DAVETLİ DERLEME (Invited Review)

A Concise Review: Ghrelin and Reproductive System

Ghrelin ve Üreme Sistemi İlişkisine Dair Kısa Bir Derleme

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Abstract
Ghrelin is a hormone, which has effects on growth hormone (GH) secretion, appetite, food intake, carbohydrate metabolism, gastrointestinal system, cardiovascular system, cell proliferation and reproductive system. Ghrelin, the endogen ligand of the GH secretagogue receptor (GHS-R), has been recently demonstrated as a pleiotropic regulator involved in a large array of endocrine and non-endocrine functions, including food intake and energy balance. The data so far available strongly suggest that, through local and /or systemic actions, ghrelin operates as a novel regulator of gonadal function that may contribute to the integrated control of energy balance and reproduction.

Anahtar kelimeler: **Mide; Grelin; İmmünohistokimya.**

Özet
Ghrelin büyüme hormonu salgılanması, iştah, gıda alımı, karbonhidrat metabolizması, gastrointestinal sistem, kardiyovasküler sistem, hücre proliferasyonu ve üreme sistemi üzerine etkileri olan bir hormondur. Büyüme hormonu (GH) salgılatıcı reseptörün endojen ligandı olan ghrelin'in son zamanlarda aralarında enerji dengesi ve üreme de dahil olmak üzere endokrin ve endokrin olmayan pek çok işlevde büyük bir düzenleyici rolü olduğu gösterilmiştir. Bulgular, aralarında enerji dengesi ve üremeyi de kapsayacak şekilde ghrelin'in gonadal fonksiyonlar üzerinde lokal ve/veya sistemik bir etkiyle düzenleyici bir rol oynadığını kuvvetle düşündürmektedir.

Key words: **Stomach; Ghrelin; Immunohistochemistry.**

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Introduction

Ghrelin is a peptide hormone produced by the gastrointestinal system and is functional in regulation of eating habit and body weight through central effect. Kojima and co-workers defined ghrelin in the gastrointestinal fundus of rats first in 1999 (1). Ghrelin is basically a hormone with a lipopeptide structure of 28 amino acids produced by X(A) cells which have endocrinal functions in the gastrointestinal fundus, and, is the legend of Growth Hormone Secretion- Receptor (GHS-R) (1, 2). It is monitored in the studies done through gene expression on humans and rats that ghrelin and its receptor are present in a wide range of body parts such as heart, kidneys, liver, lungs, pancreas, placenta, brain, pituitary and intestines (3-5). Ghrelin takes part at the secretion of growth hormone, energy balance, food intake and regulation of body weight, and shows its effect by binding to GHS-R type 1 (1).

Ghrelin and GHS-R are found in reproductive organs and placenta (6, 7). The expression of ghrelin peptide and ghrelin mRNA are shown in both human and rat placentas. It is known that human and rat placentas have a strong correlation in terms of ghrelin expression and pregnancy periods. In the case of human placenta, ghrelin as an immunohistochemical can be monitored to be expressed in main cytotrophoblasts and very little in cyncytiotrophoblasts in the first trimester. However, in the term, there has been observed no ghrelin as an immunohistochemical. On the other hand, with pregnant rats, while there has been no proof of ghrelin mRNA expression in the early period of pregnancy, a prominent increase has be shown on the 16th day of pregnancy, later decreasing in the continuing period (8).

It is stated that ghrelin and its functional receptor GHS-R 1 are expressed in adult human testicles. Ghrelin immunoreactivity has been seen in normal testicles, Leydig cells and lesser in Sertoli cells (7). Ghrelin is also expressed in ovary. While it is expressed highly in functional phase in corpus luteum, it is defined that it is expressed in lower levels in regression period (9). Observation of intense and specific ghrelin immunopositivity in steroidogenic luteal cytoplasms also supports this finding (10). Functional ghrelin receptor is found in follicular and luteal surface epithel of the ovary, and in interstitial hilus cells. Ghrelin and GHS-R expression are also seen in the endometrium. It is thought that ghrelin has paracrinal and otocrinal effects in embryonic implantation causing many mediators act in synergy, and has very complex effects (11).

The borders of the direct effects of ghrelin on reproductive system are not yet known. It is stated that ghrelin has extragonadal effects on the reproductive system. It is shown that it suppresses LH secretion and lessens the LH response to GnRH in vitro (12).

Ghrelin: Structure and Pleiotropic Functions of an Ubiquitous Molecule

Ghrelin was identified in late 1999 as the natural ligand of the GH secretagogue (GHS) receptor (1). The GHSs constitute a large family of peptidyl and non-peptidyl synthetic compounds with ability to elicit GH release in vivo and in vitro in a wide spectrum of species, including humans (13). Their endogenous counterpart, ghrelin, results from the cleavage of a precursor form (prepro-ghrelin) that is composed of 117 amino acids. In the human and rat, the mature ghrelin peptide consists of 28 amino acids, with the addition of an n-octanoyl group at Ser3 (1, 14). Such a post-translational modification (acylation) was the first of this type reported in a secreted protein, and it was originally considered as absolutely essential for the biological activities of ghrelin (14-16).

The biological actions of ghrelin are mostly conducted through interaction with its specific cell surface receptor, namely the GH-secretagogue receptor (GHS-R), which belongs to the large family of G-protein coupled, seven transmembrane domain receptors (17). Two GHS-R subtypes, generated by alternative splicing of a single gene, have been described so far: the full-length type 1a receptor and the truncated GHS-R type b (17). Whereas the GHS-R 1a is the functionally active form of the receptor, the GHS-R 1b lacks the transmembrane domains 6 and 7 and it is apparently devoid of high affinity ligand binding and signal transduction capacity (17). Thus, its functional role, if any, appears uncertain. In addition, a wealth of evidence has been recently gathered for GHS-R-independent actions of ghrelin, including some of its effects on cell proliferation and metabolism (14).

The biological actions of ghrelin have been proven much more diverse than those of originally anticipated, and include endocrine and non-endocrine effects. In terms of endocrine actions, ghrelin was originally identified by its ability to elicit GH secretion in a variety of species (14, 15). In addition, ghrelin might serve additional central neuroendocrine functions, such as modulation of lactotropic and corticotropic axes (14). An additional feature of ghrelin that has drawn considerable attention is its ability

to operate as orexigenic signal. This action appears to be conducted mostly at the hypothalamus, through regulation of several food-intake controlling neuropeptides such as neuropeptide Y (NPY), Agouti-related protein (AgRP) and orexin (14, 15). Notably, ghrelin is predominantly secreted by the stomach and its expression is mostly regulated by nutritional status and metabolic factors (e.g., it is enhanced after food deprivation). Thus ghrelin has been proposed as molecular signal for energy insuffiency, which may play a major role in the long-term control of body weight (10, 18).

Ghrelin and Reproduction: a Link Between Energy Balance and Fertility?

The neuroendocrine system governing somatic growth, energy balance and reproduction are intimately related. Such a link had been long hypothesized on the basis of the well-known need of sufficient energy stores to achieve proper pubertal development, growth and fertility (9, 19). However identification of the molecular signals responsible for such an integrated control has begun only recently. A revolutionary finding in this area was the cloning of the adipocyte-derived hormone leptin, a satiety factor produced primarily by the white adipose tissue, which signals the amount of body energy stores to the hypothalamic centers controlling food intake and energy balance (19). More importantly, leptin is now regarded as a pivotal neuroendocrine integrator, which operates as a pleiotropic mediator in a wide range of neuroendocrine systems, including the reproductive axis (16, 19-21). The data so far available make it tempting to speculate that ghrelin might be a good candidate for such a neuroendocrine integrator. Indeed leptin and ghrelin share some relevant functional features, as both molecules are peripheral factors involved in the control of food intake and somatotropic axis. Recently ghrelin might participate in the control of gonadal axis (9, 16, 22-25).

Ghrelin Expression in the Testis and Ovary

One of the reproductive facets of ghrelin that was first evaluated was its presence and actions in male gonad. Initial analyses identified a testis-specific ghrelin gene derived transcript (GGDT) in the mouse (26), and expression of ghrelin gene in human testis was preliminarily reported (3). Thus, expression of ghrelin in rat and human testis was demonstrated through molecular and immunological approaches (7, 22, 23, 27). In the rat testis, ghrelin expression was selectively detected in Leydig cells at advanced stages of maturation, regardless of their fetal or adult origin (7, 22, 27). Similarly, immunohistochemical analyses evidenced that ghrelin is strongly expressed in interstitial mature Leydig cells of the human testis (7). In the rat, ovarian expression of ghrelin gene was demonstrated throughout the estrous cycle, with the lowest levels in proestrus and peak expression at diestrus, i.e., during the luteal phase of the cycle. Moreover, ghrelin immunoreactivity was predominantly located in the luteal compartment of the ovary (9). Likewise, strong ghrelin immunostaining was observed in young and mature corpora lutea of the human ovary, whereas ghrelin signal was absent in ovarian follicles at any developmental stage (28). There are still many open questions concerning the potential reproductive actions of ghrelin. In order to shed light on these unanswered questions, we have aimed at defining, by using immunohistochemical method, how the ghrelin expression in the gastrointestinal mucosa of ovariectomized female rats with lack of estrogen may be affected. In our study that we have aimed at finding answers to unanswered question, we have tried to determine by histochemical method how the ghrelin expression in gastric mucosa of female rats that are lacked of estrogen may be affected after ovariectomy. Consequently, bilateral ovariectomy causes no histological changes in the gastric tissue while it is observed that ovariectomy is effective on gastric ghrelin immunoreactivity (29).

Recently, ghrelin implicated in modulating feeding behavior and energy metabolism, has been identified in mouse uterine fluid and endometrium as well as in morula and blastocyst stages (30).

In summary, ghrelin has recently emerged as a pleiotropic neuroendocrine modulator implicated in the control of a wide spectrum of biological functions, including body weight and energy balance. In addition, growing evidence indicates that ghrelin may participate in the regulation of different aspects of the reproductive function.

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