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Review Article

# G-protein Coupled Estrogen Receptor (GPER/GPR30) and Women's Health

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Estrogen - the female sexual hormone playing the most important role - plays a physiologically significant role, not only regulating in cell signals with second messenger but also being active in regulating transcription. Estrogen receptor (ER) which is a protein accepting estrogen not only play the role of a transcription factor combining with other genes to regulate their activity like other nuclear receptors but also performs external activities, combining with DNA, etc. G-protein coupled ER (GPER) that has been recently discovered exists as 7-membrane and has non-genomic (rapid) signaling. These functions, however, are not extensively addressed. This paper discusses the roles of GPER and its physiological mechanism. **(J Menopausal Med 2015;21:79-81)**

**Key Words:** Estradiol, Estrogens, Genomics, GTP-binding proteins

## Introduction

The primary function of estrogen which is a steroid hormone playing the most important role in men and women is to develop the secondary sexual characters of woman and establish/maintain reproductive functions. The roles of 17$\beta$-estradiol in reproductive system control uterine and mammary growth and function. Also, 17$\beta$-estradiol has varied effects on the brain, including reduction of neuronal loss following stroke, increase in neuronal connectivity as well as on many diseases and cancers. This hormone becomes active largely when it combines with estrogen receptor (ER) that remains non-active in cells. Existing estrogens trigger reaction by combining with nuclear ERs - ER-alpha (ER-$\alpha$) and ER-beta (ER-$\beta$). On the other hand, G-protein coupled ER (GPER) began to be known in recent years as a function of membrane receptors involved in the non-genomic mechanism of estrogen. In addition, subsequent studies found out that GPER is an important receptor mediating the activation of estrogen in immune system, nervous system, kidney system, vascular system, and reproductive system.[1] Accordingly, this paper examines key reactions that affect the action mechanisms of existing ERs - ER-$\alpha$ and ER-$\beta$ - and GPER that has been recently known in reference to the findings that have been made to date.

## ER and GPER

Although most ERs that are having strong affinity with estrogen are ligand-dependent transcription factors in target tissue are known to mediate the action of estrogen, recent genetic, biological, and pharmacological studies of the signal transfer path of estrogen have shed light on several processes that directly influence ER functions, indicating the complexity of the action of estrogen.[2] The first described

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ER-$\alpha$ is expressed in ovary, uterus, and mammary gland and located in chromosome 6, whereas ER-$\beta$ is expressed in the ovary of female and the reproductive system of male and located in chromosome 14. Therefore, these two ERs are manifested in different places or in a different manner. This different may result from the very low amino acid homology of A/B domain of N-terminus and E/F domain of C-terminus that are known to have transaction activation function. On the other hand, GPER which is a transmembrane receptor engaging in the non-genomic mechanism of estrogen unlike ERs known to date via what is called non-genomic signal-genetic path was discovered by Owman[3] in 1996, and referred to as GPR30 at first.[4] Membrane-dependent genomic signal is the most distinctive estrogen signal mechanism containing estradiol combined with ER-$\alpha$ and ER-$\beta$.[5] Although it is not known well yet, it has a rapid pathway containing G-protein. In addition, GPER transfers signal through $G_S$ protein, raises cyclic adenosine monophosphate (CAMP) production, increases epidermal growth factor receptor (EGFR) by raising epidermal growth factor, moves calcium within cells, activates extracellular signal-regulated kinase (ERK)1/2 and Src.[6,7] However, GPER reportedly has the characteristics of ER that has single, high-affinitive, low-capacity estrogen linker module.[8~10]

## GPER and Ligand

In a recent report it is known that some specific GPER can be activated in different aspects by specific ligands for each receptor. ER antagonist and selective ER modulator such as tamoxifen show the importance of active as GPER agonist.[11] In particular, as the selective agonist called G-1 is represented as selective GPER ligand[12] and there is a study suggesting in regard to the biological significance of GPER that G-1 stimulates the growth of endometrium, breast, vagina, and testicular cancer cell in organs including organs and tissues including cancer tissues. Some recent studies say that non-steroid GPER agonist is the action factor of GPER functions and it will be used for subsequent studies.

## GPER-Mediated Signaling

Signaling capability of GPER can have significant effect on conventional ERs in estrogen reactions. The role of GPR30 in the cell is based on the association of estrogen - mediated signal.[13,14] GPER has signal molecules having big structure in human genome[15] and GPER-dependent synthesis mediated to the estrogen of mitogen-activated protein (MAP) kinase ERK1/2 through stimulation of EGFR transcription was studied for the first time. Inter-cell transfer of calcium and activation of P13K are known to be signal pathways and, as a result, it is known that GPER stimulates EGFR transcription[11] and estrogen mediates the complex and prompt activation of cells in many aspects.

## Future Direction

GPER that has been newly discovered is an ER playing many physiologically significant roles in human body. GPER is now being studies in relation to cancer and, in particular, cancers relating to such female reproductive organs as breast, uterus, ovary, etc. where GPER exists are being studies. In addition, physiological and pathophysiologic effects of GPER are expected to play a significant role in nervous system, kidney, and blood vessel tissues. However, as the activation mechanism of receptor and the roles of active substances are not systematically identified, these need to be studied to ensure extensive understanding of them. In conclusion, as the roles and actions of assistive active substances for activating GPER are not completely understood, effects of ligand synthesized by certain GPER need to be studied in the future to pave way for more systematic study of the complex action mechanism and functions of GPER.

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## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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