

Abanico Veterinario. January-December 2019; 9:1-13. <http://dx.doi.org/10.21929/abavet2019.929>
Original article. Received: 01/02/2019. Accepted: 15/12/2019. Published: 25/12/2019.

L-Arginine, Aspartate and Glutamate, and their relationship with the ewes' reproduction. Review.

L-Arginina, Aspartato y Glutamato, y su relación con la reproducción de ovejas.
Revisión.

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ABSTRACT

In most of livestock production systems, it is important to optimize reproductive activity to increase productive efficiency. This indicator depends on environmental factors such as nutrition, which regulates the onset of puberty, ovarian follicular development, oocyte quality and as a result, embryonic development. The purpose of animal nutrition strategies is to increase reproductive efficiency, to obtain better economic income in most of livestock production systems. Recent research reports that dietary supplementation with specific amino acids such as arginine, glutamine, leucine, glycine and methionine they have beneficial effects on survival and embryonic and fetal growth by regulating key signaling and metabolic pathways. In sheep production systems, supplementation with different routes with neurostimulatory amino acids such as L-Arginine, aspartate and glutamate, improves reproductive efficiency in females in a technical and economical way, with the aim of eliminating hormonal manipulation of the animals. Therefore, the objective of the present review of the literature is to describe the neurostimulatory function of amino acids and to know the neuroendocrine response in the hypothalamic-pituitary-ovarian axis in sheep to improve productive and reproductive variables.

Keywords: neurostimulatory amino acids, neuroendocrinology, reproductive efficiency, gonadotropins, sheep production.

RESUMEN

En la mayoría de los sistemas de producción pecuaria es importante optimizar la actividad reproductiva para aumentar la eficiencia productiva. Este indicador depende de factores ambientales como la nutrición, la cual regula el inicio de la pubertad, el desarrollo folicular ovárico, la calidad de los ovocitos y, como resultado, el desarrollo embrionario. La finalidad de las estrategias de nutrición animal es incrementar la eficiencia reproductiva, para obtener mejores ingresos económicos en la mayoría de los sistemas de producción pecuaria. Investigaciones recientes reportan que la suplementación dietética con aminoácidos específicos como arginina, glutamina, leucina, glicina y metionina tiene efectos beneficiosos sobre la supervivencia y el crecimiento embrionario y fetal mediante la regulación de la señalización clave y las rutas

metabólicas. En los sistemas de producción ovina, suplementar por diferentes vías con aminoácidos neuroestimuladores como L-Arginina, aspartato y glutamato, mejora la eficiencia reproductiva en la hembra de una manera técnica y económica, en la cual se pretende eliminar la manipulación hormonal de los animales. Por lo anterior, el objetivo de la presente revisión de literatura es describir la función neuroestimuladora de los aminoácidos y conocer la respuesta neuroendocrina en el eje hipotálamo-hipófisis-ovarios en ovejas para mejorar las variables productivas y reproductivas.

Palabras clave: aminoácidos neuroestimuladores, neuroendocrinología, eficiencia reproductiva, gonadotropinas, ovinocultura.

INTRODUCTION

The ovarian activity responds to the adequate secretion of LH and FSH in the adenohipophysis, by the secretion of GnRH in the hypothalamus. This endocrine communication also occurs through the action of compounds that act as neurotransmitters, from the supply of neurostimulatory amino acids that favor the pulsatile secretion of GnRH and LH (Mahesh y Brann, 2005), such as glutamate (GLU; Brann y Mahesh, 1997), aspartate (ASP; Boni *et al.*, 2006) and arginine (ARG; Recabarren *et al.*, 1996).

The action of amino acids such as glutamine, proline, and glycine regulate the functions of health, survival, growth, development, lactation and reproduction (Wu, 2010); or affect gene expression, fertility, neurotransmission and immunity in animals (Wu, 2014). In addition, GLU, glutamine, glycine, tryptophan, and tyrosine, D-alanine, D-aspartate and D-serine regulate the development and neurological function (Fernstrom, 2012). Neurotransmitters make up the neural networks and control cellular and synaptic functions in the central nervous system (CNS), excitatory and inhibitory neurotransmission is largely mediated by GLU and gamma-aminobutyric acid (GABA), which are excitatory and inhibitory neurotransmitters, respectively (Mayor y Tymianski, 2017).

The GLU regulates the expression of sexual behavior, specifically in the medial preoptic area, through the action of dopamine due to its action on GnRH neurons (Iremonger *et al.*, 2010). In the male, to regulate testosterone secretions, which is required as a mediator of baseline dopamine concentrations to increase copulatory ability (Will *et al.*, 2014). Rodents increase neuronal activity that facilitates penile erection and mating behavior (Li *et al.*, 2013). In the control of reproduction in sheep observed that, ovarian activity responds to neuronal changes in the brain and results from complementary alterations in the control of hypothalamic function, specifically in the regulation and secretion of GnRH (Weems *et al.*, 2015). GnRH is the first messenger responsible for the initiation, restoration and cyclicity of reproductive activity in sheep and goats, and it is by different neurotransmitters regulated (Meza-Herrera, 2012). The control of the pulsatile secretion of GnRH by the hypothalamus and its ovarian response in the secretion of LH and FSH by the adenohipophysis is by the action of compounds favored that act as neurotransmitters (Brann y Mahesh, 1995) and they are improvement with the supply of neurostimulatory amino acids (AANE). Neurotransmitters and neuromodulators have

stimulatory and inhibitory properties that depend on the composition of the neurocircuit. In addition, it depends on the state of development and the hormonal environment (Terasawa y Fernández, 2001). This classification is the characteristics of the control based on, of the pulsatile release of GnRH, in the adult animal and based on the classification AANEs can be as stimulators or inhibitors described. The main CNS neurotransmitters are AANE (Urbanski *et al.*, 1994), which have specificity in the activation of postsynaptic CNS neurons. The neurotransmission of AANEs is an essential component in neuroendocrine transmission, which regulates the secretion of pituitary hormones. AANEs such as ASP and GLU are in large numbers in presynaptic areas found, of a variety of hypothalamic nuclei: arcuate, suprachiasmatic, supraoptic, paraventricular nucleus and preoptic area (Brann y Mahesh, 1994).

Studies in sheep considered management practices to improve the productive efficiency of the herds in a technical and economic way, in which it is to eliminate the pharmacological manipulation of the animals intended (Martin *et al.*, 2004). These methodologies are based on knowledge of reproductive events, socio-sexual factors and the effects of nutrition (Hawken y Martin, 2012; Scaramuzzi *et al.*, 2013); or focused feeding, based on energy and protein supplements destined in the critical moments of reproduction (Somchit-Assavacheep, 2011). Therefore, the objective of the present review of the literature is to describe the neurostimulatory function of amino acids and to know the neuroendocrine response in the hypothalamic-pituitary-ovarian axis in sheep to improve the productive and reproductive variables.

L-ARGININE AND ITS NEUROENDOCRINE ACTION IN REPRODUCTION

The amino acid L-Arginine (ARG) was first isolated in 1886, from the seeds of the legume *Lupinus* sp. (Wu y Morris, 1998). It is from glutamine, glutamate (GLU) and intestinal proline synthesized through the renal axis in most mammals (Wu, 1998). It participates in the metabolism as a substrate for protein synthesis, because it is an intermediate in the urea cycle that is in the liver performed and as a precursor for the synthesis of several metabolic molecules, such as nitric oxide (NO) and polyamines (Kim *et al.*, 2007). In the arginase pathway, polyamines are from ornithine synthesized to participate in embryogenesis and placental growth (Reynolds y Redmer, 2001).

In 1987, the scientific community discovered that the human body produces NO (Tsikas, 2007). It is known that NO is a regulator in the female reproductive process (Tamanini *et al.*, 2003), such as the development and growth of the placenta. Besides, it participates in the maintenance of pregnancy and the physiology of delivery (Kwon *et al.*, 2004), ovarian function, ovarian follicular development and ovulation; In addition, it participates in the regulation of blood pressure, immune response, platelet aggregation and neurotransmission.

ARG is the only substrate of all isoforms of nitric oxide synthetase (NOS; [Wiesinger, 2001](#)). The production of the NO is by oxidation of the amino group of ARG, which uses molecular oxygen as a co-substrate, and as a secondary product of the reaction, L-Citrulline is obtained (CIT; [Tsikas, 2007](#)). The CIT can be recycled to ARG by synthetic arginosuccinate and arginosuccinate lyase, which forms the CIT-NO cycle ([Mori y Gotoh, 2004](#)). The mechanism of action of the NO as a regulator of said processes, responds to the fact that it stimulates the soluble guanylate cyclase enzyme to synthesize cyclic guanosine monophosphate (cGMP), which is responsible for such regulation (Figure 1).

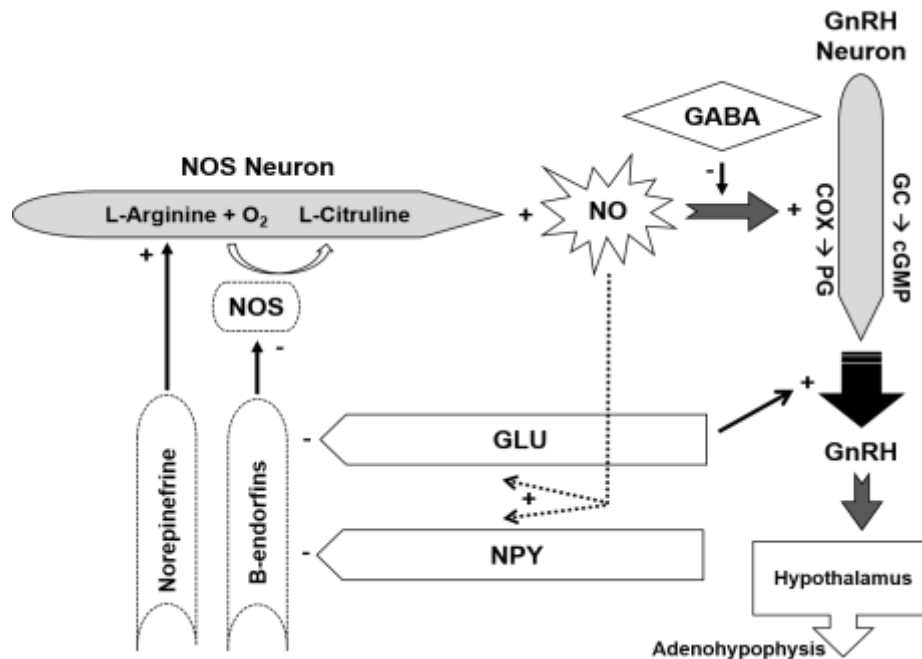


Figure 1. Action of nitric oxide (NO) in the control and release of gonadotropin-releasing hormone (GnRH). Positive effect [+], negative effect [-], GABA: Aminobutyric acid range, GC: Guanilyl cyclase, cGMP: Guanidine methyl cyclic phosphate, COX: Cyclooxygenase, PG: Prostaglandin, Glu: Glutamate, NPY: Neuropeptide, NOS: Oxide nitric synthetase (Modified by [Faletti et al., 1999](#)).

In the hypothalamus, the neurons of the NO are close to those of the GnRH, which suggests that the NO may be a regulator in the secretion of the GnRH. These neurons are located in several hypothalamic nuclei (preoptic nucleus, ventromedial hypothalamic nucleus and aquatic nucleus), and in other sites (vascular organ of the terminal lamina, preoptic area and middle eminence) related in the regulation of GnRH secretion ([Grossmann et al., 1994](#)). The NO controls the action of hormones and neurotransmitters essential to regulate reproduction, it is known by relating to the control of LH and ovulation. In addition, several inhibitory neurotransmitters and stimulators affect the NOS neurons in the hypothalamus and control the secretion of the NO ([Dixit y Parvizi, 2001](#)).

ARG supplementation in production animals improves the productive and reproductive variables. Include 1.0% of arginine hydrochloride (L-Arginine HCl, Ajinomoto) in the diet of 22 pregnant Camborough sows (30 to 114 d), increase piglet weight by 24% and increase litter size by 22% (Mateo *et al.*, 2007). In prepubertal Suffolk sheep (2 months old) infusion of 200 mL of ARG (350 mM, pH 7.4) was applied intravenously via in the jugular venipuncture for 60 min increases the average concentration of LH for 285 min after infusion with amplitude $> 1 \text{ ng mL}^{-1}$ in 13 of 17 pulses of LH. It suggests that the infusion of ARG stimulates the secretion of LH in prepubertal sheep (Recabarren *et al.*, 1996).

In estrous synchronization protocols with intravaginal sponges in adult Awassi sheep (3.5 to 4.0 years of age) was supplemented ARG (0.5 g kg⁻¹ body weight) for 15 days after sponge removal, increased the amount of luteal bodies (CL; 2.38 ± 0.67), the concentrations of E2 ($5.92 \pm 0.33 \text{ pg mL}^{-1}$) and P4 ($4.21 \pm 0.83 \text{ ng mL}^{-1}$). It was compared to the response of the control sheep: 100 ± 0.58 CL, $4.56 \pm 1.06 \text{ pg mL}^{-1}$ of E2 and $1.79 \pm 0.31 \text{ ng mL}^{-1}$ of P4, which improves the birth rate and twin deliveries due to the increase in the ovulatory rate (Al-Dabbas *et al.* 2008).

In adult hair sheep synchronized with 40 mg of fluorogestone acetate impregnated in intravaginal sponges (Cronolone-Chrono-Gest, Intervet®) for 12 d ARG supplementation (300 mg kg⁻¹ body weight) for 3 days prior to Sponge removal improves the presentation of estrus (PE; 100%), ovulatory rate (TO; 1.7 ± 0.13) and prolificacy (PROL; 1.4 ± 0.16). It was compared to the response of sheep synchronized only with oil progesterone (PE: $28.6 \pm 18.4\%$, TO: 1.4 ± 0.25 and PROL: 1.5 ± 0.5), which improves estrogen synchronization protocols with progestogens, due to the positive effects of ARG supplementation on reproductive efficiency in sheep hair (Bulbarela-García *et al.*, 2009).

In Rambouillet sheep, treated with 27 mg of L-Arginine HCl/kg of intravenous weight during maternal recognition of pregnancy was observed that the pregnancy rate was by 24% improved that suggests that ARG is related to the synthesis of NO. The treatment prior to maternal recognition of pregnancy in sheep improves early embryonic survival through the synthesis of polyamines and NO (Saevre *et al.*, 2011).

ASPARTATE AND ITS NEUROENDOCRINE ACTION IN REPRODUCTION

D-aspartic acid is a neurotransmitter that acts via the GLU receptor to stimulate the secretion of GnRH. It is naturally in the pituitary, thyroid, and ovary, adrenal and pineal; in the brain, in excretory organs such as liver and kidney, in muscle and deep tissues. At present, this D-amino acid can be to N-methyl-D-aspartic acid (NMDA) converted. It is a neuromodulator related to sexual activity, which causes the release of hypothalamic and pituitary hormones and possibly the administration of D-aspartic acid. Increase NMDA

concentrations in the nervous system; because D-aspartic acid is naturally present and is stored in the pituitary, brain and pineal gland (Boni *et al.*, 2006).

NMDA is biosynthesized endogenously from D-Aspartate by an enzyme dependent on S-adenosylmethionine, NMDA synthase and it is a potent agonist of the activity of aspartic and glutamic acids. These have a neuromodulatory activity that causes release of pituitary hormones, *in vivo* (D'aniello *et al.*, 2000^a; 2000^b) and *in vitro* (Barb *et al.*, 1993), and belongs to the group of ionotropic GLU receptors.

Estienne *et al.*(1989^a) administered intravenously NMDA (12 mg kg⁻¹ body weight; racemic mixture, Sigma Chemical co., St. Louis, MO) in castrated Hampshire rams (4 months old and 28.1±1.3 kg of weight). It observed an increase in growth hormone (GH; 185.1±20.7 ng mL⁻¹) instead of LH secretion at 15 minutes after injecting the dose, which was in the range that stimulated secretion of LH in monkeys. Therefore, they concluded that it is possible that the ram is less sensitive to NMDA and requires a larger dose to evoke the secretion of LH.

On the contrary, in ovarian-ectomized sheep, Estienne *et al.* (1989^b) demonstrated that the supply of estradiol subcutaneously (1 pg mL⁻¹ of E2; Silastic implant, polyethylene tube; Portex Ltd, Hythe, Kent) decreases the serum concentration of LH. However, intravenous application of 6, 12 or 24 mg NMDA kg⁻¹ body weight (dissolved in 0.9% saline) increases the average LH concentrations by 326% (P <0.03), 1125% (P < 0.02) and 441% (P <0.0001). Therefore, these results demonstrate that exogenous E2 suppresses the secretion of LH in ovarian-ectomized sheep in an antagonized manner by the effect of NMDA.

Sheep nutrition improved the plasma concentration of D-aspartic acid in the brain can be increased, to stimulate an increase in GnRH secretion, due to the effect of NMDA on pituitary hormone concentrations and the positive effects of D-aspartic acid on the ovulatory rate and pituitary hormone concentrations. Thus, applying D-aspartic acid (intravenously) for five days in the luteal phase of the estrous cycle does not affect the ovulatory rate, but reduces the plasma concentrations of LH and FSH in cycling sheep (Downing *et al.*, 1996). Therefore, the decrease in gonadotropin secretion in cycling sheep treated with D-aspartic acid is due to the response in the hypothalamus or adenohipophysis, which are not to the secretions of ovarian retroaction related, although it is possible that, these changes decrease the secretion of GnRH.

GLUTAMATE AND ITS NEUROENDOCRINE ACTION IN REPRODUCTION

GLU acts in the control of brain functions, because it is in large numbers at the synapses of the brain found, and by the numerous subtypes of GLU receptors found in the CNS (Brann y Mahesh, 1997). GLU and ASP are as predominant AANE classified of the CNS in mammals (Kalb, 1995). Because of GLU receptors are distributed in the hippocampus, cerebral cortex, and cerebellum; this amino acid influences various physiological processes (Brann, 1995), such as the control of gonadotropin secretion and the ovulation of the female (Brann y Mahesh, 1997).

The administration of GLU agonists stimulates the release of GnRH and LH, while GLU antagonist receptors decrease steroid induction and the pre-occupational increase of LH (Dhandapani y Brann, 2000). Thus, AANE receptors are the most abundant stimulatory neurotransmitter receptors in the CNS, also called "GLU receptors" since it is known to be the largest endogenous ligand. Brann y Mahesh (1997) reported two groups of receptors:

Ionotropic: receptors coupled to ion channels, divided into the subtypes N-methyl-D-aspartate (NMDA), kainate and propionic acid DL- α -methyl-3-hydroxy-4-isoxazole (AMPA), where its main mode of action it is through the modulation of the channels of the Na⁺, K⁺ and Ca²⁺ ions.

Metabotropic: receptors coupled to G proteins, which modulate the production of secondary messengers such as inositol phosphate and/or adenylate cyclase.

The GLU exists in four different forms: transmitter, metabolic, glial and precursor of GABA. GLU is to critical processes related such as puberty, the pulsatility of hormones and sexual behavior. Releasing the neurotransmitter NO, which potently stimulates GnRH by activating a heme-containing enzyme, guanylate cyclase (Dhandapani y Brann, 2000). GLU stimulates LH secretion Brann y Mahesh (1997) and that ionotropic GLU receptor agonists increase LH secretion after systemic or intracerebroventricular injections in rats (Zamorano *et al.*, 1998), by stimulating the secretion of GnRH. The action of these receptors underlies the rapid stimulatory synaptic transmission mediated by GLU in the CNS (Brann y Mahesh, 1994).

Recent studies indicate that GLU, ARG and glutamine play important roles in the regulation of gene expression, cell signaling, antioxidant responses and immunity. In addition, GLU, glutamine and ASP are important metabolic fuels for the small intestine and, together with glycine, regulate neurological function (Wu, 2013). In reproductive function, ARG supplementation during maternal recognition of pregnancy in sheep favors embryonic survival (Crane *et al.*, 2016) and improves pregnancy and delivery rates (Luther *et al.*, 2009). NMDA and LH increase after ASP administration, which suggests a role of this amino acid in reproductive activity in sheep (Boni *et al.*, 2006). GLU is a primary

mediator of excitatory synaptic transmission in the CNS and its receptors are located in a variety of hypothalamic nuclei, some of which are critical for reproduction and neuroendocrine function, due to their relationship with puberty, neurogenesis and reproductive behavior in the female (Meza-Herrera *et al.*, 2011).

CONCLUSION

The action of neurostimulatory amino acids stimulates the secretion of adenohipophyseal gonadotropins, and therefore regulates the control of gonadal physiological events. This knowledge can be to increase reproductive efficiency applied in sheep and improve productive and reproductive variables.

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