Review article

Changing levels of sex hormones and calcitonin gene-related peptide (CGRP) during a woman’s life: Implications for the efficacy and safety of novel antimigraine medications

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ARTICLE INFO

Keywords:
CGRP (receptor) antibodies
CGRP
Gender
Sex hormones
Migraine
Cardiovascular risk

ABSTRACT

Migraine is a neurovascular disorder that is three times more prevalent in women than in men and represents a large socio-economic burden. Therefore, the development of new preventive medications is an urgent matter. Currently, calcitonin gene-related peptide (CGRP), a neuropeptide released from trigeminal fibres, is an important target for migraine treatment. Accordingly, antibodies directed against CGRP or its receptor, as well as small-molecule CGRP receptor antagonists, have been developed for the prophylactic and acute treatment of migraine. Results from clinical phase III trials show a significant decrease in migraine days and relatively mild side-effects. However, CGRP is not only present in the trigeminal nerve, but it is also abundant in perivascular nerve fibres. Moreover, CGRP levels and hormones vary between sexes and during different life stages, and hormones affect CGRP, with a seemingly greater role for CGRP in females. In this review we discuss whether these aspects could be associated with differences in response and efficacy of drugs interfering with the CGRP pathway. Furthermore, CGRP has been described as playing a protective role in ischemic events, and CGRP seems to play a larger role in cardiac ischemic events in female patients. As cardiovascular risk is increased in female migraine patients and also increases significantly in females after menopause, further research into the risk of blocking CGRP in these patients is needed.

1. Introduction

1.1. Migraine and CGRP

Migraine is a highly prevalent, primary headache disorder. It is estimated that 15 % of the world population suffers from migraine, representing a large socioeconomic burden [1].

It is characterized by unilateral pulsating pain of moderate to severe intensity, often aggravated by physical activity and accompanied by nausea, vomiting, photophobia and phonophobia. When left untreated, typical attack duration is between 4 and 72 h [2]. A crucial role in the development of a migraine attack is attributed to the activation of the trigeminovascular system [3]. This system consists of sensory neurons of the trigeminal nucleus caudalis and the trigeminal ganglion, with the latter innervating cranial blood vessels. When activated, calcitonin gene-related peptide (CGRP) is released from the nerve endings surrounding the meningeal blood vessels causing vasodilation, further activation of the trigeminal nerve and nociceptive transmission [4,5].

During a migraine attack levels of CGRP increase in jugular blood and normalize concomitantly with headache relief [3,6]. Moreover, infusion of CGRP in migraine patients induces a migraine-like headache [7].

1.2. Migraine treatment targeting CGRP

While for the acute treatment of migraine medication is available that was specifically designed for migraine (i.e. triptans), for years prophylactic treatment consisted only of medication originally developed for diseases other than migraine, such as hypertension, epilepsy and depression. Due to their role in migraine pathophysiology, the trigeminovascular system and CGRP were identified as possible targets in

Abbreviations: CGRP, calcitonin gene-related peptide; FeRn, neonatal Fc receptor; LDL, low density lipoprotein; L-NAME, 1(Nω)-nitro-L-arginine methyl ester; NO, nitric oxide; TVS, trigeminovascular system.

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https://doi.org/10.1016/j.maturitas.2020.12.012
Received 19 May 2020; Received in revised form 17 December 2020; Accepted 30 December 2020
Available online 6 January 2021
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the treatment of migraine [3]. Simultaneously, classical (small molecule) CGRP receptor antagonists and IgG type monoclonal antibodies targeting CGRP and the CGRP receptor were developed. Phase III trials with the antibodies as preventive treatment for migraine have shown a significant improvement in migraine with a favorable tolerability profile when compared to the current prophylactics. Unfortunately, even though they were specifically developed for the treatment of migraine, not all patients benefit from these antibodies [8].

1.3. CGRP and hormonal influences

Migraine prevalence differs between men and women, with 75% of patients being women. A strongly increased incidence is seen in women after menarche, with notable changes in occurrence during life and reproductive milestones [9].

Interestingly, ovarian hormone receptors have been described in all the components of the TVS and interactions between ovarian sex hormones and CGRP levels have been described [9]. Moreover, the wide distribution of the CGRP receptors in vascular tissue points out a role for CGRP in regulation of the vascular tone. Indeed, CGRP has been described to participate in the homeostatic response to ischemic events [10]. In this review we will focus on the influence of hormones on migraine and its fluctuations throughout life, with especial focus on women, which may influence the response to CGRP-blocking medication and the possible risks which could accompany (long term) blockade of CGRP.

2. Methods

We performed an extensive search in PubMed. Our aim was to identify research papers that explored CGRP and migraine differences between sex and gender, as well as changes and potential risks through different life stages. Search terms used to identify literature included: migraine, menopause, pregnancy, cerebrovascular risk, cardiovascular risk, all separately combined with CGRP. Migraine was also combined with monoclonal antibodies. The results were filtered to show only English articles. Articles were then selected based on the abstracts. Additional articles were extracted from reference lists of original articles and review articles.

3. Gender aspects

3.1. Hormonal aspects

As mentioned above, the prevalence of migraine in women increases after menarche to a three-to-one ratio, when compared to men [11]. The symptoms men and women report differ as well, as female patients are more likely to report additional symptoms, including photophobia, phonophobia, nausea, and visual aura [11]. Moreover, for many female patients, migraine occurrence often correlates to specific phases of the menstrual cycle, the highest incidence being reported just before and during the first days of menstruation [12]. Conversely, during pregnancy, patients experience less migraine attacks. During perimenopause, patients report an increase in migraine frequency with, eventually, a postmenopausal decrease [9,13].

An interaction between ovarian sex hormones and CGRP has also been suggested. In healthy subjects it has been shown that plasma CGRP levels in women are significantly higher than in men, with even higher plasma CGRP found in women using combined hormonal contraceptives [17]. Interestingly, Ibrahimi et al. investigated the trigeminal nerve-mediated vasodilation during different phases of the menstrual cycle and showed cycle-dependent changes in healthy women, which were not observed in patients with menstrually-related migraine [14]. In the same study, estradiol levels during day 1–2 of the cycle were similar between healthy controls and patients with menstrually-related migraine, but in the luteal phase of the cycle (day 19–21), significantly lower estradiol levels were found in patients with menstrually-related migraine. Indeed, expression of sex hormone receptors has been reported in the components of the trigeminovascular system [2]. The decreased variability in estradiol levels throughout the menstrual cycle and the seemingly disturbed trigeminovascular cyclicity in the study of Ibrahimi et al. could correlate to the menstrually-related susceptibility to migraine of these patients, although the exact mechanisms remain to be determined [14].

Approximately 25% of migraine patients are men [11]. Therefore, a recent study analysed sex hormone levels in male patients and showed increased levels of estradiol in men with migraine when compared to healthy male controls [15], indicating that variations in ovarian steroid hormones could be associated with the migraine prevalence difference in both men and women.

3.2. CGRP and pregnancy

In pregnancy, important haemodynamic changes occur, such as increase of the uteroplacental blood flow and decrease of the uterine vascular resistance [16]. An impairment of the uteroplacental circulation is associated with intrauterine growth restriction and newborns small for gestational age [16,17]. CGRP has been described to be involved in the regulation of the fetoplacental vascular tone [18]. Indeed, in healthy pregnant women, CGRP levels are significantly increased throughout the pregnancy. In the postpartum phase, serum concentrations of CGRP decrease significantly to levels similar to nonpregnant women [19]. Moreover, in pregnant patients with pre-eclampsia and intrauterine growth restriction, CGRP levels are lower compared to normotensive pregnancies [20].

Certainly, migraine attacks are associated with increased levels of CGRP and an increase in CGRP is measured during pregnancy; however, migraine patients usually experience less migraine during pregnancy and puerperium [9]. This could be explained by a difference in local cranial CGRP levels that increase during migraine and systemic CGRP that plays a role in haemodynamic changes in pregnancy [9]. Alternatively, high levels of CGRP in pregnancy could lead to a desensitization of the receptor, leading to a decrease in migraine. Moreover, considering that sex hormone receptors are present in the trigeminovascular system, the fluctuations in sex hormones during pregnancy could modulate the activation of the trigeminovascular system and/or the nociceptive transmission.

3.3. CGRP and menopause

It has been shown that there is a significant increase in CGRP during hot flushes [21]. Moreover, postmenopausal women who experience hot flushes have significantly higher levels of plasma CGRP and a higher total 24 h urine secretion of CGRP than premenopausal women and postmenopausal women who do not experience hot flushes [22,23]. As CGRP has a strong vasodilatory effect, increased levels of CGRP could be correlated to vasomotor symptoms and, thus, experiencing more hot flushes.

Even though this clear relation between vasomotor symptoms and CGRP exists, the exact mechanism behind it is not completely understood. Hot flushes are experienced as being very brief, in accordance with the short biological plasma half-life of CGRP [10]. In contrast, administration of exogenous human CGRP leads to local reddening for as long as 1–6 h after administration [24,25].

A study in mice showed that blocking CGRP reduced flush-like symptoms [26], suggesting that anti-CGRP treatment, antagonists or antibodies, could potentially diminish postmenopausal vasomotor symptoms by stabilizing the CGRP fluctuations. Several studies on the effect of hormonal replacement therapy on CGRP levels have reported that after 3 months of treatment, the plasma concentration of CGRP in postmenopausal women significantly increases to levels similar to healthy fertile women [27,28], suggesting a reduced CGRP secretion.
after menopause, probably associated to sex hormone deficiency [27]. Interestingly, while most migraine patients experience a decrease of migraine attacks during postmenopause, in patients with surgical ovariectomy, a worsening in migraine attacks has been described [29]. This disparity may be explained by the abrupt and marked decline in serum estradiol levels observed in ovariectomised patients, in contrast to the initial increase in estradiol secretion followed by a continuous but irregular decline observed in patients who have a physiological meno-

4. CGRP (receptor)-antibodies in migraine

After discovering the role of CGRP in migraine, this peptide became a potential target for the development of new migraine treatments. Due to their long plasma half-life (about a month), the antibodies are only suitable for prophylactic treatment [32] and are administered monthly or once every three months. This, combined with an excellent tolera-

5. Potential risks of blocking CGRP

Due to their relatively large molecular weight, CGRP (receptor) an-
tibodies are not likely to pass the blood brain barrier and thus not likely to cause central side effects. Nonetheless, CGRP is located in both the peripheral and enteric nervous system. Although the most common adverse events reported are mild, such as local injection-site reactions (such as erythema and pain), and upper respiratory tract infections, all similar between the different antibodies, there have been a few cases of (fatal) cardiovascular events [33]. Furthermore, the long-term effects of blocking CGRP in humans are not well known [33,34]. Considering our knowledge of the presence and function of CGRP, a few potential risks that could accompany blocking CGRP will be discussed.

5.1. Potential risks in pregnancy

Because of its role in maternal haemodynamic adaptation and foetal growth, there is a theoretic risk for hypertension and foetal growth restric-
tion when blocking CGRP during pregnancy. In pregnant rats, blocking CGRP with a CGRP receptor antagonist led to an increased systolic blood pressure, foetal growth retardation and an increased foetal mortality [35]. After inducing preeclampsia by administration of CGRP receptor antagonist led to an increased growth, there is a theoretic risk for hypertension and foetal growth restric-

5.2. Potential cerebro- and cardiovascular risks

Another potential concern of blocking CGRP is an increase of car-
diovascular risk. As migraine itself has been reported to be a risk factor for ischemic stroke and cardiovascular events, especially in women, and even more when using combined oral contraceptives, it is important to study whether anti migraine treatment does not increase this risk [10]. The exact underlying mechanism for this is still unknown, which makes it difficult to assess whether adding anti-CGRP treatment would augment this risk.

Before menopausal age, the risk of cardiovascular events in women is much lower than in men. After menopause this risk increases up to similar rates as in men [10]. In postmenopausal women, higher serum total cholesterol, triglyceride and LDL levels than in premenopausal women have been described [22], which may be one of the underlying causes of the abrupt increase in cardiovascular events in post-

ment (erenumab) have been developed. In recent years multiple phase III trials have been performed [8], which have all shown a statistically significant advantage compared to placebo. About 40–60 % of partici-

patients had at least 50 % reduction in migraine days. These numbers show that not all patients benefit from this treatment. The previously described differences in plasma levels of CGRP between men and women, the hormonal influences and the changes that occur in different life stages are yet to be studied as, perhaps, a partial explanation. Nonetheless, the development of these antibodies is of great value to the advancement in the treatment of migraine.

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tion when blocking CGRP during pregnancy. In pregnant rats, blocking CGRP with a CGRP receptor antagonist led to an increased systolic blood pressure, foetal growth retardation and an increased foetal mortality [35]. After inducing preeclampsia by administration of the nitric oxide (NO) synthase inhibitor L-NAME in pregnant rats through osmotic minipumps, a significant increase in foetal mortality was observed when compared to controls. The administration of CGRP in these rats caused a substantial reduction in blood pressure and in foetal mortality [36]. In contrast, a study in which they administered erenumab during pregnancy, showed a similar rate of infant and foetal loss in the erenumab and the control group, even though they did find evidence of placental transfer [37]. The Foetal exposure to antibodies directed against CGRP or its receptor is likely to happen in the second half of pregnancy. IgG antibodies are known to be able to cross the placenta through the neonatal Fc receptor (FcRn) in syncytiotrophoblast cells, which become present after 20–22 weeks of pregnancy [38]. Thus, physicians should take into account this potential risk and consider the long half-life when prescribing these drugs.
CGRP leads to much larger vasodilatory responses to CGRP [16], is more common (Fig. 1) [47]. This difference in pathophysiology could imply a different risk for men and women when blocking CGRP. Therefore, there is an urgency for safety studies with an adequate design, including the consideration of gender differences.

6. Conclusion

The first migraine-specific prophylactic treatment, e.g. CGRP (receptor)-antibodies, has been registered. Although CGRP has been marked as a specific target for migraine, not all migraine patients benefit from treatment. Plasma CGRP levels differ between men and women and change during pregnancy and around menopause. The differences between men and women could be associated with a difference in response and a difference in risks and side effects. Although clinical trials have shown only mild side effects, the presence of CGRP throughout the body and the lack of long term data is reason for concern. The potential risks discussed in this review need to be recognized and further investigated.

Contributors

All authors participated in the writing of the review and saw and approved the final version.

Conflict of interest

SdVL has no conflict of interest to declare. ERB received travel support and/or sponsorship from Allergan, Amgen and Novartis. AMvdB received research grants, consultant or speaker fees from Amgen/Novartis, Lilly and Teva and was supported by the Dutch Research Council.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Transparency document

The Transparency document associated with this article can be found in the online version.

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