Review [Revisión]

CHARACTERIZATION OF THE METABOLIC MODULATION OF SOWS DURING PERIPARTUM AND LACTATION AND THEIR ASSOCIATION WITH THE LACTATIONAL PHYSIOLOGICAL HYPOPHAGIA: A REVIEW†

[CARACTERIZACIÓN DE LA MODULACIÓN METABÓLICA DE LAS CERDAS DURANTE EL PERIPARTO Y LACTANCIA Y SU ASOCIACIÓN CON LA HIPOFAGIA FISIOLÓGICA LACTACIONAL: UNA REVISIÓN]

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SUMMARY

Sow' digestive and metabolic adaptations during the transition pregnancy-lactation causes decreases in the voluntary feed intake (VFI), because of blood glucose increase, essential for intrauterine growth of the litter and mammary gland. Aspect (feed intake reduction) that is maintained at least during the first week post-partum. These conditions encourage the sow (post-partum) to initiate with negative energy balance, forcing the organism to mobilize body reserves to satisfy its nutritional requirements. However, under modern swine production practices, this adaptation represents an obstacle to express the reproductive and productive potential of the species; since, this potential is based on the metabolic state of the sow during lactation and post-partum, where, glucose, insulin, and other metabolites (NEFA, IGF-1 and leptin) play a predominant role. These factors have been analyzed in isolation, so it is necessary to integrate them to be clear about the strategies that must be established before the lactational hypophagia. Therefore, in this review try, to articulate the results of various researches around this topic and analyze them under a holistic perspective where both factors and interactions attributable to the phenomenon are prioritized.
Keywords: Glucose; insulin; adaptation; feeding.

RESUMEN

Las adaptaciones digestivas y metabólicas que sufre la cerda durante la transición gestación-lactancia reducen el consumo voluntario de alimento (CVA), debido al incremento de glucemia, esencial para crecimiento intrauterino de la camada y de la glándula mamaria. La reducción del CVA se mantiene al menos durante la primera semana postparto. Estas condiciones propician que la cerda durante el post-parto inicie con balance energético negativo, obligando al organismo a movilizar reservas corporales para satisfacer sus requerimientos nutricionales. No obstante, bajo las modernas prácticas de producción porcina, esta adaptación representa un obstáculo para expresar el potencial reproductivo y productivo de la especie; puesto que, este potencial está en función del estado metabólico de la cerda durante la lactación y postparto, en donde, la glucosa, insulina y otros metabolitos (NEFA, IGF-1 y leptina), juegan un papel predominante. Estos factores han sido analizados aisladamente, por lo que se requiere de su integración para tener claridad sobre las estrategias que deben establecerse ante la hipofagia lactacional. Por ello, en la presente revisión se integran los resultados de diversas investigaciones en torno a este tópico y se analizan bajo una óptica holística en donde se priorizan tanto los factores como las interacciones atribuibles al fenómeno.
Palabras clave: Glucosa; insulina; adaptación; alimentación.

INTRODUCTION

In sows, the lactation phase is a relatively short period within their productive cycle (15 to 19%), compared to other species such as bovines (Farmer *et al.*, 2007). However, the digestive and metabolic adaptations suffered by the sow during the transition period between gestation and early lactation (±10 days from farrowing) is comparable with that of a bovine producer of milk (Theil, 2015). This period is

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characterized by the reduction of the voluntary feed intake, product of metabolic changes, and digestive adaptations suffered by the sow (Park *et al.*, 2010), because in the last third of gestation it produces the maximum intrauterine growth of fetuses (up to one third of the weight) and the development of the mammary gland, without increasing the voluntary feed intake (Pére and Etienne, 2007). Conditions that, in general, encourage sows to start the lactation phase with a negative energy balance, forcing the body to mobilize its reserves to meet the energy requirements for the maintenance and milk production (Theil, 2015).

Sow' digestive and metabolic adaptations, are product of the evolutionary physiology of the species; therefore, the impact of lactational hypophagia on sow' productivity postweaning, would be minimal or null under conditions of wild state (Carey *et al.*, 2003). However, modern swine production practices establish that, if sows mobilize too much fat and body protein at lactation (>10 kg of live weight) ovarian functions will be affected as well as the productivity (Rempel *et al.*, 2015).

Since the optimal functioning of the hypothalamus-pituitary-ovary axis in the third lactation week (Britt, 1986) requires support of energy and protein for restarting ovarian function (Cools *et al.*, 2014); support which, usually, is obtained from the own sow' body reserves (Mosnier *et al.*, 2010a). Therefore, it has been established that sow' body condition postweaning should be three (considering the score from 1 to 5) so, that reproductive efficiency is not affected (Estienne *et al.*, 2000).

Prunier and Quesnel (2000) established, that postweaning sow' reproductive efficiency is determined by its metabolic state, during the lactation phase and postweaning, where, metabolites such as glucose, insulin, NEFA, insulin, IGF-1, and leptin, play a preponderant role in the restart of ovarian activity; since, this metabolites are related to hypothalamic sensors that link sow' nutritional and reproductive status. Therefore, it is essential to establish the metabolic changes that the sow present at gestation and lactation to establish appropriate strategies and streamline the productivity of this species.

Since the productive potential of swine production systems is determined by the size and weight of the litter at farrowing and weaning, as well as, by sow' reproductive intensity (Boulot *et al.*, 2008). Therefore, the objectives of this work were: i) revision of the state of the art (during the last forty years) on the factors that modulate sow' metabolism at peripartum and lactation and, ii) establish the effect of metabolic changes on voluntary feed intake of sow at peripartum and lactation.

Methodological approach

For characterize and model schematically the sow' metabolic status during the peripartum and lactation and their impact on the voluntary feed intake, the current information of the main research on this topical was used, as well as the use of classic articles generated between 1960 to 1980. The information was analyzed under the methodological approach of the general system theory (GST). Theory postulates that with the integration of different scientific disciplines is achieved the solution of problems in an integral way (Bertalanffy, 1976); since, the scenarios and processes of the biologic systems cannot be classified by their correspondence with a particular discipline because of their complex interactions which is derived in *complex systems* (García, 2006; Ortiz *et al.*, 2016).

A *complex system* represents only a portion of reality, conceptualized as an organized whole in which the elements are characterized for: 1) not to be separate, 2) have specific delimitation (feedback of mechanisms involved) and, 3) cannot be studied in isolation (Spedding, 1988; Ortiz *et al.*, 2016). Since studying a phenomenon in isolation is to eliminate of the analysis the context [*environment*] in which observable relationships are developed (Schaeffer, 2009), which is not possible; every biological system interacts directly with the environment (Ortiz *et al.*, 2016). Therefore, research on the sow' metabolic status (pre-and postpartum) and their relationship with feed intake offer disjointed visions of this phenomenon.

Complex systems, such as swine production systems, are generally composed of four elements: context, human component, animal component and technology (Van Gigch *et al.*, 1998). However, for the purposes of this review, the technological component was prioritized; since a production system of this nature is determined by its technical element. Which may be present in two areas: 1) physical, associated with alternatives used to try to control the environment and, 2) biological, associated with the knowledge generated to control variables inherent in species' biology (Gilbert *et al.*, 1980). In addition, it is not possible to balance the four components and expect the system to maintain constant productivity; because a system in total balance runs the risk of disappear, due to the precision exerted by a higher entropy contained among its components (Tyrtania, 2012); therefore, biological systems move away from equilibrium for as long as possible. Thus, for a system not to enter into entropy should: i) invest in the process increasing amounts of energy extracted from the medium by modifying the biological system [sow] through technology and; ii) transfer the price of energy loss to sub-systems by modifying the interaction between system components (Tyrtania, 2009).

Taking the considerations of the preceding paragraph, it characterized and modelled sow' metabolic regulation (during peripartum and lactation) under two schematic models of organization (Wadsworth, 1997). The first schematic model that was made around this characterization, contains an approach "*Soft*", where the factors attributable and not attributable to the phenomenon are obtained, which are susceptible to condition the functioning of the system. In the second model, a more formal approach was considered, since the information collected was analyzed considering the criterial of Goodall (1976): i) internal homogeneity with respect to a system property; ii) relative interdependence of system components and, iii) related disciplines as a basis for decomposing the system. Eliminating as much as possible the inconsistencies that skew the perception of reality.

Factors attributable and not attributable to the biological component (sow) that modify the voluntary feed intake at lactation: *Schematic model*

Context

The growing demand for protein of animal origin for human consumption places the pig as a livestock activity with potential for this purpose, due to the biological characteristics of this species, as they are: precocity, short reproductive cycle, prolificacy, among others (FAO, 2016). However, to meet the consumers pork demand, the productive potential of this species must be achieved within swine production systems (Ortiz and Ortega, 2001). Potential determined, essentially, by the sow' productivity: parties sow^{-1} $year^{-1}$ and within this indicator the size and weight of the litter at parity and weaning play a significant role (Boulot *et al.*, 2008). However, to achieve the efficiency of these indicators, sow' voluntary feed intake at lactation must be controlled and manipulated (Xie *et al.*, 2015); since, this variable, directly affects sow' productivity.

In sows, lactational physiological hypophagia is a physiological process complex to control and manipulate (Yoder *et al.*, 2012; Rempel *et al.*, 2015), because the behavior of the appetite postpartum is an evolutionary adaptation of the species and therefore involved several elements, including: changes in the metabolic and reproductive system, changes that in modern production systems are disrupted [*biologically*] for the genotype, age, health status, body condition and, [*technologically*] for the housing infrastructure and zootechnical practices applied to sow pre and postpartum (Mosnier *et al.*, 2010a). Therefore, to maximize the production of the swine production systems, the biological event to be controlled and manipulated is the sow' metabolism at the end of gestation and during lactation (Figure 1), because it not only affects the behavior of the appetite (decreases) but also sow' productivity (Parra *et al.*, 2009).

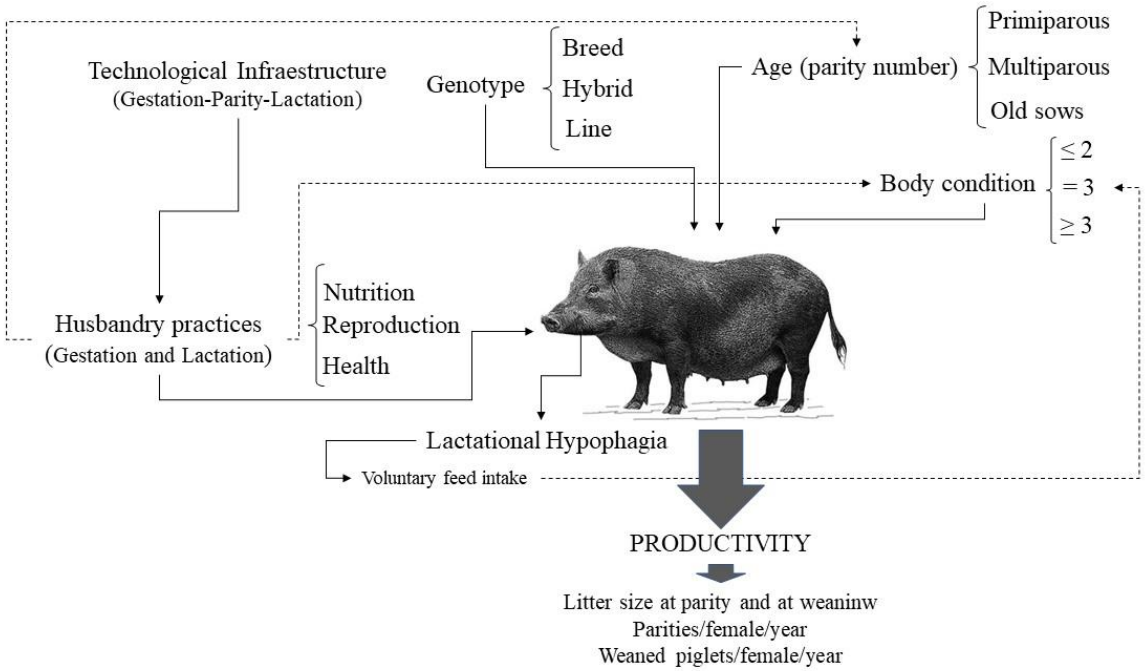

Figure 1. Schematic vision of the factors that alter or modify the biological system around the reduction of sow' feed intake at lactation. (Authors own elaboration)

Human component

Even though the pig is a widely investigated species, there are physiological peculiarities, such as the sow' metabolic changes during peripartum and lactation and its relationship with the alteration of the hypothalamic centers that are responsible for regulating the appetite (Pére and Etienne, 2007); the results on this topic have not yet been integrated to be clear about the strategies to be established on of the effects of the decrease in sow' voluntary feed intake at lactation phase (Figure 1). Because of that, is common to use zootechnical practices to mitigate the effect of lactational hypophagia with limited results in the control of this phenomenon (Gasa and Sola, 2016) without a clear understanding of the factors involved in the modulation of the sow' metabolism at lactation.

The physiological modification of the sow' appetite postpartum, under the modern systems of swine production, has productive implications. Ortiz and Ortega (2001) establish that any alteration (however small it is) is propagated to the entire system in a wave form, increasing the wavelength as it propagates. The difficulty with this manifestation is that, in general, the effect of the problem is attacked and not to the problem itself, whose origin is almost imperceptible given its low intensity characteristics. Hence, attempts to manipulate and control sow' lactational hypophagia have not had satisfactory results (Figure 2).

Animal component

Animal production systems are artificial systems where the animal depends on human to satisfy its physiological requirements (Ortiz and Ortega, 2001). Therefore, greater coverage of the needs of the biological component [animal] within the system, greater it will be the production of this; but for this, it is required as a condition the knowledge of the animal biology, not the physical presence of the same in the system (Bertalanffy, 1976). Therefore, facing the problem and its effect of the sow' lactational hypophagia implies moving from a simple system (human-animal-technology) to a system of greater complexity: modulation of the sow' energy metabolic during the transition from peripartum to lactation. Taking this point, as a departure of analysis and understanding of this phenomenon (lactational hypophagia), it will be able to control and manipulate the metabolism in this transition period waiting for the sow to increase the voluntary feed intake and improve the productivity of the same during and after of lactation (Mosnier *et al.*, 2010a).

Voluntary feed intake postpartum: sow' metabolic changes during peripartum and lactation were evolutionary adaptations of the species (Pére and Etienne, 2007). But this is not to say that it cannot be manipulated to counteract its effects on the productivity of swine production systems. However, feeding and nutritional strategies to maximize sow' feed intake during the lactation phase have not been successful (Parra *et al.*, 2009). Aspect that is reflected in the variability of feed intake *ad libitum* (with conventional diets; corn-soybean) at lactation: 3.6 to 7.0 kg average day^{-1} (Revell *et al.*, 1998; Park *et al.*, 2010; Wan *et al.*, 2016). Gasa and Sola (2016), in their review on feeding of hyperprolific sows in lactation phase, found that more than 50% of the research on this topic reported an average of feed intake less than 5.5 kg day^{-1}. Quantity that does not satisfy the nutritional requirements of sows in this phase and, is in the first week of lactation where the biggest deficit of intake is observed: the sows only achieve a maximum intake of 60% of the required (Mosnier *et al.*, 2010a). Whereas, in the following weeks, the intake is of 80% of the required, this, independently of the nutrient composition of the diet, age, and genotype of the sow (Farmer *et al.*, 2007; Yang *et al.*, 2009).

Even when the genetic improvement of the current sows has had a positive impact on the prolificacy and leanness, the feed intake at lactation has not undergone variation (Foxcroft, 2012). However, leanness has sharpened the effects of lactational hypophagia, since the body reserves (<24 mm of dorsal fat) of genetically improved sows (lines) are lower than those of hybrid or breed sows (Ordaz *et al.*, 2013), which results in less homeostatic response to the decrease in sow' voluntary feed intake at lactation (Pérez *et al*., 2015). The heterogeneity in the sow' feed intake at lactation motivated its mathematical modeling (Figure 3), that is currently an important reference when dealing with this problem (Koketsu *et al.*, 1996).

Koketsu *et al.* (1996) classify the sow' voluntary feed intake at lactation phase as: GRADUAL, progressive increase with peak at ten days without a decrease of intake post-peak (8-9 kg average day^{-1}); RAPID, rapid increase postpartum without intake drop (5.9 kg average day^{-1}); MINOR "RAPID", with postpartum drop <1.8 kg day^{-1} at least two days (5.4 kg average day^{-1}); MAJOR "RAPID"; with postpartum drop >1.8 kg day^{-1} at least two days (5.1 kg average day^{-1}); GRADUAL "HIGHER", gradual increase with intake < 2.7 kg day^{-1} during the first week of lactation (3.9 kg average day^{-1}) and, GRADUAL "LOWER", low intake throughout lactation (3.2 kg average day^{-1}). This classification of sow' voluntary feed intake postpartum, established by Koketsu *et al.* (1996) reveals the complexity of the phenomenon between the metabolic state and sow' feed intake at lactation phase (Martos *et al.*, 2006; Pére and Etienne, 2007; Cools *et al.*, 2014), since this intake depends of the behavior of the metabolites regulating the homeostasis of hunger and satiety, such as: glucose, NEFA, insulin, leptin, among others no less important (Figure 3). As well as

the interaction of these metabolites and the emergence of insulin resistance (Prunier and Quesnel, 2000; Hoving *et al.*, 2012).

Dynamics of the behavior of blood glucose pre-and postpartum: The first observations on the reduction of sow' voluntary feed intake postpartum point out to glucose as the main origin (Aherne *et al.*, 1969; Pére *et al.*, 2000). That was associated with the increased glucose requirements of the gravid uterus at late gestation; a phenomenon that persists after parity due to the increased requirements of mammary glands at lactation (Pére *et al.*, 2000). Ten days prepartum (Figure 4), glucose levels are stable and higher (36.3%) than at lactation (Aherne *et al.*, 1969; Pére and Etienne, 2007; Reynolds *et al.*, 2010).

Postpartum, glucose pre-prandial increases in the first week and decreases in subsequent weeks (Kraetzl *et al.*, 1998). At lactation phase, about 60% of the blood glucose is used to synthesis of lactose, glycerol, fatty acids (for milk), energy for the maintenance of the mammary gland and other metabolic processes (Spincer *et al.*, 1969). The production of 11.4 kg of milk require close to 2000 g of glucose (Farmr *et al.*, 2008); but, to cover this demand, insulin resistance must be implanted (Figure 4) which originate the lactational hypophagia (Reynolds *et al.*, 2010).

The degree of insulin resistance depends on certain factors such as: body condition, age, genotype, litter size, suckling intensity, nutrition and feed techniques among others (Mosnier *et al.*, 2010b).

Glucose dynamics, according to sow' body condition (without and with overweight) and type of diet (high, 19% or low, 7.9% in protein) at gestation, is equal (P=0.957): 73.8 *vs* 74.1 mg dL^{-1} for sows without and with overweight, respectively (Revell *et al.*, 1998); prepartum, both types of sows present higher levels of glucose (118.9 mg dL^{-1}) with respect to the second (59.4 mg dL^{-1}) and third (75.7 mg dL^{-1}) lactation week. All of this, regardless of diet type (Table 1) (Revell *et al.*, 1998).

Table 1. Blood glucose levels (mg dL^{-1}) at peripartum and lactation according to different factors of variation

Day/Phase	Variation factors				SEM	P-Value		Reference
	Fat/LP	Fat/HP	Lean/LP	Lean/HP		BC	Diet	
110 gestation	74.9	73.9	74.7	73.5	0.220	0.957	0.765	Revell *et al.* (1998)
14 lactation	53.2	55.6	58.7	51.9	0.372	0.946	0.917	
28 lactation	66.3	56.3	53.9	54.6	0.228	0.260	0.213	
	Genotype							
	Line	Duroc	Landrace	Yorkshire		Genotype		Farmer *et al.* (2007)
2 lactation	75.7[ab]	85.2[a]	71.7[b]	82.1[ab]	0.21	0.04		
18 lactation	67.6	75.8	69.5	74.9	0.17	0.15		
	Energy							
	Lactation 12 days		Lactation 21 days			LD	Diet	
	Restricted	*Ad libitum*	Restricted	*Ad libitum*				Koketsu *et al.* (1998)
12-21 lactation	72.9 ±2.8	84.7 ±1.8	67.2 ±2.1	73.0 ±1.7		<0.01	<0.01	
13-22 postweaning	85.6 ±3.2	75.6 ±4.9	67.2 ±3.8	73.6 ±3.0		0.51	0.75	
	Commercial Feed (CF)		CF + cactus[&]			LD	Diet	
	GLU Pre-P	GLU Post-P	GLU Pre-P	GLU Post-P				
85-110 gestation	70.3[1]±7.2	79.8[1]±8.2	75.2[1] ±7.9	83.2[1] ±6.7		<0.01	<0.01	Ordaz *et al.* (2017)
1-7 lactation	72.0 [a1] ±8.3	81.5[a1] ±9.0	59.7[a2] ±5.4	67.2[a2]±12.1		<0.01	<0.01	
8-14 lactation	71.1[a1]±8.5	81.4[a1]±10.6	46.4[a2]±7.5	58.7[b2]±5.7				
15-21 lactation	69.2[a1]±7.7	76.9[a1]±12.9	57.1[a2]±7.1	66.1[a2]±9.5				

LP = low protein level; HP = high protein level; BC = Body condition; LD = lactation duration; GLU = glucose; Pre-P = preprandial; Post-P = postprandial.

[&]addition of cactus: 1% according to the live weight of the sow on fresh base.

[a, b] Different literals indicate statistical difference (P<0.05) within column.

[1, 2] Different numerals indicate statistical difference (P<0.05) between feeding schemes for glucose pre-and postprandial, respectively.

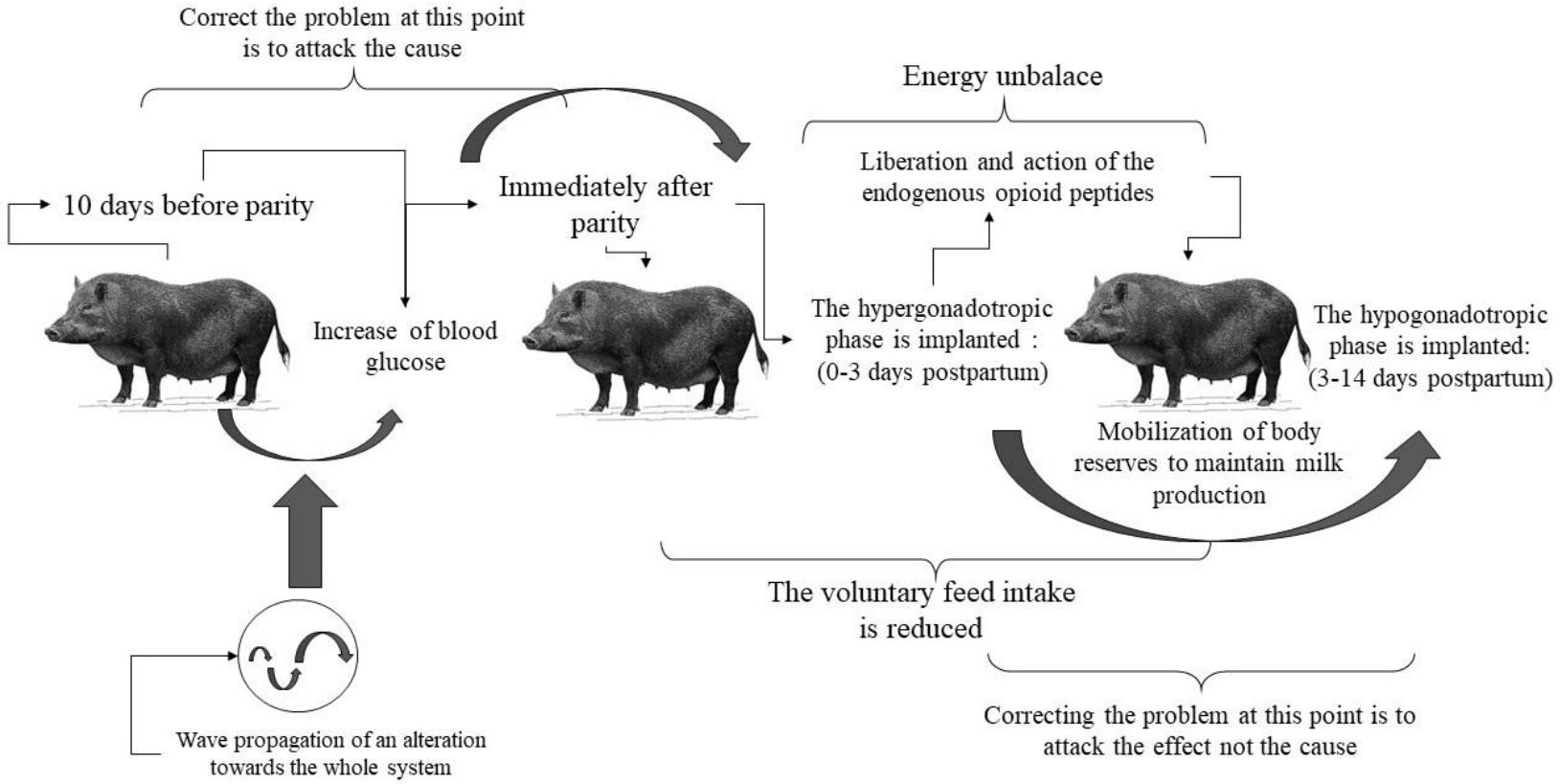

Figure 2. Blood glucose increases in sows and its effect on the voluntary feed intake reduction at lactation: schematic vision. (Authors own elaboration)

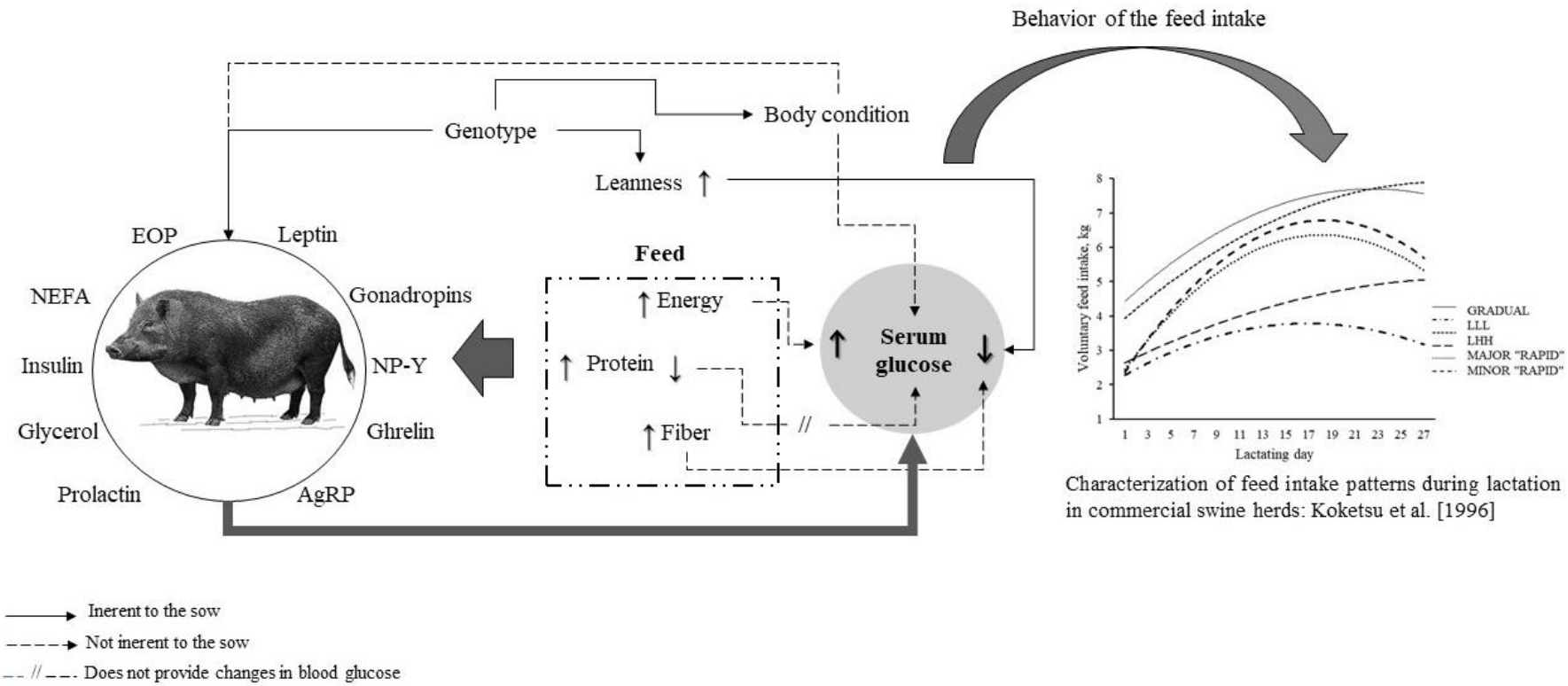

Figure 3. Reformulation of the schematic vision of the biological system around the metabolic state and its relationship with the behavior of the sow' voluntary feed intake at lactation. (Authors own elaboration).

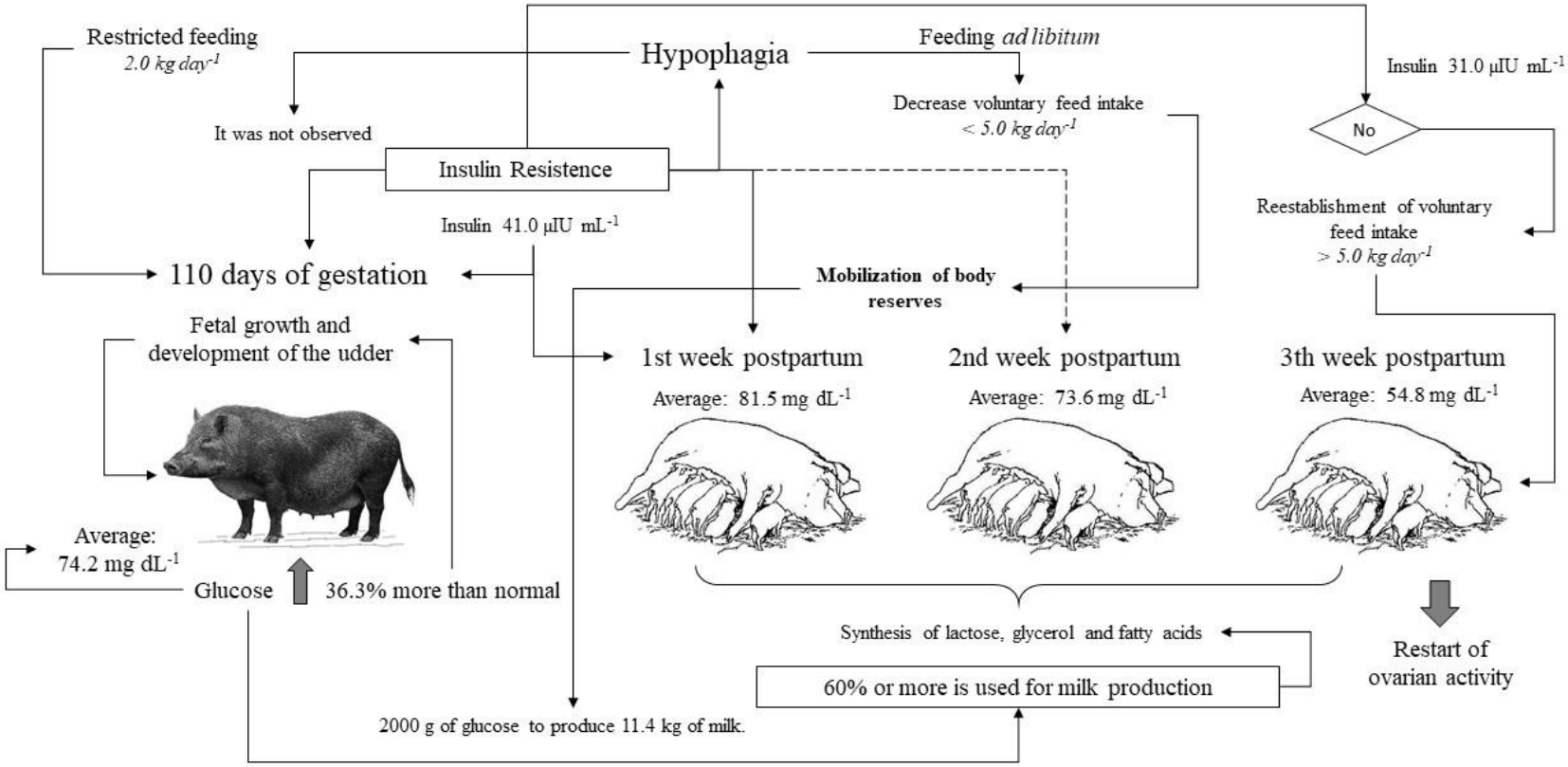

Figure 4. Blood glucose dynamics and their relationship to sow' voluntary feed intake at lactation: schematic reformulation. (Authors own elaboration).

With respect to the genotype, Farmer *et al.* (2007) have reported lower glucose levels to second day postpartum in Landrace sows (72.0±3.1 mg dL^{-1}) in contrast to Duroc, Yorkshire and synthetic lines genotypes (Table 1), the lower glucose levels was reflected in higher feed intake for Landrace sows: 5.6±0.15 *vs* 4.7, 5.3 and 5.3±0.15 kg day^{-1} for synthetic lines, Duroc and Yorkshire, respectively. With respect to the feeding scheme (*ad libitum*: 6.0 kg average day^{-1} *vs* restricted: 4.0 kg day^{-1}), lactation duration (12 *vs* 21 days) and independently of the genotype, the sows fed *ad libitum* showed higher average glucose levels at lactation ($P<0.05$): 84.7±1.8 *vs* 73.0±1.7 mg dL^{-1} for short lactation (12 days) and conventional (21 days), respectively (Table 1), in comparison to the sows fed in a restricted manner: 72.9±2.8 mg dL^{-1} for short lactation and 67.2±2.1 mg dL^{-1} for conventional lactation (Koketsu *et al.*, 1998).

In terms of lysine content in the diet (1.0 or 1.3%) at gestation and lactation phase, it is not reported (Yang *et al.*, 2009) effect of lysine level or age of sow on glucose levels ($P>0.05$): 91.99±0.92 mg dL^{-1} at parity and 89.40±0.92 mg dL^{-1} at weaning (21 days postpartum). The same behavior was observed, for adding different type of energy source to the diet: soybean oil (55 g kg^{-1}; control diet), Dextrose (54 g kg^{-1}), Sucrose (50 g kg^{-1}), Lactose (50 g kg^{-1}), Dextrose/Sucrose (54/50 g kg^{-1}), sucrose/lactose (50/50 g kg^{-1}) and beet pulp (400 g kg^{-1}); Wientjest *et al.* (2012) do not report differences ($P=0.640$) in glucose levels for treatment effect, glucose levels at ninth lactation day were between 73.2 to 71.0 mg dL^{-1}. Postweaning glucose levels, Koketsu *et al.* (1998) did not find effect on feed intake (Table 1). As for the addition of a hypoglycemic, as is the cactus (*Opuntia ficus-indica*), to sows' diet modified the dynamics of the behavior of glucose levels pre-and postprandial, immediately after parity and at lactation phase (Ordaz *et al.*, 2017) (Table 1).

The behavior of insulin pre-and postpartum shows insulin resistance, mainly, 10 days prepartum and during the first lactation week; since, despite increased insulin synthesis and release, glucose levels do not descend (Mosnier *et al.*, 2010b). Coupled with that, the growth hormone - insulin interaction (Steele *et al.*, 1985; Kusina *et al.*, 1999) is essential for the development of fetuses at last third of gestation and milk production at lactation (Pére *et al.*, 2000), aspects responsible for blood glucose fluctuations (Farmer *et al.*, 2007), lipolysis presentation, increase of NEFA and its subsequent effect on lactational hypophagia (Revell *et al.*, 1998).

Dynamics of the behavior of insulin pre-and postpartum: Insulin is the main anabolic endocrine signal and plays a critical role in the metabolism of carbohydrates, lipids and proteins (Baumgard *et al.*, 2015). Their level increases post-feeding to provide energy to the cells (Kusina *et al.*, 1999). Revel *et al.* (1998) reported insulin increase prepartum (41.0 µIU mL^{-1} average), behavior that is maintained at first week of lactation and subsequently decays in the fourth week: to 31.0 µIU mL^{-1}, regardless of the protein percentage of the sow' diet or body condition (Table 2). According to the feed intake, Koketsu *et al.* (1998) reported higher insulin levels in sows fed *ad libitum* (6.0 kg average day^{-1}) independently of lactation duration: 12 (21.3±2.7 µIU mL^{-1}) and 21 days (18.9±4.5 µIU mL^{-1}), in contrast to levels found in sows fed in a restricted manner (2.0 kg $days^{-1}$): 8.5±3.5 and 6.8±2.9 µIU mL^{-1} for lactations of 21 and 12 days, respectively.

Kusina *et al.* (1999) establish that, the deficiency in amino acids in the diet, specifically lysine decreases insulin concentrations. This is corroborated by Yang *et al.* (2009) who report higher insulin concentration in sows fed a diet rich in lysine (1.3%) at gestation and lactation: 24.4±0.4 µIU mL^{-1} average at parity and 16.4±0.4 µIU mL^{-1} average at weaning, in contrast to sows who consumed a diet with 1.0% lysine: 22.0±0.4 and 24.4±0.4 µIU mL^{-1} average at parity and weaning, respectively (Table 2). The addition of L-carnitine to the diet of lactating sows was observed (Woodworth *et al.*, 2004) higher sensitivity of insulin receptors, which improved glucose utilization due to increased GLUT4 activity (Wang *et al.*, 1999). However, the addition of L-carnitine (250 mg day^{-1}) does not increase sow' feed intake at lactation: 5.3 kg average day^{-1} *vs* 5.2 kg average day^{-1} of the control group (Birkenfeld *et al.*, 2006).

With respect to the energy substrate that is added to the diet of lactating sows on the synthesis of insulin; Wientjest *et al.* (2012) report increased insulin synthesis to ninth lactation day when the diet is added with sucrose alone or sucrose in combination with another energy substrate (Table 2). Bantle *et al.* (1992) establish that the fructose stimulates to a higher degree of insulin synthesis, which justifies greater insulin synthesis in sows fed with the diet added with sucrose, because, this monomer is hydrolyzes in glucose and fructose to be able to be absorbed.

Table 2. Insulin levels (µIU mL^{-1}) at peripartum and lactation according to different factors of variation.

Day	Variation factors				SEM	P-Value		Reference
	Fat/LP	Fat/HP	Lean/LP	Lean/LP		BC	Diet	
110 gestation	7.0	6.5	7.1	5.9	1.18	0.816	0.459	Revell *et al.* (1998)
14 lactation	5.0	3.7	4.0	4.0	1.08	0.732	0.584	
28 lactation	2.7	4.1	2.8	3.5	0.62	0.812	0.225	

Lysine level, %								
Gestation	Lactation	Age (E)	Postpartum	Weaning day		Phase	F*E	
0.8	1.0	Primiparous	21.72	14.90	0.33	0.106	0.889	Yang *et al.* (2009)
0.8	1.0	Multiparous	22.75	15.15				
0.8	1.3	Primiparous	23.17	15.47				
0.8	1.3	Multiparous	24.04	16.01				
0.6	1.0	Primiparous	21.58	14.42				
0.6	1.0	Multiparous	22.08	15.83				
0.6	1.3	Primiparous	24.95	16.56				
0.6	1.3	Multiparous	25.28	17.48				

Diet	Insulin levels at ninth lactating day	Diet	
Soybean oil, 55 g kg^{-1}, Control	16.4 ± 0.9^{ab}	<0.001	Wiensj*et al.* (2012)
Dextrose, 54 g kg^{-1}	19.0 ± 1.0^{abc}		
Sucrose, 50 g kg^{-1}	17.9 ± 1.0^{abc}		
Lactose, 50 g kg^{-1}	15.9 ± 0.9^{a}		
Dex/bag, 54/50 g kg^{-1}	19.6 ± 0.9^{c}		
Suc/Lake, 50/50 g kg^{-1}	19.1 ± 0.9^{bc}		
Beet pulp, 400 g kg^{-1}	18.4 ± 1.0^{abc}		

LP = low protein level; HP = high protein level; BC = Body condition.
[abc] Different literals indicate statistical difference (P<0.05) between row.

Insulin resistance: It is called insulin resistance to decreased uptake insulin-mediated by glucose in sensitive tissues (De Koster and Opsomer, 2013; Akbari *et al.*, 2015). It is known that the increase in plasma concentration of NEFA propitiates insulin resistance in muscle and liver (Boder, 2011). NEFA increase has negative impact on insulin secretion in the cells β of the pancreas (Kerestes *et al.*, 2009). Therefore, the insufficient capacity of the liver and skeletal muscle to oxidize fatty acids favors increase in tissue and plasma, contributing to the development of insulin resistance (Karpe *et al.*, 2011). Revell *et al.* (1998) establish that, NEFA increase it reduces the number of insulin receptors available, therefore insulin resistance is an indicator of the catabolic state of the sow associated with body reserves mobilization. Revell *et al.* (1998) and Kusina *et al.* (1999) reported that, the daily administration of insulin during the first lactation week reduces plasma glucose levels and increases voluntary feed intake, however, this administration has no effect on plasma NEFA. However, not only energy substrates and their derivatives favor the development of insulin resistance, also resistin participates in this phenomenon (Dai *et al.*, 2005).

Claire *et al.* (2001), researching the administration of recombinant resistin in mice (16.5 mg), they observed increased glucose and insulin (28%) compared to untreated mice (P=0.004); these result post-administration of resistin indicated that: a) insulin resistance is not due to a failure in the production and synthesis of insulin and, b) the resistin increases glucose levels by acting as antagonistic to insulin. Like leptin, it seems likely that the resistin did not evolve specifically to lead to insulin endurance during times when feed is abundant; rather, its physiological function focuses on the adaptive response to starvation (Ahima *et al.*, 1996). In contrast, there is evidence that during hibernation (in mammals) modifies the regulation of carbohydrates towards the metabolism of fatty acids through the enzymatic activity glycolytic (Brooks and Storey 1992). This synergy (glucose-fat) provides the substrates through the lipogenesis-lipolysis and gluconeogenesis-glycolysis to provide energy (Staples and Hochachka, 1998; Bauer *et al.*, 2001). Processes that increase anaerobic glycolysis and decrease the oxidation of glucose, by preventing glycolysis intermediate products from entering the cycle of the tricarboxylic acid (Galster and Morrison, 1975). However, it is required to hydrolyze triacylglycerol for the synthesis of glycerol and to perform the replenishment of glycogen through the gluconeogenesis (Yeh *et al.*, 1995; Store, 1997). A phenomenon that also occurs during the lactational physiological hypophagia.

Possibly, the expression of two proteins triggers the genetic mechanism of hypophagia (Andrews *et al.*, 1998): Pyruvate dehydrogenase kinase isoenzyme-4 (PDK4) and Pancreatic triacylglycerol lipase (PTL). PDK4 through the white adipose tissue activates the synthesis of pyruvate dehydrogenase (PDH) in its inactive form phosphorylation (Carey *et al.*, 2003). This modification prevents the catabolism of carbohydrates since the conversion of pyruvate into acetyl CoA is blocked. PTL, on the other hand, hydrolyzes triacylglycerol to release fatty acids for oxidation. Both PTL and PDK4 work in a coordinated manner to block the switch from the catabolism of carbohydrates and lipids. This mechanism offers a constant supply of NEFA that can re-esterify as triacylglycerol and be stored as lipids in the mitochondria for the generation of ATP (Burlington *et al.*, 1972; Bauer *et al.*, 2001).

Beckman and Llados-Eckman (1985) reported (in bats) that, the insulin level constantly increases during hibernation to promote fast-release storage once the hibernation is completed and facilitate the absorption of glucose post-feeding. In the case of lactational hypophagia in sows the increase of insulin is essential prepartum for the synthesis of growth hormone and IGF-1 essential for the development of fetuses and mammary glands (Farmer *et al.*, 2007). With regard to lactation, insulin has a role in the regulation of leptin and is associated with the energy supply of milk for piglets (Pére and Etienne, 2007). In this sense, in the hibernation phase the insulin loses its function (characteristic observed in the lactational hypophagia) since the ligand dependent of the receptor activator of the Peroxisomal Proliferase-α (PPARα) is the one that activates PDK4 (Wu *et al.*, 2001). Likewise, the expression of PDK4 is induced by natural ligands as they are NEFA of long chain: linoleic fatty acids, linolenic, and arachidonic (Kliewer *et al.*, 1998). Also, present in the lactational hypophagia due to the catabolic state in which the sows are found. This can be based on what is reported by Wu *et al.* (2000 and 2001) who establish that hypophagia and diabetes, are two conditions that share some characteristics with the state of hibernation (stimulate the expression PDK4) and these two characteristics (hypophagia and diabetes) are the central pillars of the phenomenon of lactational hypophagia.

The action of PDK4 on the modification of white adipose tissue lies in its sensitivity to dichloroacetate (pyruvate analogue), so PDK4 activity is less likely to be inhibited if there is a buildup of pyruvate during hibernation. Shoonjans *et al.* (1996) report that PPARα participates also in activating the genes involved in lipid metabolism and, this is central in hibernation; specifically, in the transport of extracellular and intracellular and mitochondrial lipids to be oxidized to fatty acids (Squire and Andrews, 2000). The activation of PPARα could therefore provide a mechanism linking the inhibition of the oxidation of carbohydrates with the increase of fat catabolism, becoming the switch for the contribution of energy during hibernation (Figure 5). Thus, NEFA product of fat metabolism they are a clear signal of catabolic state, because, only a minimum portion is derived from the feed intake (Cools *et al.*, 2014).

In pregnant sows with normal body condition the NEFA increased (30%) ($P<0.05$): 74.0 mg dL^{-1} in contrast to obese sows (57.1 mg dL^{-1}) (Revell *et al.*, 1998). This behavior is similar between 112-114 days of gestation: increases when feeding is restricted and is reduced when is *ad libitum* (Cools *et al.*, 2014). At lactation phase, Farmer *et al.* (2003) reported trend ($P>0.05$) in NEFA increased in sows with lower feed intake (3.0 kg) to second (52.2±9.0 mg dL^{-1}) and twenty-eight (59.4±7.2 mg $dL^{-}1$) lactation day, in contrast to sows fed *ad libitum* (≥5.0 kg): 45.0±5.4 mg dL^{-1} in second day and 43.2±7.2 mg dL^{-1} in twenty-eight day. The increase of crude protein in the feed (from 7.9 to 19.0%) does not affect ($P>0.05$) serum levels of NEFA: range of 67.3 to 78.1 mg dL^{-1} at parity; 72.9 to 80.3 mg dL^{-1} in the first lactation week and 61.6 to 75.8 mg dL^{-1} for the second lactation week. This, because the effect of insulin resistance persists even when the protein is increased in the diet (Yang *et al.*, 2009). With respect to sow' genotype, Farmer *et al.* (2003) determined that the levels of NEFA, at lactation phase, are 70% higher ($P=0.010$) in Asian genotypes (96.2 mg dL^{-1}) than in Europeans (55.7 mg dL^{-1}). To second postpartum day NEFA levels in Landrace sows (45.7±6.5 mg dL^{-1}) were lower ($P<0.5$) than in sows of synthetic line (65.8±6.5 mg dL^{-1}) (Farmer *et al.*, 2007). These researchers agree that the increase of NEFA was due to a lower feed intake, which propitiates catabolic state.

Another metabolite that functions as an indicator of sows' energy balance, is the glycerol, due to its association with the mobilization of NEFA, since, in the route of glycerol is the formation of triglycerides (Revell *et al.*, 1998). However, research on glycerol and its relation to catabolism at lactation was not overwhelming (Baidoo *et al.*, 1992; Revell *et al.*, 1998; Yang *et al.*, 2009). This is due to the inevitable effect of insulin resistance at lactation phase on voluntary feed intake; regardless of the nutritional composition of the diet, as well as sow' body condition (Gasa and Sola, 2016). Thus, the catabolic state of the postpartum sows apparently does not affect the triglyceride levels (Cools *et al.*, 2014).

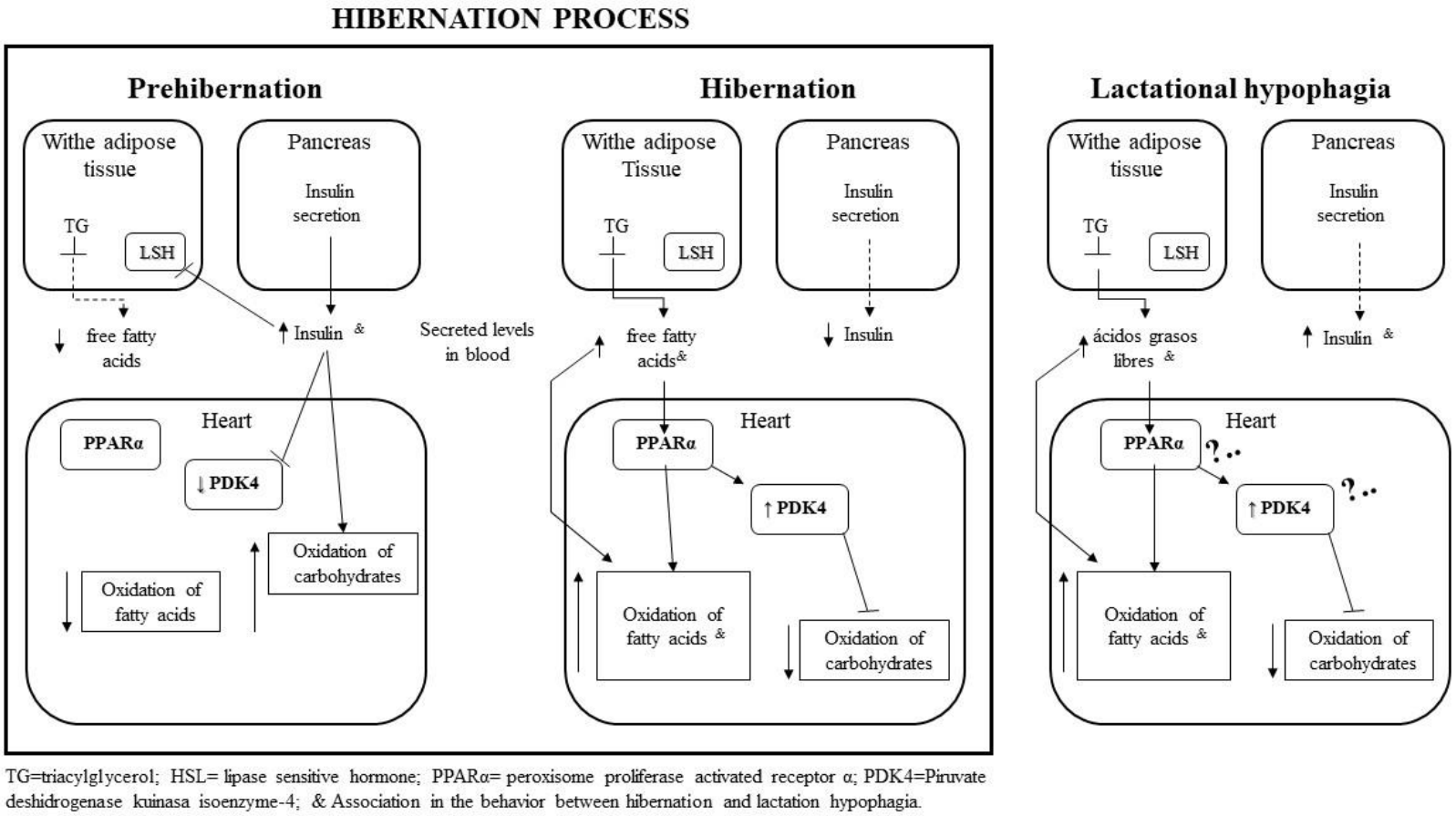

Figure 5. Molecular regulation of the use of carbon pre-and during the hibernation season and its relationship with lactational hypophagia in sows. Modified from Carey *et al.* (2003).

Behavior of the leptin at transition peripartum to lactation: Insulin has a fundamental role in leptin regulation, this observed in humans, rodents (Considine and Caro, 1997) and in pigs (*in vitro* results) (Leininger *et al.*, 2000). Ernst *et al.* (1997) reported that, leptin receptors were the product of the diabetes gene, located on chromosome six in pigs. Polymorphisms (of the LEPR gene) that were associated with insulin and glucose metabolism in obese and gestational diabetes women (Wauters *et al.*, 2001). Leptin is a mediator of the regulation of the energy balance in the long term (its levels do not increase post-feeding), likewise, it has effect on the suppression of the feed intake induces weight loss (Barb *et al.*, 2001; Martínez *et al.*, 2014). Another characteristic of leptin is that in the absence of feed or negative energy balance, its levels, in plasma and adipose tissue, decrease rapidly (Houseknecht *et al.*, 1998).

Lee *et al.* (1996) report in mice, with insulin resistance or diabetes, that the LEPR gene is spliced alternatively to produce at least six isoforms, obese Ra-obese Rf (obRa-obRf). In pigs, the expression of the mRNA of the isoform obRb is found in hypothalamus and affects the regulation of feed intake, energy balance and reproduction (Lin *et al.*, 2000), this expression is more pronounced in lactating sows due to insulin resistance present in this phase. Other isoforms present distribution in liver, heart, kidneys, lungs, small intestine, ovaries, spleen, pancreas and adipose tissue, suggesting that leptin has peripheral effects not only in regulating its secretion, in addition, regulates processes fundamentals of metabolism and reproduction (Ruiz *et al.*, 2000). Forhead and Fowden (2009) observed (in rats and humans) that, at gestation blood levels of leptin increase, due to the formation of the placenta (Forhead and Fowden, 2009). The presence of hyperleptinemia at gestation has no effect on the reduction of feed intake, due to the negative regulation of leptin receptors in the ventromedial nucleus of the hypothalamus (Kolaczynski *et al.*, 1996; Saleri *et al.*, 2005). In sows, Saleri *et al.* (2005) reported at day 7 postweaning plasma leptin values of 1.54±0.36 ng mL^{-1}, values that increase at estrus (3.74±0.98 ng mL^{-1}) to remain constant at first two thirds of gestation (2.5 to 3.0 ng mL^{-1}) and show a peak at day 107 of gestation (5.91±0.69 ng mL^{-1}) until the parity (5.84±1.72 ng mL^{-1}). Therefore, the metabolic key that develops at gestation to increase the availability of nutrients for fetuses is the leptin resistance (Tessier *et al.*, 2013; Nagaishi *et al.*, 2014; Szczesna and Zieba, 2015).

Leptin resistance at last third of gestation (107 to 112 day) was demonstrated by Cools *et al.* (2014) who evaluated the sows according to the thickness of dorsal fat found difference (P=0.003) in the synthesis of leptin average: 2.9; 3.1 and; 3.6 ng mL^{-1} for <18, 18 to 22 and 22 mm of dorsal fat, respectively, if it affects the feed intake (*ad libitum*) (P>0.05): 7.1 kg average day^{-1}. As regards the lactation phase, there is no resistance to leptin, since, in this phase is reported loss of the intracellular signal of the function of the receptors leptin and prolactin, a phenomenon that is most evident at first lactation week, propitiating hypophagia (Tessier *et al.*, 2013). At lactation, leptin levels decrease with form elapses this phase; levels of 2.2±0.3 ng mL^{-1} were reported at day 10 of lactation and 1.7±0.6 ng mL^{-1} at day 20 (Saleri *et al.*, 2015).

Regarding the genotype, it has been shown that leptin placental, as well as leptin receptors mRNA were higher in Asian sows than in European genotypes (Dyer *et al*., 1999). However, Farmer *et al.* (2007) nor report difference (P=0.14) in leptin levels to second postpartum day according to genotype (Table 3), but if at eighteen lactation day, day in which Landrace sows showed higher (P<0.05) leptin levels (3.3±0.2 ng mL^{-1}) with respect to the other genotypes evaluated (Table 3). This behavior was associated with the highest thickness of dorsal fat in Landrace sows and their association with leptin: r=0.47 and 0.63 to second and eighteen lactation day, respectively (P<0.001).

Estienne *et al.* (2000), report a correlation between dorsal grade thickness and leptin synthesis of 0.67 (P <0.001); this association was reflected in leptin synthesis 24 h before prepartum, and according to classification of sow' body condition: obese (>25 mm backfat): 4.9 ng mL^{-1}; medium condition (20 to 25 mm backfat): 3.7 ng mL^{-1} and, thin (<20 mm backfat): 2.8 ± 0.20 ng mL^{-1}. At 7, 14, and 21 lactation days leptin levels decreased, this behavior was maintained (obese sows presented the highest levels of leptin). Likewise, it was found (Mosnier *et al.*, 2010a) effect of body condition on feed intake at lactation, being the sows with lower thickness of backfat those that had the highest intake (5.4 kg day^{-1}), with respect to those with medium body condition (4.5 kg day^{-1}) and obese (4.3 kg day^{-1}).

Table 3. Leptin levels (ng mL^{-1}) at second and eighteen lactation day according to the sow' genotype

Lactation day	Lin. Synthetic	Duroc	Landrace	Yorkshire	SEM	P-Value	
2	3.48	3.56	3.83	2.99	0.27	0.140	Farmer *et al.* (2007)
18	2.36^{b}	2.75^{ab}	3.28^{a}	2.34^{b}	0.19	0.002	

[ab] Different literals indicate statistical difference (P<0.05) between columns.

Kolaczynski *et al.* (1996) stablish that, the increase in 10% of body weight results in a 300% increase in serum leptin levels, which justifies the greater leptin synthesis reported by Estienne *et al.* (2000) and Farmer *et al.* (2007) in sows with higher backfat. This behavior is also observed when they were add lipolytic compounds such as L-carnitine (1.84 ng mL^{-1}) and chromium (1.12 ng mL^{-1}) *vs* control (0.84 ng mL^{-1}), due to fat removal (Woodworth *et al.*, 2004) however, although leptin levels declined, there was no increased feed intake at lactation. In contrast, when a diet rich in fiber is added (11.0 *vs* 2.8%) at gestation, leptin levels are not only reduced (42.5 *vs* 50.5 ng mL^{-1}), but also favors the feed intake at lactation (0.94 kg more day^{-1}); the correlation reported between these two variables was -0.51 (P=0.04).

Although leptin is an important metabolic signal, other metabolic signals such as IGF-1, insulin, and glucose availability may play a role in regulating the neuroendocrine axis at periods of acute and chronic undernourishment (Barb and Hausman, 2008), and in the case of lactational hypophagia, the acute imbalance caused for hormones that trigger lactation as is the case of prolactin, interfere with the regulation of feed intake (Farmer *et al.*, 2008).

Prolactin (PRL): It is a peptide hormone with multiple biological functions, not only involved in the lactation process, also affects the metabolism, osmoregulation, ethology and immunoregulation (Farmer, 2016). In sows, PRL levels at 7 days postweaning were of 4.2±0.9 ng mL^{-1}, values that decrease when estrus is present (2.4±1.1 ng mL^{-1}),remain constant for most of gestation and increase (67.8±4.9 ng mL^{-1}) in the last 14 days of gestation, a period in which high correlation with leptin levels is observed (r=0.687; P<0.001) (Algers *et al.*, 1991; Farmer *et al.*, 1999; Saleri *et al.*, 2015). One of the most important functions of the PRL at the last third of gestation focuses on insulin secretion stimulated for glucose; two glucose sensors in the cells *β* (Glucokinase and GLUT2) are stimulated for PRL in isolated islets, an essential mechanism for increased nutrient input to the fetus (Weihaus *et al.*, 2007).

At lactation, PRL levels decrease (P<0.05): 55.4±3.1 to 39.5±1.6 ng mL^{-1} for tenth and twentieth lactating day, respectively (Saleri *et al.*, 2015). Armstrong *et al.* (1986) report in primiparous sows PRL levels of 80.0, 65.3 and 50.1 ng dL^{-1} at days 6, 12 and 20 of lactation, respectively (P<0.05).

Farmer *et al.* (2008) report that Asian genotypes present higher PRL circulation: Meishan sows present higher (P<0.05) PRL levels to seventh lactating day (36.5 ng mL^{-1}) in contrast to genotype Large White sows (24.3 ng mL^{-1}). However, PRL levels in nineteen postpartum day were equals (P>0.05): 17.8 *vs* 17.3 ng mL^{-1} for sows Meishan and Large White, respectively. Behavior associated with backfat thickness - leptin synthesis - PRL synthesis (Farmer *et al.*, 2008).

Roy *et al.* (2007) report direct effect of PRL on Neuropeptide-Y (NPY) expression, with the purpose of satisfying energy demand for milk production. At last lactation phase (≥14 days postpartum), changes in PRL levels were not reported with different dietary patterns or nutrient composition of the feed: Baidoo *et al.* (1992) do not report increased PRL levels to twenty-eight lactation day in sows fed restricted (3.0 kg day^{-1}) and to *ad libitum*; also, PRL synthesis was not modified to the nineteen lactation day in sows that were restricted whit 43% the feed (Lachance *et al.*, 2010).

Regarding energy levels in the diet, it was not found (Jones *et al.*, 2006) modification on PRL levels at day 14 of lactation with diets with high (13.7 MJ kg^{-1}) and low (13.3 MJ kg^{-1}) energy (Table 4). Results that contradict the findings of Farmer (2016), who noted highest PRL levels prepartum and at first lactation week (at the hypothalamic level), mechanisms to increase feed intake. However, this effect has been observed in the second lactation week; where it increases the voluntary feed, intake compared to the first lactation week (Ordaz *et al.*, 2017). Quesnel *et al.* (2005) and Farmer *et al.* (2008) did not find difference in PRL levels at lactation when they assessed sow weight and increased crude protein in the feed. De-Ridder *et al.* (2014) did not alter the short-term response in the average PRL levels of 7 to 10 lactation day increasing (18%) the supply of specific amino acids (isoleucine, leucine, lysine, threonine or valine) according to the daily feed intake (Table 4). In contrast, Quesnel *et al.* (2009) report in sows fed a high crude fiber diet (11.0 *vs* 2.8%) from the twenty-sixth day of gestation until parity, increases PRL levels to parity (43 *vs* 51 ng mL^{-1}). Results that suggest the potential impact of fiber on PRL concentrations.

The addition of fiber to the feed, the duration of the treatment, as well as, the composition of the dietary fiber affects the behavior of PRL (Farmer, 2016) possibly the dietary fiber modifies the speed of transit of feed bolus through the digestive tract, which reduces glucose (mechanical route) and stimulates insulin secretion (via glucose reduction) (Farmer *et al.*, 2007). López (2007) determined that the ingestion of cactus modifies lipid metabolism, because the consumption of this cactus causes hypoglycemic and hypocholesterolemic effect. In this regard, Ordaz *et al.* (2013) established that serum glucose levels were modified (P<0.05) in sows that consumed a diet added with *O. ficus-indica*. This modification (reduction) of this metabolite is probably related to the soluble fiber contained in the cactus (35%) (Ayadi *et al.*, 2009), which can create a pecti-gel and cover the lipid substances present in the feed preventing their

digestion (Urriola and Stein, 2010) and promoting the expulsion with feces. Finding that matches what was suggested by Farmer (2016), as far as dietary fiber reduces glucose and stimulates insulin secretion.

Table 4. Prolactin levels (ng mL^{-1}) at lactation according to different factors of variation

Day	Low energy 13.3 $MJkg^{-1}$	High energy 13.7 MJ kg^{-1}	SEM	P-Value	Reference
14 lactation	6.6	5.6	1.30	NS	Jones *et al.* (2006)

Day	180 kg 18.3% CP	180kg 9.3% CP	240kg 9.3% CP	SEM	Weight*Diet	
21 lactation	13.3±1.0	14.4±1.4	16.1±1.7		0.26	Quesnel *et al.* (2009)
7 postweaning	2.9±0.3	2.5±0.2	2.5±0.1			

AA Infusion	Average prolactin of 7^{th} to 10^{th} lactating day	SEM	Treatment	
Control	17.1			
Isoleucine	17.2			
Lysine	17.8			
Leucine	15.0	2.1	0.939	De-Ridder *et al.* (2014)
Threonine	17.2			
Valine	17.3			

CP = crude protein; AA = amino acid.

There is evidence to support that PRL receptors are also present in white and brown adipose tissue (Symonds *et al.*, 1998), as well as, in the islets of the pancreas (Ling *et al.*, 2003). This gives the pattern to establish that the PRL is complementary or acts as a modulator in the adipogenesis, trying to inhibit insulin resistance (Nira *et al.*, 2006). In the brown adipocytes PRL accelerates the phosphorylation of JAK2, STAT3 and 5 and regulates extracellular signals of kinase 1 and 2 (ERK1/2) which increases the activation of insulin receptors: fosfatiadilinositol- 3-kinase (IRS/PI 3-kinase) (Viengchareun *et al.*, 2004). Also, PRL-insulin coupling induces the PRL production (Ling and Billig, 2001). PRL in stimulating insulin and suppressing metabolites affecting the metabolic state (adiponectin and IL-6) reveals its involvement in the presentation of insulin resistance (Nira *et al.*, 2006); since, for increasing cell proliferation *β* (Sorenson and Brelje, 1997) causes decreased threshold for stimulation of insulin secretion in the face of increased glucose at gestation and postpartum (Hughes and Huang 2011; Carré and Binart, 2014).

Action of opioid peptides, neuropeptide-Y and ghrelin on orexigenic and anorexigenic signals: It has been established that endogenous opioid peptides stimulate PRL synthesis for suppressing dopaminergic neurons (Barb *et al.*, 1986). Mattioli *et al.* (1986) stablish that the mechanism of endogenous opioid peptides propitiates hyperprolactinemia in lactation sows. However, the role of opiates on PRL synthesis is not clear (Farmer, 2016). The action of opioid peptides (endorphins, enkephalins, and dynorphins) on the reduction of sows' feed intake is associated with the action of proopiomelacortin (POMC), as a precursor for the synthesis of *β*-endorphins (Grossman *et al.*, 1981), essential metabolites to reduce the synthesis of GnRH, FSH, and LH and metabolize higher PRL, essential for the initiation of lactation (Estienne *et al.*, 2000).

It has been accepted that, the POMC has several posttranslational metabolic pathways, not only gives rise to the *β*-endorphins (Grossman *et al.*, 1981). In addition, it synthesizes other peptides such as: corticotropic hormone (ACTH) and melacortin stimulating proteins (MSH α, β and γ). Peptides that exert their effect through receivers for melacortin (MCR), of which have been described five, being MC3R and MC4R those involved in the inhibition of feed intake (González *et al.*, 2006). In addition, these peptides are mediators of thermogenesis in the central nervous system, which induces weight loss due to the deficit of feed intake (Korner and Aronne, 2003). The α-MSH is agonist of the MC3R and MC4R, therefore, it is a anorexigenic signal of importance, likewise, the α-MSH is increased by the presence of leptin in the neurons of POMC, while inhibiting the neurons of the agouti protein (AgRP) (Pritchard *et al.*, 2001), synthesized protein in the arched nucleus of the hypothalamus with orexigenic action to mediate the effect of leptin on the suppression of appetite (Schwartz *et al.*, 2000).

In terms of Neuropeptide-Y (NPY), this is a potent regulator of feed, energy expenditure, and energy storage (Billington and Levine, 1992), in addition, it modulates part of the effect of leptin on the feed intake and hypothalamic functions (Blum, 1997). The co-localization of leptin receptors mRNA with NPY is

evidence that hypothalamic NPY are potent target for leptin, which modulates its expression (Campfield *et al.*, 1996). The leptin link to the receptors in the neurons of NPY results in an increase in energy issued and a decrease in the feed intake (Magni *et al.*, 2000). Additionally, NPY have been implicated in the regulation of GnRH/LH in rodents, primates and sheep (Kalra *et al.*, 1999). In the pig, the administration of NPY suppresses the secretion of LH (Barb *et al.*, 1991), increases the growth hormone synthesis (Barb *et al.*, 1999, 2001) and stimulates feed intake by inhibiting leptin (Barb *et al.*, 2001). The increase of the growth hormone mediated by NPY is through different signaling routes of the somatotrophs (Barb and Barrett, 2005), including extracellular modulation through Ca^{2+} in suprachiasmatic neurons (Obrietan and Van Den Pol, 1996).

In the pig, two subpopulations of somatotroph have been identified; low and high density (Ramirez *et al.*, 1996). The response of low-density somatotroph depends on the extra mobilization and intra-cellular Ca^{2+} where as, high density somatotroph are mainly Ca^{2+} dependent extracellular, this is corroborated when applying Ca^{2+} infusions in pigs (Ramirez *et al.*, 1996), which gives the pattern to establish that diets rich in Ca^{2+} they could favorably modulate the synthesis of NPY in sows and increase the feed intake during lactation.

As for ghrelin, this has a significant role in energy homeostasis, body weight control, feed intake (stimulates the start of feeding and increased appetite), positive energy balance, and reproduction (Horvath et al 2001; Anderson *et al.*, 2005; Klok *et al.*, 2007). In addition, it stimulates the synthesis of growth hormone in the pituitary gland and stimulates the secretion of gastric juices in the stomach (Hayashida *et al.*, 2001). The main receptors of this hormone are located at hypothalamic level with the NPY (Wellensen *et al.*, 1999), although they are also distributed in pituitary, brain, stomach, gonads, kidney, thyroid and lymphatic cells (Zhang *et al.*, 2007). In pigs, the largest site of action of ghrelin is in the glands of the cardiax and pylorus (Hayashida *et al.*, 2001). In sows, ghrelin levels increase in response to insufficient energy (Wertz-Lutz *et al.*, 2010), regardless of the diet (Scimgeour *et al.*, 2008) or backfat thickness (Cools *et al.*, 2014). Since, in sows at last third of gestation, no difference was found (P>0.05) in the synthesis of ghrelin when implementing restricted diets (535±306 pg mL^{-1}) *vs ad libitum* (541±349 pg mL^{-1}), or according to the thickness of backfat (P>0.05): <18 mm (554 pg mL^{-1}), 18-22 mm (528 pg mL^{-1}), and >22 mm (535 pg mL^{-1}) (Cools *et al.*, 2014).

Stimulation of growth hormone synthesis and appetite through ghrelin is mediated for the GHS-R (Sun *et al.*, 2004). In mice exempt from GHS-R, treated with ghrelin no stimulus was observed in the intake of feed or synthesis of growth hormone (Sun *et al.*, 2003). Likewise, changes induced for fasting on leptin and insulin propitiate behavior like the absence of GHS-R, which indicates that the antagonists of ghrelin (leptin and insulin) probably do not exert their function as ant-obesity agents (Anderson *et al.*, 2005). When providing infusions of insulin in mice with euglycemic observed reduction in the circulation of ghrelin concentration itself that remained at subsequent periods of hypoglycemia and hyperglycemia (Flanagan *et al.*, 2003). However, the same was not the case with growth hormone, since this hormone showed concomitant increase in form was reduced glucose, suggesting that insulin can suppress ghrelin regardless of the behavior of glucose.

Influence of sow' metabolic state on the reproductive axis: There is a clear effect of the sow' metabolic status on reproductive functions (Clarke and Arbabi, 2016), particularly, malnutrition and loss of body weight (such as that caused for lactational hypophagia) reduce pulsatile GnRH secretion (I´anson *et al.*, 2000). This suggests that the reproductive axis is engaged in low body weight animals due to the negative feedback effects of estradiol through GnRH secretion. Since, reproduction is driven for the secretion of GnRH, which stimulates the synthesis and secretion of LH and FSH (Clarke and Arbabi, 2016), also, GnRH controls and modulates a wide range of neural systems that transmit signals from sexual steroids on metabolic status (Clarke, 2014).

In pigs, the biological activity of hormones, such as leptin in the hypothalamus and pituitary, increases the synthesis of GnRH and LH, suggesting direct action of leptin on the pituitary hypothalamus axis (Barb *et al.*, 1999; Lin *et al.*, 2000). Henry *et al.* (1999), reported that leptin inhibits feed intake when they present normal body condition, and does not affect the secretion of LH. However, in lean, but not limited feed animals, leptin activates the GnRH/LH system (Henry *et al.*, 2001). This is consistent with the idea that adequate leptin levels are permissive of the normal secretion of GnRH and LH, while low levels of leptin (in lean and restricted feed animals) indicate energy deficiency. In this sense, it can be shown that sows subjected to a phase of conventional lactation or less than this (<21 days) is unlikely to recover the body condition loss during the first two weeks of lactation due to the catabolic state product of the effect of insulin resistance (hypophagia) and energy demand to sustain the increase in milk production (Pére and Etienne, 2007). Aspect that is aggravated in primiparous sows, because these unlike the multiparous, require energy not only for the processes of synthesis and production of milk but also for its maintenance and growth (Mosnier *et al.*, 2010a), from here, in this type of females is where there is an increase in reproductive

failures postweaning (Rempel *et al.*, 2015): lower litter size, lower number of parties/female/year and fewer piglets weaned/female/year (Gasa and Sola, 2016).

Fiber as a modulator of the sow' feed intake at lactation: The administrations of fibrous diets at gestation have been associated with an increase in the feed intake at lactation under conditions of equal energy intake during this physiological phase (Courboulay and Gaudré, 2001). Veum *et al.* (2009), when evaluating two diets with different levels of crude fiber (3.12 *vs* 8.26%), during three consecutive pregnancies, reported increased of feed intake at lactations (0.37 kg more day^{-1}; 1.3 Mcal EM dia^{-1}), as well as larger litter size (0.51 piglets) and piglet weight at birth (0.8 kg litter^{-1}) and weaning (3.59 kg litter^{-1}). Similar results have been reported (Van Der Peet-Schwering *et al.*, 2003) with the addition of 38% beet pulp in the feeding of pregnant sows: 0.40 kg of feed day^{-1} more and 0.5 piglets living born more litter^{-1}.

Regarding the feeding of nulliparous sows with fibrous diets at gestation, Quesnel *et al.* (2009) report higher feed intake (0.94 kg more day^{-1} or 15%) in the lactation phase when implementing a diet with 12.4% of fiber *vs* conventional diet (3.2% fiber). This intake was associated with a reduction in leptin levels in plasma prepartum: 3.0 *vs* 3.8 ng mL^{-1} for high and low-fiber diet, respectively. Guillement *et al.* (2010) report a faster transition of feed in the gestation phase with high fiber content (12.8%). Therefore, fiber can act as a modulator of the sow' metabolic status and improve feed intake at lactation (Van Der Peet-Schwering *et al.*, 2003). However, the type of fiber implemented for that purpose should be considered, since the best results have been observed when implementing high-soluble-fiber foods (Cummings *et al.*, 2004), due to the components that constitute it as they are: mucilage, pectin, flavonoids, polyphenols, structural carbohydrates among others (Halmi *et al.*, 2013).

The diet for sows in lactation phase added with cactus (Ordaz *et al.*, 2017) showed reduction of blood glucose preprandial ($P<0.05$): 55.2 ± 8.5 *vs* 70.9 ± 8.2 mg dL^{-1} of sows conventionally fed (Table 1), likewise there was observed increase of the voluntary feed intake in the sows that consumed cactus (0.9 kg more day^{-1}).The decrease of serum glucose levels through the effect of cactus has been associated with several mechanisms to exert the cactus (Lopez *et al.*, 2007; Halmi *et al.*, 2013), including: i) mechanical effect through fiber, ii) stimulates the secretion of insulin, iii) extra-pancreatic action, and iv) stimulates the resorption of glucose by different tissues. Regarding dietary fiber, not being digested or absorbed by gastrointestinal enzymes, modifies the absorption of certain substances such as bile salts, cholesterol and glucose (Frati *et al.*, 1983). This is associated with the pectin and mucilage found in the cactus, and its effect on the viscosity of the feed bolus; reducing glucose absorption via mechanics (Shapiro and Gong, 2002).

Coupled with the hypoglycemic effect produced by the ingestion of cactus, the insoluble polysaccharides (hemicelluloses strongly bonded and cellulose) present in this cactus increase the volume of feed bolus and reduce the transit time of feed through of the digestive tract (Hsu *et al.*, 2004).

With regard to the physiological mechanism for which the cactus (*O. ficus-indica*) facilitates the release of glucose-induced pancreatic insulin, it is known that leucine increases the secretion of insulin from cells β of pancreas through: 1) oxidative decarboxylation; 2) ability to activate allosterically to glutamate dehydrogenase, and 3) transamination to alpha ketoisocaproate (Manders *et al.*, 2012). Events that will later lead to the increase in the cycle of tricarboxylic acid; increased ATP/ADP ratio; closing the K^+/ATP channels; membrane depolymerization and increased Ca^{2+} stimulation (first key to stimulate insulin secretion) (Pari and Latha, 2005; Newsholme wt al., 2005). These processes indicate a direct action on the secretion of insulin in the site of the cells β of pancreas instead of an indirect action through increased blood glucose (Halmi *et al.*, 2013). According to the antecedents described above, the cactus could act as an unconventional feed strategy in lactating sows which is capable of regulating the metabolic state by which the sows travel during the peripartum and lactation and increase the voluntary feed intake.

CONCLUSIONS

According to the analysis of the evaluated literature on the metabolic modulation of the peripartum and lactation it was possible to establish that the metabolic state of the sows, during the transition from peripartum to lactation, affects the feed intake of sows in a general way, because it is an inherent evolutionary and physiological behavior of this species. However, the physiological understanding of the metabolic state pre- and postpartum of the sows would allow to develop and implement various strategies that mitigate their effects. Thus, for manipulating feeding immediately and during lactation, the effects of insulin resistance will be reduced for increasing feed intake and reducing the catabolic state in which postpartum sows enter and, in turn, avoid the removal of body reserves and loss of body weight at lactation, factors limiting the expression of the reproductive and productive potential of the species postweaning.

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