



*Bulgarian Society
of Physiological Sciences
Sofia branch*

SCIENTIFIC MEETING

ABSTRACTS

Sofia, 19 February, 2016



**BULGARIAN SOCIETY
OF PHYSIOLOGICAL SCIENCES
*SOFIA BRANCH***

**SCIENTIFIC MEETING
ABSTRACTS**

19 February, 2016, Sofia, Bulgaria

LOCAL ORGANIZING COMMITTEE

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Programme Overview

Oral presentations

- 13.30 – 13.50 Maria Lazarova, Reni Kalfin.
Neuromodulatory effects of vasoactive intestinal peptide.
- 13.50 – 14.10 Elka Popova, Petia Kупenova.
Effects of histamine and the selective H₁ receptor agonist TFMH on the ON and OFF responses of frog electroretinogram.
- 14.10 – 14.30 Rene Mileva-Popova, Nina Belova.
Methods for arterial stiffness assessment.
- 14.30 – 14.50 Irena Mihaylova.
Anandamide and its influence on CNS.
- 14.50 – 15.10 Zlatina Nenčovska, Dimitrinka Atanasova, Milena Atanasova, Lidia Kortenska, Miroslava Stefanova, Liana Alova, Nikolai Lazarov, Jana Tchekalarova.
Consequences of long-term treatment with agomelatine on depressive-like behavior and neurobiological abnormalities in pinealectomized rats.
- 15.10 – 15.30 Daniela Pechlivanova, Kiril Petrov, Rumiana Mitreva, Zlatina Nenčovska, Alexander Stoynev.
Aggravation of diabetes mellitus-induced metabolic and behavioral alterations by intracerebroventricular infusion of Angiotensin AT₂ receptor agonist in Wistar rats.

NEUROMODULATORY EFFECTS OF VASOACTIVE INTESTINAL PEPTIDE

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Vasoactive intestinal peptide (VIP) is a 28-amino acid peptide originally described in small intestine as a vasodilatator. It is widely distributed in central and peripheral nervous systems and acts as neurotransmitter/neuromodulator. VIP exerts its broad range of biological functions through specific membrane receptors, VPAC1, VPAC2 и PAC1.

It is generally accepted that the mammalian vas deferens is innervated by adrenergic neurons. Stimulation of the sympathetic nerves of the guinea pig vas deferens evokes a biphasic contractile response, which is mediated by two neurotransmitters, ATP and NA. VIP immunoreactivity has been demonstrated in cholinergic nerve supplying mammalian vas deferens. In cortex and hippocampus presence of VIP-containing neurons has been demonstrated. They are interneurons and show also GABA immunoreactivity.

We investigated the neuromodulatory effects of VIP on vegetative nervous systems in vas deferens in periphery and in cortex and hippocampus in the central nervous system. Our results showed that VIP (1 to 100 nM) inhibited, in a concentration-dependent manner, both components of neurogenically- evoked contractions in a vas deferens of guinea pig and rat *in vitro*. The effect of the peptide was more pronounced on the first components as compared to the second in guinea pig. VIP reduced the amplitude of ATP-induced contractions and stimulated NA-induced contractions in guinea pig vas deferens.

In *in vivo* experiments, VIP (0,01 to 100 nM) administered locally through the microdialysis membrane, increased the extracellular levels of ACh and reduced those of DA in rat cortex. In hippocampus VIP increased the extracellular levels of ACh, DA, NE and E.

**EFFECTS OF HISTAMINE AND THE SELECTIVE H₁ RECEPTOR AGONIST
TFMH ON THE ON AND OFF RESPONSES OF FROG ELECTRORETINOGRAM**

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Introduction: Histamine is a neurotransmitter of the retinopetal axons that originate from the tuberomammillary nucleus of the hypothalamus, but its role in visual information processing in the retina is still unknown. It has been shown that histamine influences in a different manner the activity of single retinal neurons, while no changes of the gross retinal electrical activity evaluated by electroretinogram (ERG) have been seen in knockout mice, which does not synthesize histamine. In the present work we investigated the effects of histamine and the selective H₁ receptor agonist 2-((3-Trifluoromethyl) phenyl) histamine (TFMH) upon the ON (b-wave) and OFF (d-wave) responses of frog ERG.

Methods: The experiments were carried out on dark adapted perfused frog (*Rana ridibunda*) eyecups, stimulated with intermittent diffuse white light with constant intensity. The effects of 5 μM histamine or 5 μM TFMH on the amplitude and time characteristics of the ERG b- and d-waves were followed for 25 minutes. In a control group the eyecups were perfused with Ringer solution only.

Results: Perfusion with 5 μM histamine caused a significant enhancement of the b- and d-wave amplitude in comparison with the corresponding values obtained in the control group. The effect developed within the first two minutes and remained stable until the end of the experiment. Histamine significantly shortened the implicit time of the both ERG waves. Perfusion with 5 μM TFMH also significantly increased the b- and d-wave amplitude. However, the effect on the amplitude of the ON response was smaller than that of histamine, while the effect on the OFF response was equally expressed. TFMH did not significantly change the time characteristics of the b-wave, while it shortened the implicit time of the d-wave.

Conclusion: Our results indicate that histamine has a significant role in visual information processing through the retinal ON and OFF channels and that a part of its action is mediated by H₁ receptors. Other types of histamine receptors are probably involved in its action on the ERG b-wave.

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METHODS FOR ARTERIAL STIFFNESS ASSESSMENT

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Arterial stiffness is an important marker for the assessment of cardiovascular risk, which can be measured noninvasively with different techniques. Carotid to femoral pulse wave velocity has emerged as the golden standard method for aortic pulse wave velocity evaluation.

By definition sphygmocardiography assesses the dynamic interaction between left ventricular pump function and the arterial system load. Accurate pressure recording by means of applanation tonometry from a peripheral location (e.g. the radial artery) and the use of a generalized transfer function derives the central aortic pressure waveform. Central arterial pressure waveform (at the level of the ascending aorta) is more informative than peripheral waveform since it represents the true load imposed on the left ventricle.

Pulse wave analysis (PWA) might be performed using the Sphygmocor device (AtCor Medical). Various indices can be extracted and assessed from the aortic pressure waveform: aortic systolic, diastolic, and mean blood pressure; central pulse pressure; aortic augmentation pressure and augmentation index; time to reflection; and Buckberg Index. Aforementioned indices are dependent on the velocity of pulse wave propagation, the amplitude of the reflected wave, the reflectance point, and the duration and pattern of ventricular ejection, especially with respect to changes in heart rate and ventricular contractility. In contrast to pulse wave velocity, which is a direct measure of arterial stiffness, central pressures and augmentation index are only indirect measures of arterial stiffness.

The hallmark of increased arterial stiffness is the augmentation of the central systolic peak pressure due to the increased pulse wave velocity and shortened return time for the reflected wave. These changes underlie the increased aortic pulse pressure and augmentation index as well. Monitoring of arterial stiffness progression in patients with hypertension, diabetes and/or metabolic syndrome provides more accurate data concerning the cardiovascular risk and prognosis, and the choice and efficiency of treatment.

ANANDAMIDE AND ITS INFLUENCE ON CNS

Irena Mihaylova

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Endocannabinoid system is composed by endocannabinoid receptors, their ligands and the proteins involved in the synthesis and the deactivation of the endocannabinoids. The last are known to influence a variety of physiological systems, including appetite, pain sensation, body temperature regulation, intraocular pressure, energy balance, metabolism, stress responses, motivation, memory and mood.

Essential endocannabinoid is anandamide. Its effects are due to not only the binding with anandamide's receptors but also to its interactions with a number of neuromodulators and hormones, which is the basis of many scientific studies. Here will be presented studies related to the relationship between anandamide and oxytocin as well as between anandamide and dopamine and the role of these interactions on the social activity of the individual and the pleasure center in the CNS.

The first study is composed by two parts. The first part shows the relationship between the levels of anandamide in the CNS and the social activity of the tested laboratory animals. Pharmacological stimulation of endocannabinoid signaling increases anandamide in the part of the brain responsible for the motivation and the sense of pleasure and leads to increased desire for contacts. When anandamide receptors are blocked, the pleasure of the social interaction decreases, which is a proof for anandamide influence on the social behavior. The second part reveals the role of oxytocin for the social interaction and its influence on the mobilization and production of anandamide. Their indicative role in the creating a sense of pleasure is the prevention of loss of satisfaction, blocking receptors for oxytocin by reducing the degradation of anandamide.

The second study illustrates the increase in dopamine levels in the CNS as result of the influence of anandamide and its stable metabolite methanandamide, which is associated with effects similar to those described above. Other effects of anandamide, such us increased appetite, are also described.

Keywords: endocannabinoid system, anandamide, oxytocin, center of pleasure

**CONSEQUENCES OF LONG-TERM TREATMENT WITH AGOMELATINE ON
DEPRESSIVE-LIKE BEHAVIOR AND NEUROBIOLOGICAL ABNORMALITIES
IN PINEALECTOMIZED RATS**

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Previous data have shown that the rat model of melatonin deficit can cause a number of neurobiological aberrations. The aim of the present study was to determine whether the antidepressant drug agomelatine, a MT1/MT2 melatonergic receptor agonist/5-HT_{2C} receptor antagonist is able to prevent some of the behavioral, biochemical and cellular abnormalities induced by pinealectomy.

The injection of agomelatine (40 mg/kg, i.p. for 5 weeks)/vehicle started after pinealectomy/sham procedure in Wistar rats. Animals were tested in different behavioral tests for depression during the period of agomelatine treatment.

The effect of agomelatine on KCl-evoked serotonin (5-HT) release from the hippocampus, the activity of the hypothalamic–pituitary–adrenal (HPA) axis and neuronal loss in pinealectomized rats were assessed.

Our results showed that agomelatine corrected a depressive-like behavior, alleviated the enhanced KCl-evoked 5-HT release in the hippocampus, recovered the suppressed negative feedback inhibition of HPA axis and exerted a neuroprotection in pinealectomized rats. Our findings suggest that pinealectomy can model melancholic depression disorder while the antidepressant action of agomelatine is associated with a correction of 5-HT release in the hippocampus, dysregulated HPA system and neuroprotection in limbic structures.

Key words: pinealectomy, agomelatine, depression, serotonin, HPA axis, neuronal loss

**AGGRAVATION OF DIABETES MELLITUS-INDUCED METABOLIC AND
BEHAVIORAL ALTERATIONS BY INTRACEREBROVENTRICULAR INFUSION
OF ANGIOTENSIN AT2 RECEPTOR AGONIST IN WISTAR RATS**

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Renin - Angiotensin System has an important role in the development of the pathological consequences of diabetes mellitus (DM). Recently, it was established that Angiotensin converting enzyme inhibitors and AT1 receptor blockers are capable to reduce insulin resistance and renal damage in people with DM and in rats with streptozotocin (STZ)-induced diabetes. AT2 receptor agonists also gained importance as a potential target for creating new antihypertensive and anti-inflammatory drugs. These data gives us a reason to study the effects of a selective AT2 agonist Novokinin on the development of DM. Experimental DM type 1 was induced by an injection of STZ (65 mg/kg, IP) in male Wistar rats adapted to metabolic cages. Motor activity and anxiety level were studied through “open field” and “elevated plus maze” tests.

Intracerebroventricularly (ICV) infusion of Novokinin in control rats significantly increased water and food consumption and diuresis accompanied with an initial decrease in weight gain. Symptoms of diabetes mellitus - polyuria, polydipsia and polyphagia were established in all rats injected with STZ, however ICV infusion with Novokinin augmented water intake and diuresis and decreased food intake in STZ-injected group. AT2 agonist significantly increased mortality rate in diabetic animals, decreased exploratory activity in a new environment (open field) and increased anxiety in aversive area (central in open field and open arms in elevated plus maze).

These data showed that activation of brain AT2 receptors aggravated some metabolic and behavioral consequences of DM type 1 in normotensive Wistar rats.

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