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Review article

Select nutrients and their effects on conceptus development in mammals

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ABSTRACT

The dialogue between the mammalian conceptus (embryo/fetus and associated membranes) involves signaling for pregnancy recognition and maintenance of pregnancy during the critical peri-implantation period of pregnancy when the stage is set for implantation and placentation that precedes fetal development. Uterine epithelial cells secrete and/or transport a wide range of molecules, including nutrients, collectively referred to as histotroph that are transported into the fetal-placental vascular system to support growth and development of the conceptus. The availability of uterine-derived histotroph has long-term consequences for the health and well-being of the fetus and the prevention of adult onset of metabolic diseases. Histotroph includes numerous amino acids, but arginine plays a particularly important role as a source of nitric oxide and polyamines required for fetal-placental development in rodents, swine and humans through mechanisms that remain to be fully elucidated. Mechanisms whereby arginine regulates expression of genes via the mechanistic target of rapamycin cell signaling pathways critical to conceptus development, implantation and placentation are discussed in detail in this review.

1. Introduction

One's Health Begins In Utero! Socioeconomic, biological, and environmental factors, particularly nutrition, have an impact on the realization of a positive outcome of pregnancy. Our research focuses on fetal and neontatal development and prevention of adult onset of metabolic diseases. Epigenomics is the study of how environmental factors such as nutrition, stress and gender modify structure and expression of genes. Epigenetic modifications of the genome may adversely impact fetal growth and development and metabolic activity (the metabolome) that predisposes one to adult onset of metabolic and inflammatory diseases (e.g., obesity, diabetes, and cardiovascular diseases). The aim of this research is to increase reproductive success in food animals and reproductive health in humans, as well as enhance long-term health and productivity of adolescent and adult humans. With a projected increase in the worldwide population from the current 7.2 billion to 9.6 billion by 2050, the global food crisis will receive increased attention as physiological epigenomics and metabolomics research improves reproductive performance of food animals that underpins human health and economic status of our global community. Improved reproductive performance in food animals due to reduced embryonic losses will increase the production of animal protein for the human diet, especially for some 400 million developing children of the world who are undernourished, and thereby compromised with respect to their future health.

Embryonic mortality and the pattern of development of conceptuses are similar for pigs, sheep, cattle and goats (Bazer and First, 1983; Geisert et al., 1982a, 1982b). Spherical blastocysts shed the zona pellucida, expand to large spherical blastocysts and then become tubular and finally filamentous in their morphology at they initiate implantation during pregnancy (Bazer, 2013). These dramatic changes in morphology precede initial attachment of trophectoderm to uterine luminal epithelium (LE) and initiation of a non-invasive "central-type" implantation. It is during this period of morphological and functional transition that 30 to 40 % of the conceptuses die, with many failing to elongate and/or achieve

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extensive contact of trophectoderm with uterine LE for uptake of components of histotroph from the uterine lumen. Among the species of livestock, prolific pigs and ewes suffer the greatest prenatal losses due to a suboptimal intra-uterine environment which may include inadequate uterine secretions and sub-optimal nutrition for conceptuses (embryo and its extra-embryonic membranes) (Bazer et al., 2009). In pigs, the first peak of embryonic deaths occurs between days 12 and 15 of gestation and three-fourths of prenatal losses occur in the first 25 or 30 days of gestation (Bazer and First, 1983). Then, fetal losses occur between days 30 and 75 of gestation likely as a result of inadequate development of the placenta or insufficient uterine capacity for placentation that is primarily at the expense of those conceptuses that experience insufficient elongation of the trophectoderm during the peri-implantation period of pregnancy (Bazer et al., 1969a, 1969b; Fenton et al., 1970; Webel and Dziuk, 1974).

Successful establishment and maintenance of pregnancy requires appropriate development of the conceptus for pregnancy recognition signaling to ensure maintenance of a functional corpus luteum (CL) to secrete progesterone (P4) required for an intrauterine environment that supports implantation, placentation and fetal-placental growth and development (Spencer et al., 2004). Interactions between the conceptus and various uterine cells, especially LE, superficial glandular epithelia (sGE) and glandular epithelia (GE), as well as stromal cells coordinate mechanisms that stimulate: 1) conceptus development, 2) uterine blood flow, 3) water and electrolyte transport, 4) maternal recognition of pregnancy, 5) transport of nutrients such as glucose and amino acids into the uterine lumen, and 6) secretion or selective transport of components of histotroph by uterine epithelia into the uterine lumen to meet the demands of the conceptus for growth and development (Bazer et al., 2012a, 2012b). Conceptuses may fail to develop appropriately due to lack of response to components of histotroph or deficiencies in components of histotroph that orchestrate developmental events required for conceptus signaling for pregnancy recognition, implantation and placentation (see Fig. 1). This review focuses on amino acids in histotroph of sheep with particular emphasis on arginine (Arg), leucine (Leu), and glutamine (Gln), as well as interactions between Arg and secreted phosphoprotein 1 [SPP1, also known as osteopontin (OPN)], that activate mechanistic target of rapamycin (mTOR) cell signaling that stimulates migration, hypertrophy and hyperplasia of cells of the conceptus (Guertin and Sabatini, 2009; Kim et al., 2010). Arg, Leu and Gln are abundant in the conceptus (Bazer et al., 2013; Wu et al., 2013a) and their concentrations in the uterine lumen increase markedly during the peri-implantation period of pregnancy (Gao et al., 2009a; Kim et al., 2013) (Fig. 2).

All mammalian uteri contain endometrial glands that produce/or selectively transport a complex array of proteins and related substances termed histotroph. Histotroph is a complex mixture of enzymes, growth factors, cytokines, lymphokines, hormones, transport proteins, sugars, amino acids, water, and other nutrients that affect trophectoderm development and function (Bazer, 2013). Among nutrients, amino acids play the most important roles in growth and development of the conceptus because they are essential for protein synthesis and activation of cellular functions (Kim et al., 2008; Wu, 2013a, 2013b; Wu et al., 2013b). This places amino acids at the forefront of animal health because fetal growth restriction has permanent negative impacts on neonatal adjustment to extra-uterine life, preweaning survival, postnatal growth, efficiency of feed utilization, lifetime health, tissue composition (including protein, fat, and minerals), meat quality, reproductive function, and athletic performance (Wu et al., 2006). Based on dietary needs for nitrogen balance or growth, amino acids have been traditionally classified as nutritionally essential (indispensable) or nonessential (dispensable). Nutritionally essential amino acids are those for which carbon skeletons cannot be synthesized or those which are inadequately synthesized *de novo* by the body to meet metabolic needs and must be provided in the diet to meet requirements (Wu et al., 2013b). Non-essential amino acids are defined as those amino acids which are synthesized *de novo* in adequate amounts by the body to meet requirements. Nutritionally essential amino acids are normally synthesized in adequate amounts by the organism, but must be provided in the diet to meet needs under conditions where rates of utilization are greater than rates of synthesis. Functional amino acids regulate key metabolic pathways to benefit health, survival, growth, development, lactation and reproduction of animals and humans (Wu et al., 2010). These unique nutrients include Arg, cysteine (Cys), Gln, Leu, proline (Pro) and tryptophan (Trp) which can be classified as either nutritionally essential or non-essential amino acids (Li et al., 2009; Tan et al., 2010, 2009; Wu, 2013b; Wu et al., 2013b). (Figs. 3–5).

Leu, Arg and Gln are of particular interest based on their roles in conceptus development. In mice, outgrowth of trophectoderm requires Leu or Arg for expanded blastocysts to exhibit motility and outgrowth of trophectoderm required for implantation (Gwatkin, 1966, 1969; Martin and Sutherland, 2001; Martin et al., 2003). Leu and Arg initiate cell signaling via a serine–threonine kinase and mTOR to regulate protein synthesis and catabolism, and induce expression of genes for insulin-like growth factor 2 (IGF2), nitric oxide synthases (NOS), and ornithine decarboxylase (ODC1) (Kimball et al., 1999; Murakami et al., 2004; Nielsen et al., 1995). This may allow the conceptus and uterus to coordinate differentiation of trophectoderm with development of uterine epithelia receptive to implantation. There are also differential effects of Leu, Arg and Gln on hypertrophy and hyperplasia of cells important for conceptus development during the peri-implantation period of pregnancy (Kim et al., 2011a). Physiological levels of Leu, Arg and Gln stimulate activities of mTOR and ribosomal protein S6 (RPS6) kinase, and proliferation of trophectoderm cells (Kim et al., 2013). Interestingly, the actions of Gln require the presence of physiological concentrations of glucose or fructose, supporting the view that hexosamine plays a cell signaling role in conceptus growth and development (Kim et al., 2012). Cellular events associated with elongation of ovine and porcine conceptuses during the peri-implantation period of pregnancy involve both cellular hyperplasia and hypertrophy, as well as cytoskeletal reorganization during the transition of spherical blastocysts to tubular and filamentous conceptuses (Albertini et al., 1987; Burghardt et al., 2009; Mattson et al., 1990).

Amino acids in histotroph of sheep and swine, particularly Arg, Leu, and Gln, as well as a mixture of Arg and SPP1 can activate mTOR cell signaling that stimulates migration, hypertrophy and hyperplasia of cells of the conceptus (Guertin and Sabatini, 2009; Kim et al., 2010). As noted previously, Arg, Leu and Gln are abundant in the conceptus (Bazer et al., 2013; Wu et al., 2013a) and their concentrations in the uterine lumen increase markedly during the peri-implantation period of pregnancy (Gao et al., 2009a; Kim et al., 2013). Arg is the precursor for synthesis of nitric oxide (NO) via NOS and polyamines via either the Arg : ODC1 pathway or the arginine decarboxylase (ADC) : agmatinase (AGMAT) pathway, as well as homoarginine.

2. Conceptus development and signaling for pregnancy recognition in sheep

2.1. Conceptus development in sheep

Sheep embryos enter the uterus on day 3, develop to spherical blastocysts and then transform from spherical (day 10, 0.4 mm) to