Assessment of the nitroglycerine influence on intracranial blood flow by imaging photoplethysmography in rats.

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Introduction. Migraine belongs to primary headaches and because of wide spreading and severity became important medical, social, and economic problem. The pathogenesis of migraine is still uncertain; however, the key element is an activation of trigemino-vascular system (TVS) - morpho-functional complex formed by trigeminal nerve and cranial vessels. Whereas existing methods of treatment are not effective enough, there is an unmet need in new therapy approaches and, therefore, it requires more detailed investigation of migraine pathophysiology. Various animal models are used for this purpose, particularly «nitroglycerine (NTG) model of migraine» in which NTG, being well-known headache provoker due to donation of nitrogen monoxide, plays a role of exogenic TVS activator. Against the background of an abundance of data about neuronal reactions induced by NTG, there is lack of information of its impact on intracranial, in particular, meningeal vessels, which is considered an omission due to the neuro-vascular nature of migraine. We recently demonstrated that imaging photoplethysmography (iPPG) is a reliable method to assess the dynamics of intracranial blood flow in different experimental conditions on rats. The aim of this study was to estimate the effects of systemic administration of NTG to iPPG-signals from meningeal vessels in closed cranial window (CCW) conditions.

Materials and methods. A series of experiments was performed on anesthetized (urethane + alpha-chloralose 800 mg/kg + 60 mg/kg, i.p. - ICN, USA) male Wistar rats (n = 13). Animal's trachea was intubated, left femoral artery and vein were cannulated, intraperitoneal catheter was installed. The head was fixed in stereotaxic apparatus and CCW was formed by thinning parietal bone to the state of membrane to visualize meningeal vessels. Steel needle electrodes were inserted into the muscle tissue of the rat limbs to record ECG. Myorelaxation was performed by pipecuronii bromide («Arduan», Hungary, 0,9 mg/kg, then 0,45 mg/kg, i.v.) and the rats were transferred to artificial pulmonary ventilation thereafter. Continuous recording of brain images through CCW was accomplished by a monochrome CMOS digital camera under brain illumination by incoherent green light (LEDs at the wavelength of 530 ± 25 nm). During each experiment, the vital parameters of the animal were monitored (arterial blood pressure (ABP), heart rate, end-tidal CO_2, body temperature). Simultaneous ECG monitoring was provided by a digital electrocardiograph synchronized with the camera. At the beginning of each experiment two 30 sec video were recorded with 15 minutes interval as a baseline. Next, a rat received NTG (10 mg/kg, i.p.), that was immediately followed by video recording of intracranial vessels state. Then recordings repeated every 15 minutes during 150 minutes. The experimental data were analyzed using an original software implemented in the Matlab platform.

Results. We have found that one of the PPG-waveform parameters, namely, an amplitude of the pulsatile component (APC), which characterizes an instant change in vascular tone of the intracranial arteries, increased in one subgroup (n=7) and decreased in another (n=6) in response to systemic administration of NTG. Such divergency gradually progressed in time and achieved the maximum state about 1.5 – 2 hours after drug infusion. At the same time, significant decrease in mean ABP was observed in all 13 animals immediately after NTG injection.

Conclusion. In this study we have shown for the first time that NTG can cause diametrically opposite APC changes. There are reasons to assume that divergent APC trajectories display local intracranial vascular events that hardly might be a result of systemic hemodynamic changes since ABP level significantly and steadily decreased directly after NTG administration in all cases. Apparently, such APC reactions demonstrate oppositely directed changes in tone of dural and pial small arteries, and arterioles in PPG-transillumination zone. Despite the fact that NTG is well known as a vasodilator, our study has shown that it can cause either vasodilation or vasoconstriction, at least in investigated region of biological tissue. Therefore, we have documented two types of vasomotor response to NTG by using iPPG: constricting and dilating of blood vessels, which is generally consistent with earlier sporadic studies of other authors who used different optical methods. Dilation of meningeal arterioles and venules can be explained both by direct action of NTG to the vascular wall and progressive increasing of antidromal activity of trigeminal afferents resulting in releasing from their perivascular endings of vasoactive neuropeptides, in particular, CGRP - crucial neurochemical compound of migraine pathogenesis. Constriction of

meningeal microvessels can be explained by the hypothesis that exogenous NO-donors initiate dilation of relatively large arteries and compensatory constriction of small-caliber vessels which lead to tissue hypoxia and activation of cranial nociceptors. At the same time both mechanisms can lead to headache and possibly might be altered by anti-migraine interventions, which is an extensive field for scientific research.

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