or high (High R, i.e., ~80 % 1RM) intensity resistance training programmes for 12 weeks, 3× per week (LowR, n = 9, age 74 ± 5 years; HighR, n = 8, age 68 ± 6 years). Patellar tendon properties (stiffness [K], Young’s modulus [YM], cross-sectional area [T CSA], and tendon length [T L]) were measured pre and post training using a combination of magnetic resonance imaging (MRI), B-mode ultrasonography, dynamometry, electromyography and ramped isometric knee extensions. With training K showed no significant change in the LowR group while it incremented by 57.7 % in the HighR group (p < 0.05). The 51.1 % group difference was significant (p < 0.05). These differences were still apparent when the data was normalized for T CSA and T L, i.e., significant increase in YM post-intervention in HighR (p < 0.05), but no change in LowR. These findings suggest that when prescribing exercise for a mixed genders elderly population, exercise intensities of ≤40 % 1RM may not be sufficient to affect tendon properties.
Breen L


Alterations in human muscle protein metabolism with aging: Protein and exercise as countermeasures to offset sarcopenia.

Churchward-Venne TA, Breen L, Phillips SM.

Abstract

Aging is associated with a reduction in skeletal muscle mass—sarcopenia—the etiology of which is multifactorial. One mechanism is that aging has, as one of its hallmarks, a reduced sensitivity of skeletal muscle to the normally potent anabolic effects of protein feeding and resistance exercise, and to the anticalcatabolic effects of insulin, the combination of which has been termed "anabolic resistance." However, this reduced sensitivity of skeletal muscle to anabolic stimuli may, in some cases, be overcome by providing a greater quantity of the nutrition and/or exercise stimulus. Daily habitual physical activity appears to be a primary determinant of anabolic resistance as we have recently shown that as little as 14 days of reduced ambulatory activity was sufficient to induce anabolic resistance in the elderly by attenuating the postprandial increase in muscle protein synthesis (MPS). The etiology of anabolic resistance is complex and may include alterations in amino acid uptake/utilization, cell signaling status, muscle blood flow, and microvascular perfusion (impacting amino acid delivery and availability). Further, there appears to be sexual dimorphism with advancing age in the response of MPS to amino acid/insulin provision. Maintenance of physical activity during aging is of fundamental importance for skeletal muscle to allow it to appropriately respond to the anabolic effects of nutrition.

Masud T


Effectiveness of general practice-based physical activity promotion for older adults: systematic review.

Stevens Z, Barlow C, Kendrick D, Masud T, Skelton DA, Dinan-Young S, Iliffe S.

Abstract

AIM: To review the effectiveness of physical activity interventions for adults aged 50 and above, delivered through general practice.

BACKGROUND: Physical activity has beneficial effects on the common disorders of later life. General practice is a potentially important setting for promotion of physical activity among older adults, but the effectiveness of such interventions is presently unknown.

METHODS: Studies published between January 1998 and July 2011 were identified from electronic databases. We searched for studies of tailored physical activity interventions to older adults through general practice. The search and selection process was not restricted to any outcome measures but only included studies comparing two or more groups prospectively. Two reviewers screened the studies and obtained full texts of eligible studies. Included studies were assessed for their methodological quality and public health impact.

FINDINGS: Altogether, 4170 studies met the initial search criteria but only six were included in the review, with a total of 1522 participants. The interventions ranged from six weeks to six months. One study showed a statistically significant increase in physical activity in the intervention compared with the control group (P < or = 0.007). Four studies measured quality of life using the SF-36, of which three reported inconsistent results. This review shows some evidence of the effectiveness of physical activity promotion for older adults through general practice, but not enough to warrant widespread commissioning and implementation. Large-scale developmental projects with long follow-up (beyond two years), objective measures of physical activity and comprehensive documentation of resource use, should now be conducted.
Rehabilitation aimed at improving outdoor mobility for people after stroke: a multicentre randomised controlled study (the Getting out of the House Study).


Abstract

BACKGROUND:
One-third of stroke patients are dependent on others to get outside their homes. This can cause people to become housebound, leading to increased immobility, poor health, isolation and misery. There is some evidence that outdoor mobility rehabilitation can reduce these limitations.

OBJECTIVE: To test the clinical effectiveness and cost-effectiveness of an outdoor mobility rehabilitation intervention for stroke patients.

DESIGN: Multicentre, parallel-group randomised controlled trial, with two groups allocated at a 1 : 1 ratio plus qualitative participant interviews.

SETTING: Fifteen UK NHS stroke services throughout England, Scotland and Wales.

PARTICIPANTS:
A total of 568 stroke patients who wished to get out of the house more often, mean age of 71 years: 508 reached the 6-month follow-up and 10 were interviewed.

INTERVENTION:
Control was delivered prior to randomisation to all participants, and consisted of verbal advice and transport and outdoor mobility leaflets. Intervention was a targeted outdoor mobility rehabilitation programme delivered by 29 NHS therapists to 287 randomly chosen participants for up to 12 sessions over 4 months.

MAIN OUTCOME MEASURES:
Primary outcome was participant health-related quality of life, measured by the Short Form questionnaire-36 items, version 2 (Social Function domain), 6 months after baseline. Secondary outcomes were functional ability, mobility, number of journeys (from monthly travel diaries), satisfaction with outdoor mobility (SWOM), psychological well-being and resource use (health care and Personal Social Services (PSS)) 6 months after baseline. Carer well-being was recorded. All outcome measures were collected by post and repeated 12 months after baseline. Outcomes for the groups were compared using statistical significance testing and adjusted for multiple membership to account for the effect of multiple therapists at different sites. Interviews were analysed using interpretive phenomenology to explore confidence.

RESULTS:
A median of seven intervention sessions [interquartile range (IQR) 3-7 sessions], median duration of 369 minutes [IQR 170-691.5 minutes] per participant was delivered. There was no significant difference between the groups on health-related quality of life (social function). There were no significant differences between groups in functional ability, psychological well-being or SWOM at 6- or 12-month follow-ups. There was a significant difference observed for travel journeys with the intervention group being 42% more likely to make a journey compared with the control group [rate ratio 1.42, 95% confidence interval (95% CI) 1.14 to 1.67] at 6 months and 76% more likely [rate ratio 1.76, 95% CI 1.36 to 1.95] at 12 months. The number of journeys was affected by the therapist effect. The mean incremental cost (total NHS and PSS cost) of the intervention was £3413.75 (95% CI -£448.43 to £7121.00), with an incremental quality-adjusted life-year gain of -0.027 (95% CI -0.060 to 0.007) according to the European Quality of Life-5 Dimensions and -0.003 (95% CI -0.016 to 0.006) according to the Short Form questionnaire-6 Dimensions. At baseline, 259 out of 281 (92.2%) participants in the control group were dissatisfied with outdoor mobility but at the 6-month assessment this had reduced to 77.7% (181/233), a 15% reduction. The corresponding reduction in the intervention group was slightly greater (21%) than 268 out of 287 (93.4%) participants dissatisfied with outdoor mobility at baseline to 189 out of 261 (72.4%) at 6 months. Participants described losing confidence after stroke as being detrimental to outdoor mobility. Recruitment and retention rates were high. The intervention was deliverable by the NHS but had a neutral effect in all areas apart from potentially increasing the number of journeys. This was dependent on the therapist effect, meaning that some therapists were more successful than others. The control appeared to affect change.

CONCLUSIONS:
The outdoor mobility intervention provided in this study to these stroke patients was not clinically effective or cost-effective. However, the provision of personalised information and monthly diaries should be considered for all people who wish to get out more.
The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics.

Tonge DP, Pearson MJ, Jones SW.

Abstract

Osteoarthritis (OA) is an age-related condition and the leading cause of pain, disability and shortening of adult working life in the UK. The incidence of OA increases with age, with 25% of the over 50s population having OA of the knee. Despite promising preclinical data covering various molecule classes, there is regrettably at present no approved disease-modifying OA drugs (DMOADs). With the advent of next generation sequencing technologies, other therapeutic areas, in particular oncology, have experienced a paradigm shift towards defining disease by its molecular composition. This paradigm shift has enabled high resolution patient stratification and supported the emergence of personalised or precision medicines. In this review we evaluate the potential for the development of OA therapeutics to undergo a similar paradigm shift given that OA is increasingly being recognised as a heterogeneous disease affecting multiple joint tissues. We highlight the evidence for the role of these tissues in OA pathology as different "hallmarks" of OA biology and review the opportunities to identify and develop targeted disease-modifying pharmacological therapeutics. Finally, we consider whether it is feasible to expect the emergence of personalised disease-modifying medicines for patients with OA and how this might be achieved.

Logan P, Gladman JR, Masud T


Developing the principles of chair based exercise for older people: a modified Delphi study.


Abstract

BACKGROUND: Chair based exercise (CBE) is suggested to engage older people with compromised health and mobility in an accessible form of exercise. A systematic review looking at the benefits of CBE for older people identified a lack of clarity regarding a definition, delivery, purpose and benefits. This study aimed to utilise expert consensus to define CBE for older people and develop a core set of principles to guide practice and future research.

METHODS: The framework for consensus was constructed through a team workshop identifying 42 statements within 7 domains. A four round electronic Delphi study with multi-disciplinary health care experts was undertaken. Statements were rated using a 5 point Likert scale of agreement and free text responses. A threshold of 70% agreement was used to determine consensus. Free text responses were analysed thematically. Between rounds a number of strategies (e.g. amended wording of statements, generation and removal of statements) were used to move towards consensus.

RESULTS: 16 experts agreed on 46 statements over four rounds of consultation (Round 1: 22 accepted, 3 removed, 5 new and 17 modified; Round 2: 16 accepted, 0 removed, 4 new and 6 modified; Round 3: 4 accepted, 2 removed, 0 new and 4 modified; Round 4: 4 accepted, 0 removed, 0 new, 0 modified). Statements were accepted in all seven domains: the definition of CBE (5), intended users (3), potential benefits (8), structure (12), format (8), risk management (7) and evaluation (3). The agreed definition of CBE had five components: 1. CBE is primarily a seated exercise programme; 2. The purpose of using a chair is to promote stability in both sitting and standing; 3. CBE should be considered as part of a continuum of exercise for frail older people where progression is encouraged; 4. CBE should be used flexibly to respond to the changing needs of frail older people; and 5. Where possible CBE should be used as a starting point to progress to standing programmes.

CONCLUSIONS: Consensus has been reached on a definition and a set of principles governing CBE for older people; this provides clarity for implementation and future research about CBE.
Wallis GA
Designing food structures for nutrition and health benefits.
Abstract
In addition to providing specific sensory properties (e.g., flavor or textures), there is a need to produce foods that also provide functionality within the gastrointestinal (GI) tract, over and above simple nutrition. As such, there is a need to understand the physical and chemical processes occurring in the mouth, stomach, small intestine, and large intestine, in addition to the food structure-physiology interactions. In vivo techniques and in vitro models have allowed us to study and simulate these processes, which aids us in the design of food microstructures that can provide functionality within the human body. Furthermore, it is important to be aware of the health or nutritional needs of different groups of consumers when designing food structures, to provide targeted functionality. Examples of three groups of consumers (elderly, obese, and athletes) are given to demonstrate their differing nutritional requirements and the formulation engineering approaches that can be utilized to improve the health of these individuals. Eating is a pleasurable process, but foods of the future will be required to provide much more in terms of functionality for health and nutrition.

Tsintzas K
The causal role of breakfast in energy balance and health: a randomized controlled trial in lean adults
Abstract
BACKGROUND: Popular beliefs that breakfast is the most important meal of the day are grounded in cross-sectional observations that link breakfast to health, the causal nature of which remains to be explored under real-life conditions. OBJECTIVE: The aim was to conduct a randomized controlled trial examining causal links between breakfast habits and all components of energy balance in free-living humans. DESIGN: The Bath Breakfast Project is a randomized controlled trial with repeated-measures at baseline and follow-up in a cohort in southwest England aged 21-60 y with dual-energy X-ray absorptiometry-derived fat mass indexes ≤11 kg/m² in women (n = 21) and ≤7.5 kg/m² in men (n = 12). Components of energy balance (resting metabolic rate, physical activity thermogenesis, energy intake) and 24-h glycemic responses were measured under free-living conditions with random allocation to daily breakfast (≥700 kcal before 1100) or extended fasting (0 kcal until 1200) for 6 wk, with baseline and follow-up measures of health markers (e.g., hematology/biopsies). RESULTS: Contrary to popular belief, there was no metabolic adaptation to breakfast (eg, resting metabolic rate stable within 11 kcal/d), with limited subsequent suppression of appetite (energy intake remained 539 kcal/d greater than after fasting; 95% CI: 157, 920 kcal/d). Rather, physical activity thermogenesis was markedly higher with breakfast than with fasting (442 kcal/d; 95% CI: 34, 851 kcal/d). Body mass and adiposity did not differ between treatments at baseline or follow-up and neither did adipose tissue glucose uptake or systemic indexes of cardiovascular health. Continuously measured glycemia was more variable during the afternoon and evening with fasting than with breakfast by the final week of the intervention (CV: 3.9%; 95% CI: 0.1%, 7.8%). Conclusions: Daily breakfast is causally linked to higher physical activity thermogenesis in lean adults, with greater overall dietary energy intake but no change in resting metabolism. Cardiovascular health indexes were unaffected by either of the treatments, but breakfast maintained more stable afternoon and evening glycemia than did fasting. This trial was registered at www.isrctn.org as ISRCTN31521726.
**Effects of the 5-HT2C receptor agonist meta-chlorophenylpiperazine on appetite, food intake and emotional processing in healthy volunteers.**

**Abstract**

**RATIONALE:**
The treatment of obesity is an increasing global health priority, yet few effective drug treatments are currently available. The discovery of novel anti-obesity therapies could be assisted by the validation of experimental (translational) medicine models in healthy volunteers that assess efficacy and safety at an early stage of drug development.

**OBJECTIVES:**
The aim of this study was to examine the effects of the 5-HT2C receptor agonist meta-chlorophenylpiperazine (mCPP) in an experimental medicine model assessing both appetite and mood.

**METHODS:**
Using a between-subjects, double-blind, placebo-controlled design, 24 male and 24 female participants were randomly assigned to either placebo, 15- or 30-mg mCPP treatment groups. Lunch was eaten from a Universal Eating Monitor (UEM) that measured eating rate, and the participants completed the P1vital® Oxford Emotional Test Battery (ETB) and a series of appetite and mood ratings.

**RESULTS:**
mCPP reduced appetite and, in women, enhanced measures of satiation. The drug also enhanced memory for emotional material in the word recall and recognition memory tasks of the ETB.

**CONCLUSIONS:**
The results provide new insight into the effects of mCPP on appetite, satiety and memory in humans. In addition, our data provide an illustration of the value of measuring changes in appetite and mood in healthy volunteers to determine the potential efficacy and safety of novel anti-obesity drug.

**Hypoxia modulates the phenotype of osteoblasts isolated from knee osteoarthritis patients, leading to undermineralized bone nodule formation.**

**Abstract**

**OBJECTIVE:**
To investigate the role of hypoxia in the pathology of osteoarthritic (OA) bone by exploring its effect on the phenotype of isolated primary osteoblasts from patients with knee OA.

**METHODS:**
OA bone samples were collected at the time of elective joint replacement surgery for knee or hip OA. Normal bone samples were collected postmortem from cadaver donors. Primary osteoblasts were isolated from knee OA bone chips and cultured under normoxic or hypoxic (2% O2) conditions. Alkaline phosphatase activity was quantified using an enzymatic assay, and osteopontin and prostaglandin E2 (PGE2) production was assayed by enzyme-linked immunosorbent assay. Total RNA was extracted from bone and osteoblasts, and gene expression was profiled by quantitative reverse transcription-polymerase chain reaction.

**RESULTS:**
Human OA bone tissue sections stained positively for carbonic anhydrase IX, a biomarker of hypoxia, and exhibited differential expression of genes that mediate the vasculature and blood coagulation as compared to those found in normal bone. Culture of primary osteoblasts isolated from knee OA bone under hypoxic conditions profoundly affected the osteoblast phenotype, including the expression of genes that mediate bone matrix, bone remodeling, and bone vasculature. Hypoxia also increased the expression of cyclooxygenase 2 and the production of PGE2 by OA osteoblasts. Osteoblast expression of type II collagen α1 chain, angiopoietin-like 4, and insulin-like growth factor binding protein 1 was shown to be mediated by hypoxia-inducible factor 1α. Chronic hypoxia reduced osteoblast-mineralized bone nodule formation.

**CONCLUSION:**
These findings demonstrate that hypoxia can induce pathologic changes in osteoblast functionality consistent with an OA phenotype, providing evidence that hypoxia is a key driver of OA pathology.
Theme 3

Motor Control and Motor Neuroscience

This theme focuses on the fact that age-related neurodegeneration occurs in both motor and cognitive neurones. Loss of cognitive function is accelerated by age-related reduced physical activity, obesity and inflammation, with exercise interventions giving substantial improvement. The large artery and microvascular endothelial impairments associated with inflammation and ageing may also reduce local blood perfusion in the central nervous system.

Publications

Szewczyk NJ


Protective role of DNJ-27/ERdj5 in Caenorhabditis elegans models of human neurodegenerative diseases.


Abstract

AIMS:
Cells have developed quality control systems for protection against proteotoxicity. Misfolded and aggregation-prone proteins, which are behind the initiation and progression of many neurodegenerative diseases (ND), are known to challenge the proteostasis network of the cells. We aimed to explore the role of DNJ-27/ERdj5, an endoplasmic reticulum (ER)-resident thioredoxin protein required as a disulfide reductase for the degradation of misfolded proteins, in well-established Caenorhabditis elegans models of Alzheimer, Parkinson and Huntington diseases.

RESULTS:
We demonstrate that DNJ-27 is an ER luminal protein and that its expression is induced upon ER stress via IRE-1/XBP-1. When dnj-27 expression is downregulated by RNA interference we find an increase in the aggregation and associated pathological phenotypes (paralysis and motility impairment) caused by human β-amyloid peptide (Aβ), α-synuclein (α-syn) and polyglutamine (polyQ) proteins. In turn, DNJ-27 overexpression ameliorates these deleterious phenotypes. Surprisingly, despite being an ER-resident protein, we show that dnj-27 downregulation alters cytoplasmic protein homeostasis and causes mitochondrial fragmentation. We further demonstrate that DNJ-27 overexpression substantially protects against the mitochondrial fragmentation caused by human Aβ and α-syn peptides in these worm models.

INNOVATION:
We identify C. elegans dnj-27 as a novel protective gene for the toxicity associated with the expression of human Aβ, α-syn and polyQ proteins, implying a protective role of ERdj5 in Alzheimer, Parkinson and Huntington diseases.

CONCLUSION:
Our data support a scenario where the levels of DNJ-27/ERdj5 in the ER impact cytoplasmic protein homeostasis and the integrity of the mitochondrial network which might underlie its protective effects in models of proteotoxicity associated to human ND.
Rapid acquisition of the transcranial magnetic stimulation stimulus response curve.

Mathias JP, Barsi GI, van de Ruit M, Grey MJ.

Abstract

BACKGROUND:
Transcranial magnetic stimulation is frequently used to construct stimulus response (SR) curves in studies of motor learning and rehabilitation. A drawback of the established method is the time required for data acquisition, which is frequently greater than a participant’s ability to maintain attention. The technique is therefore difficult to use in the clinical setting.

OBJECTIVE:
To reduce the time of curve acquisition by determining the minimum acquisition time and number of stimuli required to acquire an SR curve.

METHODS:
SR curves were acquired from first dorsal interosseous (FDI) and abductor digiti minimi (ADM) at 6 interstimulus intervals (ISI) between 1.4 and 4 s in 12 participants. To determine if low-frequency rTMS might affect the SR curve, MEP amplitudes were monitored before and after 3 min of 1 Hz rTMS delivered at 120% of resting motor threshold in 12 participants. Finally, SR curves were acquired from FDI, ADM and Biceps Brachii (BB) in 12 participants, and the minimum number of stimuli was calculated using a sequential MEP elimination process.

RESULTS:
There were no significant differences between curves acquired with 1.4 s ISI and any other ISI. Low frequency rTMS did not significantly depress MEP amplitude (P = 0.87). On average, 61 ± 18 (FDI), 60 ± 16 (ADM) and 59 ± 16 (BB) MEPs were needed to construct a representative SR curve.

CONCLUSIONS:
This study demonstrates that reliable SR curves may be acquired in less than 2 min. At this rate, SR curves become a clinically feasible method for assessing corticospinal excitability in research and rehabilitation settings.
Miall RC
Non-invasive cerebellar stimulation--a consensus paper.

Abstract
The field of neurostimulation of the cerebellum either with transcranial magnetic stimulation (TMS; single pulse or repetitive (rTMS)) or transcranial direct current stimulation (tDCS; anodal or cathodal) is gaining popularity in the scientific community, in particular because these stimulation techniques are non-invasive and provide novel information on cerebellar functions. There is a consensus amongst the panel of experts that both TMS and tDCS can effectively influence cerebellar functions, not only in the motor domain, with effects on visually guided tracking tasks, motor surround inhibition, motor adaptation and learning, but also for the cognitive and affective operations handled by the cerebro-cerebellar circuits. Verbal working memory, semantic associations and predictive language processing are amongst these operations. Both TMS and tDCS modulate the connectivity between the cerebellum and the primary motor cortex, tuning cerebellar excitability. Cerebellar TMS is an effective and valuable method to evaluate the cerebello-thalamo-cortical loop functions and for the study of the pathophysiology of ataxia. In most circumstances, DCS induces a polarity-dependent site-specific modulation of cerebellar activity. Paired associative stimulation of the cerebello-dentato-thalamo-M1 pathway can induce bidirectional long-term spike-timing-dependent plasticity-like changes of corticospinal excitability. However, the panel of experts considers that several important issues still remain unresolved and require further research. In particular, the role of TMS in promoting cerebellar plasticity is not established. Moreover, the exact positioning of electrode stimulation and the duration of the after effects of tDCS remain unclear. Future studies are required to better define how DCS over particular regions of the cerebellum affects individual cerebellar symptoms, given the topographical organization of cerebellar symptoms. The long-term neural consequences of non-invasive cerebellar modulation are also unclear. Although there is an agreement that the clinical applications in cerebellar disorders are likely numerous, it is emphasized that rigorous large-scale clinical trials are missing. Further studies should be encouraged to better clarify the role of using non-invasive neurostimulation techniques over the cerebellum in motor, cognitive and psychiatric rehabilitation strategies.
Szewczyk NJ


The neurodegenerative effects of selenium are inhibited by FOXO and PINK1/PTEN regulation of insulin/insulin-like growth factor signaling in Caenorhabditis elegans.

Estevez AO, Morgan KL, Szewczyk NJ, Gems D, Estevez M.

Abstract

Exposures to high levels of environmental selenium have been associated with motor neuron disease in both animals and humans and high levels of selenite have been identified in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis (ALS). We have shown previously that exposures to high levels of sodium selenite in the environment of Caenorhabditis elegans adult animals can induce neurodegeneration and cell loss resulting in motor deficits and death and that this is at least partially caused by a reduction in cholinergic signaling across the neuromuscular junction. Here we provide evidence that reduction in insulin/insulin-like (IIS) signaling alters response to high dose levels of environmental selenium which in turn can regulate the IIS pathway. Most specifically we show that nuclear localization and thus activation of the DAF-16/forkhead box transcription factor occurs in response to selenium exposure although this was not observed in motor neurons of the ventral cord. Yet, tissue specific expression and generalized overexpression of DAF-16 can partially rescue the neurodegenerative and behavioral deficits observed with high dose selenium exposures in not only the cholinergic, but also the GABAergic motor neurons. In addition, two modifiers of IIS signaling, PTEN (phosphatase and tensin homolog, deleted on chromosome 10) and PINK1 (PTEN-induced putative kinase 1) are required for the cellular antioxidant reduced glutathione to mitigate the selenium-induced movement deficits. Studies have suggested that environmental exposures can lead to ALS or other neurological diseases and this model of selenium-induced neurodegeneration developed in a genetically tractable organism provides a tool for examining the combined roles of genetics and environment in the neuro-pathologic disease process.

Miall RC


Restoring cognitive functions using non-invasive brain stimulation techniques in patients with cerebellar disorders.

Pope PA, Miall RC.

Abstract

Numerous studies have highlighted the possibility of modulating the excitability of cerebro-cerebellar circuits bi-directionally using transcranial electrical brain stimulation, in a manner akin to that observed using magnetic stimulation protocols. It has been proposed that cerebellar stimulation activates Purkinje cells in the cerebellar cortex, leading to inhibition of the dentate nucleus, which exerts a tonic facilitatory drive onto motor and cognitive regions of cortex through a synaptic relay in the ventral-lateral thalamus. Some cerebellar deficits present with cognitive impairments if damage to non-motor regions of the cerebellum disrupts the coupling with cerebral cortical areas for thinking and reasoning. Indeed, white matter changes in the dentato-rubral tract correlate with cognitive assessments in patients with Friedreich ataxia, suggesting that this pathway is one component of the anatomical substrate supporting a cerebellar contribution to cognition. An understanding of the physiology of the cerebro-cerebellar pathway previously helped us to constrain our interpretation of results from two recent studies in which we showed cognitive enhancements in healthy participants during tests of arithmetic after electrical stimulation of the cerebellum, but only when task demands were high. Others studies have also shown how excitation of the prefrontal cortex can enhance performance in a variety of working memory tasks. Thus, future efforts might be guided toward neuroenhancement in certain patient populations, using what is commonly termed "non-invasive brain stimulation" as a cognitive rehabilitation tool to modulate cerebro-cerebellar circuits, or for stimulation over the cerebral cortex to compensate for decreased cerebellar drive to this region. This article will address these possibilities with a review of the relevant literature covering ataxias and cerebellar cognitive affective disorders, which are characterized by thalamo-cortical disturbances.
Wing AM

Physiotherapy 100:108-115 Jun 2014

Attentional focus of feedback for improving performance of reach-to-grasp after stroke: a randomised crossover study

Durham, K. F.; Sackley, C. M.; Wright, C. C, Wing AM, Edwards MG, van Pliet P

Abstract

Objective: To investigate whether feedback inducing an external focus (EF) of attention (about movement effects) was more effective for retraining reach-to-grasp after stroke compared with feedback inducing an internal focus (IF) of attention (about body movement). It was predicted that inducing an EF of attention would be more beneficial to motor performance.

Design: Crossover trial where participants were assigned at random to two feedback order groups: IF followed by EF or EF followed by IF.

Setting: Research laboratory

Participants: Forty-two people with upper limb impairment after stroke.

Intervention: Participants performed three reaching tasks: (A) reaching to grasp ajar; (B) placing ajar forwards on to a table; and (C) placing ajar on to a shelf. Ninety-six reaches were performed in total over one training session.

Main outcome measures: Kinematic measures were collected using motion analysis. Primary outcome measures were movement duration, peak velocity of the wrist, size of peak aperture and peak elbow extension.

Results: Feedback inducing an EF of attention produced shorter movement durations (first feedback order group: IF mean 2.53 seconds [standard deviation (SD) 1.85]; EF mean 2.12 seconds [SD 1.63], mean difference 0.41 seconds; 95% confidence interval -0.68 to 1.5; P = 0.008), an increased percentage time to peak deceleration (P = 0.01) when performing Task B, and an increased percentage time to peak velocity (P = 0.039) when performing Task A compared with feedback inducing an IF of attention. However, an order effect was present whereby performance was improved if an EF of attention was preceded by an IF of attention.

Conclusions: Feedback inducing an EF of attention may be of some benefit for improving motor performance of reaching in people with stroke in the short term; however, these results should be interpreted with caution. Further research using a randomised design is recommended to enable effects on motor learning to be assessed.
Theme 4
Overcoming Barriers to Lifestyle Interventions

This theme is based on the importance of theory in developing, implementing and evaluating interventions centred on promoting active living and well-being, from one-on-one and small group interventions in exercise on referral schemes, to community exercise classes and workplace wellbeing programmes.

Publications

Thøgersen-Ntoumani C, Duda JL
Mental Health and Physical Activity 01/2014;
A step in the right direction? Change in mental well-being and self-reported work performance among physically inactive university employees during a walking intervention

Cecilie Thøgersen-Ntoumani, Elizabeth A. Loughren, Ian M. Taylor, Joan L. Duda, Kenneth R. Fox

Abstract

Objective
To examine well-being and work performance changes accompanying participation in a 16-week uncontrolled feasibility lunchtime walking trial.

Method
Participants were 75 (92% female; M age = 47.68) previously physically inactive non-academic employees from a large British university. Multilevel modelling analyses examined well-being and work performance trajectories from baseline to post-intervention, to four months later, controlling for group membership and trait affectivity.

Results
Increases in perceptions of health, subjective vitality, and work performance, and decreases in fatigue at work were observed. Changes were sustained four months after the end of the intervention. No changes were identified for enthusiasm, nervousness and relaxation at work.

Conclusion
Although this was a relatively small uncontrolled feasibility trial, the results suggest that participation in a walking programme may be associated with sustainable well-being benefits and improvements in perceptions of work performance.

Thøgersen-Ntoumani, C
Journal of Environmental Psychology (Impact Factor: 2.4). 01/2014;
The effect of the physical environment and levels of activity on affective states

Florence-Emilie Kinnafick, Cecilie Thøgersen-Ntoumani

Abstract

The physical environment and physical activity can independently improve positive affect. The current studies investigated the effects of two opposing environments (urban versus natural) and levels of activity (walking and sitting) on affective states in either a laboratory (study 1) or an outdoor setting (study 2). While doing each activity (walking and sitting in each environment), participants watched film clips of urban or natural outdoor settings (study 1), or were naturally immersed in an urban or a natural environment (study 2). Measures of affect were administered pre, mid and post each condition. Findings highlighted the benefits of being immersed in a natural outdoor environment with physical activity being key for positive effects on energy. Short bouts of sedentary behaviour increased state negative affect, tiredness, and decreased energy levels. Attempts by policy-makers, urban planners and public health promoters should encourage greater use of natural open space to promote acute psychological well-being.
Duda JL, Ntoumanis N, Eves FF, Rouse PC, Jolly K


Effects of a standard provision versus an autonomy supportive exercise referral programme on physical activity, quality of life and well-being indicators: a cluster randomised controlled trial.


Abstract

BACKGROUND:

The National Institute for Health and Clinical Excellence in the UK has recommended that the effectiveness of ongoing exercise referral schemes to promote physical activity should be examined in research trials. Recent empirical evidence in health care and physical activity promotion contexts provides a foundation for testing the feasibility and impact of a Self Determination Theory-based (SDT) exercise referral consultation.

METHODS:

An exploratory cluster randomised controlled trial comparing standard provision exercise referral with an exercise referral intervention grounded in Self Determination Theory. Individuals (N = 347) referred to an exercise referral scheme were recruited into the trial from 13 centres. Outcomes and processes of change measured at baseline, 3 and 6-months: Minutes of self-reported moderate or vigorous physical activity (PA) per week (primary outcome), health status, positive and negative indicators of emotional well-being, anxiety, depression, quality of life (QOL), vitality, and perceptions of autonomy support from the advisor, need satisfaction (3 and 6 months only), intentions to be active, and motivational regulations for exercise. Blood pressure and weight were assessed at baseline and 6 months.

RESULTS:

Perceptions of the autonomy support provided by the health and fitness advisor (HFA) did not differ by arm. Between group changes over the 6-months revealed significant differences for reported anxiety only. Within arm contrasts revealed significant improvements in anxiety and most of the Dartmouth CO-OP domains in the SDT arm at 6 months, which were not seen in the standard exercise referral group. A process model depicting hypothesized relationships between advisor autonomy support, need satisfaction and more autonomous motivation, enhanced well being and PA engagement at follow up was supported.

CONCLUSIONS:

Significant gains in physical activity and improvements in quality of life and well-being outcomes emerged in both the standard provision exercise referral and the SDT-based intervention at programme end. At 6-months, observed between arm and within intervention arm differences for indicators of emotional health, and the results of the process model, were in line with SDT. The challenges in optimising recruitment and implementation of SDT-based training in the context of health and leisure services are discussed.
Thompson JL


Objective indicators of physical activity and sedentary time and associations with subjective well-being in adults aged 70 and over.

Withall J, Stathi A, Davis M, Coulson J, Thompson JL, Fox KR.

Abstract

This study explored the associations of the volume and intensity of physical activity and the volume of sedentary time with subjective well-being in a diverse group of 228 older adults in the UK (111 female, mean age 78.2 years (SD 5.8)). Physical activity (PA) and sedentary behaviour were assessed by accelerometry deriving mean steps per day, mean moderate/vigorous PA minutes per hour (MVPA min · h(-1)) and minutes of sedentary time per hour (ST min · h(-1)). Lower limb function was assessed by the Short Physical Performance Battery. Subjective well-being was assessed using the SF-12 health status scale, the Ageing Well Profile and the Satisfaction with Life Scale. Linear regressions were used to investigate associations between the independent variables which included physical activity (steps and MVPA), sedentary time, participant characteristics (gender, age, BMI, education, number of medical conditions), and lower limb function and dependent variables which included mental and physical well-being. Steps, MVPA and lower limb function were independently and moderately positively associated with perceived physical well-being but relationships with mental well-being variables were weak. No significant associations between sedentary behaviours and well-being were observed. The association between objectively evaluated physical activity and function and subjective evaluations of physical well-being suggest that improving perceptions of physical health and function may provide an important target for physical activity programmes. This in turn may drive further activity participation.

Thøgersen-Ntoumani C, Duda JL

Qual Health Res. 2014 Apr 23;24(6):738-748. [Epub ahead of print]

Changing Bodies: Experiences of Women Who Have Undergone a Surgically Induced Menopause.

Pearce G, Thøgersen-Ntoumani C, Duda JL, McKenna J.

Abstract

We aimed to explore the lived experiences of women who had a surgical menopause as a result of undergoing a hysterectomy with Bilateral Salpingo-Oopherectomy (BSO). We adopted a qualitative interview design using Interpretative Phenomenological Analysis (IPA), and recruited 7 women aged 47 to 59. We conducted synchronous online semi-structured interviews using the MSN (Microsoft Network) Messenger program. In the findings, we examine the prominent and under-researched theme of body image change. We discuss the women’s journey from a deep internal bodily change, the meaning of this changing body image, through to the thoughts and behaviours involved with self-presentation concerns and coping with body image changes. A woman’s perceived attractiveness and appearance investment are important factors to consider regarding adaptation to change over this transition. The findings might have implications for interventions designed to enhance mental well-being and increase health behaviours in women experiencing gynaecological illness and/or menopause.
Follow us @CMARoBUoN

www.birmingham.ac.uk/musculoskeletal-ageing

ISSUE 1 January – June 2014
Thompson JL


Objectively Assessed Physical Activity and Subsequent Health Service Use of UK Adults Aged 70 and Over: A Four to Five Year Follow Up Study.


Abstract

OBJECTIVES:
To examine the associations between volume and intensity of older peoples’ physical activity, with their subsequent health service usage over the following four to five years.

STUDY DESIGN:
A prospective cohort design using baseline participant characteristics, objectively assessed physical activity and lower limb function provided by Project OPAL (Older People and Active Living). OPAL-PLUS provided data on numbers of primary care consultations, prescriptions, unplanned hospital admissions, and secondary care referrals, extracted from medical records for up to five years following the baseline OPAL data collection.

PARTICIPANTS AND DATA COLLECTION:
OPAL participants were a diverse sample of 240 older adults with a mean age of 78 years. They were recruited from 12 General Practitioner surgeries from low, middle, and high areas of deprivation in a city in the West of England. Primary care consultations, secondary care referrals, unplanned hospital admissions, number of prescriptions and new disease diagnoses were assessed for 213 (104 females) of the original 240 OPAL participants who had either consented to participate in OPAL-PLUS or already died during the follow-up period.

RESULTS:
In regression modelling, adjusted for socio-economic variables, existing disease, weight status, minutes of moderate-to-vigorous physical activity (MVPA) per day predicted subsequent numbers of prescriptions. Steps taken per day and MVPA also predicted unplanned hospital admissions, although the strength of the effect was reduced when further adjustment was made for lower limb function.

CONCLUSIONS:
Community-based programs are needed which are successful in engaging older adults in their late 70s and 80s in more walking, MVPA and activity that helps them avoid loss of physical function. There is a potential for cost savings to health services through reduced reliance on prescriptions and fewer unplanned hospital admissions.
Dietary changes and associations with metabolic improvements in adults with type 2 diabetes during a patient-centred dietary intervention: an exploratory analysis.

England CY, Thompson JL, Jago R, Cooper AR, Andrews RC.

Abstract
OBJECTIVES: Describe dietary intake of participants enrolled in a non-prescriptive dietary intervention and dietary changes at 6 months and explore whether these changes had a role in observed improvements in glycated haemoglobin (HbA1c), weight, lipids and blood pressure.

DESIGN: Secondary analysis of data from the Early ACTivity in Diabetes randomised controlled trial.

PARTICIPANTS: 262 patients with newly diagnosed type 2 diabetes randomised to the dietary intervention.

OUTCOMES AND ANALYSIS: Changes in energy intake, macronutrients, fibre and alcohol and in weight, waist circumference, lipids, HbA1c and blood pressure at baseline and 6 months. Multivariate models were used to examine associations between dietary changes and metabolic variables.

RESULTS: Men reported reducing mean energy intake from 1903±462 kcal to 1685 kcal±439 kcal (p<0.001), increasing carbohydrate intake from 42.4±6.6% to 43.8±6.6% (p=0.002) and reducing median alcohol intake from 13 (0-27) g to 5 (0-18) g (p<0.001). Women reported reducing mean energy intake from 1582±379 kcal to 1459±326 kcal (p<0.001) with no change to macronutrient distribution and alcohol. Fibre intake was maintained. In men (n=148), weak and clinically insignificant associations were found between increased carbohydrates and reduction in HbA1c (β=-0.003 (-0.006, -0.001); p=0.009), increased fibre and reduction in total cholesterol (β=-0.023 (-0.044, -0.002); p=0.033), decreased total fat and reduction in low-density lipoprotein (LDL)-cholesterol (β=0.024 (0.006, 0.001); p=0.011), and decreased alcohol and reduction in diastolic blood pressure (β=0.276 (0.055, 0.497); p<0.015). In women (n=75), associations were found between a decrease in trans fats and reductions in waist circumference (β=-0.029 (0.006, 0.052); p=0.015), total cholesterol (β=0.399 (0.028, 0.770); p=0.036) and LDL cholesterol (β=0.365 (0.042, 0.668); p=0.028).

CONCLUSIONS: Clinically important metabolic improvements observed in a patient-centred dietary intervention were not explained by changes in macronutrients. However, a non-prescriptive approach may promote a reduction in total energy intake while maintaining fibre consumption.

Influence of Adult Knee Height, Age at First Birth, Migration, and Current Age on Adult Physical Function of Bangladeshi Mothers and Daughters in the United Kingdom and Bangladesh

Barry Bogin, Diane Harper, Joy Merrell, Jasmin Chowdhury, Michael Heinrich, Vanja Garaj, Bablin Molik, and Janice L. Thompson

Abstract
In the United Kingdom, Bangladeshi women have the lowest self-reported levels of physical activity and some of the highest levels of metabolic disease of all ethnic groups. To better understand these risks for poor health we employed life course and intergenerational hypotheses to predict lower body physical function in a sample of 121 Bangladeshi mothers (40–70 years old) and one of their adult daughters (17–36 years old) living in Bangladesh or in the UK. For the mothers, older age and shorter knee height predicted reduced lower body physical function. Knee height is a biomarker of nutrition and health status between birth and puberty. Age at first birth did not have a significant effect. For daughters, older age and migration to the UK predicted reduced lower body physical function. We controlled for total stature and fatness in all analyses. UK-born daughters were taller than BD-born daughters living in the UK, mostly due to differences in knee height. These new findings support previous research indicating that early life health and adequate nutritional status, along with appropriate adult physical activity and diet, may decrease risks for poor physical function, morbidity, and premature mortality.
Theme 5

Systems Biology and Metabolomics

This theme aims to provide a systems-level molecular understanding of the effects of ageing on the musculoskeletal system. Projects will study the complex interactions between different biochemicals (genes, RNA, proteins and metabolites) and their influence on mechanisms of healthy and unhealthy musculoskeletal ageing.

Publications

Lavery GG


**TNFα**-mediated Hsd11b1 binding of NF-κB p65 is associated with suppression of 11β-HSD1 in muscle.

Doig CL, Bashir J, Zielinska AE, Cooper MS, Stewart PM, Lavery GG.

Abstract

The activity of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts inactive cortisone (11-dehydrocorticosterone (11-DHC)) (in mice) into the active glucocorticoid (GC) cortisol (corticosterone in mice), can amplify tissue GC exposure. Elevated TNFα is a common feature in a range of inflammatory disorders and is detrimental to muscle function in diseases such as rheumatoid arthritis and chronic obstructive pulmonary disease. We have previously demonstrated that 11β-HSD1 activity is increased in the mesenchymal stromal cells (MSCs) by TNFα treatment and suggested that this is an autoregulatory anti-inflammatory mechanism. This upregulation was mediated by the P2 promoter of the Hsd11b1 gene and was dependent on the NF-κB signalling pathway. In this study, we show that in contrast to MSCs, in differentiated C2C12 and primary murine myotubes, TNFα suppresses Hsd11b1 mRNA expression and activity through the utilization of the alternative P1 promoter. As with MSCs, in response to TNFα treatment, NF-κB p65 was translocated to the nucleus. However, ChIP analysis demonstrated that the direct binding was seen at position -218 to -245 bp of the Hsd11b1 gene's P1 promoter but not at the P2 promoter. These studies demonstrate the existence of differential regulation of 11β-HSD1 expression in muscle cells through TNFα/p65 signalling and the P1 promoter, further enhancing our understanding of the role of 11β-HSD1 in the context of inflammatory disease.
Abstract
Objective. Inflammatory arthritis is associated with systemic manifestations including alterations in metabolism. We used nuclear magnetic resonance (NMR) spectroscopy-based metabolomics to assess metabolic fingerprints in serum from patients with established rheumatoid arthritis (RA) and those with early arthritis.

Methods. Serum samples were collected from newly presenting patients with established RA who were naive for disease-modifying antirheumatic drugs, matched healthy controls, and 2 groups of patients with synovitis of 3 months’ duration whose outcomes were determined at clinical followup. Serum metabolomic profiles were assessed using 1-dimensional H-1-NMR spectroscopy. Discriminating metabolites were identified, and the relationships between metabolomic profiles and clinical variables including outcomes were examined.

Results. The serum metabolic fingerprint in established RA was clearly distinct from that of healthy controls. In early arthritis, we were able to stratify the patients according to the level of current inflammation, with C-reactive protein correlating with metabolic differences in 2 separate groups (P < 0.001). Lactate and lipids were important discriminators of inflammatory burden in both early arthritis patient groups. The sensitivities and specificities of models to predict the development of either RA or persistent arthritis in patients with early arthritis were low.

Conclusion. The metabolic fingerprint reflects inflammatory disease activity in patients with synovitis, demonstrating that underlying inflammatory processes drive significant changes in metabolism that can be measured in the peripheral blood. The identification of metabolic alterations may provide insights into disease mechanisms operating in patients with inflammatory arthritis.
The MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research is a collaborative research venture between Birmingham and Nottingham Universities that aims to understand how ageing results in loss of musculoskeletal function and strives to use this knowledge to intervene and minimise age-related musculoskeletal decline and disease. The major focus of our interventions is on exercise and diet, incorporating motivational psychology research to underpin improved uptake and adherence to lifestyle changes. The Centre will also use the facilities on both sites to train the next generation of researchers, building capacity in this vital area and ensuring older adults are able to enjoy rather than endure old age.

Centre objectives for the first 5 years are to:

- Increase understanding of molecular and cellular processes underlying musculoskeletal ageing and their systems-level effects;
- Establish a national technology platform for research and training in stable isotope tracer methods to study metabolism in musculoskeletal tissues in humans;
- Develop pharmacological and lifestyle interventions to attenuate age-related musculoskeletal decline in humans;
- Develop protocols to achieve adherence to lifestyle interventions in humans;
- Increase research and training capacity in Birmingham and Nottingham in musculoskeletal ageing through a joint, dedicated PhD programme for clinicians and non-clinicians and an MSc in Musculoskeletal Health.