EDITORIAL | Omic and Systems Biology Approaches in Neurodegenerative Diseases

Multi-omics and Alzheimer’s disease: a slower but surer path to an efficacious therapy?
Sanjay W. Pimplikar
July 1, 2017 : C1-C2
DOI: 10.1152/ajpcell.00109.2017

THEME | Omic and Systems Biology Approaches in Neurodegenerative Diseases

Applying fluid biomarkers to Alzheimer's disease
Henrik Zetterberg
July 1, 2017 : C3-C10
DOI: 10.1152/ajpcell.00007.2017

RESEARCH ARTICLE | Cell-to-Cell Communication and Signaling Pathways

MiR-9-5p promotes MSC migration by activating β-catenin signaling pathway
Xianyang Li, Lihong He, Qing Yue, Junhou Lu, Naixin Kang, Xiaojing Xu, Huihui Wang, Huanxiang Zhang
July 6, 2017 : C80-C93
DOI: 10.1152/ajpcell.00232.2016

RESEARCH ARTICLE | Regulation of Cell Signaling Pathways

Balance between S-nitrosylation and denitrosylation modulates myoblast proliferation independently of soluble guanylyl cyclase activation
Aline M. S. Yamashita, Maryana T. C. Ancillotti, Luciana P. Rangel, Marcio Fontenele, Cicero Figueiredo-Freitas, Ana C. Possidonio, Carolina P. Soares, Martha M. Sorenson, Claudia Mermelstein, Leonardo Nogueira
July 1, 2017 : C11-C26
DOI: 10.1152/ajpcell.00140.2016

RESEARCH ARTICLES

Melamine induces Ca2+-sensing receptor activation and elicits apoptosis in proximal tubular cells
Allen J. Yiu, Cliff-Lawrence Ibeh, Sanjit K. Roy, Bidhan C. Bandyopadhyay
July 1, 2017 : C27-C41
DOI: 10.1152/ajpcell.00225.2016

ENaC activity is regulated by calpain-2 proteolysis of MARCKS proteins
Ablation of S1P3 receptor protects mouse soleus from age-related drop in muscle mass, force, and regenerative capacity
Michela Bondì, Elena Germinario, Marco Pirazzini, Giulia Zanetti, Francesca Cencetti, Chiara Donati, Luisa Gorza, Romeo Betto, Paola Bruni, Daniela Danielli-Betto
July 1, 2017: C54-C67
DOI: 10.1152/ajpcell.00027.2017

Airway epithelial anion secretion and barrier function following exposure to fungal aeroallergens: role of oxidative stress
Nathan A. Zaidman, Kelly E. O’Grady, Nandadevi Patil, Francesca Milavetz, Peter J. Maniak, Hirohito Kita, Scott M. O’Grady
July 1, 2017: C68-C79
DOI: 10.1152/ajpcell.00043.2017

Primary cilia control the maturation of tubular lumen in renal collecting duct epithelium
Thomas Ernandez, Olga Komarynets, Alexandra Chassot, Soushma Sougoumarin, Priscilla Soulié, Yubao Wang, Roberto Montesano, Eric Feraille
July 6, 2017: C94-C107
DOI: 10.1152/ajpcell.00290.2016

FXYD5 (dysadherin) may mediate metastatic progression through regulation of the β-Na+-K+-ATPase subunit in the 4T1 mouse breast cancer model
Irina Lubarski-Gotliv, Kuntal Dey, Yuri Kuznetsov, Vecheslav Kalchenco, Carol Asher, Haim Garty
July 6, 2017: C108-C117
DOI: 10.1152/ajpcell.00010.2017

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RESEARCH ARTICLE | Metabolic Control by Inflammation and Immunity

Whey protein effects on energy balance link the intestinal mechanisms of energy absorption with adiposity and hypothalamic neuropeptide gene expression
Kanishka N. Nilaweera, Raul Cabrera-Rubio, John R. Speakman, Paula M. O’Connor, AnneMarie McAuliffe, Caitriona M. Guinane, Elaine M. Lawton, Fiona Crispie, Mónica Aguilera, Maurice Stanley, Serena Boscai, Susan Joyce, Silvia Melgar, John F. Cryan, Paul D. Cotter
July 1, 2017 : E1-E11
DOI: 10.1152/ajpendo.00356.2016

RESEARCH ARTICLE | Role of Adipose Tissue Nutrient/Vitamin Metabolism in Physiological and Altered Metabolic Settings

Feeding influences adipose tissue responses to exercise in overweight men
Yung-Chih Chen, Rebecca L. Travers, Jean-Philippe Walhin, Javier T. Gonzalez, Francoise Koumanov, James A. Betts, Dylan Thompson
July 7, 2017 : E84-E93
DOI: 10.1152/ajpendo.00006.2017

RESEARCH ARTICLE | Role of Gut Microbiota and Gut-Brain and Gut-Liver Axes in Physiological Regulation of Inflammation, Energy Balance, and Metabolism

GPR40 reduces food intake and body weight through GLP-1
Judith N. Gorski, Michele J. Pachanski, Joel Mane, Christopher W. Plummer, Sarah Souza, Brande S. Thomas-Fowlkes, Aimie M. Ogawa, Adam B. Weinglass, Jerry Di Salvo, Boonlert Cheewatrakoolpong, Andrew D. Howard, Steven L. Colletti, Maria E. Trujillo
July 1, 2017 : E37-E47
DOI: 10.1152/ajpendo.00435.2016

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Gonad-related factors promote muscle performance gain during postnatal development in male and female mice
Vanessa Ubershlag-Pitiot, Amalia Stantzou, Julien Messéant, Megane Lemaitre, Daniel J. Owens, Philippe Noirez, Pauline Roy, Onnik Agbulut, Daniel Metzger, Arnaud Ferry
July 1, 2017 : E12-E25
DOI: 10.1152/ajpendo.00446.2016

Effects of genetic deletion of soluble 5′-nucleotidases NT5C1A and NT5C2 on AMPK activation and nucleotide levels in contracting mouse skeletal muscles
Samanta Kviklyte, Didier Vertommen, Xavier Yerna, Harriet Andersén, Xiufeng Xu, Philippe Gailly, Mohammad Bohlooly-Y, Jan Oscarsson, Mark H. Rider
July 1, 2017 : E48-E62
DOI: 10.1152/ajpendo.00304.2016

A four-compartment compartmental model to assess net whole body protein breakdown using a pulse of phenylalanine and tyrosine stable isotopes in humans
Alvise Mason, Mariëlle P. K. J. Engelen, Ivan Ivanov, Gianna M. Toffolo, Nicolaas E. P. Deutz
July 1, 2017 : E63-E74
DOI: 10.1152/ajpendo.00362.2016

Does maternal-fetal transfer of creatine occur in pregnant sheep?
Syed Baharom, Robert De Matteo, Stacey Ellery, Paul Della Gatta, Clinton R. Bruce, Greg M. Kowalski, Nadia Hale, Hayley Dickinson, Richard Harding, David Walker, Rodney J. Snow
July 1, 2017 : E75-E83
DOI: 10.1152/ajpendo.00450.2016

Oxygen delivery and the restoration of the muscle energetic balance following exercise: implications for delayed muscle recovery in patients with COPD
Gwenael Layec, Corey R. Hart, Joel D. Trinity, Oh-Sung Kwon, Matthew J. Rossman, Ryan M. Broxterman, Yann Le Fur, Eun-Kee Jeong, Russell S. Richardson
July 7, 2017 : E94-E104
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Retraction
Raymond C. Pasek, Jennifer C. Dunn, Joseph M. Elsakr, Mounika Aramandla, Anveetha R. Matta, Maureen Gannon
July 7, 2017 : E105

DOI: 10.1152/ajpendo.zh1-7764-retr.2017

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MINI-REVIEW | Liver and Biliary Tract Physiology/Pathophysiology

Pregnancy and bile acid disorders
Vanessa Pataia, Peter H. Dixon, Catherine Williamson
July 1, 2017 : G1-G6
DOI: 10.1152/ajpgi.00028.2017

MINI-REVIEW | Microbiome and Host Interactions

From sensing to shaping microbiota: insights into the role of NOD2 in intestinal homeostasis and progression of Crohn’s disease
Iyshwarya Balasubramanian, Nan Gao
July 1, 2017 : G7-G13
DOI: 10.1152/ajpgi.00330.2016

EDITORIAL FOCUS

A new role for microbiota? Dulling the thrust of serotonin and 5-HT3 signaling cascade
Eugene B. Chang, Mrinalini C. Rao
July 1, 2017 : G14-G15
DOI: 10.1152/ajpgi.00166.2017

RESEARCH ARTICLES | Epithelial Biology and Secretion

Expression and localization of VPAC1, the major receptor of vasoactive intestinal peptide along the length of the intestine
Dulari Jayawardena, Grace Guzman, Ravinder K. Gill, Waddah A. Alrefai, Hayat Onyuksel, Pradeep K. Dudeja
July 1, 2017 : G16-G25
DOI: 10.1152/ajpgi.00081.2017

These studies for the first time present comprehensive data on the relative characterization of vasoactive intestinal peptide (VIP) receptors in the intestinal mucosa. Vasoactive intestinal peptide receptor 1 (VPAC1) was identified as the predominant receptor with higher levels in the colon.
compared with the small intestine and was mainly localized to the apical membrane. In addition, the findings in the human tissues were consistent with VPAC1 expression in the mouse intestine and open possibilities to target colonic tissues with VIP for treating diseases such as inflammatory bowel disease.

Absence of the NOD2 protein renders epithelia more susceptible to barrier dysfunction due to mitochondrial dysfunction

Alpana Saxena, Fernando Lopes, Karen K. H. Poon, Derek M. McKay
July 1, 2017 : G26-G38

DOI: 10.1152/ajpgi.00070.2017

Increased internalization of bacteria by epithelia with dysfunctional mitochondria (reduced ATP) is potentiated if the cells lack nucleotide-binding oligomerization domain 2 (NOD2), mutations in which are inflammatory bowel disease (IBD)-susceptibility traits. Uptake of bacteria was dependent on reactive oxygen species and MAP-kinase activity, and the increased viable intracellular bacteria in NOD2−/− cells likely reflect a reduced ability to recognize and kill bacteria. Thus a significant barrier defect occurs with NOD2 deficiency in conjunction with metabolic stress that could contribute to inflammation.

RESEARCH ARTICLES | Liver and Biliary Tract Physiology/Pathophysiology

Targeted inactivation of copper transporter Atp7b in hepatocytes causes liver steatosis and obesity in mice
Abigail Muchenditsi, Haojun Yang, James P. Hamilton, Lahari Koganti, Franck Housseau, Lisa Aronov, Hongni Fan, Hannah Pierson, Ashima Bhattacharjee, Robert Murphy, Cynthia Sears, James Potter, Clavia R. Wooton-Kee, Svetlana Lutsenko
July 1, 2017 : G39-G49

DOI: 10.1152/ajpgi.00312.2016

Targeted inactivation of copper-transporting ATPase 2 (Atp7b) in hepatocytes causes steatosis in the absence of inflammation.

Phosphatidylcholine transfer protein/StarD2 promotes microvesicular steatosis and liver injury in murine experimental steatohepatitis
Hayley T. Nicholls, Jason L. Hornick, David E. Cohen
July 1, 2017 : G50-G61

DOI: 10.1152/ajpgi.00379.2016

Phosphatidylcholine transport protein (PC-TP) is a highly specific phosphatidylcholine-binding protein that we previously showed to regulate hepatocellular nutrient metabolism through its interacting partner thioesterase superfamily member 2 (Them2). This study identifies a pathogenic role for PC-TP, independent of Them2, in the methionine- and choline-deficient diet model of experimental steatohepatitis. Our current observations suggest that PC-TP promotes liver injury by mediating the intermembrane transfer of phosphatidylcholines, thus stabilizing more pathogenic microvesicular lipid droplets.

RESEARCH ARTICLE | Metabolomics and Physiological Systems

Gastroparesis and lipid metabolism-associated dysbiosis in Wistar-Kyoto rats
J. E. Dalziel, Karl Fraser, Wayne Young, Catherine M. McKenzie, Shalome A. Bassett, Nicole C. Roy
July 1, 2017 : G62-G72

DOI: 10.1152/ajpgi.00008.2017

This study reveals that the stress-prone Wistar-Kyoto rat strain has a baseline physiology of gastroparesis and rapid small intestine transit, together with metabolic changes consistent with lipid metabolism-associated dysbiosis, compared with nonstress-prone rats. This suggests that the Wistar-Kyoto rat strain may be an appropriate animal model for gastroparesis.

RESEARCH ARTICLES | Neurogastroenterology and Motility

Elevated intrabolus pressure identifies obstructive processes when integrated relaxation pressure is normal on esophageal high-resolution manometry
Farhan Quader, Chanakyaram Reddy, Amit Patel, C. Prakash Gyawali
July 1, 2017 : G73-G79

DOI: 10.1152/ajpgi.00091.2017

Integrated relaxation pressure (IRP) above the upper limit of normal defines esophageal outflow obstruction using high-resolution manometry. In patients with normal IRP, elevated intrabolus pressure (IBP) can be a surrogate marker for a structural restrictive or obstructive process at the esophagogastric junction (EGJ). This has the potential to augment the clinical value of esophageal HRM by raising suspicion for a structural EGJ process when IBP is elevated.

Human-derived gut microbiota modulates colonic secretion in mice by regulating 5-HT3receptor expression via acetate production
Yogesh Bhattarai, Bradley A. Schmidt, David R. Linden, Eric D. Larson, Madhusudan Grover, Arthur Beyder, Gianrico Farrugia, Purna C. Kashyap
We found that gut microbiota alters serotonin (5-HT)-evoked intestinal secretion in a 5-HT3-receptor-dependent mechanism and gut microbiota metabolite acetate alters 5-HT3 receptor expression in colonoids.

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Cardiac myofibrillar contractile properties during the progression from hypertension to decompensated heart failure
Laurin M. Hanft, Craig A. Emter, Kerry S. McDonald
July 1, 2017 : H103-H113
DOI: 10.1152/ajpheart.00069.2017

This novel study systematically examined the power-generating capacity of cardiac myofilaments during the progression from hypertension to heart disease. Previously undiscovered changes in myofibrillar power output were found and were associated with alterations in myofilament proteins, providing potential new targets to exploit for improved ventricular pump function in heart failure.

VO₂ kinetics associated with moderate-intensity exercise in heart failure: impact of intrathecal fentanyl inhibition of group III/IV locomotor muscle afferents
Erik H. Van Iterson, Bruce D. Johnson, Michael J. Joyner, Timothy B. Curry, Thomas P. Olson
July 1, 2017 : H114-H124
DOI: 10.1152/ajpheart.00014.2017

Inhibition of locomotor muscle afferents results in rapid primary-component O₂ uptake (VO₂) on-kinetics accounting for the decreased O₂ deficit in heart failure (HF). This study revealed that abnormal musculoskeletal–neural afferents couple with pulmonary and circulatory dysfunction to provoke impaired exercise VO₂ in HF. Steady-state VO₂ cannot properly phenotype abnormal muscle afferent contributions to impaired exercise VO₂ in HF.

RESEARCH ARTICLES | Integrative Cardiovascular Physiology and Pathophysiology

Hypoxia-mediated regulation of the secretory properties of mitral valve interstitial cells
Kareem Salhiyyah, Padmini Sarathchandra, Najma Latif, Magdi H. Yacoub, Adrian H. Chester
July 1, 2017 : H14-H23
DOI: 10.1152/ajpheart.00720.2016

This study demonstrates that hypoxia regulates extracellular matrix secretion and the remodeling potential of heart valve interstitial cells. Expression of hypoxia-induced factor-1α plays a role in these effects. These data highlight the potential role of hypoxia as a physiological mediator of the complex function of heart valve cells.

Shear-mediated dilation of the internal carotid artery occurs independent of hypercapnia
Ryan L. Hoiland, Kurt J. Smith, Howard H. Carter, Nia C.S. Lewis, Michael M. Tymko, Kevin W. Wildfong, Anthony R. Bain, Daniel J. Green, Philip N. Ainslie
July 1, 2017 : H24-H31
DOI: 10.1152/ajpheart.00119.2017

Shear stress dilates the internal carotid artery in humans. This vasodilatory response occurs independent of other physiological factors, as demonstrated by our transient CO₂ test, and is strongly correlated to shear area under the curve. Assessing carotid shear-mediated dilation may provide a future avenue for assessing cerebrovascular health and the risk of cerebrovascular events.

RESEARCH ARTICLES | Muscle Mechanics and Ventricular Function

Desmin loss and mitochondrial damage precede left ventricular systolic failure in volume overload heart failure
Jason L. Guichard, Michael Rogowski, Giulio Agnetti, Lianwu Fu, Pamela Powell, Chih-Chang Wei, James Collawn, Louis J. Dell’Italia
July 1, 2017 : H32-H45
DOI: 10.1152/ajpheart.00027.2017

This study provides new evidence of early onset (24 h) and continuous (4–12 wk) desmin misarrangement and disruption of the normal sarcomeric and mitochondrial architecture throughout the progression of volume overload heart failure, suggesting a causal link between desmin cleavage and mitochondrial disorganization and damage.

Quantitative cardiac phosphoproteomics profiling during ischemia-reperfusion in an immature swine model
July 1, 2017 : H125-H137
DOI: 10.1152/ajpheart.00842.2016

We used Isobaric Tags for Relative and Absolute Quantitation technology to investigate the phosphoproteomic changes that occur in cardiac tissue under ischemia-reperfusion conditions. The results of this study provide an extensive catalog of phosphoproteins, both predicted and novel, associated with ischemia-reperfusion, thereby identifying new pathways for investigation.

Ultrasound biomicroscopy validation of a murine model of cardiac hypertrophic preconditioning: comparison with a hemodynamic assessment
We successfully developed an ultrasound biomicroscopy protocol for the serial assessment of aortic bandings and the relevant left ventricular pressure in a murine model of cardiac hypertrophic preconditioning. The protocol may be of great importance in the successful establishment of the hypertrophic preconditioning model for further mechanistic and pharmacological studies.

RESEARCH ARTICLES | Signaling and Stress Response

MK5 haplodeficiency attenuates hypertrophy and preserves diastolic function during remodeling induced by chronic pressure overload in the mouse heart
Sherin Ali Nawaito, Dharmendra Dingar, Pramod Sahadevan, Bahira Hussein, Fatiha Sahmi, Yanfen Shi, Marc-Antoine Gillis, Matthias Gaestel, Jean-Claude Tardif, Bruce G. Allen
July 1, 2017 : H46-H58
DOI: 10.1152/ajpheart.00597.2016

MAPK-activated protein kinase-5 (MK5)/p38-regulated/activated protein kinase is a protein serine/threonine kinase activated by p38 MAPK and/or the atypical MAPKs ERK3 and ERK4. MK5 immunoreactivity was detected in adult ventricular fibroblasts but not in myocytes. MK5 haplodeficiency attenuated the progression of hypertrophy, reduced collagen type 1 mRNA, and protected diastolic function in response to chronic pressure overload.

Cardiac hyporesponsiveness in severe sepsis is associated with nitric oxide-dependent activation of G protein receptor kinase
July 1, 2017 : H149-H163
DOI: 10.1152/ajpheart.00052.2016

The main novelty presented here is to show that septic shock induces cardiac hyporesponsiveness to isoproterenol by a mechanism dependent on nitric oxide and mediated by G protein-coupled receptor kinase isoform 2. Therefore, G protein-coupled receptor kinase isoform 2 inhibition may be a potential therapeutic target in sepsis-induced cardiac dysfunction.

RESEARCH ARTICLES | Vascular Biology and Microcirculation

Imaging and modeling of acute pressure-induced changes of collagen and elastin microarchitectures in pig and human resistance arteries
July 1, 2017 : H164-H178
DOI: 10.1152/ajpheart.00110.2017

This is the first study to quantitatively relate pressure-induced microstructural changes in resistance arteries to the mechanics of their wall. Principal findings using a pig model system were confirmed in human arteries. The combined methods provide a strong tool for future hypothesis-driven studies of microvascular pathologies.

Endothelial cAMP deactivates ischemia-reperfusion-induced microvascular hyperpermeability via Rap1-mediated mechanisms
Adam H. Korayem, Patricio E. Mujica, Haruo Aramoto, Ricardo G. Durán, Prerna R. Nepali, David D. Kim, Andrew L. Harris, Fabiola A. Sánchez, Walter N. Durán
July 1, 2017 : H179-H189
DOI: 10.1152/ajpheart.00002.2017

Here, we demonstrate that 1) stimulation of cAMP production deactivates ischemia-reperfusion-induced hyperpermeability in muscle and endothelial cells; 2) VEGF mRNA expression is not enhanced by brief ischemia, suggesting that VEGF mechanisms do not activate immediate postischemic hyperpermeability; and 3) deactivation mechanisms operate via cAMP-exchange protein activated by cAMP 1-Rap1 to restore integrity of the endothelial barrier.

WNT5A regulates adipose tissue angiogenesis via antiangiogenic VEGF-A165b in obese humans
Shakun Karki, Doan T. M. Ngo, Melissa G. Farb, Song Young Park, Samantha M. Saggese, Naomi M. Hamburg, Brian Carmine, Donald T. Hess, Kenneth Walsh, Noyan Gokce
July 6, 2017 : H200-H206
Wingless-related integration site 5a (WNT5A) negatively regulates adipose tissue angiogenesis via VEGF-A165b in human obesity.

**Chronic hypoxia attenuates the vasodilator efficacy of protein kinase G in fetal and adult ovine cerebral arteries**

Richard B. Thorpe, Margaret C. Hubbell, Jinjutha Silpanisong, James M. Williams, William J. Pearce

July 6, 2017 : H207-H219

DOI: 10.1152/ajpheart.00776.2016

Using measurements of contractility, protein abundance, kinase activity, and confocal colocalization in fetal and adult ovine cerebral arteries, the present study demonstrates that long-term hypoxia diminishes the ability of cGMP-dependent protein kinase (PKG) to cause vasorelaxation through suppression of its colocalization and interaction with large-conductance Ca2+-sensitive K+ (BK) channel proteins in cerebrovascular smooth muscle. These experiments are among the first to demonstrate hypoxic changes in BK subunit abundances in fetal cerebral arteries and also introduce the use of advanced methods of confocal colocalization to study interaction between PKG and its targets.

**RAPID REPORT | Mining Natural Products for Cardiovascular Benefits**

Acute beetroot juice supplementation on sympathetic nerve activity: a randomized, double-blind, placebo-controlled proof-of-concept study

Karambir Notay, Anthony V. Incognito, Philip J. Millar

July 1, 2017 : H59-H65

DOI: 10.1152/ajpheart.00163.2017

The hemodynamic benefits of dietary nitrate supplementation have been attributed to nitric oxide-mediated peripheral vasodilation. Here, we provide proof of concept that acute dietary nitrate supplementation using beetroot juice can decrease muscle sympathetic outflow at rest and during exercise in a normotensive population. These results have applications for targeting central sympathetic overactivation in disease.

**RAPID REPORT | Vascular Biology and Microcirculation**

S-nitrosylation of VASP at cysteine 64 mediates the inflammation-stimulated increase in microvascular permeability

Patricia Zamorano, Natalie Marin, Francisco Córdova, Alejandra Aguilar, Cynthia Meininger, Mauricio P. Boric, Nikola Golenhofen, Jorge E. Contreras, José Sarmiento, Walter N. Durán, Fabiola A. Sánchez

July 1, 2017 : H66-H71

DOI: 10.1152/ajpheart.00135.2017

Here, we demonstrate that S-nitrosylation of vasodilator-stimulated phosphoprotein (VASP) on C64 is a mechanism for the onset of platelet-activating factor-induced hyperpermeability. Our results reveal a dual role of VASP in endothelial permeability. In addition to its well-documented function in barrier integrity, we show that S-nitrosylation of VASP contributes to the onset of endothelial permeability.

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**Acute brain trauma, lung injury, and pneumonia: more than just altered mental status and decreased airway protection**

Parker J. Hu, Jean-Francois Pittet, Jeffrey D. Kerby, Patrick L. Bosarge, Brant M. Wagener

July 1, 2017 : L1-L15

DOI: 10.1152/ajplung.00485.2016

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**REVIEW | Translational Research in Acute Lung Injury and Pulmonary Fibrosis**

Acute brain trauma, lung injury, and pneumonia: more than just altered mental status and decreased airway protection

Parker J. Hu, Jean-Francois Pittet, Jeffrey D. Kerby, Patrick L. Bosarge, Brant M. Wagener

July 1, 2017 : L1-L15

DOI: 10.1152/ajplung.00485.2016
RESEARCH ARTICLE | Age-Related Dysfunction in Lung Barrier Function in Health and Disease

Klotho, an antiaging molecule, attenuates oxidant-induced alveolar epithelial cell mtDNA damage and apoptosis
Seok-Jo Kim, Paul Cheresh, Mesut Eren, Renea P. Jablonski, Anjana Yeldandi, Karen M. Ridge, G. R. Scott Budinger, Dong-Hyun Kim, Myles Wolf, Douglas E. Vaughan, David W. Kamp
July 1, 2017 : L16-L26
DOI: 10.1152/ajplung.00063.2017

RESEARCH ARTICLES | Biomarkers in Lung Diseases: From Pathogenesis to Prediction to New Therapies

Autophagy plays a role in FSTL1-induced epithelial mesenchymal transition and airway remodeling in asthma
Tian Liu, Yahui Liu, Marina Miller, Liuzhao Cao, Jiping Zhao, Jinxian Wu, Junfei Wang, Lin Liu, Shuo Li, Minfang Zou, Jiawei Xu, David H. Broide, Liang Dong
July 1, 2017 : L27-L40
DOI: 10.1152/ajplung.00510.2016

CD44high alveolar type II cells show stem cell properties during steady-state alveolar homeostasis
Qian Chen, Varsha Suresh Kumar, Johanna Finn, Dianhua Jiang, Jiurong Liang, You-yang Zhao, Yuru Liu
July 1, 2017 : L41-L51
DOI: 10.1152/ajplung.00564.2016

RESEARCH ARTICLES | Electronic Cigarettes: Not All Good News?

Flavored e-cigarette liquids reduce proliferation and viability in the CALU3 airway epithelial cell line
Temperance R. Rowell, Steven L. Reeber, Shernita L. Lee, Rachel A. Harris, Rachel C. Nethery, Amy H. Herring, Gary L. Glish, Robert Tarran
July 1, 2017 : L52-L66
DOI: 10.1152/ajplung.00392.2016

The effects of electronic cigarette aerosol exposure on inflammation and lung function in mice
July 1, 2017 : L67-L79
DOI: 10.1152/ajplung.00203.2016

RESEARCH ARTICLES | Translational Research in Acute Lung Injury and Pulmonary Fibrosis

Low-dose cadmium exposure induces peribronchiolar fibrosis through site-specific phosphorylation of vimentin
Fu Jun Li, Ranu Surolia, Huashi Li, Zheng Wang, Gang Liu, Rui-Ming Liu, Sergey B. Mirov, Mohammad Athar, Victor J. Thannickal, Veena B. Antony
July 1, 2017 : L80-L91
DOI: 10.1152/ajplung.00087.2017

Modified mesenchymal stem cells using miRNA transduction alter lung injury in a bleomycin model
Luai Huleihel, Jacobo Sellares, Nayra Cardenes, Diana Álvarez, Rosa Faner, Koji Sakamoto, Guoying Yu, Maria G. Kapetanaki, Naftali Kaminski, Mauricio Rojas
July 1, 2017 : L92-L103
DOI: 10.1152/ajplung.00323.2016

Nedd8 modification of Cullin-5 regulates lipopolysaccharide-induced acute lung injury
Ziyan Zhu, Lei Sun, Rui Hao, Hongchao Jiang, Feng Qian, Richard D. Ye
July 1, 2017 : L104-L114
DOI: 10.1152/ajplung.00410.2016

RESEARCH ARTICLES

Does lack of glutathione peroxidase 1 gene expression exacerbate lung injury induced by neonatal hyperoxia in mice?
Sheena Bouch, Megan O’Reilly, Judy B. de Haan, Richard Harding, Foula Sozo
July 1, 2017 : L115-L125
DOI: 10.1152/ajplung.00039.2016
Acidosis increases the susceptibility of respiratory epithelial cells to *Pseudomonas aeruginosa*-induced cytotoxicity
Iviana M. Torres, Sally Demirdjian, Jennifer Vargas, Britton C. Goodale, Brent Berwin
July 1, 2017 : L126-L137
DOI: 10.1152/ajplung.00524.2016

Immunomodulators targeting MARCO expression improve resistance to postinfluenza bacterial pneumonia
Muzo Wu, John G. Gibbons, Glen M. DeLoid, Alice S. Bedugnis, Rajesh K. Thimmulappa, Shyam Biswal, Lester Kobzik
July 1, 2017 : L138-L153
DOI: 10.1152/ajplung.00075.2017

Bitter taste receptor agonists alter mitochondrial function and induce autophagy in airway smooth muscle cells
Shi Pan, Pawan Sharma, Sushrut D. Shah, Deepak A. Deshpande
July 1, 2017 : L154-L165
DOI: 10.1152/ajplung.00106.2017

TNFa decreases mitochondrial movement in human airway smooth muscle
Philippe Delmotte, Vanessa A. Zavaletta, Michael A. Thompson, Y. S. Prakash, Gary C. Sieck
July 1, 2017 : L166-L176
DOI: 10.1152/ajplung.00058.2016

Therapeutic blockade of CD54 attenuates pulmonary barrier damage in T cell-induced acute lung injury
Julia Svedova, Antoine Ménoret, Payal Mittal, Joseph M. Ryan, James A. Buturla, Anthony T. Vella
July 1, 2017 : L177-L191
DOI: 10.1152/ajplung.00050.2017

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RESEARCH ARTICLE | Model Systems for the Study of Integrative Physiology: The Rebirth of Translational Biology

Use of the hyperinsulinemic euglycemic clamp to assess insulin sensitivity in guinea pigs: dose response, partitioned glucose metabolism, and species comparisons
Dane M. Horton, David A. Saint, Julie A. Owens, Kathryn L. Gatford, Karen L. Kind
July 1, 2017 : R19-R28
DOI: 10.1152/ajpregu.00028.2017

RESEARCH ARTICLE | Neural Control

Role of endothelial nitric oxide in control of peripheral vascular conductance during muscle metaboreflex activation
Danielle Senador, Jasdeep Kaur, Alberto Alvarez, Hanna W. Hanna, Abhinav C. Krishnan, Yasir H. Altamimi, Donal S. O'Leary
July 1, 2017 : R29-R34
DOI: 10.1152/ajpregu.00515.2016

RESEARCH ARTICLES | Physical Activity and Inactivity

Histone deacetylase activity modulates exercise-induced skeletal muscle plasticity in zebrafish (Danio rerio)
Alec I. M. Simmonds, Frank Seebacher
July 1, 2017 : R35-R43
DOI: 10.1152/ajpregu.00378.2016

Impact of acetaminophen consumption and resistance exercise on extracellular matrix gene expression in human skeletal muscle
Shivam H. Patel, Andrew C. D’Lugos, Erica R. Eldon, Donald Curtis, Jared M. Dickinson, Chad C. Carroll
July 1, 2017 : R44-R50
DOI: 10.1152/ajpregu.00019.2017

RESEARCH ARTICLE | Sex and Gender Differences in Cardiovascular, Renal and Metabolic Diseases

ETB receptor contribution to vascular dysfunction in postmenopausal women
Megan M. Wenner, Kelly N. Sebzda, Andrew V. Kuczmarski, Ryan T. Pohlig, David G. Edwards
July 1, 2017 : R51-R57
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RESEARCH ARTICLE | Mechanism and Treatment of Renal Fibrosis

β-Arrestin-biased AT1R stimulation promotes extracellular matrix synthesis in renal fibrosis
Yandao Wang, Jieli Huang, Xi Liu, Yangyang Niu, Liqin Zhao, Ying Yu, Li Zhou, Limin Lu, Chen Yu
July 1, 2017 : F1-F8
DOI: 10.1152/ajprenal.00588.2016

RESEARCH ARTICLE | Renal Hemodynamics

Physiopathological implications of P2X1 and P2X7 receptors in regulation of glomerular hemodynamics in angiotensin II-induced hypertension
Martha Franco, Rocío Bautista-Pérez, Agustina Cano-Martínez, Ursino Pacheco, José Santamaría, Leonardo del Valle Mondragón, Oscar Pérez-Méndez, L. Gabriel Navar
July 1, 2017 : F9-F19
DOI: 10.1152/ajprenal.00663.2016

RESEARCH ARTICLES

Intrarenal signaling mediated by CCK plays a role in salt intake-induced natriuresis
Hiromi Takahashi-Iwanaga, Shunsuke Kimura, Kohtarou Konno, Masahiko Watanabe, Toshihiko Iwanaga
July 1, 2017 : F20-F29
DOI: 10.1152/ajprenal.00539.2016

Identification of β-catenin-interacting proteins in nuclear fractions of native rat collecting duct cells
Jacqueline R. Hwang, Chung-Lin Chou, Barbara Medvar, Mark A. Knepper, Hyun Jun Jung
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DOI: 10.1152/ajprenal.00054.2017

Maternal separation diminishes α-adrenergic receptor density and function in renal vasculature from male Wistar-Kyoto rats
Analia S. Loria, Jeffrey L. Osborn
July 1, 2017 : F47-F54
DOI: 10.1152/ajprenal.00591.2016

Responses of distal nephron Na+ transporters to acute volume depletion and hyperkalemia
Gustavo Frindt, Lei Yang, Shinichi Uchida, Alan M. Weinstein, Lawrence G. Palmer
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DOI: 10.1152/ajprenal.00668.2016

Autophagy is activated to protect against podocyte injury in adriamycin-induced nephropathy
Mixuan Yi, Lei Zhang, Yu Liu, Man J. Livingston, Jian-Kang Chen, N. Stanley Nahman Jr., Fuyou Liu, Zheng Dong
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DOI: 10.1152/ajprenal.00114.2017

Urothelial proliferation and regeneration after spinal cord injury
July 7, 2017 : F85-F115
DOI: 10.1152/ajprenal.00064.2017

Monophosphoryl lipid A induces protection against LPS in medullary thick ascending limb through a TLR4-TRIF-PI3K signaling pathway
Bruns A. Watts III, Thampi George, Edward R. Sherwood, David W. Good
July 7, 2017 : F103-F115
DOI: 10.1152/ajprenal.00064.2017
Proximal tubule glutamine synthetase expression is necessary for the normal response to dietary protein restriction
Hyun-Wook Lee, Gunars Osis, Mary E. Handlogten, Jill W. Verlander, I. David Weiner
July 7, 2017 : F116-F125
DOI: 10.1152/ajprenal.00048.2017

Slowly cycling Rho kinase-dependent actomyosin cross-bridge “slippage” explains intrinsic high compliance of detrusor smooth muscle
Christopher J. Neal, Jia B. Lin, Tanner Hurley, Amy S. Miner, John E. Speich, Adam P. Klausner, Paul H. Ratz
July 7, 2017 : F126-F134
DOI: 10.1152/ajprenal.00633.2016

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Applied physiology: Research that makes a difference
Sue C. Bodine
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RESEARCH ARTICLE | Aging and Exercise
Lower limb explosive strength capacity in elderly women: effects of resistance training and healthy diet
Peter Edholm, Emelie Strandberg, Fawzi Kadi
July 1, 2017 : 190-196
DOI: 10.1152/japplphysiol.00924.2016

Age-related decline in lower limb explosive strength leads to impaired ability to perform daily living tasks. The present randomized controlled trial demonstrates that a healthy diet rich in n-3 polyunsaturated fatty acid (n-3 PUFA) enhances resistance training-induced gains in dynamic explosive strength capacity during isolated lower limb movements and multijoint exercises in healthy elderly women. This supports the use of strategies combining resistance training and dietary changes to mitigate the decline in explosive strength capacity in older adults.

RESEARCH ARTICLES

Blood pressure and calf muscle oxygen extraction during plantar flexion exercise in peripheral artery disease
J. Carter Luck, Amanda J. Miller, Faisal Aziz, John F. Radtka III, David N. Proctor, Urs A. Leuenberger, Lawrence I. Sinoway, Matthew D. Muller
July 1, 2017 : 2-10
DOI: 10.1152/japplphysiol.01110.2016

In this laboratory study, patients with peripheral artery disease performed plantar flexion exercise in the supine posture until symptoms of claudication occurred. Relative to age- and sex-matched healthy subjects we found that patients had a higher blood pressure response, a higher heart rate response, and a greater reduction in skeletal muscle oxygenation as determined by near-infrared spectroscopy. Our data suggest that muscle ischemia contributes to the augmented exercise pressor reflex in peripheral artery disease.

Combined effect of Bacillus coagulans GBI-30, 6086 and HMB supplementation on muscle integrity and cytokine response during intense military training
Yftach Gepner, Jay R. Hoffman, Elad Shemesh, Jeffrey R. Stout, David D. Church, Alyssa N. Varanoske, Hila Zelicha, Ilan Shelef, Yacov Chen, Hagai Frankel, Ishay Ostfeld
β-Hydroxy-β-methylbutyrate (HMB) in its free acid form was reported to attenuate inflammation and maintain muscle integrity during military training. However, this formulation was difficult to maintain in the field. In this investigation, soldiers ingested HMB calcium (CaHMB) with Bacillus coagulans (BC30) or CaHMB alone during 40 days of training. Results indicated that CaHMB attenuated the inflammatory response and that BC30 combined with CaHMB may be more beneficial than CaHMB alone in maintaining muscle integrity during intense military training.

Voluntary upregulation of reflex cough is possible in healthy older adults and Parkinson’s disease
Alexandra E. Brandimore, Karen W. Hegland, Michael S. Okun, Paul W. Davenport, Michelle S. Troche
July 1, 2017 : 19-26
DOI: 10.1152/japplphysiol.00612.2016

Aspiration pneumonia is a leading cause of death in Parkinson’s disease (PD) and results from concurrent dysphagia and dystussia (cough dysfunction). This is the first study to demonstrate that people with PD and healthy age-matched controls can volitionally upregulate induced reflex and voluntary cough effectiveness when presented with novel cueing strategies. Thus targeting upregulation of cough effectiveness via biofeedback may be a viable way to enhance airway protection in people with PD.

Optical clearing: impact of optical and dielectric properties of clearing solutions on pulmonary tissue mechanics
David Schwenninger, Hans-Joachim Priebe, Matthias Schneider, Hanna Runck, Josef Guttmann
July 1, 2017 : 27-37
DOI: 10.1152/japplphysiol.00234.2016

Investigating optical clearing in porcine lung tissue strips, we found that refractive index and dielectric constant of the clearing solution affected tissue clearing and biomechanics. By documenting the impact of the composition of the clearing solution on clearing potency and preservation of tissue mechanics, our results help to compose optimal clearing solutions. In addition, the results allow conclusions on the molecular interaction of solvents with collagen fibers in tissue, thereby consolidating existing theories about the functionality of collagen.

Prosthetic model, but not stiffness or height, affects the metabolic cost of running for athletes with unilateral transtibial amputations
Owen N. Beck, Paolo Taboga, Alena M. Grabowski
July 1, 2017 : 38-48
DOI: 10.1152/japplphysiol.00896.2016

The metabolic cost of running for athletes with unilateral transtibial amputations depends on prosthetic model and is associated with lower peak and stance average vertical ground reaction forces, longer contact times, and reduced leg stiffness. Metabolic cost is unrelated to prosthetic stiffness, height, and stride kinematic symmetry. Unlike nonamputees who decrease leg stiffness with increased in-series surface stiffness, biological limb stiffness for athletes with unilateral transtibial amputations is positively correlated with increased in-series (prosthetic) stiffness.

Impaired popliteal artery flow-mediated dilation caused by reduced daily physical activity is prevented by increased shear stress
André L. Teixeira, Jaume Padilla, Lauro C. Vianna
July 1, 2017 : 49-54
DOI: 10.1152/japplphysiol.00001.2017

We found that the impairment in popliteal artery flow-mediated dilation caused by physical inactivity can be prevented by increased shear stress. These findings indicate that reduced leg blood flow-induced shear stress during physical inactivity may be a key underlying mechanism mediating the detrimental leg vascular effects of physical inactivity. Heating the foot area may be used as a nonpharmacological therapy to combat inactivity-induced leg vascular dysfunction, especially in people who are unable or unwilling to be active.

Low-frequency blood pressure oscillations and inotrope treatment failure in premature infants
Zachary A. Vesoulis, Jessica Hao, Christopher McPherson, Nathalie M. El Ters, Amit M. Mathur
July 1, 2017 : 55-61
DOI: 10.1152/japplphysiol.00205.2017

In this study, we examine patterns of low-frequency oscillations in blood pressure variability across regulatory components of vascular tone in normotensive and hypotensive infants exposed to inotropic medications. We found that hypotensive infants who require inotropes have decreased low-frequency variability at baseline, which increases after inotrope initiation. Low-frequency spectral power does not change for those with inotrope treatment failure, suggesting dysfunctional regulation of vascular tone as a potential mechanism of treatment failure.

Increased cerebral blood volume pulsatility during head-down tilt with elevated carbon dioxide: the SPACECOT Study
Gary E. Strangman, Quan Zhang, Karina Marshall-Goebel, Edwin Mulder, Brian Stevens, Jonathan B. Clark, Eric M. Bershad
July 1, 2017 : 62-70
Cerebral blood volume (CBV) pulsatility—as measured by near-infrared spectroscopy—increases over time during −12° head-down tilt at both cardiac and Mayer wave frequencies. CBV pulsatility appeared to increase more under elevated (0.5%) CO2 at Mayer wave frequencies in some individuals. If similar dynamic pulsatility increases occur in astronauts, there is the potential to initiate vascular and possibly other remodeling processes that lead to symptoms associated with sustained increases in intracranial pressure.

**Effect of acute physiological free fatty acid elevation in the context of hyperinsulinemia on fiber type-specific IMCL accumulation**
Lisa S. Chow, Douglas G. Mashek, Qi Wang, Sam O. Shepherd, Bret H. Goodpaster, John J. Dubé
July 1, 2017 : 71-78

This novel human study examined the effects of FFA elevation in the setting of hyperinsulinemia on accumulation of fat in specific types of muscle fibers. Within the context of the hyperinsulinemic-euglycemic clamp, we found that an increase of FFAs to a physiological range sufficient to reduce insulin sensitivity is associated with preferential IMCL accumulation in type 1 fibers.

**Evidence for age-dependent air-space enlargement contributing to loss of lung tissue elastic recoil pressure and increased shear modulus in older age**
K. Subramaniam, H. Kumar, M. H. Tawhai
July 1, 2017 : 79-87

We use a structure-based mechanics analysis to correlate air-space enlargement and redistribution of elastin and collagen to age-related changes in the mechanical behavior of lung parenchyma. Our study highlights that both the cause (redistribution of elastin and collagen) and the structural effect (alveolar air-space enlargement) contribute to decline in lung tissue elastic recoil with age; these results are consistent with published data and provide a new avenue for understanding the mechanics of the older lung.

**Muscle length-dependent contribution of motoneuron Cav1.3 channels to force production in model slow motor unit**
Hoejeng Kim
July 1, 2017 : 88-105

Cav1.3 channels in motoneuron dendrites are actively involved during normal motor activities. To investigate the effects of the activation of motoneuron Cav1.3 channels on force production, a model motor unit was built based on best-available data. The simulation results suggest that force potentiation induced by Cav1.3 channel activation is strongly modulated not only by firing history of the motoneuron but also by length variation of the muscle as well as neuromodulation inputs from the brainstem.

**Sympathetic nervous system activation reduces contraction-induced rapid vasodilation in the leg of humans independent of age**
William E. Hughes, Nicholas T. Kruse, Darren P. Casey
July 1, 2017 : 106-115

Aging is associated with attenuated contraction-induced rapid onset vasodilation (ROV). Within the forearm, this attenuation is partially due to enhanced sympathetic vasoconstriction. In the current study, we found that sympathetic vasoconstriction reduces contraction-induced ROV within the leg of both young and older adults, with the magnitude of change being similar between age groups. Our current results suggest that age-related attenuations in contraction-induced ROV within the leg are not fully explained by a sympathetic vasoconstrictor mechanism.

**Assessment of tongue mechanical properties using different contraction tasks**
Wen-Yang Li, Simon Gakwaya, Didier Saey, Frédéric Sériès
July 1, 2017 : 116-125

To our knowledge, this is the first study to assess and compare tongue function using both elevation and protrusion tasks with repetitive isometric fatiguing contractions in subjects with different OSA status. Tongue mechanical performance seemed to differ between protrusion and elevation tasks and depend on the severity of OSA.

**Raising the pressure: Hemodynamic effects of splanchnic nerve stimulation**
Marat Fudim, Suraj Yalamuri, J. Taylor Herbert, Peter R. Liu, Manesh R. Patel, Aaron Sandler
July 1, 2017 : 126-127

Our case series provides the first detailed description of human hemodynamic effects with splanchnic nerve stimulation. Splanchnic nerve stimulation results in profound hemodynamic alteration with rapid onset of hypertension and blood mobilization.
Sex differences in sympathetic vasoconstrictor responsiveness and sympatholysis
Timothy P. Just, Darren S. DeLorey
July 1, 2017: 128-135
DOI: 10.1152/japplphysiol.00139.2017

Sex differences in the neurovascular regulation of blood pressure and vascular resistance have been documented. However, our understanding of the underlying mechanisms that mediate these differences is incomplete. The present study demonstrates that female rats have an enhanced capacity to inhibit sympathetic vasoconstriction during exercise (sympatholysis) and that NO mediates a portion of the enhanced sympatholysis.

Measurement of the distribution of ventilation-perfusion ratios in the human lung with proton MRI: comparison with the multiple inert-gas elimination technique
July 1, 2017: 136-146
DOI: 10.1152/japplphysiol.00804.2016

We report a comparison of a new proton MRI technique to measure regional VA/Q ratio against the multiple inert gas elimination technique (MIGET). The study reports good relationships between measures of heterogeneity derived from MIGET and those derived from MRI. Although currently limited to a single slice acquisition, these data suggest that single sagittal slice measures of VA/Q ratio provide an adequate means to assess heterogeneity in the normal lung.

Mild aerobic exercise blocks elastin fiber fragmentation and aortic dilatation in a mouse model of Marfan syndrome associated aortic aneurysm
Christine Gibson, Cory Nielsen, Ramona Alex, Kimbal Cooper, Michael Farney, Douglas Gaufin, Jason Z. Cui, Cornelis van Breemen, Tom L. Broderick, Johana Vallejo-Elias, Mitra Esfandiarei
July 1, 2017: 147-160
DOI: 10.1152/japplphysiol.00132.2017

The present study provides conclusive scientific evidence that daily exercise can improve aortic health in a mouse model of Marfan syndrome associated aortic aneurysm, and it establishes the threshold for the exercise intensity beyond which exercise may not be as protective. These findings establish a platform for a new focus on promoting regular exercise in Marfan patients at an optimum intensity and create a paradigm shift in clinical care of Marfan patients suffering from aortic aneurysm complications.

The effects of physical exercise on nonmotor symptoms and on neuroimmune RAGE network in experimental parkinsonism
July 1, 2017: 161-171
DOI: 10.1152/japplphysiol.01120.2016

This study newly shows that physical exercise (PE) corrects nonmotor symptoms of the intranasal 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of experimental parkinsonism. Additionally, we show that suppression of neuroimmune receptor for advanced glycation end products (RAGE) network occurs in frontal cortex on chemical (MPTP) and physical (PE) interventions. Finally, PE normalizes frontal cortical RAGE transcriptomics and upregulates the neuroprotective DJ-1 gene in the intranasal MPTP model of experimental parkinsonism.

Progression and variability of physiologic deterioration in an ovine model of lung infection sepsis
Farid Yaghouby, Chathuri Daluwatte, Satoshi Fukuda, Christina Nelson, John Salsbury, Michael Kinsky, George C. Kramer, David G. Strauss, Perenlei Enkhbaatar, Christopher G. Scully
July 1, 2017: 172-181
DOI: 10.1152/japplphysiol.00122.2017

Variable pulmonary response to injury results in varying outcomes in a previously reported animal model of lung injury and methicillin-resistant Staphylococcus aureus-induced sepsis. Heart rate and blood pressure variability analyses were investigated to track the varying levels of physiologic deterioration but did not discriminate early nonsurvivors from survivors.

Evidence for β-adrenergic modulation of sweating during incremental exercise in habitually trained males
Tatsuro Amano, Yosuke Shitara, Naoto Fujii, Yoshimitsu Inoue, Narihiko Kondo
July 1, 2017: 182-189
DOI: 10.1152/japplphysiol.00220.2017

We demonstrated for the first time that the β-adrenergic mechanism does modulate sweating (i.e., β-adrenergic sweating) during exercise using a localized β-adrenoceptor blockade in humans in vivo. β-Adrenergic sweating was evident in habitually trained individuals during exercise at a submaximal high relative intensity (80–90% maximal work). This observation advances our understanding of human thermoregulation during exercise and of the mechanism that underlies sweat gland adaptation to habitual exercise training.
Effect of cyclooxygenase inhibition on the inspiratory muscle metaboreflex-induced cardiovascular consequences in men
Joshua R. Smith, Kaylin D. Didier, Shane M. Hammer, Andrew M. Alexander, Stephanie P. Kurti, Steven W. Copp, Thomas J. Barstow, Craig A. Harms
July 1, 2017 : 197-204
DOI: 10.1152/japplphysiol.00165.2017

Cyclooxygenase (COX) products play a role in activating the muscle metaboreflex. It is not known whether COX products contribute to the inspiratory muscle metaboreflex. Herein, we demonstrate that COX inhibition led to greater increases in blood pressure and limb vascular resistance compared with placebo during inspiratory muscle metaboreflex activation.

Experimental dyspnea as a stressor: differential cardiovegetative responses to inspiratory threshold loading in healthy men and women
Marie-Cécile Niérat, Louis Laviolette, Anna Hudson, Thomas Similowski, Caroline Sévoz-Couche
July 1, 2017 : 205-212
DOI: 10.1152/japplphysiol.00078.2017

Breathing against the ITL induced autonomic modifications driven by sympathetic mediated responses in men, whereas women showed a greater parasympathetic modulation of cardiovascular activity, even for low load. A stress circuit could be at the origin of autonomic modifications induced by ITL. Our results would underline the role of the mechanic inspiratory load in the abnormalities in heart rate variability seen in COPD patients.

Dispelling the myth that habitual caffeine consumption influences the performance response to acute caffeine supplementation
Lívia de Souza Gonçalves, Vitor de Salles Painelli, Guilherme Yamaguchi, Luana Farias de Oliveira, Bryan Saunders, Rafael Pires da Silva, Erika Maciel, Guilherme Giannini Artioli, Hamilton Roschel, Bruno Gualano
July 1, 2017 : 213-220
DOI: 10.1152/japplphysiol.00260.2017

There has been a long-standing paradigm that habitual caffeine intake may influence the ergogenicity of caffeine supplementation. Low, moderate, and high caffeine consumers showed similar absolute and relative improvements in cycling time-trial performance following acute supplementation of 6 mg/kg body mass caffeine. Performance effects of acute caffeine were not influenced by the level of habitual caffeine consumption, suggesting that high habitual caffeine intake does not negate the benefits of acute caffeine supplementation.

Biomechanical impact of provisional stenting and balloon dilatation on coronary bifurcation: clinical implications
Henry Y. Chen, Khalid Al-Saadon, Yves Louvard, Ghassan S. Kassab
July 1, 2017 : 221-226
DOI: 10.1152/japplphysiol.00245.2017

Although the role of wall shear stress (WSS) has been well investigated, the role of circumferential wall stresses (CWS) has not been well studied in provisional stenting with and without final kissing balloon. Both fluid and solids mechanics need to be evaluated when considering various stenting techniques at bifurcations. An integrative index of bifurcation mechanics is the stress ratio that considers both CWS and WSS.

Data collection, handling, and fitting strategies to optimize accuracy and precision of oxygen uptake kinetics estimation from breath-by-breath measurements
Alan P. Benson, T. Scott Bowen, Carrie Ferguson, Scott R. Murgatroyd, Harry B. Rossiter
July 1, 2017 : 227-242
DOI: 10.1152/japplphysiol.00988.2016

We identified an unbiased method to maximize accuracy and precision of oxygen uptake kinetics (τVo2P) estimation. The optimum number of bouts to average was four; interpolation, bin, and stacking averaging methods gave similar results. Contradictory to previous advice, we found that optimal fitting procedures removed no more than 20 s of phase 1 data. Our data suggest a minimally important difference of ~5 s to determine significant changes in τVo2P during interventional and comparative studies.

Exercise training and metformin, but not exercise training alone, decreases insulin production and increases insulin clearance in adults with prediabetes
Richard Viskochil, Steven K. Malin, Jennifer M. Blankenship, Barry Braun
July 1, 2017 : 243-248
DOI: 10.1152/japplphysiol.00790.2016

Exercise is increasingly viewed as medication, creating a need to understand its interactions with other common medications. Research suggests metformin, a widely prescribed diabetes medication, may diminish the benefits of exercise when used in combination. In this study, however, metformin combined with exercise training, but not exercise alone, lowered proinsulin concentrations and increased insulin clearance in adults with prediabetes. This may directly influence personalized prescriptions of lifestyle and/or pharmacology to reduce diabetes risk.

Obesity-induced discrepancy between contractile and metabolic phenotypes in slow- and fast-twitch skeletal muscles of female obese Zucker rats
This study demonstrates a discrepancy between morphological (reduced muscle mass), contractile (shift toward a faster phenotype), and metabolic (increased mitochondrial oxidative enzyme activity) characteristics in skeletal muscles of female Zucker fatty rats. It is noteworthy that this inconsistency was comparable (in nature and extent) in muscles with different structure and function.

Lower-body negative pressure decreases noninvasively measured intracranial pressure and internal jugular vein cross-sectional area during head-down tilt

The current study provides new evidence that 25 or 50 mmHg of lower-body negative pressure reduces jugular venous pooling and intracranial pressure during simulated microgravity. Therefore, spaceflight countermeasures that sequester fluid to the lower body may mitigate cephalic venous congestion and vision impairment.

Impaired maximal fat oxidation has been linked to obesity and weight regain after weight loss. Noteworthy, maximal fat oxidation was equally high after clinical weight loss maintenance and weight regain compared with moderate weight loss. A high maximal fat oxidation after clinical weight loss maintenance was related to higher maximal oxygen uptake, content of key proteins involved in transport of lipids across the plasma membrane and β-oxidation. In contrast, a high maximal fat oxidation after weight regain was related to higher availability of lipids, i.e., general adiposity and plasma concentration of triglycerides.

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Neural mechanisms of oculomotor abnormalities in the infantile strabismus syndrome
Mark M. G. Walton, Adam Pallus, Jérome Fleuriet, Michael J. Mustari, Kristina Tarczy-Hornoch
July 1, 2017 : 280-299
DOI: 10.1152/jn.00934.2016

REVIEW | Spinal Control of Motor Outputs
The potential for understanding the synaptic organization of human motor commands via the firing patterns of motoneurons
Michael D. Johnson, Christopher K. Thompson, Vicki M. Tysseling, Randall K. Powers, Charles J. Heckman
July 1, 2017 : 520-531
DOI: 10.1152/jn.00018.2017

RESEARCH ARTICLE | Biology of Neuroengineering Interfaces
Functional remodeling of subtype-specific markers surrounding implanted neuroprostheses
Joseph W. Salatino, Bailey M. Winter, Matthew H. Drazin, Erin K. Purcell
July 1, 2017 : 194-202
DOI: 10.1152/jn.00162.2017

We report novel changes in the local expression of excitatory and inhibitory synaptic markers surrounding microelectrode arrays implanted in the motor cortex of rats, where a progressive shift toward increased inhibitory tone was observed over the 4-wk observation period. The result was driven by declining glutamate transporter expression (VGLUT1) in parallel with increasing GABA transporter expression (VGAT) over time, where a reactive VGAT+ astroglial subtype made an unexpected contribution to our findings.

RESEARCH ARTICLES | Cellular and Molecular Properties of Neurons
PICs in motoneurons do not scale with the size of the animal: a possible mechanism for faster speed of muscle contraction in smaller species
Seoan Huh, Ramamurthy Siripuram, Robert H. Lee, Vladimir V. Turkin, Derek O’Neill, Thomas M. Hamm, Charles J. Heckman, Marin Manuel
July 1, 2017 : 93-102
DOI: 10.1152/jn.00045.2017

The small size of the mouse warrants concern over whether the properties of their neurons are a scaled version of those in larger animals or instead have unique features. Comparison of spinal motoneurons in mice to cats showed unique features. Firing rates in the mouse were much higher, in large part due to relatively larger persistent inward currents. These differences likely reflect adaptations for controlling much faster muscle fibers in mouse than cat.

Glycolytic inhibition by 2-deoxy-d-glucose abolishes both neuronal and network bursts in an in vitro seizure model
Li-Rong Shao, Carl E. Stafstrom
July 1, 2017 : 103-113
DOI: 10.1152/jn.00100.2017

Neuronal activity is highly energy demanding and coupled to cellular metabolism. In this study, we demonstrate that glycolytic inhibition with 2-deoxy-d-glucose (2-DG) effectively suppresses spontaneous neuronal firing and epileptiform bursts in hippocampal slices. These data suggest that an altered metabolic state can profoundly affect cellular and network excitability, and that the glycolytic inhibitor 2-DG may hold promise as a novel treatment of drug-resistant epilepsy.

Contributions of space-clamp errors to apparent time-dependent loss of Mg2+ block induced by NMDA
Min-Yu Sun, Mariangela Chisari, Lawrence N. Eisenman, Charles F. Zorumski, Steven J. Mennerick
July 1, 2017 : 532-543
DOI: 10.1152/jn.00106.2017

We report that upon sustained activation of NMDARs in juvenile mouse hippocampal neurons there is apparent loss of Mg2+ block at negative membrane potentials. However, the phenomenon is explained by loss of dendritic voltage clamp, leading to a linear current-voltage relationship. Our results give a specific example of how spatial voltage errors in voltage-clamp recordings can readily be misinterpreted as biological modulation.

Activation mechanism of a neuromodulator-gated pacemaker ionic current
Michael Gray, Daniel H. Daudelin, Jorge Golowasch
July 1, 2017 : 595-609
DOI: 10.1152/jn.00743.2016
Neuronal rhythmic activity is generated by either network-based or cell-autonomous mechanisms. In the pyloric network of decapod crustaceans, the activation of a neuromodulator-gated pacemaker current is crucial for the generation of rhythmic activity. This current is activated by several neuromodulators, including peptides and acetylcholine, presumably via metabotropic receptors. We have previously demonstrated a novel extracellular calcium-sensitive voltage-dependence mechanism of this current. We presently report that the activation mechanism depends on intracellular and extracellular calcium-sensitive components.

Neuropeptide-Y (NPY) has been shown to act on mesolimbic dopamine circuits to increase motivated behaviors toward food, but it is unclear exactly how NPY causes these responses. Here, we demonstrate that NPY directly inhibited a subset of ventral tegmental area (VTA) dopamine neurons through the activation of G protein-coupled inwardly rectifying potassium currents, and it inhibited both excitatory postsynaptic currents and inhibitory postsynaptic currents onto subsets of dopamine neurons through a presynaptic mechanism. Thus NPY uses multiple mechanisms to dynamically control VTA dopamine neuron activity.

In this study, we are separating different kinds of possible contributors to an electroencephalogram (EEG) error correlate (Ne/ERN) in a throwing task. We tested the influence of action effect monitoring on the Ne/ERN amplitude in the EEG. We used a task that allows us to restrict movement correction and action effect monitoring and to control the onset of result feedback. We ascribe the Ne/ERN to predictive error processing where a conscious feeling of failure is not a prerequisite.

While the orderly representation of major body parts along the precentral gyrus has been known for decades, questions have been raised about the possible existence of additional more detailed aspects of somatotopy. In this study, we have investigated this question with respect to muscles of the arm and show consistent features of within-arm (intra-areal) somatotopic organization. For the first time we also show maps of how inhibitory output from motor cortex is organized.

Complementing a large body of prior work showing advantages of composing primitives to manage the complexity of motor control, this paper uncovers a limitation due to composition of behavior from dynamic primitives: while slower execution frequently makes a task easier, there is a limit and it is hard for humans to move very slowly. We suggest that this remarkable limitation is not due to inadequacies of muscle, nor to slow neural communication, but is a consequence of how the control of movement is organized.

Correcting limb movements for external perturbations is a hallmark of flexible sensorimotor behavior. While visual and mechanical perturbations are corrected in a task-dependent manner, it is unclear whether a vestibular perturbation, naturally arising when the body moves, is selectively processed in reach control. We show, using galvanic vestibular stimulation, that reach corrections to vestibular perturbations are task dependent, consistent with a prediction of optimal feedback control theory.
The modulation of two motor behaviors by persistent sodium currents in Xenopus laevis tadpoles
Erik Svensson, Hugo Jeffreys, Wen-Chang Li
July 1, 2017 : 121-130
DOI: 10.1152/jn.00755.2016

We have characterized persistent sodium currents in three groups of spinal neurons and their role in shaping spiking activity in the Xenopus tadpole. We then attempted to evaluate the role of persistent sodium currents in regulating tadpole swimming and struggling motor outputs by using low concentrations of the persistent sodium current antagonist riluzole.

Developmental profile of motor cortex transcallosal inhibition in children and adolescents
Patrick Ciechanski, Ephrem Zewdie, Adam Kirton
July 1, 2017 : 140-148
DOI: 10.1152/jn.00076.2017

Here we demonstrate that transcranial magnetic stimulation can characterize transcallosal inhibition in normal children and adolescents with effects of age, directionality, handedness, and motor performance. Interestingly, we also demonstrated sex effects, possibly related to the differing developmental profiles of boys and girls. Establishing this developmental profile of interhemispheric interactions may advance understanding and therapeutic strategies for pediatric motor disorders such as cerebral palsy.

Dynamical signatures of isometric force control as a function of age, expertise, and task constraints
Solveig Vieluf, Rita Sleimen-Malkoun, Claudia Voelcker-Rehage, Viktor Jirsa, Eva-Maria Reuter, Ben Godde, Jean-Jacques Temprado, Raoul Huys
July 1, 2017 : 176-186
DOI: 10.1152/jn.00691.2016

Stochastic and deterministic dynamical components contribute to force production. Dynamical signatures differ between force maintenance and cyclic force modulation tasks but hardly between age and expertise groups. Differences in both stochastic and deterministic components are associated with group differences in behavioral variability, and observed behavioral variability is more strongly task dependent than person dependent.

Transfer of dynamic motor skills acquired during isometric training to free motion
Alejandro Melendez-Calderon, Michael Tan, Moria Fisher Bittmann, Etienne Burdet, James L. Patton
July 1, 2017 : 219-233
DOI: 10.1152/jn.00614.2016

This study provided early evidence supporting that training movement skills without moving is possible. In contrast to previous studies, our study involves 1) exploiting cross-modal sensory interactions between vision and proprioception in a motionless setting to teach motor skills that could be transferable to a corresponding physical task, and 2) evaluates the movement skill of controlling muscle-generated forces to execute arm movements in the presence of external forces that were only virtually present during training.

Multisensory components of rapid motor responses to fingertip loading
F. Crevecoeur, A. Barrea, X. Libouton, J.-L. Thonnard, P. Lefèvre
July 1, 2017 : 331-343
DOI: 10.1152/jn.00091.2017

To grasp and manipulate objects, the brain uses touch signals related to skin deformation as well as sensory information about motion of the fingers encoded in muscle spindles. Here we investigated how these two sensory systems contribute to feedback responses to perturbation applied to the fingertip. We found distinct response components, suggesting that each sensory system engages separate sensorimotor circuits with distinct functions and latencies.

Increased neuromuscular consistency in gait and balance after partnered, dance-based rehabilitation in Parkinson’s disease
Jessica L. Allen, J. Lucas McKay, Andrew Sawers, Madeleine E. Hackney, Lena H. Ting
July 1, 2017 : 363-373
DOI: 10.1152/jn.00813.2016

We demonstrate changes in neuromuscular control of gait and balance in individuals with Parkinson’s disease after short-term, dance-based rehabilitation. Our work is the first to show that motor module distinctness, consistency, and generalizability across gait and balance are more sensitive than motor module number to improvements in motor performance following short-term rehabilitation. Our results indicate commonalities in muscle coordination improvements associated with motor skill reacquisition due to rehabilitation and motor skill acquisition in healthy individuals.

Implications of plan-based generalization in sensorimotor adaptation
The pattern of generalization is thought to reveal how the motor system represents learned actions. Recent work has made the intriguing suggestion that maximum generalization in sensorimotor adaptation tasks occurs at the location of the learned movement plan. Here we support this interpretation, develop a novel model of motor adaptation that incorporates plan-based generalization, and use the model to successfully predict surprising dynamics in the time course of adaptation across several conditions.

GABA and primary motor cortex inhibition in young and older adults: a multimodal reliability study
Ronan A. Mooney, John Cirillo, Winston D. Byblow
July 1, 2017 : 425-433
DOI: 10.1152/jn.00199.2017

γ-Aminobutyric acid (GABA) in primary motor cortex was assessed in young and older adults using magnetic resonance spectroscopy and threshold-tracking paired-pulse transcranial magnetic stimulation. Older adults exhibited reduced extrasynaptic inhibition (short-interval intracortical inhibition at 1 ms) compared with young, whereas GABA concentration and synaptic inhibition were similar between age groups. We demonstrate that magnetic resonance spectroscopy and threshold-tracking provide valid and reliable assessments of primary motor cortex GABA concentration and neurotransmission, respectively.

Muscle synergies obtained from comprehensive mapping of the primary motor cortex forelimb representation using high-frequency, long-duration ICMS
Sommer L. Amundsen Huffmaster, Gustaf M. Van Acker III, Carl W. Luchies, Paul D. Cheney
July 1, 2017 : 455-470
DOI: 10.1152/jn.00784.2016

While muscle synergies have been investigated in various muscle activity sets, it is unclear whether and how synergies may be organized in the cortex. We have investigated muscle synergies resulting from high-frequency, long-duration intracortical microstimulation (HFLD-ICMS) applied throughout M1. We compared HFLD-ICMS synergies to synergies from voluntary movement. While synergies can be identified from M1 stimulation, they are not clearly related to voluntary movement synergies and do not show an orderly topographic organization across M1.

Modulation of long-latency afferent inhibition by the amplitude of sensory afferent volley
Claudia V. Turco, Jenin El-Sayes, Hunter J. Fassett, Robert Chen, Aimee J. Nelson
July 1, 2017 : 610-618
DOI: 10.1152/jn.00118.2017

This is the first investigation of the relationship between long-latency afferent inhibition (LAI) and the sensory afferent volley. Differences exist between median and digital nerve LAI. For the median nerve, LAI increases until all sensory fibers are presumably recruited. In contrast, digital nerve LAI does not increase with the recruitment of additional sensory fibers but rather is present when a given volume of sensory afferent fibers is recruited (~50% of maximum sensory nerve action potential). This novel data provide practical guidelines and contribute to our understanding of the mechanisms underlying LAI.

Density of available striatal dopamine receptors predicts trait impulsiveness during performance of an attention-demanding task
Brian A. Anderson, Hiroto Kuwabara, Dean F. Wong, Susan M. Courtney
July 1, 2017 : 64-68
DOI: 10.1152/jn.00125.2017

Several studies have demonstrated a relationship between the density of available striatal D2/D3 receptors and trait impulsiveness. However, in each case, the availability of dopamine receptors was measured during the resting state. This complicates interpretation of previously observed correlations, which could be influenced by either stable variation in receptor density or context-dependent dopamine release. We present evidence uniquely consistent with the former interpretation, providing clarity to the nature of this brain-behavior relationship.

Spatial attention during saccade decisions
Donatas Jonikaitis, Anna Klapetek, Heiner Deubel
July 1, 2017 : 149-160
DOI: 10.1152/jn.00665.2016

We show that saccadic decisions can be tracked by measuring spatial attention. Spatial attention is allocated in parallel to the two competing saccade targets, and the time course of spatial attention differs for fast-slow and for correct-erroneous decisions. Saccade decisions take the form of a competition between potential saccade goals, which is associated with spatial attention allocation to those locations.
Entrainment of visual steady-state responses is modulated by global spatial statistics
Thomas Nguyen, Karl Kuntzelman, Vladimir Miskovic
July 1, 2017 : 344-352
DOI: 10.1152/jn.00129.2017

Rhythmically modulated visual stimuli entrain the activity of neuronal populations, but the effect of global stimulus statistics on this entrainment is unknown. We assessed entrainment evoked by 1) visual noise ensembles with different spectral slopes, 2) complex natural scenes, and 3) narrowband sinusoidal gratings. Entrainment was most effective for broadband noise with naturalistic luminance contrast. This reveals some global properties shaping stimulus-driven brain oscillations in the human visual system.

Time compression of visual perception around microsaccades
Gongchen Yu, Mingpo Yang, Peng Yu, Michael Christopher Dorris
July 1, 2017 : 416-424
DOI: 10.1152/jn.00029.2017

Here we show that humans perceive the duration of visual events as compressed if they are accompanied by microsaccades. Despite the tiny and transient nature of microsaccades, time compression extended more than ±200 ms from their occurrence. Moreover, the number, pattern, and temporal coincidence of microsaccades relative to visual events all contribute to this time misperception. Our results reveal a detailed picture of how our visual time percepts are altered by microsaccades.

RESEARCH ARTICLES | Nervous System Pathophysiology

Impaired sweating responses to a passive whole body heat stress in individuals with multiple sclerosis
Dustin R. Allen, Mu Huang, Iqra M. Parupia, Ariana R. Dubelko, Elliot M. Frohman, Scott L. Davis
July 1, 2017 : 7-14
DOI: 10.1152/jn.00897.2016

This study is the first to assess the reflex control of the thermoregulatory system in individuals living with multiple sclerosis (MS). The novel findings are twofold. First, attenuated increases in sweat rate in subjects with MS compared with healthy controls were observed in response to a moderate increase (0.8°C) in core temperature via passive whole body heat stress. Second, it appears the reflex control of the cutaneous vasculature is preserved in MS.

Loss and recovery of functional connectivity in cultured cortical networks exposed to hypoxia
Joost le Feber, Niels Erkamp, Michel J. A. M. van Putten, Jeannette Hofmeijer
July 1, 2017 : 394-403
DOI: 10.1152/jn.00098.2017

Hypoxia reduced the firing rates of cultured neurons. Depending on hypoxic depth and duration, activity recovered during hypoxia and upon return to normoxia. Recovery (partial) during hypoxia was associated with restored baseline connections rather than newly formed ones. Predominantly, baseline connections with most active postsynaptic electrodes recovered, supporting the notion of effective activity homeostasis. This compensatory mechanism remained effective during ~20 h of hypoxia. Beyond 20 h of compensation, loss of activity and connectivity became irreversible.

Cell type-specific changes in retinal ganglion cell function induced by rod death and cone reorganization in rats
Wan-Qing Yu, Norberto M. Grzywacz, Eun-Jin Lee, Greg D. Field
July 1, 2017 : 434-454
DOI: 10.1152/jn.00826.2016

This study provides novel and therapeutically relevant insights to retinal function following rod death but before cone death. To determine changes in retinal output, we used a large-scale multielectrode array to simultaneously record from hundreds of retinal ganglion cells (RGCs). These recordings of large-scale neural activity revealed that following the death of all rods, functionally distinct RGCs remain. However, the receptive field properties and spontaneous activity of these RGCs are altered in a cell type-specific manner.

RESEARCH ARTICLES | Neural Circuits

Population activity statistics dissect subthreshold and spiking variability in V1
Mihály Bányaí, Zsombor Koman, Gergő Orbán
July 1, 2017 : 29-46
DOI: 10.1152/jn.00931.2016

Neural variability and covariability are puzzling aspects of cortical computations. For efficient decoding and prediction, models of information encoding in neural populations hinge on an appropriate model of variability. Our work shows that stimulus-dependent changes in pairwise but not in
single-cell statistics can differentiate between two widely used models of neuronal variability. Contrasting model predictions with neuronal data provides hints on the noise sources in spiking and provides constraints on statistical models of population activity.

Recreational concentrations of alcohol enhance synaptic inhibition of cerebellar unipolar brush cells via pre- and postsynaptic mechanisms
Ben D. Richardson, David J. Rossi
July 1, 2017 : 267-279
DOI: 10.1152/jn.00963.2016

Genetic variability in cerebellar alcohol/ethanol sensitivity (ethanol-induced ataxia) predicts ethanol consumption phenotype in rodents and humans, but the cellular and molecular mechanisms underlying genetic differences are largely unknown. Here it is demonstrated that recreational concentrations of alcohol (10–30 mM) enhance glycinergic and GABAergic inhibition of unipolar brush cells through increases in glycine/GABA release and postsynaptic enhancement of glycine receptor-mediated responses. Ethanol effects varied across rodent genotypes parallel to ethanol consumption and motor sensitivity phenotype.

Temporal integration and 1/f power scaling in a circuit model of cerebellar interneurons
Reinoud Maex, Boris Gutkin
July 1, 2017 : 471-485
DOI: 10.1152/jn.00789.2016

The most common function attributed to inhibitory interneurons is feedforward control of principal neurons. In many brain regions, however, the interneurons are densely interconnected via both chemical and electrical synapses but the function of this coupling is largely unknown. Based on large-scale simulations of an interneuron circuit of cerebellar cortex, we propose that this coupling enhances the integration time constant, and hence the memory trace, of the circuit.

Presynaptic and extrasynaptic regulation of posterior nucleus of thalamus
Anthony Park, Ying Li, Rady Masri, Asaf Keller
July 1, 2017 : 507-519
DOI: 10.1152/jn.00862.2016

The posterior nucleus of thalamus (PO) is a key sensorimotor structure, whose activity is tightly regulated by inhibition from several nuclei. Maladaptive plasticity in this inhibition leads to severe pathologies, including chronic pain. We reveal here, for the first time in PO, multiple regulatory mechanisms that modulate synaptic transmission within PO. These findings may lead to targeted therapies for chronic pain and other disorders.

Magnitude and behavior of cross-talk effects in multichannel electrophysiology experiments
Matthew J. Nelson, Silvana Valcheva, Laurent Venance
July 1, 2017 : 574-594
DOI: 10.1152/jn.00877.2016

We develop and experimentally verify an electrical circuit model describing cross-talk that necessarily occurs between two channels. Recorded cross-talk increased with electrode impedance and signal frequency. We recorded cross-talk contamination of spike waveforms from intracellular to extracellular channels. We simulated high-density multichannel extracellular recordings and demonstrate spatial smoothing and phase shifts that cross-talk enacts on CSD measurements. However, when channels record similar-magnitude signals, effects are modest and unlikely to affect most conclusions.

RESEARCH ARTICLES | Sensory Processing

Visual and presaccadic activity in area 8Ar of the macaque monkey lateral prefrontal cortex
Kelly R. Bullock, Florian Pieper, Adam J. Sachs, Julio C. Martinez-Trujillo
July 1, 2017 : 15-28
DOI: 10.1152/jn.00278.2016

We recorded the responses of neurons in lateral prefrontal area 8Ar of macaques during a visually guided saccade task using multielectrode arrays. Neurons have Gaussian-shaped visual and movement fields in both visual hemifields, with a bias toward the contralateral hemifield. Visual neurons show contrast response functions with sigmoid shapes. Visual neurons tend to cluster at similar locations within the cortical surface; however, this organization does not appear retinotopic.

Afferent motor feedback determines the perceived location of tactile stimuli in the external space presented to the moving arm
Femke Maij, Alan M. Wing, W. Pieter Medendorp
July 1, 2017 : 187-193
DOI: 10.1152/jn.00286.2016
We show that proprioceptive feedback of arm motion rather than efferent motor signals contributes to tactile localization during an arm movement. Data further show that localization errors depend on arm velocity, not displacement per se, suggesting that instantaneous velocity feedback plays a role in the underlying computations. Model simulation using Bayesian inference suggests that these errors depend not only on spatial but also on temporal uncertainties of sensory and motor signals.

**Dynamic population codes of multiplexed stimulus features in primate area MT**
Erin Goddard, Samuel G. Solomon, Thomas A. Carlson
July 1, 2017 : 203-218

DOI: 10.1152/jn.00954.2016

Simultaneous multielectrode recordings can measure population-level codes that previously were only inferred from single-electrode recordings. However, many multielectrode recordings are analyzed using univariate single-electrode analysis approaches, which fail to fully utilize the population-level information. Here, we overcome these limitations by applying multivariate pattern classification analysis and representational similarity analysis to large-scale recordings from middle-temporal area (MT) in marmoset monkeys. Our analyses reveal a dynamic interplay of feature representations in area MT population response.

**Musculoskeletal geometry accounts for apparent extrinsic representation of paw position in dorsal spinocerebellar tract**
Raeed H. Chowdhury, Matthew C. Tresch, Lee E. Miller
July 1, 2017 : 234-242

DOI: 10.1152/jn.00695.2016

A classic experiment concluding that many dorsal spinocerebellar tract neurons encode paw position rather than joint angles has been cited by many studies as evidence for high-level computation occurring within a single synapse of the sensors. However, our study provides evidence that such a computation is not required to explain the results. Using simulation, we replicated many of the original results with purely random connectivity, suggesting that a reinterpretation of the classic experiment is needed.

**Frequency tagging to track the neural processing of contrast in fast, continuous sound sequences**
Sylvie Nozaradan, André Mouraux, Marion Cousineau
July 1, 2017 : 243-253

DOI: 10.1152/jn.00971.2016

Recent theories suggest that the basis of neurodevelopmental auditory disorders such as dyslexia might be an impaired processing of fast auditory changes, highlighting how the encoding of rapid acoustic information is critical for auditory communication. Here, we present a novel electrophysiological approach to capture in humans neural markers of contrasts in fast continuous tone sequences. Contrast-specific responses were successfully identified, even for very fine contrasts, providing direct insight on the encoding of rapid auditory information.

**Human primary somatosensory cortex is differentially involved in vibrotaction and nociception**
Cédric Lenoir, Gan Huang, Yves Vandermeeren, Samar Marie Hatem, André Mouraux
July 1, 2017 : 317-330

DOI: 10.1152/jn.00615.2016

Whereas the role of the primary somatosensory cortex (S1) in vibrotaction is well established, its involvement in nociception remains strongly debated. By assessing, in healthy volunteers, the effect of high-definition transcranial direct current stimulation over S1, we demonstrate a differential involvement of S1 in vibrotaction and nociception.

**Effect of silhouetting and inversion on view invariance in the monkey inferotemporal cortex**
N. Aparva Ratan Murty, S. P. Arun
July 1, 2017 : 353-362

DOI: 10.1152/jn.00008.2017

We easily recognize objects across changes in viewpoint, but the underlying features are unknown. Here, we show that view invariance in monkey inferotemporal cortex is driven mainly by external object contours and is not specialized for object orientation. We also find that the responses to natural objects match with that of their silhouettes early in the response, and with inverted versions later in the response—indicative of a coarse-to-fine processing sequence in the brain.

**Prediction suppression and surprise enhancement in monkey inferotemporal cortex**
Suchitra Ramachandran, Travis Meyer, Carl R. Olson
July 1, 2017 : 374-382

DOI: 10.1152/jn.00136.2017

In predictive coding models of the visual system, neurons carry signed prediction error signals. We show here that monkey inferotemporal neurons exhibit prediction-modulated firing, as posited by these models, but that the signal is unsigned. The response to a prediction-confirming image is
suppressed, and the response to a prediction-violating image may be enhanced. These results are better explained by a model in which the visual system emphasizes unpredicted events than by a predictive coding model.

**Context effects on smooth pursuit and manual interception of a disappearing target**
Philipp Kreyenmeier, Jolande Fooken, Miriam Spering
July 1, 2017: 404-415
DOI: 10.1152/jn.00217.2017

In a novel track-intercept paradigm, human observers tracked a briefly shown object moving across a textured, dynamic context and intercepted it with their finger after it had disappeared. Context motion significantly affected eye and hand movement latency and speed, but not interception accuracy; eye and hand position at interception were correlated on a trial-by-trial basis. Visual context effects may be short-lasting, affecting movement trajectories more than movement end points.

**Neural coding of time-varying interaural time differences and time-varying amplitude in the inferior colliculus**
Nathaniel Zuk, Bertrand Delgutte
July 1, 2017: 544-563
DOI: 10.1152/jn.00797.2016

Humans use time-varying binaural cues to parse auditory scenes comprising multiple sound sources and reverberation. However, the neural mechanisms for doing so are poorly understood. Our results demonstrate a potential neural correlate for the reduced detectability of fluctuations in time-varying binaural information at high speeds, as occurs in reverberation. The results also suggest that the neural mechanisms for processing time-varying binaural and monaural cues are largely distinct.

**Characterizing the effects of feature salience and top-down attention in the early visual system**
Sonia Poltoratski, Sam Ling, Devin McCormack, Frank Tong
July 1, 2017: 564-573
DOI: 10.1152/jn.00924.2016

While spatial attention allows for specific, goal-driven enhancement of stimuli, salient items outside of the current focus of attention must also be prioritized. We used 7T fMRI to compare salience and spatial attentional enhancement along the early visual hierarchy. We report additive effects of attention and bottom-up salience in early visual areas, suggesting that salience enhancement is not contingent on the observer’s attentional state.

**Cl⁻ channel is required for CXCL10-induced neuronal activation and itch response in a murine model of allergic contact dermatitis**
Lintao Qu, Kai Fu, Steven G. Shimada, Robert H. LaMotte
July 1, 2017: 619-624
DOI: 10.1152/jn.00187.2017

The ionic mechanisms underlying CXCL10-induced neuronal activation and allergic itch are largely unexplored. This study revealed that CXCL10 evoked an ionic current mainly carried by Cl⁻ channels. We suggest that Cl⁻ channels are likely key molecular candidates responsible for the CXCL10-evoked neuronal activation and itch-like behaviors in a murine model of allergic contact dermatitis induced by the antigen squaric acid dibutylester. Cl⁻ channels may emerge as a promising drug target for the treatment of allergic itch in which CXCL10/CXCR3 signaling may participate.

**Ube3a loss increases excitability and blunts orientation tuning in the visual cortex of Angelman syndrome model mice**
Michael L. Wallace, Geeske M. van Woerden, Ype Elgersma, Spencer L. Smith, Benjamin D. Philpot
July 1, 2017: 634-646
DOI: 10.1152/jn.00618.2016

Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by the loss of the gene UBE3A. Using electrophysiological recording in vivo, we describe visual cortical dysfunctions in a mouse model of AS. Aberrant cellular properties in AS model mice could be improved by reinstating Ube3a in inhibitory neurons. These findings suggest that inhibitory neurons play a substantial role in the pathogenesis of AS.

**RESEARCH ARTICLES | Spinal Control of Motor Output**

**SK channel inhibition mediates the initiation and amplitude modulation of synchronized burst firing in the spinal cord**
Amr A. Mahrous, Sherif M. Elbasiouny
July 1, 2017: 161-175
DOI: 10.1152/jn.00929.2016

This study demonstrates that cholinergic inhibition or direct blockade of small conductance Ca²⁺-activated potassium (SK) channels facilitates burst firing in spinal motoneurons. The data provide a novel mechanistic explanation for synchronized bursting initiation and amplitude modulation through SK channel inhibition. Evidence also shows that synchronized bursting is driven by NMDA (N-methyl-d-aspartate) and AMPA (α-amino-3-
hydroxy-5-methylisoxazole-4-propionate) receptors and that gap junctions do not mediate motoneuron synchronization in this behavior.

Parallel processing of internal and external feedback in the spinocerebellar system of primates
Oren Cohen, Ran Harel, Tim D. Aumann, Zvi Israel, Yifat Prut
July 1, 2017: 254-266
DOI: 10.1152/jn.00825.2016

Cerebellar coordination of voluntary movements relies on integrating feedback information to update motor output. With the use of a novel protocol, we identified spinal neurons constituting the ascending and descending components of the forelimb spinocerebellar system in behaving primates. The data suggest that descending information contributes to both motor preparation and execution, whereas ascending information conveys the spinal level motor command, such that internal and external feedback is relayed through parallel pathways.

RESEARCH ARTICLE | The Mouse Visual System

Comparison of optomotor and optokinetic reflexes in mice
Friedrich Kretschmer, Momina Tariq, Walid Chatila, Beverly Wu, Tudor Constantin Badea
July 1, 2017: 300-316
DOI: 10.1152/jn.00055.2017

We provide the first quantitation of head gain during optomotor response in mice and show that optomotor and optokinetic responses have similar psychometric curves. Head gains are far smaller than eye gains. Unrestrained mice combine head and eye movements to respond to visual stimuli, and both monocular and binocular fields are used during optokinetic responses. Mouse OMR and OKR movements are heterogeneous under optimal and suboptimal stimulation and are affected in mice lacking ON direction-selective retinal ganglion cells.

RESEARCH ARTICLE | Where Are You Going? The Neurobiology of Navigation

Interaction of compass sensing and object-motion detection in the locust central complex
Tobias Bockhorst, Uwe Homberg
July 1, 2017: 496-506
DOI: 10.1152/jn.00927.2016

Neurons of the central complex in several insects signal compass directions through sensitivity to the sky polarization pattern. In locusts, these neurons also respond to moving objects. We show here that during polarized-light presentation, responses to moving objects override their compass signaling or restore adapted inhibitory as well as excitatory compass responses. A network model is presented to explain the variations of these responses that likely serve to redirect flight or walking following evasive maneuvers.

RAPID REPORT | Neural Circuits

Development and long-term integration of MGE-lineage cortical interneurons in the heterochronic environment
Phillip Larimer, Julien Spatazza, Michael P. Stryker, Arturo Alvarez-Buylla, Andrea R. Hasenstaub
July 1, 2017: 131-139
DOI: 10.1152/jn.00096.2017

Transplanting embryonic interneurons into older brains induces a period of plasticity in the recipient animal. We find that these interneurons develop typical fast-spiking and non-fast-spiking phenotypes by the end of adolescence. However, the input-output characteristics of transplant-derived neurons diverged from endogenously developing interneurons during adulthood, and they showed lower connection rates to local pyramidal cells at all time points. This suggests a unique and ongoing role of transplant-derived interneurons in host circuits, enabling interneuron transplant therapies.

RAPID REPORT

Ion diffusion may introduce spurious current sources in current-source density (CSD) analysis
Geir Halnes, Tuomo Mäki-Marttunen, Klas H. Pettersen, Ole A. Andreassen, Gaute T. Einevoll
July 1, 2017: 114-120
DOI: 10.1152/jn.00976.2016

Standard CSD analysis does not account for ionic diffusion. Using biophysically realistic computer simulations, we show that unaccounted-for diffusive currents can lead to the prediction of spurious current sources. This finding may be of strong interest for in vivo electrophysiologists doing extracellular recordings in general, and CSD analysis in particular.
CORRIGENDA

Corrigendum
July 1, 2017 : 647
DOI: 10.1152/jn.z9k-4250-corr.2017

Corrigendum
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Felipe P. Carpes, Emmanuel Souza da Rocha, Marcos Roberto Kunzler, Pâmela Billig Mello-Carpes
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A question-based recall activity during classroom teaching for improving learning process
Rajib Biswas
September 1, 2017 : 448
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May 24, 2017: 995-1043
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Membrane and Nuclear Estrogen Receptor Alpha Actions: From Tissue Specificity to Medical Implications
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June 14, 2017: 1165-1209
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Low-Density Lipoprotein Receptor-Related Proteins in Skeletal Development and Disease
Tao Yang, Bart O. Williams
June 14, 2017: 1211-1228
DOI: 10.1152/physrev.00013.2016

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Original Research
Intimal hyperplasia induced by vascular intervention causes lipoprotein retention and accelerated atherosclerosis
Siavash Kijani, Ana Maria Vázquez, Malin Levin, Jan Borén, Per Fogelstrand
July 17, 2017 : e13334
DOI: 10.14814/phy2.13334

Vascular interventions are associated with rapid formation of atherosclerotic lesions. This study shows that intervention-induced intimal hyperplasia makes the vessel wall highly susceptible for lipoprotein retention and accelerated atherosclerosis. Furthermore, the increased lipoprotein retention in intimal hyperplasia can be targeted by LDL-mimicking peptides and immunization with glycosaminoglycan-binding antibodies.

Effect of type 2 diabetes, surgical incision, and volatile anesthesia on hemodynamics in the rat
Carol T. Bussey, Regis R. Lamberts
July 17, 2017 : e13352
DOI: 10.14814/phy2.13352

Patients with diabetes have increased perioperative cardiovascular risk. The interaction of diabetes with anesthesia and surgery, both altering blood pressure and heart rate, may be an underlying cause. In a type 2 diabetic rat model, the effect of diabetes on the interaction between hemodynamics, anesthesia, and surgical incision was determined. We found that during perioperative conditions, type 2 diabetes and surgical incision had minimal impact on short-term hemodynamic regulation, whereas anesthesia had a large impact.

Complex object motion represented by context-dependent correlated activity of visual interneurones
Paul C. Dick, Nicole L. Michel, John R. Gray
July 17, 2017 : e13355
DOI: 10.14814/phy2.13355

This work describes correlated activity of multiple neurons in the locusts visual system in response to objects moving along simple and compound trajectories. Dimensionality reduction techniques show that the number of coordinated neurons and the firing properties vary with the type of object visual motion.

Maxi-K channel (BKCa) activity veils the myogenic tone of mesenteric artery in rats
Eun Yeong Suh, Ming Zhe Yin, Haiyue Lin, Yin Hua Zhang, Hae Young Yoo, Sung Joon Kim
July 18, 2017 : e13330
DOI: 10.14814/phy2.13330

Myogenic tone (MT) in cerebral artery (CA) is larger than mesenteric artery (MA) despite the higher amplitudes of voltage-operated calcium channel (VOCC) current in MA smooth muscle cells (MASMCs) than in CA smooth muscle cells (CASMCs). Because the potassium conductance such as voltage-gated potassium channel (Kv) and big-conductance calcium-activated potassium channel (BKCa) currents are also higher in MASMCs, the hyperpolarizing outward currents was supposed to counterbalance the VOCC current. More frequent calcium sparks might underlie the higher frequency of spontaneous transient outward currents (STOCs). The larger outward potassium current via STOCs might explain the higher sensitivity to iberiotoxin as well as low MT in MA.

Ischemic preconditioning does not alter muscle sympathetic responses to static handgrip and metaboreflex activation in young healthy men
Anthony V. Incognito, Connor J. Doherty, Jordan B. Lee, Matthew J. Burns, Philip J. Millar
July 18, 2017 : e13342
DOI: 10.14814/phy2.13342

Ischemic preconditioning (IPC) has been hypothesized to reduce feedback from metabolically sensitive group III/IV muscle afferents during exercise. These afferents are known to influence central fatigue, muscle activation, and cardiovascular responses. Our results demonstrate that IPC does not attenuate central sympathetic outflow directed toward the skeletal muscle or pressor responses during static handgrip or subsequent post-exercise circulatory occlusion.

Regulation of the autophagy system during chronic contractile activity-induced muscle adaptations
Yuho Kim, David A. Hood
July 18, 2017 : e13307
DOI: 10.14814/phy2.13307

In this manuscript, we show that lysosomes are inducible by chronic exercise in skeletal muscle. This will enhance the capacity of the muscle for autophagic flux and represents an adaptation that can counter lysosomal storage diseases.
Sensory processing of deep tissue nociception in the rat spinal cord and thalamic ventrobasal complex
Shafaq Sikandar, Steven J. West, Stephen B. McMahon, David L. Bennett, Anthony H. Dickenson
July 18, 2017 : e13323
DOI: 10.14814/phy2.13323

Our study explores the central nervous system processing of deep tissue nociceptive inputs. We use electrophysiology and immunohistochemistry in rats to provide a novel characterization of the lateral spinal nucleus and its role in somatosensory processing of acute and pathological muscle activation. We also characterize the evoked activity of neurons in the thalamic ventrobasal complex and demonstrate sensitization of subpopulations of these neurons to mechanical somatosensory stimulation following muscle stimulation with hypertonic saline.

Baseline aortic pulse wave velocity is associated with central and peripheral pressor responses during the cold pressor test in healthy subjects
Anastasiya Borner, Kyle Murray, Claire Trotter, James Pearson
July 21, 2017 : e13357
DOI: 10.14814/phy2.13357

The acute risk of cardiovascular events increases with elevated aortic pulse wave velocity and central pulse pressures. The aim of this study was to examine the independent influence of baseline aortic pulse wave velocity upon acute central pressor responses to sympathetic activation via the cold pressor test (CPT) in healthy individuals. These data indicate that the acute central pulse pressure response during sympathetic activation via CPT is positively and independently associated with aortic pulse wave velocity across a wide age range.

Regional septal hinge-point injury contributes to adverse biventricular interactions in pulmonary hypertension
Eva Amalie Nielsen, Kenichi Okumura, Mei Sun, Vibeke E. Hjortdal, Andrew N. Redington, Mark K. Friedberg
July 21, 2017 : e13332
DOI: 10.14814/phy2.13332

Using two experimental models of right ventricular (RV) pressure-loading/pulmonary hypertension, we demonstrate that beyond reduced LV filling, adverse RV-LV (left) interactions occur regionally at the septal hinge-point regions where geometrical changes trigger RV and LV fibrosis and extra-cellular matrix remodeling in association with regional and global ventricular dysfunction.

Bronchial microdialysis monitoring of inflammatory response in open abdominal aortic aneurysm repair; an observational study
Stig S. Tyvold, Torbjørn Dahl, Stein Dragsund, Sigurd Gunnes, Oddveig Lyng, Jan K. Damås, Petter Aadal, Erik Solligård
July 25, 2017 : e13348
DOI: 10.14814/phy2.13348

Bronchial microdialysis is a safe method for monitoring the inflammatory responses during open abdominal aortic aneurysm repair. Levels of inflammatory cytokines in epithelial lining fluid may be predictors for immediate complications such as organ failure in patients undergoing vascular surgery.

The effects of Suramin on Ca2+ activated force and sarcoplasmic reticulum Ca2+ release in skinned fast-twitch skeletal muscle fibers of the rat
Dane W. Williams, Dimitrie George Stephenson, Giuseppe S. Posterino
July 25, 2017 : e13333
DOI: 10.14814/phy2.13333

Suramin has long been used in the treatment of various human diseases. Intravenous infusions of Suramin are commonly administered to patients over extended periods of time but there are a number of significant contraindications with peripheral muscle weakness being one of the most frequently reported. This article reports new functional effects for Suramin related to alterations in both the contractile apparatus and SR Ca2+-handling of skeletal muscle that may contribute to the peripheral muscle weakness noted in human pharmacological treatments.

The effect of dietary nitrate supplementation on the spatial heterogeneity of quadriceps deoxygenation during heavy-intensity cycling
Brynmor C. Breese, David C. Poole, Dai Okushima, Stephen J. Bailey, Andrew M. Jones, Narihiko Kondo, Tatsuro Amano, Shunsaku Koga
July 25, 2017 : e13340
DOI: 10.14814/phy2.13340

Dietary nitrate supplementation has been reported to increase locomotor muscle blood flow and microvascular O2 partial pressures during contractions in animals. In this study, we show using novel time-resolved NIRS that nitrate-rich beetroot juice supplementation increases muscle O2 diffusive capacity in humans, with this effect associated with improved O2 uptake dynamics during heavy-intensity exercise.
Unloading-induced atrophy and decreased oxidative capacity of the soleus muscle in rats are reversed by pre- and postconditioning with mild hyperbaric oxygen
Ai Takemura, Roland R. Roy, Ikumi Yoshihara, Akihiko Ishihara
July 25, 2017 : e13353
DOI: 10.14814/phy2.13353
We determined the effects of pre- and/or postconditioning with mild hyperbaric oxygen (1.25 atmospheric pressure, 36% oxygen for 3 h/day) on the properties of the soleus muscle that was atrophied by hindlimb suspension-induced unloading. A combination of pre- and postconditioning with mild hyperbaric oxygen can be effective against the atrophy and decreased oxidative capacity of skeletal muscles associated with unloading.

Nonspecific block of voltage-gated potassium channels has greater effect on distal schaffer collaterals than proximal schaffer collaterals during periods of high activity
Benjamin Owen, Rishi Reddy, Lawrence M. Grover
July 25, 2017 : e13354
DOI: 10.14814/phy2.13354
We tested the involvement of voltage-gated potassium channels in activity-dependent changes in the Schaffer collateral axons of hippocampal CA3 pyramidal neurons, and in functional differences between proximal and distal axons. We found that block of voltage-gated potassium channels profoundly altered function of distal portions of Schaffer collaterals, but proximal portions were minimally affected. Our results suggest that voltage-gated potassium channels play critical roles in maintaining excitability of distal Schaffer collaterals during periods of high activity.

Autologous minced muscle grafts improve endogenous fracture healing and muscle strength after musculoskeletal trauma
July 25, 2017 : e13362
DOI: 10.14814/phy2.13362
Volumetric muscle loss (VML) injury incited an exacerbated inflammatory response that associates with impaired muscle and concomitant fracture healing. Herein we demonstrate that repair of VML injury with autologous minced muscle grafts augments the local wound wound environment and improves skeletal muscle functional recovery as well as fracture healing.

Nongenomic modulation of the large conductance voltage- and Ca2+-activated K+ channels by estrogen: A novel regulatory mechanism in human detrusor smooth muscle
Kiril L. Hristov, Shankar P. Parajuli, Aaron Provence, Eric S. Rovner, Georgi V. Petkov
July 27, 2017 : e13351
DOI: 10.14814/phy2.13351
Here, we used human detrusor smooth muscle (DSM) specimens from open bladder surgeries on 27 patients to elucidate the mechanism by which 17β-estradiol regulates large conductance voltage- and Ca2+-activated K+ (BK) channels, the most prominent K+ channels in human DSM. We employed single BK channel recordings on inside-out excised membrane patches, perforated whole-cell patch-clamp on freshly isolated DSM cells, and isometric tension recordings on DSM-isolated strips to investigate the mechanism by which 17β-estradiol activates BK channels. Our results reveal that 17β-estradiol plays a critical role in regulating human DSM function through a direct nongenomic activation of BK channels.

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Original Research

Acylated and unacylated ghrelin do not directly stimulate glucose transport in isolated rodent skeletal muscle
Daniel T. Cervone, David J. Dyck
July 4, 2017 : e13320
DOI: 10.14814/phy2.13320
We find no evidence that either of ghrelin's two major isoforms stimulates glucose transport or increases insulin signaling in rodent skeletal muscle. Ghrelin also does not alter glucose transport in the presence of low or high concentrations of insulin. Finally, growth hormone, which is secreted in vivo in response to the spike in ghrelin, also does not directly alter glucose transport in isolated rodent muscle.

Voluntary physical activity counteracts the proliferative tumor growth microenvironment created by adipose tissue via high-fat diet feeding in...
Adipose has been shown to contribute to the cancer tumor microenvironment. We show that diet-induced obesity is associated with increased estrogen, leptin, and decreased adiponectin secretion and promotes adipose-dependent breast cancer growth. Voluntary physical activity completely abolishes this response, suggesting the preventative and therapeutic benefits of exercise for breast cancer patients.

Diabetic rats have lower renal expression of CIC-5, CFTR, TNR-CFTR, and cubilin proteins. Diabetic rats have higher urinary transferrin excretion. These results provide insights into the critical role of the proximal tubule in DN pathophysiology.

Little data is available on the tissue composition and hence energy density of short-term fluctuations in body energy stores weight. Here we report a relatively larger contribution of fat-free mass (84%; mainly body water), as compared to fat mass (16%), to the body weight fluctuations after 2-weeks of unrestricted free-living conditions. We also show that the energy density of short-term changes in body energy stores is small. Our findings are useful for short-term, near energy balance studies where body composition cannot be easily measured.

Increased FNDC5 is associated with insulin resistance in high fat-fed mice

Increased FNDC5 in adipose and muscle of high fat-fed mice is attenuated by exercise. In addition, FNDC5 levels in adipose are correlated with HOMA-IR. Together, these data suggest a compensatory increase in FNDC5 to offset obesity and insulin resistance.

Our data demonstrate that repeated radiation exposure at two different doses (26 and 46 eGy), commonly used to image bone structure, from microcomputed tomography (μCT) did not alter soleus or extensor digitorum longus (EDL) morphometrics (weight and cross-sectional area), in vitro contractile function, and most enzyme activities measured in female mice. One exception is exposure to 46 eGy resulted in a lower maximal citrate synthase activity in soleus, but not EDL. Thus, longitudinal μCT scanning to provide sufficient quality bone images should take radiation dose into consideration to not impact neighboring muscles.

Case Reports

High-intensity interval exercise and glycemic control in adolescents with type one diabetes mellitus: a case study

Current physical activity guidelines for youth with type 1 diabetes (T1D) are poorly supported by empirical evidence and the optimal dose of physical activity to improve glycemic control is unknown. This case report studies the effect of acute high-intensity interval exercise (HIIE) and
moderate-intensity exercise (MIE) on 24-h glycemic control in three youths with T1D using continuous glucose monitoring. Findings show both HIIE and MIE have the potential to improve short-term glycemic control in youth with T1D but HIIE is more enjoyable. Future work with a larger sample size is required to explore the potential for HIIE to improve health markers in youth with T1D.

Original Research

**Comparative effects of glucose and water drinks on blood pressure and cardiac function in older subjects with and without postprandial hypotension**
Laurence G. Trahair, Sharmalar Rajendran, Renuka Visvanathan, Matthew Chapman, Daniel Stadler, Michael Horowitz, Karen L. Jones
July 6, 2017 : e13341
DOI: 10.14814/phy2.13341

The comparative effects of water and glucose drinks on cardiac hemodynamics were compared in healthy older subjects and individuals with postprandial hypotension (PPH). In PPH, the hypotensive response to oral glucose was shown to be associated with inadequate compensatory increases in cardiac output and heart rate, whereas the pressor response to water ingestion is maintained and, possibly, exaggerated.

**Early sepsis does not stimulate reactive oxygen species production and does not reduce cardiac function despite an increased inflammation status**
Thibault Léger, Alice Charrier, Clarisse Moreau, Isabelle Hininger-Favier, Evangelia Mourmoura, Jean-Paul Rigaudière, Elodie Pitois, Damien Bouvier, Vincent Sapin, Bruno Pereira, Kasra Azarnoush, Luc Demaison
July 6, 2017 : e13231
DOI: 10.14814/phy2.13231

Early sepsis is accompanied by a loss of skeletal muscle mass and an activation of the inflammation process with increased plasma TNF-α concentration and cardiac expression of TNF-α and IL-1β RNAs. Despite the inflammation burst, the cardiac function is increased in the in vivo situation as well as ex vivo in the perfused heart. The improved cardiac function is associated with a lower reactive oxygen species production which can preserve the cellular energy metabolism.

**Efficacy of nutritional interventions to lower circulating ceramides in young adults: FRUVEDomic pilot study**
Alice T. Mathews, Oluremi A. Famodu, Melissa D. Olfert, Pamela J. Murray, Christopher F. Cuff, Marianne T. Downes, Norman J. Haughey, Sarah E. Colby, Paul D. Chantler, I. Mark Olfert, Joseph W. McFadden
July 10, 2017 : e13329
DOI: 10.14814/phy2.13329

Ceramide is an associative and causal mediator of insulin resistance. A nutritional intervention can lower circulating ceramide.

**Lifelong exercise, but not short-term high-intensity interval training, increases GDF11, a marker of successful aging: a preliminary investigation**
Bradley T. Elliott, Peter Herbert, Nicholas Sculthorpe, Fergal M. Grace, Daniel Stratton, Lawrence D. Hayes
July 11, 2017 : e13343
DOI: 10.14814/phy2.13343

Growth and differentiation factor (GDF11) concentration in mice at midlife predicts all cause mortality while provision of GDF11 to older mice restores grip strength. Here, we demonstrated that GDF11 concentration is higher in masters athletes, and predicts peak power output, confirming the role of GDF11 in human frailty with aging. Importantly, some masters athletes show low peak power and low GDF11, while some inactive older individuals show high peak power and high GDF11.

**Nanoparticles increase human bronchial epithelial cell susceptibility to respiratory syncytial virus infection via nerve growth factor-induced autophagy**
Sreeparna Chakraborty, Vincent Castranova, Miriam K. Perez, Giovanni Piedimonte
July 11, 2017 : e13344
DOI: 10.14814/phy2.13344

This study shows for the first time that exposure of the lower airway epithelium to nanosized environmental particles makes the respiratory tract more susceptible to subsequent respiratory syncytial virus (RSV) infection. Also, autophagy plays a critical role in modulating RSV infectivity by allowing infected cells made susceptible by prior exposure to ultrafine particles to better adapt to the stress of viral invasion, and preventing apoptotic cell death while the virus completes its replication cycle that will ultimately lead to necrotic cell lysis.
Cigarette smoke differentially affects IL-13-induced gene expression in human airway epithelial cells
Tinne C. J. Mertens, Anne M. van der Does, Loes E. Kistemaker, Dennis K. Ninaber, Christian Taube, Pieter S. Hiemstra
July 11, 2017: e13347
DOI: 10.14814/phy2.13347

In this article, we have investigated the effects of chronic whole cigarette smoke exposure on the IL-13-induced gene expression profile in primary airway epithelial cells with a focus on the T helper 2 (Th2) signature genes POSTN, SERPINB2, and CLCA1, suggested as a biomarker for patients with Th2-high asthma. Our results show that whole cigarette smoke exposure differentially affected an established IL-13-induced expression profile. Moreover, exposure of differentiating primary airway epithelial cells to whole cigarette smoke differentially affected a subsequent response to IL-13 exposure.

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