Therapeutics of neonatal asphyxia in production animals: a review

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Abstract: The aim of this review is to assess the different treatments and therapeutic protocols used for neonatal asphyxia in animal production. Perinatal asphyxia is considered to be one of the main non-infectious causes of neonatal mortality in the majority of domestic mammals. However, its incidence in intensive animal production is increasing because of a series of implemented strategies aimed at improving and increasing production. For example, through the application of genetics, an increase in size and weight in newly born animals has been achieved. Nevertheless, this has resulted in a larger incidence of dystocia associated with oxygen restriction to the foetus, which elicits metabolic and respiratory acidosis. Furthermore, aside from immediate financial implications when it comes to production, it also has an impact on the welfare of mother and offspring. Regarding the field of animal perinatology, several therapeutic strategies using respiratory and hormonal stimulants, as well as energetic supplements have been evaluated with the aim of preventing perinatal asphyxia and treating neonates with the condition, and also to diminish the incidence of stillbirths associated with it. However, during the last decades this condition has persisted mainly in porcine, equine, ovine and bovine production; for this reason, it continues to be studied extensively.

Keywords: animal perinatology; neonatal mortality; piglets; foals; calves

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1. Introduction

During the second stage of labour, foetuses go through intermittent periods of mechanical pressure provoked by uterine contractions that are part of the labour process, which lead to a temporary deprivation of oxygen for the new-born (Yli and Kjellmer 2016). However, in some cases, the intraterine pressure exercised on the foetus can increase in length and intensity until it becomes pathological. The cumulative effects of uterine contractions during pathologically prolonged labour will lead to cord damage or cord rupture as well as a premature detachment of the placenta which invariably leads to foetal hypoxia. If hypoxia persists due to dystocia, it can have serious negative long-term effects on the survival of the new-born or be immediately fatal (Martz et al. 2017). In many cases, this event has been related to the implementation of both genetic and handling strategies that have been carried out in order to increase and improve animal production – increasing the size of litters and the weight of the product/products can be given as examples (Quiniou et al. 2002; Fix et al. 2010; Vanderhaeghe et al. 2013).

What is more, the inadequate use of labour inducers or accelerants has resulted in alterations in uterine behaviour increasing the number of both stillbirths and new-borns showing evidence of having gone through severe oxygen restriction during labour (Mota-Rojas et al. 2005). However, irrespective of its aetiology one major cause of neonatal death in farm animals is intra-uterine hypoxia during labour. Therefore, from financial and welfare perspectives, there is a high motivation to reduce death rates (Martz et al. 2017). The objective of the present paper is to discuss the different treatments and the different therapeutic protocols used in the prevention and treatment of neonatal asphyxia in the main species of domestic animals used in animal production.

2. Perinatal asphyxia

In human medicine, asphyxia represents one of the main causes of death in the neonatal period; The World Health Organization has calculated that more than a million new-born babies survive asphyxia and all of these present with sequelae such as infantile cerebral palsy, learning disabilities and physical and development problems (WHO 2017). In human medicine, three causes account for three quarters of neonatal mortality cases worldwide: premature births for 29%, asphyxia for 23% and severe infections such as sepsis and pneumonia for 25% of all cases.

On the other hand, in animal production, perinatal asphyxia (PA), regardless of its aetiology, is the main cause of new-born mortality of non-infectious origin. It accounts for 10% to 20% of mortality during the first days of piglet lactation (Alonso-Spilsbury et al. 2005; Baxter et al. 2011; Muns et al. 2016), for 19.5% in foals (Pirrone et al. 2013; Carluccio et al. 2017), 17–30% in puppies (Veronesi et al. 2009; Tonnessen et al. 2012; De Cramer et al. 2017), 2.5–8.6% in calves (Bleul and Kahn 2008; Probo et al. 2012) and 20% in lambs (Robertson et al. 2018). When it comes to porcine production, the costs associated with piglets up until weaning, from gestation to labour, are close to 45.72 dollars (Seddon et al. 2013); therefore, pre-weaning mortality results in significant economic losses for this industry. In the same way, a dead calf during the stage prior to weaning translates into an approximate cost of 57.20 dollars (Retes-Lopez et al. 2013),
while that of a dead lamb in the perinatal stage is estimated at 100 dollars (Robertson et al. 2018).

Generally, as foetuses advance through the birth canal at the time of birth, they go through intermittent periods of mechanical pressure caused by uterine contractions during labour that lead to temporary oxygen deprivation for the new-born (Yli and Kjellmer 2016). Different studies have characterised uterine contractions during labour in species such as the sow. With regard to this, Olmos-Hernandez et al. (2008) reported that the intensity of uterine contractions in the sow during eutocic labour vary depending on the number of previous births. That is, sows giving birth for the first, third and sixth time presented intensities of 12.30 ± 2.18, 9.30 ± 2.45 and 10.25 ± 1.77 mmHg, respectively, with primiparous mothers showing higher intensity contractions while those giving birth for the fourth time exhibited lower intensity contractions (8.59 ± 2.01 mmHg). These data suggest that in the case of sows, the intensity of uterine contractions is dependent on the number of previous births. In bovines, the intensity of uterine contractions is higher than in sows and it is independent of the number of eutocic labours the female has had, oscillating between 19.6 up to 40 mmHg and lasting for up to 48 hours after labour has finished (Bajcsy et al. 2005).

However, both genetic and handling strategies have been implemented to increase and improve animal production: augmenting the size of the litter and the weight of the product/products represents one such strategy. This has provoked prolonged labour in which the cumulative effects of uterine contractions lead to protracted expulsion and invariably to foetal hypoxia (Martz et al. 2017). On the other hand, the inadequate use of labour inducers or accelerants elicits alterations in uterine behaviour. As an example, it has been shown that the administration of exogenous hormones such as oxytocin during labour in sows can increase uterine activity up to levels that are dangerous for piglets. Uterine over-stimulation provoked by oxytocin diminished blood flow to the uterus and resulted in a state of foetal distress (Gonzalez-Lozano et al. 2009a). In contrast, Gonzalez-Lozano et al. (2012) reported that the administration of vetrabutine hydrochloride, a spasmolytic muscular tropic drug, significantly reduced the incidence of stillborn piglets in sows with dystocia, while the number of piglets born alive without evidence of acute foetal suffering was higher in sows treated with vetrabutine hydrochloride in comparison to the control group.

Regardless of the cause, modified uterine activity during labour results in alterations to neonatal pulmonary ventilation, which in turn, provoke a decrease in the saturation of circulating oxygen and a decrease in oxygen flowing to the brain (Herrera-Marschitz et al. 2014). A reduction in the availability of oxygen is categorised in the following way: Type 1) Hypoxaemia, which involves a reduction in oxygen in arterial blood without necessarily affecting organ and cell functions. Type 2) Hypoxia, which stems from a reduction in oxygen and subsequently in anaerobic metabolism mainly in peripheral tissue and Type 3) Asphyxia, in which hypoxia is extended to central organs and may likely lead to metabolic acidosis (Yli and Kjellmer 2016). When this last type occurs during labour, it is defined as perinatal asphyxia (PA). PA occurs when the gas exchange between mother and foetus is altered and is characterised by hypoxaemia, hypercapnia and ischaemia, which provoke an immediate redistribution of blood flow to vital organs and, therefore, flow to other tissues becomes compromised (Nemeth et al. 2016; Barkhuizen et al. 2017). The indicators for the diagnosis of perinatal asphyxia in human babies and in different domestic species are defined in Table 1. Notice the recent adaptations made to the Apgar scale for its use in domestic animals and the use of equipment to assess acidosis in domestic animals.

In the majority of cases, new-borns with PA will manifest metabolic and respiratory acidosis processes (Orozco-Gregorio et al. 2010, Orozco-Gregorio et al. 2011) that exert a direct impact on well-being and with immediate financial implications for production, even in animals that manage to survive the process. Previous research has shown that those piglets which survived a PA event showed reduced consumption of milk, which is related to an increase in the time required to start suckling for the first time. As a consequence, these piglets had gained less weight by five days after birth (Trujillo-Ortega et al. 2007; Orozco-Gregorio et al. 2008). This has also been reported in calves in which, furthermore, the immunological system was compromised due to failure in the passive transferance of immunity stemming from the low consumption of colostrum after the asphyxia episode (Murray and Leslie 2013).
As well as the important economic losses caused by PA, the ever-growing awareness of animal welfare (Yeates and Main 2008; Ohl and van der Staay 2012) has resulted in increased interest in studying this phenomenon. This increased focus has the goal of enabling more definitive diagnoses in order to avoid the suffering of the mother and its young as well as to generate and promote new and more effective prevention, intervention and recovery protocols (Bleul and Kahn 2008). In human medicine, the World Health Organization stresses the importance of timing, stating that if available interventions were to reach those who need them at the right time, two thirds or more of the above-mentioned deaths could be prevented.

### 3. Therapies for oxygen re-establishment in new-borns with asphyxia

#### 3.1 Neonatal re-oxygenation post asphyxia

As pointed out above, not all mammalian foetuses experience hypoxia phases of varying severity during the birth process. However, foetal oxygen restriction can result in intrauterine respiratory stimulation which, if not dealt with through the initiation of spontaneous breathing at the moment of birth, will lead to processes of neonatal apnoea. That is why, in animals such as foals and dogs, artificial ventilation is the standard treatment for apnoea caused by asphyxia. However, because of the equipment and the number of operators needed for ventilation, these procedures cannot be carried out routinely when dealing with farm animals (Bleul et al. 2010). Furthermore, the indiscriminate or inadequate use of this type of intervention may potentially be toxic for various organs through the production of reactive oxygen species (ROS) (Figueira et al. 2016), as ROS production induces oxidative stress, which in turn affects several aspects of organismal physiological with different pathological consequences (Perrone et al. 2017).

Clinically, oxidative stress is inherent to re-oxygenation, and is a reason why the subsequent production of free radicals worsens brain lesions (Herrera-Marschitz et al. 2014). At an experimental level, it was proven that exposure to 100% oxygen for 30 minutes in new-born sheep results in a significant increase in lipid peroxidation, a key...
indicator of oxidative stress (Perrone et al. 2017). In another study, also carried out in new-born sheep, prolonged ventilation with 100% oxygen for 30 minutes caused an increase in oxygen brain tissue pressure in comparison to those sheep undergoing 3-min oxygenation (0.1 kPa–56 kPa vs 0.1 kPa–4.2 kPa, respectively). This increase in oxygen tissue pressure has only been reported under hyperbaric conditions, which suggests the need to limit oxygen exposure for asphyxiated new-borns (Perez-de-Sa et al. 2009).

In contrast, research in other species in which lower oxygen percentages were used, gave satisfactory results. For example, Herpin et al. (2001) showed that new-born piglets with PA who were administered inhaled oxygen at 40%, showed lower blood lactate concentrations in comparison to the control group (3.79 vs 6.46 mmol/l, respectively). As a consequence, blood pH values were different between the two groups (7.40 vs 7.35, respectively). The authors suggested that the results were due to an immediate supply of oxygen that stimulated oxidative metabolism and the aerobic oxidation of glucose, supplying the piglet with additional ATP (adenosine triphosphate). It is important to point out that lactate and pH are two of the main indicators of PA (Orozco-Gregorio et al. 2008; Orozco-Gregorio et al. 2011). In contrast, Zaleski and Hacker (1993) did not find differences either in the number of stillborn piglets or in new-borns with low life expectancy born to mothers to whom supplementary oxygen was provided during labour.

Also, it has been shown that the use of an air chamber during the handling protocol of the new-born can be a good option for recovery. This is due to the fact that it reduces the damage caused by free radicals that are secondary to direct oxygenation, diminishing the possibility of oxidative stress and multi-organ damage (Baxter et al. 2011). In this way, research carried out in new-born pigs with hypoxaemia and induced meconium aspiration showed that these can be reanimated in air chambers or with 100% oxygen for 120 minutes with satisfactory results in both procedures (Tollofsrud et al. 2002). However, administering oxygen at 80 or 100% for periods of eight or more hours causes irritation to the breathing passages resulting in retrosternal discomfort, nasal congestion, pharynx inflammation and cough. The results obtained suggest that O₂ toxicity is due to the production of the superoxide anion, a free radical produced by an excess of oxygen. This excess oxygen favours the transfer of xanthine dehydrogenase to xanthine oxidase using oxygen as substrate, which generates high amounts of superoxide anion, thus provoking oxidative stress (Vento et al. 2005). In the same way, the release of excitotoxic amino acids, cellular proteolysis, nitric oxide synthesis and the circulation of inflammatory substances such as cytokines, have been implicated in brain damage during PA (Xu et al. 2015) where ischaemic-hypoxic encephalopathy is one of the most severe consequences (Nemeth et al. 2016). Ischaemic-hypoxic encephalopathy is therefore the result of a combination of brain oxygen reduction (hypoxaemia) and/or the reduction in perfusion (ischaemia).

### 3.2 Methylxanthines

Methylxanthines are a group of bronchodilator drugs also known for mediating anti-inflammatory and neuroprotector effects in chronic degenerative illnesses (Lee et al. 2016; Endesfelder et al. 2017). Moreover, they have been used as respiratory stimulants in the treatment of apnoea and hypoxia in premature humans (Skourosiakou et al. 2010; Park et al. 2015), as well as in the physiometabolic recovery of foals (Wilkins 2003; Katz 2006), calves (Bleul et al. 2010) and pigs (Orozco-Gregorio et al. 2010; Orozco-Gregorio et al. 2011) with neonatal asphyxia. Four different mechanisms of action have been described for methylxanthines: (1) The mobilisation of intracellular calcium, (2) The inhibition of phosphodiesterase, (3) The modulation of GABA receptors and (4) The antagonism of adenosine receptors. The blocking of adenosine receptors, however, seems to be mainly responsible for many of the effects of methylxanthines on the central nervous system (Onatibia-Astibia et al. 2016).

In new-born foals with PA, episodes of hypoxaemia and hypercapnia are common. With respect to this, Wilkins (2003) has suggested that in those foals with abnormal breathing patterns and with periods of post-labour apnoea, the administration of caffeine either through the rectum or orally (10 mg/kg) can function as an adjuvant therapy in respiratory support. However, foals with respiratory acidosis that develops as a compensatory mechanism against metabolic alkalosis will not respond to treatment with this methylxanthine. Lu et al. (2006) suggest that in foals with respiratory depression or
hypercapnia, the administration of caffeine could improve breathing without the need to implement therapeutic protocols with mechanical ventilation.

In the case of porcine production, it has been shown that the oral administration of caffeine (20 mg and 35 mg) in new-born piglets with PA reverses the alterations in the acid-base balance related to the restriction of oxygen suffered by the animal 24 hours after its administration. This is achieved through an increase of blood triglyceride and glucose concentrations (Orozco-Gregorio et al. 2010). In another study, the administration of 35 mg subcutaneously to new-born piglets with PA resulted in an increase in glucose concentrations and a decrease in pCO₂ levels as well as weight gain that was 19% greater in comparison to the control individuals. Nevertheless, these results were observed only in new-borns whose weights exceeded 1100 g (Orozco-Gregorio et al. 2012).

The results obtained in the research mentioned above have been questioned from a practical point of view as it has been pointed out that both ways of caffeine administration (oral and subcutaneous) are difficult to carry out on porcine farms. Thus, Superchi et al. (2013) have proposed that prophylactic caffeine administration in food to pregnant sows before labour starts improves thermoregulation capacity in the newly born in comparison to the control group (39.31 ± 0.10 °C vs 38.83 ± 0.08 °C), which increases their viability. Equally, the piglets of treated sows exhibited lower concentrations of bipterin, a co-factor in the synthase of nitric oxide and which was used in this experiment as an indicator of the neuroprotective effect of caffeine in the face of adverse reactions akin to PA. More recent studies have determined the effects of 27 mg/kg caffeine intake orally in sows 24 hours before labour. In this study, caffeine did not affect the weight of piglets born to the treated mother; however, they did show a better capacity to adapt to life outside the uterus (Superchi et al. 2016). The effect of caffeine has also been assessed in species such as sheep. Recently, Robertson et al. (2018) observed that the administration of 20 mg/kg caffeine to pregnant sheep reduced lamb mortality from 30% to 9% in the first week of lambing.

Theophylline is another methylxanthine that has been assessed in the recovery of new-borns with asphyxia. In new-born bovines, Bleul et al. (2010) compared the effects of administering theophylline versus doxapram. Their results showed that doxapram – but not theophylline – led to an immediate increase in respiratory rate. Arterial pCO₂ decreased 30 seconds after doxapram administration, but decreased within 120 min after theophylline administration. Pulmonary vascular resistance also increased after doxapram administration and decreased after theophylline administration. The authors concluded that doxapram had a more pronounced and much faster effect on respiratory rate and on the elimination of CO₂ compared to theophylline. However, the administration of doxapram does carry the potential for cardiovascular side effects. Therefore, caffeine has been shown to be more effective for PA in comparison to the other methylxanthine due to the possibility daily dosing at the beginning of its therapeutic action and because of its minimum adverse effects (Park et al. 2015; Onatibia-Astibia et al. 2016). Also, the therapeutic doses of caffeine are much lower than the toxic levels (5 to 25 μg/ml and 40 μg/ml, respectively) in comparison to those of theophylline (7 to 12 μg/ml and 20 μg/ml, respectively). Its half-life in neonates is up to 103 hours versus 20 hours in theophylline, which allows for longer bio-availability in the organism (Natarajan et al. 2007).

In this way, caffeine acts to reduce the frequency of apnoea and hypoxia through the non-selective antagonism of adenosine receptors, improves respiratory functions through its bronchodilator effect, reduces diaphragmatic fatigue, and increases muscular resistance and the secretion of catecholamines (Park et al. 2015; Yadegari et al. 2016). Similarly, as it is highly liposoluble and has a low molecular weight, caffeine passes through the placental barrier easily (Yadegari et al. 2016) and can thus be used in a prophylactic way during gestation. Therefore, therapy with methylxanthines such as caffeine is highly attractive mainly in new-born farm animals with PA due to the ease of administration and to the minimal adverse effects, which means it can improve survival rates as well as neurodevelopment in new-borns.

4. Energy-focused therapies in the treatment of new-borns with asphyxia

During PA, an immediate complication stemming from the absence of oxygen is the development of encephalopathy. This is the result of the combination of a reduction in brain oxygen (hypoxaemia)
and/or a reduction of perfusion (ischaemia) and oxygenation to the brain. During the acute stage of brain damage, neuronal cell death occurs through necrosis, as a result of brain energy depletion, and even though metabolic energy levels recover in the brain after a few hours a cascade of biochemical events is activated, resulting in neuronal apoptosis and consequently severe brain damage (Filippi et al. 2012). This is why early energy supply failure is considered a very important factor in the survival of the new-born. One of the alternatives for therapeutic intervention is the administration of molecules that can affect energy production through enzymatic ways with the aim of reducing the extent of damage (Valenzuela-Peraza et al. 2014; Declerck et al. 2016; Ellery et al. 2016).

4.1 Thiamine pyrophosphate

During the acute phases of hypoxic ischemic encephalopathy (HIE), neuronal cell death occurs by necrosis occurs as a result of a depletion of brain energy. Even at a few hours post-asphyxia, after commencement of aerobic energy metabolism and replenishment of glucose levels, the previously initiated apoptosis produces severe lesions in the brain (Orozco-Gregorio et al. 2008). In regards to this, one of the therapeutic agents studied for its possible neuroprotective effect is thiamine, a vitamin that carries out its metabolic function mainly through thiamine pyrophosphate (TPP), which is an indispensable co-factor in the activation of dehydrogenase pyruvate, alpha-ceto dehydrogenase glutarate, the alpha-ceto dehydrogenase acid and the transketolase enzymes involved in energy generation through the Krebs cycle (Sicilia-Argumedo et al. 2007; Valenzuela-Peraza et al. 2014).

Research carried out by Valenzuela-Peraza et al. (2014) in neonatal rats with experimentally induced hypoxia, showed that, histologically, the animals given TPP an hour before suffering hypoxia exhibited less brain damage in the motor cortex, somatosensory cortex and in the striate cortex in comparison to the control group. In the same research, the animals given TPP after hypoxia showed no significant changes in the same brain areas. These results suggest that once the process of cellular demise has started, it is practically impossible to revert it, even though other physiometabolic parameters such as pH, PaCO₂ and PaO₂ could be stabilised regardless of when exactly TPP is administered.

Additionally, more recent research carried out in rabbit foetuses by Jiménez-Bravo et al. (2016) showed that TPP is capable of modifying some biochemical parameters during ischaemia in utero and during ensuing reperfusion. As one example, the levels of foetal glucose were lower in foetuses without treatment in comparison to those foetuses that received TPP possibly with the aim of preserving energy metabolism under hypoxic conditions.

Therefore, the neuroprotective effects of TPP can be explained through 1) The strengthening of the antioxidant system due to the capacity of TPP to capture free radicals, 2) The reduction in the excessive accumulation of excitotoxins involved in cell death such as glutamate and 3) The intracellular reduction in calcium accumulation (Valenzuela-Peraza et al. 2014). TPP research in animals has been geared towards clinical use in humans; however, in the future, it will be important to carry out research that explicitly focuses on direct use in veterinary medicine.

4.2 Creatine

Experimental studies with animals have shown that amino acids such as creatine, which are endogenously produced from glycerine, methionine and arginine in the liver, kidneys and pancreas, provide neuroprotective effects against ischaemic and oxidative alterations (Sullivan et al. 2000). The main metabolic role of creatine is to combine with a phosphate group and form phosphocreatine through creatine kinase enzymatic reactions. In this way, while ATP is degraded into ADP (adenosine diphosphate) and phosphate thus providing energy for metabolic activity, the energy released from the hydrolysis of PCr (phosphorylcreatine) can be used as a buffer to re-synthesise ATP. This helps to maintain the availability of ATP particularly under anaerobic conditions and those of extreme physical effort (Kreider et al. 2017).

Creatine has been shown to directly improve mitochondrial energy metabolism as well as to act as a weak antioxidant through the ADP re-phosphorylation via phosphocreatine. These properties mean that the reaction between creatine and phosphocreatine can prevent cytosolic acidification, particularly under hypoxic conditions, by pro-
tecting cells from the damage associated with an acute hypoxic event (Ellery et al. 2016). In regards to this, Ireland et al. (2008), using an experimental model of intra-partum hypoxia in the spiny mouse, showed that creatine added to the feed of gestating mothers (5% of creatine monohydrate in isocaloric pellets) increased neonatal survival up to 95% and also improved the growth rate of the offspring up to the 15th day after labour. Moreover, it has been shown that structural and functional hypoxic damage to the new-born’s diaphragm can be reduced by maternal supplementation with creatine probably because this amino acid provides energy for muscular contraction and allows maintenance of ATP synthesis during physical activity (de Camargo Ferraz et al. 2006; Dickinson et al. 2014).

In spiny mice whose diets were enriched with 5% creatine during gestation, exhibited a transfer of this amino acid to the foetus; levels of creatine were increased by 10% to 30% in foetal tissues such as the heart, liver, kidney and muscles without any evidence of harmful effects on the mother and the new-born after PA (Dickinson et al. 2014).

Similarly, as with the TPP described above, there has been no research carried out on animals from other species. It would be important to develop PA treatment protocols on domestic animals.

4.3 Fatty acids

When it comes to supplementing individuals with asphyxia with fatty acids, collagen peptides derived from salmon skin through hydrolysis have shown to be effective in improving physiological and neuro-behavioural development in rats that experienced PA. This manifested as better performance in learning and memory tasks that are part of the Morris water navigation task and was possibly connected with a reduced level of oxidative damage to the brain. Additionally, supplemented rats gained significantly more weight in comparison to those subjected to asphyxia without treatment (Xu et al. 2015).

However, in production animals no significant differences were found in the time required to initiate first suckling amongst piglets born to sows whose diets were augmented with tuna poly-unsaturated fatty acids from day 92 of gestation, compared to piglets born to sows without treatment and to those born to sows treated with fatty acids from the start to day 91 of gestation (Rooke et al. 2001). It is worth pointing out that the time required for neonates to begin suckling at the mammary gland has been one of the most important indicators to determine vitality and viability in new-born piglets (Herpin et al. 1996; Trujillo-Ortega et al. 2007; Orozco-Gregorio et al. 2008).

Cordoba et al. (2000) also reported a decrease in piglet mortality before weaning upon addition of salmon oil to the diet of gestating sows. Meanwhile, Declerck et al. (2016) reported that supplementation of underweight piglets (< 1 kg) with medium- and long-chain fatty acids (Vigorol®) did not have any effect on the improvement of weight upon weaning (5.15 ± 0.091 kg vs 5.69 ± 0.092 kg) nor on the colostrum consumption in comparison to the control group. The authors ascribed this to the possibility that supplementing per se reduces appetite, meaning that the treated new-borns are less likely to look for the mother’s teat. In accordance with such results, research carried out by Petzold et al. (2014) found that the addition of linoleic acid to bovine diets 21 days before labour does not modify the weight of the offspring.

In other research carried out with the aim of improving performance and vitality in calves straight after labour, Moallem and Zachut (2012) assessed supplementation with three fatty acids crucial for the development of bovine foetuses to the diets of gestating bovines and its concentrations in the plasma of new-borns: linoleic acid, docosahexaenoic acid and eicosapentaenoic acid. No differences were observed in linoleic acid and eicosapentaenoic acid concentrations in calf blood plasma. However, docosahexaenoic acid was 1.9 times larger in comparison to the control calves. According to the authors, this is probably due to the fact that docosahexaenoic acid is essential in foetal development.

In general, supplementing with energy-producing compounds in order to improve viability and vitality in new-borns is broadly applied. Nevertheless, scientific evidence regarding its efficiency is scarce (Declerck et al. 2016) and particularly, the effect observed will depend on the type of fatty acid used (Moallem and Zachut 2012).

5. Melatonin

During gestation, even in normal periods, oxygen demands go up and results in an increased
rate of reactive oxygen species production (ROS). However, the low antioxidant capacity of new-borns contributes to the pathogenesis of several prenatal conditions associated with exposure to free radicals (Marseglia et al. 2016). For this reason, melatonin seems to be an ideal alternative for these prenatal conditions because of its capacity to capture ROS, as well as its function in blocking the excitotoxic cascade and in modulating neuro-inflammatory passageways, mechanisms known to be involved in the pathogenesis of prenatal brain damage (Colella et al. 2016; Arteaga et al. 2017).

Experimental research carried out by Miller et al. (2005) in sheep foetuses exposed to an acute in utero bout of asphyxia, showed that the administration of melatonin as a prophylactic measure in gestation between 1 to 4 and 1 to 7 days resulted in a significant decrease of the free radical OH (hydroxyl free radical). In other research, Welin et al. (2007) showed that the administration of melatonin (20 mg/kg, i.v.) reduces cell death in the brain of the ovine foetus after PA, which was induced through the occlusion of the umbilical cord. In this study, the administration of melatonin to the foetus resulted in a decrease in microglia activity and in the concentration of 8-isoprostane after the occlusion of the umbilical cord in ovine foetuses. The 8-isoprostane molecule was considered to be an inflammatory marker of oxidative stress. However, melatonin did not have effects on metabolic acidosis and on blood gases associated with the oxygen restriction.

Finally, in other research carried out in piglets, the administration of intravenous melatonin (5 mg/kg/h) 10 minutes after an experimental hypoxic event resulted in increased neuroprotection through an increase in the brain’s energy metabolism as assessed by magnetic resonance spectroscopy (Robertson et al. 2013). In regards to this, Arteaga et al. (2017) proposed that the repeated dosing of melatonin for up to 24 to 48 hours after a hypoxic-ischaemic event is more effective, suggesting a dose-dependent effect in neuroprotection. However, melatonin usage in production animals is not viable on the whole due to the fact that its application is still in the experimental phase. Meanwhile, in human new-borns with PA its application is geared toward avoiding the secondary effects of asphyxia during the reperfusion period with the aim of improving neurodevelopment in individuals who suffered asphyxia during labour.

6. Implications

In polytocous species such as pigs, high productivity is defined as a large number of new-born piglets, which has increased the incidence of weakness and of stillbirths (Gonzalez-Bulnes et al. 2016). On the other hand, monotonous species such as sheep, goats, cows and horses have fewer offspring, which has allowed a larger investment in maternal care required by the offspring, maximizing survival rates (Mellor and Stratford 2004).

Several factors have considerably increased the levels of production in species destined for human consumption, which has secondary implications (Gonzalez-Bulnes et al. 2016). In regard to this, nowadays PA is a recurring phenomenon in animal production; new-borns who do not die at a primary or secondary stage as a result of hypoxia during labour, are often nevertheless no longer compatible with post-natal life, and are neither capable of thermoregulation nor of seeking the maternal teat in order to initiate suckling conduct (Dwyer 2008). Also, the new-borns that survive asphyxia episodes turn out to be the weakest in the litter and consume less food, which subsequently hampers weight gain resulting in difficulties in reaching the target weight (Gonzalez-Bulnes et al. 2016).

Therefore, neonatal mortality in animal production can be considered as an indicator of poor welfare; that is, a production system with high levels of post-partum losses is evidently not providing for adequate animal welfare (Dwyer 2008). Consequently, there is an imperative need to investigate prevention and therapeutic strategies suitable to tackle PA.

7. Conclusions

Asphyxia during the prenatal period in domestic animals has emerged as the main non-infectious cause of neonatal death. Particularly in animal production, the sequelae of a decrease in foetal and new-born oxygenation complicate the process of normal labour, which decreases the reproductive efficiency of the females. It also compromises the final commercial quality of the surviving offspring in species such as cows and pigs and increases production costs in larger species such as horses and cows as more complicated obstetric and surgical manipulations are required. Moreover, several
8. References


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