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Nutrigenomics: An emerging tool in Nutrition

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Abstract

Nutrigenomics is the study of genes interaction with dietary chemicals to alter the phenotype and conversely, how genes metabolize the nutrients. The results of the available experiments allow us to emphasize the importance of the influence of genetic-nutrition interactions on different physiological and metabolic processes with transcendence in animal production. The obtained information allows us to deepen in the knowledge of the genes and metabolic pathways affected by diet and the influence that the nutritional interventions can have on their regulation. On the other hand, the subsequent structural characterization of these genes and the identification of their allelic variation in animals present future implications of great interest both for genetic improvement of the breeds and for the understanding of the variability in the individual response to nutritional factors. This in turn may have future implications for the formulation of animal diets.

Keywords: Nutrigenomics, genes, phenotype, physiological and metabolic processes

Introduction

In modern years there has been a lot of development in molecular genetics techniques that allowing us to study the genomic function on a large scale. These recent advances have been lead to decrease in the cost and also having greater accessibility, which has been contributing to the development of new disciplines that would fall within the generic term “Nutritional Genomics”. Bioactive food compounds will interact with the genes affecting transcription factors, metabolite function and protein expression.

Nutrigenomics

The study of genes and gene products interaction with dietary chemicals to alter phenotype and conversely, how genes and their products metabolize nutrients is called Nutritional genomics or “Nutrigenomics” (Kaput *et al.*, 2005) [14].

Molecular-level interaction between the nutrients and also other dietary bioactive compounds with the genome called as Nutrigenomics.

Nutritional Genomics is divided into two different fields i.e. Nutrigenomics and Nutrigenetics. “Nutrigenomics” has emerged as novel and multidisciplinary research field in nutritional science that aims to deal with how dietary nutrients can interact with genes affecting transcription factors, RNA and protein expression, cellular homeostasis and metabolite production (genome, transcriptome, proteome metabolome).

Nutrigenetics defined as studies how structural genetic variation affects the diet effects on phenotype. There are possibly thousands of gene polymorphisms which may results in any deviations in nutritional biochemistry influencing the diet effects on metabolism.

Nutrient gene interaction

The diet has long been known as a complex mixture of natural substances that supplies both the energy and protein to develop and sustain the organism. However, nutrients will have variety of biological activities. Some nutrients will have to act as radical scavengers called as antioxidants and that are involved in protecting against many diseases. Other nutrients are also shown to be the potent signalling molecules and also act as nutritional hormones (Muller and Kersten, 2003) [26]. Some of the plant secondary metabolites are phyto chemicals that act as a modulator for production and animal health.

Many diseases and disorders are related to lower nutrition in terms of essential nutrients, imbalance of macronutrients, or event toxic concentrations of certain food compounds. There are many etiological causes of diseases that is due to interaction of different nutrients along with many genes (Mariman, 2006) [23].

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Due to notable diversity in all living beings differences in food digestion, nutrient absorption, metabolism, and excretion have been observed and genetic diseases in these processes have been seen. The functional integrity of gene will mainly depend on metabolic signals that the nucleus receives from various internal factors, e.g. hormones and external factors, e.g. nutrients, which are among the most influential of environmental stimuli. Genomes evolve in response to many types of environmental changes, including nutrition. Therefore, the expression of genetic information can be highly influenced by nutrients, micronutrients, and phytochemicals found in food (Van Ommen, 2002) [30].

The nutrient and gene interactions with the intermediate action of transcriptional regulatory factors (TF) in short to medium term and epigenetics factors in medium to long term. Bioactive nutrigenomic compounds are able to directly or indirectly activate or re-press TF. Therefore, nutrient and gene interaction is thought to be a TF-mediated interaction with the genome rather than a direct binding of nutrients to the genome. Hence to understand nutrient and gene interaction is very important to know the transcriptional regulatory factors.

Transcriptional factors with Nutrigenomics in livestock

Transcriptional regulatory factors are ligand dependent nuclear receptors and non-ligand dependent nuclear receptors. Ligand dependent nuclear receptors (LdNR) are comprising of per-oxisome proliferator activated receptors (PPAR), liver

X receptors (LXR), and hepatic nuclear factor 4 (HNF4), which are able to bind and be activated by major nutrients, including fatty acids for all (Khan and Vanden Heuvel, 2003) [15] and metabolites of cholesterol (oxysterols) for LXR (Zhao and Dahlman-Wright, 2010) [31]. The vitamin specific LdNR are among the micronutrient responders. These include retinoid X receptors (RXR) and retinoic acid receptors (RAR) activated by retinoic acids (metabolites of the vitamin A; Minucci *et al.*, 1997) [25], vitamin D receptor (VDR), and pregnane X receptor activated by vitamin E (Landes *et al.*, 2003) [19].

Non LdNR TF will control the expression of genes when activation by nutrients; however, such activation is not direct but mediated by other internal factors. These includes sterol regulatory element binding proteins sterol regulatory element-binding protein (SREBP1; gene name *SREBF1*), which are effected by long-chain fatty acids (LCFA; Georgiadi and Kersten, 2012) [10] and glucose (Uttarwar *et al.*, 2012) [29]; Spot 14 or thyroid hormone responsive protein (THRSP), which is affected by polyunsaturated fatty acids (PUFA; Cunningham *et al.*, 1998) [6]; carbohydrate responsive element binding protein (ChREBP; gene name *MLXIPL*), which is activated indirectly by glucose 6-phosphate and xylulose-5-phosphate (Li *et al.*, 2006) [20]; and CCAAT/enhancer binding protein, activating transcription factor 4, and nuclear factor kappa-light-chain-enhancer of activated B cells, which respond to amino acid deprivation.

Table 1: Ligand-dependent nuclear receptors (LdNR) with potential Nutrigenomic role

Common name	symbol	Gene symbol	Agonist	Main function
Retinoic acid receptor α	RAR α	RARA	Retinoic acid	Development, differentiation, Apoptosis
Retinoic acid receptor γ	RAR γ	RARG	Retinoic acid	Limb bud development, skeletal growth, and matrix homeostasis
Peroxisome proliferator activated receptor α	PPAR α	PPARA	Fatty acids	Fatty acid metabolism, inflammation, and tissue regeneration
Peroxisome proliferator activated receptor β/δ	PPAR β/δ	PPARD	Fatty acids	Fatty acid metabolism, tissue regeneration, and epidermal proliferation
Peroxisome proliferator activated receptor γ	PPAR γ	PPARG	Fatty acids	Adipogenesis, insulin sensitivity, and Lipogenesis
Liver X receptor α	LXR α	NR1H3	Oxysterols/fatty acids	Cholesterol homeostasis, macrophage functions, and inflammation
Liver X receptor β	LXR β	NR1H2		
Vitamin D receptor	VDR	VDR	Vitamin D	Mineral metabolism and immune response
Pregnane X receptor	PXR	NR1I2	Vitamin E	Detoxification
Hepatocyte nuclear factor 4 α	HNF4 α	HNF4A	Fatty acids	Development of the liver, kidney, and intestines
Retinoid X receptor α	RXR α	RXRA	9- <i>cis</i> -retinoic acid	Forming heterodimers with other LdNR and differentiation of leukocytes
Retinoid X receptor β	RXR β	RXRB	9- <i>cis</i> -retinoic acid	Embryonic morphogenesis and cell growth and differentiation

Techniques used in Nutrigenomics

Traditionally, Nutrigenomics studies have employed for small scale techniques (PCR and quantitative real-time PCR) that will measure the expression of a reduced number of genes. Actually new technologies of genomic analysis will allow more powerful approaches to a variety of problems in biology. The study of gene expression on a large scale is possible today, thanks to the development of microarrays and massive sequencing of the transcriptome (RNAseq). These new technologies introduced the concept of high-throughput data accumulation through automation and parallelization of protein and DNA/RNA chemistrys. The most widely adopted omics technologies have been the ones developed to gather transcriptomic, proteomic, and metabolomic data. Newly emerging bioinformatics techniques along with biological data are generated from genomics and transcriptomics studies have already allowed biologists to apply modern systems approaches to study interactions occurring inside living systems.

Nutritional genomics in ruminants

Dietary changes and nutritional strategies are key factors for influencing ruminant production. Genetic factors and nutritional strategies requires reproductive performance and fertility in dairy cattle. This is very much important during the transitional period and also early lactation, when the animal is particularly sensitive to nutritional imbalances. Byrne, (2005) [4] also reported that nutritional restriction due to intake of poor quality feeds, expression of specific genes associated with protein turnover, cytoskeletal remodeling, and metabolic homeostasis was clearly influenced by diet. Many of these changes in expression could be predicted from observation leads to change in animal growth and physiology during normal nutrient restriction. Jones *et al* (2004) [13] reported that entophyte-infected tall fescue on gene expression in luteal tissue of heifers by using rat microarray. He noticed some changes in cell they are specific differential expression of genes associated with neural functions, Transport function,

Cell cycle regulation, Programmed cell death. This clearly indicated that nutrients act on transcriptional level heifers.

Application of nutrigenomics in ruminant health and nutrition

Dietary manipulations and nutritional strategies are key tools for influencing ruminant production. Nutrition and genetic make-up strongly influences of the reproductive performance of milch animals. This is important during transition period and early lactation, when animal sensitive to nutritional imbalance. Very little information on diet on expression of genes related to productive and reproductive performance of the livestock. It may possible to begin to understand the importance of the relationship between individual nutrients and regulation of gene expression. When animal fed with selenium deficiency feeds that cause alteration of protein synthesis at transcriptional level; selenium deficiency adverse effect is enhancement of stress through up regulation of specific genes expression and signalling pathways. Genes controlling protection of oxidative damage, detoxification mechanism these consequences cause alteration of phenotype. The identification of the gene markers related to economically important trait like milk, meat, wool production etc. These traits will improved by dietary regimens (Kore et al., 2008) [18].

Nutrigenomics in ruminants for improved milk fat

Mammary synthesis of milk fat is a continuous process. This can be regulated by bioactive fatty acids (FAs). The biodegradation theory established that diet induced milk fat depression (MFD) in the dairy cow is caused by an inhibition of mammary synthesise of milk fat by specific FAs produced during ruminal biodegradation. The first such shown to affect milk fat synthesis was tran-10, cis-12 conjugated linoleic acid and effect has been characterized dose response relationship. During MFD lipogenic capacity and transcription of keys mammary lipogenic genes are co-ordinately down regulated. Result provide strong evidence for sterol response element – binding protein-1 (SREBP1) and spot 14 as bio degradation intermediate responsive lipogenic signaling pathway for ruminants and rodents. Rumen derived bioactive FAs regulate milk fat synthesis in ruminants (Bauman *et al.*, 2011) [3].

Mach *et al.* (2011) reported that fat is the most variable component in milk of dairy cows, with the amount and composition affected by genetic, physiological and environmental factors. It has been also shown that lipid metabolism in the mammary gland is highly controlled at the level of transcriptome. *Trans-10 cis-12 C18:2* FAs produced as intermediates in rumen bio hydrogenation of unsaturated FA, reduce transcription of coordinated and concerted genes, including transcriptional regulators such as sterol response element-binding protein-1 (*SREBP1*), peroxisome proliferator-activated receptor gamma (*PPARG*) or Spot14. The effect of specific rumen-derived bioactive FAs on transcription, as well as post-transcriptional and translational modifications in major lipogenic gene networks in the bovine mammary gland, can provide insights for the development of methods to alter milk fat yield and improve its FA profile.

Application of Nutrigenomics in ruminant reproduction and fertility

Reproduction performance in cattle and other species of livestock is based on dietary induced changes in specific genes function. It possible to understand relationship between

nutrients and regulation of gene expression e.g. study of dietary selenium on gene expression in mice (Rao *et al.*, 2001) [28]. He revealed selenium influences the pattern of protein synthesis in mice regulating specific gene expression at transcriptional levels.

Directly demonstrate the effects of nutritional strategies or diets on the expression of genes related to fertility in either male or female animals, it may be possible to begin to understand the importance of the relationship between individual nutrients and the regulation of gene expression. Selenium deficiencies can influence the patterns of protein synthesis in mice by regulating the expression of specific genes at the transcriptional level.

Application of nutrigenomics in poultry

1. Improving feed conversion ratio in broiler
2. To improving broiler and breeder performance by using epigenetics
3. Improved innate immunity and acquired immunity

a) Improving feed conversion rate in broiler

Genetic variation of broiler and genetic selection will also improve variety of traits to feed conversion. These factor include

1. Increase feed intake and appetite
2. Increased digestibility of feeds
3. Increased absorption of feeds
4. Decreased maintenance energy
5. Increased availability of ME for Gain
6. Decreased rate of protein turnover

Feed conversion rate of commercial flock improved by genetic, management, nutritional factors (Pym *et al.*, 1990) [27].

b) To improving broiler and breeder performance by using epigenetics

Epigenetics is the study of cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence or heritable changes in gene expression. It also refers to functionally relevant modifications to the genome that not involve a change in the nucleotide sequence. Examples of such changes are DNA methylation and histone acetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

Changes in the activity of gene are known from the environmental influences including nutrition in chicks or parents. These changes can result from the alteration the DNA of animals. If epigenetics is to be proven to work in chicken then possible to design feed ration or feeding programs for chicken that can alter gene expression this will help broiler performance. These changes will also potentially depress and also enhance health of broilers and also breeds. When feeding specific nutrients in early life of chicken which in turn affect gene and gene's regulations. The P restriction in young broilers followed by observed enhanced absorption in older broilers is possible evidence for these type of changes (Ashwell, 2010) [2].

c) Diseases resistance in poultry

Broiler strains from both Cobb and Aviagen are independently with either salmonella or campylobacter found in quantitative trait loci on several chromosomes which are associated with disease resistance. Feed additive and feed components were identified and that help to improve

resistance to many disease that includes variety of bacteria and virus. Nutritional components which may also affect the immunity includes many nutrients like energy, PUFA, Vitamin A, Vitamin C, Vitamin E, Lectin, Carotenoids and fiber. These components of feed ingredients will affect the lymphocyte responses in immune system. Nutrient affects the hormones concentration that may affect the immune responses.

Nutritional deficiencies may also reduce the immune response and that will leads to susceptibility to specific pathogen. When required nutrient level of Fe and biotin also help the restriction of pathogen growth proper use of nutrients may modulate the immune responses that requires appropriate scientific knowledge. Multiple diet acts differently in immunomodulation mechanism might be fed to help protect health of poultry from variety of pathogen. Nutrient level of iron and biotin can help restrict pathogen growth. Proper use of nutrients to modulate the immune response that requires appropriate scientific knowledge.

Nutrigenomics help to identify the genes that affect broiler disorder or diseases such as ascites, Sudden Death Syndrome (SDS), Tibial Dyschroplasia (TD) and also for use to develop desirable feeds to help reduce or manage these disorders.

Application of nutrigenomics in pig

- a. Improving Meat quality
- b. Improving reproductive performance
- c. Modulation of the Immune Response in Pig
- d. Increased immunity
- e. Increased longevity and life span

a) Improving Meat Quality

Meat qualities are quantitative traits determined by minor genes during pig growing and fattening. Formation of these characteristics depends on the breeding circumstances of pig. The nutritional factors and ingredients influences the quality of pork meat. The three most important feed additives are Ractopamine, Linoleic acid and Vitamin E. These three feed additives to enhance the composition and quality of pork. Ractopamine is a β -1 agonist that exerts its action through the pathway of cyclic adenosine monophosphate by binding to receptors on membrane of muscles fibre cells and adipocytes. Dietary supplementation with the ractopanime during this finishing phase of pigs will improve average daily gain and feed conversion efficiency but decrease carcass fatness (Anderson, 2000) ^[1] and increase carcass leanness. Maximize the effect of ractopamine, increased lean deposition without increase in feed consumption. Ractopamine can increase in shear force decrease in tenderness and ractopamine only contributed minor effects on most meat quality characteristics. CLA is protecting against

- Reduces Atherosclerosis
- Many types of cancer in laboratory animals,
- Improve the pork meat quality in pigs.
- Reducing subcutaneous fat
- Increasing intramuscular fat of loin muscle in pigs,
- Contributes positively to meat palatability

Feeding CLA can increase the fat hardness and also reverse the softening effect of feeding canola oil on subcutaneous fat in swine (Martin *et al.* 2008) ^[24].

Pork meat quality formation is affected by many factors such as breeds, nutritional status, and feeding systems of swine growing and fattening. Skeletal intramuscular fat (IMF) is

also positively related to the meat quality and it may also be one of the most important noted traits that could be selected to understand the interaction of genes and nutrition supplies during meat quality formation in swine. It also been shown that IMF along with shear force and drip loss was influenced by one recessive allele (Janss *et al.*, 1997) ^[11]. Swine carry the special genes who contribute to the certain meat quality. Thus, it is very important for selecting the special breed of pigs to identify the major genes that influence the certain meat quality trait. Porcine intramuscular fat is not influenced by genetic background and nutritional status of swine. The nutritional change is difficult to identify the major genes who affect these quantitative traits (Jing dong Yin and Defa Li, 2009) ^[12].

Effect of vitamin E on meat quality

Vitamin E is a very potent and lipid-soluble antioxidant, and its primary functions is to maintain and protect biological membranes against lipid peroxidation. Membrane phospholipids oxidation is a major cause of deterioration in meat quality and can affect many quality characteristics such as flavor, color, texture, nutritive value, and safety of the food the inclusion of Vitamin E above dietary requirements can effectively reduce quality defects associated with lipid peroxidation. In pigs, Vitamin E is generally supplemented at the 200 mg/kg of feed level to improve meat color stability and reduce drip loss during refrigerated storage without any negative effects on growth performance and carcass quality. The beneficial effects on sensory qualities involving freshness, tenderness and juiciness, and on the oxidative stability of pork improved by feeding 600 IU/kg of vitamin E to the pigs at 36 to 70 days before slaughter. Increased the pH value of longissimus muscle, improved color and juiciness of lumbar muscle (Dirinck *et al.*, 1996) ^[8].

b) Maximize fertility and reproduction in pig

The recent advances in pig productivity through genetic selection, management, health and nutritional strategies have resulted in reproductive performance once unpredictable. Feed efficiencies during the growing and finishing phase of production have increased in the range of 25% over the past 15 years (Fremaut, 2003). Sow reproductive efficiency also shown equal improvement and the biological potential of today's modern, hyper prolific genotypes is truly staggering (Close and Cole, 2001) ^[5].

The role of trace minerals in boar and sow reproduction

The trace minerals supplementation for sow and boar reproduction is extremely important and the trace mineral supplementation in swine research is very limited. Supplementation to working boars with organic trace minerals improved semen concentration and increased the number of doses of extended semen per ejaculate (Mahan *et al.*, 2002) ^[22] A trace element of interest in the enhancement of reproductive performance in sow nutrition is chromium supplementation of lactating sows increased reproductive performance and these effects were likely due to the glucose insulin relationships and consequential metabolic effects on reproduction. These novel feed ingredients will increase result in enhanced reproductive productivity under commercial conditions (Lindemann *et al.* 2004) ^[21].

c) Improves Immune Response in Pig

The change of the immune response will lead not only to

improved overall animal health but also to improve animal performance. New protein sources that provide additional nutrients to the diet of pigs have also been investigated and shown to improve reproductive performance. Formulating with yeast cell proteins (NuPro®, Alltech Inc.) into the diet of sows not only improved piglet growth rate and also weaning weight and also reduced the variation in growth and diarrhoea incidence (Kocher, 2004) [17].

d) Reduce the Mortality of pigs

Longevity in sow herds is a major focal point as culling rates and mortality in many situations are approaching about 60%. Genetics will play a major role in longevity as indicated heritability estimates were found to be very low and variable but selection for sow longevity may be possible, difficult to selection decisions for sow longevity must be carried out by pedigrees. Increasing the lifetime sow reproductive performance should be a major goal for industry indicating the genetic differences in populations of sows enable certain lines to have an increased herd life of up to one additional parity. Supplementation of sow diets with some commercial Bioplex® and Sel-Plex® trace minerals was found to increase the number of sows remaining in the herd after parity 4 (Close and cole 2001) [5].

Conclusion

The results of the available experiments allow us to emphasize the importance of the influence of genetic-nutrition interactions on different physiological and metabolic processes with transcendence in animal production. The obtained information allows us to deepen in the knowledge of the genes and metabolic pathways affected by diet and the influence that the nutritional interventions can have on their regulation. On the other hand, the subsequent structural characterization of these genes and the identification of their allelic variation in animals present future implications of great interest both for genetic improvement of the breeds and for the understanding of the variability in the individual response to nutritional factors. This in turn may have future implications for the formulation of animal diets.

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