INTERFACE BETWEEN NUTRITION AND REPRODUCTION: THE VERY BASIS OF PRODUCTION

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Keywords: Nutrition, puberty, reproduction, animal production, intermediate metabolism, GnRH, Kiss1, Kisspeptins, GPR54, leptin

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Summary

Nutrition level affects the metabolic status of animals thereby influencing reproduction fitness and, finally, production outcomes as well as the sustainability of any animal production system. In the female, the energetic drainage of reproduction is considerable and the asynchrony between food availability and reproductive function is serious and potentially life threatening to both the mother and the offspring. Certainly, if nutrition is compromised, reproductive efficiency is diminished in order not to compromise the survival of the mother and her progeny by potential starvation during pregnancy. Interestingly, in both animal and human models, an inverse relationship seems to exist between litter size and longevity. On this respect, the disposable soma theory on the evolution of ageing states that longevity requires investments in somatic maintenance that reduce the resources available for reproduction and, therefore, impacts upon productive outcomes. Food availability as external cue will define the energy balance status in both females and males, in order to ensure that reproduction is very closely aligned with nutrient support. Energy balance, on the other hand, is one of the most important internal cues for an animal to use in order to define whether or not triggering

the onset or resumption of reproductive function. The endocrine system, a system of glands, each of which secretes a type of hormone directly into the bloodstream to regulate the body, is often the mediator between changes in the external environment and the corresponding internal responses. Certainly, complex though integrated hormonal and metabolic changes characterize different reproductive-productive processes. In the face of progressive decline in insulin action, glucose homeostasis is maintained through a compensatory increase in insulin secretion. Once glycogen reserves are depleted, energy production switches from carbohydrates to lipids, making glucose available for different reproductive-productive functions. While a variable set of hormones acts throughout the intermediate metabolism, the common undisputable neuroendocrine initiator of reproductive function is the gonadotropin-releasing hormone (GnRH) pulse generator, building the key link between the brain and the reproductive system. The two gonadotropins, LH and FSH, in turn, will be released from the anterior pituitary, modulating gonadal function. Other endocrine players involved are the gonadal sex steroids, estrogen plus progesterone in females and testosterone in males. Fetal programming is another important aspect regarding the interface between nutrition-reproduction and its impact upon productive outcomes. Certainly, research suggests that undernutrition of females from mating onwards can be associated with retarded fetal growth, affecting fetal programming and therefore compromising both reproductive and productive outcomes. In adult offspring, irrespectively of gender, a low compared with high maternal nutrition reduces reproductive parameters and therefore compromises productive outcomes. Recent evidence regarding Kiss1, kisspeptin (KP) and GPR54 system has pointed out the key roles of these elements as a very effective sensory system that translates environmental (including nutritional) cues into endocrine-reproductive responses. The functions of this system include its potential involvement in the neuroendocrine control of seasonal reproduction as well as the metabolic gating of reproductive function, integrating in this way signals from internal and external environments. These novel actions of the Kiss1-KP-GPR54 system acquire particular importance in the design of new reproductive and nutritional management technologies not only in seasonal breeders, such as sheep and goats, but also in other non-seasonal animal species. The latter is of crucial importance in the development of new nutritional and reproductive strategies for increasing productive outcomes in every animal industry.

1. Introduction: The Interface between Nutrition, Reproduction & Animal Production

Considering the key role of the nutritional status of both females and males upon reproductive events, nutritional management is considered essential for optimizing reproductive performance in many species. The endocrine system is one of the key mediators between changes in the external environment and internal responses, with proven impacts not only in reproductive anatomy and physiology, but also, and consequently, on both reproductive behavior and efficiency. While a variable set of hormones is involved in the control of reproduction and its modulation by metabolic factors, the common undisputable initiator of reproductive function is the gonadotropin-releasing hormone (GnRH) pulse generator, produced by the hypothalamus (a portion of the brain that contains a number of small nucle. One of the most important functions of it is to link the nervous system to the endocrine system), GnRH is responsible for

building the major link between the brain and the reproductive system, via the release of GnRH to the hypothalamic portal vessels, and thereby, to the pituitary gland. In turn, GnRH stimulates the secretion of the two gonadotropins, LH and FSH, by the gonadotrophs in the anterior pituitary (also called adenohypophysis, is the glandular, anterior lobe of the pituitary gland. It regulates several physiological processes including stress, growth, and reproduction). Other endocrine players of such hypothalamic-pituitary-gonadal (HPG) axis are the gonadal sex steroids, mainly estrogen and progesterone in females or testosterone in males.

The cyclic or seasonal function of the HPG axis is modulated by an array of neuronal inputs, governed either by photoperiodic or thermoperiodic pathways, which ultimately modulate the neuronal activity of the GnRH releasing terminals in the hypothalamus and do also have an impact on energy homeostasis. These features provide the basis for the environmental control of either (i) the onset of reproductive function at puberty, (ii) the recurrent reproductive cycle observed in the adult female stage in non-seasonal breeder and (iii) the intermittent reproductive cycles observed in seasonal-breeder species. In all the above scenarios, the nutritional status is closely related to the function of the HPG axis. Hence, clear links exist between energy balance, the pool of metabolic fuel (glucose, pyruvate and lactate) availability and reproductive capacity. In this way, changes in the circulating levels of metabolic hormones or even metabolites are important signals that inform the central nervous system (CNS) about the nutritional status of the organism and gate its capacity to reproduce efficiently.

In addition to their ability to modulate hormonal systems with an impact of reproduction, nutritional cues are also direct regulators of seasonal reproduction and a main cue regulating fertility in cycling animals. Therefore, nutritional supply is considered an alternative to hormonal treatments in order to increase reproductive efficiency and production outcomes. Certainly, positive effects of nutrition upon reproductive yields are commonly obtained through increases in body weight and welfare of the animal, both in the long-term ("static effect", in which heavy females have higher ovulation rates) or short-term ("dynamic effect", by a higher feeding over 3–4 weeks before mating). However, reproductive efficiency may be also enhanced by supplying nutritional inputs in a very short time scale, i.e., less than 10 days, without changing body weight. This phenomenon is known as "immediate nutrient effect", "acute effect" or "focus feeding". This nutritional strategy consists, in brief, in a supplementation for 4–6 days around timing of preovulatory follicle selection (a phase of the reproductive cycle in the ovary), which increases the ovulation rate over 20–30%, without detectable changes in either body weight or body condition.

The aim of this review is to highlight the roles of nutrition as one of the main internal cues for the regulated maturation and function of HPG axis during the lifespan. Our goal is to highlight the physiologic relevance of the interface between nutrition and reproduction, which is at the very basis or a major determinant of production efficiency in different animal species. To achieve such a goal, some basic aspects on the function of the HPG axis and intermediate metabolism will be reviewed, and our current understanding of the control of the HPG system by relevant transmitters and how these interplay with major metabolic players will be summarized. In this context, the role of the recently identified Kiss1 system, as composed by kisspeptins and their receptor, GPR54, as key modulators in the activation of reproductive function at puberty and in

the cycling adult stage, as well as the paramount role of birth weight, fetal programming and reproductive and productive outcomes in adult life will be also presented.

2. Basic Aspects of Intermediary Metabolism: Hormonal Control of Energy Homeostasis

Animals, either ruminants or monogastrics, like all living organisms, require energy to survive. The basal energy consumption is used for essential muscular activity, such as that of respiratory and cardiac function, for maintenance of cell structure and the intracellular environment, including protein synthesis and ion transport, as well as for keeping extracellular homeostasis, via among other regulatory systems, the synthesis and secretion of hormones.

2.1. Basic Principles of Energy Homeostasis and Intermediate Metabolism

To meet energy needs, mammals must consume the equivalent amount of energy in the form of organic molecules that can be metabolized. The major dietary source of energy for monogastrics (animals with a simple single-chambered stomach, whereas ruminants have a four-chambered complex stomach. Examples of monogastric animals are humans, pigs, dogs, and cats), is carbohydrate, which can come in the form of simple sugars, glucose, or more commonly as disaccharides, sucrose, lactose, or polysaccharides such as starch. Fat, most of which consist of triglycerides, is the second major energy source but the most efficient one, providing twice as many calories per gram than carbohydrates. Although protein represents a relatively small percentage of the total dietary intake, it provides the amino acids that are essential components of enzymes and structural proteins.

Fuel metabolism and homeostasis can be defined by a rather simple equation: the amount of energy in the diet must be sufficient to meet the energy needs of the body. This straight relationship, however, is complicated by two important factors. First, dietary fuel intake is intermittent, not continuous. Therefore, the excess of energy ingested during a meal must be stored for its use during periods when dietary sources are not available. There are three major forms of energy storage in the body. Carbohydrates are stored as glycogen in liver and muscle. Glycogen, however, is a relatively small energy reservoir and the amount of energy that is stored as glycogen is not sufficient to meet even the needs of one day. The major site of energy storage is the adipose tissue where there is sufficient triglyceride (ester derived from glycerol and three fatty acids) to provide energy for several weeks. Consequently, during any prolonged period of fasting, the free fatty acid released from adipose tissue serve as the primary source of energy for most tissues via beta-oxidation. There is also a significant amount of energy stores as protein, primarily in muscle, although is a relatively expensive source of energy because protein serve other essential functions.

The second factor to consider and which complicates the energy balance equation is that several tissues, most notably the brain and gonads, are normally dependent on direct glucose supply as a source of energy. For this reason, it is of paramount importance to keep blood glucose concentrations above a critical threshold level. On this respect, hepatic glycogen is an important reservoir of glucose that can be used to maintain normoglycemia (the normal level of glucose in blood) during a short fasting period. However, it depletes easily and, therefore, another sources of glucose must be used at

certain metabolic conditions. Protein can be readily converted to glucose via gluconeogenesis, whereas fat cannot. Once glycogen stores are depleted, catabolism of protein and conversion of amino acids to glucose becomes the primary means for meeting the energy needs of those glucose-dependent tissues.

Upon consumption, the ingested fuels are diverted into storage as glycogen, triglyceride and protein. Between meals, these energy stores are used to provide energy and to maintain plasma glucose concentrations. The flow along these metabolic pathways is influenced by a variety of hormones including insulin, glucagon, epinephrine, cortisol, thyroid hormones and growth hormone (GH). More recently, additional hormonal players in glucose homeostasis have been identified, including leptin, resistin, adiponectin and ghrelin, among others. Some of the major actions of these hormones on fuel metabolism and/or fuel (food) intake, as well as their physiological importance, will be briefly reviewed below.

2.2. Hormonal Regulation of Fuel Metabolism and Food Intake

Under most circumstances, insulin, an anabolic hormone produced by the endocrine pancreas**,** is the dominant hormonal regulator of fuel metabolism. Insulin lowers circulating concentrations of glucose, free fatty acids and amino acids and promotes their storage in the form of glycogen, triglycerides and proteins, respectively. Some of the main actions of insulin include stimulation of glucose uptake and conversion to glycogen in liver and muscle, inhibition of lipolysis in liver and adipose tissue, and stimulation of protein synthesis in muscle. In addition, insulin is an anorectic hormone, which is likely to contribute to the cessation of appetite that follows the postprandial rise of circulating glucose after food intake. Although insulin promotes energy storage, all of its actions are readily reversible so that a fall in insulin concentrations will cause energy mobilization. Certainly, changes in insulin secretion are important to fuel metabolism both during a meal, when plasma insulin levels are elevated, and between meals, when plasma insulin is low. The importance of insulin to normal fuel metabolism is illustrated by the dramatic metabolic changes that occur in untreated diabetic patients; changes that cannot be compensated by any of the other hormones affecting fuel metabolism.

Glucagon is another important hormone, secreted by the pancreas, involved in the normal control of fuel metabolism. The primary action of glucagon is to protect against hypoglycemia by stimulating glycogenolysis and gluconeogenesis. Glucagon also stimulates lipolysis but their effects upon the muscle and adipose tissue are of limited physiological relevance. Since the effects of glucagon are opposite to those of insulin, secretion of these two hormones is usually inversely related. Consequently, insulin and glucagon normally act reciprocally to maintain glucose homeostasis.

Epinephrine, also known as adrenaline is a hormone and a neurotransmitter produced only by the adrenal glands, as glucagon, stimulates both hepatic glycogenolysis and gluconeogenesis. However, the most potent actions of epinephrine are on muscle and adipose tissue, where it stimulates glycogenolysis and lipolysis, respectively. The stimulation of lipolysis produces an increase in free fatty acids, while glycogen breakdown in muscle leads to the release of lactate, which serves as precursor for hepatic gluconeogenesis. Epinephrine plays only a minor role in the regulation of fuel

metabolism under resting conditions, but it is important for the metabolic responses to stress and exercise.

Although growth hormone(GH), a single-chain polypeptide synthesized, stored, and secreted by the somatotroph cells within the anterior pituitary gland, influences certain aspects of fuel metabolism, it is normally of little importance in the overall regulation of these processes. GH has protein anabolic effects in muscle while it conducts catabolic actions upon carbohydrate and fat metabolism. An increase in GH levels can thus elevate plasma glucose and free fatty acid levels under some circumstances. However, circulating concentrations of these factors are not normally correlated with changes in GH secretion.

The major catabolic effect of cortisol and other glucocorticoids is the stimulation of hepatic gluconeogenesis. Cortisol also promotes protein catabolism in muscle, thus increasing the supply of gluconeogenic precursors. Most of the other actions of cortisol on fuel metabolism are permissive in that it allows other hormones to exert their full effects, such as epinephrine-induced lipolysis, which is enhanced by cortisol, but does not exert independent actions. Because of these permissive effects, adequate cortisol levels are a prerequisite for normal fuel metabolism. However, changes in cortisol secretion do not contribute significantly to the metabolic responses to feeding or fasting. Nonetheless, during prolonged fasting, when an animal faces significant stress, cortisol release and actions are activated.

Regarding thyroid hormones (T3, T4), their actions are somewhat analogous to those of cortisol since they are permissive for normal metabolic responses. Thyroid hormones are mostly catabolic, since they tend to stimulate glycogenolysis, lipolysis and protein catabolism. However, because their actions are rather slow, changes in thyroid hormones are usually not important for rapid fuel homeostatic responses.

With the exception of the anabolic effects of GH on protein metabolism, all of the actions of glucagon, epinephrine, cortisol, GH and thyroid hormones are opposite to those of insulin. Because of this insulin antagonism, these five hormones have been classically referred as “counter-regulatory” or “anti-insulinic” hormones. In fact, as already noted for glucagon, the secretion of most of these hormones is normally inversely related to insulin release. The net result is that these hormones usually act in (reciprocal) concert with insulin to maintain normal fuel homeostasis.

In addition to the *classical hormones* indicated above, other endocrine factors from the adipose tissue and the gastrointestinal tract have been identified in the last two decades. The adipocyte has been classically identified as an inert deposit of fat, but it is now recognized as an important source of different endocrine and cytokine factors, globally termed asadipokines, with essential roles in the control of metabolism and food intake. Among them, leptin is an indispensable signal for energy homeostasis, as evidenced by the dramatic alterations in energy balance and body weight in conditions of defective leptin signaling. The major actions of leptin take place at the hypothalamus, where leptin inhibits food intake and enhances thermogenesis. The circulating leptin levels, as released by the white adipose tissue, are proportional to the amount of body fat stores, leptin is therefore thought to play an essential role in body weight homeostasis and in the maintenance of the energy balance equation. Notably, persistent excess of leptin, as observed in obesity, induces a state of resistance to its biological actions that is probably

a major contributing factor for perpetuation of overweight. Importantly, leptin is also a major gate signal for the metabolic control of reproduction, so that threshold levels of leptin are needed for puberty to proceed and for the maintenance of reproductive capacity in adulthood. The mechanisms for such a major role of leptin in reproduction will be summarized later in this chapter.

Other adipokines, besides leptin, have been shown to play important roles in the control of intermediate metabolism and energy balance. It is obviously beyond the scope of this chapter to provide an exhaustive summary of the plethora of hormonal and cytokine factors released by the adipocyte. As illustrative example, it can be mentioned that the adipose tissue has been shown to release resistin, as putative factor for inducing insulin resistance in conditions of obesity. Despite the major excitement caused by identification of resistin, much debate has been boosted recently on whether this molecule is actually produced by human adipocytes (or other component of the adipose tissue, such as macrophages), as well as on the actual pathophysiological roles of resistin in the control of glucose homeostasis and food intake. As another example, the adipose tissue has been demonstrated to be the source of adiponectin, a multiglobular hormone whose levels are opposite to those of leptin (i.e., decrease in obesity and increase in negative energy balance conditions) and positively correlated with insulin sensitivity. Both resistin and adiponectin, have been shown to display specific regulatory actions upon the HPG axis, and therefore may play a role in the metabolic control of reproduction as well.

In addition to the adipose tissue, our awareness of the importance of hormones from the gastrointestinal (GI) tract in the control of energy homeostasis and fuel metabolism has significantly increased in the last decades. Although the ability of endocrine cells of the GI mucosa to secrete hormones with key roles in the control of digestive processes, including gastric and pancreatic secretion and GI motility has been long recognized, several hormones secreted by the stomach and the intestine have gained momentum as key players in the hormonal control of food intake and important aspects of intermediate metabolism only recently.

Among them, the gut-secreted hormone, ghrelin, has drawn considerable interest in last years, since it is the only circulating orexigenic (appetite-promoting) hormone known so far. Of important note, ghrelin levels have been reported to rise before meals, and to decrease thereafter; hence, ghrelin is suggested to play an important role as trigger of hunger and in the initiation of food ingestion. In addition, in different conditions, mean circulating levels of ghrelin have been shown to inversely correlate with body mass index (BMI); i.e., the lower the BMI, the higher the ghrelin concentrations. This has led to the proposal that ghrelin may operate as long-term signal for situations of energy deficit, with an important role in the generation of adaptive metabolic responses to such conditions of negative energy balance. In fact, leptin, which can be considered as signal of energy abundance as its levels are proportional to the amount of fat stores, and also ghrelin, have been proposed to operate as functional antagonists to reciprocally modulate food intake and key aspects of metabolism. Indeed, this tandem may conduct also reciprocal actions on the HPG axis since. Ghrelin, contrary to leptin, has been shown to carry out predominant inhibitory actions of different reproductive parameters in various mammalian species.

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Biographical Sketches

Dr. Cesar A. Meza-Herrera (Mexico, 1959) got his Bachelor in Animal Science obtaining the Master of Science Degree in Sheep and Goat Production Systems and completing his Ph.D. studies at New Mexico State University (NMSU), USA, getting his Major in Reproductive Physiology, his Minor in Molecular Biology, with Ruminant Nutrition as tool. In 1987, he got the academic position as Professor at Chapingo Autonomous University, Universitary Regional Unit on Arid Land Studies, Bermejillo, Durango, Mexico. During the last 23 years, he has been conducted Research Projects on Caprine, Ovine and Bovine Production, getting financial support from Private and Official Institutions greater than 1,400,000.00 USD, and working in five Multi-Institutional Research Groups on Small Ruminants, whose research results have been published in more than 60 refereed articles in JCR-journals. Results of these research projects have been presented at international level in Canada, United States, Guyana, Chile, Brazil, Bolivia, Peru, Argentina, Portugal, Spain, France, Italy, Austria, Romania, Belgium, South Africa, Jordan, the Sultanate of Oman, and Japan. He has participated as adviser in both academic and research formation of several graduate and undergraduate students. In 1988, he was accepted as Member of the National Scientist System, (SNI-CONACYT-Mexico). Dr. Meza-Herrera has been Consultant in Small Ruminant Production Systems by the Inter-American Development Bank in the CARICOM region, by the International Centre for the Study of Arid and Semiarid Areas (ICARDA) in Brazil, Venezuela and Mexico, as well as by the European Commission in Argentina, Bolivia, Peru and Mexico, while participating as Invited Professor in Austria, Spain and Argentina. From 2002-2005, he carried out a Postdoctoral Research Fellowship at the National Institute for Forestry, Agricultural and Livestock Research (INIFAP-Mexico), in the Goat Production Systems Area. His current research programs are mainly focused to understand the neuroendocrine regulation of the reproductive axis, with special attention to the interaction nutrition-reproduction mainly in the ruminants specie. Current research programs of Dr. Meza-Herrera keep active scientific collaborations with several universities and research institutions worldwide..

Manuel Tena-Sempere (Spain, 1969) MD, PhD is full Professor of Physiology at the Department of Cell Biology, Physiology and Immunology of the University of Córdoba, Spain. Dr. Tena-Sempere has been visiting research fellow in the Universities of Turku (Finland) and Edinburgh (UK), and is currently member of the Maimonides Institute for Biomedical Research (Cordoba) and the Spanish Centre of Excellence for Research in Obesity and Nutrition (CIBERobn); in both institutions he serves as member of their scientific steering boards. Tena-Sempere's expertise lies in Reproductive Biology and Endocrinology, with special attention to the neuroendocrine regulation of the reproductive axis, and in particular to the neurohormonal and molecular mechanisms responsible for the control of sexual maturation and puberty onset in mammals. In addition, Tena-Sempere's work over the past ten years has allowed the characterization of novel signals involved in the integral control of energy balance and

reproduction, and their mechanisms of action, with the ultimate aim of understanding the basis for alterations in puberty onset and fertility linked to severe disturbances of body energy/metabolic status, from obesity to anorexia and cachexia. Altogether, Tena-Sempere has published over 195 articles in international peer-reviewed journals during the last 20 years. The international impact of his work is reflected by the high citation numbers of his publications, with an *H*-index of 41. In addition, Tena-Sempere has received numerous (>50) invitations to present the work of his group in international meetings over the last years, including the International/World Congresses of Endocrinology, Neuro-endocrinology and Physiology, as well as several annual Meetings of the European and American Endocrine Societies, and numerous national Endocrine and Neuroendocrine Societies worldwide. Dr. Tena-Sempere is/has been member of different editorial boards of highly-ranked scientific journals in the areas of Endocrinology and Biomedicine, and is PI of several research projects funded by regional, national (Spanish) and European agencies. The team of Dr. Tena-Sempere maintains active scientific collaborations with numerous groups worldwide.