

The effect of epigenetic changes on animal production

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Abstract

All alterations in DNA function, without alterations in DNA sequence, are referred to as epigenetics. It is associated with gene expression and the expression of different phenotypes (appearance). These modifications are influenced by environmental factors and can be transferred to the progeny in cell lines and complex organisms, including livestock. The first evidence of epigenetic inheritance in humans resulted from the Dutch famine in 1944. Children of pregnant women exposed to the famine intra-uterine during late pregnancy were smaller than average and more susceptible to health problems. Surprisingly, some of these effects remained in the children of these children. Recent research, mostly on laboratory animals, has shown that diet, toxicants and even culture media in in-vitro fertilization can mediate epigenetic changes. The initial interest in genomic imprinting and epigenetics in livestock was driven by the occurrence of a fetal overgrowth syndrome during assisted reproduction techniques in ruminants. In poultry there are initiatives to use epigenetics for improved heat tolerance and “nutrigenomic” research for optimizing future broiler and broiler breeder performance. Since both milk and beef production can be influenced by environmental factors and epigenetic mechanisms, the use of epigenetics to manipulate milk and beef production is being investigated. The idea is that ‘soft’ or epigenetic inheritance is a more pliable system for the fine tuning of the next generation to novel environments than the slow reactivity of Mendelian ‘hard inheritance’. Both genetic and epigenetic controls influence genetic expression and should be taken into account when formulating breeding programs for changing environmental conditions.

Keywords: flash evolution, gene expression, hard inheritance, phenotype, soft inheritance

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Introduction

Epigenetic mechanisms play a significant part in the development, growth, well-being and behaviour of livestock and provide a means of understanding how environmental factors may result in heritable changes in gene expression. Alterations in DNA function without alterations in DNA sequence are called epigenetics. These include events associated with differentiation and development, as well as changes associated with gene expression and the expression of different phenotypes (appearance) and are mediated through a variety of mechanisms. At the molecular level, epigenetic changes are mediated by changes to the chromatin conformation initiated by DNA methylation, histone variants, post-translational modifications of histones and histone inactivation, non-histone chromatin proteins, non-coding RNA and RNA interference (Tollefsbol, 2004).

These modifications are influenced by those factors classified in genetic terms as “of environmental origin”, which occur independently of DNA sequence; the induced changes can be transferred transgenerationally in cell lines of complex organisms, including livestock. Climate, temperature, nutrition, disease and other environmental factors can all modulate the phenotypic expression of the genome of the animal through epigenetic mechanisms. With a better understanding of these epigenetic mechanisms, the possibility arose that the result of some of these mechanisms forms part of the genotypic variance as currently determined. A modern definition of epigenetics is “Collective heritable changes in phenotype that arise independent of genotype” (Tollefsbol, 2011). The purpose of this paper is to give an overview of how performance and other behavioral traits in livestock may be influenced by epigenetic factors.

Discussion

The early embryo has always been considered to be in a primal state with regard to epigenetic modifications, implying that all previous epigenetic information was erased at the moment of conception.

The first evidence of transgenerational epigenetic inheritance in humans resulted from the Dutch famine in 1944. Children of pregnant women exposed to the famine intra-uterine were smaller than average and more susceptible to health problems. Poor maternal nutrition during gestation resulted in restricted growth of the fetus and increased susceptibility to disease in later life. Surprisingly, some of these effects remained in the children of these children (Lumey, 1992). It is now clear that all epigenetic modifications are not erased at conception and that the development of the embryo is influenced by a set of epigenetic modifications transferred from both parents. These epigenetic modifications can remain in the loop for longer than a single generation.

There are, however, mechanisms to reset epigenetic modifications. Epigenetic changes imposed on DNA sequences can successfully be erased and reset during gametogenesis, as illustrated by the phenomenon of genomic imprinting. The imprint is erased and then re-established in germline cells depending on the gender of the individual, with paternal imprints established during spermatogenesis in the developing sperm and maternal imprints during oogenesis in the developing oocytes. The imprinted alleles are silenced through epigenetic modification such that the affected genes in the offspring are only expressed from the non-imprinted allele inherited from the other parent. An example of the effect of imprinting known for thousands of years is the difference in appearance and character in hybrids between horses and donkeys. In beef cattle, ten carcass quality traits were found to be influenced by imprinting, contributing between 8 and 25% of the total additive genetic variance. The maternal contribution to the imprinting variance was larger than the paternal in six of these traits, whilst fat grade only showed a paternal contribution to the imprinting variance (Neugebauer, *et al.*, 2010).

It is postulated that environmentally induced epigenetic information, transmitted via the egg and sperm, fundamentally acts as a form of pre-programming. If the survival of the parents was influenced or restricted by environmental factors, the offspring are pre-programmed with the information required to enable it to survive in a similar unfavourable environment. However, if the environment is different from the predicted one, the mismatch may result in maladaptation (e.g. obesity or diseases). This concept forms the basis of nutrigenomics, where the existence of nutrition-epigenetic-phenotype relationships in livestock is increasingly being researched and exploited (Li, *et al.*, 2008; Neiberger & Johnson, 2012). Feeding pig boars with methyl-supplemented feed not only affected their epigenetic status and back-fat thickness, but resulted in a higher level of DNA methylation in the muscle of their offspring through the transgenerational transmission of the epimutations induced by feeding (Braunschweig *et al.*, 2012).

Animal tradition is a different form of epimutation and is acquired by the animal through a learning process, e.g. by observing a parent or parental influence. Maternal behaviour in rats is epigenetically influenced by the extent (Lambert & Kingsley, 2012) and nature (Kurian *et al.*, 2010) of parental stimuli. Maternal behaviour is established early in life as a result of methylation of the genes, depending on whether the dam is attentive or neglectful. Once such an animal tradition is established, it is perpetuated through epigenetic mechanisms irrespective of the genotypic make-up of the rat dams and transmitted transgenerational, although not through the gametes. Mothering ability in livestock is of critical importance to the survival of the young and is included in many performance recording programmes. The extent to which this and other behavioural traits in livestock are influenced by epigenetic factors requires further investigation.

In order to examine the transmission of epigenetic signals through subsequent generations via the embryo, the role of animal tradition must be eliminated. Modern poultry production practices provide an excellent model for this, as all the eggs are batch-harvested and hatched in a hatchery, with no contact between parents and offspring. In a study where nutritional stress and feeding behaviour adaptation was induced in poultry by unpredicted food access, adaptive responses in feeding behaviour were transmitted to the offspring by means of epigenetic mechanisms, which included regulation of immune genes (Nätt *et al.*, 2009). This, in essence, can prepare the offspring to cope with an unpredictable environment and may lead to innovative farm management approaches to equip the offspring for improved survival in alternative systems.

Many of the epigenetic influences on livestock production occur during the prenatal period, which is a particularly sensitive period with regard to epigenetic programming. It is evident that signals that may result in epigenetic modification during this, or during the early neonatal period, have a significant impact on the life of the animal. The occurrence of fetal overgrowth syndrome during assisted reproduction techniques in ruminants can be linked to genomic imprinting and epigenetics (Tveden-Nyborg *et al.*, 2008; Hori, *et al.*, 2010). This overgrowth is known as "large offspring syndrome". It is characterized by a significant increase

in birth weight (8% – 50%), increase in gestation length, breathing problems at birth and an increased frequency of perinatal death.

Although cloned animals are derived from a single genome, the degree of epigenetic similarity between the “parent” and “offspring”, or between “offspring”, is of interest. The use of differentiated somatic nuclei in nuclear transfer investigations pose an interesting challenge as it requires the genome of the differentiated nuclei to be remodeled to a totipotent state when transplanted into enucleated oocytes. Initially, it was uncertain whether the methylation patterns of the resulting cloned offspring would mirror the uniparental DNA. It is now clear that even though cloned animals have the same DNA sequence as the donor-somatic cell, phenotypic profiles can be markedly different from their “parent” as a result of epigenetic reprogramming, in some cases increasing the variability associated with traits (Archer, *et al.*, 2003).

Thermotolerance acquisition is part of the sensory development process during which the temperature set point is established. This occurs in chickens between day three and five days after hatching and is characterized by changes in DNA methylation (Kisliouk, *et al.*, 2010) and histone acetylation (Yossifoff, *et al.*, 2008). By exposing the birds to higher temperatures on day three after hatching (heat conditioning), thermotolerance to heat stress later in life is improved (Yahav & McMurry, 2001). Research into the manipulation of temperature at an earlier stage, during incubation of eggs in the hatchery, indicated that performance can be improved and thermotolerance induced, at least as far as the early post-hatch period is concerned (Uni, *et al.*, 2010).

Environmental factors impacts on production traits such as milk production through cell signaling and epigenetic mechanisms and the influence of epigenetic mechanisms on milk production traits are of interest. Although there is no current direct evidence for transgenerational epigenetic inheritance in dairy cows, all of the variation in some of the dairy traits cannot be accounted for by simple additive genetic effects. This deficit is likely due to epigenetic influences both within and between generations (Singh, *et al.*, 2012). Understanding the extent and scope of these mechanisms could provide opportunities to enhance milk production and mastitis resistance through manipulation of the environment whilst *in utero* or by manipulating early life nutrition.

Example

In a crossbreeding experiment that was done at the Vaalharts Research Station of the Northern Cape Department of Agricultural, Land Reform and Rural Development near Jan Kempdorp, the average 205-day adjusted weaning weight of the Angus x Nguni calves were 181 kg and that of the pure Nguni calves 146 kg. Although the adjusted weaning weight of the Angus x Nguni calves was 35 kg higher than that of pure Nguni calves, the difference was not significantly. This can be attributed to the large variation in weaning weights, with that of the pure Nguni calves ranging from 56 to 230kg and that of the Angus x Nguni calves from 105 to 303 kg (Scholtz, *et al.*, 2014).

The adjusted weaning weight increased with increase of the age of the cow until cows were 5 years, then it decreases. Remarkably, cow weight at weaning did not seem to have an effect on the weaning weights of the calves, but the herd of origin of the cow did have an effect on the weaning weight of the calves (Scholtz, *et al.*, 2014). The fact that herd of origin of the cow affects the weaning weights of her calves may indicate the presence of epigenetics. Epigenetic mechanisms can play a major role in phenotypic diversity in response to environmental conditions and the example mentioned here warrants further investigation.

Conclusion

Even though the many molecular mechanisms involved in epigenetics and its response to environmental conditions are being studied and clarified, applications in livestock production are still rare. Traditional breeding focus on Mendelian inheritance and involves long term breeding programmes. However, both genetic and epigenetic controls influence genetic expression and should be taken into account when formulating breeding programs for changing environmental conditions. Knowledge of epigenetic controls in the diverse environments should allow for more effective control and management of such effects. Taking control of genetics, independent of Mendelian inheritance, can move future breeding beyond simple breeding programs and provides new management and nutritional tools to enhance productivity. This can be done by using the environment and management to define epigenetic controls, as well as nutritional interactions. This brings about the concept of “flash evolution”. The challenge is therefore to use “soft” or

epigenetic inheritance to fine tune the next generation faster to novel environments than the slow reactivity of Mendelian or “hard inheritance”.

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