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Review

Developmental programming, adiposity, and reproduction in ruminants

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A B S T R A C T

Although sheep have been widely adopted as an animal model for examining the timing of nutritional interventions through pregnancy on the short- and long-term outcomes, only modest programming effects have been seen. This is due in part to the mismatch in numbers of twins and singletons between study groups as well as unequal numbers of males and females. Placental growth differs between singleton and twin pregnancies which can result in different body composition in the offspring. One tissue that is especially affected is adipose tissue which in the sheep fetus is primarily located around the kidneys and heart plus the sternal/neck region. Its main role is the rapid generation of heat due to activation of the brown adipose tissue-specific uncoupling protein 1 at birth. The fetal adipose tissue response to suboptimal maternal food intake at defined stages of development differs between the perirenal abdominal and pericardial depots, with the latter being more sensitive. Fetal adipose tissue growth may be mediated in part by changes in leptin status of the mother which are paralleled in the fetus. Then, over the first month of life plasma leptin is higher in females than males despite similar adiposity, when fat is the fastest growing tissue with the sternal/neck depot retaining uncoupling protein 1, whereas other depots do not. Future studies should take into account the respective effects of fetal number and sex to provide more detailed insights into the mechanisms by which adipose and related tissues can be programmed in utero.

1. Introduction

The influence of early life nutrition on the long-term reproductive and carcass quality has been alluded to in many reviews [1,2], but substantive evidence that this has a pronounced role, together with the primary biological mechanisms, remains elusive [3]. This is due to the substantial challenges of performing robust and biologically meaningful studies that are designed to look at outcomes that are directly relevant to animal production. As will be illustrated in the following section, the potential confounding effects of maternal parity, age, previous diet, together with fetal number, and sex, as well as seasonal and postnatal influences, mean very few robust studies have been undertaken using sheep [3,4]. One reason for this is that most investigations that have attempted to look at longer term outcomes have used end points that are considered relevant to human beings rather than to sheep [5]. This is in turn due to the main stimulus for such investigations namely the developmental origins of adult health and disease in humans.

The cornerstone establishing the fetal/developmental origins of later disease as an established concept is the pioneering epidemiological studies led by David Barker [6–8]. He was able to utilize a unique set of epidemiological cohorts coincident with the introduction of the National Health Service in the United Kingdom, a pronounced reduction in

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infant mortality together with a population-wide improvement in diet, health, and well-being [9,10]. Sheep as an experimental model were therefore well placed to investigate the physiological mechanism and adaptations which can occur in utero due to their long gestation. In addition, the relative similarities in birth weight and organogenesis to the human fetus [11] enabled chronic instrumentation and blood sampling of the late gestation fetus. Furthermore, from a historical perspective, the use of pregnant sheep had proved invaluable in the pioneering work of Liggins [12] and the introduction of prenatal glucocorticoid therapy to promote lung maturation in the preterm human fetus. This was, however, a much more defined and immediate end point compared with the current search for a range of mechanisms by which early development could impact on a variety of long-term noncommunicable diseases [13]. Moreover, with the increasing challenge of the potential adverse effects of maternal obesity on the offspring [14,15], current studies tend to be focused on this challenge which is not relevant to current sheep production systems.

It should also be recognized that sheep are of course ruminants. As such, the main reason they have been used for meat production is their capacity to thrive primarily on a roughage diet [16]. Their capacity to produce short-chain fatty acids, the main gluconeogenic precursors [17] is often overlooked when considering the impact of dietary manipulations but could have substantive effects on fetal growth and later body composition [18]. Most intensive sheep producers bring their flocks indoors to supervise lambing and also supplement their diet with concentrate feed. This is more important for ewes carrying multiple fetuses where the risk of pregnancy toxemia is increased [19]. The calculated metabolizable energy requirements for the ewe in late gestation [20] have been quantified and are used in most experimental studies. These would appear to be less than most ewes would eat when housed individually and allowed to eat to appetite [21] which is a further challenge to interpreting the outcomes of the offspring in later life. At the same time, when the offspring are actually reared under standard field conditions they rarely show any adverse response to prior nutritional exposure [2]. That may reflect the necessity of imposing a further challenge such as exposure to an obesogenic environment [3]. Clearly, this is not in line with standard agricultural practice and even when adopted is not always guaranteed to produce a distinct phenotype [22]. Often these phenotypic changes can take several years to become apparent and then be quite subtle [23,24]. Consequently, these types of long-term studies are not feasible under the conditions imposed by most grant funding bodies which expect studies to be completed and published over 1 to 2 years.

2. Adipose tissue development as a primary target tissue for modulation of diet in early life

One particular focus of developmental programming in sheep has been adipose tissue [25,26], which is especially important in enabling the newborn to effectively adapt to cold exposure of the extrauterine environment [18,27]. This occurs due to the rapid appearance of the brown adipose tissue-specific uncoupling protein (UCP) 1 that is activated during birth in conjunction with substantial increase in plasma circulation of endocrine stimulatory factors including catecholamines, thyroid hormones, cortisol, prolactin, and leptin [18,27]. If this process is compromised then hypothermia rapidly occurs, which if combined with a failure to feed results in death and is thus a major factor in the 1 to 4 million lambs that die annually in the United Kingdom [28]. The effect of manipulating the maternal nutritional and endocrine environment thus has the potential to promote or compromise fetal adipose tissue growth and development. Further this may also impact on later fat distribution, and in females, their subsequent reproductive performance.

An additional factor that can also influence both the mother and her fetus is the season. This will be accompanied by changes in both temperature and photoperiod [16], even within the comparatively short breeding season for sheep, that itself is driven by changes in day length. A complex interaction exists between growth and development of organs and tissue from fertilization (and the subsequent epigenetic reprogramming) up to the time of birth [1]. Ultimately, parturition is initiated by maturation of the hypothalamic-pituitary-adrenal axis [18]. It is, therefore, perhaps disappointing that the academic community has not utilized the clear translational strengths of ruminants to provide relevant insights into developmental programming by failing to conduct much more robust and repeatable studies.

3. The maternofetal metabolic environment, adipose tissue depot location, and response to maternal nutritional manipulation

The fetus grows and develops in what would normally be considered to be a metabolically compromised environment [29] in which the circulating concentrations of oxygen and most metabolites are much lower than those in the mother [18]. With the exception of acetate, these metabolites then all increase dramatically after birth, coincident with the onset of breathing, digestive function, and independent thermoregulation [18]. All short-chain fatty acids could thus decline substantially after birth and may be an important regulator of the transition in adipose tissue conformation that occurs postnatally [18].

The main metabolite that has been studied in response to nutritional perturbations of the mother is glucose, whose concentration is closely related to changes in dietary

Table 1
Summary of the differences in maternal and fetal plasma glucose and insulin concentrations between sheep, humans, and rats.

Species	Adult (male)	Adult (female)	Pregnant	Fetus	References
Glucose (mmol/L)					
Sheep	3.5 ± 0.3	3.5 ± 0.2	3.6 ± 0.6	0.6 ± 0.1	[22,32]
Human	5.2 ± 0.6		4.5 ± 0.1		[33,34]
Rat	4.8 ± 0.2	4.1 ± 0.1	5.3 ± 0.2	3.2 ± 0.1	[35–37]
Insulin (mU/L)					
Sheep	6.2 ± 1.6	5.5 ± 1.4	8.6 ± 0.3	13.8 ± 1.6	[22,32]
Human	5.0 ± 1.0		10.7 ± 0.9		
Rat	9.4 ± 2.2	10 ± 2			[35–37]