Lozić *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A1.21
http://www.intrinsicactivity.org/2015/3/S2/A1.21
published online: 9 September 2015

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

A1.21

Over-expression of V_{1A} receptors in the hypothalamic paraventricular nucleus induces baroreflex desensitization and increases cardiovascular variability during stress

Maja LOZIĆ[1], Tatjana TASIĆ[1], Andrew MARTIN[2], Michael GREENWOOD[2], Olivera ŠARENAC[1,2], Charles HINDMARCH[2], Julian F. PATON[3], David MURPHY[2,4] and Nina JAPUNDŽIĆ-ŽIGON[1,*]

[1]Institute of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Serbia; [2]Molecular Neuroendocrinology Research Group, The Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, UK; [3]School of Physiology and Pharmacology, University of Bristol, UK; [4]Department of Physiology, University of Malaya, Kuala Lumpur, Malaysia

Background: The hypothalamic paraventricular nucleus (PVN) is a key integrative site of neuroendocrine control of the circulation and of the stress response. It is also the major source of the neuropeptide vasopressin (VP), and co-expresses V_{1A} receptors (V_{1A}R). Therefore we sought to investigate the role of V_{1A}R in PVN in cardiovascular control. We hypothesized that, by increasing the number of vasopressin V_{1A}R in PVN and by selectively blocking their activity, we can modulate PVN neuronal activity involved in autonomic cardiovascular control.

Methods: Experiments were performed in conscious male Wistar rats equipped with a radiotelemetric device implanted into the abdominal aorta for registration of cardiovascular parameters. The experimental group of animals was subjected to unilateral *in vivo* gene transfer into the right PVN of adenoviral vectors (Ads) containing information necessary to induce expression of enhanced green fluorescent protein (eGFP), used as a marker, and over-expression of V_{1A}Rs. Control animals were either subjected to gene transfer of Ads containing information for eGFP or were sham-operated. Rats were recorded with and without selective blockade of vasopressin V_{1A} receptors (V_{1A}RX) in the PVN, both under baseline conditions and during exposure to acute air-jet stress. Blood pressure (BP), heart rate (HR) and their short-term variability as well as spontaneous baroreflex sensitivity (BRS) were evaluated using spectral analysis and the sequence method, respectively.

Results: Under baseline conditions, V_{1A}R over-expressing rats exhibited reduced BRS and this was antagonized by V_{1A}RX. Exposure to stress increased BP, HR, BP variability, and decreased BRS in all rats. In V_{1A}R rats, stress induced a marked increase of BP variability and HR variability, all of which were prevented by V_{1A}RX pre-treatment. In wild-type rats, V_{1A}RX did not modify cardiovascular parameters under baseline conditions but prevented stress-induced BP variability increase.

Discussion: The present findings show for the first time that V_{1A}Rs in the PVN are involved in local (autocrine/paracrine) regulation of neurons involved in the control of the baroreflex function and cardiovascular short-term variability. During exposure of wild-type rats to stress, V_{1A}Rs in the PVN were responsible for an increase of BP variability. In rats over-expressing V_{1A}R in the PVN, baroreflex was desensitized both under baseline conditions and stress, while cardiovascular variability was markedly increased by stress. These findings indicate that the level of expression (*i.e.* density) of V_{1A}R in the PVN influences cardiovascular vulnerability to stress. The findings also implicate a possible role of somato-dendritic release of VP and of V_{1A}Rs in the PVN in cardiovascular pathology, especially hypertension and heart failure, whose poor prognosis is associated with baroreflex desensitization and enhancement of cardiovascular short-term variability.

Acknowledgements: This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (grant no. III 41013) and BBSRC (BB/G006156/1 and BB/J01515/1).

*Corresponding author e-mail: *nzigon@med.bg.ac.rs*