Maturitas 145 (2021) 73–77

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

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

Simone de Vries Lentsch [a,b], Eloísa Rubio-Beltrán [b], Antoinette MaassenVanDenBrink [b,*]

[a] Department of Neurology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands
[b] Div. of Pharmacology, Dept. of Internal Medicine, Erasmus University Medical Centre, PO Box 2040, 3000 CA Rotterdam, the Netherlands

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; FcRn, neonatal Fc receptor; LDL, low density lipoprotein; L-NAME, n(ω)-nitro-L-arginine methyl ester; NO, nitric oxide; TVS, trigeminovascular system.

* Corresponding author at: Erasmus MC, PO Box 2040, 3000 CA Rotterdam, the Netherlands.
*E-mail address:* a.vanharen-maassenvandenbrink@erasmusmc.nl (A. MaassenVanDenBrink).

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

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 influences

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, vomiting 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 perimenopausal 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 menopause [30,31], but further studies should address the exact mechanisms behind.

## 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 administrated monthly or once every three months. This, combined with an excellent tolerability in clinical trials [8], will lead to a higher compliance rate when compared to the current preventive migraine treatments.

At the moment three antibodies against CGRP (fremanezumab, galcanezumab and eptinezumab), and one against the CGRP receptor (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 participants 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.

## 5. Potential risks of blocking CGRP

Due to their relatively large molecular weight, CGRP (receptor) antibodies 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 restriction 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 administrated 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.

### 5.2. Potential cerebro- and cardiovascular risks

Another potential concern of blocking CGRP is an increase of cardiovascular 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 postmenopausal women. Additionally, Gupta et al. demonstrated that adipose tissue of postmenopausal women has a significantly larger expression of β-CGRP compared to premenopausal women [39]. These changes in CGRP expression might be a physiological response to the change in lipid profile and act as a protective mechanism against cardiovascular events. No safety concerns for cerebro- or cardiovascular events have been reported in the clinical trials with CGRP (receptor) antibodies, although there have been a few reported cases of cardiovascular events during treatment with these antibodies [40–42], that were assumed not to be treatment-related by the investigators. Noteworthy, all trials excluded patients with a history of cardiovascular or cerebrovascular events.

Even though the exact physiological function of CGRP has not been fully described, it is clear that after an ischemic event, CGRP is released, causing vasodilation [10], suggesting a protective role. Moreover, during vascular inflammation, release of CGRP inhibits the proliferation of vascular smooth muscle cells, thus limiting the growth of atheromatous lesions [43]. This poses a concern as CGRP (receptor) blockade could lead to more extensive damage in an otherwise mild infarction. A small study performed in 2005 revealed no effect on cerebral blood flow or the diameter of the middle cerebral artery in the 3 h after infusion of a CGRP receptor antagonist. Additionally, no effect on the extracranial arteries or systemic haemodynamic was recorded [44]. While, indeed, in the acute phase of blocking CGRP there might be compensating physiological mechanisms to maintain cerebral blood flow [10], it remains to be demonstrated whether similar mechanisms are effective on the long term.

A recent study explored the cardiovascular safety of CGRP receptor blockade with erenumab, in a randomized, double-blind, placebo-controlled study in patients with stable angina. Patients received a single infusion of erenumab (140 mg) and subsequently performed an exercise treadmill test. No difference was found between the erenumab and placebo group regarding time to exercise-induced angina, systolic and diastolic blood pressure or heart rate [45]. This might indicate that antibodies directed against CGRP or its receptor are safe in patients with a history of cardiovascular events. However, the treadmill test took place 30 min after infusion of erenumab, while no evidence was provided to show whether the CGRP receptor was already blocked at the time of the treadmill test [46]. This could potentially have taken several hours, given the large molecular size of erenumab and the location of the CGRP receptor in the smooth muscle wall of the blood vessel. Furthermore, although the majority of migraine patients are women, the majority of patients in this trial were men with stable angina. It is important to have in mind that myocardial infarction in men is usually caused by occlusion of the proximal coronary circulation, while in women vasospasm of the small intramyocardial parts of the coronary arteries, where

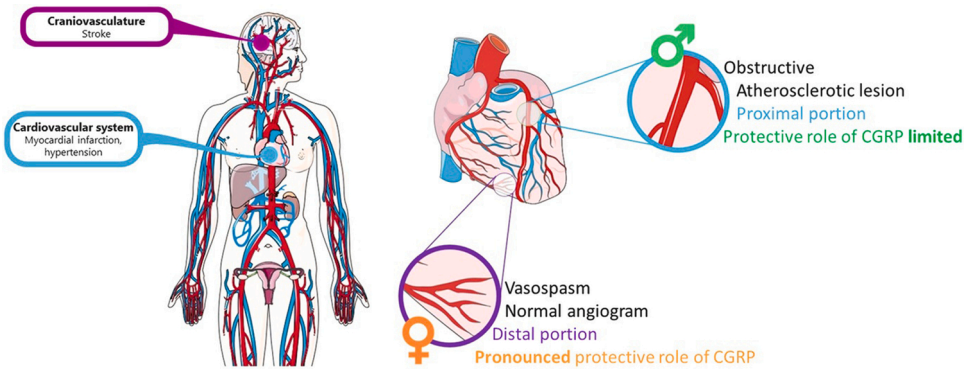


**Fig. 1.** schematic representation of the difference in pathophysiology of cardiovascular events in men and women and the potential protective role of CGRP.

CGRP leads to much larger vasodilatory responses to CGRP [10], 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.

## References

[1] K. Maasumi, R.L. Michael, A.M. Rapoport, CGRP and migraine: the role of blocking calcitonin gene-related peptide ligand and receptor in the management of migraine, Drugs 78 (9) (2018) 913–928.
[2] Headache Classification Committee of the International Headache Society, The international classification of headache disorders, 3rd edition, Cephalalgia 38 (2018) 1–211.
[3] P.J. Goadsby, L. Edvinsson, Trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cat, Ann. Neurol. 33 (1993) 48–56.
[4] T. de Vries, C.M. Villalon, A. MaassenVanDenBrink, Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans, Pharmacol. Ther. (2020), 107528.
[5] F.A. Russell, R. King, S.J. Smillie, X. Kodji, S.D. Brain, Calcitonin gene-related peptide: physiology and pathophysiology, Physiol. Rev. 94 (4) (2014) 1099–1142.
[6] P.J. Goadsby, L. Edvinsson, R. Ekman, Vasoactive peptide release in the extracerebral circulation of humans during migraine headache, Ann. Neurol. 28 (1990) 183–187.
[7] L.H. Lassen, P.A. Haderslev, V.B. Jacobsen, H.K. Iversen, B. Sperling, J. Olesen, CGRP may play a causative role in migraine, Cephalalgia 22 (2002) 54–61.
[8] H. Deng, G.G. Li, H. Nie, Y.Y. Feng, G.Y. Guo, W.L. Guo, Z.P. Tang, Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis, BMC Neurol. 20 (1) (2020) 57.
[9] A. Labastida-Ramirez, E. Rubio-Beltran, C.M. Villalon, A. MaassenVanDenBrink, Gender aspects of CGRP in migraine, Cephalalgia 39 (3) (2017) 435–444.
[10] A. MaassenVanDenBrink, J. Meijer, C.M. Villalon, M.D. Ferrari, Wiping out CGRP: potential cardiovascular risks, Trends Pharmacol. Sci. 37 (9) (2016) 779–788.
[11] D.C. Buse, E.W. Loder, J.A. Gorman, W.F. Stewart, M.L. Reed, K.M. Fanning, D. Serrano, R.B. Lipton, Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study, Headache 53 (8) (2013) 1278–1299.
[12] M.E.A. MacGregor, M.A. Frith, P.J. Ellis, B.H.L. Aspinall, M.A. Hackshaw, Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen, Neurology 67 (2006) 2154–2158.
[13] K. Ibrahimi, E.G. Couturier, A. MaassenVanDenBrink, Migraine and perimenopause, Maturitas 78 (4) (2014) 277–280.
[14] K. Ibrahimi, W.P.J. van Oosterhout, W. van Dorp, A.H. Jan Danser, I.M. Garrelds, S. A. Kushner, E.M.E.H. Lesaffre, G.M. Terwindt, M.D. Ferrari, A.H. van den Meiracker, A. Maassen Van Den Brink, Reduced trigeminovascular cyclicity in patients with menstrually related migraine, Neurology 84 (2015) 125–131.
[15] W.P.J. van Oosterhout, G.G. Schoonman, E.W. van Zwet, O.M. Dekkers, G. M. Terwindt, A. MaassenVanDenBrink, M.D. Ferrari, Female sex hormones in men with migraine, Neurology 91 (4) (2018) e374–e381.
[16] C. Yallampalli, M. Chauhan, C.S. Thota, S. Kondapaka, S.J. Wimalawansa, Calcitonin gene-related peptide in pregnancy and its emerging receptor heterogeneity, Trends Endocrinol. Metab. 13 (6) (2002) 263–269.
[17] K. Harrington, C. Goldfrad, R.G. Carpenter, S. Campbell, Transvaginal uterine and umbilical artery doppler examination of 12-16 weeks and the subsequent development of pre-eclampsia and intrauterine growth retardartion, Ultrasound Obstet. Gynecol. 9 (1997) 94–100.
[18] Y.L. Dong, S. Vegiraju, M. Chauhan, P.R. Gangula, G.D. Hankins, L. Goodrum, C. Yallampalli, Involvement of calcitonin gene-related peptide in control of human fetoplacental vascular tone, Am. J. Physiol. Heart Circulatory Physiol. 286 (1) (2004) H230–239.
[19] G. Saggese, S. Bertelloni, G.I. Baroncelli, A. Pelletti, U. Benedetti, Evaluation of a peptide family encoded by the calcitonin gene in selected healthy pregnant women. A longitudinal study, Hormone Res. 34 (5–6) (1990) 240–244.
[20] Y.L. Dong, M. Chauhan, K.E. Green, S. Vegiraju, H.Q. Wang, G.D. Hankins, C. Yallampalli, Circulating calcitonin gene-related peptide and its placental origins in normotensive and preeclamptic pregnancies, Am. J. Obstet. Gynecol. 195 (6) (2006) 1657–1667.

[21] Y.A. Wyon, A.C. Spetz, G.E. Theodorsson, M.L. Hammar, Concentrations of calcitonin gene-related peptide and neuropeptide Y in plasma increase during flushes in postmenopausal women, Menopause (New York, N.Y.) 7 (1) (2000) 25–30.
[22] P. Gupta, A. Harte, D.W. Sturdee, A. Sharma, A.H. Barnett, S. Kumar, P. G. McTernan, Effects of menopausal status on circulating calcitonin gene-related peptide and adipokines: implications for insulin resistance and cardiovascular risks, Climacteric 11 (5) (2008) 364–372.
[23] Y. Wyon, J. Frisk, T. Lundeberg, E. Theodorsson, M. Hammar, Postmenopausal women with vasomotor symptoms have increased urinary excretion of calcitonin gene-related peptide, Maturitas 30 (3) (1998) 289–294.
[24] S.D. Brain, T.J. Williams, J.R. Tippins, H.R. Morris, I. MacIntyre, Calcitonin gene-related peptide is a potent vasodilator, Nature 313 (5997) (1985) 54–56.
[25] M.A. Oliveira, W.G. Lima, D.A. Schettini, C.Q. Tilelli, V.E. Chaves, Is calcitonin gene-related peptide a modulator of menopausal vasomotor symptoms? Endocrine 63 (2) (2019) 193–203.
[26] D.B. Wilhelms, H. Dock, H.O. Brito, E. Pettersson, A. Stojakovic, J. Zajdel, D. Engblom, E. Theodorsson, M.L. Hammar, A.E. Spetz Holm, CGRP is critical for hot flushes in ovariectomized mice, Front. Pharmacol. 9 (2018) 1452.
[27] A. Valentini, F. Petraglia, D. De Vita, C. Nappi, A. Margutti, E.C. degli Uberti, A. R. Genazzani, Changes of plasma calcitonin gene-related peptide levels in postmenopausal women, Am. J. Obstet. Gynecol. 175 (3 Pt 1) (1996) 638–642.
[28] A. Spinetti, A. Margutti, S. Bertolini, F. Bernardi, G. BiFulco, E.C. degli Uberti, F. Petraglia, A.R. Genazzani, Hormonal replacement therapy affects calcitonin gene-related peptide and atrial natriuretic peptide secretion in postmenopausal women, Eur. J. Endocrinol. 137 (6) (1997) 664–669.
[29] I. Neria, F. Granellab, R. Nappi, G.C. Manzonib, F.Fa.A.R. Genazzani, Characteristics of headache at menopause: a clinico-epidemiologic study, Maturitas 17 (1993) 31–37.
[30] J.R. Guthrie, L. Dennerstein, J.R. Taffe, P. Lehert, H.G. Burger, The menopausal transition: a 9-year prospective populationbased study. The Melbourne Women's Midlife Health Project, Climacteric 7 (2004) 375–389.
[31] G.A. Laughlin, E. Barrett-Connor, D. Kritz-Silverstein, D. von Muhlen, Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study, J. Clin. Endocrinol. Metab. 85 (2000) 645–651.
[32] K. Paemeleire, A. MaassenVanDenBrink, Calcitonin-gene-related peptide pathway mAbs and migraine prevention, Curr. Opin. Neurol. 31 (3) (2018) 274–280.
[33] E. Rivera-Mancilla, C.M. Villalon, A. MaassenVanDenBrink, CGRP inhibitors for migraine prophylaxis: a safety review, Expert Opin. Drug Saf. 19 (10) (2020) 1237–1250.
[34] E. Rubio-Beltran, A. MaassenVanDenBrink, Understanding CGRP and cardiovascular risk, in: S. Brain, P. Geppetti (Eds.), Calcitonin Gene-Related Peptide (CGRP) Mechanisms. Handb Expl Pharmacol., Springer, Cham, 2019, pp. 131–140.
[35] P.R. Gangula, Y.L. Dong, S.J. Wimalawansa, C. Yallampalli, Infusion of pregnant rats with calcitonin gene-related peptide (CGRP)(8-37), a CGRP receptor antagonist, increases blood pressure and fetal mortality and decreases fetal growth, Biol. Reprod. 67 (2) (2002) 624–629.
[36] C. Yallampalli, Y.L. Dong, S.J. Wimalawansa, Calcitonin gene-related peptide reverses the hypertension and significantly decreases the fetal mortality in pre-eclampsia rats induced by N(G)-nitro-L-arginine methyl ester, Hum. Reprod. (Oxford, England) 11 (4) (1996) 895–899.
[37] J.L. Bussiere, R. Davies, C. Dean, C. Xu, K.H. Kim, H.M. Vargas, G.J. Chellman, G. Balasubramanian, E. Rubio-Beltran, A. MaassenVanDenBrink, T.M. Monticello, Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine, Regul. Toxicol. Pharmacol. 106 (2019) 224–238.
[38] C.M. Story, Neil E. Simister, Hua-Liu Chen, Joan S. Hunt, An IgG-transporting Fc receptor expressed in the syncytiotrophoblast of human placenta, Eur. J. Immunol. 26 (1996) 1526–1531.
[39] P. Gupta, A.L. Harte, N.F. da Silva, H. Khan, A.H. Barnett, S. Kumar, D.W. Sturdee, P.G. McTernan, Expression of calcitonin gene-related peptide, adrenomedullin, and receptor modifying proteins in human adipose tissue and alteration in their expression with menopause status, Menopause (New York, N.Y.) 14 (6) (2007) 1031–1038.
[40] M. Ashina, D. Dodick, P.J. Goadsby, U. Reuter, S. Silberstein, F. Zhang, J.R. Gage, S. Cheng, D.D. Mikol, R.A. Lenz, Erenumab (AMG 334) in episodic migraine: interim analysis of an ongoing open-label study, Neurology 89 (12) (2017) 1237–1243.
[41] M.E. Bigal, S. Walter, M. Bronson, A. Alibhoy, R. Escandon, Cardiovascular and hemodynamic parameters in women following prolonged CGRP inhibition using LBR-101, a monoclonal antibody against CGRP, Cephalalgia 34 (12) (2014) 968–976.
[42] D.W. Dodick, P.J. Goadsby, S.D. Silberstein, R.B. Lipton, J. Olesen, M. Ashina, K. Wilks, D. Kudrow, R. Kroll, B. Kohrman, R. Bargar, J. Hirman, J. Smith, Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial, Lancet Neurol. 13 (11) (2014) 1100–1107.
[43] Y. Li, R.R. Fiscus, J. Wu, L. Yang, X. Wang, The antiproliferative effects of calcitonin gene-related peptide in different passages of cultured vascular smooth muscle cells, Neuropeptides 31 (5) (1997) 503–509.
[44] K.A. Petersen, S. Birk, L.H. Lassen, C. Kruuse, O. Jonassen, L. Lesko, J. Olesen, The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers, Cephalalgia 25 (2) (2005) 139–147.
[45] C. Depre, L. Antalik, A. Starling, M. Koren, O. Eisele, R.A. Lenz, D.D. Mikol, A. Randomized, Double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina, Headache 58 (5) (2018) 715–723.
[46] A. MaassenVanDenBrink, E. Rubio-Beltran, D. Duncker, C.M. Villalon, Is CGRP receptor blockade cardiovascularly safe? Appropriate studies are needed, Headache 58 (8) (2018) 1257–1258.
[47] K.H. Humphries, A. Pu, M. Gao, R.G. Carere, L. Pilote, Angina with "normal" coronary arteries: sex differences in outcomes, Am. Heart J. 155 (2) (2008) 375–381.