Calcitonin gene related peptide induced changes of internal homeostatic body model; translation from TCD studies

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Abstract:

Intravenously introduced Calcitonin gene-related peptide (αCGRP) induces CGRP- induced headache (CGRP-IH) as well cerebral and systemic hemodynamic changes detectable with transcranial Doppler sonography (TCD). Therefore, elevation of CGRP in the systemic blood can evoked headache in predisposed subjects, especially in migrainours. Thus, increase of CGRP during migraine episode might be source of nociceptive sensation. Following predictive coding and interoception, this could induce painful prediction error and updates the internal homeostatic model, inducing headache, and turn subject into no fit to purpose mode which leads to disability during migraine episode. The CGRP provocation might be used for discrimination of CGRP sensitive from insensitive migraine using TCD and predict CGRP antagonism effect in migraine treatment.

Keywords: Calcitonin gene-related peptide; headache, migaine, transcranial Doppler sonography

Sažetak:

Peptidi povezani s genom kalcitonina inducirali su promjene unutarnjeg homeostatskog tjelesnog modela - translacija iz TCD studija

Intravenozno uveden peptid povezan s genom kalcitonina (αCGRP) inducira CGRP-induciranu glavobolju (CGRP-IH), kao i cerebralne i sistemske hemodinamske promjene koje se mogu otkriti transkranijalnom Doppler sonografijom (TCD). Stoga, povišenje CGRP-a u sistemskoj krvi može izazvati glavobolju kod predisponiranih ispitanika, osobito kod migrena. Stoga povećanje CGRP-a tijekom epizode migrene može biti izvor nociceptivnog osjeta. Nakon prediktivnog kodiranja i interocepcije, to bi moglo izazvati bolnu pogrešku predviđanja i ažurirati interni homeostatski model, izazivajući glavobolju i pretvoriti subjekta u način koji ne odgovara svrsi što dovodi do invaliditeta tijekom epizode migrene. CGRP provokacija se može koristiti za razlikovanje CGRP osjetljivog od neosjetljive migrene korištenjem TCD i predvidjeti učinak antagonizma CGRP u liječenju migrene.

Ključne riječi: peptid povezan s genom kalcitonina, glavobolja, migrena, transkranijalni Doppler sonografija

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Introduction

Migraine is an important neurological disease, affecting more than 10% of the population and causing significant disability. In recent years, it has been found that Calcitonin gene-related peptide (CGRP) is important for the development of migraine and CGRP antagonism can be used to treat and cope migraine. Sensitization of trigeminal ganglia appears to be initial even which lead to the most disabling phase of migraine episode, headache. According to predictive coding and interoception theories, the nociceptive drive after sensitization of trigeminal ganglia is increased which lead to error detection in trigemino-cervical complex (TCC) and updating of internal body model which produce headache which switch to mode no fit to purpose. This cause transitory disability of migrainours. Thus, CGRP could play important role in formatting of internal body homeostatic model.

Migraine and CGRP

Migraine is a common, disabling, neurovascular disorder. In Europe, the prevalence of migraine is estimated at around 10%. It mainly affects the population between the ages of 20 and 50. During a migraine episode, as many as 50% of patients are unable to work. Migraine therefore has a significant impact on work capacity as well as on the quality of life and as such represents a major socio-economic burden (1). Migraine is defined by clinically characteristic migraine attacks, among which there are asymptomatic periods of varying lengths. The central symptom of a migraine episode is a migraine headache, which is often unilateral, moderate to severe, throbbing, and lasts from a few hours to a few days. Basically, migraine episode is clinical correlate of transient central sensitization of nervous system.

The pathophysiology of migraine has not been fully elucidated to date. The findings of clinical trials suggest that the neuropeptide CGRP plays an important role in the pathophysiology of migraine. It is involved in the mechanisms of onset, persistence and deepening of migraine headaches (2, 3). Elevated serum CGRP levels in the external jugular vein have been found to occur during a migraine attack (5,6). In addition, serum interictal CGRP levels are higher in patients with chronic migraine than in patients with episodic migraine (6). Migraine medications such as onabotualinumtoxin A and sumatriptan reduce serum CGRP levels. (7,8). The importance of newer anti-CGRP target drugs for both acute and preventive treatment of migraine also speaks in favor of the importance of CGRP. CGRP receptor antagonists have been shown to be effective in the treatment of acute migraine headaches. Monoclonal antibodies against CGRP and CGRP receptors have been shown to be effective in the preventive treatment of episodic and chronic migraines. They significantly reduce the number of headache days and the use of drugs to acutely relieve migraine headaches (9). Current data indicate that CGRP target is important in migraine although exact mechanism on its action is still unclear. There are still many questions regarding anti-CGRP monoclonal antibodies since they cannot pass blood-brain barrier. There is still uncertainly whether plasma concentration (anti-CGRP mAb) of CGRP is elevated in chronic and episodic migraine. Nevertheless, anti-CGRP mAb could produce its effects through it action as scavenger of CGRP in human blood.

CGRP in human

CGRP is a neuropeptide composed of a sequence of 37 amino acids. It is formed in the nervous system in the process of alternative expression of mRNA for calcitonin. Two isoforms are known in humans: αCGRP, which is found in the peripheral and central nerves, and ßCGRP, which is found primarily in the enteric nervous system (2). CGRP is a potent vasodilator. It works by binding to the CGRP receptor, which consists of three components. CGRP and its receptor components are demonstrated in myelinated and unmylated nerve fibers involved in pain transmission, the trigeminal ganglion, its satellite glial cells, and many other central (10,11,12) nervous system structures such as the cerebral cortex, thalamus, hypothalamus, cerebellum. The pharmacokinetics of exogenous CGRP was investigated in animal and human studies. It was found that CGRP pharmacokinetics follows the first order with a plateau reached within one hour. The elimination of CGRP shows a two-phase, bi-exponential decay (13). The half-life was found to be for the first phase, 6.9 minutes, and for the second one, 26.4 minutes, which supports a modulatory role of CGRP. Indeed, CGRP level in human blood shows high individual variance and it is released by CGRP afferents, majority of which form C-fibers but a minor proportion also Aδ-fibers, have nociceptive functions and are usually co-expressing transient receptor potential (TRP) cation channels of the vanilloid 1 and ankyrin type (TRPV1 and TRPA1) (14). In peripheral blood, CGRP occurs in pico-gram levels. Thus, CGRP is permanently existing peptide in human circulation in might be increase in chronic migraine.

Cerebrovascular reactivity to CGRP (CVR-CGRP)

CGRP is a potent vasodilator of intracranial arteries. Perivascular administered CGRP induces dose dependent dilatation of many cerebral arteries. In animal models, it induces vasodilation of middle cerebral artery (MCA), basilar artery, and cortical arteries. (15,16). In vitro studies on the response of human intracranial arteries to CGRP have shown that CGRP induces dose-dependent vasodilation of human pial arteries (17).

Cerebrovascular reactivity to intravenously administer CGRP (CVR-CGRP) of anterior and posterior cerebral circulation CGRP has been elucidated. Vasodilation of the middle meningeal artery and the superficial temporal artery has been demonstrated (18,19). The results of a small number of studies on CVR-CGRP of MCA were not consistent. In patients with aura free migraine and in migraine free subjects, intravenous infusion

of CGRP induces vasodilation of MCA (19, 20). In contrast, the Asghar study did not confirm that CGRP induces vasodilation of MCA in healthy subjects (21). Recently, Visočnik et al. using Transcranial Doppler (TCD) (23) undoubtedly showed that αCGRP could induce vasodilatation of MCA probably via activation of TCC. In addition, they reported decrease of end-tidal carbon dioxide (Et-CO_2) which might reflect a compensatory decrease in arterial partial pressure of carbon dioxide (pCO_2), which underlies the normalization of cerebral blood flow during CGRP stimulation. In addition, the authors (23) found that an intravenous αCGRP infusion might induce vasodilatation not only MCA but posterior cerebral artery (PCA) as well. Furthermore, CGRP produces systemic effects with a significant decrease of mean arterial pressure (MAP) and increase of heart rate (HR). They explained Et-CO2 decrease as compensatory mechanism in preserving cerebral blood flow and intracranial pressure during CGRP stimulation. In patient with migraine CVR-CGRP is significantly enhanced and is associated with CGRP-induced headache (CGRP-IH) (22). This might indicate that patients with migraine are more prone to sensitization. Therefore, studies of CVR-CGRP suggest vasodilatatory effects of αCGRP in human blood on cerebral and systemic vessels.

Methodology for CVR-CGRP

The investigation of CVR-CGRP in our laboratory (24) is conducted a quiet room under constant conditions. During the experiment, the participants are resting in a supine position. The experiment consists of a 10 min baseline period, a 20 min period during which an intravenous infusion of αCGRP 1.5mcg/min (Calbiochem, Merck4 Biosciences, Darmstadt, Germany) is given and a 10 min period after the end of the application of αCGRP. The incidence of CGRP-IH is recorded during within 1 hour of the experiment (immediate CGRP-induced headache) and within the next 12 hours after the experiment (delayed CGRP-induced headache). Visual analog scale is used to measure intensity of CGRP-IH.

TCD with 2 MHz ultrasound probes is applied to measure mean flow velocity (vm) in left MCA and right PCA through the transtemporal acoustic windows. The signals of the MCA and PCA were defined according to the direction of the blood flow, typical depth of the signal and the response to compression. A mechanical probe holder is used to ensure a constant probe position. During the entire experiment MAP and HR are continuously measured using non-invasive plethysmography (Colin 7000, 12 Komaki-City, Japan). The Et-CO_2 is measured by a ventilation mask and an infrared capnograph (Capnograph, Model 9004, Smith medical, USA) using the standard protocol. The capnograph is connected to a computer. Et-CO_2 signals were recorded on the same time scale as other variables.

TCD Multi-Dop X4 software (DWL, Sipplingen, Germany) is used to define mean values of vmMCA, vmPCA, MAP, HR and Et-CO_2 during 5 min intervals: one interval during the baseline period (5-10 min of the experiment-measurement), two intervals during the αCGRP infusion (15-20 min and 25-30 min of the experiment) and one interval after the αCGRP infusion (35-40 min of the experiment). The mean vm MCA is calculated for each 5-min interval using the following equation:

$vm = \int vdt / (t_0 - t_5)$.

The mean values of other variables (MAP, HR, and Et-CO_2) are also calculated for the same time intervals as vmMCA and vmPCA using TCD software. We determine calculated responses to αCGRP as the differences between measuring points and responses are determined.

CGRP induced headache (CGRP-IH)

Cerebral hemodynamics is supposed to associate with migraine headache. CGRP seems to be key signaling molecule in connecting cerebral arteries with nervous system. The changes in pial cerebral arteries may be source of nociceptive signals to central nervous system. Although exact mechanism is elusive, it is well known that parenteral administration of CGRP induce CGRP-IH and even migraine like attacks in migraineurs (25). Latter study found (26) excellent response on erenumab in patients, in whom CGRP-IH with migraine futures has been evoked. Visočnik et al. established relationships between hemodynamic changes of arterial velocity changes in MCA, PCA and CGRP-IH (22).

According to concept to distal and proximal segments in cerebral circulation (27), CGRP could dilate both proximal and distal segments of cerebral circulation and consequently lower overall cerebral arterial resistance. The response to increase cerebral blood flow in order to normalize cerebral blood flow could be mediated through lowering of pCO_2 which acts on distal cerebral segment and increase cerebral resistance due to CGRP provocation (22). Therefore, decrease of vm MCA and vm PCA could be solely due to vasodilatation of MCA and PCA during normalization of cerebral blood flow after pCO_2 lowering. This finding suggests CGRP causation of CGRP-IH probably due to direct effect on hemodynamics and consequent nociception related to it.

Interoception and internal body homeostatic model

According to the predictive coding concept, human form internal models of the homeostatic states through experiences. This represents priors under the principles of predictive coding and Bayesian inference. It is predicted that central nervous system builds internal homeostatic model though the process of learning which represents template for further incoming homeostatic information. Incoming sensory data from periphery are adjusted with prediction based on current internal homeostatic model in prediction error units at different levels of central nervous system (28). We believe that the lowest prediction error unit is represented by TCC. The higher level is located in modulatory pain

system, brainstem including periaqueductal gray (PAG) with descending pathways to TCC. The highest level consists of cerebral cortex and other brain structures. Thus, central nervous system including brain, brain stem and spine represent material base for again and again changing internal homeostatic model.
In described system, the sensory input is represented by trigeminal afferents which contain CGRP. In addition, CGRP is located in peripheral as well in central nervous system. When αCGRP is delivered intravenously, the CGRP in the blood increases in accordance with pharmacokinetic principles. Thus, CGRP in systemic blood might represent nociceptive stimuli, which can induce nociceptive sensation, when the human central nervous system does not predict painful expectation. In TCC, the error unit of central nervous system, prediction error is detected and sent via ascending pathways to PAG and further to cerebral cortex. In this context, predictive error, carrying painful information, updates the internal model in set the subject to not fit purpose mode. In other words, increase CGRP in the systemic blood evokes CGRP-IH and disabled the subject. It seems, that similar situation occurs during migraine episode leading to disability.

Conclusion

TCD studies of CVR-CGRP suggested that exogenous αCGRP induces vasodilatation of cerebral vessels. This could be induced directly through peripheral access or indirectly via sensitization of TCC. Nevertheless, the CGRP-IH can serve as clinical model of migraine episode. In addition, cerebral vascular response to αCGRP can be utilized to discriminate CGRP sensitive from insensitive migraine and other headaches. Therefore, we could predict efficiency of anti-CGRP therapy in migrainours.

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