REVIEW

Molecular insights into the normal operation, regulation, and multisystemic roles of K+-Cl− cotransporter 3 (KCC3)
A. P. Garneau, A. A. Marcoux, R. Frenette-Cotton, F. Mac-Way, J. L. Lavoie, P. Isenring
November 7, 2017 : C516-C532
DOI: 10.1152/ajpcell.00106.2017

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

Muscle paralysis induces bone marrow inflammation and predisposition to formation of giant osteoclasts
Brandon J. Ausk, Leah E. Worton, Kate S. Smigiel, Ronald Y. Kwon, Steven D. Bain, Sundar Srinivasan, Edith M. Gardiner, Ted S. Gross
November 7, 2017 : C533-C540
DOI: 10.1152/ajpcell.00363.2016

RESEARCH ARTICLES | Molecular Pathways in Cell Signaling

Integration of TRPC6 and NADPH oxidase activation in lysophosphatidylcholine-induced TRPC5 externalization
Pinaki Chaudhuri, Michael A. Rosenbaum, Lutz Birnbaumer, Linda M. Graham
November 7, 2017 : C541-C555
DOI: 10.1152/ajpcell.00028.2017

Detachment-induced E-cadherin expression promotes 3D tumor spheroid formation but inhibits tumor formation and metastasis of lung cancer cells
Phattrakorn Powan, Sudjit Luanpitpong, Xiaoqing He, Yon Rojanasakul, Pithi Chanvorachote
November 7, 2017 : C556-C566
DOI: 10.1152/ajpcell.00096.2017

RESEARCH ARTICLE | Single Cell Physiology

The role of Ca2+-activated Cl− current in tone generation in the rabbit corpus cavernosum
Karen L. Hannigan, Caoimhin S. Griffin, Roddy J. Large, Gerard P. Sergeant, Mark A. Hollywood, Noel G. McHale, Keith D. Thornbury
November 1, 2017 : C475-C486
DOI: 10.1152/ajpcell.00025.2017

RESEARCH ARTICLES

Acute myotube protein synthesis regulation by IL-6-related cytokines
PLK1 regulates spindle association of phosphorylated eukaryotic translation initiation factor 4E-binding protein and spindle function in mouse oocytes
Ashley L. Severance, Keith E. Latham
November 1, 2017 : C501-C515
DOI: 10.1152/ajpcell.00075.2017

Oxidized low-density lipoprotein-induced microparticles promote endothelial monocyte adhesion via intercellular adhesion molecule 1
November 7, 2017 : C567-C574
DOI: 10.1152/ajpcell.00193.2017

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PERSPECTIVE

“Calories in, calories out” and macronutrient intake: the hope, hype, and science of calories
Scott Howell, Richard Kones
November 29, 2017 : E613-E621
DOI: 10.1152/ajpendo.00111.2016

RESEARCH ARTICLE | CNS Control of Metabolism

Central effects of insulin detemir on feeding, body weight, and metabolism in rats
Joseph R. Vasselli, F. Xavier Pi-Sunyer, Daniel G. Wall, Catherine S. John, Colin D. Chapman, Paul J. Currie
November 29, 2017 : E613-E621
DOI: 10.1152/ajpendo.00111.2016

RESEARCH ARTICLE | Mitochondria Dysfunction in Aging and Metabolic Diseases
Long-term rates of mitochondrial protein synthesis are increased in mouse skeletal muscle with high-fat feeding regardless of insulin-sensitizing treatment
Sean A. Newsom, Benjamin F. Miller, Karyn L. Hamilton, Sarah E. Ehrlicher, Harrison D. Stierwalt, Matthew M. Robinson
November 29, 2017 : E552-E562
DOI: 10.1152/ajpendo.00144.2017

RESEARCH ARTICLES | Translational Physiology

Extraovarian gonadotropin negative feedback revealed by aromatase inhibition in female marmoset monkeys
Marissa Kraynak, Matthew T. Flowers, Robert A. Shapiro, Amita Kapoor, Jon E. Levine, David H. Abbott
November 1, 2017 : E507-E514
DOI: 10.1152/ajpendo.00058.2017

Dapagliflozin slows the progression of the renal and liver fibrosis associated with type 2 diabetes
Li Tang, Yuanyuan Wu, Mi Tian, C. David Sjöström, Ulrika Johansson, Xiao-Rong Peng, David M. Smith, Yufeng Huang
November 29, 2017 : E563-E576
DOI: 10.1152/ajpendo.00086.2017

RESEARCH ARTICLES

Adaptive facultative diet-induced thermogenesis in wild-type but not in UCP1-ablated mice
Gabriella von Essen, Erik Lindsund, Barbara Cannon, Jan Nedergaard
November 1, 2017 : E515-E527
DOI: 10.1152/ajpendo.00097.2017

Circulating sex steroids coregulate adipose tissue immune cell populations in healthy men
Katya B. Rubinow, Jing H. Chao, Derek Hagman, Mario Kratz, Brian Van Yserloo, Niles W. Gaikwad, John K. Amory, Stephanie T. Page
November 1, 2017 : E528-E539
DOI: 10.1152/ajpendo.00075.2017

Cross-sex testosterone therapy in ovariectomized mice: addition of low-dose estrogen preserves bone architecture
Laura G. Goetz, Ramanaiyah Mamillapalli, Maureen J. Devlin, Amy E. Robbins, Masoumeh Majidi-Zolbin, Hugh S. Taylor
November 1, 2017 : E540-E551
DOI: 10.1152/ajpendo.00161.2017

Glucose oxidation positively regulates glucose uptake and improves cardiac function recovery after myocardial reperfusion
Tingting Li, Jie Xu, Xinghua Qin, Xuoxu Hou, Yongzheng Guo, Zhenhua Liu, Jianjiang Wu, Hong Zheng, Xing Zhang, Feng Gao
November 29, 2017 : E577-E585
DOI: 10.1152/ajpendo.00014.2017

Dihydrocapsiate improved age-associated impairments in mice by increasing energy expenditure
Kana Ohyama, Katsuya Suzuki
November 29, 2017 : E586-E597
DOI: 10.1152/ajpendo.00132.2017

Optimization of tolerability and efficacy of the novel dual amylin and calcitonin receptor agonist KBP-089 through dose escalation and combination with a GLP-1 analog
Sofie Gydesen, Kim Vietz Andreassen, Sara Toftegaard Hjuler, Lars I. Hellgren, Morten Asser Karsdal, Kim Henriksen
November 29, 2017 : E598-E607
DOI: 10.1152/ajpendo.00419.2016

Glycemic control after metabolic surgery: a Granger causality and graph analysis
Elena Previti, Serenella Salinari, Alessandro Bertuzzi, Esmeralda Capristo, Stephan Bornstein, Geltrude Mingrone
November 29, 2017 : E622-E630
DOI: 10.1152/ajpendo.00042.2017

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REVIEW

Role of G protein-coupled receptors-microRNA interactions in gastrointestinal pathophysiology
Ivy Ka Man Law, David Miguel Padua, Dimitrios Iliopoulos, Charalabos Pothoulakis
November 1, 2017 : G361-G372
DOI: 10.1152/ajpgi.00144.2017

EDITORIAL FOCUS | Epithelial Biology and Secretion

KLF-5 extends its fingers to desmosomes: the next frontier for enteric epithelial research?
Narek Israelyan, Kara Gross Margolis
November 2, 2017 : G476-G477
DOI: 10.1152/ajpgi.00298.2017

EDITORIAL FOCUS | Pancreatic Physiology/Pathophysiology

Impact of prevailing thiamin levels on thiamin pyrophosphate uptake in pancreatic acinar cells: do the shuttle!
Lindsey Kennedy, Heather Francis, Gianfranco Alpini
November 1, 2017 : G373-G375
DOI: 10.1152/ajpgi.00256.2017

RESEARCH ARTICLES | Epithelial Biology and Secretion

Overactivation of intestinal sterol response element-binding protein 2 promotes diet-induced nonalcoholic steatohepatitis
November 1, 2017 : G376-G385
DOI: 10.1152/ajpgi.00174.2017

The current study highlights the role of overactivation of intestinal SREBP-2 transcription factor in the progression of hepatic fibrosis associated with diet-induced NASH. Mice with intestine-specific overexpression of SREBP-2 demonstrated more inflammation and severe fibrosis in the liver in response to 15 wk of being fed a high-cholesterol, high-fat diet as compared with their wild-type littermates. These data demonstrate a novel link between intestinal regulatory processes of cholesterol metabolism and the pathogenesis of fatty liver diseases.

Krüppel-like factor 5 is essential for maintenance of barrier function in mouse colon
Yang Liu, Martyn Chidgey, Vincent W. Yang, Agnieszka B. Białkowska
November 2, 2017 : G478-G491
DOI: 10.1152/ajpgi.00172.2017

The study is original research on the direct function of a Krüppel-like factor on intestinal barrier function, which is commonly exerted by cell junctions, including tight junctions, adherens junctions, and desmosomes. Numerous previous studies were focused on tight junctions and adherens junctions. However, this study provided a new perspective on how the intestinal barrier function is regulated by KLF5 through DSG2, a component of desmosome complexes.
Enteric serotonin and oxytocin: endogenous regulation of severity in a murine model of necrotizing enterocolitis
Kara Gross Margolis, Jennifer Vittorio, Maria Talavera, Karen Gluck, Zhishan Li, Alina Iuga, Korey Stevanovic, Virginia Saurman, Narek Israelyan, Martha G. Welch, Michael D. Gershon
November 1, 2017 : G386-G398
DOI: 10.1152/ajpgi.00215.2017

Serotonin (5-HT) and oxytocin reciprocally regulate the severity of intestinal inflammation and hepatotoxicity in a murine model of necrotizing enterocolitis (NEC). Selective depletion of mucosal 5-HT through genetic deletion or inhibition of tryptophan hydroxylase-1 ameliorates, while deletion of the 5-HT uptake transporter, which increases 5-HT availability, exacerbates the severity of NEC. In contrast, oxytocin reduces, while the oxytocin receptor antagonist atosiban enhances, NEC severity. Peripheral tryptophan hydroxylase inhibition may be useful in treatment of NEC.

PARP2 deficiency affects invariant-NKT-cell maturation and protects mice from concanavalin A-induced liver injury
Aveline Filliol, Claire Piquet-Pellorce, Sarah Dion, Valentine Genet, Catherine Lucas-Clerc, Françoise Dantzer, Michel Samson
November 1, 2017 : G399-G409
DOI: 10.1152/ajpgi.00436.2016

The genetic inactivation of Parp2, but not Parp1, protects mice from concanavalin A hepatitis. Immune cell populations are lower in the thymus, but not in the spleen, liver, or bone marrow of Parp2-deficient mice compared with wild-type mice. Spleen and liver invariant natural killer T (NKT) lymphocytes, as well as thymic T and NKT lymphocytes, are reduced in Parp2-deficient mice.

Melatonin inhibits hypothalamic gonadotropin-releasing hormone release and reduces biliary hyperplasia and fibrosis in cholestatic rats
Matthew McMillin, Sharon DeMorrow, Shannon Glaser, Julie Venter, Konstantina Kyritsi, Tianhao Zhou, Stephanie Grant, Thao Giang, John F. Greene Jr, Nan Wu, Brandi Jefferson, Fanyin Meng, Gianfranco Alpini
November 1, 2017 : G410-G418
DOI: 10.1152/ajpgi.00421.2016

We have previously demonstrated that GnRH is expressed in cholangiocytes and promotes their proliferation during cholestasis. In addition, dark therapy, which increases melatonin, reduced cholangiocyte proliferation and fibrosis during cholestasis. This study expands these studies by investigating neural GnRH regulation by melatonin during BDL-induced cholestasis by infusing melatonin into the brain. Melatonin infusion reduced cholangiocyte proliferation and fibrosis, and these effects are due to GNRH receptor 1-dependent paracrine signaling between cholangiocytes and hepatic stellate cells.

A small population of liver endothelial cells undergoes endothelial-to-mesenchymal transition in response to chronic liver injury
Jordi Ribera, Montse Pauta, Pedro Melgar-Lesmes, Bernat Córdoba, Anna Bosch, Maria Calvo, Daniel Rodrigo-Torres, Pau Sancho-Bru, Aurea Mira, Wladimiro Jiménez, Manuel Morales-Ruiz
November 2, 2017 : G492-G504
DOI: 10.1152/ajpgi.00428.2016

A subpopulation of liver endothelial cells from cirrhotic patients and mice with liver fibrosis undergoes endothelial-to-mesenchymal transition. Liver endothelial cells from healthy mice could transition into a mesenchymal phenotype in culture in response to TGF-β1 treatment. Fibrotic livers treated chronically with BMP-7 showed lower EndMT acquisition, reduced fibrosis, and improved vascular organization.

Loss of nitric oxide-mediated inhibition of purine neurotransmitter release in the colon in the absence of interstitial cells of Cajal
Leonie Durnin, Andrea Lees, Sheerien Manzoor, Kent C. Sasse, Kenton M. Sanders, Violeta N. Mutafova-Yambolieva
November 1, 2017 : G419-G433
DOI: 10.1152/ajpgi.00045.2017

This is the first study investigating the role of nitric oxide (NO) and intramuscular interstitial cells of Cajal (ICC-IM) in modulating neural release of purines in colon. We found that NO inhibited release of purines in human, monkey, and murine colons and that colons from KitW/KitW-v (W/Wv) mice, which present with partial loss of ICC-IM, demonstrated augmented neural release of purines. Interactions between nitriergic and purinergic neurotransmission may affect motility in disease conditions with ICC-IM deficiencies.

Vagally mediated effects of brain stem dopamine on gastric tone and phasic contractions of the rat
Dopamine administration in the brain stem decreases gastric tone and phasic contractions. The gastric effects of dopamine are mediated via dopamine 2 receptors on neurons of the dorsal motor nucleus of the vagus. The inhibitory effects of dopamine are mediated via inhibition of the postganglionic cholinergic pathway.

Relationship of gastric emptying or accommodation with satiation, satiety, and postprandial symptoms in health
Houssam Halawi, Michael Camilleri, Andres Acosta, Maria Vazquez-Roque, Ibironke Oduyebo, Duane Burton, Irene Busciglio, Alan R. Zinsmeister
November 1, 2017 : G442-G447
DOI: 10.1152/ajpgi.00190.2017

A higher volume to comfortable fullness postprandially correlated with a higher calorie intake at ad libitum buffet meal. Gastric emptying of solids is correlated to satiation (volume to fullness and maximum tolerated volume) and satiety (the calorie intake at buffet meal) and symptoms of nausea, pain, and aggregate symptom score after a fully satiating meal. There was no significant correlation between gastric accommodation and either satiation or satiety indices, postprandial symptoms, or gastric emptying.

Effects of NK1 receptors on gastric motor functions and satiation in healthy humans: results from a controlled trial with the NK1 antagonist aprepitant
Deepti Jacob, Irene Busciglio, Duane Burton, Houssam Halawi, Ibironke Oduyebo, Deborah Rhoten, Michael Ryks, W. Scott Harmsen, Michael Camilleri
November 2, 2017 : G505-G510
DOI: 10.1152/ajpgi.00197.2017

Aprepitant increases fasting, postprandial, and accommodation gastric volumes. Aprepitant increases volume to fullness and maximum tolerated volume during a nutrient drink test. NK1 receptors are involved in the control of gastric volume and in determining postprandial satiation and symptoms.

RESEARCH ARTICLES | Nutrient Sensing, Nutrition, and Metabolism

Hamp1 mRNA and plasma hepcidin levels are influenced by sex and strain but do not predict tissue iron levels in inbred mice
November 2, 2017 : G511-G523
DOI: 10.1152/ajpgi.00307.2016

Both sex and strain have a significant effect on both hepcidin mRNA (primarily a sex effect) and plasma hepcidin levels (primarily a strain effect). Liver iron and diferric transferrin levels are not predictors of Hamp1 mRNA levels in mice, nor are the Hamp1 mRNA and plasma hepcidin levels good predictors of tissue iron levels, at least in males.

RESEARCH ARTICLES | Pancreatic Physiology/Pathophysiology

Adaptive regulation of pancreatic acinar mitochondrial thiamin pyrophosphate uptake process: possible involvement of epigenetic mechanism(s)
Subrata Sabui, Veedamali S. Subramanian, Rubina Kapadia, Hamid M. Said
November 1, 2017 : G448-G455
DOI: 10.1152/ajpgi.00192.2017

Our findings show, for the first time, that the mitochondrial thiamin pyrophosphate (MTPP) uptake process is adaptively regulated by the prevailing thiamin level in pancreatic acinar cells and this regulation is mediated, at least in part, by transcriptional and epigenetic mechanism(s) affecting the SLC25A19 promoter.

Roles of autophagy and metabolism in pancreatic cancer cell adaptation to environmental challenges
Sandrina Maertin, Jason M. Elperin, Ethan Lotshaw, Matthias Sendler, Steven D. Speakman, Kazuki Takakura, Benjamin M. Reicher, Olga A. Mareninova, Paul J. Grippo, Julia Mayerle, Markus M. Lerch, Anna S. Gukovskaya
November 2, 2017 : G524-G536
DOI: 10.1152/ajpgi.00138.2017

Cancer cells in the highly desmoplastic pancreatic ductal adenocarcinoma confront nutrient [i.e., amino acids (AA)] deprivation and hypoxia, but how pancreatic cancer (PaCa) cells adapt to these conditions is poorly understood. This study provides evidence that the maintenance of mitochondrial function, in particular, oxidative phosphorylation (OXPHOS), is a key mechanism that supports PaCa cell growth, both in normal
conditions and under the environmental stresses. OXPHOS in PaCa cells critically depends on autophagy and AA supply. Furthermore, the oncogenic activation mutation in GTPase Kras upregulates OXPHOS through an autophagy-dependent mechanism.

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

A novel mouse model of radiation-induced cancer survivorship diseases of the gut
Cecilia Bull, Dilip Malipatolla, Marie Kalm, Fei Sjöberg, Eleftheria Alevronta, Rita Grandér, Pedram Sultanian, Linda Persson, Martina Boström, Yohanna Eriksson, John Swanpalmer, Agnes E. Wold, Klas Blomgren, Thomas Björk-Eriksson, Gunnar Steineck
November 1, 2017 : G456-G466
DOI: 10.1152/ajpgi.00113.2017

A novel mouse model for studying the long-term trajectory of radiation-induced gut injury. The method allows for the use of high doses and multiple fractions, with minor impact on animal health for at least 3 mo. Crypt loss and a slow progression of fibrosis is observed. Crypt degeneration is a process restricted to isolated crypts. Crypt degeneration is presented as a convenient proxy endpoint for long-term radiation-induced gut injury.

INNOVATIVE METHODOLOGY | Epithelial Biology and Secretion

A simple, cost-effective method for generating murine colonic 3D enteroids and 2D monolayers for studies of primary epithelial cell function
Elizabeth H. Fernando, Michael Dicay, Martin Stahl, Marilyn H. Gordon, Andrew Vegso, Cristiane Baggio, Laurie Alston, Fernando Lopes, Kristi Baker, Simon Hirota, Derek M. McKay, Bruce Vallance, Wallace K. MacNaughton
November 1, 2017 : G467-G475
DOI: 10.1152/ajpgi.00152.2017

Primary intestinal epithelial monolayers are notoriously difficult to maintain culture, even with the recent advances in the field. We describe, in detail, the protocols required to maintain three-dimensional cultures of murine colonoids and passage these primary epithelial cells to confluent monolayers in a standardized, high-yield, and cost-effective manner.

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REVIEWS | Advances in Cardiovascular Geroscience

Vascular niche contribution to age-associated neural stem cell dysfunction
Deana M. Apple, Erzsebet Kokovay
November 1, 2017 : H896-H902
DOI: 10.1152/ajpheart.00154.2017

Dietary modulation of oxylipins in cardiovascular disease and aging
Stephanie P. B. Caligiuri, Mihir Parikh, Aleksandra Stamenkovic, Grant N. Pierce, Harold M. Aukema
November 1, 2017 : H903-H918
DOI: 10.1152/ajpheart.00201.2017

Oxylipins are an important group of fatty acid metabolites amenable to dietary manipulation. Because of the role they play in cardiovascular disease and in age-related degeneration, oxylipins are gaining recognition as viable targets for specific dietary interventions focused on manipulating oxylipin composition to control these biological processes.

Role of pattern recognition receptors of the neurovascular unit in inflamm-aging
REVIEWS | Integrative Cardiovascular Physiology and Pathophysiology

How does pressure overload cause cardiac hypertrophy and dysfunction? High-ouabain affinity cardiac Na⁺ pumps are crucial
Mordecai P. Blaustein
November 1, 2017 : H919-H930
DOI: 10.1152/ajpheart.00131.2017

An update on hormone therapy in postmenopausal women: mini-review for the basic scientist
Virginia M. Miller, S. Mitchell Harman
November 6, 2017 : H1013-H1021
DOI: 10.1152/ajpheart.00383.2017

EDITORIAL FOCUS

Mineralocorticoids: the secret of muscle reflex dysfunction in hypertension?
Han-Jun Wang
November 1, 2017 : H931-H933
DOI: 10.1152/ajpheart.00501.2017

RESEARCH ARTICLE | Advances in Cardiovascular Geroscience

Moderate-to-severe obstructive sleep apnea is associated with telomere lengthening
November 6, 2017 : H1022-H1030
DOI: 10.1152/ajpheart.00197.2017

Here, we show that moderate-to-severe obstructive sleep apnea is associated with longer telomeres, independent of age and cardiovascular risk factors, challenging the hypothesis that telomere shortening is a unidirectional process related to age/disease. A better understanding of the mechanisms underlying telomere dynamics may identify targets for therapeutic intervention in cardiovascular aging/other chronic diseases.

RESEARCH ARTICLE | Cardiac Excitation and Contraction

Effect of ovariectomy on intracellular Ca²⁺ regulation in guinea pig cardiomyocytes
Hsiang-Yu Yang, Jahn M. Firth, Alice J. Francis, Anita Alvarez-Laviada, Kenneth T. MacLeod
November 6, 2017 : H1031-H1043
DOI: 10.1152/ajpheart.00249.2017

Ovariectomized guinea pig cardiomyocytes have higher frequencies of Ca²⁺ waves, and isoprenaline-challenged cells display more early afterdepolarizations, delayed afterdepolarizations, and extra beats compared with sham myocytes. These alterations to Ca²⁺ regulation were not observed in myocytes from ovariectomized guinea pigs supplemented with 17β-estradiol, suggesting that ovarian hormone deficiency modifies cardiac Ca²⁺ regulation, potentially creating proarrhythmic substrates.

RESEARCH ARTICLES | Integrative Cardiovascular Physiology and Pathophysiology

A comparison of passive hindlimb cycling and active upper-limb exercise provides new insights into systolic dysfunction after spinal cord injury
Kathryn M. DeVeau, Kathryn A. Harman, Jordan W. Squair, Andrei V. Krassioukov, David S. K. Magnuson, Christopher R. West
November 1, 2017 : H861-H870
DOI: 10.1152/ajpheart.00046.2017

This is the first direct comparison between the cardiac changes elicited by active upper-limb or passive lower-limb exercise after spinal cord injury. Here, we demonstrate that lower limb exercise positively influences flow-derived cardiac indexes, whereas upper limb exercise does not. Furthermore, neither intervention corrects the cardiac contractile dysfunction associated with spinal cord injury.
Impact of electrical defibrillation on infarct size and no-reflow in pigs subjected to myocardial ischemia-reperfusion without and with ischemic conditioning
Andreas Skyschally, Georgios Amanakis, Markus Neuhäuser, Petra Kleinbongard, Gerd Heusch
November 1, 2017 : H871-H878
DOI: 10.1152/ajpheart.00293.2017

Ventricular fibrillation/defibrillation is associated with increased infarct size. Electrical injury is unlikely the cause of such association, since there is no dose-response relation between infarct size and number of defibrillations. Ventricular fibrillation, in turn, is associated with a larger area at risk and lower residual blood flow.

Inhibitory actions of the NRG-1/ErbB4 pathway in macrophages during tissue fibrosis in the heart, skin, and lung
Zarha Vermeulen, Anne-Sophie Hervent, Lindsey Dugaucquier, Leni Vandekerckhove, Miche Rombouts, Matthias Beyens, Dorien M. Schrijvers, Guido R. Y. De Meyer, Stuart Maudsley, Gilles W. De Keulenaer, Vincent F. M. Segers
November 1, 2017 : H934-H945
DOI: 10.1152/ajpheart.00206.2017

Our study contributes to the understanding of the antifibrotic effect of neuregulin-1 during myocardial remodeling. Here, we show that the antifibrotic effect of neuregulin-1 is at least partially mediated through anti-inflammatory activity, linked to receptor tyrosine-protein kinase erbB-4 activation in macrophages. Furthermore, we show that this effect is also present outside the heart.

Plastics and cardiovascular health: phthalates may disrupt heart rate variability and cardiovascular reactivity
Rafael Jaimes III, Adam Swiercz, Meredith Sherman, Narine Muselimyan, Paul J. Marvar, Nikki Gillum Posnack
November 6, 2017 : H1044-H1053
DOI: 10.1152/ajpheart.00364.2017

Phthalates are widely used in the manufacturing of consumer and medical products. In the present study, di-2-ethylhexyl-phthalate exposure was associated with alterations in heart rate variability and cardiovascular reactivity. This highlights the importance of investigating the impact of phthalates on health and identifying suitable alternatives for medical device manufacturing.

RESEARCH ARTICLE | Mechanisms of Exercise-Induced Amelioration of Cardiovascular Disease
Exercise of obese mice induces cardioprotection and oxygen sparing in hearts exposed to high-fat load
Neoma T. Boardman, Anne D. Hafstad, Jim Lund, Line Rossvoll, Ellen Aasum
November 6, 2017 : H1054-H1062
DOI: 10.1152/ajpheart.00382.2017

The exercise-induced cardioprotective effects in obese hearts are present under hyperlipidemic conditions, comparable to circulating levels of fatty acid occurring with an ischemic insult. Myocardial oxygen sparing is associated with this effect, despite the general notion that high fat can decrease cardiac efficiency. This highlights the role of myocardial energetics during ischemic stress.

RESEARCH ARTICLE | Translational Physiology
Shock and lethality with anthrax edema toxin in rats are associated with reduced arterial responsiveness to phenylephrine and are reversed with adefovir
Dante A. Suffredini, Yan Li, Wanying Xu, Mahtab Moayeri, Stephen Leplla, Yvonne Fitz, Xizhong Cui, Peter Q. Eichacker
November 1, 2017 : H946-H958
DOI: 10.1152/ajpheart.00285.2017

The most important aspects of the present study are the findings that 1) in vivo challenge with anthrax edema but not lethal toxin depresses arterial contractile function measured both ex vivo and in vivo and 2) adefovir inhibits the effects of edema toxin on arterial hypotension and improves survival with lethal dose of edema toxin challenge.

RESEARCH ARTICLES | Vascular Biology and Microcirculation
Temperature-dependent modulation of regional lymphatic contraction frequency and flow
Eleonora Solari, Cristiana Marcozzi, Daniela Negrini, Andrea Moriondo
November 1, 2017 : H879-H889
DOI: 10.1152/ajpheart.00267.2017

This study demonstrates to what extent lymphatic vessel intrinsic contractility and lymph flow are modulated by temperature and that this modulation is dependent on the body district that the vessels belong to, suggesting a possible functional misbehavior should lymphatic vessels be
exposed to a chronically different temperature.

Visualization of three pathways for macromolecule transport across cultured endothelium and their modification by flow
Mean Ghim, Paola Alpresa, Sung-Wook Yang, Siets T. Braakman, Stephen G. Gray, Spencer J. Sherwin, Maarten van Reeuwijk, Peter D. Weinberg
November 1, 2017 : H959-H973
DOI: 10.1152/ajpheart.00218.2017

Solute transport of increasing size crossed cultured endothelium through intercellular junctions, through tricellular junctions, or transcellularly. Cells aligned to minimize the shear stress acting across their long axis. Paracellular transport correlated with the level of this minimized shear, but transcellular transport was reduced uniformly by flow regardless of the shear profile.

Primed polymorphonuclear leukocytes from hemodialysis patients enhance monocyte transendothelial migration
Eynav Kliger, Batya Kristal, Galina Shapiro, Judith Chezar, Shifra Sela
November 1, 2017 : H974-H987
DOI: 10.1152/ajpheart.00122.2017

Primed polymorphonuclear leukocytes are key mediators in monocyte transendothelial migration, a new understanding of the initiation of endothelial dysfunction and monocyte activation, transmigration, and accumulation in the subendothelial layer.

Preconditioning with the BKCa channel activator NS-1619 prevents ischemia-reperfusion-induced inflammation and mucosal barrier dysfunction: roles for ROS and heme oxygenase-1
Hongyan Dai, Meifang Wang, Parag N. Patel, Theodore Kalogeris, Yajun Liu, William Durante, Ronald J. Korthuis
November 1, 2017 : H988-H999
DOI: 10.1152/ajpheart.00620.2016

Antecedent treatment with the large-conductance Ca2+-activated K+ channel opener NS-1619 24 h before ischemia-reperfusion limits postischemic tissue injury by an oxidant-dependent mechanism. The present study shows that NS-1619-induced oxidant production prevents ischemia-reperfusion-induced inflammation and mucosal barrier disruption in the small intestine by provoking increases in heme oxygenase-1 activity.

Chronic hypertension increases aortic endothelial hydraulic conductivity by upregulating endothelial aquaporin-1 expression
Jimmy Toussaint, Chirag Bharavi Raval, Tieuvi Nguyen, Hadi Fadaifard, Shripad Joshi, George Wolberg, Steven Quarfordt, Kung-ming Jan, David S. Rumschitzki
November 6, 2017 : H1063-H1073
DOI: 10.1152/ajpheart.00651.2016

The aortic endothelia of two high-renin hypertensive rat models express greater than two times the aquaporin-1 and, at low pressures, have greater than two times the endothelial hydraulic conductivity of normotensive rats. Data are consistent with theory predicting that higher endothelial aquaporin-1 expression raises the critical pressure for subendothelial intima compression and for artery wall hydraulic conductivity to drop.

RAPID REPORT | Integrative Cardiovascular Physiology and Pathophysiology

Endothelial cell senescence with aging in healthy humans: prevention by habitual exercise and relation to vascular endothelial function
Matthew J. Rossman, Rachelle E. Kaplon, Sierra D. Hill, Molly N. McNamara, Jessica R. Santos-Parker, Gary L. Pierce, Douglas R. Seals, Anthony J. Donato
November 1, 2017 : H890-H895
DOI: 10.1152/ajpheart.00416.2017

Our study provides novel evidence in humans of increased endothelial cell senescence with sedentary aging, which is associated with impaired vascular endothelial function. Furthermore, our data suggest an absence of age-related increases in endothelial cell senescence in older exercising adults, which is linked with preserved vascular endothelial function.

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REVIEWS | Ion Channels and Transporters in Lung Function and Disease

Influenza virus infection alters ion channel function of airway and alveolar cells: mechanisms and physiological sequelae
James David Londino, Ahmed Lazrak, James F. Collawn, Zsuzsanna Bebok, Kevin S. Harrod, Sadis Matalon
November 6, 2017 : L845-L858
DOI: 10.1152/ajplung.00244.2017

Ion channels of the lung and their role in disease pathogenesis
Rafal Bartoszewski, Sadis Matalon, James F. Collawn
November 6, 2017 : L859-L872
DOI: 10.1152/ajplung.00285.2017

REVIEW | Translational Physiology

LungMAP: The Molecular Atlas of Lung Development Program
November 1, 2017 : L733-L740
DOI: 10.1152/ajplung.00139.2017

REVIEW

Use of proper statistical techniques for research studies with small samples
Charity J. Morgan
November 6, 2017 : L873-L877
DOI: 10.1152/ajplung.00238.2017

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

Importance of kynurenine in pulmonary hypertension
Bence M. Nagy, Chandran Nagaraj, Andreas Meinitzer, Neha Sharma, Rita Papp, Vasile Foris, Bahil Ghanim, Grazyna Kwapiszewska, Gabor Kovacs, Walter Klepetko, Thomas R. Pieber, Harald Mangge, Horst Olschewski, Andrea Olschewski
November 1, 2017 : L741-L751
DOI: 10.1152/ajplung.00517.2016

Transglutaminase 2 in pulmonary and cardiac tissue remodeling in experimental pulmonary hypertension
November 1, 2017 : L752-L762
DOI: 10.1152/ajplung.00170.2017

Fra-2 negatively regulates postnatal alveolar septation by modulating myofibroblast function
Kazuyuki Tsujino, John T. Li, Tatsuya Tsukui, Xin Ren, Latifa Bakiri, Erwin Wagner, Dean Sheppard
November 6, 2017 : L878-L888
DOI: 10.1152/ajplung.00062.2017

RESEARCH ARTICLES | Ion Channels and Transporters in Lung Function and Disease

TGF-β inhibits alveolar protein transport by promoting shedding, regulated intramembrane proteolysis, and transcriptional downregulation of megalin

DOI: 10.1152/ajplung.00039.2017
Aquaporin 1-mediated changes in pulmonary arterial smooth muscle cell migration and proliferation involve β-catenin
Xin Yun, Haiyang Jiang, Ning Lai, Jian Wang, Larissa A. Shimoda
November 6, 2017 : L889-L898
DOI: 10.1152/ajplung.00247.2016

RESEARCH ARTICLE | Real-time Visualization of Lung Function: From Micro to Macro
X-ray-based lung function measurement reveals persistent loss of lung tissue elasticity in mice recovered from allergic airway inflammation
M. Andrea Markus, Sergej Borowik, Marius Reichardt, Giuliana Tromba, Frauke Alves, Christian Dullin
November 1, 2017 : L763-L771
DOI: 10.1152/ajplung.00136.2017

RESEARCH ARTICLES | Translational Physiology
Lethal avian influenza A (H5N1) virus induces ataxic breathing in mice with apoptosis of pre-Botzinger complex neurons expressing
neurokinin-1 receptor
Jianguo Zhuang, Na Zang, Chunyan Ye, Fadi Xu
November 1, 2017 : L772-L780
DOI: 10.1152/ajplung.00145.2017

Endothelial cell-related autophagic pathways in Sugen/hypoxia-exposed pulmonary arterial hypertensive rats
Fumiaki Kato, Seichiro Sakao, Takao Takeuchi, Toshio Suzuki, Rintaro Nishimura, Tadashi Yasuda, Nobuhiro Tanabe, Koichiro Tatsumi
November 6, 2017 : L899-L915
DOI: 10.1152/ajplung.00527.2016

RESEARCH ARTICLES | Translational Research in Acute Lung Injury and Pulmonary Fibrosis
FGF9 prevents pleural fibrosis induced by intrapleural adenovirus injection in mice
 Aurélien Justet, Audrey Joannes, Valérie Besnard, Joëlle Marchal-Sommé, Madeleine Jailet, Philine Bonniaud, Jean Michel Sallenave, Brigitte Solhonne, Yves Castier, Pierre Mordant, Hervé Mal, Aurélie Cazes, Raphael Borie, Arnaud A. Maillieux, Bruno Crestani
November 1, 2017 : L781-L795
DOI: 10.1152/ajplung.00508.2016

Repetitive intradermal bleomycin injections evoke T-helper cell 2 cytokine-driven pulmonary fibrosis
Brijendra Singh, Rajesh K. Kasam, Vishwaraj Sontake, Thomas A. Wynn, Satish K. Madala
November 1, 2017 : L796-L806
DOI: 10.1152/ajplung.00184.2017

CYP2E1 regulates the development of radiation-induced pulmonary fibrosis via ER stress- and ROS-dependent mechanisms
Beomseok Son, TaeWoo Kwon, Sungmin Lee, IkJoon Han, Wanyeon Kim, HyeSook Youn, BuHyun Youn
November 6, 2017 : L916-L929
DOI: 10.1152/ajplung.00144.2017

Alternative pre-mRNA splicing of Toll-like receptor signaling components in peripheral blood mononuclear cells from patients with ARDS
Rachel Z. Blumhagen, Brenna R. Hedin, Kenneth C. Malcolm, Ellen L. Burnham, Marc Moss, Edward Abraham, Tristan J. Huie, Jerry A. Nick, Tasha E. Fingerlin, Scott Alper
November 6, 2017 : L930-L939
DOI: 10.1152/ajplung.00247.2017

RESEARCH ARTICLES
Benefits of oxytocin administration in obstructive sleep apnea
Vivek Jain, Joseph Marbach, Shawn Kimbro, David C. Andrade, Arad Jain, Eleanor Capozzi, Kyle Mele, Rodrigo Del Rio, Matthew W. Kay, David
Metabolic characterization and RNA profiling reveal glycolytic dependence of profibrotic phenotype of alveolar macrophages in lung fibrosis
Na Xie, Huachun Cui, Jing Ge, Sami Banerjee, Sijia Guo, Shubham Dubey, Edward Abraham, Rui-Ming Liu, Gang Liu
November 1, 2017: L825-L833
DOI: 10.1152/ajplung.00206.2017

Oxygen-dependent changes in lung development do not affect epithelial infection with influenza A virus
William Domm, Min Yee, Ravi S. Misra, Robert Gelein, Aitor Nogales, Luis Martinez-Sobrido, Michael A. O’Reilly
November 6, 2017: L940-L949
DOI: 10.1152/ajplung.00235.2017

Levosimendan prevents bronchoconstriction and adverse respiratory tissue mechanical changes in rabbits
Barna Babik, Adam L. Balogh, Roberta Sudy, Orsolya Ivankovitsne-Kiss, Gergely H. Fodor, Ferenc Petak
November 6, 2017: L950-L956
DOI: 10.1152/ajplung.00213.2017

INNOVATIVE METHODOLOGY

Preserved right ventricular integrity in a new telemetric rat model of severe pulmonary hypertension
Catharina Schreiber, Magdalena Eilenberg, Attila Kiss, Helga Bergmeister, Bruno Podesser, Julia Mascherbauer, Diana Bonderman
November 6, 2017: L957-L963
DOI: 10.1152/ajplung.00278.2017

LETTER TO THE EDITORS | Electronic Cigarettes: Not All Good News?

Letter to the Editor: Pulmonary toxicity of electronic cigarettes: more doubts than certainties
Massimo Caruso, Colin P. Mendelsohn, Riccardo Polosa
November 6, 2017: L964-L965
DOI: 10.1152/ajplung.00402.2017

Reply to “Letter to the Editor: Pulmonary toxicity of electronic cigarettes: more doubts than certainties”
Lauren F. Chun, Farzad Moazed, Carolyn S. Calfee, Michael A. Matthay, Jeffrey E. Gotts
November 6, 2017: L966-L967
DOI: 10.1152/ajplung.00428.2017

Letter to the Editor: The effects of electronic cigarette aerosol exposure on inflammation and lung function in mice
Konstantinos Farsalinos, Kurt A Kistler, Gene Gillman
November 6, 2017: L968-L969
DOI: 10.1152/ajplung.00423.2017

Reply to “Letter to the Editor: The effects of electronic cigarette aerosol exposure on inflammation and lung function in mice”
November 6, 2017: L970-L971
DOI: 10.1152/ajplung.00448.2017

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EDITORIAL | New Investigator Review Awards

The 2017 New Investigator Review Awards
Willis K. Samson
November 9, 2017 : R583-R584
DOI: 10.1152/ajpregu.00377.2017

REVIEW | New Investigator Review Award

Filling the void: a role for exercise-induced BDNF and brain amyloid precursor protein processing
Rebecca E. K. MacPherson
November 9, 2017 : R585-R593
DOI: 10.1152/ajpregu.00255.2017

RESEARCH ARTICLES | Exploiting Environmental Factors to Improve Health and Performance

Combining remote ischemic preconditioning and aerobic exercise: a novel adaptation of blood flow restriction exercise
Justin D. Sprick, Caroline A. Rickards
November 1, 2017 : R497-R506
DOI: 10.1152/ajpregu.00111.2017

Cyclical blood flow restriction resistance exercise: a potential parallel to remote ischemic preconditioning?
Justin D. Sprick, Caroline A. Rickards
November 1, 2017 : R507-R517
DOI: 10.1152/ajpregu.00112.2017

Face cooling increases blood pressure during central hypovolemia
Blair D. Johnson, James R. Sackett, Suman Sarker, Zachary J. Schlader
November 9, 2017 : R594-R600
DOI: 10.1152/ajpregu.00253.2017

RESEARCH ARTICLE | Hypertensive Disorders of Pregnancy: Effects on Mother and Baby

Flow-mediated dilation and peripheral arterial tonometry are disturbed in preeclampsia and reflect different aspects of endothelial function
Dominique Mannaerts, Ellen Faes, Inge Goovaerts, Tibor Stoop, Jerome Cornette, Wilfried Gyselaers, Marc Spaanderman, Emeline M. Van Craenenbroeck, Yves Jacquemyn
November 1, 2017 : R518-R525
DOI: 10.1152/ajpregu.00514.2016

RESEARCH ARTICLES | Obesity, Diabetes and Energy Homeostasis

Effect of circulating glucagon and free fatty acids on hepatic FGF21 production in dairy cows
Luciano S. Caixeta, Sarah L. Giesy, Christopher S. Krumm, James W. Perfield 2nd, Anthony Butterfield, Katie M. Schoenberg, Donald C. Beitz, Yves R. Boisclair
November 1, 2017 : R526-R534
DOI: 10.1152/ajpregu.00197.2017
Energy homeostasis in apolipoprotein AIV and cholecystokinin-deficient mice
Jonathan Weng, Danwen Lou, Stephen C. Benoit, Natalie Coschigano, Stephen C. Woods, Patrick Tso, Chunmin C. Lo
November 1, 2017 : R535-R548
DOI: 10.1152/ajpregu.00034.2017

Regulation of energy metabolism during social interactions in rainbow trout: a role for AMP-activated protein kinase
K. M. Gilmour, P. M. Craig, R. S. Dhillon, G. Y. Lau, J. G. Richards
November 1, 2017 : R549-R559
DOI: 10.1152/ajpregu.00341.2016

Obesity-induced vascular inflammation involves elevated arginase activity
Lin Yao, Anil Bhatta, Zhimin Xu, JiJun Chen, Haroldo A. Toque, Yongjun Chen, Yimin Xu, Zsolt Bagi, Rudolf Lucas, Yuqing Huo, Ruth B. Caldwell, R. William Caldwell
November 1, 2017 : R560-R571
DOI: 10.1152/ajpregu.00529.2016

Diet-induced obesity accelerates blood lactate accumulation of rats in response to incremental exercise to maximum
Chiao-Nan (Joyce) Chen, Yi-Hung Liao, Shang-Ying Lin, Jun-Xian Yu, Zhen-Jie Li, Yu-Chieh Lin, Gwo-Jyh Chang, Chung-Hao Lin, Alice May-Kuen Wong
November 9, 2017 : R601-R607
DOI: 10.1152/ajpregu.00337.2016

Physiological and metabolic differences between visceral and subcutaneous adipose tissues in Nile tilapia (Oreochromis niloticus)
Ya-Wen Wang, Ji-Lei Zhang, Jian-Gang Jiao, Xiao-Xia Du, Samwel Mchele Limbu, Fang Qiao, Mei-Ling Zhang, Dong-Liang Li, Zhen-Yu Du
November 9, 2017 : R608-R619
DOI: 10.1152/ajpregu.00071.2017

RESEARCH ARTICLE | Respiration
Obesity modulates diaphragm curvature in subjects with and without COPD
Aladin M. Boriek, Michael A. Lopez, Cristina Velasco, Azam A. Bakir, Anna Frolov, Shari Wynd, Tony G. Babb, Nicola A. Hanania, Eric A. Hoffman, Amir Sharafkhaneh
November 9, 2017 : R620-R629
DOI: 10.1152/ajpregu.00173.2017

RESEARCH ARTICLE | Translational Physiology
Elucidating the role of leptin in systemic inflammation: a study targeting physiological leptin levels in rats and their macrophages
Elizabeth A. Flatow, Evlin N. Komegae, Monique T. Fonseca, Camila F. Brito, Florin M. Musteata, José Antunes-Rodrigues, Alexandre A. Steiner
November 1, 2017 : R572-R582
DOI: 10.1152/ajpregu.00171.2017

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REVIEWS

Insights into cellular and molecular basis for urinary tract infection in autosomal-dominant polycystic kidney disease
Chao Gao, Long Zhang, Ye Zhang, Darren P. Wallace, Reynold I. Lopez-Soler, Paul J. Higgins, Wenzheng Zhang
November 29, 2017 : F1077-F1083
DOI: 10.1152/ajprenal.00279.2017

Cannabinoids and the kidney: effects in health and disease
Frank Park, Praveen K. Potukuchi, Hamid Moradi, Csaba P. Kovesdy
November 29, 2017 : F1124-F1132
DOI: 10.1152/ajprenal.00290.2017

EDITORIAL FOCI

- An essential MIF-CD74 signaling axis in kidney tubular regeneration, with prospects for precision medicine and pharmacological augmentation
Idit Shachar
November 29, 2017 : F1084-F1086
DOI: 10.1152/ajprenal.00283.2017

- Sex and rigor: the TGF-β blood pressure affair
Kathryn Sandberg, Amrita V. Pai, Taylor Maddox
November 29, 2017 : F1087-F1088
DOI: 10.1152/ajprenal.00381.2017

- Stimulating bioelectronic medicine discovery for urological disorders
Peregrine B. Osborne
November 29, 2017 : F1133-F1135
DOI: 10.1152/ajprenal.00372.2017

RESEARCH ARTICLE | Gender and Hormones in Lower Urinary Tract Function

Metabolic acidosis stimulates the production of the antimicrobial peptide cathelicidin in rabbit urine
Hu Peng, Jeffrey M. Purkerson, Andy L. Schwaderer, George J. Schwartz
November 1, 2017 : F1061-F1067
DOI: 10.1152/ajprenal.00701.2016

RESEARCH ARTICLES

Stimulation of diuresis and natriuresis by renomedullary infusion of a dual inhibitor of fatty acid amide hydrolase and monoacylglycerol lipase
Ashfaq Ahmad, Zdravka Daneva, Guangbi Li, Sara K. Dempsey, Ningjun Li, Justin L. Poklis, Aron Lichtman, Pin-Lan Li, Joseph K. Ritter
November 1, 2017 : F1068-F1076
DOI: 10.1152/ajprenal.00196.2017

Effects of multiple simulated birth traumas on urethral continence function in rats
Satoru Yoshikawa, Yasuhiro Sumino, Joonbeom Kwon, Takahisa Suzuki, Takeya Kitta, Minoru Miyazato, Naoki Yoshimura
November 29, 2017 : F1089-F1096
DOI: 10.1152/ajprenal.00230.2017

Vasa recta pericyte density is negatively associated with vascular congestion in the renal medulla following ischemia reperfusion in rats
G. Ryan Crislip, Paul M. O’Connor, Qingqing Wei, Jennifer C. Sullivan
November 29, 2017 : F1097-F1105
DOI: 10.1152/ajprenal.00261.2017

Heterozygous loss-of-function mutation in Odd-skipped related 1 (Osr1) is associated with vesicoureteric reflux, duplex systems, and hydronephrosis
TRPV4 channels contribute to renal myogenic autoregulation in neonatal pigs
Hitesh Soni, Dieniffer Peixoto-Neves, Anberitha T. Matthews, Adebowale Adebiyi
November 29, 2017 : F1116-F1115
DOI: 10.1152/ajprenal.00107.2017

Preventative effects of a HIF inhibitor, 17-DMAG, on partial bladder outlet obstruction-induced bladder dysfunction
Nao Iguchi, M. İrfan Dönmez, Anna P. Malykhina, Alonso Carrasco Jr., Duncan T. Wilcox
November 29, 2017 : F11149-F11160
DOI: 10.1152/ajprenal.00300.2017

An excitatory reflex from the superficial peroneal nerve to the bladder in cats
Michelle Yu, Jamie Uy, Xuewen Jiang, Xing Li, Cameron Jones, Bing Shen, Jicheng Wang, James R. Roppolo, William C. de Groat, Changfeng Tai
November 29, 2017 : F11161-F11168
DOI: 10.1152/ajprenal.00265.2017

OAB without an overactive bladder in the acute prostaglandin E2 rat model
James A. Hokanson, Christopher L. Langdale, Arun Sridhar, Warren M. Grill
November 29, 2017 : F11169-F11177
DOI: 10.1152/ajprenal.00270.2017

RAPID REPORT
Thy-1+/− fibroblast subsets in the human peritoneum
Edyta Kawka, Janusz Witowski, Maria Bartosova, Rusan Catar, András Rudolf, Aurelie Philippe, Rafal Rutkowski, Betti Schäfer, Claus Peter Schmitt, Duska Dragun, Achim Jörres
November 29, 2017 : F11116-F11123
DOI: 10.1152/ajprenal.00274.2017

CORRIGENDUM
Corrigendum
November 29, 2017 : F11178
DOI: 10.1152/ajprenal.zh2-8359-corr.2017
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REVIEW | Edward F. Adolph Distinguished Lecture

Edward F. Adolph Distinguished Lecture: Skin-deep insights into vascular aging
W. Larry Kenney
November 1, 2017 : 1024-1038
DOI: 10.1152/japplphysiol.00589.2017

REVIEWS | Hypoxia 2017

The hypoxia-adenosine link during inflammation
Jessica L. Bowser, Jae W. Lee, Xiaoyi Yuan, Holger K. Eltzschig
November 1, 2017 : 1303-1320
DOI: 10.1152/japplphysiol.00101.2017

Oxygen metabolism and innate immune responses in the gut
Sean P. Colgan, Eric L. Campbell
November 1, 2017 : 1321-1327
DOI: 10.1152/japplphysiol.00113.2017

Determinants of hypoxia-inducible factor activity in the intestinal mucosa
Raphael R. Fagundes, Cormac T. Taylor
November 1, 2017 : 1328-1334
DOI: 10.1152/japplphysiol.00203.2017

Acute oxygen sensing by the carotid body: from mitochondria to plasma membrane
Andy J. Chang
November 1, 2017 : 1335-1343
DOI: 10.1152/japplphysiol.00398.2017

On the existence of a central respiratory oxygen sensor
Alexander V. Gourine, Gregory D. Funk
November 1, 2017 : 1344-1349
DOI: 10.1152/japplphysiol.00194.2017

Human cerebral blood flow control during hypoxia: focus on chronic pulmonary obstructive disease and obstructive sleep apnea
Andrew E. Beaudin, Sara E. Hartmann, Matiram Pun, Marc J. Poulin
November 1, 2017 : 1350-1361
DOI: 10.1152/japplphysiol.00352.2017

Epigenomics and human adaptation to high altitude
Colleen G. Julian
November 1, 2017 : 1362-1370
DOI: 10.1152/japplphysiol.00351.2017

Measuring high-altitude adaptation
Lorna G. Moore
November 1, 2017 : 1371-1385
DOI: 10.1152/japplphysiol.00321.2017

Variation in O2 transport characteristics among Andean, Tibetan, and, when available, Ethiopian high-altitude residents supports the existence of genetic adaptations that improve the distribution of blood flow to vital organs and the efficiency of O2 utilization. Genome scans and whole genome sequencing studies implicate a broad range of gene regions. Future studies are needed using phenotypes of clear relevance for reproductive success for determining the mechanisms by which naturally selected genes are acting.
EDITORIAL FOCUS | Hypoxia 2017

Drowning in a river with an average depth of 3 ft: interpreting athletic performance gains
Connie C. W. Hsia
November 1, 2017 : 1256-1257
DOI: 10.1152/japplphysiol.00733.2017

EDITORIAL FOCUS

The double-edged sword of intermittent hypoxia—can intermittent hypoxia be both deleterious and protective in OSA? Focus on “Frequency and magnitude of intermittent hypoxia modulate endothelial wound healing in a cell culture model of sleep apnea”
Lena Lavie, Peretz Lavie
November 1, 2017 : 1021-1023
DOI: 10.1152/japplphysiol.00630.2017

RESEARCH ARTICLES | Hypoxia 2017

Is normobaric hypoxia an effective treatment for sustaining previously acquired altitude acclimatization?
November 1, 2017 : 1214-1227
DOI: 10.1152/japplphysiol.00344.2017

This study demonstrates that normobaric hypoxia treatment over a 12-day period at sea level was not more effective for sustaining high-altitude (HA) acclimatization during readaptation to HA than no treatment at all. The noteworthy aspect is that athletes, mountaineers, and military personnel do not have to go to extraordinary means to retain HA acclimatization to an easily accessible and relevant altitude if reexposure occurs within a 2-wk time period.

Remote ischemic preconditioning does not prevent acute mountain sickness after rapid ascent to 3,450 m
Marc M. Berger, Franziska Macholz, Lukas Lehmann, Daniel Dankl, Marcel Hochreiter, Bernhard Bacher, Peter Bärtsch, Heimo Mairbäurl
November 1, 2017 : 1228-1234
DOI: 10.1152/japplphysiol.00505.2017

Remote ischemic preconditioning (RIPC) has been reported to improve neurologic and pulmonary outcome following an acute ischemic or hypoxic insult, yet the effect of RIPC for protecting from high-altitude diseases remains to be determined. The present study shows that RIPC, performed immediately before passive ascent to 3,450 m, does not attenuate acute mountain sickness and the degree of high-altitude pulmonary hypertension. Therefore, RIPC cannot be recommended for prevention of high-altitude diseases.

Skeletal muscle signaling, metabolism, and performance during sprint exercise in severe acute hypoxia after the ingestion of antioxidants
David Morales-Alamo, Borja Guerra, Jesús Gustavo Ponce-González, Amelia Guadalupe-Grau, Alfredo Santana, Marcos Martin-Rincon, Miriam Gelabert-Rebato, Joan A. Cadefau, Roser Cusso, Cecilia Dorado, José A. L. Calbet
November 1, 2017 : 1235-1245
DOI: 10.1152/japplphysiol.00384.2017

The glycolytic rate is increased during sprint exercise in severe acute hypoxia. This study showed that the ingestion of antioxidants before sprint exercise in severe acute hypoxia reduced the glycolytic rate and attenuated the increases of the AMP-to-ATP and the reduction of the NAD+-to-NADH.H+ ratios. This resulted in a modified muscle signaling response with a blunted Thr286-CaMKII but similar AMP-activated protein kinase phosphorylation responses in the sprints preceded by the ingestion of antioxidants.

Effects of acute hypoxia on human cognitive processing: a study using ERPs and SEPs
Hiroki Nakata, Tadayoshi Miyamoto, Shigehiko Ogoh, Ryusuke Kakigi, Manabu Shibasaki
November 1, 2017 : 1246-1255
DOI: 10.1152/japplphysiol.00348.2017

Hypoxia has the potential to impair the cognitive function, but the effects of acute hypoxia on the cognitive function remain debatable. We investigated the effects of acute hypoxia on human cognitive processing using electroencephalographic event-related potentials and somatosensory-evoked potentials. Acute normobaric hypoxia impaired neural activity in motor executive and inhibitory processing, but no significant differences were observed in neural activity in somatosensory processing.

Short-term arrival strategies for endurance exercise performance at moderate altitude
For athletes who cannot arrive at altitude, multiple days before an endurance competition to properly acclimatize, this study asked if shortening hypoxic exposure time to 2 h before a competition was more advantageous than arrival at altitude the evening before competition. Our data suggest that athletes who cannot arrive at altitude with adequate time for complete acclimatization can choose the short-term arrival strategy that best fits with the logistics of their travel.

UBC-Nepal Expedition: acute alterations in sympathetic nervous activity do not influence brachial artery endothelial function at sea level and high altitude

Michael M. Tymko, Joshua C. Tremblay, Craig D. Steinback, Jonathan P. Moore, Alex B. Hansen, Alexander Patrician, Connor A. Howe, Ryan L. Hoiland, Daniel J. Green, Philip N. Ainslie
November 1, 2017 : 1386-1396
DOI: 10.1152/japplphysiol.00583.2017

The role of the sympathetic nervous system on endothelial function remains unclear. We used lower-body negative and positive pressure to manipulate sympathetic nervous activity at sea level and high altitude and measured brachial endothelial function via flow-mediated dilation. We found that acutely altering sympathetic nervous activity had no effect on endothelial function.

RESEARCH ARTICLES

Frequency and magnitude of intermittent hypoxia modulate endothelial wound healing in a cell culture model of sleep apnea

Noelia Campillo, Bryan Falcones, Josep M. Montserrat, David Gozal, Ana Obeso, Teresa Gallego-Martin, Daniel Navajas, Isaac Almendros, Ramon Farré
November 1, 2017 : 1047-1054
DOI: 10.1152/japplphysiol.00077.2017

Intermittent hypoxia (IH) induces cardiovascular consequences in obstructive sleep apnea (OSA) patients. However, the vast array of frequencies and severities of IH previously employed in OSA-related experimental studies has led to controversial results on the effects of IH. By employing an optimized IH experimental system here, we provide evidence that the frequency and magnitude of IH markedly alter human aortic endothelial wound healing, emerging as key factors determining how cells respond in OSA.

An assessment of the autonomic nervous system in the electrohypersensitive population: a heart rate variability and skin conductance study

Soafara Andrianome, Jonathan Gobert, Laurent Hugueville, Erwan Stéphan-Blanchard, Frederic Telliez, Brahim Selmaoui
November 1, 2017 : 1055-1062
DOI: 10.1152/japplphysiol.00229.2017

This study provided analysis on the skin conductance parameters using a newly developed method (peak/min, extraction of skin conductance responses) that had not been performed previously. Additionally, the skin conductance signal was decomposed, considering tonic and phasic activities to be a distinct compound. Moreover, this is the first time a study has been designed into two steps to understand whether the autonomic nervous system is disturbed in the EHS population.

Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading

Eline Oppersma, Nima Hatam, Jonne Doorduin, Johannes G. van der Hoeven, Gernot Marx, Andreas Goetzenich, Sebastian Fritsch, Leo M. A. Heunks, Christian S. Bruells
November 1, 2017 : 1063-1070
DOI: 10.1152/japplphysiol.00095.2017

Transdiaphragmatic pressure using esophageal and gastric balloons is the gold standard to assess diaphragm effort. However, this technique is invasive and requires expertise, and the interpretation may be complex. We report that speckle tracking ultrasound can be used to detect stepwise increases in diaphragmatic effort. Strain and strain rate were highly correlated with transdiaphragmatic pressure, and therefore, diaphragm electric activity and speckle tracking might serve as reliable tools to quantify diaphragm effort in the future.

Extra- and intracranial blood flow regulation during the cold pressor test: influence of age

Daniela Flück, Philip N. Ainslie, Anthony R. Bain, Kevin W. Wildfong, Laura E. Morris, James P. Fisher
November 1, 2017 : 1071-1080
DOI: 10.1152/japplphysiol.00224.2017

Sympathetic activation evoked by a cold pressor test elicits heterogeneous extra- and intracranial blood vessel responses in young individuals that may serve an important protective role. The extra- and intracranial responses to the cold pressor test are blunted in older individuals.
Green tea epigallocatechin gallate enhances cardiac function restoration through survival signaling expression in diabetes mellitus rats with autologous adipose tissue-derived stem cells
Tung-Sheng Chen, Show-Yih Liou, Chia-Hua Kuo, Lung-Fa Pan, Yu-Lan Yeh, Jeffery Liou, V. Vijaya Padma, Chun-Hsu Yao, Wei-Wen Kuo, Chih-Yang Huang
November 1, 2017 : 1081-1091
DOI: 10.1152/japplphysiol.00471.2016
Cardiomyopathy can be induced in rats with diabetes mellitus (DM). Heart function can be restored in DM rats with adipose-derived stem cell treatment. Oral epigallocatechin gallate (EGCG) administration synergistically enhances cardiac function in DM rats with stem cell treatment. The EGCG and stem cell treatment cross-effect occurs via survival protein expression.

Effects of β-hydroxy-β-methylbutyrate on skeletal muscle mitochondrial content and dynamics, and lipids after 10 days of bed rest in older adults
Robert A. Standley, Giovanna Distefano, Suzette L. Pereira, Min Tian, Owen J. Kelly, Paul M. Coen, Nicolaas E. P. Deutz, Robert R. Wolfe, Bret H. Goodpaster
November 1, 2017 : 1092-1100
DOI: 10.1152/japplphysiol.00192.2017
Mitochondrial content and dynamics remained unchanged over 10 days of bed rest in older adults. β-Hydroxy-β-methylbutyrate (HMB) stimulated intramuscular lipid storage as triacylglycerol following 10 days of bed rest (BR) and maintained higher mitochondrial oxidative phosphorylation (OXPHOS) content and dynamics during the 8-wk resistance exercise rehabilitation program.

Acute volume loading exacerbates direct ventricular interaction in a model of COPD
November 1, 2017 : 1110-1117
DOI: 10.1152/japplphysiol.01109.2016
Volume loading may exacerbate adverse cardiopulmonary interaction in COPD however, the mechanisms remain unclear. We found that when negative intrathoracic pressure is increased, acute volume loading paradoxically reduces stroke volume. This reduction in stroke volume is considerably greater in a model of COPD, owing to the effects of lung hyperinflation.

Feedback modulation of surrounding pressure determines the onset of negative effort dependence in a collapsible tube bench model of the pharyngeal airway
Christopher Lambeth, Benjamin Kolevski, Terence Amis, Kristina Kairaitis
November 1, 2017 : 1118-1125
DOI: 10.1152/japplphysiol.00378.2017
A collapsible tube, pharyngeal airway bench model was used to study the role of surrounding pressure and longitudinal wall strain at the onset of negative effort dependence (NED). NED occurred to varying degrees across all conditions tested, but maximum airflow was achieved with 1) low initial surrounding pressure, 2) a feedback mechanism between surrounding pressure and driving pressure; and 3) a moderate amount of strain applied. Potential impacts on OSA phenotypic analyses are discussed.

Sexually dimorphic skeletal muscle and cardiac dysfunction in a mouse model of limb girdle muscular dystrophy 2i
Joseph W. Maricelli, Denali R. Kagel, Yemeserach M. Bishaw, O. Lynne Nelson, David C. Lin, Buel D. Rodgers
November 1, 2017 : 1126-1138
DOI: 10.1152/japplphysiol.00287.2017
Limb-girdle muscular dystrophy 2i is a rare dystroglycanopathy that until recently lacked an appropriate animal model. Studies with the FKRP P448L mutant mouse began assessing muscle structure and function as well as running gait. Our studies further characterize systemic muscle function using exercise and cardiac performance. They identified many markers of respiratory, cardiac and skeletal muscle function that could prove invaluable to better understanding the disease and more importantly, to preclinical drug trials.

Lower body negative pressure reduces optic nerve sheath diameter during head-down tilt
Karina Marshall-Goebel, Robert Terlević, Darius A. Gerlach, Simone Kuehn, Edwin Mulder, Jörn Rittweger
November 1, 2017 : 1139-1144
DOI: 10.1152/japplphysiol.00256.2017
This is the first study to demonstrate the ability of lower body negative pressure to directly influence cerebrospinal fluid surrounding the optic nerve, indicating potential use as a countermeasure for increased cerebrospinal fluid on Earth or in space.

Cardiac output by pulse contour analysis does not match the increase measured by rebreathing during human spaceflight
Richard L. Hughson, Sean D. Peterson, Nicholas J. Yee, Danielle K. Greaves
November 1, 2017 : 1145-1149
Noninvasive assessment of cardiac function during human spaceflight is an important tool to monitor astronaut health. This study demonstrated that pulse contour analysis of finger arterial blood pressure to estimate cardiac output failed to track the 46% increase measured by a rebreathing method. These results strongly suggest that alternative methods not dependent on pulse contour analysis are required to track cardiac function in spaceflight.

**Aerobic exercise elevates markers of angiogenesis and macrophage IL-6 gene expression in the subcutaneous adipose tissue of overweight-to-obese adults**
Douglas W. Van Pelt, Lisa M. Guth, Jeffrey F. Horowitz
November 1, 2017 : 1150-1159

Acute exercise in overweight/obese adults increased subcutaneous adipose tissue (SAT) mRNA expression of VEGFA, an important regulator of angiogenesis and capillary growth. In addition, subjects that regularly exercise had elevated SAT CD31 mRNA expression and elevated IL-6 mRNA in adipose tissue macrophages compared with nonexercisers. This study demonstrates that aerobic exercise may alter processes related to whole body metabolic outcomes in obesity, such as angiogenesis and immune response, in the SAT of overweight/obese adults.

**Blood pressure and leg deoxygenation are exaggerated during treadmill walking in patients with peripheral artery disease**
Amanda J. Miller, J. Carter Luck, Danielle Jin-Kwang Kim, Urs A. Leuenberger, David N. Proctor, Lawrence I. Sinoway, Matthew D. Muller
November 1, 2017 : 1160-1165

This is the first study to simultaneously measure skeletal muscle oxygen saturation and blood pressure (BP) during treadmill exercise in patients with peripheral arterial disease. We found that BP and leg deoxygenation responses to slow-paced, graded treadmill walking are greater in patients with peripheral arterial disease compared with healthy subjects. These data may help explain the high cardiovascular risk in patients with peripheral arterial disease.

**Impact of the localization of dendritic calcium persistent inward current on the input-output properties of spinal motoneuron pool: a computational study**
Hojeong Kim
November 1, 2017 : 1166-1187

How does the dendritic location of calcium persistent inward current (Ca-PIC) influence dendritic excitability and firing behavior across the spinal motoneuron pool? This issue was investigated developing a model motoneuron pool that reflected key motoneuron type-specific properties experimentally identified. The simulation results point out the negative relationship between the distance of Ca-PIC source from the soma and cell recruitment threshold as a basis underlying the systematic variation in input-output properties of motoneurons over the motoneuron pool.

**Peripheral ventilation heterogeneity determines the extent of bronchoconstriction in asthma**
Catherine E. Farrow, Cheryl M. Salome, Benjamin E. Harris, Dale L. Bailey, Norbert Berend, Gregory G. King
November 1, 2017 : 1188-1194

Using ventilation SPECT/CT imaging in asthmatics, we show induced bronchoconstriction leads to the development of areas of low ventilation. Furthermore, the relative volume of the low-ventilation regions was predicted by ventilation heterogeneity in diffusion-dependent acinar airways. This suggests that the pattern of regional airway narrowing in asthma is determined by acinar airway function.

**Effects of antenatal melatonin therapy on lung structure in growth-restricted newborn lambs**
Graeme R. Polglase, Jade Barbuto, Beth J. Allison, Tamara Yawno, Amy E. Sutherland, Atul Malhotra, Keith E. Schulze, Euan M. Wallace, Graham Jenkin, Sharon D. Ricardo, Suzanne L. Miller
November 1, 2017 : 1195-1203

Fetal growth restriction (FGR) results in poor respiratory outcomes, which may be caused by oxidation in utero. We investigated the contribution of oxidative stress to adverse lung development and the effects of melatonin administration, a powerful antioxidant, on lung structure in FGR lambs. FGR disrupted septation of the developing alveoli, which is not altered by melatonin administration. Oxidative stress may not be the mechanism driving altered lung structure in FGR neonates.

**Elevated airway liquid volumes at birth: a potential cause of transient tachypnea of the newborn**
Erin V. McGillick, Katie Lee, Shigeo Yamaoka, Arjan B. te Pas, Kelly J. Crossley, Megan J. Wallace, Marcus J. Kitchen, Robert A. Lewis, Lauren T. Kerr, Philip DeKoninck, Janneke Dekker, Maria Thio, Annie R.A. McDougall, Stuart B. Hooper
November 1, 2017 : 1204-1213
Transient tachypnea of the newborn reduces respiratory function in newborns and is thought to result due to elevated airway liquid volumes following birth. However, the effect of elevated airway liquid volumes on neonatal respiratory function is unknown. Using phase contrast X-ray imaging, we show that elevated airway liquid volumes have adverse effects on lung structure and function in the immediate newborn period, which may underlie the pathology of TTN in near-term babies after birth.

Acute effects of long-acting bronchodilators on small airways detected in COPD patients by single-breath N2 test and lung P-V curve
Matteo Pecchiari, Pierachille Santus, Dejan Radovanovic, Edgardo D’Angelo
November 1, 2017 : 1266-1275
DOI: 10.1152/japplphysiol.00493.2017

This is the first study investigating in stable chronic obstructive pulmonary disease patients the acute effects of two long-acting bronchodilators, a β-agonist and a muscarinic antagonist, on peripheral airways using simultaneous lung pressure-volume curve and single-breath N2 test. By lessening airway mechanical property heterogeneity, both drugs similarly reduced ventilation inhomogeneity and extent of small-airway closure, as indicated by the decrease of phase III slope, increased oxygen saturation, and fall of closing volume, often below expiratory reserve volume.

Severe energy deficit upregulates leptin receptors, leptin signaling, and PTP1B in human skeletal muscle
Ismael Perez-Suarez, Jesus Gustavo Ponce-Gonzalez, Jaime de La Calle-Herrero, Jose Losa-Reyna, Marcos Martin-Rincon, David Morales-Alamo, Alfredo Santana, Hans-Christer Holmberg, Jose A. L. Calbet
November 1, 2017 : 1276-1287
DOI: 10.1152/japplphysiol.00454.2017

This study shows that the skeletal muscle leptin receptors and their corresponding signaling cascade are upregulated in response to a severe energy deficit, contributing to increase maximal fat oxidation. The responses are more prominent in the arm muscles than in the legs but partly blunted by whey protein ingestion and high volume of exercise. This occurs despite an increase of protein tyrosine phosphatase 1B protein expression, a known inhibitor of insulin and leptin signaling.

Walking economy is predictably determined by speed, grade, and gravitational load
Lindsay W. Ludlow, Peter G. Weyand
November 1, 2017 : 1288-1302
DOI: 10.1152/japplphysiol.00504.2017

Introduced is a “minimum mechanics” model that predicts human walking economy across a broad range of conditions from only three variables: speed, surface grade, and body-plus-load mass. The derivation/validation data set includes steady-state loaded and unloaded walking trials (n = 3,414) that span a fourfold range of walking speeds on each of six different surface gradients (−6 to +9°). The accuracy of our minimum mechanics model (r² = 0.99; SEE = 1.06 ml O2·kg−1·min−1) appreciably exceeds that of currently-used standards.

Effects of anti-inflammatory (NSAID) treatment on human tendinopathic tissue
Katja Maria Heinemeier, Tommy F. Øhlenschläger, Ulla Ramer Mikkelsen, Freja Sønder, Peter Schjerling, Rene B. Svensson, Michael Kjaer
November 1, 2017 : 1397-1405
DOI: 10.1152/japplphysiol.00281.2017

Nonsteroidal anti-inflammatory drugs are widely used in the treatment of tendinopathy, but little is known of the effects of these drugs on tendon tissue. We find that 1 wk of ibuprofen treatment has no effect on gene expression of collagen and related growth factors in adult human tendinopathic tendon in vivo (in spite of relatively low levels of variation in gene expression), suggesting that tendinopathic cells are not responsive to ibuprofen.

INNOVATIVE METHODOLOGY

Imaging IGF-I uptake in growth plate cartilage using in vivo multiphoton microscopy
Maria A. Serrat, Gabriela Ion
November 1, 2017 : 1101-1109
DOI: 10.1152/japplphysiol.00645.2017

This paper describes and validates a novel method for imaging transport of biologically active, fluorescently labeled IGF-I into skeletal growth plates of live mice using multiphoton microscopy. Cellular patterns of fluorescence in the growth plate were completely distinct from our prior publications using biologically inert probes, demonstrating for the first time in vivo localization of IGF-I in chondrocytes and perichondrium. These results form important groundwork for future studies aimed at targeting therapeutics into growth plates.

VIEWPOINTS

Origin of the forward-going “backward” wave
LETTER TO THE EDITOR

Muscle Oxygen content at exercise in patients with claudication
Samir Henni, Pierre Abraham
November 1, 2017 : 1412
DOI: 10.1152/japplphysiol.00639.2017

Reply to Drs. Henni and Abraham: Muscle oxygen content at exercise in patients with claudication
J. Carter Luck, Faisal Aziz, Lawrence I. Sinoway, Matthew D. Muller
November 1, 2017 : 1413
DOI: 10.1152/japplphysiol.00706.2017

Inaccuracies in caffeine intake quantification and other important limitations in recent publication by Gonçalves et al.
J.L. Areta, C. Irwin, B. Desbrow
November 1, 2017 : 1414
DOI: 10.1152/japplphysiol.00489.2017

Reply to Areta et al.: Time to withdraw and let the myth rest
November 1, 2017 : 1415
DOI: 10.1152/japplphysiol.00567.2017

It is time to investigate acute and chronic perceptual responses to eccentric cycling
Benjamin Pageaux, Romuald Lepers, Jean-Marie Casillas, Davy Laroche
November 1, 2017 : 1416-1417
DOI: 10.1152/japplphysiol.00507.2017

Reply to Drs. Pageaux et al.: Cognitive demand of eccentric versus concentric cycling
Kazunori Nosaka, Andrew Haynes, Lauren C. Chasland, Andrew Maiorana, Louise H. Naylor, Daniel J. Green
November 1, 2017 : 1418
DOI: 10.1152/japplphysiol.00562.2017

Editorial makes unsubstantiated claims about high-load resistance training
James L. Nuzzo, Benjamin K. Barry
November 1, 2017 : 1419-1420
DOI: 10.1152/japplphysiol.00315.2017
Corrigendum

CORRIGENDUM
November 1, 2017 : 1422

DOI: 10.1152/japplphysiol.zdg-2479.corr.2017

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NEURO FORUM

Effective assessments of electroencephalography during stroke recovery: contemporary approaches and considerations
Kartik K. Iyer
November 1, 2017 : 2521-2525

DOI: 10.1152/jn.00206.2017

RESEARCH ARTICLE | 50 Years of Microneurography: Insights into Neural Mechanisms in Humans
Ventilation inhibits sympathetic action potential recruitment even during severe chemoreflex stress
Mark B. Badrov, Otto F. Barak, Tanja Mijacika, Leena N. Shoemaker, Lindsay J. Borrell, Mihajlo Lojpur, Ivan Drvis, Zeljko Dujic, J. Kevin Shoemaker
November 1, 2017 : 2914-2924

DOI: 10.1152/jn.00381.2017

The current study demonstrates that the sympathetic neural recruitment patterns observed during chemoreflex activation induced by rebreathing or apnea are restrained and/or inhibited by the act of ventilation per se, despite similar, or even greater, levels of severe chemoreflex stress. Therefore, ventilation modulates not only the timing of sympathetic bursts but also the within-burst axonal recruitment normally observed during progressive chemoreflex stress.

RESEARCH ARTICLE | Biology of Neuroengineering Interfaces

Parkinsonism and vigilance: alteration in neural oscillatory activity and phase-amplitude coupling in the basal ganglia and motor cortex
November 1, 2017 : 2654-2669

DOI: 10.1152/jn.00388.2017

Chronically implanted electrodes were used to record neural activity across multiple nodes in the basal ganglia-thalamocortical circuit simultaneously in a nonhuman primate model of Parkinson’s disease, enabling within-subject comparisons of electrophysiological biomarkers between normal and parkinsonian conditions and different vigilance states. This study improves our understanding of the role of oscillatory activity and phase-amplitude coupling in the pathophysiology of Parkinson’s disease and supports the development of more effective DBS therapies based on pathophysiological
RESEARCH ARTICLES | Cellular and Molecular Properties of Neurons

**Functional and molecular plasticity of γ and α1 GABAA receptor subunits in the dorsal motor nucleus of the vagus after experimentally induced diabetes**  
Carie R. Boychuk, Katalin C. Smith, Bret N. Smith  
November 1, 2017 : 2833-2841  
DOI: 10.1152/jn.00085.2017

Glutamate and GABA signaling in the dorsal vagal complex is elevated after several days of chronic hyperglycemia in a mouse model of type 1 diabetes. We report persistently enhanced GABAA receptor-mediated responses to the somnolent zolpidem in preganglionic vagal motor neurons. These results imply a broader impact of chronic hyperglycemia on central vagal function than previously appreciated and reinforce the hypothesis that diabetes effects in the brain can impact regulation of metabolic homeostasis.

**A role for the cystic fibrosis transmembrane conductance regulator in the nitric oxide-dependent release of Cl− from acidic organelles in amacrine cells**  
Vijai Krishnan, J. Wesley Maddox, Tyler Rodriguez, Evanna Gleason  
November 1, 2017 : 2842-2852  
DOI: 10.1152/jn.00511.2017

Although CFTR function has been studied extensively in the context of epithelia, relatively little is known about its function in neurons. We show that CFTR is involved in an NO-dependent release of Cl− from acidic organelles. This internal function of CFTR is particularly relevant to neuronal physiology because postsynaptic cytosolic Cl− levels determine the outcome of GABA- and glycinergetic synaptic signaling. Thus the CFTR may play a role in regulating synaptic transmission.

RESEARCH ARTICLE | Central Pattern Generators

**State-dependent sensorimotor gating in a rhythmic motor system**  
Rachel S. White, Robert M. Spencer, Michael P. Nusbaum, Dawn M. Blitz  
November 1, 2017 : 2806-2818  
DOI: 10.1152/jn.00420.2017

Sensory feedback influences motor systems (i.e., motor circuits and their projection neuron inputs). However, whether regulation of sensory feedback to these projection neurons is consistent across different versions of the same motor pattern driven by the same motor system was not known. We found that gating of sensory feedback to projection neurons is determined by the modulatory state of the motor system, and not simply by whether the system is active or inactive.

RESEARCH ARTICLES | Control of Movement

**Altered visual strategies and attention are related to increased force fluctuations during a pinch grip task in older adults**  
Kevin G. Keenan, Wendy E. Huddleston, Bradley E. Ernest  
November 1, 2017 : 2537-2548  
DOI: 10.1152/jn.00928.2016

The significant contributions of the study are the addition of eye movement data and an attention task to explain differences in hand motor control across different visual displays in older adults. Older participants used different visual strategies across varying feedback displays, and saccadic eye movements were related with motor performance. In addition, those older individuals with deficits in attention had impaired motor performance on two different hand motor control tasks, including the Grooved Pegboard test.

**Intermittent cortical involvement in the preservation of tremor in essential tremor**  
Sarvi Sharifi, Frauke Luft, Rens Verhagen, Tjitske Heida, Johannes D. Speelman, Lo J. Bour, Anne-Fleur van Rootselaar  
November 1, 2017 : 2628-2635  
DOI: 10.1152/jn.00848.2016

The part of the motor cortex involved in essential tremor is uncertain. The current electrophysiological study is the first to assess corticomuscular coherence systematically. The study shows a dynamic nature of corticomuscular coherence and a possible influence of cognitive states. The results elucidate the involvement of the motor cortex in tremor and help interpret the varying results in the literature. In clinical practice, the findings may guide in standardizing tremor registration and its interpretation.

**Distinct coordinate systems for adaptations of movement direction and extent**  
Eugene Poh, Timothy J. Carroll, Aymar de Rugy
Visuomotor gain and rotation adaptations generalize differently to novel movement directions, which suggests different neural mechanisms. When extrinsic and joint-based coordinates are effectively dissociated in an isometric aiming task, we find that they also generalize in different coordinate systems. Specifically, rotation generalized in extrinsic coordinates and decayed as posture departed from that adopted during adaptation. In contrast, gain generalization was expressed according to mixed extrinsic/joint-based coordinates and was not substantially reduced by postural changes.

Rapid visuomotor feedback gains are tuned to the task dynamics
Sae Franklin, Daniel M. Wolpert, David W. Franklin
November 1, 2017 : 2711-2726
DOI: 10.1152/jn.00748.2016

Here, we test whether rapid visuomotor feedback responses are selectively tuned to the task dynamics. The responses do not exhibit gain scaling, but they do vary with the level and stability of task dynamics. Moreover, these feedback gains are independently tuned to perturbations to the left and right, depending on these dynamics. Our results demonstrate that the sensorimotor control system regulates the feedback gain as part of the adaptation process, tuning them appropriately to the environment.

Variance in exposed perturbations impairs retention of visuomotor adaptation
Cesar Augusto Canaveral, Frédéric Danion, Félix Berrigan, Pierre-Michel Bernier
November 1, 2017 : 2745-2754
DOI: 10.1152/jn.00416.2017

The brain predicts the sensory consequences of motor commands through a forward model. These predictions are subject to uncertainty. We use visuomotor adaptation and modulate uncertainty in the sensory predictions by manipulating the variance in exposed rotations. Results reveal that variance does not influence the final extent of adaptation but selectively impairs the retention of motor memories. These results suggest that a more uncertain forward model is more susceptible to change or decay.

Intended arm use influences interhemispheric correlation of β-oscillations in primate medial motor areas
Toshi Nakajima, Haruka Arisawa, Ryosuke Hosaka, Hajime Mushiake
November 1, 2017 : 2865-2883
DOI: 10.1152/jn.00379.2016

We addressed interhemispheric relationships of β-oscillations during bimanual coordination. While monkeys prepared to initiate movement of the instructed arm, β-oscillations in the contralateral hemisphere showed a phase advance relative to the other hemisphere. Furthermore, the sequence of arm use influenced β-power and the degree of interhemispheric phase synchronization. Thus the dynamics of interhemispheric phases and power in β-oscillations may contribute to the specification of motor effectors in a given behavioral context.

The superior colliculus and the steering of saccades toward a moving visual target
Laurent Goffart, Aaron L. Cecala, Neeraj J. Gandhi
November 1, 2017 : 2890-2901
DOI: 10.1152/jn.00506.2017

The deep superior colliculus is involved in steering the saccade toward the current location of a moving target. During interceptive saccades, the active population consists of a continuum of cells ranging from neurons issuing commands related to past locations of the target to neurons issuing commands related to its current location. The motor burst of collicular neurons does not contain commands related to the future location of a moving target.

Vowel generalization and its relation to adaptation during perturbations of auditory feedback
Kevin J. Reilly, Chelsea Pettibone
November 1, 2017 : 2925-2934
DOI: 10.1152/jn.00702.2016

Speech adaptations to alterations, or perturbations, of auditory feedback have provided important insights into sensorimotor representations underlying speech. One finding from these studies that is yet to be accounted for is vowel generalization, which describes the effects of repeated perturbations to one vowel on the production of other vowels that were not perturbed. The present study used correlation testing to quantify the effects of changes in a perturbed vowel on neighboring (i.e., similar) nonperturbed vowels. The results identified significant correlations between the changes of adjacent, but not nonadjacent, vowel pairs. This finding suggests that generalization is partly a response to adaptation and not solely due to the auditory perturbation.

Role of digit placement control in sensorimotor transformations for dexterous manipulation
Daisuke Shibata, Marco Santello
November 1, 2017 : 2935-2943
This study was designed to understand the sensorimotor mechanisms underlying digit force-to-position modulation required for manipulation. Surprisingly, estimation of relative digit position and force-to-position modulation was accurate regardless of whether the digits were passively or actively positioned. Therefore, accurate estimation of digit position does not require an efference copy of active digit positioning, and the hypothesized advantage of active over passive movement on estimation of end-point position appears to be task and effector dependent.

RESEARCH ARTICLES | Higher Neural Functions and Behavior

Characterization of decision commitment rule alterations during an auditory change detection task
Bridgette Johnson, Rebeka Verma, Manying Sun, Timothy D. Hanks
November 1, 2017 : 2526-2536

Flexible decision stopping rules confer control over decision processes. Using an auditory change detection task, we found that alterations of decision stopping rules did not result in systematic changes in the temporal weighting of sensory information. We also found that post-error alterations of decision stopping rules depended on the type of mistake subjects make. These results provide guidance for understanding the neural mechanisms that control decision stopping rules, one of the critical components of decision making and behavioral flexibility.

Limbic-motor integration by neural excitations and inhibitions in the nucleus accumbens
Sara E. Morrison, Vincent B. McGinty, Johann du Hoffmann, Saleem M. Nicola
November 1, 2017 : 2549-2567

The nucleus accumbens (NAc) is thought to link expected rewards and action planning, but evidence for this idea remains sparse. We show that, across contexts, both excitatory and inhibitory cue-evoked activity in the NAc jointly encode reward prediction and probability of behavioral responding to the cue, as well as spatial and locomotor properties of the response. Interestingly, although spatial information in the NAc is updated quickly, fine-grained updating of reward value occurs over a longer timescale.

The neural basis of temporal individuation and its capacity limits in the human brain
Claire K. Naughtin, Benjamin J. Tamber-Rosenau, Paul E. Dux
November 1, 2017 : 2601-2613

We present novel findings into the neural bases of temporal individuation and repetition blindness (RB)—the perceptual deficit that arises when this process reaches its capacity limit. Specifically, we found that temporal individuation is a widely distributed process in the brain and identified a number of candidate brain regions that appear to underpin RB. These findings enhance our understanding of how these fundamental perceptual processes are reflected in the human brain.

Face percept formation in human ventral temporal cortex
Kai J. Miller, Dora Hermes, Franco Pestilli, Gagan S. Wig, Jeffrey G. Ojemann
November 1, 2017 : 2614-2627

Philosophers have puzzled for millennia about how humans build abstract conceptual objects (house/face/tool) from the simple features of the world they see around them (line/patch/lighting). Understanding the biological foundation of this process requires detailed knowledge of the spatial-temporal characteristics of cerebral cortex. By examining the physiology of the human temporal lobe from implanted electrodes while showing subjects noise-degraded images, we find that face percept formation happens in specific subregions within known face-processing areas.

Sequential hemifield gating of α- and β-behavioral performance oscillations after microsaccades
Joachim Bellet, Chih-Yang Chen, Ziad M. Hafed
November 1, 2017 : 2789-2805

We investigated long-term microsaccadic influences on visual processing and found rhythmic oscillations in behavioral performance at α- and β-frequencies (~8–20 Hz). These oscillations were pulsed at a much lower frequency across visual hemifields, first occurring in the same hemifield as the microsaccade direction vector for ~400 ms before switching to the opposite hemifield for a similar interval. Our results suggest that saccades temporally organize visual processing and that such organization can sequentially switch hemifields.

Asymmetric vestibular stimulation reveals persistent disruption of motion perception in unilateral vestibular lesions
November 1, 2017 : 2819-2832
A novel vestibular stimulus, combining asymmetric slow and fast sinusoidal half cycles, revealed persistent vestibuloperceptual dysfunction in unilateral vestibular lesion (UVL) patients. The compensation of motion perception after UVL was slower than that of vestibulo-ocular reflex. Perceptual but not vestibulo-ocular reflex deficits correlated with dizziness-related handicap.

RESEARCH ARTICLE | Nervous System Pathophysiology

Time-of-day influences on respiratory sequelae following maximal electroshock-induced seizures in mice
Benton S. Purnell, Michael A. Hajek, Gordon F. Buchanan
November 1, 2017: 2592-2600
DOI: 10.1152/jn.00039.2017

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy. SUDEP frequently occurs during the night, which has been attributed to an effect of sleep. We have shown that sleep state does indeed influence survival following a seizure. That SUDEP occurs during the night could also implicate a circadian influence. In this study we found that time of day independently affects the physiological consequences of seizures.

RESEARCH ARTICLES | Neural Circuits

Intrinsic frequency biases and profiles across human cortex
Monika S. Mellem, Sophie Wohltjen, Stephen J. Gotts, Avniel Singh Ghuman, Alex Martin
November 1, 2017: 2853-2864
DOI: 10.1152/jn.00061.2017

The organization of rhythmic neural activity is not well understood. Whereas it has been postulated that rhythms are organized in a hierarchical manner across brain regions, our novel analysis allows comparison of full cortical maps across different frequency bands, which demonstrate that the rhythmic organization is more complex. Additionally, data-driven methods show that rhythms of multiple frequencies or timescales occur within a particular region and that this nonhierarchical organization is widespread.

Firing rate estimation using infinite mixture models and its application to neural decoding
Ryohei Shibue, Fumiyasu Komaki
November 1, 2017: 2902-2913
DOI: 10.1152/jn.00818.2016

We propose a new neural decoding method using infinite mixture models and nonparametric Bayesian statistics. The proposed method improves decoding performance in terms of accuracy and computation speed. We have successfully applied the proposed method to position decoding from spike trains recorded in a rat hippocampus.

RESEARCH ARTICLES | Sensory Processing

Altered tactile sensitivity in children with attention-deficit hyperactivity disorder
Nicolaas A. J. Puts, Ashley D. Harris, Mark Mikkelsen, Mark Tommerdahl, Richard A. E. Edden, Stewart H. Mostofsky
November 1, 2017: 2568-2578
DOI: 10.1152/jn.00087.2017

This manuscript presents the first tactile psychophysical study testing different aspects of tactile processing in attention-deficit hyperactivity disorder (ADHD), using large cohort sizes of 67 children with ADHD and 65 Typically Developing Children. This study demonstrates impaired tactile processing in children with ADHD, on some, but not all tasks (showing this is not just due to attention), related to impaired cortical mechanisms. Furthermore, both IQ and soft motor skill abnormalities (common in ADHD) are correlated with tactile abnormalities.

Induced cortical oscillations in turtle cortex are coherent at the mesoscale of population activity, but not at the microscale of the membrane potential of neurons
Mahmood S. Hoseini, Jeff Pobst, Nathaniel Wright, Wesley Clawson, Woodrow Shew, Ralf Wessel
November 1, 2017: 2579-2591
DOI: 10.1152/jn.00375.2017

Coherent oscillatory neural activity has long been hypothesized as a potential mechanism for communication across locations in the brain. In this study we confirm the existence of coherent oscillations at the mesoscale of integrated cortical population activity. However, at the microscopic level of neurons, we find no evidence for coherence among oscillatory membrane potential fluctuations. These results raise questions about the applicability of the communication through coherence hypothesis to the level of the membrane potential.
Unbounded evidence accumulation characterizes subjective visual vertical forced-choice perceptual choice and confidence
Koeun Lim, Wei Wang, Daniel M. Merfeld
November 1, 2017 : 2636-2653
DOI: 10.1152/jn.00318.2017

We found that choice confidence data show dynamics consistent with evidence accumulation for a forced-choice subjective visual vertical task. We also found that the evidence accumulation appeared unbounded when judging confidence, which suggests that the brain utilizes mechanisms consistent with signal detection theory to determine choice confidence.

Muscle proprioceptors in adult rat: mechanosensory signaling and synapse distribution in spinal cord
Jacob A. Vincent, Hanna M. Gabriel, Adam S. Deardorff, Paul Nardelli, Robert E. W. Fyffe, Thomas Burkholder, Timothy C. Cope
November 1, 2017 : 2687-2701
DOI: 10.1152/jn.00497.2017

Muscle sensory neurons signal information necessary for controlling limb movements. The information encoded and transmitted by muscle proprioceptors to networks in the spinal cord is known in detail only for the cat, but differences in size and behavior of other species challenge the presumed generalizability. This report presents the first findings detailing specializations in mechanosensory signaling and intraspinal targets for functionally identified subtypes of muscle proprioceptors in the rat.

Hyperalgesia and sensitization of dorsal horn neurons following activation of NK-1 receptors in the rostral ventromedial medulla
Sergey G. Khasabov, Patrick Malecha, Joseph Noack, Janneta Tabakov, Glenn J. Giesler Jr., Donald A. Simone
November 1, 2017 : 2727-2744
DOI: 10.1152/jn.00478.2017

It is known that activation of neurokinin-1 (NK-1) receptors in the rostral ventromedial medulla (RVM), a main output area for descending modulation of pain, produces hyperalgesia. Here we show that activation of NK-1 receptors produces hyperalgesia by sensitizing nociceptive dorsal horn neurons. Targeting this pathway at its origin or in the spinal cord may be an effective approach for pain management.

Tests of the sorption and olfactory “fovea” hypotheses in the mouse
David M. Coppola, Brittaney E. Ritchie, Brent A. Craven
November 1, 2017 : 2770-2788
DOI: 10.1152/jn.00455.2017

Two classical ideas concerning olfaction’s receptor-surface two-dimensional organization—the sorption and olfactory fovea hypotheses—were found wanting in this study that afforded unprecedented comparisons between electrophysiological recordings in the mouse olfactory epithelium and computational fluid dynamic simulations of nasal airflow. Alternatively, it is proposed that the olfactory receptor layouts in macrosmatic mammals may be an evolutionary contingent state devoid of the functional significance found in other sensory epithelia like the cochlea and retina.

Surface electrodes record and label brain neurons in insects
Konstantinos Kostarakos, Berthold Hedwig
November 1, 2017 : 2884-2889
DOI: 10.1152/jn.00490.2017

We show that surface suction electrodes can be used to monitor the activity of auditory neurons in the cricket brain. They also allow delivering electrophoretically a fluorescent tracer to label the structure of the recorded neurons and the local neuropil to which the electrode was attached. This new extracellular recording and labeling technique is a versatile and useful method to explore neural processing in invertebrate sensory and motor systems.

RESEARCH ARTICLES | Spinal Control of Motor Outputs

Intermittent apnea elicits inactivity-induced phrenic motor facilitation via a retinoic acid- and protein synthesis-dependent pathway
Nathan A. Baertsch, Tracy L. Baker
November 1, 2017 : 2702-2710
DOI: 10.1152/jn.00212.2017

We identify spinal retinoic acid and protein synthesis as critical components in the cellular cascade whereby repetitive reductions in respiratory neural activity elicit rebound increases in phrenic inspiratory activity.

Spinal BDNF-induced phrenic motor facilitation requires PKCθ activity
Ibis M. Agosto-Marlin, Gordon S. Mitchell
November 1, 2017 : 2755-2762
We demonstrate that BDNF-induced pMF requires downstream signaling via PKCθ but not MEK/ERK or PI3K/Akt signaling. These data are essential to understand the sequence of the cellular cascade leading to BDNF-dependent phrenic motor plasticity.

Constitutive activity of 5-HT2C receptors is present after incomplete spinal cord injury but is not modified after chronic SSRI or baclofen treatment
V. M. Tysseling, D. A. Klein, R. Imhoff-Manuel, M. Manuel, C. J. Heckman, M. C. Tresch
November 1, 2017 : 2944-2952

DOI: 10.1152/jn.00190.2017

After spinal cord injury (SCI), most people will develop muscle spasms below their level of injury that can severely impact function. In this work, we examine the adaptations that occur within the spinal cord after SCI that contribute to these motor dysfunctions. We also evaluate one hypothesis about how these adaptations develop, which will potentially lead to intervention strategies to improve functional outcomes in persons with SCI.

INNOVATIVE METHODOLOGY | The Mouse Visual System

Method to remove photoreceptors from whole mount retina in vitro
Steven T. Walston, Yao-Chuan Chang, James D. Weiland, Robert H. Chow
November 1, 2017 : 2763-2769

DOI: 10.1152/jn.00578.2017

This study reports a method for removing photoreceptors from rodent whole mount retina while preserving the architecture of the inner retina. The method enables easier access to the inner retina for studies of neural processing, such as by patch clamp recording.

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Addison W. Woll, Frederick W. Quelle, Curt D. Sigmund
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Frank Park, Duane D. Miller
November 1, 2017 : 659-666

DOI: 10.1152/physiolgenomics.00070.2017

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Anna Alexanian, Andrey Sorokin
November 1, 2017 : 667-681

DOI: 10.1152/physiolgenomics.00086.2017

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Autonomic regulation of the immune system in cardiovascular diseases
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Effectiveness of interprofessional education in renal physiology curricula for health sciences graduate students
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Lecture attendance improves success in medical physiology
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Chloride Channels Take Center Stage in Acute Regulation of Excitability in Skeletal Muscle: Implications for Fatigue
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Wanshu Ma, Guillermo Oliver
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Lactic Acid: No Longer an Inert and End-Product of Glycolysis
Shiren Sun, Heng Li, Jianghua Chen, Qi Qian
October 11, 2017 : 453-463
DOI: 10.1152/physiol.00016.2017

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Vascular Smooth Muscle Cells and Arterial Stiffening: Relevance in Development, Aging, and Disease
Patrick Lacolley, Véronique Regnault, Patrick Segers, Stéphane Laurent
September 27, 2017 : 1555-1617
DOI: 10.1152/physrev.00003.2017

Hippocampal GABAergic Inhibitory Interneurons
Kenneth A. Pelkey, Ramesh Chittajallu, Michael T. Craig, Ludovic Tricoire, Jason C. Wester, Chris J. McBain
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Letters to the Editor

PROPERTIES OF THE TRPV4 ACTIVATOR GSK1016790A AND the TRPV4 ANTAGONIST GSK2193874
Kevin S. Thorneloe, Mui Cheung, Dennis A. Holt, Robert N. Willette
August 9, 2017 : 1231-1232
DOI: 10.1152/physrev.00019.2017

REPLY TO THORNELOE ET AL.
John P. M. White, Mario Cibelli, Laszlo Urban, Bernd Nilius, Graham McGeown, Istvan Nagy
August 9, 2017 : 1233-1234
DOI: 10.1152/physrev.00020.2017

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All articles for this journal are open access.

November 2017; volume 5, issue 22

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Original Research

Modeling search movements of an insect's front leg
Tibor I. Tóth, Eva Berg, Silvia Daun
November 15, 2017 : e13489
DOI: 10.14814/phy2.13489

In this work, we have set out to mimic search movements of insects using an existing model of insect locomotion. Using physiological reasonable assumptions, we could achieve good qualitative agreement between experimental and simulation results. Owing to this modeling work, we can provide a prospective tool to tell apart and characterize different functional modes of an insect leg.

Acute hypoxia-reoxygenation and vascular oxygen sensing in the chicken embryo
Riazuddin Mohammed, Carlos E. Salinas, Dino A. Giussani, Carlos E. Blanco, Angel L. Cogolludo, Eduardo Villamor
November 15, 2017 : e13501
DOI: 10.14814/phy2.13501
We hypothesized that exposure to acute hypoxia-reoxygenation induces alterations in vascular O2 sensing/signaling as well as in endothelial function in the chicken embryo pulmonary artery (PA), mesenteric artery (MA), femoral artery (FA), and ductus arteriosus (DA). However, ex vivo hypoxic contraction of PA and MA, hypoxic relaxation of FA, and normoxic contraction of DA were not significantly affected by previous exposure to hypoxia-reoxygenation. This suggests that direct effects of acute hypoxia-reoxygenation on vascular function does not play a role in the pathophysiology of hypoxic cardiovascular injury in the perinatal period.

- Change in hydration indices associated with an increase in total water intake of more than 0.5 L/day, sustained over 4 weeks, in healthy young men with initial total water intake below 2 L/day
  Jodi D. Stookey, Janice Hamer, David W. Killilea
  November 16, 2017 : e13356
  DOI: 10.14814/phy2.13356
  This secondary data analysis addressed gaps in knowledge about effects of chronic water intake on hydration indices. The results warrant work to determine if sustained higher water intake increases total body water through gradual isotonic retention of potassium and/or sodium, and if saliva osmolality is a sensitive and specific index of this effect.

- Subtype-specific effects of dopaminergic D2 receptor activation on synaptic trains in layer V pyramidal neurons in the mouse prefrontal cortex
  Jonna M. Leyrer-Jackson, Mark P. Thomas
  November 16, 2017 : e13499
  DOI: 10.14814/phy2.13499
  We characterized the effects of D2 receptor (D2R) activation on short-term excitatory postsynaptic potential (EPSP) dynamics evoked at varying frequencies in the two subtypes of layer V pyramidal neurons in mouse mPFC. All significant effects of D2 receptor activation were confined to type I (corticopontine) cells. Overall, our results suggest that D2R activation may modulate memory functions by inhibiting ‘top-down’ influences from apical tuft inputs activated at low frequencies, while promoting ‘top-down’ influences from inputs activated at higher frequencies.

- Cholesterol depletion does not alter the capacitance or Ca handling of the surface or t-tubule membranes in mouse ventricular myocytes
  Hanne C. Gadeberg, Cherrie H. T. Kong, Simon M. Bryant, Andrew F. James, Clive H. Orchard
  November 16, 2017 : e13500
  DOI: 10.14814/phy2.13500
  We show that cholesterol depletion using MβCD has no effect on t-tubule structure or function and does not alter surface or t-tubular membrane capacitance. These data suggest that the functional differences observed between the surface and t-tubular membranes are not due to differences in cholesterol content.

- Effects of short-lasting supramaximal-intensity exercise on diet-induced increase in oxygen uptake
  Katsunori Tsuji, Yuzhong Xu, Xin Liu, Izumi Tabata
  November 19, 2017 : e13506
  DOI: 10.14814/phy2.13506
  High-intensity intermittent exercise (HIIE) enhances diet-induced oxygen uptake to values equal to oxygen uptake during HIIE and excess postexercise oxygen consumption measured during the first 1.5 h after HIIE; this effect is related to the cardiorespiratory fitness of subjects.

- Cardiovascular effects of small peptides of the renin angiotensin system
  November 21, 2017 : e13505
  DOI: 10.14814/phy2.13505
  A direct vasodilator effect of small peptides from the renin angiotensin system in coronary bed of rats has not been fully established, as well as, the mechanisms underlying this action. Our present results showed that small fragments derived from angiotensin peptides hold biological activities in coronary bed of rats. Among the peptides evaluated, Ang-(1–2) presented the higher vasodilator effect, which was mediated by angiotensin-converting enzyme, nitric oxide release and activation of Mas receptor.

- Validity and variability of xBRS: instantaneous cardiac baroreflex sensitivity
  Karel H. Wesseling, John M. Karemaker, Paolo Castiglioni, Emil Toader, Andrei Cividjian, Jos J. Settels, Luc Quintin, Berend E. Westerhof
  November 26, 2017 : e13509
  DOI: 10.14814/phy2.13509
We validated our method of measuring instantaneous cross-correlation Baroreflex Sensitivity (BRS) xBRS by comparison to the “Gold Standard” of BRS: injection of a vasoconstritor (phenylephrine) or vasodilator (nitroprusside) drug, to which it compared favorably. Special attention was directed to the variability of xBRS numbers in each recording. The xBRS variability is not random, but shows very low-frequency oscillations, in the order of 20–50 sec; this is the same periodicity as has been observed in normal respiratory control oscillations.

Decoding spatial attention with EEG and virtual acoustic space
Yue Dong, Kaan E. Raif, Sarah C. Determan, Yan Gai
November 26, 2017 : e13512
DOI: 10.14814/phy2.13512

Decoding spatial attention based on brain signals has wide applications in brain–computer interface (BCI). The present study explored the possibility of using virtual acoustic space and a visual-auditory matching paradigm to overcome this issue.

Repeated bouts of resistance exercise with short recovery periods activates mTOR signaling, but not protein synthesis, in mouse skeletal muscle
Junya Takegaki, Riki Ogasawara, Yuki Tamura, Ryo Takagi, Yuki Arihara, Arata Tsutaki, Koichi Nakazato, Naokata Ishii
November 26, 2017 : e13515
DOI: 10.14814/phy2.13515

We investigated the consequences of shortening the recovery time between bouts of resistance exercise on protein synthesis and related processes in mouse skeletal muscles. Repeated bouts of resistance exercise with excessively short recovery did not activate protein synthesis, despite activation of the mTOR signaling pathway, which likely involves oxidative stress.

Validation of whole room indirect calorimeters: refinement of current methodologies
Russell Rising, Thomas Foerster, Avigdor D. Arad, Jeanine Albu, Xavier Pi-Sunyer
November 26, 2017 : e13521
DOI: 10.14814/phy2.13521

Propane gas combustions of various durations was compared to precision gas blending tests of similar lengths to determine the best methodology for validating whole room indirect calorimeters. It was found that a 10-h propane combustion test was sufficient for validating whole room indirect calorimeters utilized for 24-h metabolic studies verses that of precision gas blending and best emulated the metabolic processes of a human subject.

Motor module activation sequence and topography in the spinal cord during air-stepping in human: Insights into the traveling wave in spinal locomotor circuits
Hikaru Yokoyama, Kohtaroh Hagio, Tetsuya Ogawa, Kimitaka Nakazawa
November 26, 2017 : e13504
DOI: 10.14814/phy2.13504

In this study, we showed indirect evidence that neural mechanisms of rostrocaudally traveling wave of neural activation exist in human spinal locomotor circuits as in other vertebrates.

Deep-targeted sequencing of endothelial nitric oxide synthase gene exons uncovers exercise intensity and ethnicity-dependent associations with post-exercise hypotension
November 26, 2017 : e13510
DOI: 10.14814/phy2.13510

We sequenced NOS3 exons for associations with post-exercise hypotension among obese (30.9±3.6kg.m-2) African American (n = 14) [AF] and Caucasian (n = 9) adults 42.0 ± 9.8 year with hypertension (139.8 ± 10.4/84.6 ± 6.2 mmHg) who performed three random experiments: bouts of vigorous and moderate intensity cycling and control. NOS3 variants exhibited associations with PEH after vigorous, but not moderate intensity exercise among AF only. NOS3 should be studied further for its effects on PEH in a large, ethnically diverse sample of adults with hypertension to confirm our findings.

Influence of residual force enhancement and elongation of attached cross-bridges on stretch-shortening cycle in skinned muscle fibers
Atsuki Fukutani, Venus Joumaa, Walter Herzog
November 26, 2017 : e13477
DOI: 10.14814/phy2.13477
Stretch shortening cycle enhances performance of human movements. This study confirmed that residual force enhancement and elongation of attached cross bridges contributed to the force enhancement by stretch shortening cycle.

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**Original Research**

- **Organ-level validation of a cross-bridge cycling descriptor in a left ventricular finite element model: effects of ventricular loading on myocardial strains**
  Sheikh Mohammad Shavik, Samuel T. Wall, Joakim Sundnes, Daniel Burkhoff, Lik Chuan Lee
  November 8, 2017 : e13392
  DOI: 10.14814/phy2.13392
  Left ventricular finite ‘element’ model with a detailed cross-bridge descriptor coupled to a closed-loop lumped parameter circulatory model.

- **A comparison of postoperative morphometric and hemodynamic changes between saphenous vein and left internal mammary artery grafts**
  Tingting Fan, Yundi Feng, Feng Feng, Zhongjie Yin, Dayou Luo, Yuan Lu, Yingjin Xu, Wenchang Tan, Yunlong Huo
  November 8, 2017 : e13487
  DOI: 10.14814/phy2.13487
  The retrospective study showed morphometric and hemodynamic changes in SVGs and LIMA grafts of 132 patients for ~1 year, 5 and 10 years after revascularization. The findings showed that the vicious cycle of increased SAR-TAWSS and decreased lumen size with time is a major risk factor for long-term SVG occlusion albeit SVG arterialization and high SAR-TAWSSG contribute to the vascular remodeling in the anastomosis within the initial years after grafting.

- **DNPEP is not the only peptidase that produces SPAK fragments in kidney**
  Rainelli Koumangoye, Eric Delpire
  November 8, 2017 : e13479
  DOI: 10.14814/phy2.13479
  Two DNPEP mouse models were used to test whether the peptidase promote SPAK cleavage in kidney.

- **Dietary weight loss-induced changes in RBP4, FFA, and ACE predict weight regain in people with overweight and obesity**
  Roel G. Vink, Nadia J. Roumans, Edwin C. Mariman, Marleen A. van Baak
  November 8, 2017 : e13450
  DOI: 10.14814/phy2.13450
  Adipokines and other biomarkers were previously identified with roles in energy expenditure, appetite, satiety and adiposity. Dietary weight loss-induced changes in angiotensin-converting enzyme activity, FFA and RBP4 independently contribute to weight regain prediction.

- **Pregnancy-adapted uterine artery endothelial cell Ca2+ signaling and its relationship with membrane potential**
  Roxanne E. Alvarez, Derek S. Boeldt, Bikash R. Pattnaik, Hannah L. Friedman, Ian M. Bird
  November 8, 2017 : e13452
  DOI: 10.14814/phy2.13452
  P-UAEC and NP-UAEC show a greater synchronization in cell monolayer coordinated [Ca2+]i response in the form of (1) synchronous monolayer [Ca2+]i bursting and (2) [Ca2+]i waves propagating across the cell monolayer. P-UAEC and NP-UAEC appear to have similar baseline cell electrical properties, and ATP-stimulated [Ca2+]i bursting in confluent cell monolayers is not tightly/temporally dependent on correspondingly rapid Vm changes. Instead, overall mobilization of [Ca2+]i seems to drive only a small progressive change in Vm, with NP-UAEC > P-UAEC. The relevance of these findings is discussed.

- **Characterization of age-related penile microvascular hemodynamic impairment using laser speckle contrast imaging: possible role of increased fibrogenesis**
  Seung-Ryeol Lee, Ki-Ho Kim, Ho-Song You, Johnny Fu, Tung-Chin (Mike) Hsieh, Valmik Bhargava, M. Raj Rajasekaran
  November 8, 2017 : e13481
We evaluated a novel laser speckle contrast imaging (LSCI) technique to determine age-related changes in penile microvascular perfusion (PMP) and tested the role of cavernosal muscle (CC) fibrosis mediated by Wnt-TGF β1 signaling pathways in a mouse model. Ten young (2–3 months) and old (24–28 months) wild-type C57BL6 male mice were subjected to PMP was measured using a LSCI system. Penile blood flow (PBF, peak systolic velocity) was also measured using a color Doppler ultrasound for comparison.

**Diminished dynamic cerebral autoregulatory capacity with forced oscillations in mean arterial pressure with elevated cardiorespiratory fitness**

Lawrence Labrecque, Kevan Rahimaly, Sarah Imhoff, Myriam Paquette, Olivier Le Blanc, Simon Malenfant, Samuel J. E. Lucas, Damian M. Bailey, Jonathan D. Smirl, Patrice Brassard

November 8, 2017 : e13486

DOI: 10.14814/phy2.13486

This study examined the impact of cardiorespiratory fitness on the dynamic cerebral autoregulatory capacity using a multimetrics approach. We observed an intact ability of the cerebral vasculature of trained individuals to react to slow rhythmical blood pressure oscillations, but a diminished capability to buffer rapid and large blood pressure changes.

**MiR-335 overexpression impairs insulin secretion through defective priming of insulin vesicles**

Vishal A. Salunkhe, Jones K. Ofori, Nihkil R. Gandasi, Sofia A. Salő, Sofia Hansson, Markus E. Andersson, Anna Wendt, Sebastian Barg, Jonathan L. S. Esguerra, Lena Eliasson

November 8, 2017 : e13493

DOI: 10.14814/phy2.13493

Earlier reports have proposed reduced granular priming as the cause of reduced first-phase insulin secretion during prediabetes. Here, we show a negative correlation between miR-335 expression and insulin secretion index during this transition period. Moreover, overexpression of miR-335 in β-cells resulted in decreased glucose-stimulated insulin secretion, reduced Ca2+-dependent exocytosis through effects on granular priming, and concomitant reduction in three exocytotic proteins: SNAP25, Syntaxin-binding protein 1 (STXBP1), and synaptotagmin 11 (SYT11). PM, plasma membrane; VDCC, voltage-dependent calcium channel.

**Whole-body heat stress and exercise stimulate the appearance of platelet microvesicles in plasma with limited influence of vascular shear stress**

Eurico N. Wilhelm, José González-Alonso, Scott T. Chiesa, Steven J. Trangmar, Kameljit K. Kalsi, Mark Rakobowchuk

November 8, 2017 : e13496

DOI: 10.14814/phy2.13496

We show that exercise and whole-body heat stress increase platelet but not endothelial-derived microvesicles. However, this occurred both within the vascular beds of exercising and nonexercising limbs suggesting a limited role of shear stress.

**Frequent drinking of small volumes improves cardiac function and survival in rats with chronic heart failure**

Can Zheng, Meihua Li, Toru Kawada, Masashi Inagaki, Kazunori Uemura, Masaru Sugimachi

November 8, 2017 : e13497

DOI: 10.14814/phy2.13497

Rats with myocardial infarction tend to increase per drinking volume, and this drinking style may be a vicious factor which related with the short lifespan. Modulation drinking behavior to drink frequently with small volume may improve cardiac function and survival.

**Prefrontal oxygenation correlates to the responses in facial skin blood flows during exposure to pleasantly charged movie**

Kanji Matsukawa, Kana Endo, Ryota Asahara, Miho Yoshikawa, Shinya Kusunoki, Tomoko Ishida

November 8, 2017 : e13488

DOI: 10.14814/phy2.13488

Positively charged emotional stimulation decreased prefrontal oxygenation and facial skin blood flow, whereas negatively charged or neutral emotional stimulation did not alter or slightly decreased them. The reduction in prefrontal oxygenation during positively charged emotional stimulation suggests a decrease in prefrontal neural activity, which may in turn elicit neurally mediated vasoconstriction of facial skin blood vessels.

**The soluble (Pro)renin receptor does not influence lithium-induced diabetes insipidus but does provoke beiging of white adipose tissue in mice**

Kevin T. Yang, Fei Wang, Xiaoan Lu, Kexin Peng, Tianxin Yang, J. David Symons

November 14, 2017 : e13410

DOI: 10.14814/phy2.13410
We first reported that the recombinant soluble (pro) renin receptor sPRR-His upregulates renal aquaporin-2 (AQP2) expression, and attenuates polyuria associated with nephrogenic diabetes insipidus (NDI) induced by vasopressin type 2 receptor (V2R) antagonism. In this study, we showed that sPRR-His has no effect on lithium-induced polyuria but remarkably induces conversion of white to brown adipose tissue. This finding suggests a novel role of sPRR in regulating adipocyte biology.

Editorial

The complexities of lithium
Benjamin Ko
November 14, 2017 : e13405
DOI: 10.14814/phy2.13405

This is an editorial focus written to highlight the findings by Yang et al in the article “The Soluble (Pro)Renin Receptor Does Not Influence Lithium-Induced Diabetes Insipidus but Does Provoke Beiging of White Adipose Tissue in Mice.”

Original Research

Tadalafil, a long acting phosphodiesterase inhibitor, promotes bone marrow stem cell survival and their homing into ischemic myocardium for cardiac repair
Ibrahim Elmadbouh, Muhammad Ashraf
November 14, 2017 : e13480
DOI: 10.14814/phy2.13480

Tadalafil prolonged MSCs survival in vitro and in vivo, and increased MSCs mobilization and their homing into infarcted myocardium resulting in improved cardiac repair and function.

Comparative effects of intraduodenal amino acid infusions on food intake and gut hormone release in healthy males
Robert E. Steinert, Sina S. Ullrich, Lori Geary, Lori Asarian, Marco Bueter, Michael Horowitz, Christine Feinle-Bisset
November 14, 2017 : e13492
DOI: 10.14814/phy2.13492

To better understand the relative effects of individual amino acids on eating, and to gain insights into the potential mechanisms that may lead to differential satiating effects, we compared the effects of premeal ID infusion of tryptophan (TRP), leucine (LEU), phenylalanine (PHE) or glutamine (GLN) on appetite, GI-hormone responses, and meal size, using data from identically-designed, randomized, double-blind, placebo-controlled tests that have in part been previously published. Under our experimental conditions, intraduodenal TRP and LEU were more satiating than PHE and GLN. The greater satiating efficacy of LEU versus PHE was significantly dissociated from the effects of these AAAs on PYY, while the greater satiating potency of TRP versus PHE was significantly dissociated from the effects of these AAAs on insulin and glucagon. In contrast, ghrelin and CCK, and potentially other mechanisms, including central sensing of individual AAAs, appear to be stronger candidate mechanisms for the relative satiating effects obtained.

Epileptic pilocarpine-treated rats exhibit aberrant hippocampal EPSP-spike potentiation but retain long-term potentiation
Ezekiel Carpenter-Hyland, Edyta K. Bichler, Mathew Smith, Robert S. Sloviter, Morris Benveniste
November 14, 2017 : e13490
DOI: 10.14814/phy2.13490

Synaptic and nonsynaptic plasticity were assessed in rat hippocampal neurons from chronically epileptic pilocarpine-treated rats. Although plasticity-inducing protocols generated long-term potentiation at excitatory synapses in both control and pilocarpine-treated rats, epileptic rats were deficient in nonsynaptic plasticity. Despite mutual dependence on intracellular Ca2+, synaptic and nonsynaptic plasticity were found to be uncorrelated, and the degree of nonsynaptic plasticity was dependent on the number of action potentials elicited during plasticity induction.

Toll-like receptor 2 has a prominent but nonessential role in innate immunity to Staphylococcus aureus pneumonia
Shawn J. Skerrett, Marissa H. Braff, H. Denny Liggitt, Craig E. Rubens
November 15, 2017 : e13491
DOI: 10.14814/phy2.13491

Mice lacking Toll-like receptor 2 exhibited significant reductions in the intrapulmonary production of pro-inflammatory cytokines and chemokines, the recruitment of neutrophils to the lungs, the release of cathelicidin into the airspaces, and bacterial killing by alveolar macrophages after airway challenge with Staphylococcus aureus in comparison with wild-type controls. However, bacterial clearance and survival after infection were not
adversely affected by the absence of Toll-like receptor 2.

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Original Research

- Peripheral chemosensitivity is not blunted during 2 h of thermoneutral head out water immersion in healthy men and women
  James R. Sackett, Zachary J. Schlader, Suman Sarker, Christopher L. Chapman, Blair D. Johnson
  October 19, 2017: e13472
  DOI: 10.14814/phy2.13472
  We tested the hypothesis that peripheral chemosensitivity to hypoxia and hypercapnia is blunted during head out water immersion. Our findings indicate that peripheral chemosensitivity is not changed during head out water immersion.

- Acoustic change complex in background noise: phoneme level and timing effects
  Curtis J. Billings, Leslie D. Grush, Nashrah Maamor
  October 19, 2017: e13464
  DOI: 10.14814/phy2.13464
  In background noise, the neural response to /s/ in /sɑ/ disappears but the response to /ɑ/ remains stable across SNRs if presented in syllable context. The interaction between context and SNR effects may be attributed to neural refractoriness.

- Transport-associated pathway responses in ovine fetal membranes to changes in amniotic fluid dynamics
  Cecilia Y. Cheung, Debra F. Anderson, Robert A. Brace
  October 19, 2017: e13455
  DOI: 10.14814/phy2.13455
  The gene expression profiles for transport-associated molecules in the fetal membranes are consistent with the amnion as the rate-limiting layer for intramembranous absorption. Tubulin-α, component of microtubules, in the amnion may be an important regulator of transcellular vesicular transport of amniotic fluid and thus regulate the rate of intramembranous absorption across the amnion. Intramembranous absorption rate across the amnion is the primary determinant of amniotic fluid volume.

- Effect of renal denervation on urine angiotensinogen excretion in prenatally programmed rats
  Asifhusen Mansuri, Susan K. Legan, Jyoti Jain, Issa Alhamoud, Jyothsna Gattineni, Michel Baum
  October 19, 2017: e13482
  DOI: 10.14814/phy2.13482
  We have demonstrated that prenatal programming is associated with an increase in renal sympathetic nerve activity and an increase in the intrarenal renin–angiotensin system. This manuscript examines if the increased renal sympathetic nerve activity in programmed rats mediates the increase in urinary angiotensinogen, a marker for the intrarenal RAS.

- Consequences of advanced aging on renal function in chronic hyperandrogenemic female rat model: implications for aging women with polycystic ovary syndrome
  Chetan N. Patil, Lorraine C. Racusen, Jane F. Reckelhoff
  October 19, 2017: e13461
  DOI: 10.14814/phy2.13461
  In this manuscript, we have evaluated the consequences of chronic long-term androgens in a rat model of women who have had polycystic ovary syndrome prior to menopause. Advanced aging in this model causes significant reductions in GFR, RPF, Filtration fraction, increases in proteinuria and KIM-1 excretion and reductions in nitrate/nitrite excretion. The data suggest that with advanced age, women who have had PCOS and still have elevated androgen levels may have chronic kidney disease.

- Body temperature and cold sensation during and following exercise under temperate room conditions in cold-sensitive young trained females
  Naoto Fujii, Erii Aoki-Murakami, Bun Tsuji, Glen P. Kenny, Kei Nagashima, Narihiko Kondo, Takeshi Nishiyasu
  October 22, 2017: e13465
We show that at room temperature conditions (i.e., 23.5°C) young trained females who are sensitive to cold exhibit augmented whole-body cold sensation during rest only, whereas they also exhibit augmented extremity cold sensation during rest that persists during and following exercise. Hence, warming the fingers and toes (e.g., wearing socks and gloves) during and following exercise under cool or cold environments might minimize augmented cold sensation thereby contributing to better subsequent exercise performance in these individuals.

Alveolar air and oxidative metabolic demand during exercise in healthy adults: the role of single-nucleotide polymorphisms of the β2AR gene
Erik H. Van Iterson, Eric M. Snyder, Bruce D. Johnson
October 22, 2017 : e13476

DOI: 10.14814/phy2.13476

β2ARs are the predominating βAR subtype expressed on alveolar tissue and play an important role in pulmonary gas exchange. This study demonstrates the homozygous Arg16Arg single-nucleotide polymorphism (SNP) of the β2AR gene is associated with reduced alveolar volume (i.e., smaller alveolar surface area) contributions to total ventilatory and oxidative metabolic demand during submaximal exercise in healthy adults.

Prolonged leg bending impairs endothelial function in the popliteal artery
Lauren K. Walsh, Robert M. Restaino, Luis A. Martinez-Lemus, Jaume Padilla
October 22, 2017 : e13478

DOI: 10.14814/phy2.13478

This work supports arterial bending as a potential causative factor to sitting-induced leg endothelial dysfunction. Spending excessive time with legs bent and immobile, irrespective of whether this is in the setting of sitting or lying-down, may be disadvantageous for leg vascular health.

Abundance, localization, and functional correlates of the advanced glycation end-product carboxymethyl lysine in human myocardium
Martin M. LeWinter, Douglas Taatjes, Takamaru Ashikaga, Bradley Palmer, Nicole Bishop, Peter VanBuren, Stephen Bell, Cameron Donaldson, Markus Meyer, Kenneth B. Margulies, Margaret Redfield, David A. Bull, Michael Zile
October 24, 2017 : e13462

DOI: 10.14814/phy2.13462

We studied the abundance and localization of the advanced glycation end-product carboxymethyl lysine (CML) in human myocardium in human myocardium obtained during coronary bypass grafting in patients with hypertension, hypertension + diabetes mellitus or neither (controls) using a quantitative, high resolution immuno-electron microscopic method. We found that CML was abundant in the cytoplasm of cardiomyocytes but very sparse in the extracellular matrix. CML counts did not differ between the three groups and were significantly correlated with left atrial volume, an index of diastolic function.

Muscle oxygenation profiles between active and inactive muscles with nitrate supplementation under hypoxic exercise
Masahiro Horiuchi, Junko Endo, Shohei Dobashi, Yoko Handa, Masataka Kiuchi, Katsuhiro Koyama
October 24, 2017 : e13475

DOI: 10.14814/phy2.13475

Muscle deoxygenation profiles were suppressed at moderate work rates during leg cycling exercise with nitrate supplementation. The results of lower muscle deoxygenation appeared to have more muscle O2 extraction reserve, which resulted in the extension of time-to-exhaustion under hypoxic exercise.

Physiological effects of high-altitude trekking on gonadal, thyroid hormones and macrophage migration inhibitory factor (MIF) responses in young lowlander women
Vittore Verratti, Francesca Ietta, Luana Paulesu, Roberta Romagnoli, Ilaria Ceccarelli, Christian Doria, Giorgio Fanò Illic, Camillo Di Giulio, Anna M. Aloisi
October 24, 2017 : e13400

DOI: 10.14814/phy2.13400

This study highlights the changes that young women (temporarily exposed to high-altitude zones) might undergo, probably due to the change in oxygen saturation during the ascent to high altitude, and suggests possible factors involved in reproductive impairment.

Cardiac and renal upregulation of Nox2 and NF-κB and repression of Nox4 and Nrf2 in season- and diabetes-mediated models of vascular oxidative stress in guinea-pig and rat
Anna Gajos-Draus, Monika Duda, Andrzej Beręsewicz
October 29, 2017 : e13474
In seasonal and diabetic models of oxidative stress, superoxide-forming Nox'es and NF-kappaB pathway versus Nox4 and Nrf2 pathway are regulated oppositely in guinea-pig and rat hearts and in rat kidneys. These data suggest that chronic oxidative stress not only comes from upregulation of some Nox'es but also from downregulation of Nox4 and Nrf2 pathway.

Linking metabolic and contractile dysfunction in aged cardiac myocytes
Gregory P. Barton, Willem J. de Lange, John C. Ralphe, Judd Aiken, Gary Diffee
October 29, 2017 : e13485
DOI: 10.14814/phy2.13485

Aging is associated with declining cardiac contractile function as well as changes in metabolism and mitochondrial function. The purpose of this study was to examine the relationship between age-related changes in cellular metabolism and contractile function. Our results demonstrate stress-induced contractile dysfunction in aged myocytes which may be related to altered cellular energetics.

You have access
Novel description of the large conductance Ca2+-modulated K+ channel current, BK, during an action potential from suprachiasmatic nucleus neurons
John R. Clay
October 29, 2017 : e13473
DOI: 10.14814/phy2.13473

This report describes for the first time the behavior during an action potential of the large conductance, Ca2+-modulated K+ current IBK. The kinetics of this component are sensitive to changes in the intracellular Ca2+ concentration adjacent to the membrane surface. The analysis is consistent with a delay of a few milliseconds before the effect of a change in Ca2+ fully occurs. A model of the action potential (AP) will need to include an equation describing this behavior.

Corticospinal control from M1 and PMv areas on inhibitory cervical propriospinal neurons in humans
Louis-Solal Giboin, Sina Sangari, Alexandra Lackmy-Vallée, Arnaud Messé, Pascale Pradat-Diehl, Véronique Marchand-Pauvert
October 29, 2017 : e13387
DOI: 10.14814/phy2.13387

In humans, inhibitory cervical propriospinal neurons have diffuse projections on upper limb motoneurons and may be good candidates to transmit diffuse descending inhibition to prevent unwilling muscle activity. Propriospinal inhibition was enhanced when peripheral nerve stimuli were combined to TMS over M1 or PMv, and inhibition from PMv was unchanged after a reversible functional disruption of M1. M1 and PMv can depress the excitability of spinal motoneurons and avoid muscle activity through inhibitory cervical propriospinal neurons.
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Alec M. DeSimone, Anna Pakula, Angela Lek, Charles P. Emerson
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Leena P. Bharath, Blanche C. Ip, Barbara S. Nikolajczyk
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Adipose Tissue in HIV Infection
John R. Koethe
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Insights into cellular and molecular basis for urinary tract infection in autosomal-dominant polycystic kidney disease
Chao Gao, Long Zhang, Ye Zhang, Darren P. Wallace, Reynold I. Lopez-Soler, Paul J. Higgins, Wenzheng Zhang
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Vascular niche contribution to age-associated neural stem cell dysfunction
Deana M. Apple, Erzsebet Kokovay
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DOI: 10.1152/ajpheart.00154.2017

Dietary modulation of oxylipins in cardiovascular disease and aging
Stephanie P. B. Caligiuri, Mihir Parikh, Aleksandra Stamenkovic, Grant N. Pierce, Harold M. Aukema
November 1, 2017 : H903-H918
DOI: 10.1152/ajpheart.00201.2017

Oxylipins are an important group of fatty acid metabolites amenable to dietary manipulation. Because of the role they play in cardiovascular disease and in age-related degeneration, oxylipins are gaining recognition as viable targets for specific dietary interventions focused on manipulating oxylipin composition to control these biological processes.

Role of pattern recognition receptors of the neurovascular unit in inflamm-aging
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Ion channels of the lung and their role in disease pathogenesis
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The hypoxia-adenosine link during inflammation
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DOI: 10.1152/japplphysiol.00101.2017

Oxygen metabolism and innate immune responses in the gut
Sean P. Colgan, Eric L. Campbell
November 1, 2017 : 1321-1327
DOI: 10.1152/japplphysiol.00113.2017
Variation in O2 transport characteristics among Andean, Tibetan, and, when available, Ethiopian high-altitude residents supports the existence of genetic adaptations that improve the distribution of blood flow to vital organs and the efficiency of O2 utilization. Genome scans and whole genome sequencing studies implicate a broad range of gene regions. Future studies are needed using phenotypes of clear relevance for reproductive success for determining the mechanisms by which naturally selected genes are acting.

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Eric Seidel, Ute I. Scholl
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* Does not include *Physiology* or *Physiological Reviews*