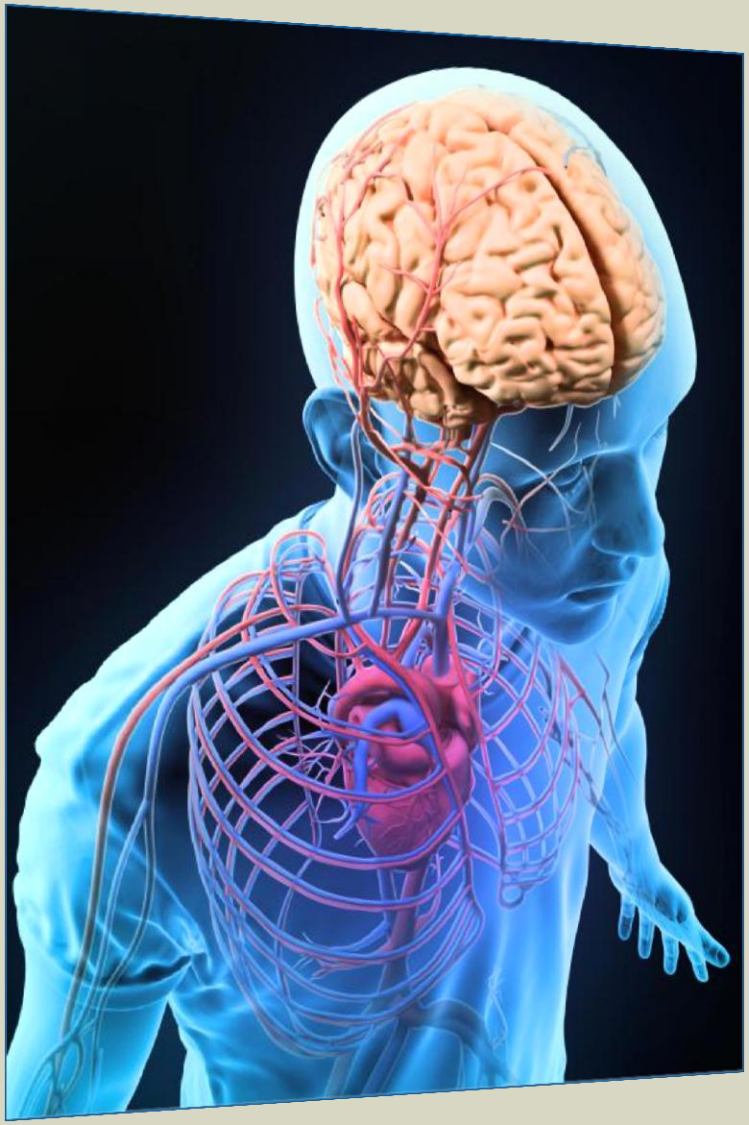
Mission of the Institute / Introduction



Since its establishment, the Institute of Normal and Pathological Physiology, Slovak Academy of Sciences has been continually focused on investigation of

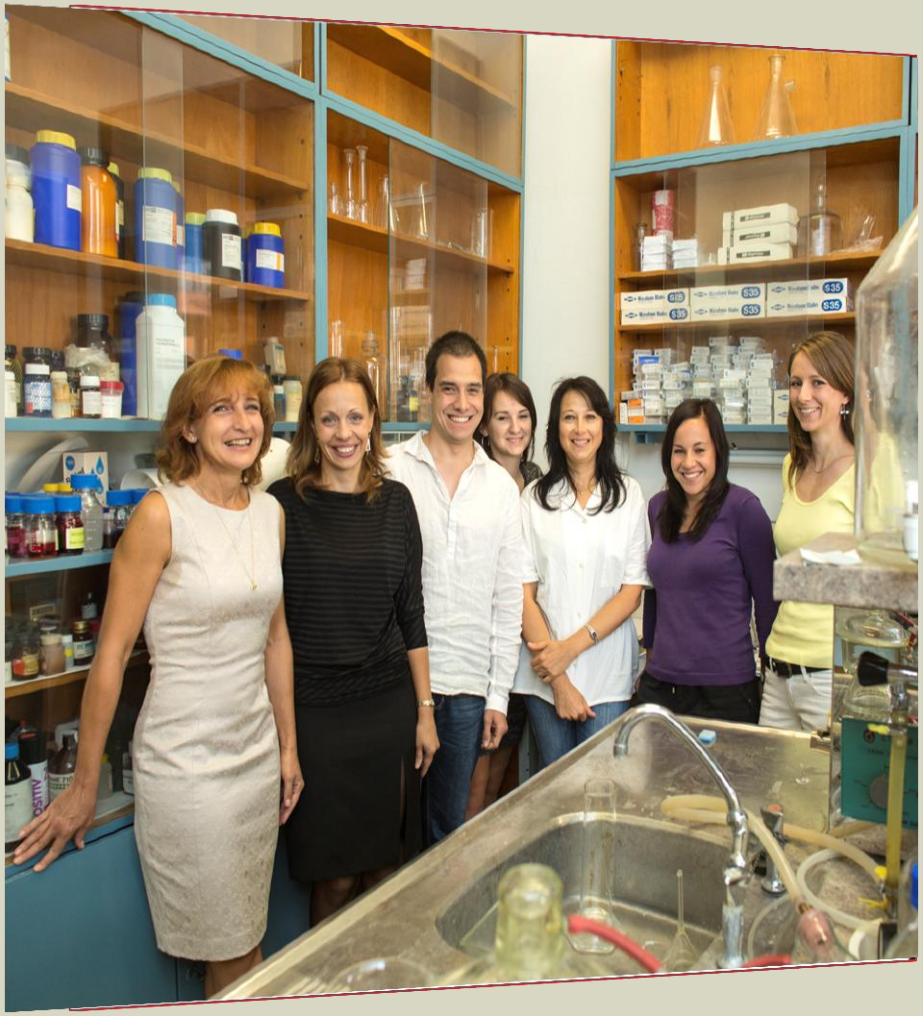
- **cardiovascular system**
- **nervous system**

under both normal, and pathological conditions.

Over the last three decades – from the discovery of the physiological function of nitric oxide, the research has been oriented towards molecular mechanisms of

nitric oxide signaling and its role at the systemic level.

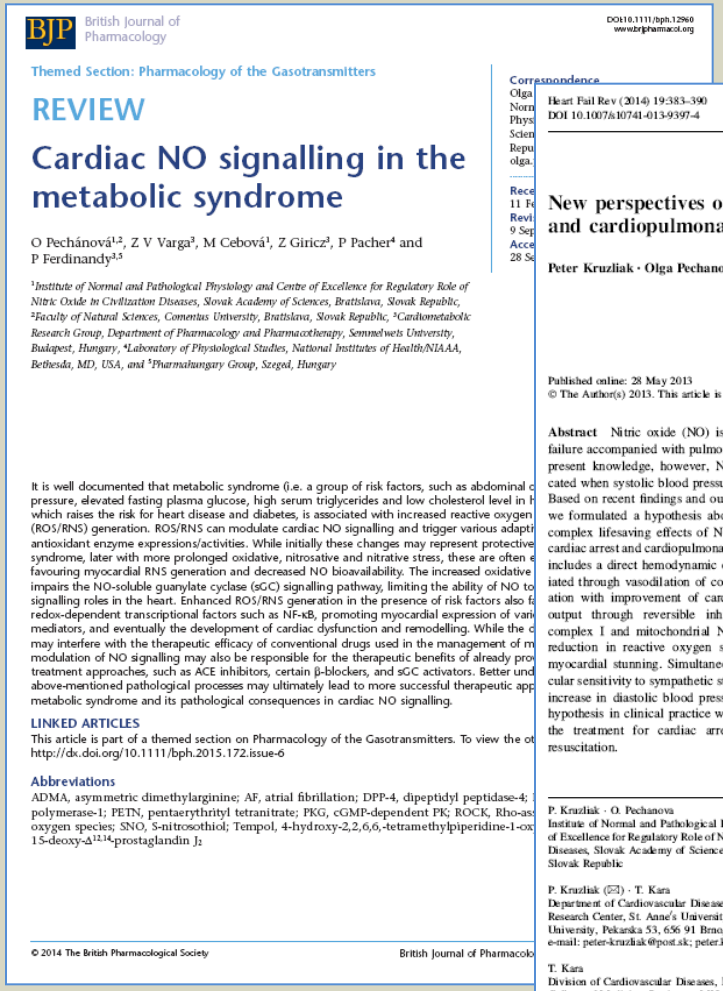
Mission of the Institute / Laboratory of Neuro-Cardiovascular Interactions



The assessment period can be characterised by:

- **development of a new myocardial infarction model**
- **study of new mechanisms leading to cardiovascular protection**
- **preparation, analysis, and monitoring of active antihypertensive and antilipidemic agents bound to various polymeric nanoparticles**
- **analysis, from a transdisciplinary point of view, of magnesium nanocomposites for biodegradable medical implants**

Mission of the Institute / Laboratory of Neuro-Cardiovascular Interactions



British Journal of Pharmacology

DOI:10.1111/bph.12960
www.brjpharmacol.org

Themed Section: Pharmacology of the Gasotransmitters

REVIEW

Cardiac NO signalling in the metabolic syndrome

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It is well documented that metabolic syndrome (i.e. a group of risk factors, such as abdominal o pressure, elevated fasting plasma glucose, high serum triglycerides and low cholesterol level in H which raises the risk for heart disease and diabetes, is associated with increased reactive oxygen (ROS/RNS) generation. ROS/RNS can modulate cardiac NO signalling and trigger various adapti antioxidant enzyme expressions/activities. While initially these changes may represent protective syndrome, later with more prolonged oxidative, nitrosative and nitrative stress, these are often e favouring myocardial RNS generation and decreased NO bioavailability. The increased oxidative impairs the NO-soluble guanylate cyclase (sGC) signalling pathway, limiting the ability of NO to signalling roles in the heart. Enhanced ROS/RNS generation in the presence of risk factors also f redox-dependent transcriptional factors such as NF-κB, promoting myocardial expression of vari mediators, and eventually the development of cardiac dysfunction and remodelling. While the c may interfere with the therapeutic efficacy of conventional drugs used in the management of m modulation of NO signalling may also be responsible for the therapeutic benefits of already pro treatment approaches, such as ACE inhibitors, certain β-blockers, and sGC activators. Better und above-mentioned pathological processes may ultimately lead to more successful therapeutic app metabolic syndrome and its pathological consequences in cardiac NO signalling.

LINKED ARTICLES

This article is part of a themed section on Pharmacology of the Gasotransmitters. To view the ot http://dx.doi.org/10.1111/bph.2015.172.issue-6

Abbreviations

ADMA, asymmetric dimethylarginine; AF, atrial fibrillation; DPP-4, dipeptidyl peptidase-4; polymerase-1; PETN, pentaerythrityl tetranitrate; PKG, cGMP-dependent PK; ROCK, Rho-as oxygen species; SNO, S-nitrosothiol; Tempol, 4-hydroxy-2,2,6,6,-tetramethylpiperidine-1-ox 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2

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Heart Fail Rev (2014) 19:383–390
DOI 10.1007/s10741-013-9397-4

New perspectives of nitric oxide donors in cardiac arrest and cardiopulmonary resuscitation treatment

Peter Kruzliak · Olga Pechanova · Tomas Kara

Published online: 28 May 2013

Abstract Nitric oxide (NO) is often used to treat heart failure accompanied with pulmonary edema. According to present knowledge, however, NO donors are contraindicated when systolic blood pressure is less than 90 mmHg. Based on recent findings and our own clinical experience, we formulated a hypothesis about the new breakthrough complex lifesaving effects of NO donors in patients with cardiac arrest and cardiopulmonary resuscitation therapy. It includes a direct hemodynamic effect of NO donors mediated through vasodilation of coronary arteries in cooperation with improvement of cardiac function and cardiac output through reversible inhibition of mitochondrial complex I and mitochondrial NO synthase, followed by reduction in reactive oxygen species and correction of myocardial stunning. Simultaneously, an increase in vascular sensitivity to sympathetic stimulation could lead to an increase in diastolic blood pressure. Confirmation of this hypothesis in clinical practice would mean a milestone in the treatment for cardiac arrest and cardiopulmonary resuscitation.

Keywords Nitric oxide · Nitric ox
Adenosine · Cardiac arrest · Cardio
Resuscitation

Introduction

Research of over two decades has sh
to be a ubiquitous modulator of biolo
cell signal to effector and from phy
ology. The involvement of NO in
has contributed significantly to our
plex disease states including athero
pulmonary hypertension, endotoxic
cardiomyopathy, myocardial infarct
allograft rejection. The dichotomy
represents the "double-edged sword
systems. The balance between cy
effects of NO may lie in the tissue
produced, the particular NO synthas
vation, and the complex interaction
such as superoxide [1, 2]. All four
thelial NOS (eNOS), neuronal NO
NOS (iNOS) and mitochondrial NOS
shown to be present in the human m
activated in response to hypoxia o
experimental myocardial infarcti
increased expression of iNOS, eNOS
the heart, together with increased pl
nitrate and nitrite, the oxidation pro
form specific amount of NO generate
for physiological versus pathologic
concentrations are associated with
concentrations with cytotoxicity. A
the dichotomous effects of NO m

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Magnetic poly(D,L-lactide) nanoparticles loaded with aliskiren: A promising tool for hypertension treatment

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ARTICLE INFO

Available online 23 October 2014

Keywords:
Magnetite nanoparticles
Poly(D,L-lactide)
Aliskiren
Optimization
Hypertension

ABSTRACT

In this study anti-hypertensive drug called aliskiren was encapsulated in magnetic poly(D,L-lactide) nanoparticles by the modified nanoprecipitation method. The effect of magnetite and drug concentrations on the size distribution and zeta potential of polymer nanoparticles was investigated. The optimized loadings were as follows: theoretical magnetite loading was 20 mg/100 mg polymer nanoparticles and aliskiren was encapsulated in magnetic poly(D,L-lactide) nanoparticles at theoretical loading 0.6 mg aliskiren/100 mg magnetic polymer nanoparticles. The physicochemical characteristics of nanoparticles were studied, with spherical shape of nanoparticles sized between 58 and 227 nm being one of the observed results. Differential scanning calorimetry and infrared spectroscopy confirmed that aliskiren was successfully identified in the magnetic poly(D,L-lactide) nanoparticles. The in vivo experiments indicated that encapsulated aliskiren decreased blood pressure of the studied male spontaneously hypertensive rat even more significantly than common administered drug.

1. Introduction

In the early 21st century, hypertension (high blood pressure) is a global public health issue contributing to the burden of heart disease, stroke and kidney failure and premature death and disability [1]. The renin–angiotensin–aldosteron system (RAAS) is a coordinated hormonal cascade that governs cardiovascular, renal, and adrenal functions by regulating fluid and electrolyte balance as well as arterial blood pressure. Aliskiren is a direct renin inhibitor that works by binding to the active site of renin, the initial step of RAAS, and decreases production of vasoconstrictors in this cascade including Angiotensin II. Thus, blood vessels can normally relax and the heart can pump blood more efficiently. However, the limiting factor in clinical practice is relatively low bioavailability of aliskiren (2–3%) [2]. One of various ways to increase aliskiren bioavailability and maximize the effect of aliskiren on kidney function is nanoencapsulation of aliskiren. Polymer nanoparticles (PLA-NP) created by poly(D,L-lactide) (PLA) were used for drug encapsulation. PLA polymers based on polyesters belong to the class of biodegradable materials extensively used in controlled drug delivery systems. Their main advantage is that they easily undergo degradation due to the hydrolysis of the ester bond and the hydrolysis products are metabolized and removed from the body via normal metabolic pathways [3,4].

The aim of this study was to formulate, characterize and analyze aliskiren entrapped in magnetic poly(D,L-lactide) nanoparticles and to study the effect of encapsulated aliskiren on systolic blood pressure of male spontaneously hypertensive rats.

2. Materials and experimental methods

2.1. Materials

Aliskiren was a generous gift from Novartis Pharma AG, Switzerland. Poly(D,L-lactide) with molecular weight 75000 g/mol, Pluronic F68 were purchased from Sigma company and sodium oleate was obtained from Riedel-de Haën.

2.2. Instrumentations

Prepared samples were observed by Scanning Electron Microscopy (SEM) to obtain information on the morphology and particle size of the polymer nanoparticles. While SEM gives us detailed

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Mission of the Institute / Lab. of Neurohumoral Regulation of Hemodynamics

The assessment period can be characterised by:

determination of the sex- and age-dependent impact of chronic social stress produced by crowding on endothelial function and oxidative load of rats with various genetic predispositions to hypertension.

Mission of the Institute / Lab. of Neurohumoral Regulation of Hemodynamics

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Long-term social stress induces nitric oxide-inde dysfunction in normotensive rats

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Institute of Normal and Pathological Physiology, Centre of Excellence for Examination Oxide in Civilisation Diseases, Slovak Academy of Sciences, Bratislava, Slovak Repub

(Received 15 May 2012; revised 30 July 2012; accepted 24 August 2012)

Abstract

As chronic stress is a significant risk factor for several cardiovascular disorders, this long-term stress produced by crowding may lead to alterations in nitric oxide (NO) pro in the course of stress, resulting in endothelial dysfunction and hypertension in Wistar male WKY rats were divided into control (480 cm^2/rat, four rats/cage, $n = 8$) and $n = 10$) groups for 8 or 12 weeks. Vasorelaxation was evaluated *in vitro* as a response to pre-contracted by serotonin, before and after NO synthase inhibition (N^G-nitro- Crowding increased plasma corticosterone concentration but failed to affect blo plethysmography) of rats. NO production was unchanged in the hypothalamus and however it was significantly elevated in the aorta. Maximal ACh-induced relaxation stress, but reduced after 12 weeks. Stress elevated the NO-dependent componer component of ACh-induced relaxation in both crowded groups. However, a reducti was more pronounced after 12-week versus 8-week stress. In conclusion, elevated observed after 8-week stress, while the extension of stress exposure resulted in a reducti a more pronounced decrease of its NO-independent component. Thus, elevation relaxation can be considered as an adaptation mechanism, and impairment of NO-inde step in chronic stress-induced cardiovascular disorders.

Keywords: *Acetylcholine, blood pressure, endothelial dysfunction, hypertension, L-NA*

Introduction

Stress affecting the cardiovascular system is a significant risk factor for several cardiovascular disorders, including myocardial infarction (Ohlin et al. 2004). However, despite many experimental and population-based observational studies, there is still conflicting information regarding the causal relationship between stress and hypertension.

There is a general agreement that the acute stress response does not produce sustained elevation of blood pressure (BP) in humans or animals, while studies investigating the effects of chronic stress on BP have produced ambiguous results (Sparrenberger et al. 2008). Available literature data indicate that chronic stress is likely to contribute to the development of hypertension (Spru disorders (Toda humans. The result on the mechanis hypertension are h positive and negativ of stress in the de inconsistency may animal strain (Toot 2006), sex (Ueno et genetic predisposit 2007a). Additional sistency may result regarding their r

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Research Communication

(–)-Epicatechin Reduces Blood Pressure and Improves Vasorelaxation in Spontaneou Hypertensive Rats by NO-mediated Me

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Iveta Bernatova[2]
Angelika Puzserova[2]

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[2]*Institute of Normal and Pathological Physiology, Centre of Excellence for Examination of Regulatory Role of Nitric Oxide in Civilisation Diseases, Slovak Academy of Sciences, Bratislava, Slovak Republic*

Abstract

Studies in humans have found consumption of certain flavanoid-containing foods to be associated with improvement in endothelial function and with reduction of blood pressure (BP). (–)-Epicatechin is a compound representative of the flavanols (a subfamily of flavonoids), abundant in cocoa seeds, which is preserved during the industrialization process to chocolate. The antihypertensive effect of dietary (–)-epicatechin was investigated on spontaneously hypertensive rats (SHRs). Consumption of (–)-epicatechin-supplemented diet (3 g (–)-epicatechin/kg diet) decreased BP in SHR by 27 and 23 mm Hg on days 2 and 6, respectively. On day 6, a 173% increase of nitric oxide synthase (NOS) activity was observed in the aorta of EPI-SHR as compared to nonsupplemented SHR ($P<0.05$). Responses to acetylcholine (ACh) were then examined in of L-NAME, mediated rel ent mechani ent relaxatio EPI-SHR than ent compone ent relaxatio nitroprusside experimental vascular smo port to the hypertension

Keywords: *flavonoids; hypertension; nitric oxide; phytonutrients; cocoa; chocolate; endothelial dysfunction*

Abbreviations: *ACh, acetylcholine; AUC, area under the curve; BP, blood pressure; eNOS, endothelial nitric oxide synthase; L-NAME, N*ω*-nitro-L-arginine methyl ester; NOS, nitric oxide synthase; SNP, sodium nitroprusside; SHR, spontaneously hypertensive rats; WKY, Wistar–Kyoto rats.*

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Introduc
Studies in hu noid-containi endothelial fu (1–6). Severa sive effect of cocoa (7–10). lation betwe ucts and (–)-e nol abundant industrializat
In humar tion, as evalu

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 598271, 14 pages
http://dx.doi.org/10.1155/2014/598271

Hindawi

Review Article

Endothelial Dysfunction in Experimental Models of Arterial Hypertension: Cause or Consequence?

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Academic Editor: Silvia M. Arribas

Hypertension is a risk factor for other cardiovascular diseases and endothelial dysfunction was found in humans as well as in various commonly employed animal experimental models of arterial hypertension. Data from the literature indicate that, in general, endothelial dysfunction would not be the cause of experimental hypertension and may rather be secondary, that is, resulting from high blood pressure (BP). The initial mechanism of endothelial dysfunction itself may be associated with a lack of endothelium-derived relaxing factors (mainly nitric oxide) and/or accentuation of various endothelium-derived constricting factors. The involvement and role of endothelium-derived factors in the development of endothelial dysfunction in individual experimental models of hypertension may vary, depending on the triggering stimulus, strain, age, and vascular bed investigated. This brief review was focused on the participation of endothelial dysfunction, individual endothelium-derived factors, and their mechanisms of action in the development of high BP in the most frequently used rodent experimental models of arterial hypertension, including nitric oxide deficient models, spontaneous (pre)hypertension, stress-induced hypertension, and selected pharmacological and diet-induced models.

1. Introduction

Cardiovascular diseases account for about one-third of premature deaths in men and one-quarter of premature deaths in women, and arterial hypertension is one of the most significant risk factors for cardiovascular diseases. Despite current knowledge and extensive clinical and experimental research, the cause of hypertension remains unknown in about 95% of all cases. There are several factors that—alone or in combination—can increase the risk of developing primary hypertension in humans. In general, these include genetic and environmental factors.

Genetic association studies have identified polymorphisms in several candidate genes (e.g., angiotensinogen, angiotensin-converting enzyme, alpha-adducin, beta-adrenergic receptors, endothelial nitric oxide synthase (NOS), cytochrome P_{450} 2C19, and nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase)) and several genomic sites that may include other genes contributing to primary hypertension [1–11]. However, none of these genetic abnormalities seems to be responsible for a significant portion of hypertension in the general population. Yet the influence of genetic factors may be accentuated and disease can be triggered by interaction of several gene polymorphisms or with environmental inputs such as sedentary life style, smoking, dietary factors (high salt, sugar, fat/cholesterol and alcohol intake, and low potassium and calcium intake) and chronic stress.

It is well known that pathophysiological characteristics of essential hypertension involve, besides other factors, increased total peripheral resistance. Thus, several experimental models of hypertension have been developed in rodents to study the mechanisms of blood pressure (BP) regulation in order to better understand the cause and consequences of human arterial hypertension [12]. These experimental models allow not only to modify all potential factors—diet, surrounding environment, and genetic information (by using specific gene knock-out or transgenic models)—but also to study the influence of interaction of specific risk factors in the etiology of hypertension. Moreover,

Mission of the Institute / Laboratory of Vascular Disorders Etiopathogenesis

The assessment period can be characterised by:

- **study of new signal pathways triggered by NO alone, and by mutual interaction of NO with hydrogen sulfide (H2S)**
- **study of paracrine vasoactive functions of perivascular adipose tissue**
- **analysis of vasoactivity of human arteries under different conditions, and exploring correlations between findings from humans and animal models**

Mission of the Institute / Laboratory of Vascular Disorders Etiopathogenesis

JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2013, 64, 2, 241-247
www.jpp.krakow.pl

S. CACANYIOVA, I. DOVINOVA, F. KRISTEK

THE ROLE OF OXIDATIVE STRESS IN ACETYLCHOLINE-
OF ENDOTHELIUM-DENUDED ARTE

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in Civilization Diseases, Slovak Academy of Sciences, Bratislava,

Nitric oxide (NO) is produced in the endothelium in response to vasorelaxants,
smooth muscle cells to induce vasorelaxation. Previously, we found that the
arteries expresses functional NO synthase. We hypothesized that the destruction
denuding arteries of their endothelial layers causes the vessels to become inse
oxidative stress. In this study, we examined whether the acetylcholine-
endothelialized arteries is mediated by NO and/or affected by oxidative stress. F
thoracic aorta and pulmonary artery of male Wistar rats were used. Vessel super
and endothelium-denuded arteries by the lucigenin chemiluminescence meth
acetylcholine evoked vasorelaxation; this effect was inhibited in endothelium-de
with the free-radical scavenger tempol improved acetylcholine-induced relaxa
administration of 1H-[1,2,4]oxadiazolo[4,3-α]quinoxalin-1-one (ODQ), an inh
arginine methylester (L-NAME), an inhibitor of NO synthase. The chemilu
denudation of both vessel types increased the production of superoxide radica
administration. Our results show that non-endothelial NO could represent an add
and that the insensitivity of endothelium-denuded vessels to vasodilators could
findings question the concept that endothelial cells play an obligatory role in va

Key words: *vasorelaxation, nitric oxide, endothelial denudation, oxidative stres*
Nω-nitro-L-arginine methylester

INTRODUCTION

Vascular smooth muscle cells are regarded as passive recipients of nitric oxide (NO) from the endothelium. The assumption that NO acts in a paracrine fashion has been challenged by the growing evidence for an autocrine function of NO in the vasculature. Buchwalow *et al.* (1), employing immunocytochemical labeling, electron microscopy, Western blotting, and RT-PCR, found that endothelial NO synthase was expressed in rat vascular smooth muscle cells in both elastic and muscular type vessels. Additionally, neuronal NO synthase was shown to be expressed in the vascular smooth muscle cells of several types of arteries (1, 2). Although these studies confirmed that vascular smooth muscle does express both constitutive isoforms of NO synthase, the principal question, *i.e.*, whether NO generation by arterial muscle is physiologically relevant, remains unanswered. Charpie and Webb (3) were some of the first investigators to provide functional evidence for a role of muscle-derived NO by showing that myocyte-derived NO modulates the vascular tone of the rat thoracic aorta. A potential role for smooth muscle NO synthase was confirmed by Schwarz *et al.* (4) who showed that NO synthase and NO synthesized in smooth muscle, in addition to endothelial NO synthase, can control vascular tone.

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Nitric Oxide 46 (2015) 123–130

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Nitric Oxide

journal homepage: www.elsevier.com/locate/

The reaction products of sulfide and S-nitrosoglutathion
vasorelaxants

Andrea Berenyiova [a], Marian Grman [b,c], Ana Mijuskovic [d], Andrej Stasko
Peter Nagy [f], Elena Ondriasova [g], Sona Cacanyiova [a], Vlasta Brezova [e], Ma
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ARTICLE INFO

Article history:
Available online 18 December 2014

Keywords:
Hydrogen sulfide
Nitric oxide
Nitrosopersulfide
Polysulfides
Aorta relaxation
Uterus

ABSTRACT

The chemical interaction of sodium sulfide (Na_2S) with
been described to generate new reaction products, inclu
via intermediacy of thionitrous acid (HSNO). The aim o
lar effects of the longer-lived products of the Sulfide/GS
of this reaction relax precontracted isolated rings of ra
lesser degree rat uterus) with a >2-fold potency compared
Na_2S and polysulfides have little effect at 1–5 μM. The
was 7–10 times faster in aorta and mesenteric arteri
(100–500 nM) was blocked by an inhibitor of soluble gu
NO scavenger cPTIO (100 μM), but less affected by p
N-acetylcysteine (1 mM) or methemoglobin (20 μM he
reaction products (100–500 nM based on the starting m
only slightly decreased by cPTIO, more markedly inhibi
abolished by acidification before addition to the organ
ate NO as detected by EPR spectroscopy using N-(dithio
spin trap. In conclusion, the Sulfide/GSNO reaction produ
than GSNO itself. We conclude that in addition to NO for
polysulfides may give rise to nitroxyl (HNO) and be inv
the Sulfide/GSNO cross-talk.

1. Introduction

Endogenously synt
nized as an important g
(NO) – influences many
ing and intracellular
interaction of NO with
reservoir for NO [2]. Sim
sulfur and transported
stimulus [3]. A number
interaction between H_2
NO were found to coop
ing a neuroendocrine

Abbreviations: ABS, absorbance; AS, Angeli's salt; AUC, area under the curve; cPTIO, 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide; GSNO, S-nitrosoglutathione; EPR, electron paramagnetic resonance; MGD, N-(dithiocarboxy)-N-methyl-D-glucamine; NAC, N-acetyl-L-cysteine; ODQ, 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one; Phen, (R)-(-)-phenylephrine hydrochloride; sGC, soluble guanylyl cyclase; Sx, polysulfides; SNP, nitroprusside; SSNO⁻, nitrosopersulfide.

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1089-8603/

Oxidative Stress

Role of Nitric Oxide Synthase Uncoupling at Rostral Ventrolateral Medulla in Redox-Sensitive Hypertension Associated With Metabolic Syndrome

Kay L.H. Wu, Yung-Mei Chao, Shiow-Jen Tsay, Chen Hsiu Chen, Samuel H.H. Chan, Ima Dovinova, Julie Y.H. Chan

Abstract—Metabolic syndrome (MetS), which is rapidly becoming prevalent worldwide, is long known to be associated with hypertension and recently with oxidative stress. Of note is that oxidative stress in the rostral ventrolateral medulla (RVLM), where sympathetic premotor neurons reside, contributes to sympathoexcitation and hypertension. This study sought to identify the source of tissue oxidative stress in RVLM and their roles in neural mechanism of hypertension associated with MetS. Adult normotensive rats subjected to a high-fructose diet for 8 weeks developed metabolic traits of MetS, alongside increases in sympathetic vasomotor activity and blood pressure. In RVLM of these MetS rats, the tissue level of reactive oxygen species was increased, nitric oxide (NO) was decreased, and mitochondrial electron transport capacity was reduced. Whereas the protein expression of neuronal NO synthase (nNOS) or protein inhibitor of nNOS was increased, the ratio of nNOS dimer/monomer was significantly decreased. Oral intake of pioglitazone or intracisternal infusion of tempol or coenzyme Q_{10} significantly abrogated all those molecular events in high-fructose diet–fed rats and ameliorated sympathoexcitation and hypertension. Gene silencing of protein inhibitor of nNOS mRNA in RVLM using lentivirus carrying small hairpin RNA inhibited protein inhibitor of nNOS expression, increased the ratio of nNOS dimer/monomer, restored NO content, and alleviated oxidative stress in RVLM of high-fructose diet–fed rats, alongside significantly reduced sympathoexcitation and hypertension. These results suggest that redox-sensitive and protein inhibitor of nNOS–mediated nNOS uncoupling is engaged in a vicious cycle that sustains the production of reactive oxygen species in RVLM, resulting in sympathoexcitation and hypertension associated with MetS. (*Hypertension*. 2014;64:815-824.) • Online Data Supplement

Key Words: hypertension ■ metabolic cardiovascular syndrome ■ nitric oxide ■ reactive oxygen species ■ sympathetic nervous system

Metabolic syndrome (MetS), defined as a cluster of ≥3 disorders that include insulin resistance, dyslipidemia, hypertension, hypercholesterolemia, and abdominal obesity,[1,2] is associated with the risk of developing type 2 diabetes mellitus, coronary heart disease, stroke, and cardiovascular-related mortality.[3,4] MetS affects >20% of adults in Western populations. However, given the acculturation of Western diet in the developing world, the burden of MetS is highly prevalent worldwide. Although insulin resistance is generally accepted as the main underlying pathogenic mechanism, increasing evidence links excessive reactive oxygen species (ROS) production and tissue oxidative stress to the pathogenesis of MetS and the progression of its complications.[5,6] A recent cross-sectional study reported that subjects with more MetS components exhibit higher levels of oxidative stress.[7] Better understanding of the significance of the redox signaling in MetS is therefore warranted.

The brain uses large amounts of oxygen and ATP for its normal functions and is therefore highly susceptible to oxidative stress. Reports on brain oxidative stress in the pathogenesis of MetS, however, are sporadic. Of the few studies reported, oxidative stress in the hypothalamus is involved in the progression of obesity-induced hypertension.[8] In the rostral ventrolateral medulla (RVLM), where sympathetic premotor neurons reside,[9] oxidative stress induces sympathoexcitation in rats with obesity-induced hypertension.[10] ROS are products of normal cellular metabolism and are derived from many sources in different cellular compartments. In RVLM, we[11,12] and others[13,14] have demonstrated that ROS generated from nicotinamide adenine

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.114.03777/-/DC1.
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Mission of the Institute / Laboratory of Cognitive Neuroscience

The assessment period can be characterised by:

by the use of human electrophysiological methods in the study of visual-spatial and sensorimotor brain processing, as well as in the neural mechanisms of social cognition. The laboratory began research in endophenotypes of mental disorders by combining methods of behavioural genetics and animal models of human psychopathology.

Mission of the Institute / Laboratory of Cognitive Neuroscience

Brain and Cognition 83 (2013) 163–170

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Visual image retention does not contribute to modul
of event-related potentials by mental rotation

Igor Riečanský[a,b,*], Livia Tomova[a], Stanislav Katina[b,d], Herbert Bau
Claus Lamm[a]

ARTICLE INFO

ABSTRACT

1. Introduction

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Beta oscillations reveal ethnicity ingroup
sensorimotor resonance to pain of others

Igor Riečanský,[1,2] Nina Paul,[1,*] Sarah Kölble,[1,*] Stefan Stieger,[3,4] and Claus Lamm
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University of Vienna, Vienna, Austria, and [4]Research Methods, Assessment, and iScience, Department
Konstanz, Germany

People evaluate members of their own social group more favorably and empathize more strongly with their
ography (EEG), we explored whether resonant responses of sensorimotor cortex to the pain of others are m
White participants watched video clips of ethnic ingroup and outgroup hands, being either penetrated by a n
while EEG was recorded. Time-frequency analysis was applied to Laplacian-transformed signals from the sen
to assess event-related desynchronization and synchronization (ERD/ERS) of sensorimotor mu (7–12 Hz) and
needle injections, beta ERD was significantly stronger for ingroup compared with outgroup hands. This ethnici
beta ERD for ingroup and outgroup hands neither differed when observing no-pain videos, nor during present
Such vicarious sensorimotor activation could play a role in social interaction by enhancing the understanding
hence facilitating behavioral coordination among group members.

Keywords: empathy; ingroup favoritism; racial bias; mu rhythm; mirror neurons

INTRODUCTION

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CrossMark

Placeb analgesia and its opioidergic regulation
suggest that empathy for pain is grounded in self pain

Markus Rütgen[a], Eva-Maria Seidel[a], Giorgia Silani[b,c], Igor Riečanský[a,d], Allan Hummer[a,f], Christian Windischberger[a,f], Predrag Petrovic[g], and Claus Lamm[a,1]

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Empathy for pain activates brain areas partially overlapping with those underpinning the first-hand experience of pain. It remains unclear, however, whether such shared activations imply that pain empathy engages similar neural functions as first-hand pain experiences. To overcome the limitations of previous neuroimaging research, we pursued a conceptually novel approach: we used the phenomenon of placebo analgesia to experimentally reduce the first-hand experience of pain, and assessed whether this results in a concomitant reduction of empathy for pain. We first carried out a functional MRI experiment ($n = 102$) that yielded results in the expected direction: participants experiencing placebo analgesia also reported decreased empathy for pain, and this was associated with reduced engagement of anterior insular and midcingulate cortex: that is, areas previously associated with shared activations in pain and empathy for pain. In a second step, we used a psychopharmacological manipulation ($n = 50$) to determine whether these effects can be blocked via an opioid antagonist. The administration of the opioid antagonist naltrexone blocked placebo analgesia and also resulted in a corresponding "normalization" of empathy for pain. Taken together, these findings suggest that pain empathy may be associated with neural responses and neurotransmitter activity engaged during first-hand pain, and thus might indeed be grounded in our own pain experiences.

pain | empathy | placebo | fMRI | psychopharmacology

Significance

Empathy is of major importance for everyday social interaction. Recent neurosdentific models suggest that pain empathy relies on the activation of brain areas that are also engaged during the first-hand experience of pain. These models rely on rather unspecific and correlational evidence. Here, we show that inducing pain analgesia also reduces pain empathy, and that this is associated with decreased activation of empathy-related brain areas. We then document that blocking placebo analgesia via an opioid antagonist also blocks placebo analgesia effects on pain empathy. This finding suggests that pain empathy is grounded in neural responses and neurotransmitter activity related to first-hand pain.

Author contributions: M.R., E.-M.S., G.S., I.R., A.H., C.W., P.P., and C.L. designed research; M.R., E.-M.S., I.R., and A.H. performed research; M.R., E.-M.S., I.R., A.H., and C.W. analyzed data; and M.R., E.-M.S., G.S., I.R., A.H., C.W., P.P., and C.L. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. N.I.E. is a guest editor invited by the Editorial Board.

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Mission of the Institute / Laboratory of Motor Control

The assessment period can be characterised by

- **development of a new method using sensory biofeedback for balance improvement**
- **study of sensory/brain stimulation to enhance postural performance in healthy elderly humans and patients with neurological movement disorders**
- **analyses of postural mechanisms and kinematics during step initiation in obese subjects and in healthy aging subjects**

Mission of the Institute / Laboratory of Motor Control

J Neurophysiol 116: 1468–1479, 2016.
First published July 13, 2016; doi:10.1152/jn.00057.2016.

Velocity dependence of vestibular information for pos surfaces

Fay B. Horak,[1,2] JoAnn Kluzik,[3] and Frantisek Hlavacka[4]
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Horak FB, Kluzik J, Hlavacka F. Velocity dependence of vestibular information for postural control on tilting surfaces. *J Neurophysiol* 116: 1468–1479, 2016. First published July 13, 2016; doi:10.1152/jn.00057.2016.—Vestibular information is known to be important for postural stability on tilting surfaces, but the relative importance of vestibular information across a wide range of surface tilt velocities is less clear. We compared how tilt velocity influences postural orientation and stability in nine subjects with bilateral vestibular loss and nine age-matched, control subjects. Subjects stood on a force platform that tilted 6 deg, toes-up at eight velocities (0.25 to 32 deg/s), with and without vision. Results showed that visual information effectively compensated for lack of vestibular information at all tilt velocities. However, with eyes closed, subjects with vestibular loss were most unstable within a critical tilt velocity range of 2 to 8 deg/s. Subjects with vestibular deficiency lost their balance in more than 90% of trials during the 4 deg/s condition, but never fell during slower tilts (0.25–1 deg/s) and fell only very rarely during faster tilts (16–32 deg/s). At the critical velocity range in which falls occurred, the body center of mass stayed aligned with respect to the surface, onset of ankle dorsiflexion was delayed, and there was delayed or absent gastrocnemius inhibition, suggesting that subjects were attempting to actively align their upper bodies with respect to the moving surface instead of to gravity. Vestibular information may be critical for stability at velocities of 2 to 8 deg/s because postural sway above 2 deg/s may be too fast to elicit stabilizing responses through the graviceptive somatosensory system, and postural sway below 8 deg/s may be too slow for somatosensory-triggered responses or passive stabilization from trunk inertia.

vestibular; postural stability; human; surface tilt; somatosensory; proprioception

NEW & NOTEWORTHY

The relative use of vestibular vs. somatosensory information for human balance control is unclear. When standing with eyes closed, subjects with vestibular loss were most unstable within a critical surface tilt velocity range of 2 to 8 deg/s. We propose that the vestibular system is critical for controlling balance at tilt velocities around normal postural sway, whereas graviceptive control is used at lower velocities, and proprioceptively triggered automatic postural responses are used at higher velocities.

THE RELATIVE IMPORTANCE OF vestibular information for postural control depends on task and environmental conditions (Fitzpatrick et al. 2002; Hlavacka et al. 1995; Horak et al. 2002; Inglis et al. 1995; M vestibular informatio posture on a stationary the support surface ca posture control (Inglis Inglis 1993; Mergner Vestibular informatio priately timed postura tions of a horizontal sensory feedback (Ho 1995; Inglis et al. 19 ever, vestibular inform tant for balance whe oscillating or sway-re available (Allum and al. 2000; Nashner et a

Vestibular informat attempt to balance o velocities that are di system, normally the disequilibrium (Peterk at about the same rat somatosensory systen between body sway o stable body (Mergner faster than natural bo signal the surface pe slowly than natural b (graviception) can sig when the surface is ti falls (around 4 deg/s), most important becau able (assuming vision

Although the effec steady-state postural 2008; Maurer et al. 2 tion has systematicall discrete, surface-tilt v with vestibular loss. with vestibular loss an cycles if the tilting ar 2008; Maurer et al. contrast, discrete, ram tage of testing subje velocity range witho maintained for only o

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Age-Related Changes of Human Balance dur

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Institute of Normal and Pathological Physiology, Slovak Acade

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Summary

Certain aspects of balance control change with age, resulting in a slight postural instability. We examined healthy subjects between 20-82 years of age during the quiet stance under static conditions: at stance on a firm surface and/or on a compliant surface with eyes either open or closed. Body sway was evaluated from centre of foot pressure (CoP) positions during a 50 sec interval. The seven CoP parameters were evaluated to assess quiet stance and were analyzed in three age groups: juniors, middle-aged and seniors. The regression analysis showed evident increase of body sway over 60 years of age. We found that CoP parameters were significantly different when comparing juniors and seniors in all static conditions. The most sensitive view on postural steadiness during quiet stance was provided by CoP amplitude and velocity in AP direction and root mean square (RMS) of statokinesigram. New physiological ranges of RMS parameter in each condition for each age group of healthy subjects were determined. Our results showed that CoP data from force platform in quiet stance may indicate small balance impairment due to age. The determined physiological ranges of RMS will be useful for better distinguishing between small postural instability due to aging in contrast to pathological processes in the human postural control.

Key words
Age • Human balance • Body sway • Quiet stance

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Introducti

For inevitably ac independent 1993). The p systems (som system and s involves con systems (Hora known to be of the ability Aging is ass sensory syste Du Pasquier diminished m mass, loss of (Porter *et al.* 1992) and dec

Adec integration information o of sensitivity reported so fr disease that t consequence the somatose indicated sig older adults generalized re vision has be increased ri Comparison related decre 1999). Adult

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Effectiveness of different visual biofeedback signals for human balance improvement

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ABSTRACT

The aim of this study was to examine the effectiveness of visual biofeedback (VBF) signals from a force platform and accelerometer sensors placed on different body segments. The study was performed on 20 young subjects during standing on a firm and foam support surface with a VBF signal sensed from CoP, lower trunk (L5) and upper trunk (Th4). The VBF signal was controlled by 2D-movement of chosen body segment, which was presented as a red point on a monitor screen. Location of VBF signal had a significant effect on each postural parameter of CoP and trunk segments. RMS and amplitudes of postural sway in medial–lateral and anterior–posterior directions decreased during standing on both types of support surface due to VBF. L5-VBF and CoP-VBF significantly reduced CoP displacements and lower trunk tilts. Th4-VBF reduced upper trunk tilts. Frequency analysis of postural sway revealed a decrease of power spectral density (PSD) values in low frequency range (0.02–0.3 Hz) and an increase of PSD values in higher frequency range (0.5–1.4 Hz) in the VBF conditions during the stance on the firm surface in anterior–posterior direction. Reduction of body sway was the most significant in the body segment from which the VBF signal was sensed. The CoP position and L5 position provided the best signals for VBF. Changes in frequency ranges of body sway suggest voluntary activation of balance control. The results open new opportunities to optimize VBF system for balance improvement using accelerometers.

1. Introduction

Undisturbed upright stance control is a complex task based on an integration process involving visual, vestibular and proprioceptive information [1]. Postural stability is often evaluated by outputs from the force platform, which measures the centre of foot pressure (CoP) variability. However, posturography has its limitations because human body is multi-segmental and does not always act as an inverted pendulum. Upper body segments are often more independent from lower body segments, especially in challenged situations [2].

Visual biofeedback (VBF) consists of supplying individuals with additional artificial visual information about body motion to supplement the natural visual information and improve human balance [3]. The use of real-time visual biofeedback (VBF) from CoP during a standing task is a common tool incorporated in evaluation and training of the postural control [4]. The CoP position is presented in real time on a monitor screen and the subject is required to confine it to the narrowest possible zone [5].

The sensor of body motion is, besides the processor and interface, one of the main components of each biofeedback device [6]. The question of optimal sensor location for VBF has not been examined yet, despite the fact that accelerometers allow to measure inclination of body segment with respect to the vertical position. They can be attached to any part of the body. Body tilts measured by the accelerometer could be displayed on a monitor screen as well as outputs from a force platform. That offers new possibilities for VBF experiments.

In the present study, the effectiveness of VBF sensed from accelerometers attached to upper and lower trunk and VBF sensed from CoP were investigated. It was hypothesized that VBF from accelerometer attached to lower trunk would have similar influence on the body sway as VBF from CoP, because both reflect similar postural activities.

2. Methods

Twenty young subjects (9 men and 11 women) within the range of 20–33 years (mean age 22.6 years, mean BMI 21 kg m^{-2}) participated in the study. Subjects did not report any neurological, orthopaedic, or balance impairments. They gave their informed

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Mission of the Institute / Important Numbers

Fig. 1.

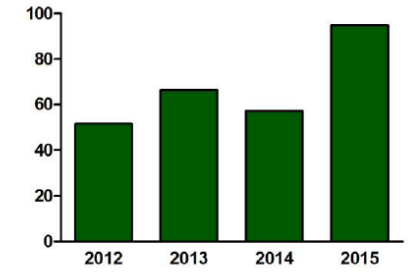


Fig. 2.

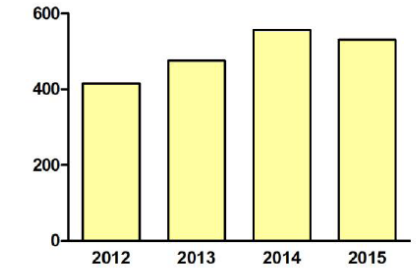
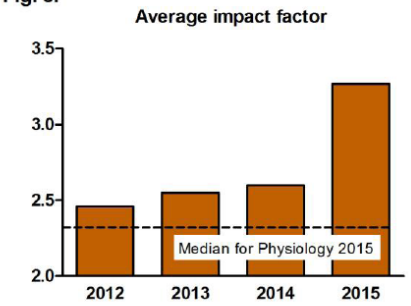


Fig. 3.



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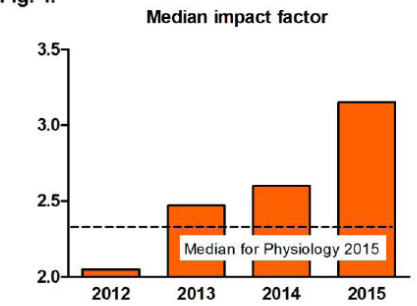


Fig. 5.

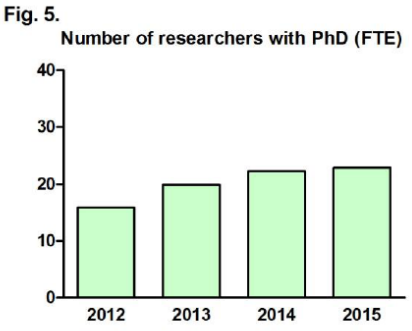
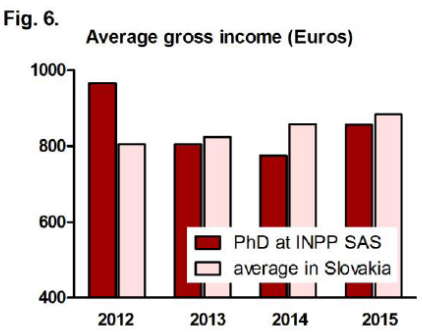


Fig. 6.



Average impact factor

2.5 → **2.9**

Citations

296 → **494**

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The SAS-CONICET (Argentina) programme: Metabolic syndrome: inflammation in hypertension and the effect of polyphenols, project leader: Oľga Pecháňová

The SAS-TUBITAK (Turkey) programme: Magnesium Nanocomposites for Biodegradable Medical Implants, project leader: Oľga Pecháňová

EU Commission - DG SANCO, European Network for Workplace Health Promotion (ENWHP): Promoting healthy work for employees with chronic illness - public health and work (EAHC No 20101208), coordinator at INPP SAS: Fedor Jagla

Joint laboratories and cooperation agreements:
Charité – Universitätsmedizin in Berlin, Germany
Faculty of Medical Sciences at University of Kragujevac, Serbia
Faculty of Psychology at University of Vienna in Austria
Balance Disorders Laboratory in the Department of Neurology, School of Medicine at Oregon Health and Science University, Portland, USA.

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Centre of Excellence for Examination of Regulatory Role of Nitric Oxide in Civilisation Diseases (NOREG)

Ministry of Health projects
- Signal pathway of nitric oxide and hydrogen sulfide, its disturbances and participation in development of hypertension and atherosclerosis, No: 2012/51-SAV-1
- The influence of variability of NOS1 and DAT1 genes on sensorimotor gating in humans: the implications for the pathophysiology of schizophrenia, No: 2012/52-SAV-2

Slovak Society of Cardiology projects
- Effect of aging on the endothelial function in experimental hypertension, No: SKS2015 grant
- Cardiovascular effects of nanoencapsulated simvastatin and CoQ10 in experimental hyperlipidemia, No: SKS2015

Slovak psychiatric society project
The effect of variability in NOS-1 gene on sensorimotor gating: implications for pathophysiology of schizophrenia

National Programme for Prevention of Cardiovascular Diseases
Healthy heart for Slovakia

Structural Funds
- Centre of Excellence for Research and Development of Constructive Composite Materials II (CEKOMAT II) - Number of project: ITMS NFP26240120006, Duration of the project: 1.1.2011 - 31.12.2014
- BIOMED PARK - Number of project: ITMS 26240220087, Duration of the project: 1.1.2013 - 31.12.2015

APVV Projects: 4 projects coordinated by the Institute + 4 projects with the Institute participation
VEGA Projects: 20 projects coordinated by the Institute + 5 projects with the Institute participation

Mission of the Institute / Networking/ International Conferences

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C.I.A.N.S. CONFERENCE 2012, Congress Centre of the SAS, Stará Lesná with chairman Fedor Jagla

LIFESTYLE AND RISK FACTORS IN DISEASES OF CIVILISATION, Congress Centre of the SAS, Stará Lesná, chair: Oľga Pecháňová

2013:

EXPLORING THE BIOLOGICAL MECHANISMS OF DECISION MAKING BY BRAIN STIMULATION within the 55th Conference of Experimental Psychologists TeaP 2013 with chairs Jürgen Pripfl (University of Vienna) and Igor Riečanský

COST SYMPOSIUM 2013, Congress Centre of the SAS, Smolenice with chairperson Oľga Pecháňová

Bilateral Slovak – Czech symposium MODULATION OF VASCULAR WALL FUNCTION AS A THERAPEUTIC TARGET IN HYPERTENSION, Bratislava with chairperson Iveta Bernátová

NEUROTRANSMITTERS AND THEIR ROLE – an invited international symposium within the XIIIth Psychopharmacological Symposium, Congress Centre of the SAS, Smolenice with chairman Igor Riečanský.

2014:

RENIN INHIBITOR–ALISKIREN: PRESENT KNOWLEDGE PROMISING FOR FUTURE within the 7th International Congress of Pathophysiology of the ISP, Rabat, Morocco with chairperson Oľga Pecháňová

JOINT MEETINGS OF THE **8th SYMPOSIUM NITRIC OXIDE** AND 2ND SYMPOSIUM GENETIC AND ENVIRONMENTAL FACTORS IN HYPERTENSION, Croatia, Vrsar with chairperson Iveta Bernátová

2015:

THE 7th INTERNATIONAL POSTURE SYMPOSIUM: POSTURE AND GAIT IN RESEARCH, CLINIC AND SPORT, Congress Centre of the SAS, Smolenice Castle with chairpersons: František Hlavačka and Jana Lobotková

Mission of the Institute / Among the Leaders

COST – management committee member

European Council for Cardiovascular research, ECCR – members of executive committee

International Society for Physiology, ISP – president elect

Collegium Internationale Activitatis Nervosae Superioris, CIANS – president

European Commission, DG Research & Innovation – evaluator

European Academy for Science and Art – elected member

Scientific Program Committee members – (IACS, FEPS, SFRBM, ISP, COST, Conference of Experimental Psychologists, CIANS, Fapronatura, etc.)

Key note presentations, Visiting professors, Members of editorial boards, Member of the Faculty Scientific Boards, Members of working group of the Ministry of Education, Science, Research and Sport of the Slovak Republic, Scientific awards, etc.

Mission of the Institute / PhD study

PhD study programmes:

- Normal and Pathological Physiology in cooperation with the Faculty of Medicine
- Animal Physiology in cooperation with the Faculty of Natural Sciences,
  both of which are part of Comenius University in Bratislava.

Within the PhD programmes INPP SAS has been able to accept PhD students from different faculties like Faculty of Natural Sciences, Faculty of Mathematics, Physics and Informatics, Faculty of Psychology at Comenius University, University of Veterinary Medicine and Pharmacy in Košice, and others.

INPP SAS also hosted master's students from the University of Vienna's Faculty of Psychology,

Fund of Stefan Schwarz - internal funding for two students

In addition to PhD study programmes, INPP SAS is currently hosting Dr. Jasminka Majdandţić, previously appointed by the University of Vienna, within the programme SASPRO - Mobility Programme of the Slovak Academy of Sciences, which began in May 2015.

INPP SAS 's former PhD students have been also appointed by different foreign universities and have excellent results.

Mission of the Institute / Social Impact

Programmes:

National Programme for Prevention of Cardiovascular Disease
National Programme for Prevention of Overweight and Hypertension, Part Children and Juveniles
Programme Healthy Heart for Slovakia

European network for workplace health promotion - national contact office

Research:

Early detection of motor control disorders was developed.
Nanoencapsulation for targeting treatment was applied.
Treatment of cigarette cravings was studied.
New materials for biomedical applications were analysed.
Utilisation of markers of cardiovascular diseases for eHealth in cooperation with SWAN, a.s.

Vision of the Institute / The Aim

Global trends in cardiovascular and neurophysiological research have been concentrated on studies elucidating the etiopathogenesis of serious civilisation diseases.

Therefore, the research groups at INPP SAS will continue with their investigations of their current research project topics, however, this will be done using new, state-of-art techniques and methodological approaches.

Research at INPP SAS is also increasingly shifting towards applied and transdisciplinary research, which is reflected by strengthened cooperation with institutions primarily focused on applied and clinical research.

Vision of the Institute / The Strategy

To be excellent: prepare quality articles with the ambition to publish them in the leading journals

To be international: increase international impact, involvement in EU projects and consortia, and create an inspiring platform for PhD students and young scientists from abroad

To be a team: as a community of scientists, post-doctoral students, PhD and diploma students, work together to promote an open, inclusive, diverse, and supportive workplace

To be integrative: continue in the development of integrative physiology in strong connection with molecular biology and modern genomic and proteomic approaches, in order to determine molecular mechanisms of diseased states

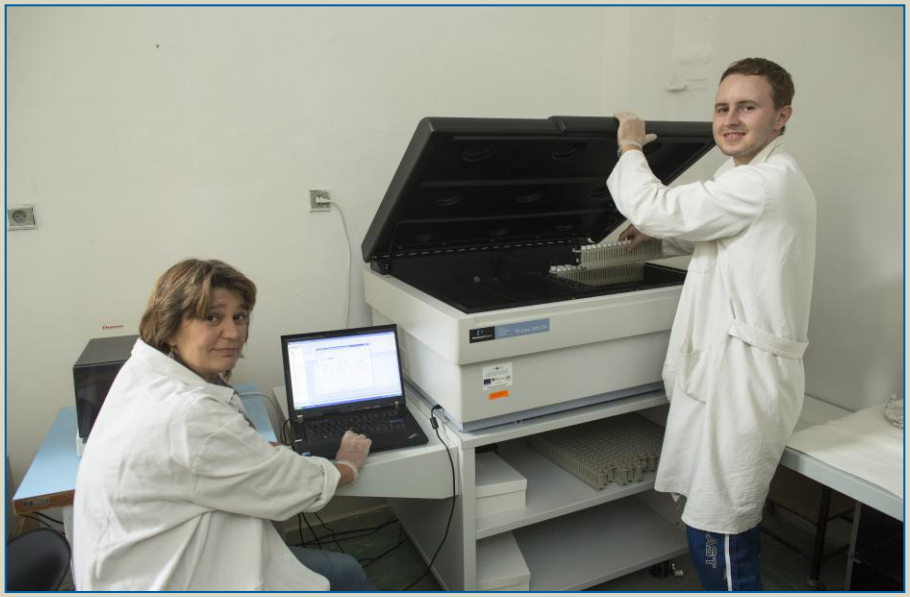
To be transdisciplinary: to continue in the first successful transdisciplinary projects to meet the applied research objectives

To be competitive: to develop new research methods, models and approaches that will increase INPP SAS's level of specialisation in the field of integrative physiology. Such specialisation would help INPP SAS be more competitive, and make it a more desirable partner for EU projects

To be open to young people and new trends: in cooperation with the Presidium of the SAS, to simplify administration procedures associated with the admission of foreign PhD students and post-doctoral students interested in studying at INPP SAS

To be beneficial for society: based on the current international projects and national cooperation with the Ministry of Health of the Slovak Republic and the National Health Information Centre to contribute to improving the quality of life

Infrastructure



Biochemical analysis

Assays for enzyme activity
Measurement of NO/ROS production
Determination of plasma/serum profile
Electrochemical methods

Bioanalysis of DNA, RNA and proteins

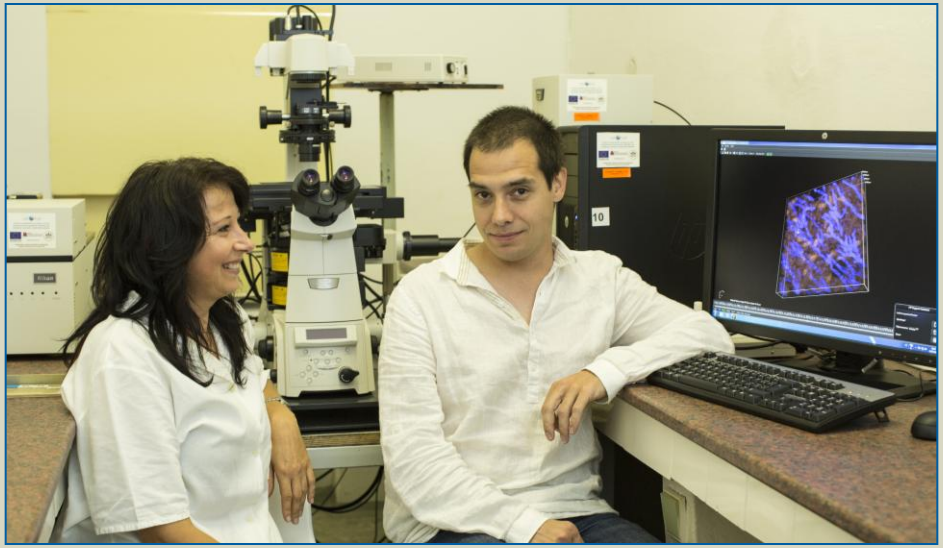
Electrophoretic analysis
Western blotting
Quantitative PCR analysis of nucleic acids

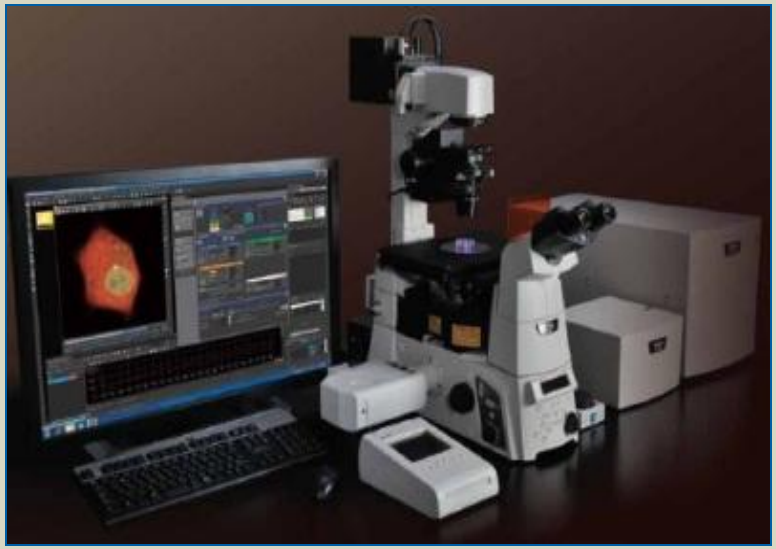
Infrastructure

Microscopy /Histology / Immunohistochemistry

Light microscopy
Fluorescent microscopy
Confocal microscopy
Transmission electron microscopy

Histological preparations
Immunohistochemistry staining





Infrastructure

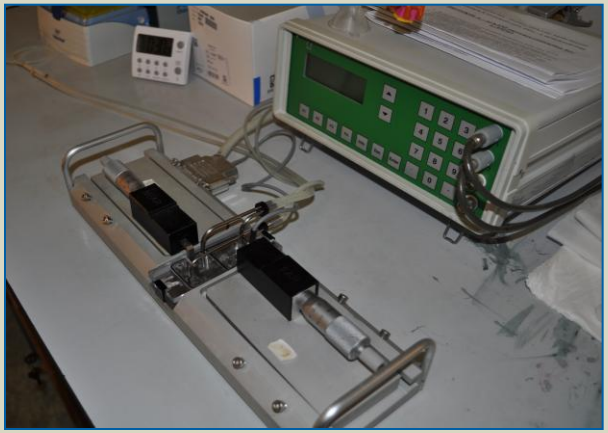
Cardiovascular physiology

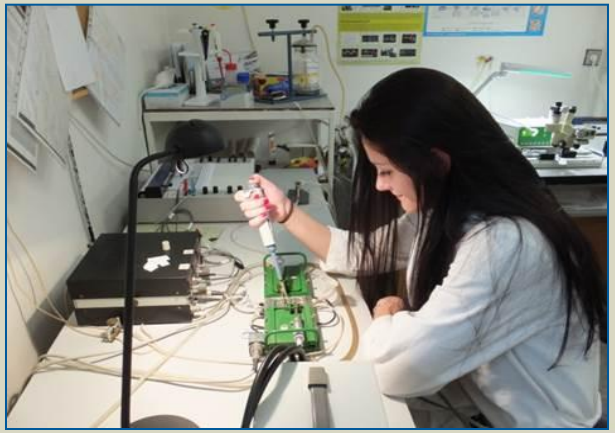
Direct measurement of blood pressure, heart rate and other biological signals

Equipment for tail-cuff plethysmography
Analysis of vasoactivity *in vitro* (multi-channel vascular organ bath systems and Mulvany´s wire myographs)

Electrocardiography for small animals

Langendorff perfusion apparatus





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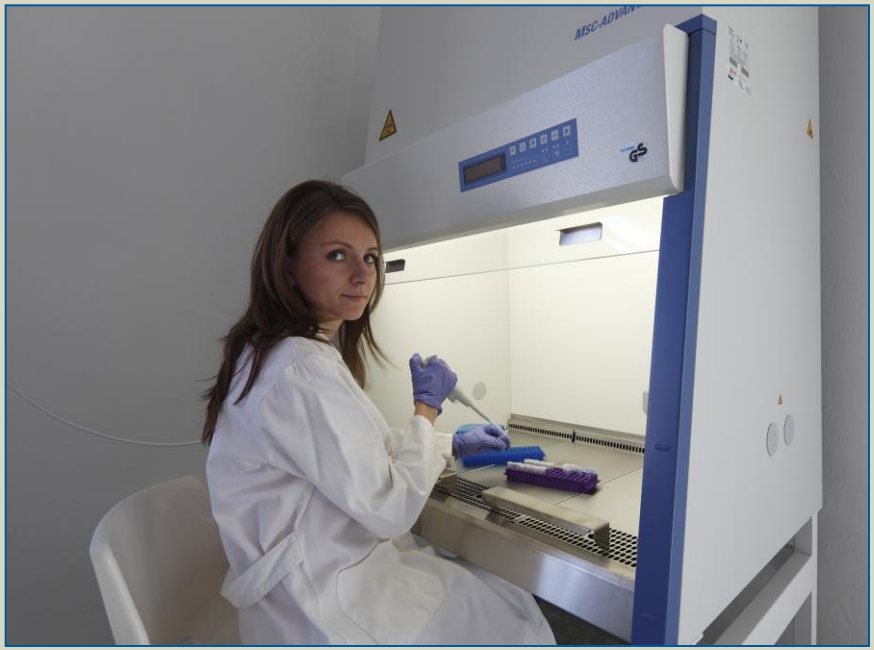

Cell culture system

Behavioural analysis in rodents

Equipment for various behavioural studies
Pepulse inhibition and startle reflex apparatus
Any-maze software for analyses of animal behaviour