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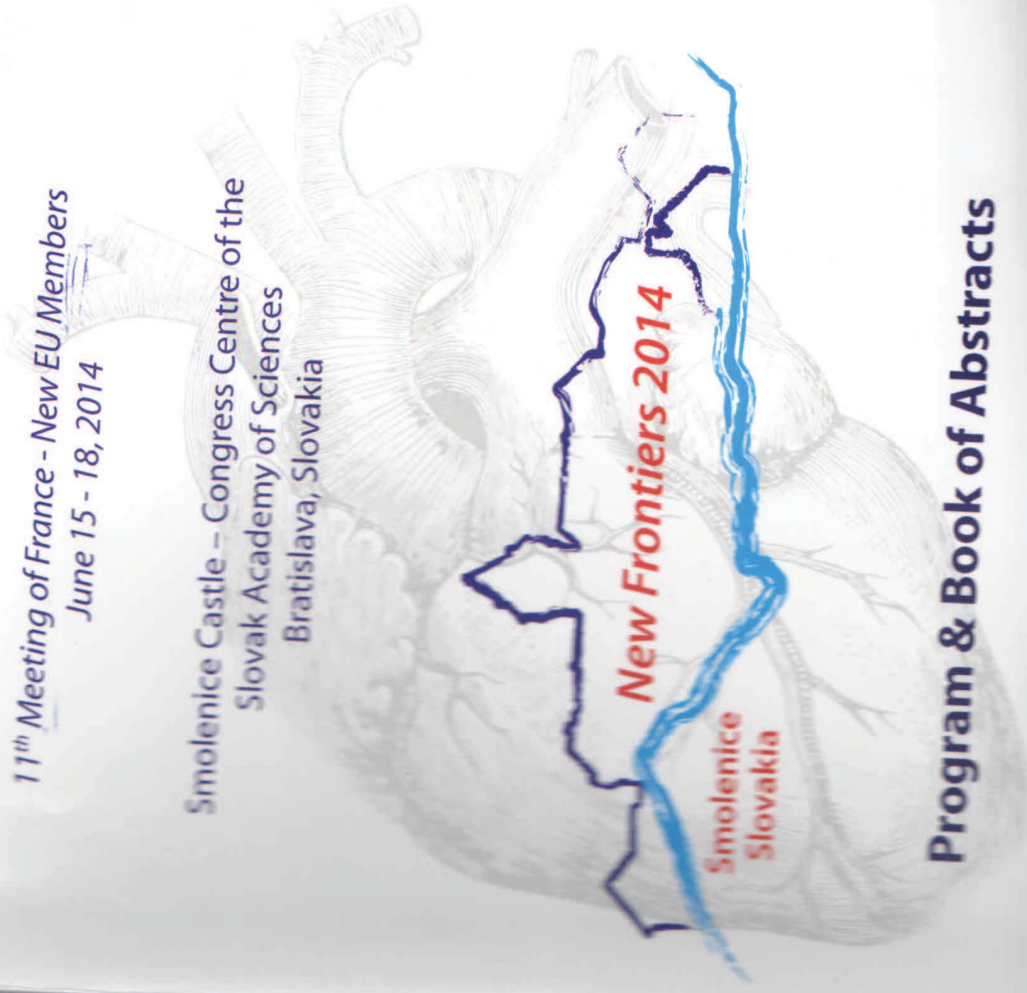
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# NEW FRONTIERS IN BASIC CARDIOVASCULAR RESEARCH 2014

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**Program & Book of Abstracts**

# EFFECT OF CHRONIC CONTINUOUS HYPOXIA ON MITOCHONDRIAL ENZYMES IN HEARTS OF SPONTANEOUSLY HYPERTENSIVE RATS (SHR) AND IN CONPLASTIC STRAIN SHR-mt<sup>BN</sup>

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Continuous normobaric hypoxia (CNH) is cardioprotective phenomenon, where cardiac mitochondria play an important role. Aim of study was to investigate whether adaptation to CNH affects expression and activity of selected mitochondrial proteins in SHR and in novel conplastic strain SHR-mt<sup>BN</sup>, which contains nuclear genome of SHR and mitochondrial genome of more ischemia tolerant Brown Norway.

Rats were adapted to CNH (10% O<sub>2</sub>) for 21 days. Left ventricular homogenate was used to assess the activity of mitochondrial enzymes. Protein and mRNA expression of subunits of oxidative phosphorylation complexes (CI - Ndufa9, CII - SdhA, CIII-Uqcrc2, CIV - COX-4 and MTCO1, CV - Atp5a1) were evaluated using immunoblotting and RT-PCR.

Normoxic SHR-mt<sup>BN</sup> had lower protein expression of CIV subunit MTCO1 (encoded by BN) compared to normoxic SHR. Adaptation to CNH attenuated CIV subunit protein levels in both strains compared to normoxic controls. In addition, malate dehydrogenase activity decreased only in chronically hypoxic SHR. Hypoxic SHR-mt<sup>BN</sup> demonstrated higher malate dehydrogenase activity and protein amount of Ndufa9, whereas protein content of COX-4 and MTCO1 were lower compared to hypoxic SHR. Hypoxic SHR-mt<sup>BN</sup> had decreased mRNA level for citrate synthase as well as cytochrome oxidase isoforms COX 4.1 and COX 4.2 compared to normoxic controls. However, in hypoxic SHR, the decrease in mRNA level was found only for COX 4.1.

Adaptation to CNH differently affects myocardial expression and activity of mitochondrial proteins in SHR rats and in conplastic SHR-mt<sup>BN</sup> strain.

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# VASOCONSTRICTIVE AND VASODILATATIVE EFFECTS OF TRANSIENT RECEPTOR POTENTIAL MELASTATIN-4 (TRPM4) MODULATION

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Transient Receptor Potential Melastatin-4 (TRPM4) is activated by the elevation of intracellular Ca<sup>2+</sup>-concentration, and it is permeable to Na<sup>+</sup> and K<sup>+</sup>-ions when activated. It is considered to participate in pressure-induced membrane depolarization and vasoconstriction (basal myogenic tone).

Our aim was to study role of the receptor in arteriolar diameter regulation. In order to find out, experiments were performed on MOVAS vascular smooth muscle cells, skeletal muscle arteries and mesenteric arteries, human saphenic veins, and data was also acquired in an in vivo measurement system.

During in vivo experiments the carotid artery of male Wistar-Kyoto (WKY) rats were cannulated for invasive measurement of the blood pressure. The TRPM4 antagonist 9-Phenanthrol caused a transient decrease in blood pressure, and blood pressure increasing effect of norepinephrine was also attenuated after the treatment with the TRPM4 inhibitor.

In experiments performed under isometric conditions human saphenic veins that remained after bypass surgery were used. After precontraction with 10μM norepinephrine the TRPM4 antagonist decreased the contractile force of the vessel ring by 67.1±20.9%.

On MOVAS (mouse vascular smooth muscle) cells the intracellular Ca<sup>2+</sup>-concentration could be measured in experiments, and the supposed TRPM4 activator A23187 caused elevation of intracellular Ca<sup>2+</sup>-concentration (1μM A23187 caused the elevation of 340/380 ratio from 0.71±0.05 to 0.81±0.04, p<0.05).

Our data confirms that TRPM4 may have a major role in vascular smooth muscle contraction. Possibly, the activation of the receptor causes membrane depolarization and that results in the opening of the voltage dependent Ca<sup>2+</sup>-channels, which increases intracellular Ca<sup>2+</sup>-concentration and leads to contraction.