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S-nitrosylation/denitrosylation regulates myoblast proliferation. Focus on “Balance between S-nitrosylation and denitrosylation modulates myoblast proliferation independently of soluble guanylyl cyclase activation”
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August 1, 2017: C131-C133
DOI: 10.1152/ajpcell.00127.2017

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Sarcomere mechanics in striated muscles: from molecules to sarcomeres to cells
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DOI: 10.1152/ajpcell.00050.2017

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Regulation of ATP production: dependence on calcium concentration and respiratory state
Brian D. Fink, Fan Bai, Liping Yu, William I. Sivitz
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RESEARCH ARTICLE | Pathophysiology of Skeletal Muscle Loss

Effects of sarcolipin deletion on skeletal muscle adaptive responses to functional overload and unload
Val A. Fajardo, Bradley A. Rietze, Paige J. Chambers, Catherine Bellissimo, Eric Bombardier, Joe Quadrilatero, A. Russell Tupling
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DOI: 10.1152/ajpcell.00291.2016

RESEARCH ARTICLE | Single Cell Physiology

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Recruitment of endosomal signaling mediates the forskolin modulation of guinea pig cardiac neuron excitability
Jean C. Hardwick, Todd A. Clason, John D. Tompkins, Beatrice M. Girard, Caitlin N. Baran, Laura A. Merriam, Victor May, Rodney L. Parsons
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Is FoxO1 the culprit, partner in crime, or a protector in systemic inflammation?
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August 3, 2017: C239-C241
DOI: 10.1152/ajpcell.00194.2016

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Menin and PRMT5 suppress GLP1 receptor transcript and PKA-mediated phosphorylation of FOXO1 and CREB
Abdul Bari Muhammad, Bowen Xing, Chengyang Liu, Ali Naji, Xiaosong Ma, Rebecca A. Simmons, Xianxin Hua
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DOI: 10.1152/ajpendo.00241.2016

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The Niemann-Pick C1 gene interacts with a high-fat diet to promote weight gain through differential regulation of central energy metabolism pathways
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Roux-en-Y gastric bypass surgery enhances contraction-mediated glucose metabolism in primary human myotubes
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Cyp8b1 ablation prevents Western diet-induced weight gain and hepatic steatosis because of impaired fat absorption
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Low-dose leptin infusion in the fourth ventricle of rats enhances the response to third-ventricle leptin injection
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DOI: 10.1152/ajpendo.00044.2017

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The NLRP3 inflammasome contributes to sarcopenia and lower muscle glycolytic potential in old mice

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DOI: 10.1152/ajpgi.00333.2016
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August 1, 2017: G102-G116
DOI: 10.1152/ajpgi.00452.2016

RESEARCH ARTICLES | Epithelial Biology and Secretion

- **FFA2 activation combined with ulcerogenic COX inhibition induces duodenal mucosal injury via the 5-HT pathway in rats**
  Yasutada Akiba, Koji Maruta, Kazuyuki Narimatsu, Hyder Said, Izumi Kaji, Ayaka Kuri, Ken-ichi Iwamoto, Atsukazu Kuwahara, Jonathan D. Kaunitz
  August 1, 2017: G117-G128
  DOI: 10.1152/ajpgi.00041.2017

Luminal free fatty acid receptor 2 agonists stimulate enterochromaffin cells and release serotonin, which enhances mucosal defenses in rat duodenum. However, overdriving serotonin release with high luminal concentrations of free fatty acid 2 ligands such as short-chain fatty acids injures the mucosa by decreasing mucosal blood flow. These results are likely implicated in serotonin-related dyspeptic symptom generation because of small intestinal bacterial overgrowth, which is hypothesized to generate excess short-chain fatty acids in the foregut, overdriving serotonin release from enterochromaffin cells.

- **A common NHE3 single-nucleotide polymorphism has normal function and sensitivity to regulatory ligands**
  Jianyi Yin, Chung-Ming Tse, Boyoung Cha, Rafiquel Sarker, Xinjun C. Zhu, Anna Walentinsson, Peter J. Greasley, Mark Donowitz
  August 1, 2017: G129-G137
  DOI: 10.1152/ajpgi.00044.2017

This study reports results on the functional significance of human NHE3-799C under basal conditions and in response to regulatory ligands, including a novel NHE3 inhibitor called tenapanor. We demonstrate that NHE3-799C is a common variant of NHE3 that is enriched in Asian populations; however, in contrast to our previous studies using rabbit NHE3, its presence seems to have limited clinical significance in humans and is not associated with compromised function or abnormal transport regulation.

RESEARCH ARTICLE | Physiology of Gastrointestinal, Hepatic, and Pancreatic Cancer

- **CD151 supports VCAM-1-mediated lymphocyte adhesion to liver endothelium and is upregulated in chronic liver disease and hepatocellular carcinoma**
  August 1, 2017: G138-G149
  DOI: 10.1152/ajpgi.00411.2016

Chronic hepatitis is characterized by lymphocyte accumulation in liver tissue, which drives fibrosis and carcinogenesis. Here, we demonstrate for the first time that the tetraspanin CD151 supports lymphocyte adhesion to liver endothelium. We show that CD151 is upregulated in chronic liver disease and hepatocellular cancer (HCC) and is regulated on endothelium by tissue remodeling and procarcinogenic factors. These regulatory and functional studies identify CD151 as a potential therapeutic target to treat liver fibrosis and HCC.

RESEARCH ARTICLE | Stem Cells, Tissue Engineering, Development, and Cancer

- **Long non-coding RNA NEAT1 promotes hepatocellular carcinoma cell proliferation through the regulation of miR-129-5p-VCP-IκB**
  Luo Fang, Jiao Sun, Zongfu Pan, Yu Song, Like Zhong, Yiwen Zhang, Yujia Liu, Xiaowei Zheng, Ping Huang
  August 1, 2017: G150-G156
  DOI: 10.1152/ajpgi.00426.2016

The results provide strong evidence that upregulated NEAT1 promotes the proliferation of cancer cells in hepatocellular carcinoma (HCC) and this regulatory mechanism depends on the microRNA (miR)-129-5p-valosin-containing protein-IκB axis. The study also indicates that NEAT1 could be a potential therapeutic target for HCC.

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EDITORIAL

Why publish in the American Journal of Physiology—Heart and Circulatory Physiology?
August 1, 2017: H221-H223
DOI: 10.1152/ajpheart.00329.2017

REVIEW | Heart Failure: Novel Therapeutic Pathways Emerging from Basic Science

Autophagy modulation: a potential therapeutic approach in cardiac hypertrophy
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The PRKAG2 gene and hypertrophic cardiomyopathy: an energetically imbalanced relationship
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DOI: 10.1152/ajpheart.00316.2017

Cyp2c44-mediated decrease of 15-HETE exacerbates pulmonary hypertension
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State-space representation of the extended Guyton's model
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DOI: 10.1152/ajpheart.00315.2017

Radiation-induced HFpEF model as a potential tool for the exploration of novel therapeutic targets
Osamu Tsukamoto, Masafumi Kitakaze
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RESEARCH ARTICLE | Advances in Cardiovascular Geroscience

Age or ischemia uncouples the blood flow response, tissue acidosis, and direct current potential signature of spreading depolarization in the rat brain
Ákos Menyhárt, Dániel Zülei-Szénási, Tamás Puskás, Péter Makra, Ferenc Bari, Eszter Farkas
August 11, 2017: H328-H337
DOI: 10.1152/ajpheart.00222.2017

The hyperemic element of the cerebral blood flow response to spreading depolarization is effectively modulated by tissue pH in the young intact rat cerebral cortex. This coupling becomes dysfunctional with age or under ischemia, and tissue acidosis lasts disproportionally longer in the aged cortex, making the tissue increasingly more vulnerable.

RESEARCH ARTICLE | Cardiac Excitation and Contraction

β-Adrenergic receptor stimulation inhibits proarrhythmic alternans in postinfarction border zone cardiomyocytes: a computational analysis
Jakub Tomek, Blanca Rodriguez, Gil Bub, Jordi Heijman
August 11, 2017: H338-H353
DOI: 10.1152/ajpheart.00094.2017

We integrated, for the first time, postmyocardial infarction electrical and autonomic remodeling in a detailed, validated computer model of β-adrenergic stimulation in ventricular cardiomyocytes. Here, we show that β-adrenergic stimulation inhibits alternans and provide novel insights into underlying mechanisms, adding to a recent controversy about pro-/antiarrhythmic effects of postmyocardial infarction hyperinnervation.

RESEARCH ARTICLE | Cardiovascular Actions of Hydrogen Sulfide and Other Gasotransmitters

Role of thiosulfate in hydrogen sulfide-dependent redox signaling in endothelial cells
Anna Leskova, Sibile Pardue, John D. Glawe, Christopher G. Kevil, Xinggui Shen
August 1, 2017: H256-H264
DOI: 10.1152/ajpheart.00723.2016

This report provides new evidence that different levels of exogenous thiosulfate dynamically change discrete sulfide biochemical metabolite bioavailability in endothelial cells under normoxia or hypoxia, acting in a slow manner to modulate sulfide metabolites. Moreover, our findings also reveal that thiosulfate surprisingly inhibits VEGF-dependent endothelial cell proliferation associated with a reduction in cystathionine-γ-lyase protein levels.

RESEARCH ARTICLE | Energetics and Metabolism

Acetylation of mitochondrial proteins by GCN5L1 promotes enhanced fatty acid oxidation in the heart
Dharendra Thapa, Manling Zhang, Janet R. Manning, Danielle A. Guimarães, Michael W. Stoner, Robert M. O’Doherty, Sruti Shiva, Iain Scott
August 1, 2017: H265-H274
DOI: 10.1152/ajpheart.00752.2016

Recent research has shown that acetylation of mitochondrial fatty acid oxidation enzymes has greatly contrasting effects on their activity in different tissues. Here, we provide new evidence that acetylation of cardiac mitochondrial fatty acid oxidation enzymes by GCN5L1 significantly upregulates their activity in diet-induced obese mice.

RESEARCH ARTICLES | Heart Failure: Novel Therapeutic Pathways Emerging from Basic Science

Myocardial overexpression of TIMP3 after myocardial infarction exerts beneficial effects by promoting angiogenesis and suppressing early proteolysis
August 1, 2017: H224-H236
Here, we report that tissue inhibitor of metalloproteinase 3 overexpression after myocardial infarction improves myocardial structural remodeling and function by promoting angiogenesis and inhibiting early proteolysis. This demonstrates the therapeutic potential of preserving the local balance of tissue inhibitor of metalloproteinase 3 in the heart given its diverse functions in modulating different processes involved in the adverse postmyocardial infarction remodeling.

Cervical vagus nerve stimulation augments spontaneous discharge in second- and higher-order sensory neurons in the rat nucleus of the solitary tract
Eric Beaumont, Regenia P. Campbell, Michael C. Andresen, Stephanie Scofield, Krishna Singh, Imad Libbus, Bruce H. KenKnight, Logan Snyder, Nathan Cantrell
August 11, 2017 : H354-H367

DOI: 10.1152/ajpheart.00070.2017

Acute vagus nerve stimulation elevated activity in neurons located in the medial nucleus of the solitary tract. Such stimuli directly activated only myelinated vagal afferents but indirectly activated a subpopulation of second- and higher-order neurons, suggesting that afferent mechanisms and central neuron activation may be responsible for vagus nerve stimulation efficacy.

EET intervention on Wnt1, NOV, and HO-1 signaling prevents obesity-induced cardiomyopathy in obese mice
August 11, 2017 : H368-H380

DOI: 10.1152/ajpheart.00093.2017

The mechanism by which EET acts on obesity-induced cardiomyopathy is unknown. Here, we describe a previously unrecognized function of EET infusion that inhibits nephroblastoma overexpressed (NOV) levels and activates Wnt1, hence identifying NOV inhibition and enhanced Wnt1 expression as novel pharmacological targets for the prevention and treatment of cardiomyopathy and heart failure.

RESEARCH ARTICLES | Integrative Cardiovascular Physiology and Pathophysiology
Noninvasive evaluation of left ventricular elastance according to pressure-volume curves modeling in arterial hypertension
Benjamin Bonnet, Franck Jourdan, Guilhem du Cailar, Pierre Fesler
August 1, 2017 : H237-H243

DOI: 10.1152/ajpheart.00086.2017

The use of real-time three-dimensional echocardiography-derived left ventricular volumes in conjunction with carotid tonometry was found to be reproducible and sensitive enough to detect expected differences in left ventricular elastance in atrial hypertension. Because of its noninvasive nature, this methodology may have clinical implications in various disease states.

Variability in coronary artery anatomy affects consistency of cardiac damage after myocardial infarction in mice
Jiqiu Chen, Delaine K. Ceholski, Lifan Liang, Kenneth Fish, Roger J. Hajjar
August 1, 2017 : H275-H282

DOI: 10.1152/ajpheart.00127.2017

In the present study, we demonstrate that left coronary artery diversity in mice is one of the primary causes of variable myocardial infarction size and cardiac functional parameters in the left coronary artery ligation model. Recognition of anatomic diversity is essential to improve reliability and reproducibility in heart failure research.

GBT1118, a potent allosteric modifier of hemoglobin O2 affinity, increases tolerance to severe hypoxia in mice
Kobina Dufu, Ozlem Yalcin, Eilleen S. Y. Ao-ieong, Athiwat Hutchaleelala, Qing Xu, Zhe Li, Nicholas Vlahakis, Donna Oksenberg, Josh Lehrer-Graiwer, Pedro Cabrales
August 11, 2017 : H381-H391

DOI: 10.1152/ajpheart.00772.2016

This study establishes that pharmacological modification of hemoglobin O2 affinity can be a promising and novel therapeutic strategy for the treatment of hypoxic hypoxia and paves the way for the clinical development of molecules that prevent hypoxemia.

Experimental cardiac radiation exposure induces ventricular diastolic dysfunction with preserved ejection fraction
Hirofumi Saiki, Gilles Moulay, Adam J. Guenzel, Weibin Liu, Teresa D. Decklever, Kelly L. Classic, Linh Pham, Horng H. Chen, John C. Burnett, Stephen J. Russell, Margaret M. Redfield
August 11, 2017 : H392-H407

DOI: 10.1152/ajpheart.00124.2017
Cardiac radiation exposure during radiotherapy increases the risk of heart failure with preserved ejection fraction. In a novel rodent model, cardiac radiation exposure resulted in coronary microvascular rarefaction, oxidative stress, impaired PKG signaling, myocardial fibrosis, mild cardiomyocyte hypertrophy, left ventricular diastolic dysfunction, and elevated left ventricular filling pressures despite preserved ejection fraction.

**Right atrial pressure and venous return during cardiopulmonary bypass**
Per W. Moller, Bernhard Winkler, Samuel Hurni, Paul Philipp Heinisch, Andreas Bloch, Soren Sondergaard, Stephan M. Jakob, Jukka Takala, David Berger
August 11, 2017 : H408-H420
DOI: 10.1152/ajpheart.00081.2017

Venous return responds immediately to changes in right atrial pressure. Concomitant volume shifts within the systemic circulation due to an imbalance between cardiac output and venous return have negligible effects on the mean systemic filling pressure. Guyton’s model of circulatory equilibrium can qualitatively predict the resulting changes in dynamic conditions with right atrial pressure as backpressure to venous return.

**Spinal cord stimulation reduces ventricular arrhythmias during acute ischemia by attenuation of regional myocardial excitability**
Kimberly Howard-Quijano, Tatsuo Takamiya, Érica A. Dale, Jasmine Kipke, Yukiko Kubo, Tristan Grogan, Andyshea Afyouni, Kalyanam Shivkumar, Aman Mahajan
August 11, 2017 : H421-H431
DOI: 10.1152/ajpheart.00129.2017

In a porcine model of ventricular ischemia, spinal cord stimulation decreased sympathetic nerve activation regionally in ischemic myocardium with no effect on normal myocardium, demonstrating that the antiarrhythmic effects of spinal cord stimulation are likely due to attenuation of local sympathoexcitation in the ischemic myocardium and not changes in global myocardial electrophysiology.

**RESEARCH ARTICLES | Metabolism, Cell Signaling and Disease**

**A novel, de novo mutation in the PRKAG2 gene: infantile-onset phenotype and the signaling pathway involved**
Yanchun Xu, A. Gray, D. Grahame Hardie, Alper Uzun, Sunil Shaw, James Padbury, Chanika Phornphutkul, Yi-Tang Tseng
August 1, 2017 : H283-H292
DOI: 10.1152/ajpheart.00813.2016

We identified a novel, de novo PRKAG2 mutation (K475E) in the cystathionine β-synthase 3 repeat, a region critical for AMP binding but with no previous reported mutation. Our data suggest the mutation affects AMP-activated protein kinase activity, activates cell growth pathways, and results in cardiac hypertrophy, which can be reversed with rapamycin.

**Metabolism and acetylation contribute to leucine-mediated inhibition of cardiac glucose uptake**
Edith Renguet, Audrey Ginion, Roselle Gélinas, Laurent Bultot, Julien Aquier, Isabelle Robillard Frayne, Caroline Daneault, Jean-Louis Vanoverschelde, Christine Des Rosiers, Louis Hue, Sandrine Horman, Christophe Beauleoye, Luc Bertrand
August 11, 2017 : H432-H445
DOI: 10.1152/ajpheart.00738.2016

Catabolism of the branched-chain amino acid leucine into ketone bodies efficiently inhibits cardiac glucose uptake through decreased translocation of glucose transporter 4 to the plasma membrane. Leucine increases protein acetylation. Pharmacological inhibition of acetylation reverses leucine’s action, suggesting acetylation involvement in this phenomenon.

**RESEARCH ARTICLES | Vascular Biology and Microcirculation**

**Cyp2c44 gene disruption is associated with increased hematopoietic stem cells: implication in chronic hypoxia-induced pulmonary hypertension**
Ryota Hashimoto, Sachindra Raj Joshi, Houli Jiang, Jorge H. Capdevila, Ivan F. McMurtry, Michal Laniado Schwartzman, Sachin A. Gupte
August 1, 2017 : H293-H303
DOI: 10.1152/ajpheart.00785.2016

This study demonstrates that cytochrome P-450 2C44 plays a critical role in controlling the phenotype of hematopoietic stem cells and that when this enzyme is knocked out, stem cells are differentiated. These stem cells give rise to increased circulating monocytes and macrophages and contribute to the pathogenesis of chronic hypoxia-induced pulmonary artery remodeling and hypertension.

**Mechanical behavior and matrisome gene expression in the aneurysm-prone thoracic aorta of newborn lysyl oxidase knockout mice**
Marius Catalin Staiculescu, Jungsil Kim, Robert P. Mecham, Jessica E. Wagenseil
August 11, 2017 : H446-H456
DOI: 10.1152/ajpheart.00712.2016
Absence of lysyl oxidase (Lox) causes thoracic aortic aneurysms. The aortic mechanical behavior of Lox−/− mice is consistent with reduced elastin and collagen cross-linking but demonstrates vascular location-specific differences. Lox−/− aortas show upregulation of matrix remodeling genes and location-specific differential expression of other matrix and smooth muscle cell gene sets.

CORRIGENDA

Corrigendum
August 11, 2017 : H457
DOI: 10.1152/ajpheart.00817.2015-corr.2017

Corrigendum
August 11, 2017 : H458
DOI: 10.1152/ajpheart.00597.2017-corr.2017

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Reduced carboxylesterase 1 is associated with endothelial injury in methamphetamine-induced pulmonary arterial hypertension
Mark E. Orcholski, Artyom Khurshudyan, Elya A. Shamskhou, Ke Yuan, Ian Y. Chen, Sean D. Kodani, Christophe Morisseau, Bruce D. Hammock, Ellen M. Hong, Ludmila Alexandrova, Tero-Pekka Alastalo, Gerald Berry, Roham T. Zamanian, Vinicio A. de Jesus Perez
August 1, 2017 : L240-L251
DOI: 10.1152/ajplung.00523.2016

Marijuana smoke induces severe pulmonary hyperresponsiveness, inflammation, and emphysema in a predictive mouse model not via CB1 receptor activation
August 1, 2017 : L267-L277
DOI: 10.1152/ajplung.00354.2016

RESEARCH ARTICLE | Electronic Cigarettes: Not All Good News?
Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function
Phillip W. Clapp, Erica A. Pawlak, Justin T. Lackey, James E. Keating, Steven L. Reeber, Gary L. Glish, Ilona Jaspers
August 1, 2017 : L278-L292
DOI: 10.1152/ajplung.00452.2016

RESEARCH ARTICLE | Ion Channels and Transporters in Lung Function and Disease
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Chun-Chun Hsu, You Shuei Lin, Ruei-Lung Lin, Lu-Yuan Lee
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RESEARCH ARTICLE | Real-Time Visualization of Lung Function: From Micro to Macro
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DOI: 10.1152/ajplung.00048.2017

RESEARCH ARTICLES | Translational Research in Acute Lung Injury and Pulmonary Fibrosis
Surfactant replacement therapy reduces acute lung injury and collapse induration-related lung remodeling in the bleomycin model
Lilian Steffen, Clemens Ruppert, Heinz-Gerd Hoymann, Manuela Funke, Simone Ebener, Christina Kloth, Christian Mühlfeld, Matthias Ochs, Lars Knudsen, Elena Lopez-Rodriguez
August 1, 2017 : L313-L327
DOI: 10.1152/ajplung.00033.2017

A novel role for primary cilia in airway remodeling
Carol S. Trempus, Wei Feng Song, Ahmed Lazrak, Zhihong Yu, Judy R. Creighton, Bethany M. Young, Rebecca L. Heise, Yen Rei Yu, Jennifer L. Ingram, Robert M. Tighe, Sadis Matalon, Stavros Garantziotis
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miR-29b supplementation decreases expression of matrix proteins and improves alveolarization in mice exposed to maternal inflammation and neonatal hyperoxia
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EETs promote hypoxic pulmonary vasoconstriction via constrictor prostanoids
Sharath Kandhi, Bin Zhang, Ghezal Froogh, Jun Qin, Norah Alruwaili, Yicong Le, Yang-Ming Yang, Sung Hee Hwang, Bruce D. Hammock, Michael S. Wolin, An Huang, Dong Sun
August 1, 2017 : L350-L359
DOI: 10.1152/ajplung.00038.2017

Brain-derived neurotrophic factor and airway fibrosis in asthma
Michelle R. Freeman, Venkatachalem Sathish, Logan Manlove, Shengyu Wang, Rodney D. Britt Jr., Michael A. Thompson, Christina M. Pabelick, Y. S. Prakash
August 1, 2017 : L360-L370
DOI: 10.1152/ajplung.00580.2016

Peroxisome proliferator-activated receptor-γ enhances human pulmonary artery smooth muscle cell apoptosis through microRNA-21 and programmed cell death 4
David E. Green, Tamara C. Murphy, Bum-Yong Kang, Brahmesheta Bedi, Zhihong Yuan, Ruxana T. Sadikot, C. Michael Hart
August 1, 2017 : L371-L383
DOI: 10.1152/ajplung.00532.2016

Integrin αβ5 inhibition protects against ischemia-reperfusion-induced lung injury in an autophagy-dependent manner
Dan Zhang, Chichi Li, Yuanlin Song, Jian Zhou, Yuping Li, Jing Li, Chunxue Bai
August 1, 2017 : L384-L394
DOI: 10.1152/ajplung.00391.2016

Transgenerational transmission of asthma risk after exposure to environmental particles during pregnancy
David J. Gregory, Lester Kobzik, Zhiping Yang, Connor C. McGuire, Alexey V. Fedulov
August 1, 2017 : L395-L405
DOI: 10.1152/ajplung.00035.2017

GABAA receptor α4-subunit knockout enhances lung inflammation and airway reactivity in a murine asthma model
Gene T. Yocum, Damian L. Turner, Jennifer Danielsson, Matthew B. Barajas, Yi Zhang, Dingbang Xu, Neil L. Harrison, Gregg E. Homanics, Donna L. Farber, Charles W. Emala
August 1, 2017 : L406-L415
DOI: 10.1152/ajplung.00107.2017

RAPID REPORT

Effect of long-term maternal smoking on the offspring’s lung health
Surpon Sukjamnong, Yik Lung Chan, Razia Zakarya, Sonia Saad, Pawan Sharma, Rachana Santiyanont, Hui Chen, Brian G. Oliver
August 1, 2017 : L416-L423
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EDITORIAL FOCUS

Heads you gain, tails you lose
K. M. Gilmour
August 1, 2017: R65-R66
DOI: 10.1152/ajpregu.00208.2017

RESEARCH ARTICLE | Cardiovascular and Renal Integration

Xanthine oxidase inhibition protects against Western diet-induced aortic stiffness and impaired vasorelaxation in female mice
August 1, 2017: R67-R77
DOI: 10.1152/ajpregu.00483.2016

RESEARCH ARTICLES | Fluid and Electrolyte Homeostasis

Flexible ammonia handling strategies using both cutaneous and branchial epithelia in the highly ammonia-tolerant Pacific hagfish
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DOI: 10.1152/ajpregu.00351.2016

Sustained increases in skin blood flow are not a prerequisite to initiate sweating during passive heat exposure
Nicholas Ravanelli, Ollie Jay, Daniel Gagnon
August 14, 2017: R140-R148
DOI: 10.1152/ajpregu.00033.2017

RESEARCH ARTICLES | Hormones, Reproduction and Development

CRF and urocortin 3 protect the heart from hypoxia/reoxygenation-induced apoptosis in zebrafish
Tegan A. Williams, Jillian C. Bergstrome, Juliana Scott, Nicholas J. Bernier
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DOI: 10.1152/ajpregu.00045.2017

Enhanced insulin secretion and insulin sensitivity in young lambs with placental insufficiency-induced intrauterine growth restriction
Leticia E. Camacho, Xiaochuan Chen, William W. Hay Jr., Sean W. Limesand
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Circulating motilin, ghrelin, and GLP-1 and their correlations with gastric slow waves in patients with chronic kidney disease
Gao-Jue Wu, Xu-Dong Cai, Jie Xing, Guang-Hui Zhong, Jiande D. Z. Chen
August 14, 2017: R149-R157
DOI: 10.1152/ajpregu.00317.2016

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

Effect of resistance exercise under conditions of reduced blood insulin on AMPKα Ser485/491 inhibitory phosphorylation and AMPK pathway activation
Kohei Kido, Takumi Yokokawa, Satoru Ato, Koji Sato, Satoshi Fujita
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RESEARCH ARTICLE | Neural Control

Sedentary conditions and enhanced responses to GABA in the RVLM: role of the contralateral RVLM
Maryetta D. Dombrowski, Patrick J. Mueller
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DOI: 10.1152/ajpregu.00063.2017

RESEARCH ARTICLES | Obesity, Diabetes and Energy Homeostasis

The performing animal: causes and consequences of body remodeling and metabolic adjustments in red knots facing contrasting thermal environments
François Vézina, Alexander R. Gerson, Christopher G. Guglielmo, Theunis Piersma
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Maternal and postnatal high-fat diet consumption programs energy balance and hypothalamic melanocortin signaling in nonhuman primate offspring
Elinor L. Sullivan, Heidi M. Rivera, Cadence A. True, Juliana G. Franco, Karalee Baquero, Tyler A. Dean, Jeanette C. Valleau, Diana L. Takahashi, Tim Frazee, Genevieve Hanna, Melissa A. Kirigiti, Leigh A. Bauman, Kevin L. Grove, Paul Kievit
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Cerebral oxygenation and regional cerebral perfusion responses with resistance breathing during central hypovolemia
Victoria L. Kay, Justin D. Sprick, Caroline A. Rickards
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DOI: 10.1152/ajpregu.00385.2016

Tissue-specific seasonal changes in mitochondrial function of a mammalian hibernator
Ashley B. Heim, Dillon Chung, Gregory L. Florant, Adam J. Chicco
August 14, 2017 : R180-R190
DOI: 10.1152/ajpregu.00427.2016

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Inflammatory cytokines regulate renal sodium transporters: how, where, and why
Allison E. Norlander, Meena S. Madhur
August 1, 2017: F141-F144
DOI: 10.1152/ajprenal.00465.2016

Gender difference in kidney electrolyte transport. I. Role of AT1a receptor in thiazide-sensitive Na+-Cl− cotransporter activity and expression in male and female mice
Jing Li, Ryo Hatano, Shuhua Xu, Laxiang Wan, Lei Yang, Alan M. Weinstein, Lawrence Palmer, Tong Wang
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DOI: 10.1152/ajprenal.00087.2017

PERSPECTIVE
Renal cell carcinoma: new insights and challenges for a clinician scientist
Roman Shingarev, Edgar A. Jaimes
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DOI: 10.1152/ajprenal.00480.2016

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Coping with nephron loss: transport at a price
Alan M. Weinstein
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Novel contrast mixture improves bladder wall contrast for visualizing bladder injury
Pradeep Tyagi, Joseph J. Janicki, T. Kevin Hitchens, Lesley M. Foley, Mahendra Kashyap, Naoki Yoshimura, Jonathan Kaufman
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Intravital imaging of the kidney in a rat model of salt-sensitive hypertension
Bradley T. Endres, Ruben M. Sandoval, George J. Rhodes, Silvia B. Campos-Bilderback, Malgorzata M. Kamocka, Christopher McDermott-Roe, Alexander Staruschenko, Bruce A. Molitoris, Aron M. Geurts, Oleg Palygin
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RESEARCH ARTICLE | Inflammation and Inflammatory Mediators in Kidney Disease
IL-6 promotes epithelial-to-mesenchymal transition of human peritoneal mesothelial cells possibly through the JAK2/STAT3 signaling pathway
Jing Xiao, Yanan Gong, Ying Chen, Dahai Yu, Xiaoyang Wang, Xiaoxue Zhang, Yanna Dou, Dong Liu, Genyang Cheng, Shan Lu, Wenming Yuan, Yansheng Li, Zhanzheng Zhao
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RESEARCH ARTICLE | Mechanism and Treatment of Renal Fibrosis
Urinary adenosine excretion in type 1 diabetes
Harindra Rajasekeran, Yuliya Lytvyn, Andrea Bozovic, Julie A. Lovshin, Eleftherios Diamandis, Daniel Catrnan, Mansoor Husain, Bruce A. Perkins, Andrew Advani, Heather N. Reich, Vathany Kulasingam, David Z. I. Cherney
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Inhibition of cholinergic neurotransmission by β3-adrenoceptors depends on adenosine release and A1-receptor activation in human and rat urinary bladders
Isabel Silva, Ana Filipa Costa, Silvia Moreira, Fátima Ferreirinha, Maria Teresa Magalhães-Cardoso, Isabel Calejo, Miguel Silva-Ramos, Paulo Correia-de-Sá
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DOI: 10.1152/ajprenal.00392.2016

Sex-specific computational models of the spontaneously hypertensive rat kidneys: factors affecting nitric oxide bioavailability
Ying Chen, Jennifer C. Sullivan, Aurélie Edwards, Anita T. Layton
August 1, 2017: F174-F183
DOI: 10.1152/ajprenal.00482.2016

Adaptive functional change of the contralateral kidney after partial nephrectomy
Se Young Choi, Sangjun Yoo, Dalsan You, In Gab Jeong, Cheryn Song, Bumsik Hong, Jun Hyuk Hong, Hanjong Ahn, Choung-Soo Kim
August 1, 2017: F192-F198
DOI: 10.1152/ajprenal.00058.2017

Effect of sodium nitrite on renal function and sodium and water excretion and brachial and central blood pressure in healthy subjects: a dose-response study
Jeppe Bakkestroem Rosenbaek, Safa Al Therwani, Janni Maigaard Jensen, Frank Holden Mose, Christine Wandall-Frostholm, Erling Bjerregaard Pedersen, Jesper Noegaard Bech
August 2, 2017: F378-F387
DOI: 10.1152/ajprenal.00400.2016

Adaptive changes in GFR, tubular morphology, and transport in subtotal nephrectomized kidneys: modeling and analysis
Anita T. Layton, Aurélie Edwards, Volker Vallon
August 1, 2017: F199-F209
DOI: 10.1152/ajprenal.00018.2017

MicroRNA-148b regulates megalin expression and is associated with receptor downregulation in mice with unilateral ureteral obstruction
Lu Wen, Pia K. Andersen, Dina M. U. Husum, Rikke Nørregaard, Zhanzheng Zhao, Zhangsuo Liu, Henrik Birn
August 1, 2017: F210-F217
DOI: 10.1152/ajprenal.00585.2016

Accounting for oxygen in the renal cortex: a computational study of factors that predispose the cortex to hypoxia
Chang-Joon Lee, Bruce S. Gardiner, Jennifer P. Ngo, Saptarshi Kar, Roger G. Evans, David W. Smith
August 1, 2017: F218-F236
DOI: 10.1152/ajprenal.00657.2016

A pseudo-three-dimensional model for quantification of oxygen diffusion from preglomerular arteries to renal tissue and renal venous blood
Chang-Joon Lee, Jennifer P. Ngo, Saptarshi Kar, Bruce S. Gardiner, Roger G. Evans, David W. Smith
April 5, 2017: F237-F253
DOI: 10.1152/ajprenal.00659.2016

PGF2α regulates the basolateral K channels in the distal convoluted tubule
Lijun Wang, Chengbiao Zhang, Xiao-Tong Su, Dao-Hong Lin, Peng Wu, Michal L. Schwartzman, Wen-Hui Wang
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DOI: 10.1152/ajprenal.00102.2017

Severe acute dehydration in a desert rodent elicits a transcriptional response that effectively prevents kidney injury
Matthew David MacManes
Urinary DcR2 is a novel biomarker for tubulointerstitial injury in patients with diabetic nephropathy
Jia Chen, Wei-Wei Zhang, Ke-Hong Chen, Li-Rong Lin, Huan-Zi Dai, Kai-Long Li, Jian-Guo Zhang, Lu-Quan Zheng, Bi-Qiong Fu, Ya-Ni He
August 1, 2017 : F273-F281
DOI: 10.1152/ajprenal.00579.2016

Hypoxia-inducible factor-1α activation improves renal oxygenation and mitochondrial function in early chronic kidney disease
Joanna L. Thomas, Hai Pham, Ying Li, Elanore Hall, Guy A. Perkins,Sameh S. Ali, Hemal H. Patel, Prabhleen Singh
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DOI: 10.1152/ajprenal.00689.2017

PDGF receptor-β uses Akt/mTORC1 signaling node to promote high glucose-induced renal proximal tubular cell collagen I (α2) expression
Falguni Das, Nandini Ghosh-Choudhury, Balachandar Venkatesan, Balakuntalam S. Kasinath, Goutam Ghosh Choudhury
August 1, 2017 : F309-F325
DOI: 10.1152/ajprenal.00066.2016

Sodium storage in human tissues is mediated by glycosaminoglycan expression
Michael Fischereder, Bernhard Michalke, Elisa Schmöckel, Antje Habicht, Raphael Kunisch, Ivana Pavelic, Bernadette Szabados, Ulf Schönermarck, Peter J. Nelson, Manfred Stangl
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DOI: 10.1152/ajprenal.00703.2017

Cross-sex transplantation alters gene expression and enhances inflammatory response in the transplanted kidneys
Lei Wang, Jiaping Song, Shaohui Wang, Jacenthal Buggs, Rongjun Chen, Jie Zhang, Liqing Wang, Song Rong, Wenbin Li, Jin Wei, Ruisheng Liu
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DOI: 10.1152/ajprenal.00688.2016

Magnesium improves cisplatin-mediated tumor killing while protecting against cisplatin-induced nephrotoxicity
Gopal Kumar, Malvika H. Solanki, Xiangying Xue, Rachel Mintz, Swati Madankumar, Prodyot K. Chatterjee, Christine N. Metz
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DOI: 10.1152/ajprenal.00039.2017

Architecture of the rat nephron-arterial network: analysis with micro-computed tomography
August 1, 2017 : F351-F360
DOI: 10.1152/ajprenal.00092.2017

Ovariectomy uncovers purinergic receptor activation of endothelin-dependent natriuresis
Eman Y. Gohar, Malgorzata Kasztan, Bryan K. Becker, Joshua S. Speed, David M. Pollock
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DOI: 10.1152/ajprenal.00098.2017

Developmental changes in contractile responses to cholinergic stimuli: role of calcium sensitization and related pathways
Young Jae Im, Jung Keun Lee, Sun Hee Lee, Seung-June Oh, Kwanjin Park
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DOI: 10.1152/ajprenal.00597.2017

Protein phosphatase 2C is responsible for VP-induced dephosphorylation of AQP2 serine 261
Pui W. Cheung, Lars Ueberdhk, Jack Day, Richard Bouley, Dennis Brown
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DOI: 10.1152/ajprenal.00004.2017

Apigenin ameliorates streptozotocin-induced diabetic nephropathy in rats via MAPK-NF-κB-TNF-α and TGF-β1-MAPK-fibronectin pathways
Salma Malik, Kapil Suchal, Sana Irfan Khan, Jagriti Bhatia, Kamal Kishore, Amit Kumar Dinda, Dharamvir Singh Arya
August 2, 2017 : F414-F422
ATP-citrate lyase is essential for high glucose-induced histone hyperacetylation and fibrogenic gene upregulation in mesangial cells
Dilip K. Deb, Yinyin Chen, Jian Sun, Youli Wang, Yan Chun Li
August 2, 2017 : F423-F429

Podocyte-specific knockout of cyclooxygenase 2 exacerbates diabetic kidney disease
Liming Wang, Yonggang Sha, Jingyi Bai, William Eisner, Matthew A. Sparks, Anne F. Buckley, Robert F. Spurney
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Luminal ANG II is internalized as a complex with AT1R/AT2R heterodimers to target endoplasmic reticulum in LLC-PK1 cells
Fernanda M. Ferrão, Luiza H. D. Cardoso, Heather A. Drummond, Xiao C. Li, Jia L. Zhuo, Dayene S. Gomes, Lucienne S. Lara, Adalberto Vieyra, Jennifer Lowe
August 2, 2017 : F440-F449

The effects of angiotensin-(1–7) on the exchanger NHE3 and on [Ca2+]i in the proximal tubules of spontaneously hypertensive rats
Regiane Cardoso Castelo-Branco, Deise C. A. Leite-Dellova, Fernanda Barrinha Fernandes, Gerhard Malnic, Margarida de Mello-Aires
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Protein disulfide isomerase regulates renal AT1 receptor function and blood pressure in rats
Xitao Wang, Mohammad Asghar
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Characterization of the transport activity of SGLT2/MAP17, the renal low-affinity Na+-glucose cotransporter
Michael J. Coady, Bernadette Wallendorff, Jean-Yves Lapointe
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The tryptophan/kynurenine pathway, systemic inflammation, and long-term outcome after kidney transplantation
Laura V. de Vries, Isidor Minović, Casper F.M. Franssen, Martijn van Faassen, Jan-Stephan F. Sanders, Stefan P. Berger, Gerjan Navis, Ido P. Kema, Stephan J. L. Bakker
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Urine RAS components in mice and people with type 1 diabetes and chronic kidney disease
Jan Wysocki, Anne Goodling, Mar Burgaya, Kathryn Whitlock, John Ruzinski, Daniel Batlle, Maryam Afkarian
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Role for reactive oxygen species in flow-stimulated inner medullary collecting duct endothelin-1 production
Will Wheatley, Donald E. Kohan
August 10, 2017 : F514-F521

Arginase-2 mediates renal ischemia-reperfusion injury
Wesley M. Raup-Konsavage, Ting Gao, Timothy K. Cooper, Sidney M. Morris Jr, W. Brian Reeves, Alaa S. Awad
August 10, 2017 : F522-F534

Altered expression and modulation of the two-pore-domain (K2P) mechan gated potassium channel TREK-1 in overactive human detrusor
Ricardo H. Pineda, Balachandar Nedumaran, Joseph Hypolite, Xiao-Qing Pan, Shandra Wilson, Randall B. Meacham, Anna P. Malykhina
August 10, 2017 : F535-F546
Acute exercise does not impair renal function in nondialysis chronic kidney disease patients regardless of disease stage
Davi A. Santana, Jacques R. Poortmans, Egidio Lima Dórea, Juliana Bannwart de Andrade Machado, Alan Lins Fernandes, Ana Lúcia Sá-Pinto, Bruno Gualano, Hamilton Roschel
August 10, 2017 : F547-F552
DOI: 10.1152/ajprenal.00131.2017

A model-specific role of microRNA-223 as a mediator of kidney injury during experimental sepsis
James F. Colbert, Joshay A. Ford, Sarah M. Haeger, Yimu Yang, Kyrie L. Dailey, Kristen C. Allison, Viola Neudecker, Christopher M. Evans, Vanessa L. Richardson, Kelley S. Brodsky, Sarah Faubel, Holger K. Eltzschig, Eric P. Schmidt, Adit A. Ginde
August 10, 2017 : F553-F559
DOI: 10.1152/ajprenal.00493.2016

INNOVATIVE METHODOLOGY
Functional assessment of sodium chloride cotransporter NCC mutants in polarized mammalian epithelial cells
Lena L. Rosenbaek, Federica Rizzo, Nanna MacAulay, Olivier Staub, Robert A. Fenton
August 2, 2017 : F495-F504
DOI: 10.1152/ajprenal.00088.2017

CORRIGENDUM
Corrigendum
August 10, 2017 : F560
DOI: 10.1152/ajprenal.zh2-8242-corr.2017
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Exercise training in heart failure: which training modality works best?
Stephan Gielen
August 22, 2017: 442-443
DOI: 10.1152/japplphysiol.00444.2017

RESEARCH ARTICLE | Aging and Exercise

Effect of calf-raise training on rapid force production and balance ability in elderly men
Ryoichi Ema, Shunsuke Ohki, Hirokazu Takayama, Yuji Kobayashi, Ryota Akagi
August 10, 2017: 424-433
DOI: 10.1152/japplphysiol.00539.2016
Calf-raise training with the intent to move rapidly, without special equipment or venue, induces an improvement of explosive plantar flexion force, which is attributable to neuromuscular rather than musculotendinous adaptations. Although the training effect on balance performance was trivial, we found a sign of improvement (i.e., neuromuscular adaptations during standing). In conclusion, functional neuromuscular capacity can be enhanced by home-based calf-raise exercise in elderly men, which may protect against mobility loss with aging.

Effect of exercise timing on elevated postprandial glucose levels
Yoichi Hatamoto, Ryoma Goya, Yosuke Yamada, Eichi Yoshimura, Sena Nishimura, Yasuki Higaki, Hiroaki Tanaka
August 1, 2017: 278-284
DOI: 10.1152/japplphysiol.00608.2016
This was the first study to investigate the effect of different exercise timing (brief periodic vs. preprandial vs. postprandial exercise) on postprandial glucose (PPG) attenuation in active healthy men. We demonstrated that brief periodic exercise attenuated peak PPG levels more than preprandial and postprandial exercise, particularly in the morning. Additionally, PPG rebounded soon after discontinuing postprandial exercise. Thus, brief periodic exercise may be better than preprandial and postprandial exercise at attenuating PPG levels.

Ventricular action potential adaptation to regular exercise: role of β-adrenergic and KATP channel function
Xinrui Wang, Robert H. Fitts
August 1, 2017: 285-296
DOI: 10.1152/japplphysiol.00197.2017
Our data demonstrated that regular exercise prolonged the action potential and Ca2+ transient durations in myocytes isolated from apex and base regions at 1-Hz and shortened both at 10-Hz stimulation. Novel findings were that wheel running shifted the β-adrenergic receptor agonist dose-response curve rightward compared with controls by reducing β1-adrenergic receptor responsiveness and that, at the high activation rate, myocytes from trained animals showed higher KATP channel function.

Inflammatory responses to acute elevations of carbon dioxide in mice
Stephen R. Thom, Veena M. Bhopale, JingPing Hu, Ming Yang
August 1, 2017: 297-302
DOI: 10.1152/japplphysiol.00343.2017
Elevated levels of CO2 are often found in indoor air and cause adverse health effects, but the mechanisms have not been identified. In a murine model, environmentally relevant levels of CO2 were found to cause diffuse vascular damage because neutrophils are stimulated to produce microparticles that contain high concentrations of interleukin-1β.

Aortic arch compliance and idiopathic unilateral vocal fold paralysis
Reza Behkam, Kara E. Roberts, Andrew J. Bierhals, M. Eileen Jacobs, Julia D. Edgar, Randal C. Paniello, Gayle Woodson, Jonathan P. Vande Geest, Julie M. Barkmeier-Kraemer
August 1, 2017: 303-309
DOI: 10.1152/japplphysiol.00239.2017
Unilateral vocal fold paralysis results from impaired function of the recurrent laryngeal nerve (RLN) impacting breathing, swallowing, and voice production. A large proportion of adults suffering from this disorder have an idiopathic etiology (i.e., unknown cause). The current study determined that individuals diagnosed with left-sided idiopathic vocal fold paralysis exhibited significantly greater compliance than age- and sex-matched controls. These seminal findings suggest a link between aortic arch compliance levels and RLN function.

Ten days of repeated local forearm heating does not affect cutaneous vascular function
We show for the first time that 10 days of repeated forearm heating is not sufficient to improve cutaneous vascular responsiveness in recreationally active young adults. In addition, this is the first study to investigate cutaneous cholinergic sensitivity and forearm blood flow following repeated local heat exposure. Our data add to the limited studies regarding repeated local heating of the cutaneous vasculature.

Exercise training in Tgαq*44 mice during the progression of chronic heart failure: cardiac vs. peripheral (soleus muscle) impairments to oxidative metabolism

Functional impairments in exercise performance, cardiac function, and soleus muscle mitochondrial respiration were observed in transgenic chronic heart failure mice, evaluated in the critical period between the occurrence of an impairment of cardiac function and the terminal stage of the disease. Exercise training improved exercise performance and cardiac function, but it did not affect the impaired mitochondrial respiration. Factors “upstream” of mitochondria, including an enhanced cardiovascular O2 delivery, were mainly responsible for the functional improvement.

Beta-1 vs. beta-2 adrenergic control of coronary blood flow during isometric handgrip exercise in humans

In this study, we evaluated the role of vascular β1 vs. β2 receptors in coronary exercise hyperemia in a single-blind, randomized, crossover study in healthy men. In response to isometric handgrip exercise, blood flow velocity in the left anterior descending coronary artery was significantly greater with esmolol compared with propranolol. These findings increase our understanding of the individual and combined roles of coronary β1 and β2 adrenergic receptors in humans.

Nonlinearities of heart rate variability in animal models of impaired cardiac control: contribution of different time scales

Although heart rate variability (HRV) dynamics is widely assumed to be nonlinear, nonlinearity tests are rarely used to check this hypothesis. By adopting multiscale entropy (MSE) and refined MSE (RMSE) as the discriminating statistic for nonlinearity test, we show that nonlinear dynamics varies with time scale and the type of cardiac dysfunction. Moreover, as complexity metrics and nonlinearities provide complementary information, we strongly recommend using the test for nonlinearity as an additional index to characterize HRV.

The impact of ocular hemodynamics and intracranial pressure on intraocular pressure during acute gravitational changes

A significant percentage of astronauts present anatomical changes in the posterior eye tissues after spaceflight. Hypothesized increases in ocular blood volume and intracranial pressure (ICP) in space have been considered to be likely factors. In this work, we provide a novel numerical model of the eye that incorporates ocular hemodynamics, gravitational forces, and ICP changes. We find that changes in ocular hemodynamics govern the response of intraocular pressure during acute gravitational change.

Physical activity modulates corticospinal excitability of the lower limb in young and old adults

Transcranial magnetic stimulation was used to determine whether achieving the recommended 10,000 steps/day for optimal health influenced the excitability of the corticospinal tract projecting to the knee extensor muscles. Irrespective of age and sex, individuals who achieved >10,000 steps/day had lower corticospinal excitability than those who performed <10,000 steps/day, possibly representing greater control of inhibitory and excitatory networks. Physical activity involving >10,000 steps/day may mediate its effects on the nervous system by decreasing corticospinal excitability.
Influence of sex, menstrual cycle, and oral contraceptives on cerebrovascular resistance and cardiorespiratory function during Valsalva or standing
Syed Abidi, Misha Nili, Stephania Serna, Simon Kim, Christopher Hazlett, Heather Edgell
August 3, 2017 : 375-386
DOI: 10.1152/japplphysiol.00035.2017
We have found sex differences in the cerebrovascular response to the Valsalva maneuver and standing. Men have greater cerebral vasoconstriction (or women have greater cerebral vasodilation) during late phase II of the Valsalva maneuver, and the cerebrovascular resistance index increases in men, but not in women, during standing. Furthermore, our findings indicate that both the menstrual cycle and oral contraceptive use can influence cardiovascular function both at rest and during active standing.

Individual hemoglobin mass response to normobaric and hypobaric “live high–train low”: A one-year crossover study
August 3, 2017 : 387-393
DOI: 10.1152/japplphysiol.00932.2016
This is the first study to compare individual hemoglobin mass (Hbmass) response to normobaric and hypobaric live high-train low using a same-subject crossover design. The main findings indicate that hypobaric and normobaric hypoxia evoked a similar mean increase in Hbmass following 18 days of live high-train low. Notable variability and reproducibility in individual Hbmass responses between athletes was observed, indicating the importance of evaluating individual Hbmass response to altitude training.

Increased left ventricular extracellular volume and enhanced twist function in type 1 diabetic individuals
August 3, 2017 : 394-401
DOI: 10.1152/japplphysiol.00012.2017
Individuals with type 1 diabetes, with normal left ventricular structure and function (ejection fraction and strain), have signs of interstitial fibrosis, measured with MRI as increased extracellular volume fraction and increased native myocardial T1, which significantly correlated with a number of measures of augmented left ventricular twist function. These measures may be useful in detecting the early stages of diabetic cardiomyopathy.

Effect of age, diet, and tissue type on PCr response to creatine supplementation
Marina Yazigi Solis, Guilherme Giannini Artioli, Maria Concepción García Otaduy, Claudia da Costa Leite, Walquiria Arruda, Raquel Ramos Veiga, Bruno Gualano
August 10, 2017 : 407-414
DOI: 10.1152/japplphysiol.00248.2017
A standardized creatine supplementation protocol (0.3 g·kg−1·day−1 for 7 days) effectively increased muscle, but not brain, phosphorylcreatine. Older participants responded better than younger participants whereas vegetarians responded better than omnivores. Responses to supplementation are thus dependent on age, tissue, and diet. This suggests that a single “universal” protocol, originally designed for increasing muscle creatine in young individuals, may lead to heterogeneous muscle responses in different populations or even no responses in tissues other than skeletal muscle.

Ocular changes over 60 min in supine and prone postures
August 10, 2017 : 415-423
DOI: 10.1152/japplphysiol.00687.2016
We show that gravity has pronounced transient and sustained effects on the eye by making detailed ocular measurements over 60 min in the supine and prone postures. These data inform our understanding of how gravitational forces can affect ocular structures, which is essential for hypothesizing how ocular changes could occur with microgravity exposure.

Experimental intermittent ischemia augments exercise-induced inflammatory cytokine production
August 10, 2017 : 434-441
DOI: 10.1152/japplphysiol.01006.2016
We demonstrate that ischemic, small-muscle endurance exercise elicits local inflammatory cytokine production compared with nonischemic exercise. The present study advances our knowledge of the inflammatory response to exercise in a partial ischemic state, which may be relevant for understanding the therapeutic effects of exercise training for people with ischemic cardiovascular disease-associated comorbidities.

Postmeal exercise blunts postprandial glucose excursions in people on metformin monotherapy
Melissa L. Erickson, Jonathan P. Little, Jennifer L. Gay, Kevin K. McCully, Nathan T. Jenkins
The interactive effects of metformin and exercise on key physiological outcomes remain an area of controversy. Findings from this study show that the combination of metformin monotherapy and moderate-intensity postmeal exercise led to beneficial reductions in postprandial glucose excursions. Postmeal exercise may be a useful strategy for the management of postprandial glucose in people on metformin.

Postexercise cold water immersion modulates skeletal muscle PGC-1α mRNA expression in immersed and nonimmersed limbs: evidence of systemic regulation
Robert Allan, Adam P. Sharples, Graeme L. Close, Barry Drust, Sam O. Shepherd, John Dutton, James P. Morton, Warren Gregson
August 22, 2017 : 451-459
DOI: 10.1152/japplphysiol.00096.2017

We report for the first time that postexercise cold water immersion of one limb also enhances PGC-1α expression in a contralateral, nonimmersed limb. We suggest that increased systemic β-adrenergic stimulation, and not localized cooling per se, exerts regulatory effects on local signaling cascades, thereby modulating PGC-1α expression. Therefore, these data have important implications for research designs that adopt contralateral, nonimmersed limbs as a control condition while also increasing our understanding of the potential mechanisms underpinning cold-mediated PGC-1α responses.

Skeletal muscle morphology, protein synthesis, and gene expression in Ehlers-Danlos syndrome
Rie H. Nygaard, Jakob K. Jensen, Nicol C. Voermans, Katja M. Heinemeier, Peter Schjerling, Lars Holm, Jakob Agergaard, Abigail L. Mackey, Jesper L. Andersen, Lars Remvig, Michael Kjaer
August 22, 2017 : 482-488
DOI: 10.1152/japplphysiol.01044.2016

This study is the first of its kind to systematically investigate muscle biopsies from Ehlers-Danlos patients, focusing on muscle structure and function. These patients suffer from severe muscle symptoms, but in our study they show surprisingly normal muscle findings, which points toward indirect muscle symptoms originating from the surrounding connective tissue. These findings have basal physiological importance and implications for future physiotherapeutic treatment options for these patients.

Reflex cardiorespiratory events from esophageal origin are heightened by preterm birth
Stéphanie Nault, Nathalie Samson, Charlène Nadeau, Djamal Djeddi, Jean-Paul Praud
August 22, 2017 : 489-497
DOI: 10.1152/japplphysiol.00915.2016

Preterm birth heightens the cardiorespiratory events triggered by esophageal stimulation. The most extensive cardiorespiratory events are induced by simultaneous stimulation of the proximal and distal esophagus.

INNOVATIVE METHODOLOGIES

A model for in vivo analysis of sudomotor sympathetic C-fiber activation and human sweat gland output
Gary W. Mack
August 3, 2017 : 317-325
DOI: 10.1152/japplphysiol.01070.2016

A model for quantitative assessment of C-fiber function in human skin using intradermal electrical stimulation and local sweat rate measurements has been developed. This new electrically induced sweating model is nonpainful and allows for a complete stimulus-response curve plotting the area under the local sweat rate-time curve vs. the log10 stimulus frequency. The model has good reproducibility and should provide a means of assessing the progression of small C-fiber peripheral neuropathy in humans.

Comparison of the vasodilatory effects of sodium nitroprusside vs. nitroglycerin
Sushant M. Ranadive, Andy R. Eugene, Gabrielle Dillon, Wayne T. Nicholson, Michael J. Joyner
August 10, 2017 : 402-406
DOI: 10.1152/japplphysiol.00167.2017

We compared the vasodilatory capacities of NTG vs. SNP at similar concentration doses and rates into the forearm. Based on the results of the study, it may be feasible to use intra-arterial NTG as a measure of endothelial-independent vasodilator in research studies. However, NTG dosing may need to be higher if used as an endothelial-independent vasodilator due to significant differences in the vasodilatory effects during higher doses of SNP compared with NTG.

Application of Euclidean distance mapping for assessment of basement membrane thickness distribution in asthma
Leila Mostaco-Guidolin, Soheil Hajimohammadi, Dragoș M. Vasilescu, Tillie-Louise Hackett
The described application of Euclidean distance mapping provides an unbiased approach to study the extent and thickness distribution of changes in tissue structures. This approach will enable researchers to use computer-aided analysis of structural changes within lung tissue to understand the heterogeneity of airway remodeling in lung diseases.

LETTER TO THE EDITORS

Rethinking Vo2max: right problem, wrong solution (Letter to the Editor regarding Poole and Jones’ “Measurement of the maximum oxygen uptake Vo2max: Vo2peak is no longer acceptable”)
Dan M. Cooper
August 22, 2017: 498

Reply to Cooper’s letter in reference to: Measurement of the maximum oxygen uptake Vo2max: Vo2peak is no longer acceptable
David C. Poole, Andrew M. Jones
August 22, 2017: 499

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NEURO FORUM | Control of Movement

Using theoretical models from adult stroke recovery to improve use of noninvasive brain stimulation for children with congenital hemiparesis
Yin-Liang Lin, Kelsey A. Potter-Baker
May 24, 2017: 1435-1438

RESEARCH ARTICLE | Biology of Neuroengineering Interfaces

Activation of ganglion cells and axon bundles using epiretinal electrical stimulation
May 31, 2017: 1457-1471

RESEARCH ARTICLE | Control of Coordinated Movements
Contrasting speed-accuracy tradeoffs for eye and hand movements reveal the optimal nature of saccade kinematics
Atul Gopal, Sumitash Jana, Aditya Murthy
July 5, 2017 : 1664-1676
DOI: 10.1152/jn.00329.2017

The optimality of saccade kinematics has been suggested by modeling studies but experimental evidence is lacking. However, we observed that, when subjects voluntarily modulated their hand velocity, the velocity of saccades accompanying these hand movements was also modulated, suggesting a shared kinematic plan for eye and hand movements. We leveraged this modulation to show that saccades had less endpoint accuracy when their velocity decreased, illustrating that normometric saccades have optimal speed and accuracy.

RESEARCH ARTICLE | Control of Homeostasis
The proinflammatory cytokine tumor necrosis factor-α excites subfornical organ neurons
Nick J. Simpson, Alastair V. Ferguson
June 21, 2017 : 1532-1541
DOI: 10.1152/jn.00238.2017

Considerable recent evidence has suggested important links between inflammation and the pathological mechanisms underlying hypertension. The present study describes cellular mechanisms through which acute and long-term exposure of tumor necrosis factor-α (TNF-α) influences the activity of subfornical organ neurons by modulating the voltage-gated transient Na+ current. This provides critical new information regarding the specific pathological mechanisms through which inflammation and TNF-α in particular may result in the development of hypertension.

RESEARCH ARTICLES | Control of Movement
Dynamics of human subthalamic neuron phase-locking to motor and sensory cortical oscillations during movement
Witold J. Lipski, Thomas A. Wozny, Ahmad Alhourani, Efstatios D. Kondylis, Robert S. Turner, Donald J. Crammond, Robert Mark Richardson
June 7, 2017 : 1472-1487
DOI: 10.1152/jn.00964.2016

Current models of basal ganglia-thalamocortical networks do not adequately explain simple motor functions, let alone dysfunction in movement disorders. Our findings provide data that inform models of human basal ganglia function by demonstrating how movement is encoded by networks of subthalamic nucleus (STN) neurons via dynamic phase synchronization with cortex. The data also demonstrate, for the first time in humans, a mechanism through which the premotor and sensory cortices are functionally connected to the STN.

Interhemispheric interactions between trunk muscle representations of the primary motor cortex
Loyda Jean-Charles, Jean-Francois Nepveu, Joan E. Deffeyes, Guillaume Elgbeili, Numa Dancause, Dorothy Barthélemy
June 14, 2017 : 1488-1500
DOI: 10.1152/jn.00778.2016

The mechanisms involved in the bilateral coordination of axial muscles during unilateral arm movement are poorly understood. We thus investigated the nature of interhemispheric interactions in axial muscles during arm motor tasks in healthy subjects. By combining different methodologies, we showed that trunk muscles receive both inhibitory and facilitatory cortical outputs during activation of arm muscles. We propose that inhibition may be conveyed mainly through interhemispheric mechanisms and facilitation by subcortical mechanisms or ipsilateral pathways.

Timing during transitions in Bengalese finch song: implications for motor sequencing
Todd W. Troyer, Michael S. Brainard, Kristofer E. Bouchard
June 21, 2017 : 1556-1566
DOI: 10.1152/jn.00296.2017

Bengalese finch songs consist of probabilistic sequences of syllables. Previous studies revealed a strong negative correlation between transition probability and the duration of intersyllable gaps. We show here that the negative correlation is inconsistent with previous suggestions that timing at syllable transitions is governed by a race between competing alternatives. Rather, the data suggest that syllable selection happens early during the gap, with gap timing determined chiefly by the latency to syllable initiation.

Long-interval intracortical inhibition is asymmetric in young but not older adults
A.-M. Vallence, E. Smalley, P. Drummond, G. R. Hammond
June 21, 2017 : 1581-1590
DOI: 10.1152/jn.00794.2016

In younger adults, more sensitive and more powerful long-interval intracortical inhibitory circuits are evident in the hemisphere controlling the more dexterous hand; this is not the case in older adults, for whom long-interval intracortical inhibitory circuits are symmetric and more variable than in younger adults. We speculate that the highly sensitive and powerful long-interval intracortical inhibition circuits in the dominant hemisphere play a
The role in manual dexterity.

**RESEARCH ARTICLES | Higher Neural Functions and Behavior**

Comparison of the VTA and LC response to methylphenidate: a concomitant behavioral and neuronal study of adolescent male rats
Tahseen J. Karim, Cruz Reyes-Vazquez, Nachum Dafny
June 14, 2017 : 1501-1514
DOI: 10.1152/jn.00145.2017

The same dose of 0.6, 2.5, and 10 mg/kg methylphenidate (MPD) elicits either behavioral sensitization or tolerance in adolescent rats. There is a direct correlation between the ventral tegmental area (VTA) and locus coeruleus (LC) neuronal response to chronic MPD exposure. Both the VTA and LC are involved in the behavioral and neurophysiological effects of chronic MPD.

Task-specific, dimension-based attentional shaping of motion processing in monkey area MT
Bastian Schledde, F. Orlando Galashan, Magdalena Przybyla, Andreas K. Kreiter, Detlef Wegener
June 28, 2017 : 1542-1555
DOI: 10.1152/jn.00183.2017

Cortical processing serving visual perception prioritizes information according to current task requirements. We provide evidence in favor of a dimension-based attentional mechanism addressing all neurons that process visual information in the task-relevant feature domain. Behavioral tasks required monkeys to attend either color or motion, causing modulations of response strength, variability, latency, and baseline activity of motion-selective monkey area MT neurons irrespective of the attended motion direction but specific to the attended feature dimension.

Caffeine accelerates recovery from general anesthesia via multiple pathways
Robert Fong, Suhail Khokhar, Atif N. Chowdhury, Kelvin G Xie, Josiah Hiu-Yuen Wong, Aaron P. Fox, Zheng Xie
June 28, 2017 : 1591-1597
DOI: 10.1152/jn.00393.2017

Currently, there is no method to accelerate emergence from anesthesia. Patients “wake” when they clear the anesthetic from their systems. Previously, we have shown that caffeine can accelerate emergence from anesthesia. In this study, we show that caffeine is effective even at high levels of anesthetic. We also show that caffeine operates by both elevating intracellular cAMP levels and by blocking adenosine receptors. This complicated pharmacology makes caffeine especially effective in accelerating emergence from anesthesia.

The cerebellum does more than sensory prediction error-based learning in sensorimotor adaptation tasks
Peter A. Butcher, Richard B. Ivry, Sheng-Han Kuo, David Rydz, John W. Krakauer, Jordan A. Taylor
June 21, 2017 : 1622-1636
DOI: 10.1152/jn.00451.2017

Individuals with cerebellar pathology are impaired in sensorimotor adaptation. This deficit has been attributed to an impairment in error-based learning, specifically, from a deficit in using sensory prediction errors to update an internal model. Here we show that these individuals also have difficulty in discovering an aiming solution to overcome their adaptation deficit, suggesting a new role for the cerebellum in sensorimotor adaptation tasks.

**RESEARCH ARTICLE | Neural Circuits**

Regulation of axonal regeneration following spinal cord injury in the lamprey
Jessica A. Benes, Kylie N. House, Frank N. Burks, Kris P. Conaway, Donald P. Julien, Jeffrey P. Donley, Michael A. Iyamu, Andrew D. McClellan
May 3, 2017 : 1439-1456
DOI: 10.1152/jn.00986.2016

Lampreys with rostral spinal cord injury (SCI) exhibited greater axonal regeneration of descending brain neurons and more rapid recovery of locomotor muscle activity below the lesion site compared with animals with caudal SCI. In addition, following rostral SCI, most injured reticulospinal (RS) neurons displayed the “injury phenotype,” whereas following caudal SCI, most injured neurons had normal electrical properties. We hypothesize that following caudal SCI, the spared synapses of injured RS neurons might limit axonal regeneration and behavioral recovery.

**RESEARCH ARTICLES | Sensory Processing**

Dynamic mechanisms of visually guided 3D motion tracking
Kathryn Bonnen, Alexander C. Huk, Lawrence K. Cormack
June 21, 2017 : 1515-1531
We characterize motion perception continuously in all directions using an ecologically relevant, manual target tracking paradigm we recently developed. This approach reveals a selective impairment to the perception of motion-through-depth. Geometric considerations demonstrate that this impairment is not consistent with previously observed spatial deficits (e.g., stereomotion suppression). However, results from an examination of disparity processing are consistent with the longer latencies observed in discrete, trial-based measurements of the perception of motion-through-depth.

Sensitivity of neurons in the middle temporal area of marmoset monkeys to random dot motion
June 21, 2017: 1567-1580

We report the activity of neurons in marmoset MT in response to random-dot motion stimuli of varying coherence. The information carried by individual MT neurons was comparable to that of the macaque, and the maximum firing rates were a strong predictor of sensitivity. Our study provides key information regarding the neural basis of motion perception in the marmoset, a small primate species that is becoming increasingly popular as an experimental model.

The visual encoding of purely proprioceptive intermanual tasks is due to the need of transforming joint signals, not to their interhemispheric transfer
Léo Arnoux, Sebastien Fromentin, Dario Farotto, Mathieu Beraneck, Joseph McIntyre, Michele Tagliabue
June 14, 2017: 1598-1608

Why does the brain encode goal-oriented, intermanual tasks in a visual space, even in the absence of visual feedback about the target and the hand? We show that the visual encoding is not due to the transfer of proprioceptive signals between brain hemispheres per se, but to the need, due to the mirror symmetry of the two limbs, of transforming joint angle signals of one arm in different joint signals of the other.

Effect of whisker geometry on contact force produced by vibrissae moving at different velocities
George E. Carvell, Daniel J. Simons
August 29, 2017: 1637-1649

This study describes the geometry of facial whiskers distributed across the mystacial pad with emphasis on velocity encoding of object strikes. Findings indicate how the shapes, lengths, and thicknesses of individual hairs can contribute to sophisticated vibrissa-based tactile discrimination.

Integration of visual and tactile information in reproduction of traveled distance
Jan Churan, Johannes Paul, Steffen Klingenhoefer, Frank Bremmer
August 29, 2017: 1650-1663

This study shows that tactile and visual information can be integrated to improve the estimates of the parameters of self-motion. This, however, happens only if the two sources of information are congruent—as they are in a natural environment. In contrast, an incongruent tactile stimulus is still used as a source of information about self-motion but it is not integrated with visual information.

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

Effect of eye position during human visual-vestibular integration of heading perception
Benjamin T. Crane
June 14, 2017: 1609-1621

In multiple cortical areas visual heading is represented in retinotopic coordinates while inertial heading is in body coordinates. It remains unclear whether multisensory integration occurs in a common coordinate system. The experiments address this using a multisensory integration task with eccentric gaze positions making the effect of coordinate systems clear. The results indicate that the coordinate systems remain separate to the perceptual level and that during the multisensory task the perception depends on relative stimulus reliability.

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Original Research

Lack of direct effect of adiponectin on vascular smooth muscle cell BKCa channels or Ca2+ signaling in the regulation of small artery pressure-induced constriction
Rachael Baylie, Majid Ahmed, Adrian D. Bonev, David C. Hill-Eubanks, Thomas J. Heppner, Mark T. Nelson, Adam S. Greenstein
August 21, 2017: e13337
DOI: 10.14814/phy2.13337

Adiponectin is a major adipose-derived cytokine contributing to the influence of perivascular adipose tissue on vascular contractility. Contrary to expectation we found very little effect of adiponectin on calcium signaling or ion channel activity in vascular smooth muscle cells of resistance arteries. The results point to a more nuanced role for this adipokine in the regulation of vascular tone.

Exercise training prevents skeletal muscle plasma membrane cholesterol accumulation, cortical actin filament loss, and insulin resistance in C57BL/6J mice fed a western-style high-fat diet
Ashley G. Ambery, Lixuan Tackett, Brent A. Penque, Joseph T. Brozinick, Jeffrey S. Elmendorf
August 15, 2017: e13363
DOI: 10.14814/phy2.13363

Physical activity is known to enhance insulin action, yet mechanisms involved remain imperfectly understood. An emerging appreciation is that cholesterol accumulation in the plasma membrane impairs cortical filamentous actin structure important for insulin action. Data presented in this article suggest that an insulin-sensitizing aspect of exercise is correction of plasma membrane cholesterol and actin defects.

A computational model of 1,5-AG dynamics during pregnancy
Seyedeh M. Zekavat, Slava Butkovich, Grace J. Young, David M. Nathan, Danny Petrasek
August 17, 2017: e13375
DOI: 10.14814/phy2.13375

The importance of 1,5-anhydroglucitol (1,5-AG) as an intermediate biomarker for diabetic pregnancy is multi-fold: (1) it serves as a reliable indicator of moderate-level glycemic control, especially during early gestation; (2) it has been associated with increased risk of diabetes, independent of HbA1c and fasting glucose; and (3) it is an independent risk factor for the development of eclampsia during pregnancy. However, the clinical use of this biomarker during pregnancy has been underutilized due to physiological changes in glomerular filtration rate, plasma volume, and other hemodynamic parameters which have been hypothesized to bias gestational serum 1,5-AG concentrations. Here, we develop an in-silico model of gestational 1,5-AG by combining pre-existing physiological data in the literature with a two-compartment mathematical model, quantitatively characterizing how renal and hemodynamic factors impact measured 1,5-AG during normal pregnancy and during pregnancy with gestational diabetes and diabetes mellitus.

Involvement of midkine in the development of pulmonary fibrosis
Kenichi Misa, Yoshinori Tanino, Xintao Wang, Takefumi Nikaido, Masami Kikuchi, Yuki Sato, Ryuichi Togawa, Mishie Tanino, Shinya Tanaka, Kenji Kadomatsu, Mitsuru Munakata
August 15, 2017: e13383
DOI: 10.14814/phy2.13383
Midkine is involved in the development of pulmonary fibrosis by regulating inflammatory cell migration into the lung, and TNF-α and transforming growth factor-β expression.

**Hypoxia decreases creatine uptake in cardiomyocytes, while creatine supplementation enhances HIF activation**
Lucia Santacruz, Antonio Jose Luis Arciniegas, Marcus Darrabie, Jose G. Mantilla, Rebecca M. Baron, Dawn E. Bowles, Rajashree Mishra, Danny O. Jacobs
August 17, 2017 : e13382
DOI: 10.14814/phy2.13382

Creatine, phosphocreatine, and creatine kinases comprise an energy shuttle linking ATP production in mitochondria with cellular consumption sites. Myocytes depend on uptake by a specialized transporter to maintain intracellular creatine levels. Here we demonstrate that hypoxia rapidly decreases creatine transport in cardiomyocytes in culture. Creatine supplementation of cardiomyocytes prior to exposure to hypoxia increases the cellular content of ATP and phosphocreatine and enhances the HIF-1-mediated adaptive physiological responses to hypoxia.

**Alterations in fatty acid metabolism and sirtuin signaling characterize early type-2 diabetic hearts of fructose-fed rats**
Phing-How Lou, Eliana Lucchinetti, Katrina Y. Scott, Yiming Huang, Manoj Gandhi, Martin Hersberger, Alexander S. Clanachan, Hélène Lemieux, Michael Zaugg
August 21, 2017 : e13388
DOI: 10.14814/phy2.13388

In this study, we examined the impact of fructose feeding on cardiac fatty acid metabolism and oxidative stress. We found that sirtuin function does not necessarily reflect the degree of change in protein abundance. This may represent one of the earliest events in the development of biochemical derangements that will ultimately lead to inflammation and remodeling in the diabetic heart.

**Evidence for ammonium conductance in a mouse thick ascending limb cell line**
Soojung Lee, Jonathan Park, Jun Ming Li, Kathy Li, Inyeong Choi
August 21, 2017 : e13379
DOI: 10.14814/phy2.13379

In this study, we examined an ammonium conductance in a mouse thick ascending limb cell line. The conductance we identified is different from the previously reported ammonium conductance in the thick ascending limb of the nephron and suggests that the protein responsible for this conductance might be a new ammonium channel.

**Acute heat stress activated inflammatory signaling in porcine oxidative skeletal muscle**
Shanthi Ganesan, Olga Volodina, Sarah C. Pearce, Nicholas K. Gabler, Lance H. Baumgard, Robert P. Rhoads, Joshua T. Selsby
August 21, 2017 : e13397
DOI: 10.14814/phy2.13397

Heat stress activated inflammatory signaling in the porcine semitendinosus red muscle via the AP-1 pathway and early activation of the NF-κB pathway.

**Nfib hemizygous mice are protected from hyperoxic lung injury and death**
Vasantha H. S. Kumar, Joseph Chaker El Khoury, Richard Gronostajski, Huamei Wang, Lori Nielsen, Rita M. Ryan
August 21, 2017 : e13398
DOI: 10.14814/phy2.13398

Adult Nfib hemizygous mice are relatively resistant to hyperoxia compared to wild-type littermates. Mechanisms contributing to this resistance are not clear; however, transcription factors such as Nfib may regulate cell survival and play a role in modulating postnatal lung development.

**Paradoxical effect of IKKβ inhibition on the expression of E3 ubiquitin ligases and unloading-induced skeletal muscle atrophy**
Svetlana P. Belova, Boris S. Shenkman, Tatiana Y. Kostrominova, Tatiana L. Nemirovskaya
August 24, 2017 : e13291
DOI: 10.14814/phy2.13291

IMD 0354 treatment during unloading: had no effect on loss of muscle mass; increased mRNA levels of MuRF1 and MAFb; increased levels of pFoxO3; and had no effect on levels of Bcl alpha3, p105, and p50 proteins. Our study for the first time showed that inhibiting IKKβ in vivo during 3-day unloading failed to inhibit expression of ubiquitin ligases and prevent muscle atrophy.
Original Research

Bayesian estimation of physiological parameters governing a dynamic two-compartment model of exhaled nitric oxide
Patrick Muchmore, Edward B. Rappaport, Sandrah P. Eckel
August 3, 2017 : e13276
DOI: 10.14814/phy2.13276

In this work, we drop the steady-state assumption in the classic two-compartment model. Instead, we have developed a new parameter estimation approach based on measuring and adjusting for a continuously varying flow rate over the entire FeNO maneuver. We have developed a Bayesian inference framework for the parameters of the partial differential equation underlying this model. Based on multiple flow FeNO data from the Southern California Children's Health Study, we use observed and simulated NO concentrations to demonstrate that our approach has reasonable computation time and is consistent with existing steady-state approaches, while our inferences consistently offer greater precision than current methods.

Renoprotective effect of topiroxostat via antioxidant activity in puromycin aminonucleoside nephrosis rats
Yosuke Kawamorita, Takeshi Shiraishi, Yoshifuru Tamura, Takanori Kumagai, Shigeru Shibata, Yoshihide Fujigaki, Makoto Hosoyamada, Takahiko Nakagawa, Shunya Uchida
August 3, 2017 : e13358
DOI: 10.14814/phy2.13358

Topiroxostat ameliorates proteinuria and renal injury independently of serum UA level in PAN-induced nephrotic rats. Topiroxostat exerts a renoprotective effect owing to its antioxidant effects and property to lower UA levels in the kidney cortex.

Molecular and functional characterization of the voltage-gated proton channel in zebrafish neutrophils
Adisorn Ratanayotha, Takafumi Kawai, Shin-ichi Higashijima, Yasushi Okamura
August 3, 2017 : e13345
DOI: 10.14814/phy2.13345

We investigated for the first time the molecular and functional characteristics of voltage-gated proton channel (Hv1/VSOP) in zebrafish neutrophils. We also found that zebrafish Hv1, unlike its mammalian orthologs, is less sensitive to zinc ion. This phenomenon appears to be correlated with high concentration of zinc in blood serum of zebrafish.

Cerebrovascular and ventilatory responses to acute normobaric hypoxia in girls and women
Laura E. Morris, Daniela Flück, Philip N. Ainslie, Ali M. McManus
August 3, 2017 : e13372
DOI: 10.14814/phy2.13372

We observe for the first time in children, that cerebral perfusion of the extracranial arteries increases in response to an acute 1 h about of hypoxia. This response is mediated by greater increases in anterior flow in girls, opposed to posterior flow in women. Furthermore, the increase in ventilation and respiratory drive were comparable between girls and women, though the pattern of breathing differed.

Energy expenditure responses to exercise training in older women
Xuewen Wang, Kimberly P. Bowyer, Ryan R. Porter, Charity B. Breneman, Sabra S. Custer
August 3, 2017 : e13360
DOI: 10.14814/phy2.13360

Aerobic exercise training did not change total daily energy expenditure, resting metabolic rate, nonexercise activity thermogenesis, or total physical activity in a sample of older women. Dose of exercise did not influence any of the responses. However, exploratory analyses suggested that compensatory changes in behavioral and physiological aspects of physical activity occurred in a subgroup of women.

Vitamin D supplementation of initially vitamin D-deficient mice diminishes lung inflammation with limited effects on pulmonary epithelial integrity
We report no beneficial effects on lung epithelial integrity by vitamin D supplementation of initially vitamin D-deficient mice. However, signs of lung inflammation induced by deficiency were diminished by subsequent supplementation with vitamin D.

Human lactoferrin induces asthmatic symptoms in NC/Nga mice
Kenjiro Nagaoka, Tatsuo Ito, Keiki Ogino, Eri Eguchi, Yoshihisa Fujikura
August 3, 2017 : e13365
DOI: 10.14814/phy2.13365

Lactoferrin is a glycoprotein that has anti-bacterial and anti-viral effects, and is commercially used as a supplement. Intranasal administration of human lactoferrin into NC/Nga mice induced allergic airway inflammation including increase in airway hyperresponsiveness, increase in inflammatory cells in bronchoalveolar fluid and lung tissue, and detection of specific IgG. These findings suggest that further study is needed for commercial uses of lactoferrin supplements.

Do anabolic nutritional supplements stimulate human growth hormone secretion in elderly women with heart failure?
Ellen T. H. C. Smeets, Scott E. Schutzler, Jeanne Y. Wei, Gohar Azhar, Robert R. Wolfe
August 4, 2017 : e13366
DOI: 10.14814/phy2.13366

Human growth hormone (HGH) concentration was increased in elderly women with heart failure following consumption of a mixture of protein, carbohydrate and fat, but not following consumption of a mixture of essential amino acids. The stimulatory effect of the protein/carbohydrate/fat mixture was presumably mediated by factors other than increases in free amino acid concentrations, as amino acid concentrations were elevated to a greater extent following ingestion of the essential amino acids.

The effect of different acute muscle contraction regimens on the expression of muscle proteolytic signaling proteins and genes
Satoru Ato, Yuhei Makanae, Kohei Kido, Kohei Sase, Naomi Yoshii, Satoshi Fujita
August 4, 2017 : e13364
DOI: 10.14814/phy2.13364

We investigated the effect of different modes of contraction during resistance exercise with standardized force–time integral on proteolytic signaling in skeletal muscle. Results indicate that divergent mode of contraction itself does not influence proteolytic signaling under the same force–time integral.

Endurance performance is enhanced by intermittent hyperbaric exposure via up-regulation of proteins involved in mitochondrial biogenesis in mice
Junichi Suzuki
August 4, 2017 : e13349
DOI: 10.14814/phy2.13349

Exercise training with intermittent hyperbaric exposure represents a beneficial strategy for increasing endurance performance by facilitating oxidative and glycolytic capacities and the expression of proteins involved in mitochondrial biogenesis in the hindlimb muscles.

Cardiorespiratory physiological phenotypic plasticity in developing air-breathing anabantid fishes (Betta splendens and Trichopodus trichopterus)
Jose F. Mendez-Sanchez, Warren W. Burggren
August 4, 2017 : e13359
DOI: 10.14814/phy2.13359

Developmental plasticity of cardiorespiratory physiology was determined in two air-breathing anabantid fishes (Betta splendens and Trichopodus trichopterus) by chronic rearing in nocturnal hypoxia. Hypoxic rearing increased hypoxic tolerance in Betta, which inhabits temporary ponds with nocturnal hypoxia. Trichopodus, inhabiting more permanent oxygenated bodies of water, showed few responses to hypoxia, reflecting a lower degree of developmental phenotypic plasticity.

Using the Portapres® for the measurement of toe arterial blood pressure during movement: is it valid and reliable?
Joshua A. Goreham, Derek S. Kimmerly, Michel Ladouceur
August 7, 2017 : e13369
This article investigates the validity of using the Portapress for the measurement of toe blood pressure during movements. This article reports a moderate correlation with changes in toe height during cycling, good concurrent validity, and good interday reliability. As such, the Portapress can be a good measuring instrument for investigating changes in toe blood pressure during movements.

**Tracking of unfamiliar odors is facilitated by signal amplification through anoctamin 2 chloride channels in mouse olfactory receptor neurons**
Franziska Neureither, Nadine Stowasser, Stephan Frings, Frank Möhrlen
August 7, 2017 : e13373

When confronted with an unfamiliar odor at low concentration, mice require a special signal amplification mechanism for tracking that odor. The calcium-activated chloride channel anoctamin 2 provides that amplification in olfactory receptor neurons. Anoctamin 2 knockout mice are unable to find the scented reward.

**Intramuscular stimulation of tibialis anterior in human subjects: the effects of discharge variability on force production and fatigue**
Michael Leitch, Rachael Brown, Vaughan G. Macefield
August 7, 2017 : e13326

Intramuscular stimulation of tibialis anterior revealed that irregular trains of stimulation generate greater force responses that regular trains of the same mean frequency.

**The effects of heat stress on morphological properties and intracellular signaling of denervated and intact soleus muscles in rats**
Takashi Ohira, Akira Higashihata, Masaya Seki, Yoichi Kurata, Yayoi Kimura, Hisashi Hirano, Yoichiro Kusakari, Susumu Minamisawa, Takashi Kudo, Satoru Takahashi, Yoshinobu Ohira, Satoshi Furukawa
August 7, 2017 : e13350

Repeated heat stress application to rats using a warm water bath (42°C, 30 min/day, every other day) promoted growth-related hypertrophy in sham-operated soleus muscles and attenuated atrophy in denervated soleus muscles. The results indicated that the beneficial effects of heat stress on the morphological properties of muscles were induced regardless of innervation. However, the responses of intracellular signalings to the heat stress were distinct between the innervated and denervated muscles.

**Expression of the aquaglyceroporin HC-9 in a freeze-tolerant amphibian that accumulates glycerol seasonally**
Brian Stogsdill, James Frisbie, Carissa M. Krane, David L. Goldstein
August 7, 2017 : e13331

We describe a homolog of the aquaglyceroporin protein AQP9 from a freeze-tolerant amphibian that accumulates glycerol as a cryoprotectant. HC-9 mRNA and protein are expressed in many tissues but are uniquely upregulated in liver during cold conditions. We suggest that glycerol transport via HC-9 contributes to the cellular mechanisms required to survive the thermal challenges of cold, freezing, and thawing.

**Enhanced maximal exercise capacity, vasodilation to electrical muscle contraction, and hind limb vascular density in ASIC1a null mice**
Heather A. Drummond, Lusha Xiang, Alejandro R. Chade, Robert Hester
August 7, 2017 : e13368

Metabolic factors, such as extracellular acidosis, contribute to local vasodilation and hyperemia during skeletal muscle contraction. Here, we show that ASIC1a, a protein that forms ion channels gated by extracellular protons, negatively contributes to local control of skeletal muscle vascular diameter, blood flow, and exercise capacity.

**Ingesting a small amount of beer reduces arterial stiffness in healthy humans**
Masato Nishiwaki, Naoki Kora, Naoyuki Matsumoto
August 7, 2017 : e13381

Epidemiological studies report that arterial stiffness is lower in mild-to-moderate drinkers than in heavy drinkers and nondrinkers, but this is the first
study to examine whether ingesting a small amount of beer (200 or 350 mL), such as might be consumed every day by mild drinkers, reduces arterial stiffness acutely. Our findings suggest that ingesting a small amount of beer does exert positive effects (reduction) on arterial stiffness.

Effects of plyometric and isometric training on muscle and tendon stiffness in vivo
Keitaro Kubo, Tomonobu Ishigaki, Toshihiro Ikebukuro
August 10, 2017 : e13374
DOI: 10.14814/phy2.13374

This is the first study to examine the effect of plyometric on muscle stiffness under active condition and tendon properties during ballistic contractions. The muscle stiffness under active condition significantly increased after plyometric training. The elongation of tendon structures during ballistic contractions increased after plyometric training. These results suggested that changes in the mechanical properties of muscle and tendon after plyometric training would be related to the enhancement of performance during stretch-shortening cycle exercise.

Torque depression following active shortening is associated with a modulation of cortical and spinal excitation: a history-dependent study
Jordan Grant, Chris J. McNeil, Leah R. Bent, Geoffrey A. Power
August 14, 2017 : e13367
DOI: 10.14814/phy2.13367

Torque depression (TD) occurs when the steady-state isometric torque which follows a shortening muscle contraction is less than that of a purely isometric contraction at the same muscle length and level of activation. The purpose of this study was to determine whether or not motoneurone and motor cortical excitability are influenced by this depressed state. We found there is a modulation of corticospinal pathways in the shortening-induced torque depressed state.

Effect of densely ionizing radiation on cardiomyocyte differentiation from human-induced pluripotent stem cells
August 10, 2017 : e13308
DOI: 10.14814/phy2.13308

Human-induced pluripotent stem cells (hiPSCs) maintained in culture are exposed to low fluences of α-particles. Irradiated hiPSCs were then differentiated into beating cardiomyocytes (hiPSC-CMs), and molecular, morphological, and functional assessments were conducted. We report that low mean absorbed doses of α-particles applied to hiPSCs does not affect their capacity to become beating cardiomyocytes, but has direct consequences on spontaneous Ca2+ beating and number of the differentiated cardiomyocytes obtained.

Evidence that central pathways that mediate defecation utilize ghrelin receptors but do not require endogenous ghrelin
Ruslan V Pustovit, Brid Callaghan, Mitchell T Ringuet, Nicole F Kerr, Billie Hunne, Ian M Smyth, Claudio Pietra, John B. Furness
August 10, 2017 : e13385
DOI: 10.14814/phy2.13385

Centrally penetrant ghrelin receptor agonists act at the defecation centers in the spinal cord to trigger propulsive contractions of the colorectum and bowel emptying. However, although the ghrelin receptor is physiologically involved in defecation control, ghrelin is not.

XOR inhibition with febuxostat accelerates pulmonary endothelial barrier recovery and improves survival in lipopolysaccharide-induced murine sepsis
Mahendra Damarla, Laura F. Johnston, Gigi Liu, Li Gao, Lan Wang, Lidenys Varela, Todd M. Kolb, Bo S. Kim, Rachel L. Damico, Paul M. Hassoun
August 10, 2017 : e13377
DOI: 10.14814/phy2.13377

Xanthine oxidase inhibition with febuxostat does not prevent pulmonary vascular permeability but rather accelerates recovery of the endothelial barrier integrity. Further, xanthine oxidase inhibition with febuxostat improves survival following lipopolysaccharide-induced murine sepsis.
Network Supervision of Adult Experience and Learning Dependent Sensory Cortical Plasticity

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- **Inflammatory cytokines regulate renal sodium transporters: how, where, and why?**
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Jing Li, Ryo Hatano, Shuhua Xu, Laxiang Wan, Lei Yang, Alan M. Weinstein, Lawrence Palmer, Tong Wang
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