INTERACTIONS BETWEEN ENERGY BALANCE AND OVARIAN ACTIVITY IN HIGH YIELDING DAIRY COWS EARLY POSTPARTUM: A REVIEW

Energiebalans en ovariële activiteit bij melkvee: metabole interacties

T. Vanholder[1], J.L.M.R. Leroy[2], G. Opsomer[2], A. de Kruif[2]

[1]Someren Veterinary Centre, Slievenstraat 16, 5711 PK Someren
The Netherlands
[2]Department of Reproduction, Obstetrics and Herd Health, Faculty of Veterinary Medicine,
Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium

T.Vanholder@vc-someren.nl

ABSTRACT

The negative energy balance (NEB) during the early postpartum period in high yielding dairy cows has clearly been linked to diminished reproductive performance. As for follicular growth and development, nearly half of all modern dairy cows suffer from an ovarian dysfunction during the first weeks after calving. Several hormones and metabolites may act as metabolic cues for the NEB, thereby affecting follicular development at both the hypothalamic and the ovarian levels. The main metabolic cue for the hypothalamus seems to be metabolic fuel availability, i.e. glucose, and hormones like insulin and leptin may have a direct permissive effect on gonadotrophin secretion or an indirect effect by affecting fuel partitioning and availability. At the ovarian level, NEB can affect follicle growth by the reduced insulin, insulin-like growth factor I and leptin concentrations. Metabolites like non-esterified fatty acids may influence follicle growth at both the hypothalamic and the ovarian levels.

SAMENVATTING

De negatieve energiebalans (NEB) die heel typisch optreedt bij hoogproductieve melkkoeien tijdens de eerste weken na het afkalven, heeft ontegensprekelijk een nadelige invloed op de vruchtbaarheid. Zo heeft haast één op twee melkkoeien een afwijkende ovariële activiteit tijdens de vroege postpartum periode. Verschillende hormonen en metabolieten fungeren als boodschapper van de NEB en beïnvloeden de folliculaire ontwikkeling op zowel het niveau van de hypothalamus als op het niveau van het ovarium zelf. Het belangrijkste metabole signaal voor de hypothalamus is het tekort aan brandstof in de vorm van lage glucoseconcentraties in het bloed die op hun beurt gepaard gaan met lage insuline- en insulin-like growth factor (IGF1)-concentraties. Net zoals leptine hebben insuline en IGF-1 daarenboven een belangrijke stimulerende functie in het ovarium (stimulatie follikelgroei en steroïdproductie). Tenslotte blijkt uit onderzoek dat metabolieten zoals vrije vetzuren, die het resultaat zijn van de toegenomen perifere lipolyse, de follikelgroei kunnen tegenhouden door hun remmend effect ter hoogte van de hypothalamus en/of het ovarium.

INTRODUCTION

Reproductive performance in high yielding dairy cows has declined worldwide over the past few decades (Lucy, 2001). This decline in reproductive performance is linked to the increased genetic selection for milk yield (reviewed by Pryce and Veerkamp, 2001) and the important underlying factor seems to be the negative energy balance (NEB) (Beam and Butler, 1999; Butler, 2003). Although milk yield and feed intake show a positive genetic correlation, the increased yield cannot be entirely compensated by increased intake. Consequently, ongoing selection for production further decreases energy balance (Veerkamp *et al.*, 2003).

Several stages of the reproductive process such as follicular development and ovulation, fertilization and pregnancy seem impaired (Lucy, 2001). As for follicular development and ovulation, nearly half (49%) of modern dairy cows suffer from an ovarian dysfunction during the (early) postpartum period, leading to a prolonged interval between calving and first ovulation (Opsomer *et al.*, 1998; Shresta *et al.*, 2004). The NEB is a major risk factor for the occurrence of delayed cyclicity (Beam and Butler, 1999; Opsomer *et al.*, 2000), and this effect seems to be exerted through the metabolic and hormonal adaptations

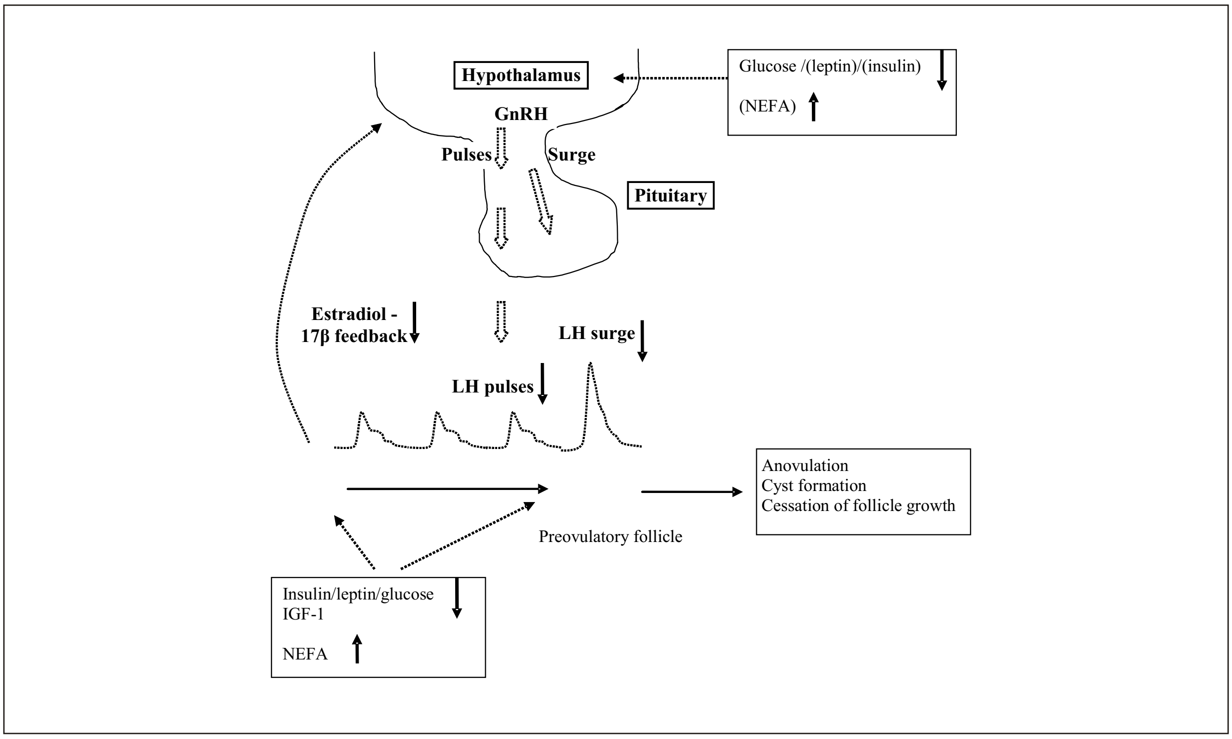

Figure 1. Schematic representation of the metabolic pathways through which the NEB may affect ovarian function. Reduced glucose availability either by or in combination with low insulin and leptin concentrations and high NEFA concentrations suppress the GnRH pulse generator in the hypothalamus. Subsequent LH pulse frequency is reduced and follicular development is insufficiently stimulated. At the ovarian level, low insulin, leptin, IGF-1 and glucose concentrations and high NEFA concentrations hamper follicular development, resulting in insufficient positive feedback of estrogen on the hypothalamus. Depending on the severity of the NEB, the disturbed neuro-endocrine regulation results in the cessation of follicular development, which leads to anovulation or cyst formation.

that accompany the NEB. Several metabolites and hormones act as metabolic messengers on the hypothalamic/pituitary axis and the ovaries (Diskin *et al.*, 2003; Lucy, 2003; Wade and Jones, 2004). This review will focus on the different hormonal and metabolic pathways by which the NEB seems to affect follicular development and ovulation. In Figure 1 the metabolic pathways through which the negative energy balance (NEB) may affect ovarian function are represented.

FOLLICULAR DEVELOPMENT AND OVULATION

Before reviewing the existing literature on the interactions between the energy balance and follicular development and ovulation, the normal endocrine regulation of follicular development and ovulation in cattle will be briefly discussed.

Follicular development results from a complex interaction between the hypothalamic-pituitary axis and the ovaries. In addition, both hormonal and metabolic factors influence this process locally at the ovarian level through paracrine/autocrine regulation. From the hypothalamus, Gonadotrophin Releasing Hormone (GnRH) is transported to the anterior pituitary where it stimulates the production and the release of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (Roche *et al.*, 1996). These latter two hormones (FSH and LH) are crucial at the ovarian level for the purpose of stimulating follicular growth and further promoting the development of the dominant follicle into the preovulatory stage.

Generally, the bovine estrous cycle exhibits two or three waves of follicular development (Savio *et al.*, 1988). The following three important growth phases are described: recruitement, selection and deviation, growth and dominance. Each new follicle wave is preceded by an FSH surge (Ginther *et al.*, 1999) since follicles require FSH support to be recruited from the gonadotropin sensitive pool of small follicles (2-4 mm) and to grow beyond a size of 4 mm in diameter. In a follicular wave, each follicle has the potency to acquire dominancy, but the future dominant follicle starts to grow 6 h before the future subordinate ones and, therefore, has a small advantage in size (Gibbons *et al.*, 1997). Selection and deviation of the dominant follicle occur when the largest follicle reaches a size of 8.5 mm (Ginther, 2000). At deviation, the largest follicle (dominant) continues to grow while the growth rate of the smaller (subordinate) follicles decreases. Moreover, at this particular time in the cycle, the FSH concentration has fallen below the critical level that is necessary to sustain follicle growth. However, the dominant follicle acquires even more LH receptors in the granulosa cells, thus enabling the use of increased LH concentrations for continued growth and development. Furthermore, the dominant follicle consolidates its dominance by reducing FSH release through a negative feedback by estradiol and inhibin, thereby preventing the further growth and development of any subordinate follicles (Ginther *et al.*, 2000; Ginther *et al.*, 2001).. In addition, the future dominant follicle exhibits changes in the insulin-like Growth Factor (IGF) System shortly before the processes of selection and deviation. Decreased concentrations of binding proteins result in an increase of the bio-available fraction of IGF-1 and 2 in the follicular fluid of the dominant follicle (Mihm *et al.*, 2000; Austin *et al.*, 2001; Beg *et al.*, 2001). Both growth factors stimulate cell proliferation and estradiol production and augment granulosa cell sensitivity for FSH (Spicer *et al.*, 2001), thereby enabling the dominant follicle to further use the now very low FSH concentration in its process of continued growth. Other intrafollicular factors such as inhibin, activin and follistatin may (Martin *et al.*, 1991; Austin *et al.*, 2001) or may not (Lopez-Diaz and Bosu, 1992; Beg *et al.*, 2001) play a role in the process of selection and deviation of the dominant follicle.

Subsequently, the dominant follicle will either ovulate, become atretic or develop into a cyst (Butler, 2003). To be able to ovulate, the dominant follicle must elicit a pre-ovulatory LH surge through increased estradiol production (reviewed by Mahesh and Brann, 1998). In the postpartum cow, FSH is not a limiting factor for the initiation of follicular development and hence the follicular wave since secretion is generally observed as early as day 5 postpartum. Reestablishment of pulsatile LH secretion, on the other hand, seems to be more variable and the amplitude and frequency of its pulsatile release determine the dominant follicle's fate (Roche *et al.*, 1996). Especially a disturbed LH pulse frequency leads to the cessation of follicular growth. Furthermore, the absence or the bad timing of the preovulatory LH surge results in the anovulation of the dominant follicle.

METABOLIC CUES OF NEB

Glucose and insulin

During the NEB in the early postpartum period, circulating glucose and insulin concentrations are low and peripheral insulin resistance occurs (Beck *et al.*, 1983; Staufenbiel *et al.*, 1992; Sano *et al.*, 1993). These alterations affect metabolic fuel partitioning, as they limit glucose uptake by the peripheral tissues, guaranteeing glucose availability for lactose production by the mammary gland, an organ which does not require insulin for glucose uptake (Collier, 1985).

However, metabolic fuel availability is crucial for fertility: information on metabolic fuel availability is signaled to the hypothalamus and forebrain, through which it affects GnRH and subsequent LH release (Wade and Schneider, 1992; Wade *et al.*, 1996). Although several (metabolic) hormones may have a signalling function, it seems that mainly glucose (Clarke *et al.*, 1990; Medina *et al.*, 1998; Diskin *et al.*, 2003; Ohkura *et al.*, 2004) and insulin (Miller *et al.*, 1995; Miller *et al.*, 1998; Tanaka *et al.*, 2000) affect GnRH release at the hypothalamic level. Energy restriction seems to activate specific neurons in the forebrain, which suppress the hypothalamic GnRH pulse generator through the release of specific peptides such as NeuroPeptide Y (Ichimaru *et al.*, 2001; Diskin *et al.*, 2003) and cathecholamines (Wade and Jones, 2004), resulting in reduced pulsatile LH release from the pituitary. The role of insulin, however, in regulating GnRH and LH pulsatility is controversial, since insulin may indirectly influence gonadotropin secretion by altering the availability of oxidizable fuels such as glucose (reviewed by Wade and Jones, 2004).

In addition, low insulin levels may directly affect follicle growth at the ovarian level. Insulin is a potent stimulator of follicle cell steroidogenesis and proliferation in vitro (Matamaros *et al.*, 1990; Spicer and Echternkamp, 1995; Campbell *et al.*, 1996; Gutierrez-Aguilar, 1997; Price and Silva, 1999) and *in vivo* (Simpson *et al.*, 1994; Armstrong *et al.*, 2002). Moreover, insulin is important for follicular maturation (Landau *et al.*, 2000) and normal ovarian function postpartum (Miyoshi *et al.*, 2001), as it increases the steroidogenic capacity of the dominant follicle (Butler *et al.*, 2004).

The importance of insulin for postpartum ovarian function is illustrated by the association between low circulating insulin concentrations and aberrant ovarian function (Pushpakumara *et al.*, 2003) such as the formation of cystic ovarian follicles in the early postpartum dairy cow (Vanholder *et al.*, 2005), although this was not observed by Beam (1995). In addition, isoenergetic diets that stimulate insulin release have a beneficial effect on ovarian function and reproductive performance in high yielding dairy cows, without affecting LH release (Gong *et al.*, 2002).

In conclusion, glucose and likely insulin as well are important metabolic cues influencing follicle growth at both the hypothalamic level and at the ovarian level. Insulin may exert its effects either directly or else indirectly by affecting metabolic fuel availability.

Growth hormone and IGF system

During the early postpartum period, circulating concentrations of Growth Hormone (GH) are increased. High GH concentrations support milk production, as reflected by the increased levels in high genetic merit cows compared to low genetic merit animals (Bonczek *et al.*, 1988). Although early studies reported a positive effect of exogenous GH on ovarian follicle development (Gong *et al.*, 1991; Gong *et al.*, 1993), later studies revealed that this effect was mediated through increased peripheral concentrations of insulin and IGF-1 (Gong *et al.*, 1997).

Contrary to the high GH concentrations, IGF-1 concentrations are decreased during NEB. This may seem contradictory, since GH stimulates IGF-1 production and release by the liver, by binding to its receptor GHR1. However, expression of GHR1 in the liver is down regulated during early lactation (Kobayashi *et al.*, 1999) due to the low insulin concentrations, hence uncoupling the GH-IGF-1 pathway (Butler and Butler, 2001).

As mentioned earlier, the IGF system plays an important role in follicular growth and development (Beam and Butler, 1999; Webb *et al.*, 1999). Consequently, low circulating IGF-1 concentrations are linked to a retarded onset of ovarian activity (Beam and Butler, 1997; Pushpakumara *et al.*, 2003) and the development of cystic ovarian follicles (Zulu *et al.*, 2002).

In conclusion, IGF-1 may be a metabolic cue at the ovarian level. However, in view of the role of insulin in coupling IGF-1 production by the liver to increased GH concentrations, it may be that insulin plays a more important role as a metabolic hormone in the postpartum dairy cow.

Leptin

Leptin is a recently "new" hormone. It is produced by adipocytes, and is regarded as the ultimate factor linking metabolic status to reproduction (Barash *et al.*, 1996). During the early postpartum period, leptin concentrations are reduced in accordance with the NEB (Block *et al.*, 2001). Depending on the metabolic state of the animal, leptin has either a stimulatory effect or no effect at all on hypothalamic-pituitary function in cattle (Williams *et al.*, 2002; Amstalden *et al.*, 2005). Spicer (2001) hypothesized that above a certain threshold level, leptin acts as a trigger to initiate hypothalamic-pituitary gonadotropin secretion. However, as already mentioned for insulin, leptin may indirectly influence gondotropin release by affecting the availability of oxidizable fuel, i.e. glucose and fatty acids (Shneider, 2004).

Besides its effects on the central nervous system, this hormone also seems capable of modulating ovarian function by acting directly on follicular cells (Spicer *et al.*, 1997; 1998). The effects on steroidogenesis and cell proliferation, however, are dependent on the levels of circulating concentrations of IGF-1, LH and insulin (Spicer *et al.*, 1997; 1998; 2000).

In the postpartum dairy cow, a clear relationship between leptin profiles and first postpartum ovulation is lacking (Liefers *et al.*, 2003), although a minimum permissive level of leptin seems required to induce the first postpartum LH surge and hence the first postpartum ovulation (Huszenicza *et al.*, 2001; Liefers *et al.*, 2003).

In conclusion, leptin does not seem to play an essential role in linking energy status to reproduction, although a permissive effect is exerted (reviewed by Wade and Jones, 2004).

Non-esterified fatty acids (NEFAs) and ketones

A NEB is also characterised by elevated NEFA and ketone concentrations (Rukkwamsuk *et al.*, 2000). At the hypothalamic-pituitary level, NEFAs may act as metabolic messengers, affecting gonadotropin secretion (Canfield and Butler, 1990), although more recent research does not support the idea of NEFAs being a metabolic cue for the GnRH pulse generator, at least not in well fed goats (Ohkura *et al.*, 2004**)**. Due to the limited number of publications on the topic, the involvement of NEFAs as metabolic cues for the central nervous system cannot be excluded (reviewed by Wade and Jones 2004).

At the ovarian level, NEFAs may directly affect follicular growth and development by acting on follicle cells. Recently, it was demonstrated in vitro that the addition of NEFAs, at concentrations measured in the follicular fluid during the NEB (Leroy *et al.*, 2005), have a detrimental effect on granulosa en theca cell viability and function (Jorritsma *et al.*, 2004; Vanholder *et al.*, 2005; Vanholder *et al.*, 2006b). In vivo, both the delayed onset of ovarian activity during the early postpartum period (Huszenicza *et al.*, 1988; Beam and Butler, 1997) and the formation of cystic ovarian follicles (Huszenicza *et al.*, 1988; Zulu *et al.*, 2002) have been associated with increased NEFA concentrations. In addition, in view of the importance of insulin for reproduction, NEFAs may affect ovarian function indirectly as they are capable of reducing insulin release from the pancreas in rats (Mason *et al.*, 1999).

Besides NEFA, increased serum ketone concentrations are associated with delayed resumption of ovarian cyclicity after parturition (Huszenicza *et al.*, 1988; Opsomer *et al.*, 2000; Reist *et al.*, 2000) and with the formation of ovarian cysts (Dohoo and Martin, 1984; Andersson *et al.*, 1991). However, there is no clear evidence, either at the hypothalamic level (Wade and Jones, 2004) or at the ovarian level (Vanholder *et al.*, 2006a), that ketones may act as metabolic cues.

CONCLUSION

The NEB seems to affect follicular development and ovulation at the level of the hypothalamus mainly through changes in metabolic fuel availability. Altered insulin and leptin concentrations may exert a direct effect on gonadotropin secretion, although their indirect effect through the regulation of fuel partitioning and availability seems more important. At the ovarian level, reduced concentrations of insulin, leptin and IGF-1, together with reduced fuel availability and high NEFA concentrations, mediate the negative effect of the NEB on follicle growth and development.

Although the occurrence of an NEB in high yielding dairy cows early postpartum is inevitable, the aim of an optimal dairy management program should be to limit the severity and duration of the negative energy balance. To achieve this, the transition period is crucial. Recent research in the U.S. (Drackley, personal communication) has shown that the level of feeding already in the early dry period plays an important role in determining feed intake after parturition. In addition, feeding "insulinogenic" diets after parturition over a longer period seems to result in an earlier resumption of ovarian activity leading to better fertility. Consequently, future research should focus on optimizing lactation diets with a view to inducing higher levels of glucose and hormones such as insulin and IGF-1.

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