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Developmental programming in the preimplantation period: can it be exploited to enhance postnatal function in cattle?

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Abstract

The concept of developmental programming states that the function of an adult animal depends on environmental conditions to which it was exposed to before birth. Developmental programming can occur in the preimplantation period. Accordingly, certain environmental signals, acting either on the mother (for pregnancies established *in vivo*) or on the embryo directly (for cultured embryos), can program development of the preimplantation embryo to have effects on postnatal life. It is proposed that research on developmental programming in cattle could lead not only to elimination of adverse outcomes associated with *in vitro* production of embryos but also to discovery of approaches to produce a neonatal animal with superior prospects for achieving optimal production later in life.

Keywords: developmental programming, environment, livestock production, preimplantation embryo.

Introduction

Programming of the preimplantation embryo – A seldom-travelled frontier for the animal scientist

It has long been the goal of animal scientists to devise means to improve the efficiency at which agriculturally-important animals produce products useful for man. Most commonly, enhanced production has been achieved through a combination of selection of genes that are optimal for production and provision of an environment that maximizes the opportunity for those genes to be expressed. Thus, for example, the increase in milk yield in dairy cattle breeds such as the Holstein and Jersey has depended upon intensive and accurate selection for genes conferring females with the capacity to produce large amounts of milk as well as provision of cattle with nutrients, housing and other environmental conditions that optimize milk yield.

The function of an adult animal depends not only on the environment to which it was exposed after birth but also on environmental conditions it was exposed to before birth. This concept, which has been variously termed developmental programming, fetal programming or developmental origins of health and disease, has been documented not only in mammals (Roseboom *et al*., 2001; Ganu *et al*., 2012; Walker and Ho, 2012; Fleming *et al*., 2015), but also amphibians (Berg *et al*., 2009), reptiles (Schwanz*et al*., 2013) and fish (Meier *et al*., 2010; Celeghin *et al*., 2011). For mammals, the environment of the conceptus is established by its mother and changes in maternal environment can alter postnatal phenotype of the developing organism.

Postnatal function can be programmed by alterations in maternal environment throughout the length of gestation, including as early as the preimplantation period (Kwong *et al*., 2000; Calle *et al*., 2012) and as late as the final stages of gestation (Li *et al*., 2013; Tao *et al*., 2014; Master *et al*., 2015). Indeed, there is experimental evidence that alterations in parental function affecting male gametes (Lane *et al*., 2014; Master *et al*., 2015) can influence postnatal phenotype of the offspring.

Those who work with the *in vitro* produced (IVP) embryo are well aware that an inadequate environment during the preimplantation period can adversely change the developmental outcome of the embryo. Some of the specific consequences of exposure of the embryo to an inadequate culture environment will be detailed in a subsequent section. Not all programming events during the preimplantation period need be harmful, however. Although the evidence is fragmentary, it is hypothesized that certain environmental signals, acting either on the mother (for pregnancies established *in vivo*) or on the embryo directly (for pregnancies established *in vitro*), can program development of the preimplantation embryo to have beneficial effects on postnatal life. The purpose of this paper is to encourage research directed towards this hypothesis because, if true, both the animal manager and the embryologist will have new tools with which to optimize animal production.

Lessons from the mouse regarding developmental programming in the preimplantation period

The mouse has been the preeminent species used to document the idea that changes in the maternal environment during the preimplantation period can alter development of the embryo in a way that alters postnatal phenotype. The best studied example is for offspring born to mothers that were fed a low protein diet during the first 3.5 days of gestation (i.e., through the period of blastocyst formation). An example of representative results is shown in Fig. 1. As for many other cases of developmental programming, consequences of being gestated in a mother fed a low protein diet during the

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preimplantation period depend on the sex of the embryo. Female offspring of females fed a low protein diet during the first 3.5 days of gestation experienced increased body weight (Watkins*et al*., 2008, 2011), decreased ratio of heart weight to body weight (Watkins *et al*., 2008), higher expression of *Insr* and *Igf1r* in retroperitoneal fat (Watkins *et al*., 2011), and altered behavioral responses (Watkins *et al*., 2008). Male offspring displayed attenuated vasodilation response in mesenteric arteries (Watkins *et al*., 2010). For both sexes, being derived from mothers fed a low protein diet during the preimplantation period resulted in increased systolic blood pressure (Watkins *et al*., 2008, 2011), elevated amounts of angiotensin converting enzyme in the lung (Watkins *et al*., 2010), and lower expression of *Ucp1* in retroperitoneal fat (Watkins *et al*., 2011).

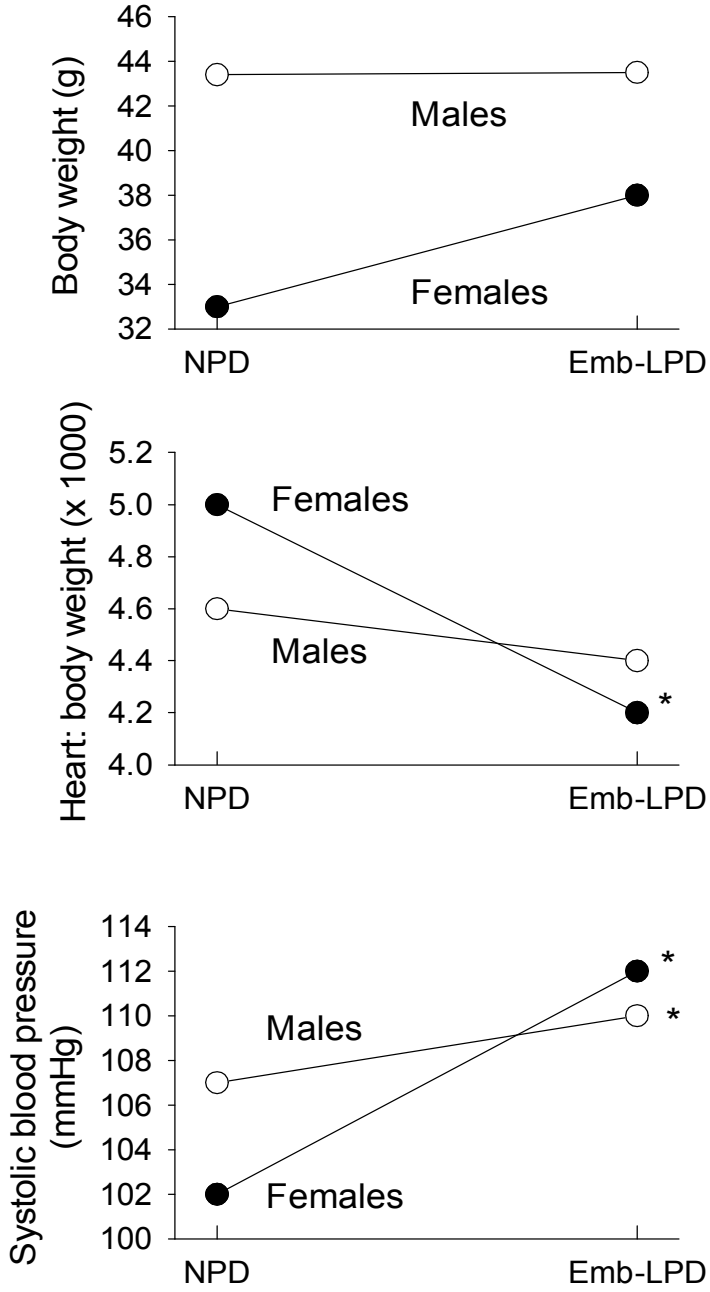

Figure 1. Developmental programming in the mouse caused by maternal protein nutrition in the preimplantation period. Female mice were fed a diet containing 18% casein throughout gestation (normal protein diet; NPD) or were fed a diet containing 9% casein from mating to day 3.5 of gestation and then fed an 18% casein diet thereafter (embryo low protein diet; Emb-LPD). Shown in the figure are data on the male (open circles) and female (closed circles) offspring at 21 days of life. Asterisks represent significant effects of Emb-LPD ($P < 0.05$). Note that, while effects on body weight at 21 days were not significant, Emb-LPD females were significantly heavier than NPD females at other times examined (results not shown). Data are from Watkins *et al*. (2008).

Other maternal events during the preimplantation period that have been reported to affect postnatal phenotype in mice are lipopolysaccharide (LPS) challenge (Williams *et al*., 2011) and mating of female to males in which seminal vesicles were removed surgically (Bromfield *et al*., 2014). For these stimuli, also, alterations in postnatal function depended on sex. For example, males born as a result of mating females to vesiculoectomized males were fatter than control males whereas there was no effect on adiposity for females (Bromfield *et al*., 2014).

It is possible that maternal events during the preimplantation period do not reflect alterations of embryonic function directly but rather changes in maternal physiology that effect the conceptus later in pregnancy. This is not the case for low protein feeding or mating to vesiculoectimized males because alterations in postnatal phenotype remain when embryos are recovered from affected females and transferred to control recipients (Watkins *et al*., 2008; Bromfield *et al*., 2014). At least some of the alteration in conceptus development caused by low protein feeding and mating to vesiculoectomized males is probably caused by altered placental function because both treatments alter placental growth (Bromfield *et al*., 2014; Watkins *et al*., 2015) and, for low protein feeding, function of trophectoderm (Sun *et al*., 2014) and primitive endoderm (Watkins *et al*., 2008; Sun *et al*., 2015). Accompanying alterations in placental function are changes in gene expression and DNA methylation of *Gata6* in primitive-endoderm-like embryoid bodies derived from embryos harvested from mothers fed low protein diets (Sun *et al*., 2015).

Taken together then, the lesson from the mouse is that changes in maternal environment during the preimplantation period can alter subsequent development in a sex-dependent manner that results in a change in phenotype in adult life.

The *in vitro* produced embryo – A sometimes victim of developmental programming

There are many alterations in embryonic function associated with IVP. These include changes in morphology (Crosier *et al*., 2001; Rizos *et al*., 2002a), gene expression (Driver *et al*., 2012), cryotolerance (Enright *et al*., 2000; Al-Katanani *et al*., 2002), and competence to establish pregnancy after transfer to females (Pontes *et al*., 2009; Siqueira *et al*., 2009). At least some of these defects are caused by the culture environment during the preimplantation period rather than to problems derived from the oocyte or induced in the fertilization process. Transfer of IVP embryos to the sheep oviduct improved survival to cryopreservation (Rizos *et al*., 2002c) and made gene expression more similar to embryos produced *in vivo* (Rizos *et al*., 2002b).

The IVP bovine embryo can also experience alterations in development later in pregnancy as indicated by occurrence of fetal growth abnormalities (Farin *et al*., 2006), loss of imprinting (Chen *et al*., 2015), and increased neonatal mortality (Bonilla *et al*., 2014). Clearly, then, the *in vitro* produced embryo can experience abnormal developmental programming.

What is not clear in the bovine is whether consequences of IVP extend into the postnatal period. The one study to examine this question, using small numbers of animals, did not find any difference between calves produced by IVP with calves produced by artificial insemination in terms of calf growth, age at first service, percent of heifers pregnant at first service, or milk yield or composition in the first 120 days of the first lactation (Bonilla *et al*., 2014). However, results from embryos produced *in vitro* in the mouse and human are indicative that the question should be examined more closely. Thus, in the mouse, alterations in culture conditions can cause sex-dependent changes in adult phenotype (Fernández-Gonzalez *et al*., 2004; Sjöblom *et al*., 2005; Serrano *et al*., 2014). Results in the human are more difficult to interpret because of the overrepresentation of older and more infertile couples as parents of children derived from *in vitro* fertilization (IVF) as compared to children from natural conceptions. With this caveat in mind, it is important to note that there are reports from a Dutch cohort of singleton children aged 8-18 that derivation by IVF was associated with increased body fatness (Ceelen *et al*., 2007), systolic and diastolic blood pressure (Ceelen *et al*., 2008), and fasting concentrations of glucose (Ceelen *et al*., 2008). In another study of Swiss singleton children, Scherrer *et al*. (2012) found evidence of vascular dysfunction for children born following IVF or intracytoplasmic sperm injection (average age 11) as compared to those born following natural conception (average age 13). There were no differences in body weight or fatness, circulating concentrations of lipid, glucose or insulin, glucose tolerance or glucose resistance (Scherrer *et al*., 2012).

Unfortunately, too few experiments with IVP embryos in cattle monitor pregnancies to term or ascertain the function of the resultant offspring during later life. This oversight should be corrected whenever feasible because it is possible that there are negative consequences of IVP on postnatal health, growth, reproduction or lactation. It might even be that there are specific culture conditions used for IVP that have beneficial effects on specific physiological functions important for optimal production.

Alterations in maternal environment during the periconceptional period can change adult phenotype in ruminants – lessons from the sheep

The fact that fetal development in the cow can be disrupted following IVP (Farin *et al*., 2006; Bonilla *et al*., 2014; Chen *et al*., 2015) is indicative that preimplantation developmental programming can occur in cattle. To date, however, there are no reports from cattle as to whether alteration of maternal environment during the preimplantation period can also modify postnatal characteristics of the offspring. Results from another ruminant, the sheep, would indicate that such a phenomenon can occur.

The first such study in sheep indicating the importance of the periconceptional environment of the mother for characteristics of the offspring in adulthood utilized a model in which ewes serving as embryo donors were fed a diet deficient in cobalt and sulfur designed to reduce capacity for DNA methylation (Sinclair *et al*., 2007). The experimental diet was fed from 8 weeks before breeding until 6 days afterwards. Embryos were then flushed from the uterus and transferred to control females to ensure effect of maternal diet reflected actions on the embryo. At day 90 of gestation, there were diet-associated differences in methylation status of 4% of 1000 CpG islands examined in fetal liver. Also, animals that were derived from females fed the experimental diet had several altered physiological characteristics in adulthood. For both sexes, body weight was greater in the treated group. For males only, offspring from mothers fed the experimental diet were fatter, had greater haptoglobin response to ovalbumin immunization, increased insulin resistance and elevated diastolic blood pressure.

The design of the experiment by Sinclair *et al*. (2007) did not make it possible to determine whether actions of maternal feeding were on the embryo itself or the oocyte from which it was derived. However, the potential for manipulating postnatal function of animals by modifying maternal diet in the periconceptional period was made clear. Moreover, there are other reports where an alteration in maternal environment either in the preovulatory period and early pregnancy or in early pregnancy alone changed postnatal outcomes in offspring. Results are summarized in Table 1. Changes in maternal environment reported to cause changes in postnatal phenotype of the offspring are undernutrition (Gardner *et al*., 2004, 2006; Poore *et al*., 2007, Hernandez *et al*., 2010) and injection with sustained release growth hormone (GH) ~3 days before estrus (Costine *et al*., 2005; Koch *et al*., 2010). The phenotype caused by these manipulations of the maternal system are less profound than for the study of Sinclair *et al*. (2007), probably because the strategy of limiting DNA methylation employed in the latter study caused a larger change in the fetal epigenome than that caused by undernutrition or activation of the GH-IGF1 axis.

Colony Stimulating Factor 2 – A maternal signal that modifies the developmental program of the preimplantation embryo

Actions of the mother to alter the developmental program of the preimplantation embryo are likely mediated in part by embryo regulatory molecules produced by the oviduct or endometrium. These molecules, which in the cow include activin, CSF2, DKK1, EGF, FGF2, IGF1, IL1B, LIF and TGFB (Hansen *et al*., 2014a), have been termed embryokines because of their capacity to regulate embryo growth and differentiation (Hansen *et al*., 2014a, b). One of these molecules, CSF2, can exert actions on the preimplantation embryo that alter development later in gestation and in postnatal life.

The first indications that CSF2 can regulate the developmental program of the preimplantation embryo was the finding of Sjöblom *et al*. (2005) in the mouse that addition of CSF2 to culture medium prevents the otherwise deleterious effects of embryo culture on postnatal phenotype. Addition of CSF2 to culture medium from the two-cell to blastocyst stages reduced or prevented effects of culture on postnatal growth in females and males, relative brain mass in males and placental weight of female progeny when they themselves became pregnant. There was no alleviation of the effect of culture on fatness of males.

Treatment of bovine embryos from day 5 to 7 of development with CSF2 also affects later development in a manner that varies between female and male embryos (Dobbs *et al*., 2014). After culture, embryos were transferred to cows and flushed from the reproductive tract 8 days later, at day 15 of gestation. Day 15 was chosen because the bovine embryo is undergoing rapid elongation of the trophoblast and secretion of the antiluteolytic molecule IFNT (Spencer *et al*., 2007). There was aninteraction between sex and treatment for conceptus length and concentrations of IFNT in the uterine lumen (an indirect measurement of embryonic production of IFNT). CSF2 decreased embryo length and intrauterine accumulation of IFNT in females but increased length and IFNT in males (Fig. 2). In addition, effects of IFNT on gene expression and DNA methylation in the trophoblast also varied between female and male embryos.

Table 1.Changes in postnatal phenotype in sheep caused by alterations in maternal environment during the preovulatory period and/or early pregnancy.

Maternal treatment	Age examined	Altered postnatal phenotype			Notes	Reference
		Both sexes	Females only	Males only		
Restricted feed intake from day 1-30 of gestation	1 year	• increased pulse pressure • reduced rate pressure product • lack of tachycardia after angiotensin II infusion • reduced baroreflex sensitivity during angiotensin II infusion			Sex differences not determined	Gardner *et al*., 2004
Restricted feed intake from day 1-30 of gestation	1 year		• increased resting cortisol • reduced ACTH and cortisol response to CRH and vasopressin	• increased ACTH and cortisol response to CRH and vasopressin		Gardner *et al*., 2006
Restricted feed intake, day 1-31 of gestation	1.5 and 2.5 years			• increased insulin resistance (1.5 years only)	most effects not significant	Poore *et al*., 2007
Reduced feed intake, day -2 to 30 after mating	4 months			• increased cortisol response to isolation • increased escape attempts, behavioral test		Hernandez *et al*., 2010
Sustained release GH, ~ day -3 before breeding	30-75 days		• increased body weight	not examined	only females examined	Costine *et al*., 2005
Sustained release GH, ~ day -3 before breeding	100 days		• increased body weight • Decreased IGF1 response to GHRH challenge	not examined	only females examined	Koch *et al*., 2010

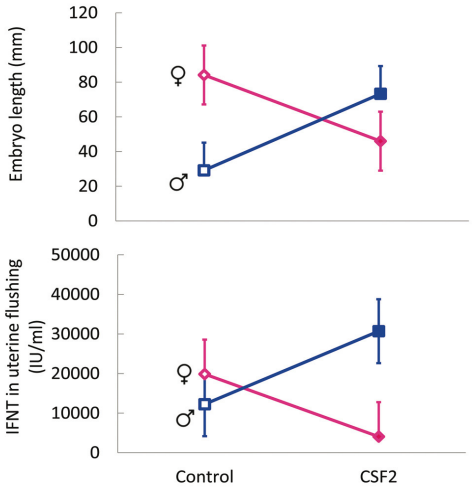

Figure 2.Sex of embryo affects actions of CSF2 treatment from day 5-7 of development on conceptus length and concentration of IFNT in uterine flushing at day 15 of pregnancy. The figure is reproduced from Biology of Reproduction(Dobbs *et al*., 2014).

Where do we go from here?

The focus of this paper has been on the preimplantation period. This is not the only time in pregnancy when alterations in maternal environment can change the characteristics of development to affect postnatal function of the offspring. In cattle, for example, diet in the second or third trimester can affect fertility (Martin *et al*., 2007) and carcass characteristics (Micke *et al*., 2010a, b, 2011) of the offspring. The fact that maternal events can affect the developmental program of the conceptus means that opportunity exists for shaping postnatal function of livestock through manipulation of maternal environment during gestation. Even though there has long been interest in exploring prospects for regulating offspring characteristics of livestock species by manipulating events during pregnancy (see Everett, 1964 for one early example), the field remains small in relation to the potential for gain in animal productivity. More should be done.

As compared to other times in pregnancy, the preimplantation period offers unique advantages. Not only is it possible to modify maternal function during this period of pregnancy but, in cases of IVP, the embryo spends part of the preimplantation period outside the mother. Experiments with CSF2 (Sjöblom *et al*.,2005; Dobbs *et al*., 2014)show that it is possible to alter the environment of the cultured embryo to change the trajectory of development. Unfortunately, exposure of the embryo to culture conditions often causes the developmental program to become dysregulated (Farin *et al*., 2006). With more research focused on outcomes of IVP beyond the establishment of pregnancy or even calving, it may be possible to not only eliminate adverse outcomes associated with IVP but to also produce a neonatal animal with superior prospects for achieving optimal production later in life.

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