A new action of peptide hormones for survival in a low-nutrient environment

Takahiro Sato1), Takahiro Nemoto2), Kazuya Hasegawa3), Takanori Ida4) and Masayasu Kojima1)

1) Molecular Genetics, Institute of Life Science, Kurume University, Kurume, Fukuoka 830-0011, Japan
2) Department of Physiology, Nippon Medical School, Bunkyo-ku, Tokyo 113-8602, Japan
3) Faculty of Nutritional Science, The University of Morioka, Takizawa, Iwate 020-0694, Japan
4) Division for Searching and Identification of Bioactive Peptides, Department of Bioactive Peptides, Frontier Science Research Center, University of Miyazaki, Kiyotake, Miyazaki 889-1692, Japan

Abstract. Malnutrition occurs when nutrient intake is too low for any reason and occurs regardless of gender or age. Therefore, besides loss of eating or digestive functionality due to illness, malnutrition can occur when a healthy individual undergoes an extreme diet and halves their nutrition, or when athletes exert more energy than they can replenish through food. It has recently been reported that in Japan, the mortality rate of leaner individuals is equal to or higher than that of obese people. It is important to understand what homeostatic maintenance mechanism is behind this when the body is under hypotrophic conditions. Such mechanisms are generally endocranially controlled. We address this fundamental concern in this paper by focusing on peptide hormones. We introduce a mechanism for survival in a malnourished state via the regulation of food intake and temperature. Additionally, we will discuss the latest findings and future prospects for research on changes in the endocrine environment associated with malnutrition associated with exercise. We also review changes in next-generation endocrine environments when caused by malnutrition brought on by dieting.

Key words: Peptide hormones, Ghrelin, Milieu, Thrifty phenotype, GH resistance

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Introduction

In order to maintain a good level of health; the necessary calories and nutrients must be absorbed from our food daily. If there is an imbalance between intake calorie and nutrient requirements, malnutrition will ensue: classed as either over- or under-nutrition. Until now, adverse effects such as obesity (from over-nutrition) have been studied in the context of lifestyle-related diseases. Obesity has now been revealed to cause health problems such as diabetes, impaired glucose tolerance, dyslipidemia, hypertension and others [1]. When considering malnutrition, both over-nutrition and under-nutrition need to be considered. This review article focuses on under-nutrition which has recently garnered attention from researchers.

Malnutrition (under-nutrition) is a condition in which there is a shortage of calories or one or more essential nutrients. It is a physiological condition which occurs when the intake of nutrients is less than physiologically required. Specifically, it is caused by the inability to obtain or cook food, having a disease that is difficult to eat or absorb food, or having a significantly increased caloric requirement. There are two known malnutrition states: marasmus and kwashiorkor [2]. Marasmus (protein-energy malnutrition) is caused by both calorie and protein deficiency, and when severe leads to severe developmental defects and significant weight loss. It has been observed when nutrition has not occurred for a long time, such as during starvation and digestive system malignancy. Anorexia nervosa also is within this classification. Conversely, kwashiorkor (protein malnutrition) is a state in which protein is depleted more heavily than calories. It is characterized by a bloated stomach and is found in infants in underdeveloped countries in Africa and Southeast Asia. Under any condition, malnutrition leads to loss of defense against infection, delayed wound healing, and metabolic disorders. Therefore, any malnutrition status remains the same in terms of health complications and life prognosis.

Although it is easy to imagine that such forms of malnutrition are due to starvation and diseases, it has been found that malnutrition is not limited to these situations.
It may also occur in people who seem apparently healthy. For example, in diet-oriented young women, repeated dieting and novel extreme diets result in poor nutrition. It is feared that young women’s ‘desire to be thin’ may increase the risk of many health problems, and that malnutrition among young and pregnant women may increase the risk of lifestyle-related diseases in the next generation of children. In addition, an individual can in fact be under-nourished despite a perceived healthy appearance when maintaining a diet consisting of only fats and carbohydrates but which lacks other nutrients such as protein. Furthermore, if a large amount of energy is consumed (such as by an athlete) and even if apparent sufficient energy is consumed through eating food, the athlete can be malnourished.

Malnutrition is therefore a physical condition that can occur regardless of gender or age. A recent study which compared the mortality rates between obese and lean people found that rates tend to be equal or higher for leaner people [3]. Therefore, there is an increasing phenomenon requiring further understanding: how is homeostasis maintained when the body is experiencing a low nutrient intake. Malnutrition has long been studied and is known to reduce energy consumption while simultaneously promoting energy intake during hunger. However, it is unknown what factors and which pathways are regulated when the body is in this state. Recent studies, however, have shown that this mechanism requires a starvation signal initiated by the peptide hormone ghrelin secreted from the stomach; we will discuss the details of this paper. Additionally, we will discuss the latest findings and future prospects for research on changes in the endocrine environment associated with malnutrition linked to exercise. We also review potential changes in the next-generation’s endocrine environments when caused by maternal malnutrition brought on by dieting.

**Ghrelin, A Key Peptide Hormone to Survive in a Low-Nutrient State**

Peptide hormones are peptides that are secreted into the bloodstream; they have an endocrine function. Neuropeptides present in both the central and peripheral nervous systems and are also peptide hormones. R. Gyillemien and A. V. Schally won the Nobel Prize in 1977 for their ‘discovery of peptide hormone production in the brain’. To date, about 100 peptide hormones have been identified. They are known to regulate endocrine function, feeding and reproduction, learning and memory, and pain sensation. Furthermore, recently, new physiological actions of peptide hormones such as controlling sighing and controlling lacrimal secretion have been revealed one after another with the development of novel research technology [4, 5].

Under malnutrition conditions, peptide hormones focus on their role during energy intake, such as activating the food-promoting system and promoting food searching behavior. However, recently, during malnutrition, it has been revealed that the peptide hormone acts as a factor linking to the regulation of food intake and temperature [6]. The role of the peptide hormone in the regulation of energy expenditure has also been noted.

Homeothermal animals can produce heat via metabolic processes to maintain their body temperature. However, as the amount of energy consumed for this heat production increases, so does the required food intake. Essentially, it is quite natural that the regulation of food intake and body temperature are closely linked: to control energy metabolism during malnutrition. This mechanism however is not well understood. Here we introduce the latest knowledge about food intake and the regulation of body temperature and other factors under endocrinial control during malnutrition.

During starvation, the expression of orexigenic peptides is increased, and the expression of anorexigenic peptides is reduced [7-9]. The food regulation by these peptide hormones is well understood due to its connection with obesity research. However, starvation induced torpor (a hibernation state accompanied by hypothermia and decreased activity) in small rodents such as mice and hamsters [10, 11]. It is understood that this is an energy retention mechanism when energy intake is difficult, but its mechanism is not yet clear [12]. It has been predicted that some peptide hormones may sense the nutritional status of the body due to alterations in the secretion of various peptide hormones occurring during malnourished states. Furthermore, it has also been predicted that such peptide hormones could be involved in the regulation of food intake and temperature during malnutrition. Ghrelin, a hormone secreted from the stomach, is regarded as one of the candidate hormones [13]. This is due to ghrelin being known to enhance physiological feeding processes; inhibiting the action of ghrelin results in inhibiting torpor [14-18]. Thus, it was thought that ghrelin could be a fluid transfer factor that senses the body’s nutritional status during hunger and conveys that information to the brain.

The mechanism of ghrelin-mediated feeding has been analyzed in detail including by this study’s research team [14-16]. In a state of starvation, ghrelin is released from the stomach into the blood and activates neuropeptide Y (NPY)-containing neurons present in the hypothalamic arcuate nucleus. NPY-containing neurons also project to the hypothalamic paraventricular nucleus, where the release of NPY suppresses heat production in brown adipose tissue and simultaneously induces feeding behavior.
That is, when NPY acts on the hypothalamic paraventricular nucleus in response to the transmission of starvation hormone from the periphery to the brain, a “starvation signal” in the brain is generated to trigger a starvation reaction for surviving starvation.

It was unknown what kind of neural circuit simultaneously caused different starvation responses such as the promotion of food intake and suppression of heat production by this starvation signal, but recently, the neuron group that is key to the mechanism has been discovered [6]. This group of neurons consists of a γ-aminobutyric acid (GABA)ergic neuron distributed in a part of the reticular body of the medulla [6]. It is activated by a starvation signal from the hypothalamic paraventricular nucleus and projects axons to sympathetic premotor neurons in the medullary raphe nucleus [6]. Therefore, during starvation, starvation signals from the hypothalamus activate reticular GABAergic neurons. This group of neurons then suppresses sympathetic premotor neurons in the bulbar nucleus and suppresses heat production in brown adipose tissue [6]. Interestingly, stimulation of the reticular neurons not only suppresses brown fat heat production, but also induces chewing movements and enhances salivation [6]. Since it is believed that the reticular body has a local neural circuit involved in the rhythm formation of chewing movements, the reticular GABAergic neurons activated by the starvation signal may be part of it. Thus, the bulbar reticular body is an important center of action for reducing energy expenditure and simultaneously promoting energy intake during starvation.

These facts indicate that the signal from the peptide hormone ghrelin links feeding regulation and thermoregulation under low-nutrient conditions (Fig. 1). Furthermore, it clearly shows that the peptide hormone controls energy balance and maintains homeostasis under the same conditions. It can thus be assumed that the peptide hormone is itself a key factor for surviving starvation.

Henceforth furthering understanding of the induction and mechanism of torpor, which is mainly found in only small rodents, as well as of the phenomenon of hibernation, is expected to contribute to innovative medical care by opening up new avenues for research such as organ preservation.

**Regulation of Energy Metabolism by Peptide Hormones in Relative Energy Deficiency in Sport**

Exercise moves the body by contracting muscles using energy. Energy consumption increases as exercise intensity increases. For example, according to a survey of
male triathlon players, the energy consumption in the ultra-endurance event was about 11,000 kcal [19]. In a study of women’s college teams, the daily energy consumption of Lacrosse athletes was approximately 2,800 kcal [20]. The energy consumption of these athletes is very high compared to ordinary people of the same physique. Top athletes need a large amount of food to supplement their energy consumption. Therefore, athletes, even if they eat food until satiation, will exhaust energy if they cannot compensate for their energy expenditure. This is different from the general image of poor nutrition from hunger or diet. Furthermore, athletes are required to have high physical activity even when in an energy-deficient condition. This next section outlines the relationship of peptide hormones, especially energy metabolism, when in an energy deficit due to exercise.

The inability to meet nutritional needs during competitive sports is prevalent among athletes. Energy deficiency is often found in aesthetic sports such as gymnastics and events that consume a large amount of energy such as cycling, long-distance running and weight-limited sports such as combat sports [21, 22]. According to several studies with track and field athletes, the percentage of athletes diagnosed with energy deficiency was between 18%–58%, with the majority being long-distance runners and jump athletes [21]. Relative energy deficiency in sport is a new term introduced by the International Olympic Committee in 2014 [22]. This refers to the potential effects on health and performance due to inappropriate energy intake; exercise under energy starvation decreases endurance. Furthermore, it has been suggested that long-term maintenance of this condition may adversely affect performance due to increased recovery time after exercise and decreased skeletal muscle mass [21].

In addition to the above, athletes’ energy deficiencies have some features that are different from general energy deficiency. Changes in body composition differ between general energy deficiency and the energy deficiencies athletes experience. Skeletal muscle and adipose tissue are decreased during more general energy deficiency cases such as starvation, but athletes experience decreased adipose tissue with their muscles preserved up to an extent [23]. It has been reported that this phenomenon is caused by the suppression of skeletal muscle protein degradation during energy deficiency due to a high protein diet and exercise stimulation [23]. In addition, exercise-induced energy deficiency is associated with a high blood free fatty acid concentration compared to diet-induced energy deficit [24]. When in energy deficits, the athlete’s body tries to adapt by suppressing anabolism and reproductive functionality and extracting energy from adipose tissue and the liver. The adaptive response of energy metabolism to relative energy deficiency during sport is controlled by many hormones centered on GH and insulin-like growth factor (IGF-1) (Table 1) [25-31]. GH is a peptide hormone secreted from the anterior pituitary, and its secretion is regulated by several factors, including GHRH, somatostatin, ghrelin, IGF-1, and insulin. GH regulates various physiological processes including muscle and bone anabolism in addition to energy metabolism [32, 33]. The anabolism of GH is largely mediated by IGF-1 (produced in the liver) [32-34]. IGF-1 is a hormone that is structurally similar to insulin and is involved in the proliferation, differentiation, and glycemic regulation via the activation of signaling pathways including RAS/RAF/MEK and PI3K/AKT [34]. Since GH secretion is strongly induced by exercise, GH concentrations in healthy athletes after exercise are generally high [35-37]. Furthermore, blood levels of GH increase with fasting. Similarly, energy deficits in athletes also increases the blood GH levels. Therefore, blood GH levels increase during general energy deficits as well as during the energy deficits experienced by athletes. This increase in blood GH is caused by the enhancement of the pathway via the growth hormone secretagogues receptor (i.e., the ghrelin receptor) which is induced by ghrelin when the body is in an energy deficit; in addition to the feedback mechanism of IGF-1 [34, 38]. In an energy deficient state, GH produces energy by catabolism in adipose tissue and the liver. Within adipose tissue, GH promotes lipolysis by activating hormone-sensitive lipase, resulting in the influx of free fatty acids (FFA) from adipose tissue into the circulation [39-41]. As mentioned above, it has been reported that exercise-related energy deficits increase the free fatty acid concentration in the blood more so than dietary-related

| Hormone     | Response | Reference |
|-------------|----------|-----------|
| GH          | ↑        | [7, 8]    |
| IGF-1       | ↓        | [7, 9, 10]|
| IGFBP1      | ↑        | [8]       |
| insulin     | ↓        | [8, 10]   |
| ghrelin     | ↑        | [11, 12]  |
| PYY         | ↑        | [11]      |
| oxytocin    | ↓        | [13]      |
| leptin      | ↓        | [9, 12]   |
| adiponectin | →        | [11, 12]  |

GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP1, Insulin-like growth factor-binding protein 1; PYY, Peptide YY
energy deficits [24]. However, there is no evidence that this feature is controlled by GH. In contrast, GH promotes cellular uptake of FFA by enhancing the activity of lipoprotein lipase in skeletal muscle [40, 41]. Additionally, in the liver, GH increases glucose production by enhancing glycogenolysis and gluconeogenesis. This phenomenon involves enhanced autophagy and increased expression of the gluconeogenic genes phosphoenolpyruvate carboxykinase and glucose 6 phosphatases [42, 43].

Conversely, despite the increase in GH secretion due to energy deprivation, circulating levels of IGF-1 congruently decrease. For example, limiting energy intake in non-athlete women who regularly menstruate has resulted in increases in GH with decreases in IGF-1 [44, 45]. In addition, male cyclists participating in a 1,230 km ultra-durable event were found to have a sharp decrease in IGF-1 due to an energy deficiency [27]. In a male bodybuilder study, IGF-1 decreased during the 11-week weight loss period prior to a competition [38]. Furthermore, an observational study of wrestlers found that study subjects had increased GH levels and significantly decreased IGF-1 levels at the end of their competitive season [25]. This reduction in IGF-1 is strongly correlated with an energy deficit when exercise was or was not performed [46, 47]. The decrease in IGF-1 due to energy deficiency is caused by the fact that the production of IGF-1 by GH is for some unknown reason inhibited. Elevated levels of GH due to energy deficiency are important tools for mobilizing body fat and glycogen in order to maintain normal blood sugar levels. However, if IGF-1 levels are elevated under malnutrition, an increase in energy expenditure due to anabolism will result in a survival disadvantage. Therefore, the reduction of IGF-1 due to GH resistance is considered an adaptive response to maintain homeostasis under malnutrition conditions.

Recently, fibroblast growth factor 21 (FGF21) and SIRT1 have been found to be one of the major regulators of GH resistance in nutrient deprivation states. FGF-21, a member of the fibroblast growth factor protein family, is a physiologically active peptide produced primarily in the liver. In an energy deficient state, production of FGF-21 is triggered by enhancement of the PPAR-α mediated pathway in the liver. IGF-1 is produced via the GH receptor (GHR)/janus activating kinase 2 (JAK2)/signal transducer and activator of transcription 5 (STAT5) pathway. GH phosphorylates STAT5 via JAK2 by binding to GHR. Phosphorylated STAT5 translocates to the nucleus and promotes transcription of target genes (including IGF-1, and produces IGFB1) [47, 48]. FGF21 induces GH resistance by blocking the transcription of IGF-1 by inhibiting the phosphorylation of STAT5 in the liver. In addition, FGF-21 also induces the expression of peroxisome proliferator-activated receptor co-activator 1α (PGC1α) and is also involved in the up-regulation of fatty acid oxidation and gluconeogenesis.

Sirtuin-1 (SIRT1) is a class III histone deacetylase that promotes gluconeogenesis and fatty acid oxidation during energy deficits. Recently, SIRT1 has been shown to act on GH resistance during starvation. SIRT1 interacts with STAT5 and deacetylates STAT5. Deacetylated STAT5 has a reduced ability to interact with phosphorylated Tyr residues in GHR and thus nuclear translocation is inhibited [49].

Decreased IGF-1 due to GH resistance is not only caused during energy deficiency but also during deficiencies of ingested protein, vitamin A, vitamin B6, zinc and magnesium. For example, adults who ate a protein deficient diet after fasting have less of an increase in IGF-1 levels than adults who ate a protein-rich diet [50]. Furthermore, in animal models with vitamin A, vitamin B6, zinc, and magnesium deficiencies, IGF-1 levels are reduced relative to normal GH levels [50-53]. GH resistance due to these deficiencies has not been reported in athletes but needs to be understood for nutritional support when recovering from an energy deficient state.

In recent years, the prevalence and impact of relative energy deficits associated with exercise have gradually become understood. Adaptive responses in energy deficits are controlled by many hormones, including GH, IGF-1, and IFG21. It is difficult to reveal the difference in endocrine effects between general energy deficits and athletes’ energy deficits. This is due to reports that hormones in the blood fluctuate in the same direction. However, with regard to an athlete’s lack of energy, several physiological stresses, such as exercise stimulation and dehydration, may be affecting the hormonal response associated with the energy deficit. For example, energy deficiency reduces blood IGF-1 but exercise training decreases IGF-1 even if an energy balance is maintained [54]. Leptin, an orexigenic adipose hormone, has lower blood levels during both diet and exercise energy deficits. However, diet-related energy deficits eliminate circadian rhythms of blood leptin levels, whereas exercise-related energy deficits maintain circadian rhythms [55]. In addition, dehydration exacerbates the catabolic response under exercise-related energy deficits and further increases cortisol, norepinephrine, blood glucose levels and glycerol [56]. It is thought that the lack of energy in athletes is affected not only by diet and exercise but also by physiological stresses such as dehydration and temperature. However, there are only a few reports of cross-sectional studies, interventionistic studies and animal studies that study energy metabolism and endocrine changes associated with multiple physiological stresses. Therefore, the endocrine effects of energy deficiency due to multiple physiological stresses includ-
Athletes yet to be addressed (Table 2). A more comprehensive understanding of the effects of hormones due to relative energy deficits associated with exercise is necessary to better appreciate this physiological relationship and to take effective action improving health and athletic performance. Also, peptide hormones, including GH, IGF-1, and ghrelin, are registered as banned substances in sports [57]. However, the blood levels of these hormones change constantly due to multiple physiological stresses including exercise. Furthermore, it is difficult to evaluate doping detection because it cannot distinguish between endogenous and exogenous hormones administered [58]. Therefore, elucidating the dynamics of a wide range of hormones in the relative energy deficits associated with exercise will also help set standard values of anti-doping of the peptide hormones.

Currently, a physiological condition questionnaire is being developed as a method for screening for relative energy deficits in sports [22]. Early detection of athletes who are at risk from a lack of energy is important for preventing health sequelae such as detrimental effects on long-term menstrual functionality, bone health, immunity as well as prevention of cardiovascular disease [22]. Therefore, early detection and immediate treatment are important to minimize energy damage and induce quick recovery. However, it is difficult to accurately measure energy intake and kinetic energy consumption via self-reporting strategies. Furthermore, because changes in physical findings and body composition are due to long-term effects, it is difficult to use as an early detection tool. The hormonal response acts to maintain homeostasis from the early stages of an energy deficit. Therefore, hormones present in the blood may be useful for early screening of energy deficits. In terms of future prospects, blood screening is expected to be used as an early screening marker of hormone levels.

### Developing Diseases Caused by Nutrition and Hormonal Milieu

Maternal nutritional status and hormone levels affect both the growth and development of children. In particular, insufficient calorie intake during pregnancy greatly affects the hormone level and metabolism of the developing child; acquiring a thrifty phenotype is a possibility [59]. The thrifty phenotype compensates for a smaller body to protect the brain size and functions [60]. This compensation works well if the postnatal environment is the same as in the uterus, but if it is exposed to hypernutrition after growth, there is a mismatch between constitution and environment and the risk of developing various non-communicable diseases (NCDs) increases [61]. Many metabolic adaptations during pregnancy are regulated by placental hormones (e.g., placental estrogen and progesterone) which undergo dramatic changes during pregnancy [62]. Placental hormone expression is thought to interact with fetal growth through polymorphism or epigenetic regulation of placental growth hormone. Additionally, somatomammotropin expression can induce insulin or IGF-I to alter the expression of other important hormones. Postnatal growth of the child is regulated by the action of GH-IGF-1 for bone elongation and muscle development. IGF-1 has a longer half-life in blood as it forms a trimer with insulin-like growth factor binding protein-3 (IGF-BP3) and insulin-like growth factor-binding protein complex acid labile subunit (IGF-ALS). During the ligation of the uterine artery at the end of pregnancy, the change in the methylation of the IGF-1 gene reduces the amount of IGF-1 produced and leads to short body length [63]. Changes in DNA methylation of IGF-BP3 can lead to children being small for gestational age and can lead to short stature [64]. Gene expression is regulated by DNA methylation as well as histone protein methylation and acetylation. However, no clear association has been found between the degree of changes induced by DNA methylation and the degree of gene expression in transcriptional regulation as compared to

| Table 2 | Areas for further research of endocrine on relative energy deficiency in sports |
|---------|--------------------------------------------------------------------------------|
| Determine hormones affected by relative energy deficiency across different sports. |
| Acute and chronic effects of endocrine response by relative energy deficiency in sports. |
| Effects of dietary factors other than energy intake (e.g., carbohydrates, proteins, vitamins, minerals) on the endocrine response relative energy deficiency in different sports. |
| Endocrine response changes caused by multiple physiological stress factors including temperature and dehydration in relative energy deficiency in sports. |
| Searching for initial screening markers of energy deficit in athletes. |
| Individual differences in sensitivity of endocrine response in relative energy deficiency in sports. |
| Changes in endocrine metabolism during the athlete’s game season cycle. |
| Determine the effects of health and performance after adulthood by chronic exposure to exercise-related energy deficits in childhood. |
| Investigate the effects of endocrine response due to energy deficiencies on performance on athletes. |
the changes in DNA methylation during cell differentiation. A systematic review reports that there was conflicting evidence of possible association between IGF-related epigenetic changes (i.e., lower IGF2 methylation) and adverse body weight or gestational age outcomes [65]. What must also be considered is methodologies, genome size, and gene dynamics when evaluating this relationship. It could be considered that the recent development of global DNA methylation technology will be a viable method for identifying specific loci involved in low birth weight induced NCDs and as well in other disease related studies. We hope to be able to examine larger populations using more rigorous methods. While IGF-1 changes the expression of other genes through the acetylation of histone proteins, it has been reported that in utero the trophic environment changes the expression of IGF-1 by epigenetic modifications [66]. Although it has been reported that environmental factors alter DNA methylation [67], it is not clear how changes in the epigenome cause a mismatch between constitution and environment. Additionally, it has not been clarified how the accumulation of the mismatch causes the epigenetic modification-induced diseases. Thus, it is difficult to know about not only these correlations but also their causality. Changes in nutrition and epigenetic modifications are closely correlated with hormone secretion, but it may be necessary to study in more detail the time axis to further clarify these causal relationships.

The thrifty phenotype hypothesis proposes that changes in the endocrine system develop; one could propose that a better indicator of changes to overall health is to look at constantly changing hormones. Environmental factors strongly influence an individual’s hormonal milieu; changes in the hormonal milieu affect growth and development. Examining hormonal milieu aid in determining the development and risk of future disease. It is known that changes in hormone levels such as maternal cortisol and thyroid hormone also affect the size and development of the child’s brain [68]. In addition to the prenatal maternal hormone levels the postnatal offspring’s hormonal environment also affects the child’s risk of future NCDs. For instance, leptin, which results in strong satiety signaling and increased energy expenditure through sympathetic activation produces a surge-like secretion shortly after birth, but this abnormal secretion results in leptin resistance in the offspring [69]. Obstruction of leptin signaling via leptin resistance leads to obesity and increases the risk of developing type 2 diabetes, hypertension, dyslipidemia, etc. [70]. Changes in the early life hormonal milieu such as in NPY, α-melanocyte-stimulating hormone, corticotropin-releasing factor, leptin, and glucocorticoids have been reviewed to affect subsequent food consumption not only in mammals but also in amphibians and many other animal species [71]. Furthermore, there is a critical period for such post-growth effects in which changes in the hormonal milieu can develop [72]. Many hormones have anabolic or catabolic effects, and increasing hormone levels can dramatically alter blood metabolite levels. As many studies of carcinogenesis caused by type 2 diabetes have recently reported, adipose tissue dysfunction may also promote metabolic reprogramming events that favor cell transformation. Many of the changes in glucose, lipid and amino acid metabolism observed in breast cancer can be caused by certain aspects of type 2 diabetes [73]. To further elucidate upon this we need to know “when” and “how long” changes in the hormonal milieu occurred. We also must clarify the causal relationship among changes in nutrient metabolism, hormonal milieu and the increased risk of disease onset.

In Japan, a decrease in average birth weight and an increase in low birth weight birth rate have been reported [74]. In the future, there is a concern about the increase in low birth weight induced NCDs; it is desirable to establish pre-emptive medicine aiming at early identification of risk patients and early intervention for at-risk patients. However, highly precise and specific test items and interventional methods for patient identification have not been developed yet. If the causal relationship with changes in nutritional metabolism, changes in hormonal milieu, and an increased risk of onset is clarified, then it will be possible to identify high-risk groups with a higher accuracy. Additionally, accuracy for early intervention will be possible depending on “when and what” (hormones) to measure. We strongly hope that further hormonal milieu research will contribute to the establishment of pre-emptive medicine.

In conclusion, nutrients change hormone levels, but changes in hormone levels also change metabolism. Malnutrition affects not only the individual hormone level and metabolites but also the hormone levels and phenotypes of the offspring if there is maternal malnourishment during pregnancy. Further study of these causal relationships will provide indications as to the mechanisms of onset of not only NCDs in low birth weight infants but also various other non-hereditary diseases.

Summary

In this paper, we have discussed the role of peptide hormones and how our body responds to survive when in a poor nutritional state and what kind of hormonal effects may occur. Although peptide hormones often have diverse functions, they are required to link functionality among multiple organs, regulate multiple physiological processes and maintain homeostasis under
specific physiological conditions. Ghrelin, which has been regarded as a hyperphagic hormone, is also involved in the thermoregulatory system, and when the body is in a low-nutritional state. It is part of mechanism which aids in adjusting energy intake and energy retention by regulating food intake and temperature. Therefore, the secretion of peptide hormones can be a marker of malnutrition due to exercise but can also contribute to the establishment of pre-emptive care. Malnutrition is a change in the body’s environment that can occur in anyone, and if not properly managed, its effects continue into the next generation. On the other hand, if it is possible to clarify the mechanisms of hibernation and torpor, which are indications for malnutrition, it may also contribute to our understanding of this area and may aid in improving health. In the future, it will be clarified how various hormones including peptide hormones are secretion-regulated and multi-functional linked when malnutrition occurs under various conditions. It is important that our understanding of this physiological phenomenon contributes to future medical care and overall human health.

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