CGRP-induced headache and hemodynamic response for prediction of therapy based on CGRP antagonism

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Abstract:

Migraine is increasingly recognized as a disorder of the calcitonin gene-related peptide (CGRP) pathway. However, other factors are involved in migraine pathophysiology such as vasoactive intestinal peptide (VIP) and PACAP-38. Indeed, the CGRP-test can discriminate migraine from non-migraine and other non-CGRP induced migraine using CGRP-induced headache (CGRP-IH) and cerebral hemodynamic changes. Recent studies support the evidence of CGRP susceptible migraine prone to CGRP antagonism. Therefore, the CGRP-test may have an important role in therapeutic decisions regarding anti-CGRP monoclonal antibodies and gepants. This may improve the clinical effects of CGRP antagonism in migraine patients and increase therapeutic adherence. From the perspective of pain medicine may improve placebo response which can enhance favourable therapeutic outcomes.

Keywords: migraine, calcitonin gene-related peptide (CGRP), transcranial Doppler (TCD), migraine susceptible to CGRP

Sažetak:

CGRP-om inducirana glavobolja i hemodinamski odgovor kao predskazatelj terapije zasovane na CGRP antagonizmu

Migrene su sve više prepoznate kao poremećaj puta kalcitonin-gen-povezanog peptida (CGRP). Međutim, drugi čimbenici su uključeni u patofiziologiju migrena, poput vazoaktivnog crijevnog peptida (VIP) i PACAP-38. CGRP test može razlikovati migrenu od nemigrenozne glavobolje i drugih migrena koje nisu inducirane CGRP-om pomoću CGRP-om inducirane glavobolje (CGRP-IH) i cerebralnih hemodinamskih promjena. Nedavne studije podržavaju dokaze CGRP osjetljivih migrena podložnih antognizmu CGRP-a. Stoga, CGRP test može imati važnu ulogu u terapijskim odlukama vezanih za anti-CGRP monoklonska protutijela i gepante. Ovaj test bi mogao poboljšati kliničke učinke CGRP antagonizma u bolesnika s migrenom i povećati adherenciju na terapiju. Iz perspektive analgezije, mogao bi biti poboljšan placebo odgovor koji može pospiješiti povoljne terapijske ishode.

Ključne riječi: migrena, kalcitonin-gen povezani peptid (CGRP), transkranijalni dopler, migrena podložna CGRP-u

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Introduction

Understanding migraine through calcitonin gene-related peptide represents (CGRP) (1) a great step in our knowledge of functional disorders in pain medicine. Although, the research goes back to the eighties of the last century, clinical applicability has reached in recent years. The role of CGRP in human physiology is not clearly explained. It is supposed that is important in the dangerous physiologic states such as ischemia of the central nervous system. In the peripheral nervous system, it contributes to neurogenic inflammation to decrease damage and initiate healing of the tissue. Nevertheless, CGRP consists of a defense response to actual or potential damage. From the perspective of migraine, we can consider the CGRP as the part of potential damage response because our brain predicts future unsafe situations and can form the response to virtual brain lesions leading to migraine attacks.

Exogenous CGRP

CGRP is an endogenous signaling molecule formed in the neurons in the body's periphery as well as in the central nervous system. It could be detected in the peripheral blood in pico levels. It is elevated after migraine attack and chronic migraine (2, 3). Therefore, we can consider that intracranial structures are an important source of CGRP. It is believed that the trigeminovascular system is an important generator of CGRP. According to current knowledge, the nociceptive activity in migraine originates from a complex consisting of trigeminal ganglia, its peripheral projections, and arteries innervated with them. It is still a mystery what is a primer for increased activity of the trigeminovascular system. Using the human model of migraine (4), CGRP was applied in the form of intravenous infusion. They established the clinical and hemodynamic responses to exogenous CGRP. Indeed, not all migraineurs show responses to exogenous CGRP. It is known that CGRP is not the only agent that can trigger migraine attacks. In a human model, another molecule such as pituitary adenylate cyclase-activating peptide-38 (PACAP-38) and vasoactive intestinal polypeptide (VIP) can evoke the migraine attack (5). This indicates migraine as a heterogeneous and multifactorial brain disorder with different pathways for increasing trigeminovascular activity. Thus, the response to exogenous CGRP could be useful for determining the therapeutic effect of CGRP antagonism, such as treatment with anti-CGRP monoclonal antibodies.

CGRP-test

CGRP-test appears to discriminate migraine from non-migraine (6). The test includes the clinical response of CGRP-induced headache (CGRP-IH) and hemodynamic responses related to cerebral vascular and systemic cardiovascular responses detected by polymodal monitoring. CGRP-IH is a phenomenon, subject to neurocognitive features of individuals and could be independent of biological reactions to CGRP. On the other hand, hemodynamic responses associated with CGRP should be more biological, specific to the CGRP mechanism. However, the discriminative power of hemodynamic variables such as arterial velocity in a middle cerebral artery (vm MCA) and posterior cerebral arteries (vm PCA) appears to be low (6). Indeed, during the CGRP test, End-tidal carbon dioxide (Et-CO_2), besides vm in MCA in PCA showed a significant response to CGRP. Thus, the combination of hemodynamic response to CGRP could be useful for testing the susceptibility of migraine to CGRP antagonism.

Methodology for CGRP testing

The methods used to determine suitability to CGRP-antagonism were described in detail in a publication of our research group (6), Therefore, only the essentials are listed here. For cerebral circulation variables, TCD sonography with 2 MHz probes applies to measure the vm MCA through the left and vm PCA through the right temporal acoustic window. During the experiment, the mean blood pressure (MAP) and heart rate (HR) are continuously measured using noninvasive plethysmography. An infrared capnograph measures the Et-CO_2. All variables are recorded simultaneously, enabling to comparison of the signals and conducting correlations between them. This is a multichannel recording technology developed in our laboratory (7). The experiment lasts 40 min, consisting of a 10-minute baseline period, a 20-minute period during which an intravenous infusion of exogenous CGRP is administered, and 10 minutes after the end of the application of CGRP. The average values of all parameters (vm MCA and vm PCA, MAP, HR, and Et-CO_2) were calculated during 5-minute intervals.

Important findings of CGRP-test

CGRP-test produces CGRP-induced headache (CGRP-IH) in migraineurs and non-migraineurs. However, the migranours have a significantly higher proportion of CGRP-IH. This means that CGRP-IH is not specific to migraines, the CGRP does not induce CGRP-IH in every patient with a migraine. CGRP-IH is supposed to be a homeostatic feeling based on the neurocognitive process of each individual. From this perspective, CGRP-IH is dependent on multiple sensory inputs and internal states related to previous experiences. In addition, beliefs and expectations concerning nocebo or placebo may be influencial.

Biological response to CGRP-test including cerebral and systemic hemodynamic alternations during CGRP infusion. The main finding of the study was a significant decrease of vm MCA and vm PCA during the exogenous CGRP infusion (6). This is explained by proximal arterial vasodilatation and drop of vm because of constant cerebral blood flow during CGRP infusion. The constancy of cerebral blood flow is provided by an additional drop of Et-CO_2 (8). According to the segmental concept of cerebral vasculature

regulation (9), the distal segment including cerebral arterioles and microcirculation compensates for vasodilatation on a proximal part. Thus, exogenous CGRP induces cerebral vasodilatation of the proximal segment which is evident from experimental studies, (10). From the physiology of cerebral circulation, It is known that partial carbon dioxide in arterial blood has a potent vasoconstrictor effect on cerebral circulation, acting predominantly on the distal segment. That's why we can consider a change of Et-CO_2 after CGRP infusion as a compensatory response.

On the other side, an enhanced response of vm MCA is observed in migraine with a positive relationship between vm MCA responses and migraine (11). According to the previous explanation, hemodynamic changes in cerebral circulation after CGRP infusion are attributed to an enhanced vasodilatation of proximal large arteries in migraine (12). Thus, the vm MCA can be used for discrimination of migranous susceptible to CGRP from others, migranours and non-migranours.

Regarding systemic variables such as mean arterial pressure (MAP) and heart rate (HR). intravenous infusion of exogenous CGRP significantly decreases MAP. The maximal decrease of MAP at the end of the infusion. Changes in HR are significant and in the opposite direction to the changes in MAP (13). However, the study concluded that CGRP does not have direct significant effects on MAP in migraine (11). This is by the finding that blocking CGRP does not affect systemic blood pressure in healthy volunteers (14). In addition, associations were found between MAP and vm MCA, as well as between MAP and vm PCA, which indicates uncoupling between cerebral flow and systemic arterial pressure and therefore normal regulation of cerebral blood flow during CGRP stimulation. Accordingly, MAP and HR can not discriminate between migranours who have specific responses to CGRP and others.

For the reasons described in previous paragraphs both, vm MCA and Et-CO2 can be used as discriminatory factors. In addition, if we use them together, we can get a stronger discriminator and predict the migraineurs susceptible to CGRP antagonism. For this reason, we introduced the product of vm MCA and Et-CO2 to augment CGRP effects on cerebral circulation and use it for discriminative factors. Analysis of ROC curves for the product vm MCA and Et-CO2 showed a significant area under the curve of the product migraineurs and non-migraineurs (15). Therefore, hemodynamic parameters of CGRP effects on cerebral circulation might be used to accurately discriminate migraine susceptible to CGRP from non-susceptible CGRP migraineurs and non-migraineurs. Therefore, hemodynamic changes during CGRP provocation might predict the efficiency of CGRP antagonism. CGRP-IH seems to be affected by non-nociceptive, subjective factors. However, some authors proposed CGRP-IH as a test for predicting response to anti-CGRP mAb (16), but it has not been tested yet. Nevertheless, the product of vm MCA and Et-CO2 appears promising discriminator with better sensitivity and specificity compared to CGRP-IH.

Other possible discriminants for migraine

The current concept considers trigeminovascular reflex (TVR) with CGRP release should be the fundamental generator of migraine headache and source of central sensitization of brain structures. According to this concept, CGRP in plasma should be increased even in the interictal period as was found in chronic migraine (2). On the other hand, increased levels of vasoactive intestinal peptide (VIP) in addition to CGRP were found elevated in plasma interictally (17) It is attributed to activation of not only sensory and parasympathetic arms of the TVS. The infusion of VIP provoked migraine (18), but the effect on cerebral and systemic hemodynamic factors is not known. In addition, intravenous infusions of the neuropeptide PACAP-38 induced delayed migraine-like headaches (19). Nevertheless, the hemodynamic effect of PACAP-38 is not known. Thus, the CGRP mechanism is neither sufficient nor necessary to evoke migraine. Blocking CGRP pathways seems not to be successful in every migraine. This supports the concept of non-CGRP and CGRP susceptible migraine phenotype as suggested previously (20). Accordingly, PACAP-38 and VIP could be useful discriminators for other than CGRP migraine types.

Conclusions

In conclusion, our studies showed that hemodynamic changes during CGRP provocation might predict the efficiency of CGRP antagonism. CGRP-IH seems to be affected by non-nociceptive factors. However, some authors proposed CGRP-IH as a test for predicting response to anti-CGRP mAb (20), but it has not been tested yet. Nevertheless, the product vm MCA and Et-CO_2 appears as promising, objective discriminator with better sensitivity and specificity compared to CGRP-IH for migraine susceptible to CGRP.

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