NEW MOLECULES USEFUL IN THE MIGRAINE TREATMENT

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Abstract: Migraine is a neurovascular condition characterized by episodes of severe headache with inter-individual variability. Inflammation of neurogenic origin contributes to the mechanism of occurrence of migraine and other primary headaches. Neurovascular headache is a condition in which neural events have as a result dilation of blood vessels and the appearance of painful sensation. CGRP (calcitonin-gene-related peptide) is a neuropeptide widespread both in the central and peripheral nervous system, being one of the most potent vasodilator substances with important role in controlling blood pressure in both normal and abnormal conditions. The releasing of perivascular peptides relaxes cerebral arteries while stimulating cAMP accumulation or release of EDRF (endothelium derived relaxing factor). An alternative to acute treatment of migraine used so far is the CGRP receptor blockade with selective antagonists. They represent potential therapeutic molecules with superior advantages to triptans and a longer duration of action.

INTRODUCTION

Primary headache include migraine, tension-type and the cluster type headache and can be defined as independent diseases which are not caused by other diseases or trauma.
Migraine is a neurovascular disorder with a high prevalence which is characterized by severe headache, unilateral, pulsating type associated with anorexia, nausea, vomiting, phono/photophobia and in some cases of diarrhea (Goadsby P. et al., 2002).
The mechanism of headaches appearance consist in activation of nociceptors, nerve endings located in the wall of intracranial blood vessels, which respond by antidromic release of vasoactive neuronal messengers (the main source of pain in headache). The nociceptors are in connection with second-order neurons in the trigeminal sensory complex nuclei in the brainstem and upper cervical spine. Local or antidromic stimulation of sensory nerve endings causes dilation of the peripheral blood vessels via substance P and of the isomer peptide corresponding to calcitonin gene (CGRP - calcitonin gene related peptide) from trigeminovascular system in humans.
Recent theories indicate that an additional component of neurogenic inflammation, neurogenic vasodilation mediated by CGRP plays an important role in the pathogenesis of migraine. Neurogenic vasodilation, mediated by nociceptors activation from the trigeminal C fibers (depolarization) or by agents that induce migraine attacks is completely abolished by CGRP receptor antagonists (Goadsby P. et al. 1988).

MIGRAINE MANAGEMENT

Antimigrain treatment consists in the usage of two large classes of compounds that concern even the crisis treatment or the background treatment designed for the interval between the crises. The first category of drugs is designed for the most of the migraineurs, while the second category is used by a narrower category. Thus, the substances that have proven the efficacy in migraine crisis are:

- nonspecific treatments: antalgic drugs and NSAIDs (nonsteroidal antiinflamatory drugs)
- specific treatments: triptans and ergot derivatives.

Other substances, such as caffeine, antiemetic drugs and psychotropic substances have proven useful as adjuvants (Massion H. 2010).
Specific antimigraine compounds, including older generations of ergot derivatives and recently triptans inhibits sensory neuropeptide release from trigeminal neurons. (Figure 1).

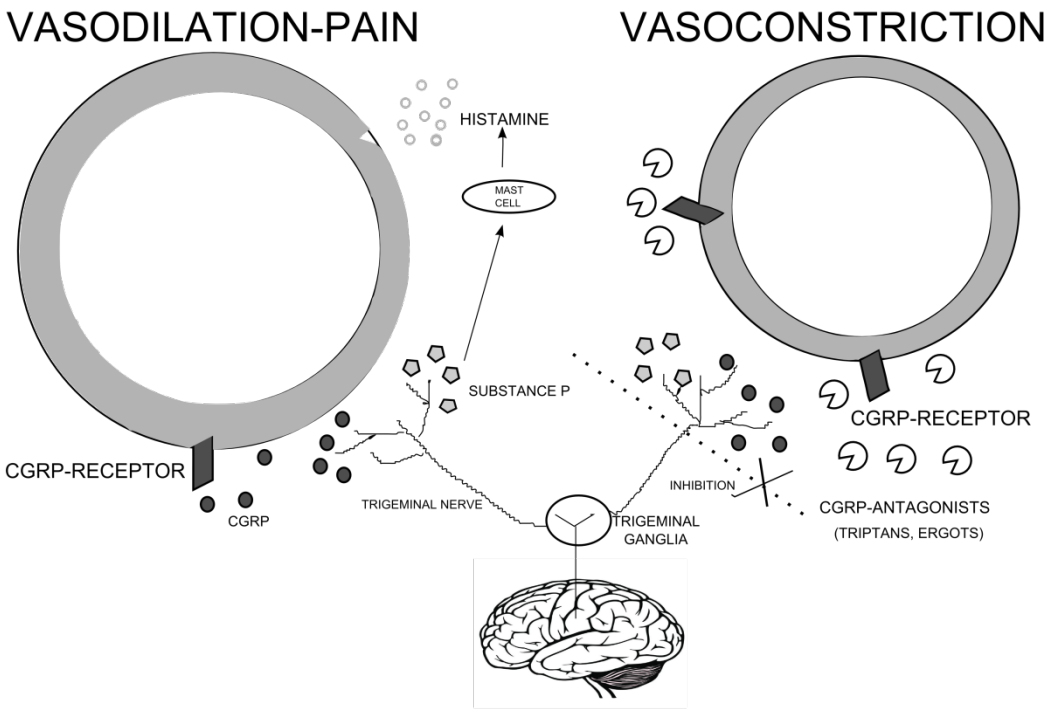

Figure 1. The action of CGRP antagonists

NO donors, who are known to be inducers of migraine attacks, release CGRP from the trigeminal nerve fibers. It was demonstrated that infusion of CGRP in volunteers can induce to a significant proportion of migraine patients, along with a number of moderate cardiovascular effects (hypotension and tachycardia), the emergence of a migraine type headache (Benemei S. et al. 2009).

Among the drugs used in migraine attacks, triptans represented a big step forward with effects that have greatly improved the lives of patients but their side effects, vasoconstrictor type, limit a lot their usage in patients with multiple vascular risk factors. (Dahlhof C. 2002).

Despite major therapeutic advances represented by triptans, there are some patients who do not respond in crisis to any treatment or do not tolerate it. These patients should benefit in future of new therapies, such as currently open perspectives for the development of a new class of drugs, the CGRP receptor antagonists.

CGRP (CALCITONIN GENE RELATED PEPTIDE)

Calcitonin gene encodes two different forms of mRNA (α-CGRP and β-CGRP) depending on the anatomical location. While transcription product of the calcitonin gene predominates in the thyroid, α-CGRP prevails in nerve tissue, these being a key molecule in the occurrence of headaches. It was emphasized also a second form, β-CGRP which is expressed in the intestine and internal organs. In humans, these two forms differ in their structure by three amino acids, but have similar effects on blood vessels motricity (both forms are powerful natural vasodilators) (Mulderry P.K. et al 1988).

The peptides of this family which includes adrenomedullin, amylin and calcitonin possess various biological functions, both at the CNS level and the peripheral one.

CGRP is a neuropeptide consisting of 37 amino acids present in the central and peripheral nervous systems and is often co-located with other peptides in the of the C type nervous fibers. CGRP is a potent vasodilator although the role it plays in the cardiovascular system remains incomplete known. It is known, however, that on the peripheral blood vessels act on smooth muscle cells, causing myorelaxation (non-endothelial mechanism) by activating adenylate cyclase (Quayle J.M et al., 1994).

The releasing of perivascular peptides relaxes cerebral arteries in the same time with stimulation of cAMP accumulation or releasing of EDRF (*endothelium derived relaxing factor*). Clinical and experimental studies have shown that injection of CGRP is responsible for inducing migraine headache (in migraine sufferer subjects).

CGRP RECEPTORS

CGRP receptor family shows a great complexity because their activity is regulated by receptor activity modifying protein, RAMP (*receptor activity-modifying protein*) and RAMP1 type is a compulsory subunit of CGRP receptors, being involved in determining their functional phenotype. High levels of RAMP-1 may sensitize certain individuals to the action of CGRP in migraine (Zhang Z.et al., 2007). For the beginning, CGRP receptors have been divided into two subclasses, CGRP-1 and CGRP-2, but recently is a tendency towards accepting a single type of receptor, namely CGRP (Hay D.L. et al., 2008).

The mRNA for CGRP receptor is expressed throughout the human intracranial arteries. CGRP functional receptors are located in the vascular smooth muscle cells of cranial arteries in particular, this being supported by the fact that in the cerebral veins territory CGRP response is very weak (Petersen K.A. et al. 2005). The basic mechanism of vascular headache involves CGRP receptor components present in brain and middle meningeal arteries. Thus, it was revealed that these arteries with cerebral capillaries express mRNA for RAMP-1.3 (Edvinsson L. et al. 2010). Induced vascular biological action in response to the activation of CGRP receptors is mediated by an increase of the intracellular levels of the second messenger cAMP (Benemei S. et al., 2007).

The answer of the muscular wall of various cranial blood vessels to stimulation of CGRP receptors is different. Pharmacological studies performed on brain and meningeal arteries revealed that CGRP receptors have a dominant role of inducing a cerebral artery dilatation, stronger effect compared with the middle meningeal artery. At the same time, responses to amylin and adrenomedullin are much lower, but are themselves mediated by CGRP receptor (Sams A. et al., 1998).

CGRP ROLE IN NOCICEPTION

As emphasise the evidence obtained so far, CGRP neurotransmitter confirm it widespread in the central and peripheral nervous system which modulates the function of other neurotransmitters (Messlinger K. et al. 1995). Satellite glial cells in the gasserian trigeminal ganglion can also express CGRP receptors, these cells having an important role in the modulation of neuronal metabolism through gap junction (Ceruti S. et al., 2011). Regarding clinical data on peripheral actions of this peptide, they are related to neurovascular inflammation which appears to have a major importance in migraine. The release of CGRP from trigeminal nerve endings is not limited only to inducing the vasodilatation occurrence, but implicitly to degranulation of mast cells and edema, associations that contribute to neurogenic inflammation.

Peripheral neurons (1^{st} order neurons) containing CGRP, both in trigeminal ganglia and other areas, correspond to multimodal nociceptors that are present in all peripheral tissues and send primary afferent signals to the 2^{nd} order neurons in the cervical-spinal horn (C1-C2), trigeminal caudalis subnucleus and the nucleus of the solitary tract (Bigal M.E., 2013). At the 2nd order neurons on the way of cephalic sensitivities (somatic and visceral) CGRP acts postsynaptic mediating the transmission of pain signals from the brain stem sensory nuclei of the cranial nerves, mainly of the trigeminal cranial nerve, to the thalamus (3^{rd} order neurons) (Eftekhari S. et al., 2011).

Brainstem trigeminal sensory nuclei and especially through the area of cervical spinal C1-C2 corresponding to trigeminal caudalis subnucleus (subcomponent of the spinal trigeminal nucleus which also contains at bulbo-pontine level oralis and interpolaris subnuclei which also have significant actions in the integration of the pain in cephalic territory) plays a major role in the pathophysiology of migraine. It is shown that stimulation of these structures with certain intensities of the excitant, duration and frequency of its application, determines both the activation of trigemino-neuralgic, and trigemino-vascular system, which will trigger the peripheral release of CGRP and the development of neurogenic type inflammation. Furthermore, the prolonged stimulation and in repeated volleys is frequently associated with alteration of the sensory perception (exteroceptive, interoceptive, proprioceptive) called allodynia, in which painless stimulation is perceived as painful, as well as hypersensitisation of second order neurons (cervical spinal and brain stem) and third order (thalamus) on sensory pathways (Sun R.Q. et al. 2003). If migraine is considered to be the combined result of altered perception of stimuli that are not normally painful, plus activation the neurovascular dilator mechanism in the territory of the trigeminal nerve ophthalmic, appears probable the involvement of CGRP in migraine pathophysiology, both at central and peripheral level.

CGRP appears to play an important role in determining neuronal plasticity and the formation of synapses, both through direct action on neurons and by indirect action on the glial cells mediated by its modulatory effects (Galeaza M.T. et al., 1995).

Current therapeutic management strategies try reducing painful sensation by blocking CGRP both centrally and peripherally bringing into question the possibility that diffusion of blocking substances in the brain is not essential to the

analgesic properties of CGRP antagonists. The penetration of therapeutic active molecules at this level can have a direct influence on photophobia and other neurological symptoms of migraine with importance in its acute treatment, but not necessarily in the preventive treatment.
A reverse of penetration of CGRP antagonists in the meningo-cerebral vascular territory could be the disturbance of homeostatic physiological role of CGRP existing naturally in neurons, including its action on neuroplasticity. Another problem is unequal actions as importance and magnitude played by CGRP in different nerve structures suspected to participate in the circuitry of migraine.
To this aspect is relatively easier to answer because the identification of markers of CGRP presence induces a heightened possible functional significance. On this line, is first mentioned as recent immunohisto-reactivity research in confocal microscopy have revealed using labeled antibodies, the presence of both components of CGRP receptor, and RAMP1 protein highly expressed in cerebellar Purkinje cell soma and their branching endings. It is so believed such a strong involvement of the cerebellum in modulating the nociception process, involvement that make him even a potential therapeutic target to prevent complications of migraine such as migraine stroke. (Moulton E.A. et al., 2010)
Sporadic administration of CGRP antagonists which can penetrate the brain in acute treatment of migraine, most likely would not affect homestasis however at this level, but chronic administration in order to achieve a preventive treatment requires more studies to assess both benefit and secure their administration.

CGRP RECEPTORS ANTAGONISTS

It is known that the adverse effect of triptans in migraine therapy but also limiting their use in patients with cardiovascular disease derives from their ability to maintain a vasoconstrictor activity. Under these circumstances a judicious alternative in the treatment of migraine by restriction on inflammatory neurogenic vasodilatation consists of CGRP receptor blockade by selective antagonists. (Geppetti P. et al., 2005).
Effectiveness of two CGRP receptor antagonists, *olcegepant* and *telcagepant* (the new gepants class) has recently been demonstrated, but the precise location of their action remains to be revealed. There are three possible targets, namely: intracranial vessels, trigeminal nerve endings in the central or peripheral and central nervous structures (Massion H., 2010). It seems that both antagonists act on the RAMP1 elements from central and peripheral sites alleviating signaling at trigeminal pathway level. Antagonist molecules have a high specificity for CGRP receptors, clinical studies already having some positive results (Olesen J. et al., 2004). However, although *in vitro* results showed a high potency *in vivo* has revealed that large quantities are required to obtain a significant antimigrain effect (Edvinsson L. et al., 2007).
The studies also showed that increased levels of RAMP1 protein increase CGRP receptor activity and moreover, may sensitize trigeminal ganglia of migraine patients to CGRP actions. RAMP1 effects include increasing CGRP synthesis and increased neurogenic inflammatory process, which enhances the nociceptive action of CGRP in migraine.
The antagonist *olcegepant* appears to have similar efficacy in reducing acute migraine pain similar to triptans, but has a longer duration of action and also fewer side effects (Edvinsson L. et al., 2010).
Regarding the place of *gepants* class action, were delimited four possible areas - target relevant to the treatment antimigrain:

- cerebral and extracerebral blood vessels, the area where CGRP receptors induce an vasodilator response which can be blocked by *olcegepant* and *telcagepant in vitro* and *in vivo*;
- dural mast cells can be degranulate by CGRP (because they contain CGRP receptors) triggering the release of histamine, bradykinin and serotonin which will cause the release of cytokines and inflammatory agents involving neurogenic inflammation appearance;
- second order sensory neurons in the trigeminal nucleus of the brainstem, but particularly appropriate in trigeminal neural caudalis subnucleus areas present in the marrow spino-cervical C1-C2 levels (otherwise involved in major trigeminal neuralgia), which were proved that postsynaptic CGRP receptors can be blocked by *olcegepant* and *telcagepant*;
- nociceptive sensory neurons of the Gasser trigeminal ganglion, where CGRP stimulates the release of the gaseous neurotransmitter nitric oxide (NO) and several pro-inflammatory cytokines (Edvinsson L. et al., 2012).

Possible consequences of CGRP antagonists in the treatment of migraine
Taking in consideration the physiological role of CGRP and its cardiovascular effects are taken into account the following consequences they might have the use of CGRP antagonists in therapeutic anti-migraine management:

- *the risk of vasoconstriction appearance*: the inhibition of CGRP, vasoconstriction may occur mainly in the small blood vessels. However, clinical trials in humans have revealed that *olcegepant* has no effect on global blood flow or the cerebral or over the blood flow velocity in the middle cerebral artery. It has also been revealed that these anatagonists seem to restore the normal tone at the already dilated arteries without causing an abnormal constriction;
- *the risk of suppressing the actions of the associated antihypertensive medications:* to see whether CGRP antagonism may affect vasodilation produced by certain antihypertensive agents has been conducted a series of clinical studies which revealed that the administration of *telcagepant* after nitroglycerin, these had no vasoconstrictor effect;

- *the risk of inhibiting the compensatory vasodilation by ischemia*: in clinical studies, the supra-therapeutic doses of *telcagepant* in patients with angina, it was revealed that compensatory vasodilator response is preserved during myocardial ischemia even in presence of CGRP receptor antagonists. (Bigal M.E. et al., 2013).

CONCLUSIONS

The possibility as CGRP receptor antagonists to be beneficial in the treatment of migraine leads to the hypothesis that migraine pain has a unique mechanism, which in part is responsive to common analgesics (eg. non-steroidal anti-inflammatory analgesics) but mainly it seems that respond to medications which are not used in other types of pain.
After drugs making based on triptans and ergot derivatives, the development of a third generation of antimigraine drugs make great progress. Preclinical and clinical data obtained so far show that CGRP and its receptor represent a major route into the mechanism of migraine, but certain conclusions about the real benefits of this new class of CGRP receptor antagonists will be set only after achieving clinical trials phase III type which is currently underway. With all important data obtained so far, it is prudent to conclude that studies can not specify more precisely the complete role of CGRP and specific place of action for antagonists in the complex mechanisms of migraine.
In terms of CGRP antagonists, in the future, remains to be seen whether the inhibition of peripheral release at the sensory nerves level is sufficient for their anti-migraine action or contrary, the CGRP inhibition at central level will play a major role in their clinical effectiveness.

REFERENCES

Benemei S., Nicoletti P., Capone J.A., Geppetti P., (2009): CGRP receptors in the control of pain and inflammation, Curr. Opin. in Pharmacol, 9:9-14
Benemei S., Nicoletti P., Capone J.A., Geppetti P., (2007): Pain pharmacology in migraine: focus on CGRP and CGRP receptors, Neurol. Sci., 28:589-593
Bigal M.E., Walter S., Rapoport A.M., (2013): Calcitonin Gene Related Peptide (CGRP) and Migraine Current Understanding and State of Development, Headache, 53:1230-1244
Ceruti S., Villa G., Fumagali M. Et al., (2011): Calcitonin gene – related peptide mediated enhancement of purinergic neuron/glia communication by the algogenic factor bradykinin in mouse trigeminal ganglia from wild type and R192QCav.2.1 knock-in mice: Implications for the basic mechanisms of migraine pain, J. Neurosci., 31:3638-3649
Dahlőf C., (2002): Integrating the triptans into clinical practice, Curr. Opin. Neurol., 15:317-322
Edvinsson L., Ho T.W., (2010): CGRP receptor antagonism and migraine, The American Society for Experimental Neurotherapeutics, Inc., 7: 164-175
Edvinsson L., Nilsson E., Jansen-Olesen I., (2007): Inhibitory effectof BIBN4096BS, a CGRP8-37, a CGRP antibody and a RNA-Spigelmer on CGRP induced vasodilation in the perfused and non-perfused rat middle cerebral artery, Br. J. Pharmacol 150:633-640
Edvinnsson L., Villalon C.M., VanDenBrink A.M., (2012): Basic mechanism of migraine and its acute treatment, Pharmacology&Therapeutics, 136:319-333
Eftkhari S., Edvinsson L., (2011): Calcitonin gene-related peptide (CGRP) and its receptor components in human and rat trigeminal nucleus and spinal cord at C1-level, Neurosci., 12:112
Galeaza M.T., Garry M.G., Yost H.J., Strait K.A., Hargreaves K.M., Seybold U.S., (1995): Plasticity in the synthesis and storage of substance P and calcitonin gene-related peptide in primary afferent neurons during peripheral inflammation, Neuroscience, 66:443-458
Geppetti P., Capone J.G., Trevisani M., Nicoletti P., Zagli G., Tola M.R., (2005): CGRP and migraine: neurogenic inflammation revisited, J. Headache Pain, 6:61-70
Goadsby P., Lipton R.B., Ferrari M.D., (2002), Migraine-current understanding and treatment, N .Engl. J. Med., 346:257-270
Goadsby P., Edvinson L., Ekman R., (1988), Release of vasoactive peptides in the extracerebral circulation of humans during activation of the trigeminovascular system, Ann. Neurol., 23:193-196
Hay D.L., Poyner D.R., Quirion R., (2008), Status of calcitonin gene-related peptide subtype 2 receptor, Pharmacol. Rev., 60:143-145
Massion H., (2010): Traitement de la migarine: présent et avenir, La revue de Médicine interne, 31 :399-402
Mulderry P.K., Ghatei M.A., Spokes R.A. et al., (1988), Differential expression of α-CGRP and β-CGRP by primary sensory neurons and enteric autonomic neurons of the rat, Neuroscience, 25:195-205
Messlinger K., Hanesch V., Kurosawa M., Pawlak M., Schmidt R.T., (1995): Calcitonin gene related peptide released from dural nerve fibers mediates increase of meningeal blood flow in the rat, 73:1020-1024

Moulton E.A., Schmahman J.D., Becerra L., Brosook D., (2010): The cerebellum and pain: Passive integrator or active participator?, Brain. Res. Rev., 65:14-27
Olesen J., Diener H.C, Hussted J.W., Goadsby P., Hall D., Meier U. et al., (2004): Calcitonin gene related peptide receptor antagonist BIBN4096BS for acute treatment of migraine, N. Engl. J. Med., 350:1104-1110
Petersen K.A., Nilsson E., Olesen J., Edvinson L., (2005): Presence and function of the calcitonin gene related petide receptor on rat pial arteries investigated in vitro and in vivo, Cephalgia, 25:424-432
Quayle J.M., Boner A.D., Brayden J.E., Nelson M.T., (1994): Calcitonin gene-related peptide activated ATP-sensitive K+ currents in rabbit arterial smooth muscle via protein kinase, A. J. Physiol., 475:9-13
Sams A., Jansen-Olesen I., (1998): Expression of calcitonin receptor-like and receptor activity modifying proteins in human cranial arteries, neurosci. Lett., 258:41-44
Sun R.Q., Lawland N.B., Willis W.D., (2003): The role of calcitonin gene-related peptide (CGRP) in the generation and maintenance of mechanical allodynia and hyperalgesia in rats after intradermal injection of capsaicin, Pain, 104:201-208
Zhang Z., Winborn C.S., Marquez de Prado B., Russo A.F., (2007): Sensitization of calcitonin gene-related peptide receptors by receptor activity modifying protein-1 in the trigeminal ganglion, J. Neurosci., 27:2693-2703

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