REVIEW ARTICLE

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# Calcitonin gene-related peptide and menopause

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## ABSTRACT

The review summarizes recent findings with respect to pathophysiological role of calcitonin gene-related peptide (CGRP), in postmenopausal symptoms and diseases, which has opened horizons in understanding pathophysiology of menopause in a better way. Current evidences strongly propose a need to develop CGRP receptor antagonists, which may prove beneficial in many prevalent menopausal symptom/diseases such as vasomotor symptoms, cardiovascular risk, obesity, and major depressive disorder, in which CGRP levels are elevated.

**Key Words:** Calcitonin gene-related peptide, menopause, vasomotor symptoms

## INTRODUCTION

Calcitonin gene-related peptide (CGRP), identified in 1982, belongs to the calcitonin family of neuropeptides which also include adrenomedullin (AM), amylin, calcitonin, intermedin, and calcitonin receptor-stimulating peptide. CGRP results from the tissue-specific alternative splicing of the primary RNA transcripts of the calcitonin gene. It is a 37-amino acid neuropeptide with widespread expression such as in the heart, blood vessels, pituitary, thyroid, lung, and gastrointestinal tract and has a wide array of biological effects including neuromodulation, vasodilatation, cardiac contractility, bone growth, and mammalian development. The peptide is released from motor neurons at the neuromuscular junction and sensory neurons of spinal cord. There are two isoforms available as alpha-CGRP and beta–CGRP derived from different genes.[1] Potent subtype selective nonpeptide agonists and antagonists for CGRP are being developed for therapeutic use in hypertension, cardiac failure, migraine headaches, Reynaud's syndrome, preeclampsia, and diabetes.[1]

The main goal of present review is to summarize recent findings with respect to pathophysiological role of CGRP, in various postmenopausal symptoms. However, recognition of its role in postmenopausal women has really opened horizons in understanding pathophysiology of menopause in better way and potential role of newer therapies.

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## HOT FLUSH

Although the hot flush is generally recognized by women and the medical profession as the most characteristic and often a very distressing symptom of the climacteric, it remains an enigma. The physiological changes associated with the hot flush are different from any other flushing condition, i.e. an increased peripheral blood flow, increased heart rate, and in particular a decrease in galvanic skin resistance, which is unique to the flush. Flushing occurs as a result of disturbance of the temperature regulating mechanism situated in the hypothalamus, and probably a reduction in the thermoneutral zone. Many other factors have been implicated, including hormone releasing factors, gonadotrophins, and neurohumorals. However, the role of estrogen is critical.

In 1998 first time a study[2] from Sweden elucidated role of CGRP in menopausal symptoms. Thirteen postmenopausal women with and 13 women without vasomotor symptoms were included in the study. Urine was collected over 24 h, and CGRP excretion was measured utilizing radioimmunoassay technique. Twenty-four hour CGRP excretion was also measured

in 10 fertile women with regular cycles in early follicular, preovulatory, and midluteal phase. Twenty-four hour urinary excretion of CGRP was significantly higher in women with vasomotor symptoms compared to nonflushing women ($P = 0.028$). CGRP concentrations were stable throughout the ovulatory cycles, thereby, indicating for the first time that the 24-h urinary excretion of CGRP is higher in women with vasomotor symptoms than in women without these symptoms. These findings suggest that CGRP may be the mediator of vasodilator signals originating from the thermoregulatory center.[2]

This was confirmed in year 2000 in another study[3] that not only plasma concentrations of CGRP, but also of other neurohormones like neuropeptide Y (NPY) increase to 73% ($P = 0.018$) and 34% ($P = 0.028$), respectively, during hot flushes in postmenopausal women with vasomotor symptoms. Hence pathophysiological role of CGRP and NPY is implicated in causation of vasomotor symptoms.

In an recent meta-analysis,[4] five studies have measured plasma CGRP concentrations in postmenopausal women who suffer from flushes; all demonstrated elevations of between 170% and 320% over control. Three of the studies showed a temporal relationship between flushes and CGRP elevation. A further study has shown that CGRP is elevated in the urine of women who suffer from flushes. Only a single study has investigated flushes in premenopausal women, where no elevation of CGRP was observed. Even it is suggested in one of the studies that administration of CGRP or AM can cause facial flushing, suggesting that the peptides may be important in hot flushes experienced particularly by postmenopausal women. Thus, overall, there is good evidence to show that flushes in postmenopausal women are accompanied by an increase in CGRP.

The neurohormone behind these symptoms was poorly understood. The evidence of various recent studies supports the role of CGRP as a predominant neurohormone involved in vasomotor symptoms and possibly are due to release of this vasodilatory peptide CGRP from perivascular nerves.[1,5] CGRP could act centrally on the thermoregulatory center of the hypothalamus as well as peripherally to cause vasodilation and sweating.[4]

## CARDIOVASCULAR DISEASES

The global burden of CVD is rapidly increasing. CVD is the leading cause of death in women around the world. Hypertension affects more men than women until 55 years of age. However, after age 55, the percentage of women is higher. More than 450,000 women succumb to heart disease annually, and 250,000 die of coronary artery disease. Estrogen deficiency has been linked to the rapid increase in CVD in women who have undergone natural or surgical menopause. CVD risk increases after the menopause, which may be related to metabolic and hormonal changes. Menopause is a risk factor for CVD, because estrogen withdrawal has a detrimental effect on cardiovascular function and metabolism. The menopause compounds many traditional CVD risk factors, including changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction, and vascular inflammation.[6]

However, the role of CGRP to influence cardiovascular risk factor in postmenopausal women has been recently recognized. In one of the studies to determine, the effects of menopausal status on circulating CGRP levels and the correlation between circulating CGRP levels and biomarkers for CVD, a cross-sectional study on healthy premenopausal and postmenopausal women was conducted.[7] Mean circulating CGRP levels were higher in the postmenopausal women compared with premenopausal women. Among women who were experiencing hot flushes, the postmenopausal women had significantly higher CGRP levels than the premenopausal women ($P = 0.028$). Thus, serum CGRP levels positively correlated with serum insulin levels ($P = 0.016$). These data show that circulating CGRP levels are influenced by menopausal status and suggest additional mechanisms through which the increased risk of hyperinsulinemia and CVD may arise in postmenopausal women. However, no statistical correlation was made between postmenopausal status/CGRP and other CVS risk factors such as resistin, leptin, adiponectin, and lipids in the study.

To investigate the relationship among serum CGRP, homocysteine (Hcy), sex hormone, and coronary heart disease (CHD) in postmenopausal women in another cross-sectional study,[8] serum CGRP, estradiol (E(2)), progesterone (P) and Hcy levels of 144 postmenopausal women undergoing diagnostic CHD (75 with CHD and 69 without CHD) and 66 healthy young women were measured. The occurrence of CHD was correlated with high Hcy level and low CGRP level. The mean serum CGRP level was significantly lower in postmenopausal women with CHD than in women without CHD ($P < 0.01$). The mean serum Hcy level was significantly higher in CHD than in without CHD postmenopausal

women ($P < 0.01$). Hcy is an independent risk factor of CHD. *CGRP, E(2), and P are independent protective factors of CHD*. There was no relationship between Hcy, CGRP and E(2), and P.[9]

## POSTMENOPAUSAL OBESITY

Postmenopausal women have an increased tendency for gaining weight. It is as yet unclear whether the menopausal transition itself leads to weight gain, but it is certain that the physiological withdrawal of estrogen brings about changes in fat distribution, together with physical inactivity. Other contributing factors include ethnicity, reduced lean mass, resting metabolic rate, and treatment with certain drugs, e.g. steroids, insulin, and glitazones. Moreover, estrogen withdrawal during menopause has a detrimental effect on metabolism and brings changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased blood pressure, increased sympathetic tone, endothelial dysfunction, and vascular inflammation.[10]

However, recently one very interesting fact has been elucidated. A study determined that CGRP, ADM, and receptor activity-modifying proteins are expressed in abdominal fat, adipocytes, and preadipocytes. CGRP and ADM mRNA levels were increased in abdominal subcutaneous fat in postmenopausal women compared with premenopausal women. This offers a potential mechanism to explain the role of CGRP in menopausal vasomotor symptoms and the increased risk of CVD in postmenopausal women.[11]

## POSTMENOPAUSAL DEPRESSION

Another important finding suggested that proinflammatory cytokines, NPY, substance P, and calcitonin-gene-related peptide were significantly higher while vasoactive intestinal peptide, a marker of parasympathetic activity, was significantly lower in patients of depression as compared to controls, and thus depressive symptomatology strongly correlated with biomarker levels, suggesting that major depressive disorder (MDD) is inconsistently in postmenopausal women is associated with elevations in proinflammatory cytokines and neuropeptides.[12]

Premenopausal women with MDD, mostly in remission, exhibited several fold elevations of proinflammatory cytokines, sympathetic (NPY), and sensory (SP and CGRP) neuropeptides, and diminished parasympathetic-associated neuropeptide, vasoactive intestinal peptide (VIP), in sweat. These levels strongly correlated with depressive and anxiety symptomatology, even after controlling for BMI, suggesting that symptom severity rather than disease classification *per se* may be related to biomarker expression. The elevated levels of SP and CGRP are consistent with other previous reports of these peptides' role in pain perception, and of painful somatic symptoms correlating with depression severity in up to two-thirds of patients with MDD.[13]

## CONCLUSION

CGRP receptor antagonists may prove beneficial in many prevalent menopausal symptoms/diseases such as vasomotor symptoms, CVS diseases, obesity, and MDD, in which CGRP levels are elevated. Future research with respect to complete cloning of CGRP and its peptide receptors is greatly awaited in order to fully elucidate its role in various systems and pathophysiological conditions. It is also necessary to develop highly potent and selective analogues that will permit further characterization and the functional role(s) of each of the CGRP receptor subtypes. Current evidences of role of molecule CGRP in pathophysiology of menopausal symptoms really stimulate us further for the assessment of role CGRP receptor antagonists such as olcegepant and telcagepant in ameliorating various postmenopausal symptoms. Japanese herb has also been tried (Kampo). Studies need to be conducted in the direction evaluating the role of CGRP in predicting the face of menopause in women much early before their menopause starts and to evaluate that can this biomarker help in predicting severity, nature, character of the vasomotor, and other menopausal symptoms, so that timely and suitable treatment can be planned for in anticipation. Similarly, can urinary 24 CGRP excretion estimation be useful bedside investigation in assessing/evaluating menopause-related problems and can this be useful investigation for predicting outcome of treatment response in menopause is equally a matter of interest.

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