In vivo studies on the effect of neuropeptides on rat intracranial arteries

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ABSTRACT

The present PhD study was performed at the Department of Neurology in locations of Glostrup Research Institute, Glostrup Hospital.

Headache disorders, which are on par with other chronic conditions, have an enormous impact on the quality of patients' life and on the society. A migraine attack may be caused by activation of perivascular trigeminal nerves innervating intra- and extracranial vasculature together with sympathetic- and parasympathetic nerves. Upon stimulation of the nerve endings various peptides are released, such as calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP), resulting in vasodilatation.

Previous human studies described the putative migraine inducing effect of CGRP, adrenomedullin (ADM), VIP and PACAP. The PhD project addresses the same peptides, putative antagonists and CGRP scavengers in an animal model and describes the involvement of the peptides in dilatation of rat intracranial arteries. In order to delineate their role the peptides are examined in the in vivo genuine- and improved closed cranial window model, which during i.v. and intracarotid (i.c.) infusion of drugs, respectively, allows visualization of the intracranial arteries and measurements of blood pressure. The improved model is developed to explore the possibility of i.c. administration. Thus, drop in blood pressure, which contributes to the autoregulatory mechanisms and use of high drug dosages are avoided. Also, mRNA expression and protein localization in rat middle meningeal artery (MMA) was investigated for diverse receptors mediating various peptides' effect.

The results demonstrate effective CGRP- and ADM-receptor antagonists against ADM induced responses on dural artery whereas antagonists against PAC and VPAC agonists showed weak responses. Presence of PAC and VPAC receptors on rat MMA are revealed through expression of mRNA and protein localization. The CGRP scavengers are effective in significant blockage of i.v. CGRP induced dural dilatation, while effect on pial artery is inhibited only after RNA-Spiegelmer infusion. No effect of the scavengers on CGRP released by electrical stimulation is observed. I.c. infusion remarkably demonstrates increased efficacy of all compounds, except ADM, without affecting blood pressure, as compared with i.v. infusion. Thus, linking the present animal studies with previous human studies it is shown that CGRP and ADM exert vasodilatory responses in rat intracranial vasculature, however only CGRP elicits migraine attacks in humans. Similarly, both VIP and PACAP induce dilatation in rat dural arteries, but in human subjects just PACAP has shown to induce headache/migraine.

The improved model is a step forward in the development of an experimental animal model which offers a resemblance of the physiological conditions in migraineurs during an attack.