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Stromal cell-derived factor-1 (SDF-1) as a target in liver diseases
Anke Liepelt, Frank Tacke
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DOI: 10.1152/ajpgi.00193.2016

Neurogastroenterology and Motility

High-fat diet-induced obesity alters nitric oxide-mediated neuromuscular transmission and smooth muscle excitability in the mouse distal colon
Yogesh Bhattarai, David Fried, Brian Gulbransen, Mark Kadrofske, Roxanne Fernandes, Hui Xu, James Galligan
August 1, 2016: G210-G220
DOI: 10.1152/ajpgi.00085.2016

Distribution and trafficking of the μ-opioid receptor in enteric neurons of the guinea pig
Joslyn Lay, Simona E. Carbone, Jesse J. DiCello, Nigel W. Bunnell, Meritxell Canals, Daniel P. Poole
August 1, 2016: G252-G266
DOI: 10.1152/ajpgi.00184.2016

This article provides a detailed characterization of the μ-opioid receptor (MOR) in the enteric nervous system of the guinea pig. The distribution of MOR within neurochemically defined neuronal subtypes is correlated with the established physiological effects of MOR agonists. The ability of clinically and experimentally relevant MOR ligands to induce endocytosis of MOR in enteric neurons is also examined, with key differences in the kinetics and magnitude of internalization observed between agonists.

Stem Cells, Tissue Engineering, Development, and Cancer

PAR2-dependent activation of GSK3β regulates the survival of colon stem/progenitor cells
Imen Nasri, Delphine Bonnet, Bailey Zwarycz, Emilie d'Aldebert, Sokchea Khou, Raoudha Mezghani-Jarraya, Muriel Quaranta, Corinne Rolland, Chrystelle Bonnart, Emmanuel Mas, Audrey Ferrand, Nicolas Cenac, Scott Magness, Laurianne Van Landeghem, Nathalie Vergnolle, Claire Racaud-Sultan
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DOI: 10.1152/ajpgi.00328.2015
Hepatocyte nuclear factor 4α is required for cell differentiation and homeostasis in the adult mouse gastric epithelium
Benjamin D. Moore, Shrada S. Khurana, Won Jae Huh, Jason C. Mills
August 1, 2016 : G267-G275

DOI: 10.1152/ajpgi.00195.2016

The transcription factor (TF) HNF4α is known to be expressed in stomach, but its function was unknown. We show here that inducing deletion of HNF4α caused increased proliferation and collapse of chief cell endoplasmic reticulum (ER) and secretory architecture. We show HNF4α binds and upregulates the known ER-regulating TF XBP1. As we have previously shown XBP1 governs expression of the TF MIST1, we now show chief cell maturation depends on a HNF4α→XBP1→MIST1 transcriptional sequence.

Liver and Biliary Tract Physiology/Pathophysiology
GGsTop, a novel and specific γ-glutamyl transpeptidase inhibitor, protects hepatic ischemia-reperfusion injury in rats
Kaneto Tamura, Nobuhiko Hayashi, Joseph George, Nobuyuki Toshikuni, Tomiyasu Arisawa, Jun Hiratake, Mutsumi Tsuchishima, Mikihiro Tsutsumi
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DOI: 10.1152/ajpgi.00439.2015

Inflammation, Immunity, and Infection
Contribution of programmed cell death receptor (PD)-1 to Kupffer cell dysfunction in murine polymicrobial sepsis
Fei Wang, Xin Huang, Chun-Shiang Chung, Yaping Chen, Noelle A. Hutchins, Alfred Ayala
August 1, 2016 : G237-G245
DOI: 10.1152/ajpgi.00371.2015

Platelet interaction with lymphatics aggravates intestinal inflammation by suppressing lymphangiogenesis
Hirokazu Sato, Masaaki Higashiyama, Hideaki Hozumi, Shingo Sato, Hirotaka Furuhashi, Takeshi Takajo, Koji Maruta, Yuichi Yasutake, Kazuyuki Narimatsu, Kenichi Yoshikawa, Chie Kurihara, Yoshikiyo Okada, Chikako Watanabe, Shunsuke Komoto, Kengo Tomita, Shigeaki Nagao, Soichiro Miura, Ryota Hokari
August 1, 2016 : G276-G285
DOI: 10.1152/ajpgi.00455.2015

Ablation of interaction between IL-33 and ST2+ regulatory T cells increases immune cell-mediated hepatitis and activated NK cell liver infiltration
Gregory Noel, Muhammad Imran Arshad, Aveline Filliol, Valentine Genet, Michel Rauch, Catherine Lucas-Clerc, Agnès Lehuen, Jean-Philippe Girard, Claire Piquet-Pellorce, Michel Samson
August 1, 2016 : G313-G323
DOI: 10.1152/ajpgi.00097.2016

Ursodeoxycholic acid inhibits TNFα-induced IL-8 release from monocytes
Aoife M. O'Dwyer, Natalia K. Lajczak, Jennifer A. Keyes, Joseph B. Ward, Catherine M. Greene, Stephen J. Keely
August 1, 2016 : G334-G341
DOI: 10.1152/ajpgi.00406.2015

The secondary bile acid, ursodeoxycholic acid (UDCA), specifically inhibits TNF-α-induced release of the proinflammatory cytokine, IL-8, from monocytes. The effects of the bile acid appear to be mediated by inhibition of TRAF-2-mediated NFκB activation and subsequent downregulation of IL-8 mRNA expression. Such actions of UDCA would serve to dampen mucosal immune responses in vivo, suggesting it may provide an alternative approach to the current use of biologics for prevention of TNF-α-induced inflammation in IBD patients.

Nutrient Sensing, Nutrition, and Metabolism
Activation of bile acid signaling improves metabolic phenotypes in high-fat diet-induced obese mice
Joseph F. Pierre, Kristina B. Martinez, Honggang Ye, Anuradha Nadimpalli, Timothy C. Morton, Jinghui Yang, Qiang Wang, Noelle Patno, Eugene B. Chang, Deng Ping Yin
August 1, 2016 : G286-G304
DOI: 10.1152/ajpgi.00202.2016

Bile diversion (BD) improves obesity, glycemic control, thermogenesis, and energy expenditure, and alters the gut microbiota, thereby increasing the microbe Akkermansia muciniphila, which is correlated with circulating bile acids in this study and is associated with leanness. Whereas oral bile acid gavage reverses mucosal hypertrophy and proliferation during BD, this approach fails to abrogate metabolic benefits, suggesting that bile acids in the distal intestine, but not proliferation in the proximal intestine, contribute to improved glycemic control.
Milk diets influence doxorubicin-induced intestinal toxicity in piglets
Rene L. Shen, Peter E. L. Pontoppidan, Mathias Rathe, Pingping Jiang, Carl Frederik Hansen, Randal K. Buddington, Peter M. H. Heegaard, Klaus Müller, Per T. Sangild
August 1, 2016 : G324-G333
DOI: 10.1152/ajpgi.00373.2015

In this study, preweaned pigs were used as models to study intestinal complications after doxorubicin as models for pediatric oncology patients receiving chemotherapy. This study shows that the type of enteral nutrition is an important factor that can influence the toxic responses related to doxorubicin treatment. Compared with formula, bovine colostrum nutrition provided beneficial effects against the intestinal injury, which occurred early after doxorubicin administration.

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Coronary blood flow in humans is responsive to both changes in cardiac effort and arterial blood gases. Using echocardiographic assessment and a noninvasively derived index of cardiac work, we present an estimation of the relative contributions to coronary reactivity during CO2 and O2 challenges.

**CALL FOR PAPERS | Small Vessels-Big Problems: Novel Insights into Microvascular Mechanisms of Diseases**

Attenuated rapid onset vasodilation with greater force production in skeletal muscle of caveolin-2−/− mice
Charmain A. Fernando, Yajun Liu, Grzegorz Sowa, Steven S. Segal
August 1, 2016 : H415-H425
DOI: 10.1152/ajpheart.00082.2016

In skeletal muscle of mice lacking caveolin-2 (Cav2−/−), microvascular diameters and vasomotor responses to norepinephrine, ACh, and rhythmic contractions were not different from wild-type. However, rapid onset vasodilation to tetanic contraction was diminished by approximately half, while active force increased by 40%, revealing novel physiological roles for Cav2 in skeletal muscle.

Cardiovascular Neurohormonal Regulation

Renal denervation improves cardiac function in rats with chronic heart failure: Effects on expression of β-adrenoceptors
Hong Zheng, Xuefei Liu, Neeru M. Sharma, Kaushik P. Patel
August 1, 2016 : H337-H346
DOI: 10.1152/ajpheart.00999.2015

This study shows in a comprehensive way that renal denervation initiated after a period of chronic heart failure enhances cardiac contractility and the responsiveness of hearts to isoproterenol stimulation, and these effects are due in part to renal denervation-induced increase in β-adrenoceptor protein and function.

Sympathetic neural reactivity to mental stress in offspring of hypertensive parents: 20 years revisited
Ida T. Fonkoue, Min Wang, Jason R. Carter
August 1, 2016 : H426-H432
DOI: 10.1152/ajpheart.00378.2016

Subjects with a family history of hypertension (FHH) demonstrate a significantly greater muscle sympathetic nerve activity (MSNA) reactivity to mental stress than those without FHH. This greater sympathoexcitation was observed despite comparable blood pressure (BP) reactivity between groups, and both groups demonstrate a marked dissociation between MSNA and BP responsiveness.

Stimulation of the hypothalamic arcuate nucleus increases brown adipose tissue nerve activity via hypothalamic paraventricular and dorsomedial nuclei
Vineet C. Chitravanshi, Kazumi Kawabe, Hreday N. Sapru
August 1, 2016 : H433-H444
DOI: 10.1152/ajpheart.00176.2016

Chemical stimulation of the arcuate nucleus (ARCN) elicited increases in interscapular brown adipose tissue sympathetic nerve activity and temperature of brown adipose tissue. These responses were mediated via the release of α-melanocyte-stimulating hormone (α-MSH) and glutamate in the dorsomedial nucleus (DMN) and the paraventricular nucleus. Subpopulations of ARCN neurons projecting directly to the DMN and containing proopiomelanocortin, α-MSH, and vesicular glutamate transporter-3 were identified.

Energetics and Metabolism

Acetylation and succinylation contribute to maturational alterations in energy metabolism in the newborn heart
Arata Fukushima, Osama Abo Alrob, Liyan Zhang, Cory S. Wagg, Tariq Altamimi, Sonia Rawat, Ivan M. Rebeyka, Paul F. Kantor, Gary D. Lopaschuk
August 1, 2016 : H347-H363
DOI: 10.1152/ajpheart.00900.2015

The present study is the first showing that alterations in acetylation and succinylation control of metabolic enzymes contribute to the dramatic shift in cardiac energy metabolism from glycolysis to fatty acid β-oxidation seen during maturation. Our results suggest that lysine acetylation enhances cardiac fatty acid β-oxidation and inhibits glycolysis during maturation.

Integrative Cardiovascular Physiology and Pathophysiology
Sympathetic nervous response to ischemia-reperfusion injury in humans is altered with remote ischemic preconditioning
Elisabeth A. Lambert, Colleen J. Thomas, Robyn Hemmes, Nina Eikelis, Atul Pathak, Markus P. Schlaich, Gavin W. Lambert
August 1, 2016 : H364-H370
DOI: 10.1152/ajpheart.00369.2016

Muscle sympathetic nervous system (SNS) increases during forearm ischemia-reperfusion (IR) in healthy individuals. When remote ischemic preconditioning (RIPC) was applied before IR, the SNS response was delayed and attenuated, indicating that modulation of the SNS may play a role in the beneficial effects afforded by RIPC.

Ataxia telangiectasia-mutated kinase deficiency exacerbates left ventricular dysfunction and remodeling late after myocardial infarction
Laura L. Daniel, Stephanie L. C. Scofield, Patsy Thrasher, Suman Dalal, Christopher R. Daniels, Cerrone R. Foster, Mahipal Singh, Krishna Singh
August 1, 2016 : H445-H452
DOI: 10.1152/ajpheart.00338.2016

Ataxia telangiectasia-mutated kinase (ATM) deficiency attenuates cardiac dysfunction early postmyocardial infarction (post-MI). Here, we provide evidence that ATM deficiency is associated with worse late post-MI outcomes in terms of function, fibrosis, apoptosis, and hypertrophy. Further identification of molecular targets involved in cell survival and growth may help explain the role of ATM in myocardial remodeling post-MI.

PlanHab: hypoxia exaggerates the bed-rest-induced reduction in peak oxygen uptake during upright cycle ergometry
Michail E. Keramidas, Roger Köllegård, Igor Mekjavic, Ola Eiken
August 1, 2016 : H453-H464
DOI: 10.1152/ajpheart.00304.2016

Hypoxia exacerbated the bed-rest-induced reduction in peak O2 uptake during upright cycling, probably due to a reduction in convective O2 transport, as indicated by the lower peak values of cardiac output and stroke volume, presumably secondary to a more pronounced bed-rest-induced hypovolemia in hypoxia.

Muscle Mechanics and Ventricular Function

A post-MI power struggle: adaptations in cardiac power occur at the sarcomere level alongside MyBP-C and RLC phosphorylation
Christopher N. Toepfer, Markus B. Sikkel, Valentina Caorsi, Anupama Vydyanath, Iratxe Torre, O'Neal Copeland, Alexander R. Lyon, Steven B. Marston, Pradeep K. Luther, Kenneth T. Macleod, Timothy G. West, Michael A. Ferenczi
August 1, 2016 : H465-H475
DOI: 10.1152/ajpheart.00899.2015

OPEN ACCESS ARTICLE
Compensation postchronic myocardial infarction (CMI) in rats is characterized in trabeculae as increased force and power production during physiological shortening, which occurs alongside classical hypertrophy. Sarcomeric contractile gain is influenced by mechanisms involving reduced myosin binding protein C (MyBP-C) and raised regulatory light chain (RLC) phosphorylation.

Signal and Stress Response

Carvedilol-responsive microRNAs, miR-199a-3p and -214 protect cardiomyocytes from simulated ischemia-reperfusion injury
Kyoung-mi Park, Jian-peng Teoh, Yongchao Wang, Zuzana Broskova, Ahmed S. Bayoumi, Yaoliang Tang, Huabo Su, Neal L. Weintraub, Il-man Kim
August 1, 2016 : H371-H383
DOI: 10.1152/ajpheart.00807.2015

Carvedilol upregulates microRNA (miR)-199a-3p and miR-214 in cardiomyocytes. This miR activation is a mechanism for carvedilol-mediated p-Akt activation. The action of these carvedilol-responsive miRs on cardiomyocyte survival is mediated in part by the repression of the predictive or known targets Ddit4 and Ing4, subsequently activating Akt-Sox2 prosurvival axis.

Moesin is activated in cardiomyocytes in experimental autoimmune myocarditis and mediates cytoskeletal reorganization with protrusion formation
Akimitsu Miyawaki, Yusuke Mitsuhara, Aya Orimoto, Yusuke Nakayasu, Shin-ichi Tsunoda, Masanori Obana, Makiko Maeda, Hiroyuki Nakayama, Yasuo Yoshioka, Yasuo Tsutsumi, Yasushi Fujio
August 1, 2016 : H476-H486
DOI: 10.1152/ajpheart.00180.2016

In spite of the limited regenerative capacity of the heart, myocardial restoration is observed in the postinflammatory phase of experimental autoimmune myocarditis (EAM). We analyzed the cardiomyocyte dynamics by shotgun proteomics and identified moesin as a cytoskeletal regulator that induces cardiomyocyte protrusions, a critical process of myocardial healing.
Vascular Biology and Microcirculation

Hyperplasia, de novo lymphangiogenesis, and lymphatic regression in mice with tissue-specific, inducible overexpression of murine VEGF-D
Gabriela M. Lammoglia, Carolynn E. Van Zandt, Daniel X. Galvan, Jose L. Orozco, Michael T. Dellinger, Joseph M. Rutkowski
August 1, 2016 : H384-H394
DOI: 10.1152/ajpheart.00208.2016

A new mouse model of inducible murine VEGF-D expression drives lymphatic expansion. Lung, kidney, or brown adipose tissue (BAT) VEGF-D overexpression causes lymphatic hyperplasia and in white adipose tissue a de novo lymphatic network. New adipose lymphatics rapidly regress with basal VEGF receptor-3 signaling, providing a mechanistic model of adult lymphatic remodeling.

Cell adhesion during bullet motion in capillaries
Naoki Takeishi, Yohsuke Imai, Shunichi Ishida, Toshihiro Omori, Roger D. Kamm, Takuji Ishikawa
August 1, 2016 : H395-H403
DOI: 10.1152/ajpheart.00241.2016

In contrast to a large number of previous studies of leukocyte and tumor cell rolling, little is known about bullet motion in capillaries. We found that bullet motion allowed the cell to firmly adhere to the wall even under the weak ligand-receptor interaction between P-selectin glycoprotein ligand-1 (PSGL-1) and P-selectin.

Symmetry recovery of cell-free layer after bifurcations of small arterioles in reduced flow conditions: effect of RBC aggregation
Yan Cheng Ng, Bumseok Namgung, Sim Leng Tien, Hwa Liang Leo, Sangho Kim
August 1, 2016 : H487-H497
DOI: 10.1152/ajpheart.00223.2016

This study demonstrates that the asymmetry of cell-free layer widths in small arterioles persists up to six vessel-diameter downstream of a bifurcation under reduced flow conditions. The symmetry recovery is further retarded by red blood cell (RBC) aggregation and seems to be unapparent within the limited interbifurcation distances in arteriolar networks.

The adipokine chemerin amplifies electrical field-stimulated contraction in the isolated rat superior mesenteric artery
Emma S. Darios, Brittany M. Winner, Trevor Charvat, Antoni Krasinski, Sreenivas Punna, Stephanie W. Watts
August 1, 2016 : H498-H507
DOI: 10.1152/ajpheart.00998.2015

This research is noteworthy, in that it supports a new mechanism by which chemerin can act to modify blood pressure. This expands the repertoire of functions assigned to this adipokine and forces us to enlarge our view of the role adipokines play in blood pressure regulation.

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Late intervention with the small molecule BB3 mitigates postischemic kidney injury
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Danielle E. Soranno, Christopher B. Rodell, Christopher Altmann, Jane Duplantis, Ana Andres-Hernando, Jason A. Burdick, Sarah Faubel
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Estimating postvoid residual volume without measuring residual bladder volume during serial cystometrograms
Zachary C. Danziger, Warren M. Grill
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Charles M. Tipton
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Lifelong strength training mitigates the age-related decline in efferent drive
Runar Unhjem, Mona Nygård, Lene T. van den Hoven, Simranjit K. Sidhu, Jan Hoff, Eivind Wang
August 1, 2016 : 415-423
DOI: 10.1152/japplphysiol.00117.2016

This cross-sectional study shows that efferent drive to contracting muscle is compromised with age. Furthermore, it shows that old subjects involved in long-term strength training mitigate this decline in efferent drive. In contrast, no difference in efferent drive was observed between recreationally
active and sedentary old subjects. This indicates that strength training in particular may be beneficial for counteracting the age-related loss of efferent drive.

**Faster and stronger manifestation of mitochondrial diseases in skeletal muscle than in heart related to cytosolic inorganic phosphate (Pi) accumulation**

Bernard Korzeniewski  
August 1, 2016: 424-437

DOI: 10.1152/japplphysiol.00358.2016

A novel mechanism contributing to a faster (at lower OXPHOS deficiencies) and stronger manifestation of mitochondrial diseases in skeletal muscle than in heart, namely a much higher cytosolic inorganic phosphate (Pi) accumulation that causes muscle fatigue even at low/moderate exercise intensity, is proposed.

**The effects of a roundtrip trans-American jet travel on physiological stress, neuromuscular performance, and recovery**

August 1, 2016: 438-448

DOI: 10.1152/japplphysiol.00429.2016

This study demonstrated trans-American jet travel going from east to west to participate in a rigorous simulated sport competition had dramatic effects on hormonal responses, sleep quality, and neuromuscular performances. Return travel to the east after the simulated sport competition resulted in muscle tissue damage and delays in neuromuscular and muscle tissue recovery upon return home. The use of extended wear whole body compression garments reduced the recovery times upon the homebound arrival.

**Qualitative dimensions of exertional dyspnea in adults with cystic fibrosis**

Bradley S. Quon, Sabrina S. Wilkie, Andrew H. Ramsook, Michele R. Schaeffer, Joseph H. Puyat, Pearce G. Wilcox, Jordan A. Guenette  
August 1, 2016: 449-456

DOI: 10.1152/japplphysiol.00391.2016

This is the first study to characterize the evolution of the qualitative descriptors of exertional dyspnea in cystic fibrosis (CF). Adults with CF experience greater ventilatory constraints, have an earlier onset of unsatisfied inspiration, and are more likely to report chest tightness during exercise relative to controls. This study provides new insight into the qualitative dimensions of dyspnea in CF and may aid clinicians in tailoring therapies to manage dyspnea during physical activity.

**Antiapoptotic effect of exercise training on ovariectomized rat hearts**

Chih-Yang Huang, Yi-Yuan Lin, Chih-Chao Hsu, Shiu-Min Cheng, Woei-Cherng Shyu, Hua Ting, Ai-Lun Yang, Tsung-Jung Ho, Shin-Da Lee  
August 1, 2016: 457-465

DOI: 10.1152/japplphysiol.01042.2015

Cardiac widely dispersed apoptosis was found after ovariectomy. Exercise training on treadmill could prevent ovariectomy-induced cardiac widely dispersed apoptosis in Fas receptor-dependent apoptotic pathway (TNF-α, TNFR1, Fas-L, Fas, activated caspase-8, and activated caspase-3) and mitochondria-dependent apoptotic pathway (t-Bid, Bad, Bak, Bax, cytosolic cytochrome c, activated caspase-9, and activated caspase-3). Exercise training has antiapoptotic effects on ovariectomized rat hearts via both Fas receptor-dependent and mitochondria-dependent apoptotic pathways.

**Regional activation within the vastus medialis in stimulated and voluntary contractions**

Alessio Gallina, Tanya D. Ivanova, S. Jayne Garland  
August 1, 2016: 466-474

DOI: 10.1152/japplphysiol.00050.2016

This study showed, for the first time, that regional activation induced by intramuscular stimulation in vastus medialis is relatively unaffected by changes in knee angle. When examined in voluntary dynamic contractions, there were shifts in regional activation that were not attributable to anatomic factors. The difference in EMG amplitude distribution between concentric and eccentric contractions provides preliminary evidence that regions within the VM can be preferentially recruited according to the mechanical demands of the task.

**Rate modulation of human anconeus motor units during high-intensity dynamic elbow extensions**

Brianna L. Cowling, Brad Harwood, David B. Copithorne, Charles L. Rice  
August 1, 2016: 475-482

DOI: 10.1152/japplphysiol.00131.2016

We recorded single MUFRs during a high-intensity fatiguing dynamic elbow extension task. Because of unique features, the anconeus muscle (an accessory elbow extensor) facilitates tracking of units during rapid maximal effort concentric contractions at a moderately high load. Despite baseline dynamic rates being higher than those recorded during isometric maximum contractions, there was a decrease in MUFRs over the 80-s
fatiguing protocol, indicating rate reduction is a common feature to both isometric and dynamic high-intensity fatiguing tasks.

Effect of 23-day muscle disuse on sarcoplasmic reticulum Ca\(^{2+}\) properties and contractility in human type I and type II skeletal muscle fibers
C. R. Lamboley, V. L. Wyckelsma, B. D. Perry, M. J. McKenna, G. D. Lamb
August 1, 2016 : 483-492

DOI: 10.1152/japplphysiol.00337.2016

This study identified for the first time a number of important cellular adaptations in human skeletal muscle fibers following 23 days of disuse, such as 1) a lower sarcoplasmic reticulum (SR) Ca\(^{2+}\)content in both fiber types and 2) an early upregulation of SR Ca\(^{2+}\) handling proteins, in particular an increase in SERCA1 and calsequestrin content, which precedes any transition in myosin heavy chain isoforms from slow to fast.

The slow component of pulmonary O2 uptake accompanies peripheral muscle fatigue during high-intensity exercise
Daniel A. Keir, David B. Copithorne, Michael D. Hodgson, Silvia Pogliaghi, Charles L. Rice, John M. Kowalchuk
August 1, 2016 : 493-502

DOI: 10.1152/japplphysiol.00249.2016

Quadriiceps muscle torque production in response to electrically stimulated contractions (a measure of peripheral muscle fatigue) progressively decreases with greater durations of high-intensity constant-load cycling, and the time course and magnitude of this response mirrors that of the p slow component and peripheral muscle fatigue suggests that mechanisms contributing to muscle fatigue also contribute to an increased O2 cost of exercise.

Intermuscular adipose tissue and thigh muscle area dynamics during an 18-month randomized weight loss trial
August 1, 2016 : 518-527

DOI: 10.1152/japplphysiol.00309.2016

This 18-mo randomized controlled trial among 273 sedentary adults considered yet to be addressed questions on the long-term effects of different lifestyle intervention strategies on the dynamics of both intermuscular adipose tissue and thigh muscle area, and their associations with cardiometabolic risk factors and abdominal subdepots. We found that intermuscular adipose tissue largely reflects body weight change per se, whereas moderate weight loss induced a significant decrease in thigh muscle area.

The effect of 1 year of Alagebrium and moderate-intensity exercise training on left ventricular function during exercise in seniors: a randomized controlled trial
Graeme Carrick-Ranson, Naoki Fujimoto, Keri M. Shafer, Jeffrey L. Hastings, Shigeki Shibata, M. Dean Palmer, Kara Boyd, Benjamin D. Levine
August 1, 2016 : 528-536

DOI: 10.1152/japplphysiol.00021.2016

Exercise for 1 yr improved stroke volume and effective arterial elastance during exercise in previously sedentary seniors; however, these adaptations were not enhanced by the advanced glycation end-product cross-link breaker Alagebrium. Exercise plus Alagebrium for 1 yr failed to restore exercising left ventricular function to levels associated with lifelong exercise, despite a similar exercise frequency.

Elevation of iron storage in humans attenuates the pulmonary vascular response to hypoxia
Nicole K. Bart, M. Kate Curtis, Hung-Yuan Cheng, Sara L. Hungerford, Ross McLaren, Nayia Petousi, Keith L. Dorrington, Peter A. Robbins
August 1, 2016 : 537-544

DOI: 10.1152/japplphysiol.00032.2016

OPEN ACCESS ARTICLE

This study shows that a single dose of intravenous iron reduces the effects of hypoxia on the pulmonary circulation in a manner that persists for at least several weeks. This is long after the foreign iron-sugar complex has been cleared from the blood. It raises the possibility that manipulating iron stores, even in people who are not initially iron deficient, could be used for therapeutic gain in some forms of pulmonary hypertension.

Intermittent hypoxia promotes recovery of respiratory motor function in spinal cord-injured mice depleted of serotonin in the central nervous system
Dragana Komnenov, Julia Z. Solarewicz, Fareeza Afzal, Kwaku D. Nantwi, Donald M. Kuhn, Jason H. Mateika
August 1, 2016 : 545-557

DOI: 10.1152/japplphysiol.00448.2016

In the present investigation we showed that exposure to intermittent hypoxia promotes the recovery of respiratory motor function in a spinal cord-injured mouse model. Moreover, we demonstrated that the recovery of respiratory motor function after spinal cord injury can occur despite the depletion of serotonin in the central nervous system.
This study provides evidence regarding a physiological mechanism that determines the lung mean capillary PCO that drives pulmonary CO excretion and functions as “back pressure” during CO uptake. Relevant to findings that CO is an intracellular signaling molecule and that there are clinical trials under way evaluating CO therapy, the goal of this study was to obtain a better understanding of the physiology of pulmonary CO exchanges that determine the body CO stores and intracellular PCO values.

A methodological approach for quantifying and characterizing the stability of agitated saline contrast: implications for quantifying intrapulmonary shunt
Heather K. Hackett, Lindsey M. Boulet, Paolo B. Dominelli, Glen E. Foster
August 1, 2016 : 568-576
DOI: 10.1152/japplphysiol.00422.2016

Indicator dilution theory can quantify agitated saline contrast and be used to characterize the stability of agitated saline contrast. Agitated saline IPAVA should consider transpulmonary transit time. Gases with high density and low blood solubility sufficiently stabilize saline contrast. Because of contrast instability, IPAVA is likely underestimated at rest.

Innovative Methodology
Correcting the dynamic response of a commercial esophageal balloon-catheter
Troy J. Cross, Kenneth C. Beck, Bruce D. Johnson
August 1, 2016 : 503-511
DOI: 10.1152/japplphysiol.00155.2016

Measurement of esophageal pressure affords calculation of many insightful and clinically important parameters of respiratory mechanics. It is recommended that an esophageal balloon-catheter possess an adequate frequency response up to 15 Hz. In this report we show that when this requirement is not met, it is possible to digitally compensate for the dynamic response of an esophageal balloon-catheter using an exponential model correction, or Wiener deconvolution (whereby superior results are obtained via the latter method).

Predicting metabolic rate during level and uphill outdoor walking using a low-cost GPS receiver
Pierre-Yves de Müllenheim, Rémy Dumond, Marie Gernigon, Guillaume Mahé, Audrey Lavenu, Sandrine Bickert, Jacques Prioux, Bénédicte Noury-Desvaux, Alexis Le Faucheur
August 1, 2016 : 577-588
DOI: 10.1152/japplphysiol.00224.2016

This is the first study to characterize the direct relationship between global positioning system (GPS) speed and grade and the metabolic rate while walking outdoors under different controlled speed and grade conditions. Using GPS speed and grade yields accurate metabolic rate predictions during level and uphill outdoor walking, particularly when GPS grade is corrected. Moreover, when using GPS parameters with published speed/grade-based equations, the metabolic rate predictions were close to those obtained using actual speed and grade values.

Highlighted Topic | Hypoxia 2015
Physiological impact of patent foramen ovale on pulmonary gas exchange, ventilatory acclimatization, and thermoregulation
Andrew T. Lovering, Jonathan E. Elliott, James T. Davis
August 1, 2016 : 512-517
DOI: 10.1152/japplphysiol.00192.2015

Physiological impact of patent foramen ovale on pulmonary gas exchange, ventilatory acclimatization, and thermoregulation
Andrew T. Lovering, Jonathan E. Elliott, James T. Davis
August 1, 2016 : 512-517
DOI: 10.1152/japplphysiol.00192.2015

Perspectives
Could lobar flow sequencing account for convection-dependent ventilation heterogeneity in normal humans?
Sylvia Verbanck, Manuel Paiva
August 1, 2016 : 589-591
DOI: 10.1152/japplphysiol.01049.2015

Commentaries on Viewpoint: Could lobar flow sequencing account for convection-dependent ventilation heterogeneity in normal humans?
Guilhem Collier, Li Zuo, Felix Horn, Jim Wild, Tingyang Zhou

DOI: 10.1152/japplphysiol.01049.2015

Commentaries on Viewpoint: Could lobar flow sequencing account for convection-dependent ventilation heterogeneity in normal humans?
Guilhem Collier, Li Zuo, Felix Horn, Jim Wild, Tingyang Zhou

DOI: 10.1152/japplphysiol.01049.2015
Last Word on Viewpoint: Could lobar flow sequencing account for convection-dependent ventilation heterogeneity in normal man?
Sylvia Verbanck, Manuel Paiva
August 1, 2016 : 593
DOI: 10.1152/japplphysiol.00513.2016

The rigorous study of exercise adaptations: why mRNA might not be enough
Benjamin F. Miller, Adam R. Konopka, Karyn L. Hamilton
August 1, 2016 : 594-596
DOI: 10.1152/japplphysiol.00509.2016

Commentaries on Viewpoint: The rigorous study of exercise adaptations: Why mRNA might not be enough
August 1, 2016 : 597-600
DOI: 10.1152/japplphysiol.00137.2016

Last Word on Viewpoint: On the rigorous study of exercise adaptations: why mRNA might not be enough?
Benjamin F. Miller, Adam R. Konopka, Karyn L. Hamilton
August 1, 2016 : 601
DOI: 10.1152/japplphysiol.00505.2016

Letter to the Editor
“Kilometer hours” hypoxic dose: one size fits all
Matiram Pun
August 1, 2016 : 602
DOI: 10.1152/japplphysiol.00556.2016

Corrigendum
Corrigendum
August 1, 2016 : 603
DOI: 10.1152/japplphysiol.zdg-1941.corr.2016

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August 2016; volume 116, issue 2

The below Table of Contents is available online at: http://jn.physiology.org/content/116/2

Review
Neural and neurochemical basis of reinforcement-guided decision making
Abbas Khani, Gregor Rainer
August 1, 2016 : 724-741
Comparison of updating performance across active, passive, and cancellation head movement conditions reveals that vestibular signals dominate auditory spatial updating. However, neck proprioceptive and/or efference copy signals also play a role and appear to be responsible for inaccurate updating during normal active head turns, consistent with overestimation of head turn angle.

Cochlear implants are neuroprosthetic devices that provide hearing to deaf patients. However, outcomes can be highly variable from patient to patient, and it is unclear how these devices stimulate the central auditory system or the degree to which plasticity in the auditory system is important for successful cochlear implant use. To overcome these challenges, we developed a new behaviorally and physiologically validated system for multichannel implant use in trained rats.

Recording in vivo from the same neuron with two different methods is difficult. It requires blindly moving each probe to within 100 μm of one another and for this reason such “dual-recordings” are rare. However, comparing the signals measured by different techniques is necessary to understand what they measure. We developed a method to precisely align the axes of two manipulators and used it to gather a “ground truth” dataset for dense extracellular polytrodes.

Current advances in invertebrate vision: insights from patch-clamp studies of photoreceptors in apposition eyes

Functional connectivity as a means to delineate differences between treatment-resistant and treatment-responsive schizophrenia

Respiratory and autonomic dysfunction in congenital central hypoventilation syndrome
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Beyond cones: an improved model of whisker bending based on measured mechanics and tapering
Samuel Andrew Hires, Adam Schuyler, Jonathan Sy, Vincent Huang, Isis Wyche, Xiuye Wang, David Golomb
August 1, 2016 : 812-824
DOI: 10.1152/jn.00026.2016

We find that mouse whiskers are thinner in the middle than a linearly tapered cone. They bend more than the standard model of whisker bending during touches in the middle of the whisker and less in distal locations. This taper affects touch-evoked forces and how whiskers slip past objects, which impacts the neural algorithms of object localization. We provide a corrective function that improves the quantification of touch-evoked forces in the whisker system.

Cellular and Molecular Properties of Neurons

Influence of cortical synaptic input on striatal neuronal dendritic arborization and sensitivity to excitotoxicity in corticostriatal coculture
Caodu Buren, Gaqi Tu, Matthew P. Parsons, Marja D. Seperis, Lynn A. Raymond
August 1, 2016 : 380-390
DOI: 10.1152/jn.00933.2015

Corticostriatal coculture from embryonic mouse brain was used to study the effect of varying cortical-to-striatal neuron ratio on striatal neuronal properties at 18 days in vitro. Reduced cortical-striatal plating ratio resulted in enhanced loss of striatal spiny projection neurons (SPNs), reduced SPN dendritic complexity and length, altered synaptic/extrasynaptic NMDA receptor distribution, and increased susceptibility to excitotoxic death. Thus cortical-striatal plating ratio influences SPN structure and function, which should be considered in experimental design.

HCN hyperpolarization-activated cation channels strengthen virtual nicotinic EPSPs and thereby elevate synaptic amplification in rat sympathetic neurons
Paul H. M. Kullmann, Kristine M. Sikora, K. Lyles Clark, Irene Arduini, Mitchell G. Springer, John P. Horn
August 1, 2016 : 438-447
DOI: 10.1152/jn.00223.2016

With the use of dynamic clamp to create virtual synapses, this study shows that hyperpolarization-activated cation current (h-current; Ih) strengthens fast excitatory postsynaptic potentials and synaptic amplification in sympathetic neurons. The manipulation of the voltage dependence of a virtual Ih also shifted gain. These results reveal a new physiological role for hyperpolarization-activated cation channels in the sympathetic motor system.

Knockout of the BK β4-subunit promotes a functional coupling of BK channels and ryanodine receptors that mediate a fAHP-induced increase in excitability
Bin Wang, Vladislav Bugay, Ling Ling, Hui-Hsui Chuang, David B. Jaffe, Robert Brenner
August 1, 2016 : 456-465
DOI: 10.1152/jn.00857.2015

There have been numerous studies demonstrating a paradoxical proexcitatory role for BK potassium channels in some neurons. This study provides the first demonstration functional coupling that underlies this unusual proexcitatory effect in dentate gyrus granule neurons. Functional coupling occurs during a single action potential that enhances the fast afterhyperpolarization amplitude and reduces the interspike interval. Given their broad expression, these findings may be relevant to many neurons of the central nervous system.

Assessment of the expression and role of the α1-nAChR subunit in efferent cholinergic function during the development of the mammalian cochlea
Isabelle Roux, Jingjing Sherry Wu (武靜靜), J. Michael McIntosh, Elisabeth Glowatzki
August 1, 2016 : 479-492
DOI: 10.1152/jn.01038.2015

In addition to the well characterized α9- and α10-nicotinic acetylcholine receptors (nAChRs), the “muscle-type” α1-nAChR subunit is expressed in developing cochlear hair cells (HCs) (Scheffer et al. 2007). The study here finds that HCs do not express nAChR8 with the same pharmacology as “muscle-type” nAChRs. Remarkably, the onset of α1-expression and efferent synaptic function occur simultaneously. Yet, α1-expression is not necessary for synapse formation as shown in α1-deficient mice.

A biophysical model examining the role of low-voltage-activated potassium currents in shaping the responses of vestibular ganglion neurons
Ariel E. Hight, Radha Kalluri
August 1, 2016 : 503-521
DOI: 10.1152/jn.00857.2015
The vestibular nerve comprises two neuronal groups that are identified by differences in the regularity of their spontaneous discharge. The mechanisms driving this hallmark difference have long been debated but remain poorly understood. We use a point-neuron model to test if variation in the density of low-voltage-gated potassium currents can account for spike-timing regularity. The model predicts how ion channels and morphology may work together to shape the responses of vestibular afferents.

**Differences in chloride gradients allow for three distinct types of synaptic modulation by endocannabinoids**
Yanqing Wang, Brian D. Burrell
August 1, 2016: 619-628

Endocannabinoids are important signaling molecules that depress both excitatory synapses leading to decreases in neural circuit output and inhibitory synapses leading to increases in circuit output due to disinhibition. In this study, differences in Cl− gradients were found to strongly influence whether endocannabinoids ultimately decrease or increase circuit output. These findings may explain the pro- and antinociceptive effects of endocannabinoids. The role of Cl− gradient may also be relevant to other modulatory transmitters as well.

**Heat pulse excitability of vestibular hair cells and afferent neurons**
Richard D. Rabbitt, Alan M. Brichta, Hessam Tabatabaee, Peter J. Boutros, JoongHo Ahn, Charles C. Della Santina, Lauren A. Pippi, Rebecca Lim
August 1, 2016: 825-843

In the present report we demonstrate that electrical excitability in sensory hair cells is thermodynamically sensitive and poised to respond to <1 zJ (10−21 J) of thermal energy. We identify key thermosensitive ion channels in hair cells and describe how the Gibbs free energy governing protein conformational state transitions and membrane electrochemistry leads to sensitivity. New experimental and theoretical methods exploit temperature as an independent thermodynamic variable to rapidly manipulate and examine excitability, in the same way voltage is routinely controlled for analogous purposes.

**Control of Movement**

**Sensory reweighting dynamics following removal and addition of visual and proprioceptive cues**
Lorenz Assländer, Robert J. Peterka
August 1, 2016: 272-285

Novel methods were applied to investigate the time course of changes in sensory contributions to balance (sensory reweighting) following a sudden addition and removal of visual or proprioceptive orientation information. Results demonstrate the influence of reweighting in adjusting to changes in sensory conditions but also reveal the influence of additional mechanisms, including an effect of expectation of upcoming changes, that affect balance control behavior when environmental conditions change.

**A motor planning stage represents the shape of upcoming movement trajectories**
Aaron L. Wong, Jeff Goldsmith, John W. Krakauer
August 1, 2016: 296-305

This work demonstrates that to produce an intentionally curved movement, it is necessary to invoke a unique process that plans the shape of the desired movement path of the endpoint effector. The existence of such an abstract representation of kinematics may explain the large human repertoire of complex movements and may help explain the dissociation seen between simple endpoint-directed movements and complex tool-use and imitative actions in ideomotor apraxia.

**Saccadic adaptation to a systematically varying disturbance**
Carlos R. Cassanello, Sven Ohl, Martin Rolfs
August 1, 2016: 336-350

Saccadic adaptation maintains the mapping between rapid eye movements and their visual targets. We studied the dynamics of this process, using an intrasaccadic target displacement that changed in size as a sinusoidal function of the trial number. The oculomotor response displayed two independent components—a delayed periodic change in saccade gain superimposed on a drift toward higher hypometria (despite the displacements’ zero mean). We quantified this response and discuss possible origins and underlying learning processes.

**Target size matters: target errors contribute to the generalization of implicit visuomotor learning**
Maayan Reichenthal, Guy Avraham, Amir Karniel, Lior Shmuelof
August 1, 2016: 411-424
Implicit motor adaptation is considered to be driven by the mismatch between a subject's aiming direction and the perceived feedback and not by the distance of the cursor from the target (target error). Using an unconstrained reaching task, we show that while the size of the target does not affect the adaptation to a gradual rotation, it does affect postrotation “blind” reaching movements. This result suggests that implicit adaptation of internal models is sensitive to target errors.

Influence of the contractile properties of muscle on motor unit firing rates during a moderate-intensity contraction in vivo
Michael A. Trevino, Trent J. Herda, Andrew C. Fry, Philip M. Gallagher, John P. Vardiman, Eric M. Mosier, Jonathan D. Miller
August 1, 2016 : 552-562
DOI: 10.1152/jn.01021.2015

It is suggested the physical properties of the motor unit (MU) influence firing rate characteristics; however, no study has examined firing rate characteristics in relation to the physical properties of the MU in vivo. In this study, there was a strong relationship between MU firing rate characteristics, particularly of higher-threshold MUs, at a target force level and type I percent myosin heavy chain isoform content of the vastus lateralis during a moderate-intensity contraction.

Motor learning and cross-limb transfer rely upon distinct neural adaptation processes
Tino Stöckel, Timothy J. Carroll, Jeffery J. Summers, Mark R. Hinder
August 1, 2016 : 575-586
DOI: 10.1152/jn.00225.2016

In the present study we observed that noninvasive brain stimulation interacted differently with motor practice when applied to the motor cortex projecting to the trained vs. the untrained limb. This suggests that distinct neural processes underlie learning obtained via direct motor practice and learning conferred indirectly from practice with the opposite limb (i.e., cross-limb transfer). The results provide a step forward in the use of noninvasive brain stimulation methods to promote cross-limb transfer in motor rehabilitation.

Preferential distribution of nociceptive input to motoneurons with muscle units in the cranial portion of the upper trapezius muscle
Jakob L. Dideriksen, Ales Holobar, Deborah Falla
August 1, 2016 : 611-618
DOI: 10.1152/jn.01117.2015

By evaluating adjustments in the behavior of motor units located in different regions of the upper trapezius to experimentally induced pain, we observed differential changes, depending on the region of the muscle, that were not dependent on pain location. These findings indicate that nociceptive synaptic input is distributed in a nonuniform way across regions of the muscle, suggesting a fixed response to muscle pain, possibly with the aim of protecting the more sensitive muscle region.

Short-latency afferent inhibition determined by the sensory afferent volley
Aaron Z. Bailey, Michael J. Asmussen, Aimee J. Nelson
August 1, 2016 : 637-644
DOI: 10.1152/jn.00276.2016

This is the first investigation of the relationship between short-latency afferent inhibition (SAI) and the sensory afferent volley and the first to examine the relationship between SAI and somatosensory evoked potentials (SEPs). The data indicate that 1) SAI increases with the recruitment of sensory fibers and 2) its stimulus-response profile is correlated with SEPs. These novel data provide practical guidelines and also contribute to our understanding of SAI mechanisms.

Arousal dynamics drive vocal production in marmoset monkeys
Jeremy I. Borjon, Daniel Y. Takahashi, Diego C. Cervantes, Asif A. Ghazanfar
August 1, 2016 : 753-764
DOI: 10.1152/jn.00136.2016

We investigated the role of arousal during naturally occurring vocal production in marmoset monkeys. The timing of vocal production was tightly correlated to an autonomic nervous system rhythm known as the Mayer wave. A state space of arousal dynamics during vocalization illustrated that perturbations to the resting state increase the likelihood of a call occurring. Arousal dynamics are critical for spontaneous primate vocal production, acting as the foundation on which vocal behavior can unfold.

Role of expected reward in frontal eye field during natural scene search
Joshua I. Glaser, Daniel K. Wood, Patrick N. Lawlor, Pavan Ramkumar, Konrad P. Kording, Mark A. Segraves
August 1, 2016 : 645-657
DOI: 10.1152/jn.00119.2016

As expected, reward affects the latency and vigor (velocity) of eye movements (saccades); it is crucial to parse apart the effects of motor variables...
and expected reward on neural activity. We recorded from frontal eye field in monkeys while they searched for a target (associated with reward) in natural scenes. Although frontal eye field activity did represent latency and vigor, it represented expected reward above and beyond those motor parameters.

On the nature of unintentional action: a study of force/moment drifts during multifinger tasks
Behnoosh Parsa, Daniel J. O'Shea, Vladimir M. Zatsiorsky, Mark L. Latash
August 1, 2016 : 698-708
DOI: 10.1152/jn.00180.2016

We suggest a mechanism of unintentional changes in finger forces based on the idea of control with referent coordinates. Nontrivial predictions of this scheme are tested, including drifts in total force and total moment of force as well as finger force drifts in opposite directions depending on the total moment of force. The drifts were smaller in the nondominant hand suggesting its advantage in ensuring stable performance of steady-state tasks.

Proactive modulation of long-interval intracortical inhibition during response inhibition
Matthew J. Cowie, Hayley J. MacDonald, John Cirillo, Winston D. Byblow
August 1, 2016 : 859-867
DOI: 10.1152/jn.00144.2016

The ability to cancel a preplanned movement, termed response inhibition, is essential for adaptable motor control. Participants performed a bimanual anticipatory response inhibition task while single- and paired-pulse transcranial magnetic stimulation was delivered. The modulation of motor evoked potential amplitude during partial response trials reflected anticipation, suppression, and subsequent reinitiation of movement. Importantly, suppression was present across all stop trial types, indicative of a “default” nonselective inhibitory process.

Higher Neural Functions and Behavior

CaMKII mediates stimulus specificity in early odor preference learning in rats
Shirin Modarresi, Bandhan Mukherjee, John H. McLean, Carolyn W. Harley, Qi Yuan
August 1, 2016 : 404-410
DOI: 10.1152/jn.00176.2016

This is the first work to show that CaMKII activation and subsequent AMPA receptor insertion mediates stimulus-specific odor memory and its blockade prevents such memory, therefore supporting the hypothesis that CaMKII serves as the synaptic tag mediating input specificity in natural memory formation as it has been shown to do in long-term potentiation.

Prefrontal and anterior cingulate cortex neurons encode attentional targets even when they do not apparently bias behavior
Stephanie Westendorff, Daniel Kaping, Stefan Everling, Thilo Womelsdorf
August 1, 2016 : 796-811
DOI: 10.1152/jn.00027.2016

Prefrontal and anterior cingulate cortex (ACC/PFC) neurons are likely “top-down” sources of attention by encoding locations of relevant stimuli. However, we show that such spatial attention selectivity is only to about one-third consistent with a role in biasing attention and behavior. The other two-thirds of attention signals in ACC/PFC indicate spatial targets even when they are not correctly attended, suggesting that they counterfactually encode and monitor possible relevant information.

Megamap: flexible representation of a large space embedded with nonspatial information by a hippocampal attractor network
Kathryn R. Hedrick, Kechen Zhang
August 1, 2016 : 868-891
DOI: 10.1152/jn.00856.2015

The megamap is a quasi-continuous attractor network built on the experimental fact that each place cell has multiple, irregularly spaced place fields in a large environment. This flexibility allows the megamap to seamlessly cover much larger environments than standard rigid continuous attractor models. The megamap has additional inherent properties, such as robustness to degraded inputs and ease of storing nonspatial information, that render it suitable as a basic building block for modeling hippocampal activity.

Nervous System Pathophysiology

Role of Fyn-mediated NMDA receptor function in prediabetic neuropathy in mice
Meng Suo, Ping Wang, Mengyuan Zhang
August 1, 2016 : 448-455
DOI: 10.1152/jn.00229.2016
Our study is the first to report that Fyn kinase is critical for the development of tactile allodynia in the state of prediabetes. Furthermore, the increased expression/function of NR2B subunit-containing N-methyl-d-aspartate receptors in the spinal cord may contribute to the progression of neuropathy in type 2 diabetes.

**Maintaining balance against force perturbations: impaired mechanisms unresponsive to levodopa in Parkinson's disease**

Irene Di Giulio, Rebecca J. St George, Eirini Kallioli, Amy L. Peters, Patricia Limousin, Brian L. Day

August 1, 2016 : 493-502

DOI: 10.1152/jn.00996.2015

**OPEN ACCESS ARTICLE**

We introduce a new method to investigate postural instability in Parkinson's disease (PD) using computer-controlled motors to deliver precise pulls to the shoulders of subjects while standing. It mimics the clinical pull test but uses forces with unpredictable timing, direction, and magnitude. It revealed a number of balance control deficits in PD. Notably, the identified deficits were not significantly altered by levodopa medication, suggesting that disruption to nondopaminergic systems contributes to postural instability in PD.

**Neural Circuits**

**Cooperation and competition of gamma oscillation mechanisms**

Atthaphon Viriyopase, Raoul-Martin Memmesheimer, Stan Gielen

August 1, 2016 : 232-251

DOI: 10.1152/jn.00493.2015

**A comparison of computational methods for detecting bursts in neuronal spike trains and their application to human stem cell-derived neuronal networks**

Ellese Cotterill, Paul Charlesworth, Christopher W. Thomas, Ole Paulsen, Stephen J. Eglen

August 1, 2016 : 306-321

DOI: 10.1152/jn.00093.2016

**OPEN ACCESS ARTICLE**

We provide an unbiased quantitative assessment of eight existing methods for identifying bursts in neuronal spike trains. We reveal limitations in a number of commonly used burst detection techniques and provide recommendations for the best practice for accurate identification of bursts using existing techniques. An analysis of the ontogeny of bursting activity in a novel data set of recordings from human induced pluripotent stem cell-derived neuronal networks, using the highest-performing burst detectors from our study, is also presented.

**Synchronized gamma-frequency inhibition in neocortex depends on excitatory-inhibitory interactions but not electrical synapses**

Garrett T. Neske, Barry W. Connors

August 1, 2016 : 351-368

DOI: 10.1152/jn.00071.2016

Using the active barrel cortex slice preparation, we show that inhibitory interneurons spike synchronously during spontaneous cortical Up states. Synchronized inhibition depends minimally on electrical synapses between interneurons and most likely arises from excitatory-inhibitory interactions. Our results suggest that when local excitatory cells activate interneurons, interneuron spike synchrony does not rely on inhibitory-inhibitory interactions or electrical synapses. Our study provides new mechanistic insights into the nature of gamma-synchronized inhibition in local cortical circuits.

**Spontaneous activations follow a common developmental course across primary sensory areas in mouse neocortex**

Charles G. Frye, Jason N. MacLean

August 1, 2016 : 431-437

DOI: 10.1152/jn.00172.2016

To evaluate the developmental ontogeny of spontaneous circuit activity, we compared two different areas of sensory cortex that are also differentiated by sensory inputs that follow different developmental timelines. We imaged neuronal populations in acute coronal slices of mouse neocortex taken from postnatal days 3 through 15. We observed a consistent developmental trajectory of spontaneous activity suggesting a consistent pattern for cortical microcircuit development: anatomical modules are wired together by coherent activations into functional circuits.

**Granule cell excitability regulates gamma and beta oscillations in a model of the olfactory bulb dendrodendritic microcircuit**

Boleslaw L. Osinski, Leslie M. Kay

August 1, 2016 : 522-539

DOI: 10.1152/jn.00988.2015
Gamma (40–100 Hz) and beta (15–30 Hz) oscillations in mammalian olfactory bulbs represent differential involvement of higher order brain areas and different cognitive networks. In a computational model of the olfactory bulb, we find that changes in granule cell excitability can gate fast transitions from gamma to beta during odor sampling. Increased granule cell excitability, produced in many ways, releases stronger graded inhibition, which supports beta as a very stable state in disparate circumstances.

Auditory Golgi cells are interconnected predominantly by electrical synapses
Daniel B. Yaeger, Laurence O. Trussell
August 1, 2016 : 540-551
DOI: 10.1152/jn.01108.2015

The dorsal cochlear nucleus contains a population of GABAergic Golgi cells that are proposed to control processing of multisensory signals in the auditory system. In this study, Golgi cells are shown to form a highly interconnected interneuron network using gap junctions but not chemical synapses.

Heterosynaptic modulation of evoked synaptic potentials in layer II of the entorhinal cortex by activation of the parasubiculum
Daniel W. Sparks, C. Andrew Chapman
August 1, 2016 : 658-670
DOI: 10.1152/jn.00095.2016

Layer II of the entorhinal cortex receives the major output projection of the parasubiculum and also provides the hippocampus with its cortical sensory input. Here, we show that the parasubiculum has strong short-term and long-term heterosynaptic modulatory effects on layer I inputs to the medial entorhinal cortex layer II. Thus the parasubiculum may modulate the nature of sensory input that the hippocampus receives from the entorhinal cortex.

Paired associative transspinal and transcortical stimulation produces plasticity in human cortical and spinal neuronal circuits
Luke Dixon, Mohamed M. Ibrahim, Danielle Santora, Maria Knikou
August 1, 2016 : 904-916
DOI: 10.1152/jn.00259.2016

We examined changes on human neuronal circuits by pairing transspinal and transcortical stimulation. Transspinal-transcortical paired associative stimulation (PAS) decreased intracortical inhibition and increased intracortical facilitation and corticospinal excitability. Transcortical-transspinal PAS did not affect intracortical circuits and decreased corticospinal excitability. Both protocols altered the excitation thresholds of Ia afferents and motor axons. This new PAS paradigm bears a significant physiological impact, because it can concomitantly alter the excitability of cortical circuits, corticospinal neurons, afferents, and motor axons in humans.

Sensory Processing

Visual-vestibular processing in the human Sylvian fissure
Sebastian M. Frank, Anna Maria Wirth, Mark W. Greenlee
August 1, 2016 : 263-271
DOI: 10.1152/jn.00009.2016

In this paper we examine vestibular and visual processing at the center of human vestibular cortex in the Sylvian fissure. We find that two areas, referred to as parieto-insular vestibular cortex (PIVC) and posterior insular cortex (PIC), are located in the Sylvian fissure and exhibit different functional specializations. Our results suggest a more complex organization at the putative core of human vestibular cortex than previously assumed.

Brain potentials evoked by intraepidermal electrical stimuli reflect the central sensitization of nociceptive pathways
August 1, 2016 : 286-295
DOI: 10.1152/jn.00013.2016

Secondary mechanical punctate hyperalgesia is a cardinal sign of central sensitization (CS), an important mechanism of chronic pain. Our study demonstrates that hyperalgesia from intraepidermal electrical stimulation coexists with mechanical punctate hyperalgesia and elicits electroencephalographic (EEG) potentials that predict the occurrence of punctate hyperalgesia in a human experimental model of CS. These findings inform clinical development of EEG-based biomarkers of CS.

Tactile length contraction as Bayesian inference
Jonathan Tong, Vy Ngo, Daniel Goldreich
August 1, 2016 : 369-379
DOI: 10.1152/jn.00029.2016
A growing body of evidence—particularly from visual research—has suggested that perception may be a Bayesian best guess, in which the brain interprets imprecise sensory inputs in light of expectations forged from experience. Passive tactile perception has rarely been studied from a Bayesian perspective. Here we show that the perception of tactile spatiotemporal stimuli conforms to the predictions of a Bayesian observer model that incorporates a low-velocity expectation.

Inhibitory modulation of optogenetically identified neuron subtypes in the rostral solitary nucleus
Z. Chen, S. P. Travers, J. B. Travers
August 1, 2016 : 391-403
DOI: 10.1152/jn.00168.2016

Optogenetic identification of GABAergic and non-GABAergic (putative projection) neurons within the solitary nucleus suggests that hyperpolarization-sensitive channels impact the transfer of information across the synapse. GABAergic neurons transfer afferent information with less fidelity compared with non-GABAergic neurons; however, the fidelity of GABAergic neurons with Ih is similar to that of non-GABAergic neurons. In non-GABAergic neurons with IA, the interaction between the IA current and inhibition suppresses the transfer of information proportionally compared with non-GABAergic neurons without IA.

Rare human nerve growth factor-β mutation reveals relationship between C-afferent density and acute pain evaluation
Irene Perini, Mitra Tavakoli, Andrew Marshall, Ian Minde, India Morrison
August 1, 2016 : 425-430
DOI: 10.1152/jn.00667.2015

This study investigates the relationship of nociceptive afferent density and subjective pain evaluation. Using subjective pain reports alongside corneal confocal microscopy of small-diameter afferents, we show that lower pain estimates are related to lower peripheral nerve density. These findings provide an integrative perspective on pain processing and highlight a multilevel approach to understanding how physiology influences pain experience.

Temporal dynamics of visual category representation in the macaque inferior temporal cortex
Mohammad-Reza A. Dehaqani, Abdol-Hossein Vahabie, Roozbeh Kiani, Majid Nili Ahmadabadi, Babak Nadjar Araabi, Hossein Esteky
August 1, 2016 : 587-601
DOI: 10.1152/jn.00018.2016

Decades of research indicate a temporal dynamic of visual-object categorization, depending on the level of category abstraction. To understand the neural mechanism of the temporal course of object categorization, we studied responses of neurons in inferotemporal cortex of macaque monkeys to presentation of natural object images. We observed that inferior temporal neurons represent mid-level categories (e.g., human faces) earlier than superordinate (e.g., animal)- and subordinate (e.g., face identity)-level categories.

Does gravity influence the visual line bisection task?
A. Drakul, C. J. Bockisch, A. A. Tarnutzer
August 1, 2016 : 629-636
DOI: 10.1152/jn.00312.2016

In this study we investigated the potential impact of direction of gravity on visual line bisection tasks. Measuring line bisections along either an Earth-horizontal or a body-horizontal axis in 20 subjects, we found no impact of gravity on line bisection errors or trial-to-trial variability. This suggests that, for the present setup, gravity does not influence the line bisection task.

Ubiquitin ligase Nedd4-2 modulates Kv1.3 current amplitude and ion channel protein targeting
Patricio Vélez, Austin B. Schwartz, Subashini R. Iyer, Anthony Warrington, Debra Ann Fadool
August 1, 2016 : 671-685
DOI: 10.1152/jn.00874.2015

Potassium ion (K) channels are the dampeners of excitation and a novel means of regulating this excitation is through interaction with protein partners that can control channel density at the membrane. An enzyme that tags K channels for degradation is found to interact with discreet residues on the COOH-terminal domain to mediate ubiquitination and functional loss of channel current. The presence of an adaptor protein to the enzyme can reverse this modulation.

Dopamine D1 receptor modulation of calcium channel currents in horizontal cells of mouse retina
Xue Liu, James C. R. Grove, Arlene A. Hirano, Nicholas C. Brecha, Steven Barnes
August 1, 2016 : 686-697
DOI: 10.1152/jn.00990.2015

We report inhibition of Ca channels in horizontal cells by dopamine, a retinal neuromodulator regulated by light and the circadian clock. The work reveals that dopamine type 1 receptors mediate inhibition of Ca channels via a direct, voltage-dependent inhibition by Gβγ subunits. With Ca channels mediating horizontal cell neurotransmission, these results suggest that dopamine reduces inhibition of bipolar cells and photoreceptors,
altering regulation of synaptic gain and lateral inhibition in visual processing in the retina.

Spontaneously active NaV1.5 sodium channels may underlie odor sensitivity
Vincent E. Dionne
August 1, 2016 : 776-783
DOI: 10.1152/jn.00114.2016

Olfactory sensory neurons inform about odor, providing reliable responses to even trace odor concentrations. Yet how weak stimuli can elicit a graded output from these neurons remains unclear. Computed responses of a recently discovered population of NaV1.5 sodium channels clustered at the dendritic ending of the sensory neurons suggest that these spontaneously active channels can transduce small odor-elicited receptor potentials into a change in firing rate to resolve the problem.

Subspace mapping of the three-dimensional spectral receptive field of macaque MT neurons
Mikio Inagaki, Kota S. Sasaki, Hajime Hashimoto, Izumi Ohzawa
August 1, 2016 : 784-795
DOI: 10.1152/jn.00934.2015

Neurons in the middle temporal (MT) visual area are thought to represent the velocity of visual motion. Our findings suggest that both well-organized excitatory inputs and broad suppressive inputs contribute significantly to the invariant and reliable representation of velocity in MT. Although suppression tends to be broadly distributed, total sum of suppression often exceed that of excitation. Furthermore, suppression sharpened the velocity tuning and appears to improve the reliability of velocity representation.

Innovative Methodology

Neurophysiological analytics for all! Free open-source software tools for documenting, analyzing, visualizing, and sharing using electronic notebooks
David M. Rosenberg, Charles C. Horn
August 1, 2016 : 252-262
DOI: 10.1152/jn.00137.2016

To boost reproducible research, neurophysiology analysis is performed with free, open-source software within the Jupyter electronic notebook. These notebooks use Python and R programming languages, with real experimental data, in the analysis of neural signals and generation of publication-quality graphics. This approach documents all steps of analysis, which can be shared in easily readable formats including PDF, HTML, and a web-based computer environment (an example provided) capable of regenerating the analysis directly from raw data.

Accommodation to hyperpolarization of human axons assessed in the frequency domain
James Howells, Hugh Bostock, David Burke
August 1, 2016 : 322-335
DOI: 10.1152/jn.00019.2016

The low-frequency response of human axons was studied in vivo using a novel application of frequency-domain and threshold-tracking techniques. Studying the response to subthreshold oscillatory input currents at different membrane potentials allows the separation of relative ion channel contributions to axonal excitability based on their voltage dependence and gating kinetics. At hyperpolarized membrane potentials, hyperpolarization-activated conductances, which flow through hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, are responsible for low-frequency resonance in human axons, and this is modulated by leak conductances.

Recording extracellular neural activity in the behaving monkey using a semichronic and high-density electrode system
Germán Mendoza, Adrien Peyrache, Jorge Gámez, Luis Prado, György Buzsáki, Hugo Merchant
August 1, 2016 : 563-574
DOI: 10.1152/jn.00116.2016

This paper demonstrates high-density, chronic recordings of single units at different depths in behaving monkeys, which have been achieved until now only in rodents. We also show how two, and potentially many, silicon probes can be implanted effectively and at low cost in primates. Using different analytical tools on simultaneously recorded cells, we were able to identify inhibitory and principal cells, so that functionally connected cortical assemblies can be studied during task performance.

Rapid Reports

Brain-derived neurotrophic factor differentially modulates excitability of two classes of hippocampal output neurons
August 1, 2016 : 466-471
DOI: 10.1152/jn.00186.2016
We show that BDNF mediates acute and long-lasting changes in intrinsic neuronal excitability in two classes of subicular pyramidal neurons (EB and LB neurons). Although BDNF plays similar roles in the induction of synaptic plasticity in these two cell types, it differentially and bidirectionally affects intrinsic excitability and burst plasticity in EB and LB neurons. These cell type-specific effects represent new avenues by which BDNF can influence the well-established information storage function of the hippocampus.

Synaptic integration of transplanted interneuron progenitor cells into native cortical networks
MacKenzie A. Howard, Scott C. Baraban
August 1, 2016 : 472-478
DOI: 10.1152/jn.00321.2016

We have explored how transplanted interneurons, which have potential therapeutic value for treating a variety of neurological and psychiatric diseases, integrate into the neural circuitry of the recipient brain. We found that exogenous cells develop rapidly to exhibit intrinsic properties and send and receive synapses appropriate to their specific cell subtype. These findings indicate that transplanted cells are fully able to contribute to neural information processing while therapeutically increasing inhibitory synaptic tone.

Shared and distinct retinal input to the mouse superior colliculus and dorsal lateral geniculate nucleus
Erika M. Ellis, Gregory Gauvain, Benjamin Sivyer, Gabe J. Murphy
August 1, 2016 : 602-610
DOI: 10.1152/jn.00227.2016

Our results suggest that the mouse superior colliculus (SC) has access to input from most of the retinal ganglion cells (RGCs) that innervate the dorsal lateral geniculate nucleus (dLGN). By comparison, a number of RGC types appear to innervate the SC but not the dLGN; these RGCs generally exhibit more transient responses and respond best to small stimuli.

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Preeclampsia, of mice and women
Jenny L. Sones, Robin L. Davisson
August 1, 2016 : 565-572
DOI: 10.1152/physiolgenomics.00125.2015

Genome-wide identification of quantitative trait transcripts for blood traits in the liver samples of a White Duroc × Erhualian F₂ pig resource population
Pan Xu, Leilei Cui, Tao Huang, Zhen Zhang, Bin Yang, Congying Chen, Lusheng Huang, Yanyu Duan
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DOI: 10.1152/physiolgenomics.00123.2015

Comprehensive coverage of cardiovascular disease data in the disease portals at the Rat Genome Database
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Comparative, Statistical, and Computational Genomics and Model Organism Databases

Rapid conditional targeted ablation model for hemolytic anemia in the rat
Marina M. Hanson, Fengming Liu, Shen Dai, Alison Kearns, Xuebin Qin, Elizabeth C. Bryda
August 1, 2016 : 626-632
DOI: 10.1152/physiolgenomics.00026.2016

General Interest

Transcriptome meta-analysis of three follicular compartments and its correlation with ovarian follicle maturity and oocyte developmental competence in cows
Daulat Raheem Khan, David A. Landry, Éric Fournier, Christian Vigneault, Patrick Blondin, Marc-André Sirard
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DOI: 10.1152/physiolgenomics.00050.2016

Early steatohepatitis in hyperlipidemic mice with endothelial-specific gain of TRPC3 function precedes changes in aortic atherosclerosis
Kathryn Smedlund, Prabhatachandra Dube, Guillermo Vazquez
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Genetic and Genomics Investigation of Structure and Function of the Kidney

Serum response factor provokes epithelial-mesenchymal transition in renal tubular epithelial cells of diabetic nephropathy
Long Zhao, Lingzhen Chi, Jun Zhao, Xueling Wang, Zhixiong Chen, Linghang Meng, Gang Liu, Guangju Guan, Fei Wang
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Genomic and “Polyomic” Studies of Cardiovascular and Inflammatory Diseases

Relationship of disease-associated gene expression to cardiac phenotype is buffered by genetic diversity and chromatin regulation
Elahieh Kharbassi, Emma Monte, Douglas J. Chapski, Rachel Lopez, Manuel Rosa Garrido, Joseph Kim, Nicholas Wisniewski, Christoph D. Rau, Jessica J. Wang, James N. Weiss, Yibin Wang, Aldons J. Lusis, Thomas M. Vondriska
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Corrigendum
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DOI: 10.1152/physiolgenomics.zh7-4118-corr.2016

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Original Research

Estrogen receptor alpha activation enhances mitochondrial function and systemic metabolism in high-fat-fed ovariectomized mice
Dale J. Hamilton, Laurie J. Minze, Tanvi Kumar, Tram N. Cao, Christopher J. Lyon, Paige C. Geiger, Willa A. Hsueh, Anisha A. Gupte
August 30, 2016 : e12913
DOI: 10.14814/phy2.12913

Loss of ovarian estrogen in hyperlipidemic middle-aged female mice leads to dramatic down-regulation of metabolism, greater weight gain, insulin resistance, and mitochondrial dysfunction when given a high-fat diet. Specific activation of estrogen receptor alpha can enhance metabolism, prevent weight gain, increase insulin sensitivity, and increase mitochondrial function. Activation of estrogen receptor alpha enhances expression of genes in mitochondrial biogenesis and function, glucose metabolism, and fatty acid metabolism pathways.

EZH2 enhances the differentiation of fibroblasts into myofibroblasts in idiopathic pulmonary fibrosis
Xiao Xiao, Lakmini K. Senavirathna, Xuxu Gou, Chaoqun Huang, Yurong Liang, Lin Liu
August 30, 2016 : e12915
DOI: 10.14814/phy2.12915

Enhancer of zeste homolog 2 (EZH2) is upregulated in the lungs of patients with idiopathic pulmonary fibrosis (IPF). EZH2 induces the differentiation of fibroblasts to myofibroblasts by enhancing Smad2/3 nuclear translocation.

Saturated high-fat diet-induced obesity increases adenylate cyclase of myocardial β-adrenergic system and does not compromise cardiac function
August 30, 2016 : e12914
DOI: 10.14814/phy2.12914

The aim of this study was to test the hypothesis that obesity promotes cardiac dysfunction due to changes in components of myocardial β-adrenergic pathway. Obese rats showed higher protein levels of adenylate cyclase, whereas the other components were unchanged. These results suggest that saturated high-fat diet-induced obesity was not effective in triggering cardiac dysfunction and impair the beta-adrenergic signaling.

Autologous subcutaneous adipose tissue transplants improve adipose tissue metabolism and reduce insulin resistance and fatty liver in diet-induced obesity rats
August 30, 2016 : e12909
DOI: 10.14814/phy2.12909

Autologous subcutaneous adipose tissue transplanted into two specific intraabdominal cavity sites (omentum and retroperitoneal adipose tissue) improved insulin sensitivity, reduced hypertrophic adipocytes, and reduced hepatic lipid content and fasting serum-free fatty acid concentrations in obese rats induced by high-fat or high-carbohydrate diets. Moreover, part of the metabolic improvement was mediated by changes in the adipose tissue lipolytic metabolism. The transplant procedure, which is an innovate method, permits to integrate physically and metabolically the transplanted adipose tissue.

Original Research

Progesterone has rapid positive feedback actions on LH release but fails to reduce LH pulse frequency within 12 h in estradiol-pretreated women
Eleanor G. Hutchens, Katherine A. Ramsey, Louisa C. Howard, Michelle Y. Abshire, James T. Patrie, Christopher R. McCartney
August 17, 2016 : e12891
DOI: 10.14814/phy2.12891

In estradiol-pretreated women in the late follicular phase, a single dose of progesterone did not inhibit LH pulse frequency within 10 h. However, progesterone acutely amplified mean LH, LH pulse amplitude, and mean FSH. Compared to an earlier study in which progesterone was administered at 1800, progesterone administration at 0600 was associated with a less pronounced increase in LH pulse amplitude, suggesting that the positive
feedback effect of progesterone may be influenced by sleep status and/or time of day.

**Oxidative stress increases the risk of pancreatic β cell damage in chronic renal hypertensive rats**
Shan Gao, Byung M. Park, Seung A. Cha, Ui J. Bae, Byung H. Park, Woo H. Park, Suhn H. Kim
August 17, 2016 : e12900

DOI: 10.14814/phy2.12900

Sustained hypertension induces abnormal islet morphology and insulin secretion in response to high glucose and increases oxidative stress in the pancreas. These effects were reversed by captopril or a-lipoic acid treatment. A close correlation between blood pressure and oxidative stress in pancreatic tissue.

**Comparison of regional skeletal muscle tissue oxygenation in college athletes and sedentary control subjects using quantitative BOLD MR imaging**
Mitchel R. Stacy, Christopher M. Caracciolo, Maolin Qiu, Prasanta Pal, Tyler Varga, Robert Todd Constable, Albert J. Sinusas
August 17, 2016 : e12903

DOI: 10.14814/phy2.12903

This study is the first to utilize a transient ischemia and reactive hyperemia paradigm that applies BOLD MR imaging to non-invasively assess and compare microvascular skeletal muscle tissue oxygenation within specific calf muscles in athletes and sedentary healthy subjects. Furthermore, peak hyperemic BOLD responses in the gastrocnemius muscle were significantly and positively related to maximal vertical and broad jumping ability, suggesting an association between skeletal muscle vascular function and lower extremity functional capacity.

**Hyperinsulinemia augments endothelin-1 protein expression and impairs vasodilation of human skeletal muscle arterioles**
August 22, 2016 : e12895

DOI: 10.14814/phy2.12895

Compensatory hyperinsulinemia associated with insulin resistance is a risk factor for cardiovascular disease. We investigated the effects of acute experimental hyperinsulinemia using a 40 mU/m²/min hyperinsulinemic-euglycemic clamp coupled with skeletal muscle biopsies and ex vivo study of isolated skeletal muscle microvascular function. We found that hyperinsulinemia disturbed flow induced dilation of isolated microvessels, increased the protein expression of endothelin-1 and disturbed the balance between endothelin type A and type B receptors.

**Case Reports**

**Exercise capacity following a percutaneous endoscopic gastrostomy in a young female with cystic fibrosis: a case report**
Owen W. Tomlinson, Alan R. Barker, Patrick J. Oades, Craig A. Williams
August 22, 2016 : e12904

DOI: 10.14814/phy2.12904

This case report presents the role of cardiopulmonary exercise testing in assessing clinically relevant outcomes following a percutaneous endoscopic gastrostomy and supplemental feeding in an adolescent female with cystic fibrosis. This is the first such report to utilise such exercise-related factors and identifies varied directions and magnitudes between clinically relevant variables.

**Original Research**

**BMI1 is downregulated by the natural compound curcumin, but not by bisdemethoxycurcumin and dimethoxycurcumin**
Temitope A. Adeyeni, Natasha Khatwani, KayKay San, Uthayashanker R. Ezekiel
August 22, 2016 : e12906

DOI: 10.14814/phy2.12906

BMI1 regulation by curcumin and its analogues.

**Acute resistance exercise-induced IGF1 expression and subsequent GLUT4 translocation**
Kohei Kido, Satoru Ato, Takumi Yokokawa, Yuhei Makanae, Koji Sato, Satoshi Fujita
August 22, 2016 : e12907

DOI: 10.14814/phy2.12907

The regulation of glucose uptake by acute resistance exercise is unclear. Muscle IGF-1 expression is increased by an acute bout of RE but not by AE. RE induced prolonged IGF-1 expression and GLUT4 translocation as compared with AE.

**Astrocyte-mediated regulation of multidrug resistance p-glycoprotein in fetal and neonatal brain endothelial cells: age-dependent effects**
Stephanie Baello, Majid Iqbal, William Gibb, Stephen G. Matthews
The age-dependent effects of astrocytes on p-glycoprotein (P-gp) function and expression at the fetal and post-natal blood-brain barrier.

**Post-exercise syncope: Wingate syncope test and visual-cognitive function**
Dylan C. Sieck, Matthew R. Ely, Steven A. Romero, Meredith J. Luttrel, Pedro M. Abdala, John R. Halliwill
August 22, 2016 : e12883
DOI: 10.14814/phy2.12883

We investigated whether standing upright after very intense exercise generates reductions in cerebral blood velocity of a sufficient magnitude that they result in reduced visual-cognitive abilities. Our findings show that intense exercise, without proper cool-down, can result in reduced cerebral blood velocity to the extent that visual-cognitive deficits in the peripheral visual field are present.

**Sleep restriction during pregnancy and its effects on blood pressure and renal function among female offspring**
Rogério Argeri, Erika E. Nishi, Rildo A. Volpini, Beatriz D. Palma, Sergio Tufik, Guiomar N. Gomes
August 22, 2016 : e12888
DOI: 10.14814/phy2.12888

Repercussion of sleep restriction during pregnancy on blood pressure and renal function of female offspring.

**Expression of polycomb protein BMI-1 maintains the plasticity of basal bronchial epithelial cells**
Elizabeth Torr, Meg Heath, Maureen Mee, Dominick Shaw, Tyson V. Sharp, Ian Sayers
August 23, 2016 : e12847
DOI: 10.14814/phy2.12847

The airway epithelium is altered in respiratory disease however the isolation of bronchial epithelial cells from patients for study is invasive and cells have a limited lifespan. We have developed an approach to delay cell senescence and provide extensive characterisation of the plasticity of these engineered cells including the ability of cells to differentiate. These cells retain properties of wild-type cells and may be useful to characterise respiratory disease mechanisms in vitro over sustained periods.

**ADAM17 and EGFR regulate IL-6 receptor and amphiregulin mRNA expression and release in cigarette smoke-exposed primary bronchial epithelial cells from patients with chronic obstructive pulmonary disease (COPD)**
Marta Stolarczyk, Gimano D. Amatngalim, Xiao Yu, Mieke Veltman, Pieter S. Hiemstra, Bob J. Scholte
August 24, 2016 : e12878
DOI: 10.14814/phy2.12878

Whole cigarette smoke induces more pronounced ADAM17-mediated shedding of the EGFR agonist amphiregulin and the interleukin-6 receptor in differentiated bronchial epithelial cells from COPD patients than controls, potentially affecting pathology. CS-induced shedding involves intracellular phospho-ADAM17-substrate interactions. Substrate shedding and mRNA levels are tightly regulated by both EGFR and ADAM17 activity, and sensitive to inhibition by experimental drugs.

**Erratum**

**Erratum**
August 24, 2016 : e12954
DOI: 10.14814/phy2.12954

**Original Research**

**Podocyte NF-κB is dispensable for the pathogenesis of renal ischemia-reperfusion injury**
Maho Yamashita, Tadashi Yoshida, Matsuhiko Hayashi
August 25, 2016 : e12912
DOI: 10.14814/phy2.12912

This study shows that inhibition of the NF-κB signaling in podocytes does not play a significant role in renal ischemia-reperfusion injury, although systemic inhibition of NF-κB attenuates the injury in mice.

**Increasing fetal ovine number per gestation alters fetal plasma clinical chemistry values**
Micaela Zywicki, Sharon E. Blohowiak, Ronald R. Magness, Jeffrey L. Segar, Pamela J. Kling
August 25, 2016 : e12905
In late gestation multifetal gestation fetuses, we observed both placental excretory dysfunction with rising fetal plasma cholesterol and fetal excretory dysfunction with rising plasma creatinine. Understanding these biochemical adaptations to an adverse fetal environment may help explain altered metabolic programming in fetal growth restriction.

**August 2016; volume 4, issue 15**

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### Original Research

**5-HT<sub>2B</sub> receptor antagonists attenuate myofibroblast differentiation and subsequent fibrotic responses in vitro and in vivo**

Anna Löfdahl, Kristina Rydell-Törmänen, Catharina Müller, C. Martina Holst, Lena Thiman, Gunilla Ekström, Christina Wenglén, Anna-Karin Larsson-Callerfelt, Gunilla Westergren-Thorsson  
August 1, 2016 : e12873  
DOI: 10.14814/phy2.12873

5-HT<sub>2B</sub> receptor antagonists have potential to prevent myofibroblast differentiation, in vitro and in vivo, with subsequent effect on matrix deposition, suggesting 5-HT<sub>2B</sub> receptors as novel targets for the treatment of pulmonary fibrosis.

**Aspirate from human stented saphenous vein grafts induces epicardial coronary vasoconstriction and impairs perfusion and left ventricular function in rat bioassay hearts with pharmacologically induced endothelial dysfunction**

Helmut R. Lieder, Theodor Baars, Philipp Kahler, Petra Kleinbongard  
August 1, 2016 : e12874  
DOI: 10.14814/phy2.12874

Human coronary arterial aspirate, retrieved after stent implantation during percutaneous coronary intervention, induces vasoconstriction in isolated epicardial rat coronary arteries and impairs coronary flow and left ventricular function in isolated perfused rat hearts with pharmacologically induced endothelial dysfunction.

**Immobilization rapidly induces muscle insulin resistance together with the activation of MAPKs (JNK and p38) and impairment of AS160 phosphorylation**

Emi Kawamoto, Keiichi Koshinaka, Tatsuhiko Yoshimura, Hiroyuki Masuda, Kentaro Kawanaka  
August 1, 2016 : e12876  
DOI: 10.14814/phy2.12876

Inactivity-induced rapid development of insulin resistance for glucose uptake in immobilized muscle is related to decreased basal phosphorylation of AS160. In addition, enhanced activation of JNK and/or p38 MAPK can account for inactivity-induced insulin resistance.

**Beneficial effects of combined resveratrol and metformin therapy in treating diet-induced insulin resistance**

Scott Frendo-Cumbo, Rebecca E. K. MacPherson, David C. Wright  
August 1, 2016 : e12877  
DOI: 10.14814/phy2.12877

We have compared the individual and combined effects of resveratrol and metformin in treating insulin resistance. Dual therapy treatment led to improvements in glucose tolerance that was associated with increases in insulin signalling in subcutaneous adipose tissue.

**Feedforward consequences of isometric contractions: effort and ventilation**

Billy L. Luu, Janette L. Smith, Peter G. Martin, Rachel A. McBain, Janet L. Taylor, Jane E. Butler  
August 1, 2016 : e12882  
DOI: 10.14814/phy2.12882

Our aim was to determine how the relationships between ventilation and perception of effort are affected by simultaneous contractions of multiple muscle groups. We examined the ventilatory response and perceived effort of contraction during separate and simultaneous isometric contractions of the contralateral elbow flexors and of an ipsilateral elbow flexor and knee extensor. The ventilatory response and the sense of effort at the onset of muscle activity are not related to the total output of the motor pathways, or the working muscles, but arise from cortical regions upstream from the motor cortex.

**Astaxanthin intake attenuates muscle atrophy caused by immobilization in rats**

Tsubasa Shibaguchi, Yusuke Yamaguchi, Nobuyuki Miyaji, Toshinori Yoshihara, Hisashi Naito, Katsumasa Goto, Daijiro Ohmori, Toshitada Yoshioka, Takao Sugiura
In this study, we demonstrated that dietary astaxanthin intake attenuated the rate of immobilization-induced soleus muscle atrophy in rats by inhibiting oxidative stress and proteolysis via three major proteolytic pathways. These findings indicate that astaxanthin supplementation could be an effective countermeasure against disuse muscle atrophy.

Acute arterial baroreflex-mediated changes in plasma catecholamine concentrations in a chronic rat model of myocardial infarction
Toru Kawada, Tsuyoshi Akiyama, Meihua Li, Can Zheng, Michael J. Turner, Mikiyasu Shirai, Masaru Sugimachi
August 5, 2016 : e12880
DOI: 10.14814/phy2.12880
Plasma catecholamine concentrations are significantly elevated in a chronic rat model of myocardial infarction. However, the catecholamine levels are still under the influence of carotid sinus baroreflex-mediated changes in sympathetic nerve activity, which may provide additional rationale for sympathetic suppression via the baroreflex activation therapy in patients with chronic heart failure.

Bidirectional variability in motor cortex excitability modulation following 1 mA transcranial direct current stimulation in healthy participants
Wolfgang Strube, Tilmann Bunse, Michael A. Nitsche, Alexandra Nikolaeva, Ulrich Palm, Frank Padberg, Peter Falkai, Alkomiet Hasan
August 5, 2016 : e12884
DOI: 10.14814/phy2.12884
1mA anodal and cathodal transcranial direct current stimulation display a significant inter-subject variability. Response clusters showing increases or decreases in corticospinal excitability following both anodal and cathodal tDCS can be extracted allowing for a separation of different response patterns. Regardless of polarity, clusters of increased corticospinal excitability following anodal or cathodal tDCS are characterized by steeper cortical recruitment. Our results help to better understand the individual response heterogeneity to standard motor-cortical transcranial direct current stimulation.

Treadmill exercise within lower body negative pressure protects leg lean tissue mass and extensor strength and endurance during bed rest
Suzanne M. Schneider, Stuart M. C. Lee, Alan H. Feiveson, Donald E. Watenpaugh, Brandon R. Macias, Alan R. Hargens
August 5, 2016 : e12892
DOI: 10.14814/phy2.12892
The effectiveness of exercise against lower body negative pressure to maintain leg lean mass and strength was evaluated during 30 days of bed rest in male and female identical twins. This aerobic exercise maintained leg lean mass and extensor, but not flexor, strength and endurance. Women had smaller changes than men due to their lower pre-bed rest values. The use of monozygous twins improved the power of many of our statistical comparisons.

Libby amphibole-induced mesothelial cell autoantibodies bind to surface plasminogen and alter collagen matrix remodeling
Robert Hanson, Caryn Evilia, John Gilmer, Linda Woods, Brad Black, Raja Flores, Jean C. Pfau
August 12, 2016 : e12881
DOI: 10.14814/phy2.12881
Serum from patients exposed to Libby amphibole (LA) asbestos contain autoantibodies that induce collagen production by mesothelial cells (Met5A), indicated as absorbance in a cell-based ELISA for collagen Type 1. Commercial plasminogen blocking antibodies have the same effect of inducing collagen production. Clearing IgG from the patient serum suppresses the collagen-inducing effect of the mesothelial cell autoantibodies (MCAA).

Extrapancreatic effects of incretin hormones: evidence for weight-independent changes in morphological aspects and oxidative status in insulin-sensitive organs of the obese nondiabetic Zucker rat (ZFR)
Ides M. Colin, Henri Colin, Ines Dufour, Charles-Edouard Gielen, Marie-Christine Many, Jean Saey, Bernard Knoops, Anne-Catherine Gérard
August 10, 2016 : e12886
DOI: 10.14814/phy2.12886
Beyond the well-known insulinotropic actions of incretins, the results presented in this article suggest that incretins may also favorably influence glucose metabolism by improving insulin sensitivity in insulin-sensitive organs (liver, adipocytes, and myocytes).

Mitochondrial function assessed by 31P MRS and BOLD MRI in non-obese type 2 diabetic rats
Yuchi Liu, Xunbai Mei, Jielei Li, Nicola Lai, Xin Yu
August 10, 2016 : e12890
DOI: 10.14814/phy2.12890
The current study aimed at delineating the development of metabolic abnormalities in the skeletal muscle of non-obese, insulin resistant rats.
Mitochondrial function and muscle oxygenation in response to ischemia-reperfusion were assessed by magnetic resonance spectroscopy and imaging. The results suggest that insulin resistance leads to alterations in tissue metabolism without impaired mitochondrial oxidative capacity in insulin-resistant rats.

The response of muscle protein synthesis following whole-body resistance exercise is greater following 40 g than 20 g of ingested whey protein
Lindsay S. Macnaughton, Sophie L. Wardle, Oliver C. Witard, Chris McGlory, D. Lee Hamilton, Stewart Jeromson, Clare E. Lawrence, Gareth A. Wallis, Kevin D. Tipton
August 10, 2016 : e12893
DOI: 10.14814/phy2.12893

We aimed to determine the influence of lean body mass on the response of muscle protein synthesis to protein ingestion following resistance exercise. The response of muscle protein synthesis following whole body resistance exercise is greater with ingestion of 40 g versus 20 g of whey protein in young, resistance-trained men.

The role of $G_{\alpha}O$-mediated signaling in the rostral ventrolateral medulla oblongata in cardiovascular reflexes and control of cardiac ventricular excitability
Richard Ang, Joel Abramowitz, Lutz Birbaumer, Alexander V. Gourine, Andrew Tinker
August 15, 2016 : e12860
DOI: 10.14814/phy2.12860

This study aimed to determine the role of inhibitory heterotrimeric G proteins in the central mechanisms underlying autonomic control of the heart and its potential role in arrhythmogenesis. Mice with $G_{\alpha}O$ deletion in the pre-sympathetic area of the rostral ventral lateral medulla (RVLM) exposed to stressful conditions (novel environment, hypoxia or hypercapnia) had exaggerated heart rate responses and an increased baroreflex gain. This was associated with shortening of the ventricular effective refractory period. $G_{\alpha}O$ deficiency in the RVLM is associated with exaggerated cardiovascular responses to stress, altered cardiovascular reflexes and electrical properties of the heart.

Age- and sex-related changes in rat renal function and pathology following neonatal hyperoxia exposure
Megan R. Sutherland, Chanel Béland, Marie-Amélie Lukaszewski, Anik Cloutier, Mariane Bertagnolli, Anne Monique Nuyt
August 15, 2016 : e12887
DOI: 10.14814/phy2.12887

Preterm neonates are prematurely exposed to high oxygen levels at birth which may adversely impact ongoing renal development. In a rat model of neonatal hyperoxia exposure, animals exhibited impaired renal functional capacity and an increased susceptibility to renal disease (glomerular crescents) in adulthood, with findings dependent on age and sex.

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