



## ON THE COVER:

Translating experimental findings in rodents to new treatment for pain in people is difficult. In this issue we highlight a new and promising translational development—treating clinical pain in our pets to improve their care while helping develop treatment for their owners.

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- Wiese *et al.*: Intrathecal Substance P-Saporin in the Dog: Distribution, Safety, and Spinal Neurokinin-1 Receptor Ablation, p. 1163
- Brown and Agnello: Intrathecal Substance P-Saporin in the Dog: Efficacy in Bone Cancer Pain, p. 1178

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### Substance P-Saporin for Bone Cancer Pain in Dogs: Can Man's Best Friend Solve the Lost in Translation Problem in Analgesic Development?

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## ■ PERIOPERATIVE MEDICINE

- ◆◆🌐 **Simultaneous Electroencephalographic and Functional Magnetic Resonance Imaging Indicate Impaired Cortical Top-Down Processing in Association with Anesthetic-induced Unconsciousness** 1031  
*Denis Jordan, Rüdiger Ilg, Valentin Riedl, Anna Schorer, Sabine Grimberg, Susanne Neufang, Adem Omerovic, Sebastian Berger, Gisela Untergehrer, Christine Preibisch, Enrico Schulz, Tibor Schuster, Manuel Schröter, Victor Spoomaker, Claus Zimmer, Bernhard Hemmer, Afra Wohlschläger, Eberhard F. Kochs, and Gerhard Schneider*  
 Both *simultaneous* electroencephalographic and functional magnetic resonance imaging measurement confirmed a decreased connectivity in frontoparietal feedback networks with propofol-induced unconsciousness. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- ◆🌐 **Using Exome Data to Identify Malignant Hyperthermia Susceptibility Mutations** 1043  
*Stephen G. Gonsalves, David Ng, Jennifer J. Johnston, Jamie K. Teer, NISC Comparative Sequencing Program, Peter D. Stenson, David N. Cooper, James C. Mullikin, and Leslie G. Biesecker*  
 In 870 volunteers not ascertained for malignant hyperthermia susceptibility, numerous variants in *RYR1* and *CACNA1S* genes were observed, some consistent and others inconsistent with presumed pathogenicity in current databases. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*
- ◆ **Exome Sequencing Reveals Novel Rare Variants in the Ryanodine Receptor and Calcium Channel Genes in Malignant Hyperthermia Families** 1054  
*Jerry H. Kim, Gail P. Jarvik, Brian L. Browning, Ramakrishnan Rajagopalan, Adam S. Gordon, Mark J. Rieder, Peggy D. Robertson, Deborah A. Nickerson, Nickla A. Fisher, and Philip M. Hopkins*  
 Exome sequencing of DNAs from four pedigrees associated with malignant hyperthermia identified novel genetic variant in each. The increased sensitivity of exome sequencing combined with allele frequency data is a powerful approach to identify rare genetic variants—associated malignant hyperthermia.
- Realizing Improved Patient Care through Human-centered Operating Room Design: A Human Factors Methodology for Observing Flow Disruptions in the Cardiothoracic Operating Room** 1066  
*Gary Palmer II, James H. Abernathy III, Greg Swinton, David Allison, Joel Greenstein, Scott Shappell, Kevin Juang, and Scott T. Reeves*  
 There were an average of about 100 flow disturbances per case. One third of the disturbances were related to operating room layout and design.
- Positive End-expiratory Pressure Influences Echocardiographic Measures of Diastolic Function: A Randomized, Crossover Study in Cardiac Surgery Patients** 1078  
*Peter Juhl-Olsen, Johan Fridolf Hermansen, Christian Alcaraz Frederiksen, Linda Aagaard Rasmussen, Carl-Johan Jakobsen, and Erik Sloth*  
 Individual pulsed wave Doppler and tissue Doppler indices of left ventricular diastolic function are subject to change with increasing positive end-expiratory pressure in postoperative cardiac surgery patients. The presence of positive pressure ventilation should thus be taken into account when evaluating echocardiographic indices of diastolic function.
- MA🌐 **Assessment of Homology Templates and an Anesthetic Binding Site within the  $\gamma$ -Aminobutyric Acid Receptor** 1087  
*Edward J. Bertaccini, Ozge Yoluk, Erik R. Lindahl, and James R. Trudell*  
 Molecular modeling revealed a putative intersubunit binding site for propofol that predicted the potency of propofol congeners for receptor potentiation. This approach might provide the basis for high-throughput *in silico* screening of novel anesthetic compounds. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

## **Bumetanide, an Inhibitor of Cation-chloride Cotransporter Isoform 1, Inhibits $\gamma$ -Aminobutyric Acidergic Excitatory Actions and Enhances Sedative Actions of Midazolam in Neonatal Rats**

1096

*Yukihide Koyama, Tomio Andoh, Yoshinori Kamiya, Satoshi Morita, Tomoyuki Miyazaki, Kazuhiro Uchimoto, Takahiro Mihara, and Takahisa Goto*

Bumetanide, a selective inhibitor of the transporter NKCC1, reduced neuroexcitatory effects in hippocampal slices and increased sedation by midazolam in neonatal rat. The neuroexcitatory effects and reduced sedative activity of midazolam in neonatal rats appear to involve increased intracellular chloride produced by NKCC1.

## **Effect of Hemorrhage and Hypotension on Transcranial Motor-evoked Potentials in Swine**

1109

*Jeremy A. Lieberman, John Feiner, Russ Lyon, and Mark D. Rollins*

Treatment of hemorrhage-induced hypotension and reductions in potential amplitude was less effective with phenylephrine than with epinephrine, which also increased cardiac output and oxygen delivery. This animal model suggests that monitoring cardiac output facilitates treatment of hemorrhage-induced reductions in motor-evoked potentials in spine surgery.

### ■ CRITICAL CARE MEDICINE

## **$^{13}\text{C}$ NMR Metabolomic Evaluation of Immediate and Delayed Mild Hypothermia in Cerebrocortical Slices after Oxygen–Glucose Deprivation**

1120

*Jia Liu, Mark R. Segal, Mark J. S. Kelly, Jeffrey G. Pelton, Myungwon Kim, Thomas L. James, and Lawrence Litt*

Spectroscopy in a highly controlled brain oxygen–glucose-deprivation slice model using neonatal rats was used during three different mild hypothermia protocols. Starting mild hypothermia simultaneously with oxygen–glucose-deprivation compared with delayed or no hypothermia is associated with higher pyruvate carboxylase throughput. This suggests that glial integrity is one key component of the neuroprotective effect of mild hypothermia. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

## **Neuroprotection against Traumatic Brain Injury by Xenon, but Not Argon, Is Mediated by Inhibition at the *N*-Methyl-D-Aspartate Receptor Glycine Site**

1137

*Katie Harris, Scott P. Armstrong, Rita Campos-Pires, Louise Kiru, Nicholas P. Franks, and Robert Dickinson*

Given after traumatic injury to hippocampal slices, xenon (and argon to a lesser degree) halves the secondary neuronal injury. *N*-methyl-D-aspartate antagonism is an important component of this protective effect.

### ■ PAIN MEDICINE

## **Nocturnal Intermittent Hypoxia Is Independently Associated with Pain in Subjects Suffering from Sleep-disordered Breathing**

1149

*Anthony G. Doufas, Lu Tian, Margaret Frances Davies, and Simon C. Warby*

In a review of over 634 individuals in the Cleveland Family Study, a study of genetics in obstructive sleep apnea, nocturnal oxyhemoglobin desaturation was independently associated with morning headache, headache disrupting sleep, chest pain while in bed, and pain disrupting sleep.

## **Intrathecal Substance P-Saporin in the Dog: Distribution, Safety, and Spinal Neurokinin-1 Receptor Ablation**

1163

*Ashley J. Wiese, Michael Rathbun, Mark T. Butt, Shelle A. Malkmus, Philip J. Richter, Kent G. Osborn, Qinghao Xu, Samantha L. Veasart, Joanne J. Steinauer, Denise Higgins, Douglas A. Lappi, Brian Russell, and Tony L. Yaksh*

Lumbar intrathecal injection of substance P-saporin, 15  $\mu\text{g}$ , resulted in loss of neurons in the spinal cord dorsal horn expressing the neurokinin-1 receptor. A larger dose, 150  $\mu\text{g}$ , resulted in progressive lower limb paresis and loss of motor neurons in the ventral horn expressing the neurokinin-1 receptor. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

## ◆◆ Intrathecal Substance P-Saporin in the Dog: Efficacy in Bone Cancer Pain 1178

*Dorothy Cimino Brown, and Kimberly Agnello*

Substance P-saporin (SAP) is a chemical conjugate of substance P, a tachykinin neuropeptide, and saporin, a recombinant version of a ribosomal-inactivating protein, that selectively destroys superficial neurokinin-1 receptor bearing cells in the spinal dorsal horn when it is administered intrathecally. Bone cancer is commonly associated with severe pain that evolves over time and is refractory to conventional pain therapies in both dogs and humans. Seventy companion dogs with bone cancer pain were randomly assigned to receive standard analgesic therapy alone or with intrathecally administered SAP. Intrathecally administered SAP produced a time-dependent antinociceptive effect; owners requested unblinding and additional intervention by 6 weeks in 74% of control dogs and 24% of SAP-treated dogs. There was no evidence of deafferentiation in the SAP-treated dogs, but hind limb weakness and ataxia were observed in some dogs receiving cisternal injections of SAP before doses for animals with front limb tumors were decreased.

## Effect of Deep Tissue Incision on pH Responses of Afferent Fibers and Dorsal Root Ganglia Innervating Muscle 1186

*Kanta Kido, Mamta Gautam, Christopher J. Benson, He Gu, and Timothy J. Brennan*

Using a muscle-nerve preparation from the rat hind paw, the authors were able to demonstrate that incision sensitizes afferent nerve fibers serving deep tissues. Acid-sensing ion channels may be responsible for this pain-related sensitization.

## Epigenetic Regulation of Spinal CXCR2 Signaling in Incisional Hypersensitivity in Mice 1198

*Yuan Sun, Peyman Sahbaie, De-Yong Liang, Wen-Wu Li, Xiang-Qi Li, Xiao-You Shi, and J. David Clark*

In mice, histone modification as one epigenetic mechanism is important to hypersensitivity after incision, and at least one epigenetic target after incision is change in CXCR2 expression.

## ■ EDUCATION

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*Vincent K. Lew and Andrew T. Gray*

#### A Preoperative Headache 1210

*Ferdia Bolster, Ian Crosbie, Jonathan Ryan, Frances Colreavy, and Fiona Carty*

### ANESTHESIA LITERATURE REVIEW 1211

### CLINICAL CONCEPTS AND COMMENTARY

#### CME Perioperative Gabapentinoids: Choice of Agent, Dose, Timing, and Effects on Chronic Postsurgical Pain 1215

*Peter C. Schmidt, Gabriela Ruchelli, Sean C. Mackey, and Ian R. Carroll*

This article summarizes the current evidence for the use of gabapentinoids in the perioperative setting and provides useful clinical recommendations regarding dosing, timing, and choice of agent.

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