

The Journal of
PHARMACOLOGY
And Experimental Therapeutics

A Publication of the American Society for Pharmacology and Experimental Therapeutics

April 2008

Vol. 325, No. 1

Contents

PERSPECTIVES IN PHARMACOLOGY

- Exploiting Complexity and the Robustness of Network Architecture for Drug Discovery Marc K. Hellerstein 1

BEHAVIORAL PHARMACOLOGY

- Early Postnatal Stress Alters Place Conditioning to Both μ - and κ -Opioid Agonists Clifford C. Michaels and Stephen G. Holtzman 313

CARDIOVASCULAR

- Design of Mutant β_2 Subunits as Decoy Molecules to Reduce the Expression of Functional Ca^{2+} Channels in Cardiac Cells Sabine Télémaque, Swapnil Sonkusare, Terrie Grain, Sung W. Rhee, Joseph R. Stimers, Nancy J. Rusch, and James D. Marsh 37

- Sphingosine 1-Phosphate Inhibits Nitric Oxide Production Induced by Interleukin-1 β in Rat Vascular Smooth Muscle Cells Takuji Machida, Yukihiro Hamaya, Sachiko Izumi, Yumika Hamaya, Kenji Iizuka, Yasuyuki Igarashi, Masaru Minami, Roberto Levi, and Masahiko Hirafuji 200

- Andrographolide Up-Regulates Cellular-Reduced Glutathione Level and Protects Cardiomyocytes against Hypoxia/Reoxygenation Injury Anthony Y. H. Woo, Mary M. Y. Waye, Stephen K. W. Tsui, Sandy T. W. Yeung, and Christopher H. K. Cheng 226

- Orally Available Levosimendan Dose-Related Positive Inotropic and Lusitropic Effect in Conscious Chronically Instrumented Normal and Heart Failure Dogs Satoshi Masutani, Heng-Jie Cheng, Minja Hyttilä-Hopponen, Jouko Levijoki, Aira Heikkilä, Arja Vuorela, William C. Little, and Che-Ping Cheng 236

- Evoked Changes in Cardiovascular Function in Rats by Infusion of Levosimendan, OR-1896 [(R)-N-(4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)acetamide], OR-1855 [(R)-6-(4-Aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one], Dobutamine, and Milrinone: Comparative Effects on Peripheral Resistance, Cardiac Output, dP/dt, Pulse Rate, and Blood Pressure Jason A. Segreti, Kennan C. Marsh, James S. Polakowski, and Ryan M. Fryer 331

CELLULAR AND MOLECULAR

- Activation and Inhibition of Adenylyl Cyclase Isoforms by Forskolin Analogs Cibele Pinto, Dan Papa, Melanie Hübner, Tung-Chung Mou, Gerald H. Lushington, and Roland Seifert 27

- Phosphorylation Increases Affinity of the Phosphodiesterase-5 Catalytic Site for Tadalafil Emmanuel P. Bessay, Mitsi A. Blount, Roya Zoraghi, Alfreda Beasley, Kennard A. Grimes, Sharron H. Francis, and Jackie D. Corbin 62

- Proteasome-Dependent Pharmacological Rescue of Cystic Fibrosis Transmembrane Conductance Regulator Revealed by Mutation of Glycine 622 Caroline Norez, Frédéric Bilan, Alain Kitzis, Yvette Mettey, and Frédéric Becq 89

The Journal of Pharmacology and Experimental Therapeutics (ISSN 0022-3565) is published monthly by the American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995; email: info@aspet.org; web site: www.aspet.org. Periodicals postage paid at Bethesda, MD, and at additional mailing offices. POSTMASTER: Send address changes to The Journal of Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995. Subscription rates: U.S.: \$893.00 for institutions and \$389.00 for non-ASPET members. Outside the U.S.: \$1,049.00 for institutions and \$545.00 for non-ASPET members.

Single copy: \$79.00. GST Tax Number for Canadian subscribers: BN: 13489 2330 RT. Indexed or abstracted by *Biochemistry & Biophysics Citation Index*®, *Biological Abstracts*, *BIOSIS Previews Database*, *BioSciences Information Services*, *Current Awareness in Biological Sciences*, *Current Contents/Life Sciences*, *EMBASE/Excerpta Medica*, *Index Medicus*, *Medical Documentation Service*®, *PsycINFO*, *Reference Update*®, *Research Alert*®, *Science Citation Index*®, *SciSearch*®, and *SIIC Data Bases*. Copyright © 2008 by the American Society for Pharmacology and Experimental Therapeutics. All rights reserved. Printed in the U.S.A.

Paradoxical Behavior of Neuromedin U in Isolated Smooth Muscle Cells and Intact Tissue	Paul J. Brighton, Alan Wise, Narinder B. Dass, and Gary B. Willars	154
G Protein Coupling and Ligand Selectivity of the D_{2L} and D₃ Dopamine Receptors	J. Robert Lane, Ben Powney, Alan Wise, Stephen Rees, and Graeme Milligan	319
Mapping the Structural Requirements in the CB₁ Cannabinoid Receptor Transmembrane Helix II for Signal Transduction	Ankur Kapur, Patrick Samaniego, Ganesh A. Thakur, Alexandros Makriyannis, and Mary E. Abood	341
CHEMOTHERAPY, ANTIBIOTICS, AND GENE THERAPY		
Design and Evaluation of S-Nitrosylated Human Serum Albumin as a Novel Anticancer Drug	Naohisa Katayama, Keisuke Nakajou, Hisakazu Komori, Kunitoshi Uchida, Jun-ichi Yokoe, Norikiyo Yasui, Hisashi Yamamoto, Toshiya Kai, Makoto Sato, Takenobu Nakagawa, Motohiro Takeya, Toru Maruyama, and Masaki Otagiri	69
ENDOCRINE AND DIABETES		
☐ (R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a Novel Xanthine-Based Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors	Leo Thomas, Matthias Eckhardt, Elke Langkopf, Moh Tadayyon, Frank Himmelsbach, and Michael Mark	175
GASTROINTESTINAL, HEPATIC, PULMONARY, AND RENAL		
☐ Discovery and Characterization of Novel Tryptophan Hydroxylase Inhibitors That Selectively Inhibit Serotonin Synthesis in the Gastrointestinal Tract	Qingyun Liu, Qi Yang, Weimei Sun, Pete Vogel, William Heydorn, Xiang-Qing Yu, Zhixiang Hu, Wangsheng Yu, Brandie Jonas, Randy Pineda, Valerie Calderon-Gay, Michael Germann, Emily O'Neill, Robert Brommage, Emily Cullinan, Ken Platt, Alan Wilson, Dave Powell, Arthur Sands, Brian Zambrowicz, and Zhi-cai Shi	47
Pharmacological Properties of N-(3,5-Diamino-6-chloropyrazine-2-carbonyl)-N'-4-[4-(2,3-dihydroxypropoxy)phenyl]butyl-guanidine Methanesulfonate (552-02), a Novel Epithelial Sodium Channel Blocker with Potential Clinical Efficacy for Cystic Fibrosis Lung Disease	Andrew J. Hirsh, Jim Zhang, Andra Zamurs, Jacquelyn Fleegle, William R. Thelin, Ray A. Caldwell, Juan R. Sabater, William M. Abraham, Mark Donowitz, Boyoung Cha, Kevin B. Johnson, Judith A. St. George, M. Ross Johnson, and Richard C. Boucher	77
Inhibitory Phosphorylation of Soluble Guanylyl Cyclase by Muscarinic m2 Receptors via Gβγ-Dependent Activation of c-Src Kinase	Karnam S. Murthy	183
5-Amino-6-chloro-N-[(1-isobutylpiperidin-4-yl)methyl]-2-methylimidazo[1,2-α]pyridine-8-carboxamide (CJ-033,466), a Novel and Selective 5-Hydroxytryptamine₄ Receptor Partial Agonist: Pharmacological Profile in Vitro and Gastroprokinetic Effect in Conscious Dogs	Tadayoshi Mikami, Yasuo Ochi, Keiko Suzuki, Toshiyuki Saito, Yutaka Sugie, and Minoru Sakakibara	190
Regulation of Renal Ectophosphodiesterase by Protein Kinase C and Sodium Diet	Edwin K. Jackson and Zaichuan Mi	210
Rutaecarpine Induces Chloride Secretion across Rat Isolated Distal Colon	DaZheng Wu and ZhiBi Hu	256
INFLAMMATION, IMMUNOPHARMACOLOGY, AND ASTHMA		
Anti-Inflammatory and Analgesic Potency of Carboxamidotriazole, a Tumorostatic Agent	Lei Guo, Caiying Ye, Wenying Chen, Hua Ye, Ru Zheng, Juan Li, Huifen Yang, Xiaoli Yu, and Dechang Zhang	10
☐ Treatment of Sepsis-Induced Acquired Protein C Deficiency Reverses Angiotensin-Converting Enzyme-2 Inhibition and Decreases Pulmonary Inflammatory Response	Mark A. Richardson, Akanksha Gupta, Lee A. O'Brien, David T. Berg, Bruce Gerlitz, Samreen Syed, Ganesh R. Sharma, Martin S. Cramer, Josef G. Heuer, Elizabeth J. Galbreath, and Brian W. Grinnell	17
The Carbon Monoxide-Releasing Molecule Tricarbonyldichlororuthenium(II) Dimer Protects Human Osteoarthritic Chondrocytes and Cartilage from the Catabolic Actions of Interleukin-1β	Javier Megías, María Isabel Guillén, Antonio Bru, Francisco Gomar, and María José Alcaraz	56
Evidence for the Role of Mitogen-Activated Protein Kinase Signaling Pathways in the Development of Spinal Cord Injury	Tiziana Genovese, Emanuela Esposito, Emanuela Mazzon, Carmelo Muià, Rosanna Di Paola, Rosaria Meli, Placido Bramanti, and Salvatore Cuzzocrea	100

<p>☐ Differential High-Affinity Interaction of Dectin-1 with Natural or Synthetic Glucans Is Dependent upon Primary Structure and Is Influenced by Polymer Chain Length and Side-Chain Branching</p>	<p>Elizabeth L. Adams, Peter J. Rice, Bridget Graves, Harry E. Ensley, Hai Yu, Gordon D. Brown, Siamon Gordon, Mario A. Monteiro, Erzsebet Papp-Szabo, Douglas W. Lowman, Trevor D. Power, Michael F. Wempe, and David L. Williams</p>	<p>115</p>
<p>Thiopental Protects Human T Lymphocytes from Apoptosis in Vitro via the Expression of Heat Shock Protein 70</p>	<p>Martin Roesslein, David Schibilsky, Laurent Muller, Ulrich Goebel, Christian Schwer, Matjaz Humar, Rene Schmidt, Klaus K. Geiger, Heike L. Pahl, Benedikt H. J. Pannen, and Torsten Loop</p>	<p>217</p>
<p>METABOLISM, TRANSPORT, AND PHARMACOGENOMICS</p>		
<p>☐ Aberrant Splicing Caused by Single Nucleotide Polymorphism c.516G>T [Q172H], a Marker of CYP2B6*6, Is Responsible for Decreased Expression and Activity of CYP2B6 in Liver</p>	<p>Marco H. Hofmann, Julia K. Bliedernicht, Kathrin Klein, Tanja Saussele, Elke Schaeffeler, Matthias Schwab, and Ulrich M. Zanger</p>	<p>284</p>
<p>NEUROPHARMACOLOGY</p>		
<p>Development and Preclinical Testing of a High-Affinity Single-Chain Antibody against (+)-Methamphetamine</p>	<p>Eric C. Peterson, Elizabeth M. Laurenzana, William T. Atchley, Howard P. Hendrickson, and S. Michael Owens</p>	<p>124</p>
<p>Correlating Efficacy in Rodent Cognition Models with in Vivo 5-Hydroxytryptamine_{1A} Receptor Occupancy by a Novel Antagonist, (R)-N-(2-Methyl-(4-indolyl-1-piperazinyl)ethyl)-N-(2-pyridinyl)-cyclohexane Carboxamide (WAY-101405)</p>	<p>Warren D. Hirst, Terrance H. Andree, Suzan Aschmies, Wayne E. Childers, Thomas A. Comery, Lee A. Dawson, Mark Day, Irene B. Feingold, Steven M. Grauer, Boyd L. Harrison, Zoë A. Hughes, John Kao, Michael G. Kelly, Heidi van der Lee, Sharon Rosenzweig-Lipson, Annmarie L. Saab, Deborah L. Smith, Kelly Sullivan, Stacey J. Sukoff Rizzo, Cesario Tio, Mei-Yi Zhang, and Lee E. Schechter</p>	<p>134</p>
<p>A Neuronal Microtubule-Interacting Agent, NAPVSIPQ, Reduces Tau Pathology and Enhances Cognitive Function in a Mouse Model of Alzheimer's Disease</p>	<p>Yasuji Matsuoka, Yan Jouroukhin, Audrey J. Gray, Li Ma, Chiho Hirata-Fukae, Hui-Fang Li, Li Feng, Laurent Lecanu, Benjamin R. Walker, Emmanuel Planel, Ottavio Arancio, Illana Gozes, and Paul S. Aisen</p>	<p>146</p>
<p>Nanomolar Propofol Stimulates Glutamate Transmission to Dopamine Neurons: A Possible Mechanism of Abuse Potential?</p>	<p>Ke-Yong Li, Cheng Xiao, Ming Xiong, Ellise Delphin, and Jiang-Hong Ye</p>	<p>165</p>
<p>Calcitonin Gene-Related Peptide₈₋₃₇ Antagonizes Capsaicin-Induced Vasodilation in the Skin: Evaluation of a Human in Vivo Pharmacodynamic Model</p>	<p>B. J. Van der Schueren, A. Rogiers, F. H. Vanmolkot, A. Van Hecken, M. Depré, S. A. Kane, I. De Lepeleire, S. R. Sinclair, and J. N. de Hoon</p>	<p>248</p>
<p>Reversal of Chronic Inflammatory Pain by Acute Inhibition of Ca²⁺/Calmodulin-Dependent Protein Kinase II</p>	<p>Fang Luo, Cheng Yang, Yan Chen, Pradeep Shukla, Lei Tang, Lili X. Wang, and Zaijie Jim Wang</p>	<p>267</p>
<p>Haloperidol and Clozapine Differentially Affect the Expression of Arrestins, Receptor Kinases, and Extracellular Signal-Regulated Kinase Activation</p>	<p>Mohamed Rafiuddin Ahmed, Vsevolod V. Gurevich, Kevin N. Dalby, Jeffrey L. Benovic, and Eugenia V. Gurevich</p>	<p>276</p>
<p>Dysregulation of Dopamine Transporter Trafficking and Function after Abstinence from Cocaine Self-Administration in Rats: Evidence for Differential Regulation in Caudate Putamen and Nucleus Accumbens</p>	<p>Devadoss J. Samuvel, Lankupalle D. Jayanthi, Senthilvelan Manohar, Kolanjiappan Kaliyaperumal, Ronald E. See, and Sammanda Ramamoorthy</p>	<p>293</p>
<p>Differential Role of Nicotinic Acetylcholine Receptor Subunits in Physical and Affective Nicotine Withdrawal Signs</p>	<p>K. J. Jackson, B. R. Martin, J. P. Changeux, and M. I. Damaj</p>	<p>302</p>

☐ Supplemental material is available online at <http://jpet.aspetjournals.org>.

About the cover: Fundamental reason for high attrition of drug candidates: outputs of complex biochemical networks are unpredictable and are the true therapeutic targets. See the article by Hellerstein on page 1 of this issue.