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DIRECTOR´S ADDRESS

Yet Another Decennium of the Institute of Physiology: A Dynamic Interplay of Innovative Approaches and 60 Years of Tradition

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I am pleased to introduce this special issue of Physiological Research published on the occasion of the 60th anniversary of the Institute of Physiology. It is only a second issue of this kind, the previous one being *Physiological Research* 53 (Suppl. 1) 2004. Since then, the Institute contributed its expertise to modern fields of physiology such as cardiovascular physiology, neurophysiology, energy metabolism, membrane transport, chronobiology, as well as relevant methodology. Diverse local and international collaboration has augmented such effort, as summarized in the attached *Synopsis* outlining the most significant achievements of Institute's departments during the past ten years. I very much hope that achievements of this kind will become Institute's tradition justifying at least equally optimistic forthcoming special issues in the decades to come.

Synopsis

The last decade has witnessed a considerable progress in experimental **cardiovascular research** focused on multifactorial polygenic diseases such as hypertension, ischemic heart disease, atherosclerosis, arrhythmias, heart failure or vascular disease. New approaches were also developed for the replacement of damaged blood vessels.

A great progress in the genetic analyses of complex pathophysiological traits in the BXH/HXB recombinant inbred (RI) strains developed from spontaneously hypertensive rat (SHR) and Brown Norway (BN) progenitors in the *Department of Genetics of Model Diseases*, has been achieved owing to an international collaborative effort supported by two EU project grants (EURATools and EURATRANS). Recent technical advances, including the next-generation sequencing technology, transcriptome analysis, genomic variation analysis, methylation-sequencing and ChIP-seq, quantitative proteomics, metabonomics, advanced bioinformatics as well as new tools for manipulating the rat genome, made it possible to identify the molecular basis of the first genetic determinants predisposing the SHR to hypertension (Pravenec *et al*. 2008), left ventricular hypertrophy (McDermott-Roe *et al*. 2011) or cardiac fibrosis (Liška *et al*. 2014).

An increasing attention has been paid to the expression of genetic abnormalities into pathophysiological alterations responsible for abnormal vascular tone and high blood pressure. The estimation of a quantitative contribution of certain vasoactive systems to blood pressure control in the *Department of Experimental Hypertension* yielded a study evaluating the contribution of calcium influx and calcium sensitization to vascular tone control, the interplay of these two 'contractile' pathways and their modulation by distinct vasoconstrictor and vasodilator systems (Pintérová *et al.* 2010, Behuliak *et al.* 2013).

Considering high blood pressure as a major risk factor of the ischemic heart disease, the alterations of myocardial tolerance to ischemia-reperfusion injury in distinct forms of systemic hypertension have been studied in the *Department of Developmental Cardiology* (Neckář *et al.* 2012). In addition, a significant progress has been made in delineating the molecular mechanisms underlying high ischemic tolerance of immature and chronically hypoxic hearts, with a particular attention paid to the role of various mitochondrial proteins and redox-dependent protective signaling pathways (Borchert *et al.* 2011).

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The *Department of Functional Morphology* studied whether a chronic administration of red palm oil (RPO, rich in antioxidants) and n-3 polyunsaturated fatty acids (n-3 PUFA, EPA/DHA Omacor) can ameliorate pathophysiological changes including cardiac arrhythmias and lipid level alterations induced by thyroid hormones. Using hyperthyroid and hypothyroid rats as "models of a diseased organism", it has been established that RPO and n-3 PUFA can partly ameliorate changes in cardiac tissue remodeling, cell-to-cell communication, expression of Cx43 and protein kinases or in myosin heavy chain composition induced by thyroid hormone level alterations (Radosinska *et al.* 2013, Rauchová *et al.* 2013).

Developmental arrhythmology is a dynamically expanding field, in part owing to the advent of new tools such as high-speed cameras for optical mapping, as well as new markers of the developing cardiac conduction system. The analysis of several mutant mouse strains in the *Department of Cardiovascular Morphogenesis* shed new light on the function of the cardiac conduction system during embryonic development. Connexin40, a dominant connexin expressed in the His bundle, bundle branches and Purkinje fibers, has been found to be crucial for the right bundle branch conductivity only during later embryonic and postnatal stages (Sankova *et al.* 2012). An analysis of mice with myocardial-specific deletion of Pitx2C has demonstrated that their hearts have dual sinoatrial nodes, both acting as functional cardiac pacemakers (Ammirabile *et al.* 2012). Finally, overexpression of a dominant negative mutant form of Kcnq1 potassium channel in a mouse model of human long QT syndrome results in ventricular conduction system dysmorphogenesis and dysfunction (de la Rosa *et al.* 2013).

The *Department of Biomaterials and Tissue Engineering* concentrates on the reconstruction of irreversibly damaged blood vessels. This is achieved by either innovating synthetic polymeric vascular prostheses currently used in clinical practice or by constructing new bioartificial vascular replacements using tissue engineering methods. The existing vascular prostheses are innovated mainly by coating their inner surface with specific protein layers, particularly fibrin-based ones, which is then followed by *in vitro* endothelialization (Filová *et al.* 2009). The construction of novel bioartificial blood vessels utilizes synthetic or natural polymers functionalized with nanoparticles or various ligands for cell adhesion receptors as well as nanofibrous or nanoporous scaffolds as carriers for the attachment, growth and phenotypic maturation of vascular endothelial and smooth muscle cells (Bačáková *et al.* 2007, Novotná *et al.* 2013). A special attention has also been paid to the development of periadventitial drug delivery system into blood vessels (Filová *et al.* 2011).

In the field of **energy metabolism**, mechanistic studies on specific aspects of mitochondrial energy conversion and its regulation have been extended to a research more strongly focused on either integrative cell biology or direct links to medicine, namely to mitochondrial diseases as well as obesity and diseases associated with it. Thus, recent studies of mitochondrial uncoupling proteins in the *Department of Membrane Transport Biophysics* revealed an antioxidant synergy of the mitochondrial uncoupling protein 2 (UCP2) and mitochondrial phospholipase $iPLA_{2\gamma}$ preventing oxidative stress in tissues such as lung, and lipotoxicity in pancreatic ß-cells. The role of mitochondria and redox regulations in glucose-stimulated insulin secretion upon cell hypoxic adaptation and in tumorigenesis is also subject to investigation (Jabůrek *et al.* 2013, Tauber *et al.* 2013).

Mitochondrial diseases, a previously underscored cause of fatal outcomes in childhood belong to the most severe inborn metabolic diseases. Identification of genes responsible for them, uniquely including also the mitochondrial genome, and elucidation of the relevant molecular pathogenic mechanisms had established the basis for the diagnostics and prevention of these yet untreatable diseases, and led to a significant progress in the understanding of mammalian mitochondrial biology. The *Department of Bioenergetics* has significantly contributed to the characterization of mechanisms of biogenesis of multi-subunit enzyme complexes of the mitochondrial oxidative phosphorylation system while studying inherited disorders of ATP synthase, the key component of mitochondrial energy provision. Identification of two new genes responsible for nuclear genetic defects of the ATP synthase, manifesting themselves as neonatal encephalocardiomyopathy, paved the way to the discovery of a novel biogenetic factor specific for higher eukaryotes (Čížková *et al.* 2008, Mayr *et al.* 2010).

Research conducted in the *Department of Adipose Tissue Biology* has focused on the systemic effects of the induction of mitochondrial oxidative capacity in white adipose tissue in response to omega-3 fatty acids and other factors. This line of investigation was prompted by the discovery that an enhanced energy expenditure in white adipose tissue induced by mitochondrial uncoupling in transgenic mice can

counteract obesity. Recent results documenting the role of mitochondrial oxidative phosphorylation in a healthy phenotype of white adipocytes revealed important details about the mechanisms of the beneficial health effects of omega-3 fatty acids, and suggested yet unexplored potential of omega-3 fatty acids in treating obesity and associated diseases (Jelenik *et al.* 2010, Flachs *et al.* 2013).

While studying the role of **membrane transporters** in cell cation and pH homeostases, a number of novel results have been obtained in the *Department of Membrane Transport*. A combination of molecular biology (cloning of genes and their heterologous expression), biophysics (measurements of relative membrane potential or intracellular pH and their changes) and chemistry (estimation of cation content and fluxes) made it possible to identify, clone and characterize new alkali-metal-cation transporters involved in the regulation of cation homeostasis in yeast cells (Petrezsélyová *et al.* 2013), to describe the structural properties of cation/proton antiporters (Kinclová-Zimmermannová *et al.* 2005, 2006) and to identify new regulatory proteins involved in cation homeostasis (Zahrádka *et al.* 2012).

Research of the *Department of Protein Structure* is focused on the molecular basis of the 14-3-3 protein-dependent regulation of three important 14-3-3 binding partners: the yeast neutral trehalase Nth1, the regulator of G-protein signaling 3 (RGS3) and phosducin (Veisova *et al.* 2012, Rezabkova *et al.* 2011, 2012, Macakova *et al.* 2013). The mechanisms under investigation feature a common aspect – a conformational change induced by binding to the 14-3-3 protein molecule takes place in regions that are remote from the segment containing the phosphorylated 14-3-3 binding motif(s). This confirms that the interactions between 14-3-3 and their ligands extend beyond the ligand-binding groove. This may explain the isoform-specific interactions between 14-3-3 proteins and their ligands. In addition, these studies have also revealed that the 14-3-3 proteins sterically block the binding surface of RGS3 and phosducin, thus inhibiting their interactions with other binding partners.

A significant progress has been made by several research groups at the Institute in the rapidly expanding field of **neurophysiology.** Recent evidence suggests that abnormal regulation of membrane receptors plays a fundamental role in the development of many neurological and psychiatric disorders, including Parkinson's, Alzheimer's, and Huntington's diseases, epilepsy, anxiety, depression, bipolar disorder, schizophrenia, lupus erythematosus and ischemia. Proper understanding of the fundamental mechanisms regulating the membrane receptors in the mammalian nervous system is thus essential if novel approaches for treating these disorders are to be successfully developed.

Research into the mechanisms underlying the effects of so-called allosteric modulators affecting the activity of a receptor at a site different from the receptor's active site represent a topic of shared interest in the field of ion channel and G-protein coupled receptor research, in both peripheral and central nervous systems. Specifically, studies on the N-methyl-D-aspartic acid (NMDA) subgroup of ionotropic glutamate receptors have focused on the identification of clinically relevant antagonists capable of preferentially blocking the excitotoxic receptor activation, without interfering with its functions essential for a normal synaptic transmission and neural plasticity. Research at the *Department of Cellular Neurophysiology* has considerably extended the knowledge on function, structure, trafficking, molecular genetics, and pharmacology of ligand-gated ion channels including glutamate, acetylcholine, and pain-related transient receptor potential channels (Lindovsky *et al.* 2008, Boukalova *et al.* 2010, Borovska *et al.* 2012, Kaniakova *et al.* 2012, Marsakova *et al.* 2012).

The *Department of Neurochemistry* has contributed to the understanding of the allosteric pharmacology of muscarinic receptors (Jakubík *et al.* 2011, Janíčková *et al.* 2013) whereas the physiological role of purinergic receptors and identification of the molecular mechanisms underlying the action of ivermectin, a positive allosteric regulator of several ligand-gated ion channels including the P2X4 subtype, has been reported by the *Department of Cellular and Molecular Neuroendocrinology* (Jelínková *et al.* 2008, Bhattacharya *et al.* 2013). The progress in both fields may have implications for the development of new compounds for treating cognitive disorders and pain, and improving learning and memory.

The *Department of Functional Morphology* has demonstrated that transient receptor potential vanilloid receptors (TRPV1) located on presynaptic endings of primary afferents in the spinal cord dorsal horn play a significant role in the development of acute and chronic pain states. Their modulatory role is potentiated under pathological conditions when their activity may be affected by a number of cytokines, and their sensitivity to endogenous agonists is increased (Spicarova and Palecek 2009, Spicarova *et al.* 2011).

The *Department of Biochemistry of Membrane*

Receptors has reported that the plasma membrane-enriched fraction isolated from the cerebral cortex of rats exposed to increasing doses of morphine (10-50 mg/kg) for 10 days contained a high amount of adenylcyclase ACI and ACII. The other isoforms (ACIII-X) remained unaltered (Ujcikova *et al.* 2011). The increase of ACI and II hydrophobic membrane interior (Brejchová *et al.* 2012).

In cognitive neuroscience, the *Department of Neurophysiology of Memory* has described an intriguing phenomenon of a continuous updating of a changing information, by employing a task involving avoidance of a small programmable robot, and the role of hippocampus in this behavior has been determined (Telensky *et al.* 2011). It has been also discovered that hippocampus is critical for recognition of objects projected onto a computer screen (such as "virtual reality in rats") (Levcik *et al.* 2013). In collaboration with other research groups, a novel neuroprotective steroidal derivative has been successfully patented (Rambousek *et al.* 2011).

The *Department of Computational Neuroscience* has mainly focused on neuronal coding and information processing. Both invertebrate and vertebrate olfactory sensory systems have been studied, and sensory-motor coupling in insect flight control analyzed. Various aspects of information representation in the temporal character of neuronal signals have been investigated in order to identify potential information coding modes (Kostal *et al*. 2007). Furthermore, methods enabling advanced statistical analysis of experimental data have been proposed (Kostal *et al.* 2013).

Using a complex approach, the *Department of Developmental Epileptology* has demonstrated that an intense epileptic activity leads to both acute and long-lasting morphological and functional alterations, often of progressive nature, in rats younger than two weeks (Kubová and Mareš 2013). Mechanisms responsible for the damage in immature brain include oxidative stress and mitochondrial dysfunction. Oxidative stress is apparently due to both increased free radical production and limited antioxidant defense (Folbergrová *et al.* 2012). Metabotropic glutamate receptors also play an important role in the generation of epileptic activity and neuronal damage. Agonists of groups II and III, as well as antagonists of group I of the metabotropic glutamate receptor exhibited an anticonvulsant and neuroprotective effect (Folbergrová *et al*. 2008, Lojková-Janečková *et al*. 2009).

Recent progress in **chronobiology** is already having far-reaching consequences in other fields of physiology. From a relatively specialized field focusing on the properties of the circadian clock in the brain and its output rhythms (mostly behavioral and humoral), the scope of chronobiology has broadened enormously owing to the discovery of the temporal regulation of cellular processes and its vital importance for cell survival. The cellular clocks are hierarchically organized at the systemic level into a circadian system. The disruption of communication among its individual components and/or the system's communication with the external environment result in the malfunction of the temporal regulation of physiological processes in general, with serious health consequences. Using the molecular biology tools, the *Department of Neurohumoral Regulations* discovered how the circadian system and its individual components develop during ontogenesis (Sumová *et al.* 2012*)*. In collaboration with the *Department of Epithelial Physiology*, the studies on the circadian regulation in the gastrointestinal system revealed a specific function of the circadian clock in the colonic epithelial cells, and the mechanisms of entraining these clocks with the external environment (Sládek *et al.* 2007, Polidarová *et al.* 2011). Importantly, the clock malfunction has been associated with colorectal cancer development (Soták *et al.* 2013). Our recent studies in humans have revealed that neuropsychiatric disorders are associated with malfunctioning of the circadian system at the level of molecular clock regulation (Nováková *et al*. 2012). These findings may contribute to new chronotherapeutic approaches to various diseases.

A dramatic progress in the development of **new technologies and methodological approaches** has also been reflected by achievements of the Institute. Recent imaging and tissue preparation techniques provide high-resolution 3D image data. The *Department of Biomathematics* is engaged in the development of new microscopic visualization (Pelc *et al*. 2008) and image analysis methods, and their applications to microscopic architecture of various tissues such as blood capillaries in brain, muscles and placenta. Recent achievements are exemplified by a more efficient software for registration of neighboring physical slices (of microscopy specimens) suffering from discontinuities (Michálek and Čapek 2013), and a comparative study on length measurement of tubular structures in 3D (Kubínová *et al.* 2013).

A progress in analytical separation methods and their application to physiologically important compounds (e.g., steroids or pigments) at the *Department of Analysis of Biologically Important Compounds* is exemplified by the recent development of a gold nanoparticles-based

stationary phase approach (Mikšík *et al.* 2012, Pataridis *et al.* 2013). The proteomes of various biological material such as teeth, avian eggshells and human mummy, as well as non-enzymatic modifications of proteins have also been studied.

References

AMMIRABILE G, TESSARI A, PIGNATARO V, SZUMSKA D, SUTERA SARDO F, BENES J JR, BALISTRERI M, BHATTACHARYA S, SEDMERA D, CAMPIONE M: Pitx2 confers left morphological, molecular, and functional identity to the sinus venosus myocardium. *Cardiovasc Res* **93**: 291-301, 2012.

BAČÁKOVÁ L, FILOVÁ E, KUBIES D, MACHOVÁ L, PROKS V, MALINOVÁ V, LISÁ V, RYPÁČEK F: Adhesion and growth of vascular smooth muscle cells in cultures on bioactive RGD peptide-carrying polylactides. *J Mater Sci Mater Med* **18**: 1317-1323, 2007.

BEHULIAK M, PINTÉROVÁ M, BENCZE M, PETROVÁ M, LÍŠKOVÁ S, KAREN P, KUNEŠ J, VANĚČKOVÁ I, ZICHA J: Ca^{2+} sensitization and Ca^{2+} entry in the control of blood pressure and adrenergic vasoconstriction in conscious Wistar-Kyoto and spontaneously hypertensive rats. *J Hypertens* **31**: 2025-2035, 2013.

BHATTACHARYA A, VAVRA V, SVOBODOVA I, BENDOVA Z, VEREB G, ZEMKOVA H: Potentiation of inhibitory synaptic transmission by extracellular ATP in rat suprachiasmatic nuclei. *J Neurosci* **33**: 8035-8044, 2013.

BORCHERT GH, YANG C-T, KOLÁŘ F: Mitochondrial BK_{Ca} channels contribute to protection of cardiomyocytes isolated from chronically hypoxic rats. *Am J Physiol Heart Circ Physiol* **300**: H507-H513, 2011.

BOROVSKA J, VYKLICKY V, STASTNA E, KAPRAS V, SLAVIKOVA B, HORAK M, CHODOUNSKA H, VYKLICKY L JR: Access of inhibitory neurosteroids to the NMDA receptor. *Br J Pharmacol* **166**: 1069-1083, 2012.

BOUKALOVA S, MARSAKOVA L, TEISINGER J, VLACHOVA V: Conserved residues within the putative S4-S5 region serve distinct functions among thermosensitive vanilloid transient receptor potential (TRPV) channels. *J Biol Chem* **285**: 41455-41462, 2010.

BREJCHOVÁ J, SÝKORA J, DLOUHÁ K, ROUBALOVÁ L, OSTAŠOV P, VOŠAHLÍKOVÁ M, HOF M, SVOBODA P: Fluorescence spectroscopy studies of HEK293 cells expressing DOR- $G_i1\alpha$ fusion protein; the effect of cholesterol depletion. *Biochim Biophys Acta* **1808**: 2819-2829, 2011.

ČÍŽKOVÁ A, STRÁNECKÝ V, MAYR JA, TESAŘOVÁ M, HAVLÍČKOVÁ V, PAUL J, IVÁNEK R, KUSS AW, HANSÍKOVÁ H, KAPLANOVÁ V, VRBACKÝ M, HARTMANNOVÁ H, NOSKOVÁ L, HONZÍK T, DRAHOTA Z, MAGNER M, HEJZLAROVÁ K, SPERL W, ZEMAN J, HOUŠTĚK J, KMOCH S: TMEM70 is a novel factor of ATP synthase biogenesis and its mutations cause isolated enzyme deficiency and neonatal mitochondrial encephalo-cardiomyopathy. *Nat Genet* **40**: 1288-1290, 2008.

DE LA ROSA AJ, DOMÍNGUEZ JN, SEDMERA D, SANKOVA B, HOVE-MADSEN L, FRANCO D, ARÁNEGA AE: Functional suppression of Kcnq1 leads to early sodium channel remodelling and cardiac conduction system dysmorphogenesis. *Cardiovasc Res* **98**: 504-514, 2013.

FILOVÁ E, BRYNDA E, RIEDEL T, BAČÁKOVÁ L, CHLUPÁČ J, LISÁ V, HOUSKA M, DYR JE: Vascular endothelial cells on two- and three-dimensional fibrin assemblies for biomaterial coatings. *J Biomed Mater Res* **A 90A**: 55-69, 2009.

FILOVÁ E, PAŘÍZEK M, OLŠOVSKÁ J, KAMENÍK Z, BRYNDA E, RIEDEL T, VANDROVCOVÁ M, LISÁ V, MACHOVÁ L, SKALSKÝ I, SZARSZOI O, SUCHÝ T, BAČÁKOVÁ L: Perivascular sirolimus-delivery system. *Int J Pharm* **404**: 94-101, 2011.

FLACHS P, ROSSMEISL M, KUDA O, KOPECKY J: Stimulation of mitochondrial oxidative capacity in white fat independent of UCP1: A key to lean phenotype. *Biochim Biophys Acta* **1831**: 986-1003, 2013.

FOLBERGROVÁ J, DRUGA R, HAUGVICOVÁ R, MAREŠ P, OTÁHAL J: Anticonvulsant and neuroprotective effect of (S)-3,4-dicarboxyphenylglycine against seizures induced in immature rats by homocysteic acid. *Neuropharmacology* **54**: 665-675, 2008.

FOLBERGROVÁ J, OTÁHAL J, DRUGA R: Brain superoxide anion formation in immature rats during seizures: Protection by selected compounds. *Exp Neurol* **233**: 421-429, 2012.

JABŮREK M, JEŽEK J, ZELENKA J, JEŽEK P: Antioxidant activity by a synergy of redox-sensitive mitochondrial phospholipase A2 and uncoupling protein-2 in lung and spleen. *Int J Biochem Cell Biol* **45**: 816-825, 2013.

JAKUBÍK J, JANÍČKOVÁ H, EL-FAKAHANY EE, DOLEŽAL V: Negative cooperativity in binding of muscarinic receptor agonists and GDP as a measure of agonist efficacy. *Br J Pharmacol* **162**: 1029-1044, 2011.

JANÍČKOVÁ H, RUDAJEV V, ZIMČÍK P, JAKUBÍK J, TANILA H, EL-FAKAHANY EE, DOLEŽAL V: Uncoupling of M1 muscarinic receptor/G-protein interaction by amyloid beta(1-42). *Neuropharmacology* **67**: 272-283, 2013.

JELENIK T, ROSSMEISL M, KUDA O, MACEK JILKOVA Z, MEDRIKOVA D, KUS V, HENSLER M, JANOVSKA P, MIKSIK I, BARANOWSKI M, GORSKI J, HÉBRARD S, JENSEN TE, FLACHS P, HAWLEY S, VIOLLET B, KOPECKY J: AMPK-activated protein kinase alpha 2 subunit is required for the preservation of hepatic insulin sensitivity by n-3 polyunsaturated fatty acids. *Diabetes* **59**: 2737-2746, 2010.

JELÍNKOVÁ I, VÁVRA V, JINDŘICHOVÁ M, OBŠIL T, ZEMKOVÁ HW, ZEMKOVÁ H, STOJILKOVIC SS: Identification of $P2X_4$ receptor transmembrane residues contributing to channel gating and interaction with ivermectin. *Pflügers Arch* **456**: 939-950, 2008.

KANIAKOVA M, KRAUSOVA B, VYKLICKY V, KORINEK M, LICHNEROVA K, VYKLICKY L, HORAK M: Key amino acid residues within the third membrane domains of NR1 and NR2 subunits contribute to the regulation of the surface delivery of N-methyl-D-aspartate receptors. *J Biol Chem* **287**: 26423-26434, 2012.

KINCLOVÁ-ZIMMERMANNOVÁ O, ZAVŘEL M, SYCHROVÁ H: Identification of conserved prolyl residue important for transport activity and the substrate specificity range of yeast plasma membrane Na^+/H^+ antiporters. *J Biol Chem* **280**: 30638-30647, 2005.

KINCLOVA-ZIMMERMANNOVA O, ZAVREL M, SYCHROVÁ H: Importance of the seryl and threonyl residues of the fifth transmembrane domain to the substrate specificity of yeast plasma membrane Na^+/H^+ antiporters. *Mol Membr Biol* **23**: 349-361, 2006.

KOSTAL L, LANSKY P, POKORA O: Measures of statistical dispersion based on Shannon and Fisher information concepts. *Inform Sci* **235**: 214-223, 2013.

KOSTAL L, LANSKY P, ROSPARS J-P: Review: Neuronal coding and spiking randomness. *Eur J Neurosci* **26**: 2693-2701, 2007.

KUBÍNOVÁ L, MAO XW, JANÁČEK J: Blood capillary length estimation from three-dimensional microscopic data by image analysis and stereology. *Microsc Microanal* **19**: 898-906, 2013.

KUBOVÁ H, MAREŠ P: Are morphologic and functional consequences of status epilepticus in infant rats progressive? *Neuroscience* **235**: 232-249, 2013.

LEVCIK D, NEKOVAROVA T, STUCHLIK A, KLEMENT D: Rats use hippocampus to recognize positions of objects located in an inaccessible space. *Hippocampus* **23**: 153-161, 2013.

LINDOVSKÝ J, KANIAKOVÁ M, SVOBODOVÁ L, VYSKOČIL F, KRŮSEK J: Role of negatively charged amino acids in beta 4 F-loop in activation and desensitization of alpha 3 beta 4 rat neuronal nicotinic receptors. *Biochim Biophys Acta* **1778**: 864-871, 2008.

LIŠKA F, MANCINI M, KRUPKOVÁ M, CHYLÍKOVÁ B, KŘENOVÁ D, ŠEDA O, ŠILHAVÝ J, MLEJNEK P, LANDA V, ZÍDEK V, D' AMATI G, PRAVENEC M, KŘEN V: Plzf as a candidate gene predisposing the spontaneously hypertensive rat to hypertension, left ventricular hypertrophy, and interstitial fibrosis. *Am J Hypertens* **27**: 99-106, 2014.

LOJKOVÁ-JANEČKOVÁ D, NG J, MAREŠ P: Antagonists of group I metabotropic glutamate receptors and cortical afterdischarges in immature rats. *Epilepsia* **50**: 2123-2129, 2009.

MACAKOVA E, KOPECKA M, KUKACKA Z, VEISOVA D, NOVAK P, MAN P, OBSIL T, OBSILOVA V: Structural basis of the 14-3-3 protein-dependent activation of yeast neutral trehalase Nth1. *Biochim Biophys Acta* **1830**: 4491-4499, 2013.

MARSAKOVA L, TOUSKA F, KRUSEK J, VLACHOVA V: Pore helix domain is critical to camphor sensitivity of transient receptor potential vanilloid 1 channel. *Anesthesiology* **116**: 903-917, 2012.

MAYR JA, HAVLÍČKOVÁ V, ZIMMERMANN F, MAGLER I, KAPLANOVÁ V, JEŠINA P, PECINOVÁ A, NŮSKOVÁ H, KOCH J, SPERL W, HOUŠTĚK J: Mitochondrial ATP synthase deficiency due to a mutation in the ATP5E gene for the F1 epsilon subunit. *Hum Mol Genet* **19**: 3430-3439, 2010.

McDERMOTT-ROE C, YE J, AHMED R, SUN XM, SERAFÍN A, WARE J, BOTTOLO L, MUCKETT P, CAÑAS X, ZHANG J, ROWE GC, BUCHAN R, LU H, BRAITHWAITE A, MANCINI M, HAUTON D, MARTÍ R, GARCÍA-ARUMÍ E, HUBNER N, JACOB H, SERIKAWA T, ZÍDEK V, PAPOUŠEK F, KOLÁŘ F, CARDONA M, RUIZ-MEANA M, GARCÍA-DORADO D, COMELLA JX, FELKIN LE, BARTON PJ, ARANY Z, PRAVENEC M, PETRETTO E, SANCHIS D, COOK SA: Endonuclease G is a novel determinant of cardiac hypertrophy and mitochondrial function. *Nature* **478**: 114-118, 2011.

MICHÁLEK J, ČAPEK M: A piecewise monotone subgradient algorithm for accurate L1-TV based registration of physical slices with discontinuities in microscopy. *IEEE Trans Med Imaging* **32**: 901-918, 2013.

MIKŠÍK I, LACINOVÁ K, ZMATLÍKOVÁ Z, SEDLÁKOVÁ P, KRÁL V, SÝKORA D, ŘEZANKA P, KAŠIČKA V: Open-tubular capillary electrochromatography with bare gold nanoparticles-based stationary phase applied to separation of trypsin digested native and glycated proteins. *J Separation Sci* **35**: 994-1002, 2012.

NECKÁŘ J, KOPKAN L, HUSKOVÁ Z, KOLÁŘ F, PAPOUŠEK F, KRAMER HJ, HWANG SH, HAMMOCK BD, IMIG JD, MALÝ J, NETUKA I, OŠŤÁDAL B, ČERVENKA L: Inhibition of soluble epoxide hydrolase by cis-4-[4-(3-adamantan-1-yl-ureido)cyclohexyl-oxy]benzoic acid exhibits antihypertensive and cardioprotective actions in transgenic rats with angiotensin II-dependent hypertension. *Clin Sci* **122**: 513-525, 2012.

NOVÁKOVÁ M, NEVŠÍMALOVÁ S, PŘÍHODOVÁ I, SLÁDEK M, SUMOVÁ A: Alteration of the circadian clock in children with Smith-Magenis syndrome. *J Clin Endocrinol Metab* **97**: E312-E318, 2012.

NOVOTNÁ K, BAČÁKOVÁ M, SLEPIČKOVÁ KASÁLKOVÁ N, SLEPIČKA P, LISÁ V, ŠVORČÍK V, BAČÁKOVÁ L: Adhesion and growth of vascular smooth muscle cells on nanostructured and biofunctionalized polyethylene. *Materials* **6**: 1632-1655, 2013.

PATARIDIS S, ŠTASTNÁ Z, SEDLÁKOVÁ P, MIKŠÍK I: Monotopic modifications derived from in vitro glycation of albumin with ribose. *Electrophoresis* **34**: 1757-1763, 2013.

PELC R, HOSTOUNSKÝ Z, OTAKI T: Correlation between off-axis illumination and apodized phase contrast: Two complementary microscopic phase-imaging modes. *J Biomed Opt* **13**: 054067, 2008.

PETREZSÉLYOVÁ S, ZIMMERMANNOVÁ O, SYCHROVÁ H: Vhc1, a novel transporter belonging to the family of electroneutral cation-Cl^- cotransporters, participates in the regulation of cation content and morphology of *Saccharomyces cerevisiae* vacuoles. *Biochim Biophys Acta* **1828**: 623-631, 2013.

PINTÉROVÁ M, KAREN P, KUNEŠ J, ZICHA J: Role of nifedipine-sensitive sympathetic vasoconstriction in maintenance of high blood pressure in SHR: effect of Gi-protein inactivation by pertussis toxin. *J Hypertens* **28**: 969-978, 2010.

POLIDAROVÁ L, SLÁDEK M, SOTÁK M, PÁCHA J, SUMOVÁ A: Hepatic, duodenal and colonic circadian clocks differ in their persistence under conditions of constant light and in their entrainment by restricted feeding. *Chronobiol Int* **28**: 204-215, 2011.

PRAVENEC M, CHURCHILL PC, CHURCHILL MC, VIKLICKY O, KAZDOVA L, AITMAN TJ, PETRETTO E, HUBNER N, WALLACE CA, ZIMDAHL H, ZIDEK V, LANDA V, DUNBAR J, BIDANI A, GRIFFIN K, QI N, MAXOVA M, KREN V, MLEJNEK P, WANG J, KURTZ TW: Identification of renal Cd36 as a determinant of blood pressure and risk for hypertension. *Nat Genet* **40**: 952-954, 2008.

RADOSINSKA J, BACOVA B, KNEZL V, BENOVA T, ZURMANOVA J, SOUKUP T, ARNOSTOVA P, SLEZAK J, GONCALVESOVA E, TRIBULOVA N: Dietary omega-3 fatty acids attenuate myocardial arrhythmogenic factors and propensity of the heart to lethal arrhythmias in a rodent model of human essential hypertension. *J Hypertens* **31**: 1876-1884, 2013.

RAMBOUSEK L, BUBENIKOVA-VALESOVA V, KACER P, SYSLOVA K, KENNEY J, HOLUBOVA K, NAJMANOVA V, ZACH P, SVOBODA J, STUCHLIK A, CHODOUNSKA H, KAPRAS V, ADAMUSOVA E, BOROVSKA J, VYKLICKY L, VALES K: Cellular and behavioural effects of a new steroidal inhibitor of the N-methyl-D-aspartate receptor 3α5β-pregnanolone glutamate. *Neuropharmacology* **61**: 61-68, 2011.

RAUCHOVÁ H, VOKURKOVÁ M, PAVELKA S, BEHULIAK M, TRIBULOVÁ N, SOUKUP T: N-3 polyunsaturated fatty acids supplementation does not affect changes of lipid metabolism induced in rats by altered thyroid status. *Horm Metab Res* **45**: 507-512, 2013.

REZABKOVA L, KACIROVA M, SULC M, HERMAN P, VECER J, STEPANEK M, OBSILOVA V, OBSIL T: Structural modulation of phosducin by phosphorylation and 14-3-3 protein binding. *Biophys J* **103**: 1960-1969, 2012.

REZABKOVA L, MAN P, NOVAK P, HERMAN P, VECER J, OBSILOVA V, OBSIL T: Structural basis for the 14-3-3 protein-dependent inhibition of the regulator of G protein signaling 3 (RGS3) function. *J Biol Chem* **286**: 43527-43536, 2011.

SANKOVA B, BENES J JR, KREJCI E, DUPAYS L, THEVENIAU-RUISSY M, MIQUEROL L, SEDMERA D: The effect of connexin40 deficiency on ventricular conduction system function during development. *Cardiovasc Res* **95**: 469-479, 2012.

SLÁDEK M, RYBOVÁ M, JINDRÁKOVÁ Z, ZEMANOVÁ Z, POLIDAROVÁ L, MRNKA L, O'NEIL J, PÁCHA J, SUMOVÁ A: Insight into circadian clock within the rat colonic epithelial cells. *Gastroenterology* **133**: 1240-1249, 2007.

SOTÁK M, POLIDAROVÁ L, ERGANG P, SUMOVÁ A, PÁCHA J: An association between clock genes and clock-controlled cell cycle genes in murine colorectal tumors. *Int J Cancer* **132**: 1032-1041, 2013.

SPICAROVA D, NERANDZIC V, PALECEK J: Modulation of spinal cord synaptic activity by tumor necrosis factor alpha in a model of peripheral neuropathy. *J Neuroinflammation* **8**: 177, 2011.

SPICAROVA D, PALECEK J: The role of the TRPV1 endogenous agonist N-Oleoyldopamine in modulation of nociceptive signaling at the spinal cord level. *J Neurophysiol* **102**: 234-243, 2009.

SUMOVÁ A, SLÁDEK M, POLIDAROVÁ L, NOVÁKOVÁ M, HOUDEK P: Circadian system from conception till adulthood. *Prog Brain Res* **199**: 83-104, 2012.

TAUBER J, DLASKOVÁ A, ŠANTOROVÁ J, SMOLKOVÁ K, ALÁN L, ŠPAČEK T, PLECITÁ-HLAVATÁ L, JABŮREK M, JEŽEK P: Distribution of mitochondrial nucleoids upon mitochondrial network fragmentation and network reintegration in HEPG2 cells. *Int J Biochem Cell Biol* **45**: 593-603, 2013.

TELENSKY P, SVOBODA J, BLAHNA K, BURES J, KUBIK S, STUCHLIK A: Functional inactivation of the rat hippocampus disrupts avoidance of a moving object. *Proc Natl Acad Sci USA* **108**: 5414-5418, 2011.

UJCIKOVA H, DLOUHA K, BOUROVA L, VOSAHLIKOVA M, KAGAN D, SVOBODA P: Up-regulation of adenylylcyclase I and II induced by long-term adaptation of rats to morphine fades away 20 days after morphine withdrawal. *Biochim Biophys Acta* **1810**: 1220-1229, 2011.

VEISOVA D, MACAKOVA E, REZABKOVA L, SULC M, VACHA P, SYCHROVA H, OBSIL T, OBSILOVA V: Role of individual phosphorylation sites for the 14-3-3-protein-dependent activation of yeast neutral trehalase Nth1. *Biochem J* **443**: 663-670, 2012.

ZAHRÁDKA J, VAN HEUSDEN GPH, SYCHROVÁ H: Yeast 14-3-3 proteins participate in the regulation of cell cation homeostasis via interaction with Nha1 alkali-metal-cation/proton antiporter. *Biochim Biophys Acta* **1820**: 849-858, 2012.