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Leptin: the link between adipose tissue and reproductive system

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Interest in the regulation of body weight and the pathological physiology of obesity has been rekindled by the cloning of the obese(ob) gene and identification of its product, leptin, in 1994. The first publication appeared in Nature and is a milestone of obesity research. The remarkable metabolic effects of leptin in rodents are: a) inhibition of food intake, b) stimulation of energy expenditure, and c) reversal of obesity. These effects, though mostly desirable, have not been fully demonstrated in humans. The central action of leptin in the regulation of body weight includes two pathways in rodents: a) When the body weight increasing, more leptin is secreted from adipose tissue, which acts on hypothalamus, probably through a POMC or MSH pathway via M4 receptor, initiates a series of response to obesity, i.e. sympathetic tone increased, energy expenditure enhanced and food intake reduced. b) When body weight reduced, leptin concentration decreased with the shrinkage of fat mass, which may also act on the hypothalamus, probably through a NPY-Y5 receptor pathway. Then a cascade of response to hungry was induced, i.e. increase of parasympathetic tone and food intake, decrease of energy expenditure and body temperature, as well as shut-down of the reproductive function.

However, further studies during the past 9 years since its discovery have demonstrated that leptin has numerous biological effects distinct from those expected of an adipostatic, anti-obesity hormone.

Actually, it has been found that leptin is a pleotropic peptide, a multifunctional hormone. It involves at least in the following fields: a) Food consumption and energy balance, b) Glucose and lipid metabolism, c) Neuroendocrine events, e) Inflammation, f) Bone formation, g) Stress, h) Hypertension, i) Sports medicine, j) Insulin resistance, k) Pathogenesis of tumor and leukemia, and l) Reproduction.

It is well known that fertility in mammals requires adequate nutrition and reserves of metabolic fuel. People experiencing severe dietary restriction, (e.g., anorexia nervosa), wasting diseases (e.g., type 1 diabetes, cancers) or who are high performance athletes or ballet dancers encounter severe impairment of reproductive system.

The effect of nutritional status on reproduction is postulated to reflect the action of metabolic signals that are recognized by the brain and serves as indices of metabolic status. Leptin provides a window in the understanding of a potential feedback loop between adipocytic and hypothalamic factors governing appetite, energy balance and reproduction. Leptin receptors have been identified in the hypothalamus, gonadotrophe cells of the anterior pituitary, and ovarian follicular cells, as well as Leydig cells. Furthermore, overweight children, especially girls, tend to mature earlier than lean children. Hence the hypothesis arises that the degree of body fatness may trigger the neuroendocrine events that lead to the onset of puberty. Attainment of a particular proportion of fat is a prerequisite for the onset of puberty in girls and mutations of the genes encoding leptin or leptin receptor, result in the delay or absence of pubertal

development in both boys and girl.

All these facts indicate that leptin may act directly on the hypothalamus-pituitary-gonad axis.

A. Hypothalamic level:

At the hypothalamic level, we investigated leptin effect on GnRH pulse generator and on GnRH secretion from GT_{1-7} cell line. The rhesus monkeys were fitted with bilateral recording electrode arrays, each consisting of nine nichrome wires chronically implanted in the mediobasalhypothalamus with an intracerebroventricular (ICV) cannulae implanted in the 3rd ventricle for drug infusion, and with chronic indwelling cardiac catheter for blood sampling. The correlation between LH pulses as determined by bioassay of LH in blood samples taken every 10 min, and hypothalamic MUA volleys assessed in the animal before study. A unitary correlation between MUA Volleys and LH pulses has been absolute and invariable, permitting the conclusion that LH pulses and MUA volleys both represent manifestations of the activity of the GnRH pulse generator.

ICV infusion of artificial cerebrospinal fluid (aCSF) served as control. ICV infusion of leptin at 1.5 μ g/kg/h did not change the MUA volley frequency, although the baseline activity seems elevated. With ICV infusion of aCSF, intravenous injection of morphine immediately inhibited hypothalamic firing for about two hours and this effect was repeatable. If aCSF was replaced by leptin started from the initiation of the experiment, the inhibitory potency of morphine is obviously reduced (Fig. 1), indicating that leptin is able to prevent GnRH pulse generator from opium inhibition[1].

Targeting SU40 T antigen to GnRH neuron in a transgenic mouse developed GT1-7

cell line. GT_{1-7} cell line possesses all the characters of GnRH neuron in the secretion of GnRH. In our experiments, GT_1 cell were incubated with leptin at the concentration from 2 ng to 2 μ g/ml for durations of 15, 30 and 60 min respectively. GnRH released into the medium was determined by radioimmunoassay. A direct stimulation of leptin on GnRH secretions was found at 20 to 200 ng/ml levels for 15 min, 20 ng/ml for 30 min, as well as 200 ng for 60 min[2] (Fig.2).

B. Pituitary level:

The direct access to the effect of leptin on the LH synthesis and secretion of the pituitary is made possible by a method developed by Dr. Zhou's group in Shanghai Institute of Planned Parenhood Research, published in Acta Physiologica Sinica. It was demonstrated that LH specifically existed in the vacuoles of pituitary cells. The vacuoles represent the storage of LH and there are two different patterns of LH secretion: granule secretion (at small amount of LH) and vacuoles secretion (at large amount of LH). This method was used for leptin effect on pituitary cells from ovariectomized rats. Leptin, at lower concentration induced LH release, while at a higher level, it facilitated the storage in the vacuole. The estrogen primed pituitary cells are more sensitive to leptin, a 10 times lower level of leptin induced vacuole secretion as well as storage, as compared to the cells from ovariectomized rat without estrogen priming. Thus, the effect of leptin on pituitary LH cells is in accordance with, though independent of, its action on GnRH cells.

C. During Pregnancy

It is understandable that plasma leptin level are higher during gestation than that in

non-pregnant women, in view of leptin is produced from different sources, i.e. the adipose tissue, the fetus and the placenta. Although with a higher leptin level, the energy expenditure was not increasing, indicating the coexistence of leptin resistant status during pregnancy, which seems beneficial to both mother and fetus. In addition, the leptin level reaches a peak just before delivery along with elevated prolactin level[3] (Fig.3). Taking together of that in vitro study, that prolactin stimulates leptin secretion, suggesting that PRL may play a role in the elevation of leptin level during gestation.

In humans, after puberty the leptin levels are consistently higher in females than in males, which reminded us as if we can predict genders of fetus by measuring leptin concentrations in maternal blood, cord blood or amniotic fluid. However our data for more than 300 deliveries suggest that fetal sexes could not be revealed by leptin concentrations from these three sources of samples (Tab 1).

Nevertheless, the leptin levels in maternal and cord blood do reflect the body weight of newborns, being highest in those neonates whose body weight is larger to gestation age, and lowest in neonates with smaller to gestation age.

D. Puberty

The mechanism for the initiation of puberty remains unclear, but it is most likely multi-factorial. The wake of GnRH pulse generator plays an essential role in its initiation. Children with mutations of leptin gene or leptin receptor gene lack of development of sex maturation, indicating that leptin appears to be a key or permissive role in pubertal development.

We cross-sectionally investigated leptin levels in 104 boys and 118 girls at different

Tanner stages around puberty. It was found that the serum leptin is continuously increasing in girls and increases initially, then decreases, right after the onset of puberty in boys (Fig.4), which suggests that leptin may play a triggering role in promoting puberty of both sexes and it is also an essential element in completing puberty and in maintaining reproductive functions for the females [4,5].

E. Conclusions:

Leptin is an important hormone communicating nutritional status to the reproductive system, which is suggested by numerous investigations in different levels [6] also confirmed from following observations:

1. Leptin is an important factor in maintaining the activity of GnRH pulse generator, at least, in certain circumstances, partially protects latter from inhibition;
2. Leptin stimulates GnRH secretion from GnRH neurons and LH secretion from pituitary cells;
3. Leptin may play a role in pregnancy-related event, but has no relationship with the gender of fetus;
4. Leptin seems one of the key factors in the pubertal development.

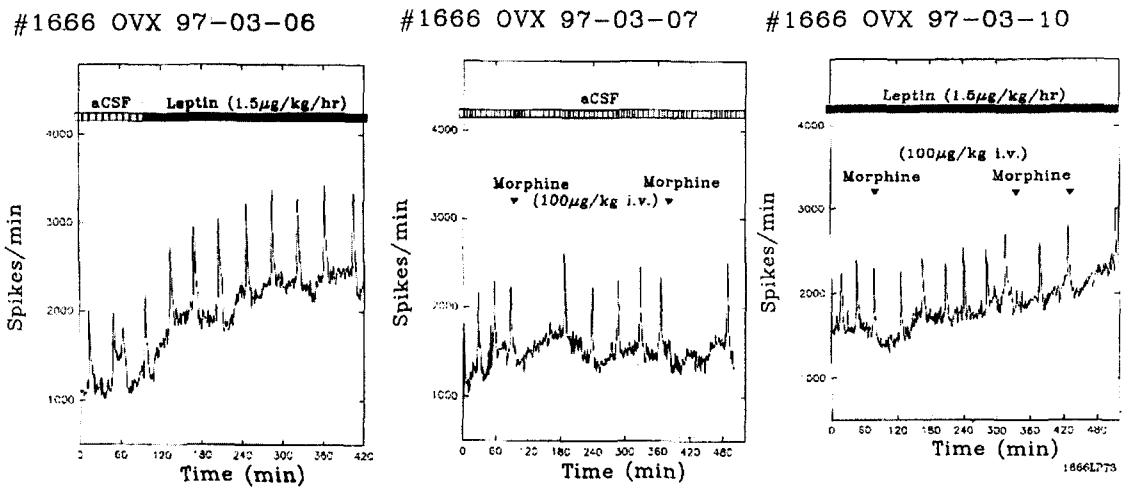

Fig.1. morphine on GnRH pulse generator

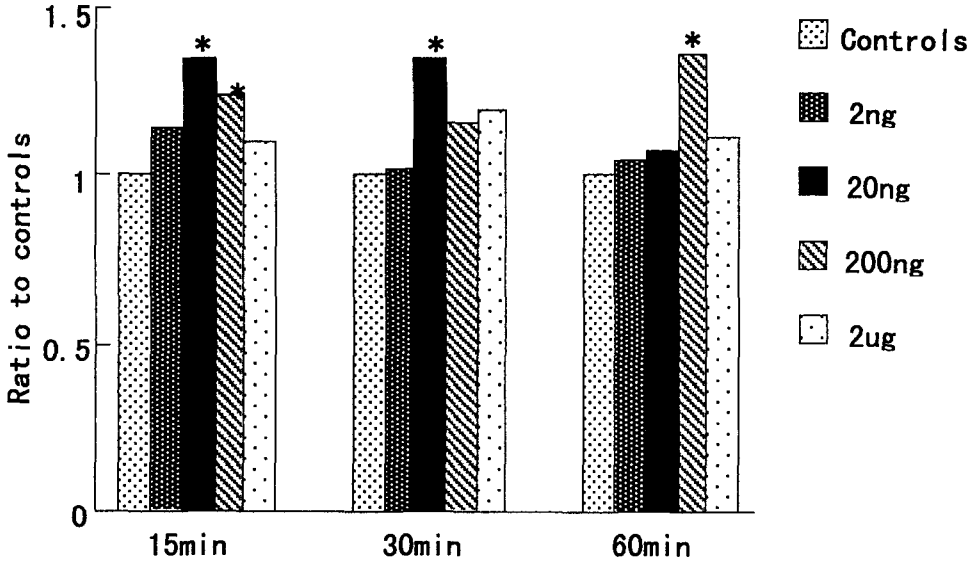

Fig.2 Effects of Leptin on GnRH Secretion from GT1－7 cell line

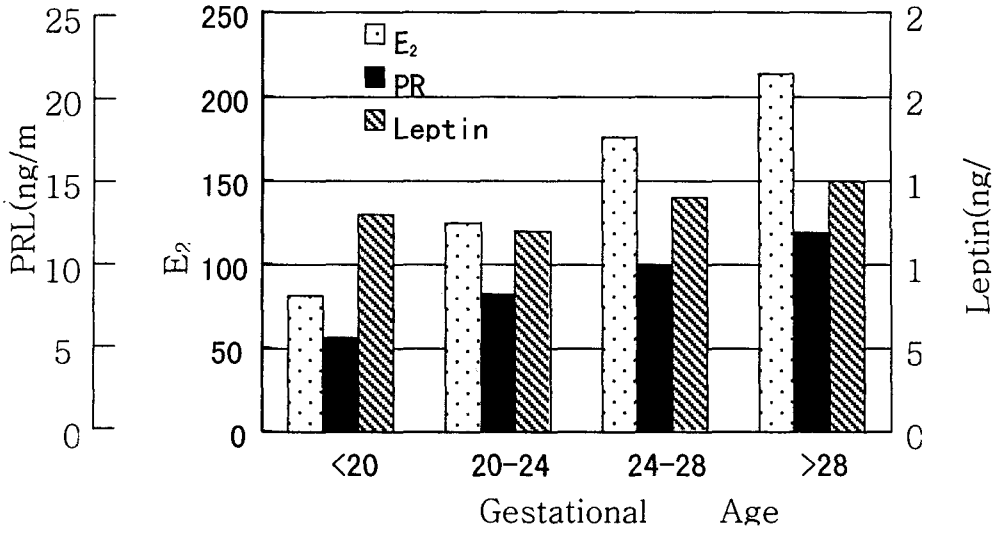

Fig.3 Leptin, PRL, E2 concentration during pregnancy

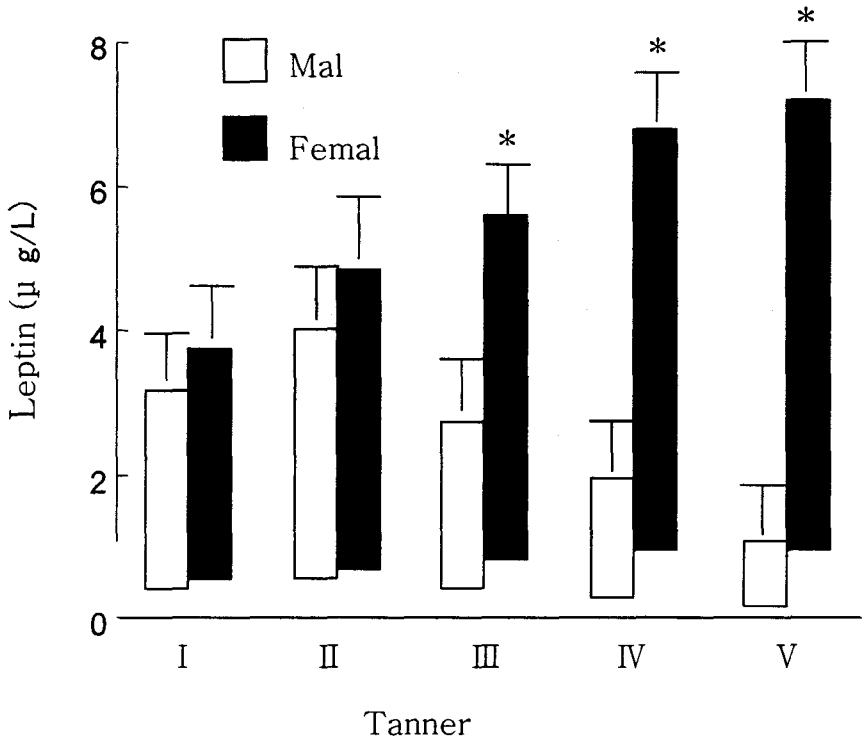

Fig.4 Leptin levels in boys and girls during puberty

Table 1. Leptin in maternal blood, umbilical blood and amniotic fluid

(relation with the newborn sexes)

	Case	Maternal blood	Umbilical blood	Amniotic Fluid
Male newborn	152	21.6±10.6	11.5±9.3	3.6±3.2
Female newborn	169	19.1±9.7	11.7±7.6	3.1±1.6

Reference

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