LEPTIN, THE MEDIATOR OF ENERGY RESERVE HAS ROLE IN FERTILITY: A REVIEW

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ABSTRACT

Leptin, an adipocytokine was discovered in 1994 as putative hormone involved in appetite control acting at hypothalamic level. Since its discovery lot of work has been done over this novel molecule and in variety of physiological domains. Previously it was speculated that fertility, which is the basis of species progression has link with total body mass and energy. Leptin which is involved both in appetite regulation and reproductive process is thought to be have role in fertility regulation. Leptin is secreted from adipose tissue, which is marker of energy reserve of the body. In this review the role of leptin in regulation of fertility has been discussed.

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INTRODUCTION

Leptin, the obese (*ob*) gene product, is synthesized and secreted exclusively by adipocytes (1). Serum leptin levels correlate with the amount of body fat in rodents and humans (2, 3) and regulate the amount of food intake by monitoring energy reserves through interaction with hypothalamic leptin receptors (4). Leptin binds to its receptors on the cell membrane and is involved in the activation of signal transducer and activator of transcription-3 (STAT3), a member of the signal transducer and activator of transcription family of proteins (5). In humans at least four types of splice variants of OB-R messenger ribonucleic acid (mrna) encoding proteins have been identified; they differ in the length of their cytoplasmic domains (6). Although the long form, referred to as OB-RL, has the full-length variant, three types of short forms, B219.1 to B219.3, lack several sequences that are responsible for intracellular signaling (6). In addition to the action on energy metabolism, leptin appears to influence various reproductive functions. Injecting leptin into *ob/ob*mice that are infertile and with low levels of gonadotropin increases the weight of the uterus and ovaries and the number of follicles (7), resulting in restoration of fertility (8). Administering leptin treatment to normal female mice accelerates puberty (9), and in humans higher leptin levels have been shown to relate to the earlier onset of menarche (10). These actions of leptin are considered to be mediated mainly through brain OB-R. In contrast, the m-rnaand protein of leptin and OB-R m-rnaare also expressed in peripheral reproductive tissue, including granulosa cells (11, 12), cumulus cells (6, 11) of human preovulatory follicles, oocytes and embryos (11), and human placental trophoblasts (13, 14). These findings suggest that leptin plays a physiological role in early reproductive development.

LEPTIN AS A SIGNAL OF NUTRITIONAL STATUS LINKED TO THE REPRODUCTIVE PROCESS

The amount of body fat stored is known to influence fertility, indicating a link between adipose tissue and reproductive system (15). An interesting hypothesis is that leptin is a peripheral signal indicating the adequacy of nutritional status for reproductive function (16). Therefore it seems possible that low leptin concentrations indicate a status of inadequate nutritional stores and could prevent an unwanted pregnancy which demands additional energy to support a growing fetus.

It is relatively well documented that leptin's central action is mediated via hypothalamic NPY gene expression (17). In response to energy restriction or fasting, it is proposed that NPY gene expression increases in response to a reduction in circulating leptin levels. In support of this hypothesis, Ob-Rb is coexpressed in NPY neurons in the arcuate nucleus of the hypothalamus in mice (18). The increase in NPY production has been postulated to decrease the stimulatory input to downstream neural pathways that ultimately reach the GnRHneurons. The evidence for neuroendocrine effects of leptin on GnRHrelease is convincing. Increased gonadotropin secretion consistently occurs as a result of leptin treatment in ob/ob mice and undernourished animals, presumably removing the inhibition of GnRH release by NPY (7, 8). Therefore, leptin communicates the size of the adipose reserve to the hypothalamus. Leptin is also synthesized in the reproductive tissues and it is related

to the hypothalamus-pituitary-ovary axis function. Gonadotrophin releasing harmoneand LH pulses can be related to leptin actions. Leptin affects directly the function of reproductive organs via paracrine effects, and may regulate oestradiol synthesis. In addition, oestradiol concentrations could also influence leptin synthesis. Leptin may be a signal of metabolic status to the reproductive system.

ROLE OF LEPTIN IN IMPLANTATION

Leptin is a small pleiotropic peptide (16 k Da) composed of 146 amino acid that was previously supposed to be related with homeostasis of energy and food consumption and fertility (19) . But some animal studies has also supported its role in implantation. As we know that embryonic implantation is a crucial event in reproductive success and is dependent on the interaction between the embryo and receptive endometrium. Study supporting this is that in 1994 (1) demonstrated I ob/obknock out mice that deficiency in leptin synthesis is related to obesity and sterility. The fertility of these animals is recovered with exogenous leptin treatment and not by food restriction, suggesting that leptin is necessary for normal reproductive function(8). This was further supported that leptin is crucial for implantation process in mouse (20).

There exist a considerable data with respect to probable involvement of leptin in human embryonic implantation process. The expression of the leptin receptor in human endometrium has been described (21, 22) .

ROLE OF LEPTIN IN MALE REPRODUCTIVE SYSTEM

Recently one animal study observed the role of Leptin in leydig cell function and spermatogenesis. Administration of subphysiological to physiological doses of leptin to leptin deficient obese mouse, improved Leydig cell function and spermatogenesis (23).

CONCLUSION

Leptin, an adipocytokine was discovred as having role in appetite control also has been found to be involved in reproductive physiology. So from above discussion it is evident that a sufficient body mass and energy level in the body is directly related to fertility status. Leptin being involved in both appetite regulation and male and female reproductive process is putative mediator and link between these physiological process.

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