

# Activation of the Renin–Angiotensin–Aldosterone System in Mares around Ovulation

KATY SATUÉ<sup>1\*</sup>, PALOMA MONTESINOS<sup>1</sup>, ANA MUÑOS<sup>2</sup>

<sup>1</sup>Department of Animal Medicine and Surgery, Faculty of Veterinary Medicine, Cardinal Herrera University, Valencia, Spain

<sup>2</sup>Equine Sport Medicine Center CEMEDE, Department of Animal Medicine and Surgery, Faculty of Veterinary Medicine, University of Córdoba, Córdoba, Spain

\*Corresponding author: [ksatue@uchceu.es](mailto:ksatue@uchceu.es)

## ABSTRACT

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Many physiological events occurring during the estrous cycle, including folliculogenesis, oocyte maturation, ovulation, follicular atresia, corpus luteum development, luteolysis, steroidogenesis, and angiogenesis are associated with an increased expression of the renin–angiotensin–aldosterone system (RAAS) in uterus and ovarian follicles. This enhanced expression leads to a rise in plasma concentrations of these hormones in women and laboratory animals, and the same might happen in the mare. This study aims to assess if an activation of the RAAS occurs in mares around ovulation and if this activation is related to the diameter of the predominant follicle (DPF), packed cell volume (PCV), and electrolyte concentrations. Twenty-five healthy Spanish Purebred mares were sampled during the five days before ovulation, the day of ovulation, and the first five days after ovulation. Renin (REN) concentrations increased progressively during the five days before ovulation, achieving the highest values on the day of ovulation. Angiotensin (ANG) concentrations showed a sharp decrease after ovulation, with the lowest values the fifth day after it. Aldosterone (ALD) concentrations increased progressively, from the fifth day before ovulation until the fifth day after ovulation. The highest PCV values were found on the day of ovulation. There were no relevant correlations between the RAAS components and electrolytes concentrations. Before ovulation, there was a positive relationship between REN and ALD ( $r = 0.760$ ) and after ovulation, a negative correlation between ANG and ALD ( $r = -0.660$ ). The DPF was correlated with REN ( $r = 0.740$ ) and with ALD ( $r = 0.800$ ) concentrations. Ovulation in the mare is associated with high plasma REN concentrations, and therefore, with an activation of the RAAS. In addition, after ovulation, the sharp decrease in plasma REN and ANG concentrations might be a reflex of the modulation of the previously activated RAAS, although plasma ALD concentrations increased during this period.

**Keywords:** estrous; mare; renin–angiotensin–aldosterone system (RAAS)

The components of the renin–angiotensin–aldosterone system (RAAS) have specific physiological roles during the estrous cycle. They act in folliculogenesis, oocyte maturation, ovulation, follicular atresia, corpus luteum development, luteolysis, steroidogenesis, and angiogenesis (Sneeringer et al. 2011). These processes are related with increased

expression of renin (REN), angiotensin (ANG), and aldosterone (ALD) in uterus, and in granulosa and thecal cells of ovarian follicles (Portela et al. 2011). As a result, there are increased circulating concentrations of these hormones in women (Chapman et al. 1997; Chidambaram et al. 2002; Szmuiłowicz et al. 2006). In addition, it has been

demonstrated that plasma REN, ANG, and ALD concentrations differ between the different phases of the estrous or the menstrual cycle (Szmuiłowicz et al. 2006).

In women and laboratory animals, pre-ovulatory rises of plasma REN, ANG, and ALD have been described (Szmuiłowicz et al. 2006). The increase in ALD concentrations, however, is not constant in all the cycles. ANG is a potent vasoconstrictor, modulating blood flow to the ovary during ovulation. ANG also stimulates vascular proliferation around the follicular antrum. In laboratory animals and human beings, after the peak of luteinizing hormone (LH), ANG modulates blood flow to the follicles for ovulation and maturation (Sneeringer et al. 2011).

During the follicular phase of the estrous cycle, there is an increase of prorenin, a REN precursor. This increase has been associated with the release of gonadotropins, mainly LH, at the time of ovulation, and the stimulating effect of estrogens on the synthesis of angiotensinogen. Additional factors involved in prorenin release are acute hemodynamic modifications, changes in sodium concentration in the renal macula densa cells, and alterations in the local sympathetic activity. Furthermore, it has been suggested that an increase in adrenocorticotrophic hormone (ACTH) might contribute to the pre-ovulatory peak of plasma REN activity and ALD concentrations, because ACTH regulates synthesis of ALD (Szmuiłowicz et al. 2006).

In normotensive women, elevated concentrations of REN and ALD have been described in the luteal phase of the menstrual cycle compared with the follicular phase (Sealey et al. 1994; Chapman et al. 1997; Chidambaram et al. 2002). However, a proportional increase in ANG concentration was not found. Because of this finding, Chapman et al. (1997) and Chidambaram et al. (2002) considered that the rise in ALD concentrations during the luteal phase could result from other pathways rather than from the activation of the RAAS. A sustained secretion of progesterone by the corpus luteum might be the main source of REN and ALD during the luteal phase (Chapman et al. 1997; Chidambaram et al. 2002).

Previous studies have described the changes in plasma REN, ANG, and ALD concentrations in mares during parturition (Broughton Pipkin et al. 1982) and pregnancy (Satue and Domingo

2011) and in both situations, an activation of the RAAS was found. It is currently unknown whether mares also present an activation of this system during the estrous cycle. As described before, the RAAS during the estrous cycle has been thoroughly evaluated in primates and non-primate animals and women (Harewood et al. 1996; Chapman et al. 1997; Chidambaram et al. 2002; Szmuiłowicz et al. 2006; Sneeringer et al. 2011), but not in mares.

The current research was pursued to investigate the physiological changes shown by the components of the RAAS around ovulation in mares. Abnormal values of the hormones of this axis have been described in women with polycystic ovary syndrome (Alphan et al. 2013), and pregnancy hypertension and preeclampsia (Verdonk et al. 2015). Abnormal changes in the RAAS might also happen in mares with disturbed fertility and cyclicity, and this idea deserves future investigations. However, firstly the differences in plasma concentrations of these hormones during the phases of the estrous cycle should be clearly defined. Based on the results obtained in other species, we hypothesized that significant differences in plasma REN, ANG, and ALD would be found before, at, and after ovulation in regular cycling mares and these differences might be associated with changes in electrolyte concentrations.

## MATERIAL AND METHODS

**Mares.** This research was approved by the CEU-Cardenal Herrera University (Valencia, Spain) Animal Ethics Committee.

Twenty-five healthy Spanish Purebred mares, aged between 5 and 15 years, were included in the study. The mares were randomly selected among those that met the following criteria: (1) regularity of estrous cycles, normal parturitions, viable foals at parturition, absence of reproductive disorders, including endometritis, placentitis, mastitis or other pathological situations associated with loss of fertility before the experiment and, (2) absence of inflammatory and infectious diseases or other pathological events that had required medical or surgical treatment, at least one month before the onset and during the study. Mares older than 15 years and/or with defects of perineal and vulvar conformation, pneumovagina, endometritis, ovarian neoplasms, endometrial cysts or with history of previous dystocia or loss of fertility were excluded.

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**Experimental protocol, blood sampling, and management.** The mares were subjected to daily rectal and ultrasound examinations (SonoSite 180-Plus; SonoSite Inc., USA) after showing estrous signs. The diameter of the predominant follicle (DPF) was recorded until the time of ovulation. After ovulation, the development and maturation of the corpus luteum were followed ultrasonographically until the 5<sup>th</sup> day post-ovulation. Hormonal treatments in order to synchronize reproductive cycles were not used, and therefore, only natural cycles were included in the current research.

This study was carried out in spring, during the months of March and April. Blood samples were taken daily during the five days pre-ovulation (from day –5 to day –1), on the day of ovulation (day 0), and the five days post-ovulation (from day +1 to day +5). In order to limit the effects of circadian rhythms on hormone concentrations, blood samples were collected between 09:00 and 10:30 h, at rest, and always by the same researcher.

After extraction of 20 ml of venous blood, samples were divided into three fractions. The first fraction (8 ml) was placed into chilled tubes containing 0.125 M EDTA (Vacutainer 6450; Becton-Dickinson Ltd., USA) and 0.025 M o-phenanthroline (199 µl/ml plasma) (P-9375; Sigma-Aldrich, USA), centrifuged at 1000 g for 15 min at 4°C. Plasma was immediately obtained and used to measure ANG concentrations. These samples were placed in a liquid nitrogen-cooled CryoPac shipper (–196°C) and transported to the laboratory, where they were stored at –70°C until analysis. The second fraction of blood (10 ml) was pipetted into glass tubes without anticoagulant (Tapval, Spain) and heparin-containing tubes for measuring ALD, packed cell volume (PCV), and electrolytes (sodium Na<sup>+</sup>, chloride Cl<sup>–</sup>, and potassium K<sup>+</sup>, respectively). PCV was measured immediately after blood extraction. The third fraction of blood was pipetted into EDTA tubes (2 ml) for REN measurements. Heparin and EDTA samples were centrifuged at 1000 g for 5 min at room temperature, within the first hour after collection, plasma was harvested and stored at –20°C. These samples were transported to the laboratory on dry ice, transport duration was shorter than 3 h upon arrival to the laboratory. The period of time between freezing and analysis was shorter than 6 months.

**Analytical techniques.** Plasma REN concentrations were measured with an immunoradiometric sandwich technique for detection of active REN.

Polystyrene tubes coated in rabbit anti-REN polyclonal antibodies (7929-9930; Biogenesis/Morpho-Sys, France) and a secondary antibody labelled with I-125 (DRG Diagnostics GmbH, Germany) were used. This procedure showed a high specificity for REN (percentage of recovery = 95–105%). Cross reactions of the first polyclonal antibody and the second I-125-labelled antibody with pro-REN were of 3.0% and 1.8%, respectively. The sensitivity of this technique was 1 pg/ml. Intra- and inter-analysis coefficients of variation (CV) were < 5% and 15%, respectively.

Plasma ANG concentrations were determined using a competitive ELISA method, based on the biotin–streptavidin–peroxidase system, using ELISA assay plates coated with a primary antibody (polyclonal antibody anti-ANG, RAB 002-12), a secondary antibody, biotinylated ANG, and streptavidin-peroxidase (EK-SA-HRP) (Phoenix Pharmaceuticals, Inc., USA). This method has a high specificity for ANG (percentage recovery = 98.5%). The sensitivity was 100 pg/ml, with intra- and inter-analysis CVs of < 5% and 14%, respectively.

Plasma ALD concentrations were also measured with a competitive ELISA. Polyclonal antibody AD97 and the combination ALD 3CMO-HRP were used (Endocrinology Laboratory, Department of Physiology, College of Veterinary Medicine, Complutense University of Madrid, Spain). This test also shows high specificity for ALD (percentage recovery = 97.6%). It shows cross reaction of the polyclonal antibody with 11-deoxycorticosterone (1.1%) and cortisone, corticosterone, 11-deoxycortisol, and 21-deoxycortisol (< 0.1% for the latter). The sensitivity of this technique was of 15 pg/ml, and the intra- and inter-analysis CVs were 4.7–6.4% and 8.5–9.6%, respectively.

These methods were validated for horses and have been used in previous researches (Munoz et al. 2010; Satue and Domingo 2011; Satue et al. 2011).

Because electrolytes and PCV are tightly associated with the RAAS, these parameters were also measured. For PCV, a volume of 0.1 ml of heparinized blood was introduced into a microhematocrit tube and centrifuged (microhematocrit centrifuge Q222H<sup>®</sup>, Quimis Aparelhos Científicos, Brasil). Plasma Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>–</sup> concentrations were measured with an electrolyte analyzer (VetLyte<sup>®</sup>; IDEXX, USA), using specific electrodes for these electrolytes provided by the same manufacturer.

**Statistical analysis.** The statistical study was made with the program SPSS 12.01 for Windows (SPSS Inc., USA). Data are presented as mean  $\pm$  SD. Normality was checked with the Kolmogorov–Smirnov test and all the studied variables followed a Gaussian distribution. Differences between the days were assessed with an ANOVA for repeated measurements. When statistical significance was reached, a post-hoc analysis was made (Tukey's test) in order to evaluate on which specific days there had been significant differences. A linear correlation (Pearson's correlation) was performed in order to analyze the relationships between the analyzed parameters before and after ovulation. Differences were considered significant at  $P < 0.05$ .

## RESULTS

Daily plasma concentrations of REN, ANG, and ALD during the study are drawn in Figure 1. From

day  $-5$  to day  $0$ , a progressive rise in REN and ALD concentrations was observed. The highest REN concentrations were detected on day  $0$  and after that, a progressive reduction was observed until the end of the study (Figure 1A). On the contrary, plasma ALD concentrations increased progressively, from day  $-5$  to day  $+5$  (Figure 1B). Plasma ANG concentrations did not change significantly between day  $-5$  and day  $+4$ . ANG concentrations were lower on day  $+4$  compared to day  $0$ , and the lowest values were observed on day  $+5$ , with values significantly different compared to those found at other times (Figure 1C).

The mean value of DPF on day  $-5$  was  $24.73 \pm 2.20$  mm, attaining the highest diameters on the day of ovulation, with a mean of  $40.23 \pm 1.36$  mm.

PCV and electrolyte concentrations are presented in Figure 2. On days  $-5$ ,  $-4$ , and  $-2$ , PCV was significantly lower than on day  $0$ . Plasma  $\text{Na}^+$  concentrations on day  $-1$  ( $138.9 \pm 0.99$  mmol/l) were significantly lower than on day  $+3$  ( $142.2 \pm 3.28$  mmol/l). Plasma  $\text{K}^+$  concentrations reached

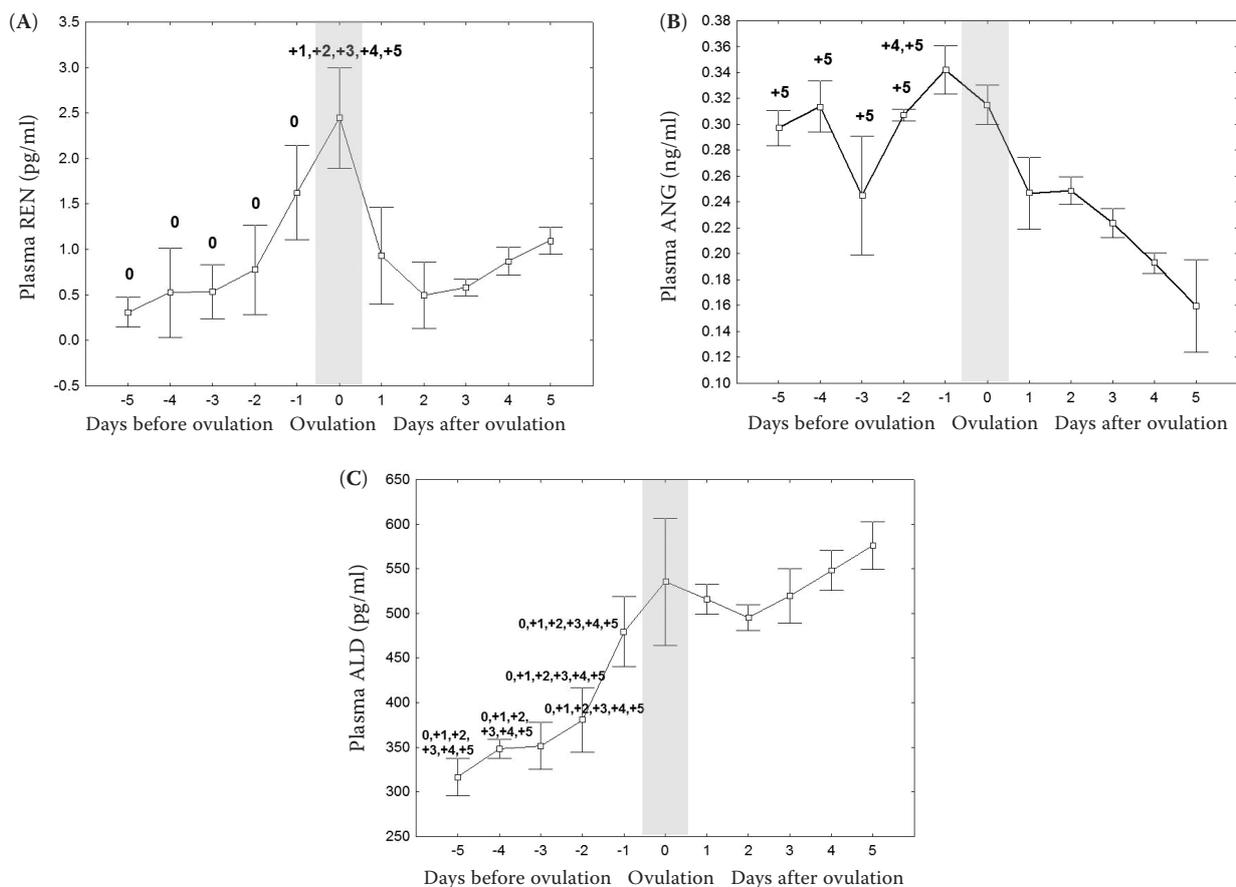


Figure 1. Plasma concentrations of renin (REN) (A), angiotensin (ANG) (B), and aldosterone (ALD) (C) in mares before ovulation (from day  $-5$  to day  $-1$ ), on the day of ovulation (day  $0$ ), and after ovulation (from day  $+1$  to day  $+5$ ) (numbers indicate the days between which significant differences were found);  $P < 0.05$

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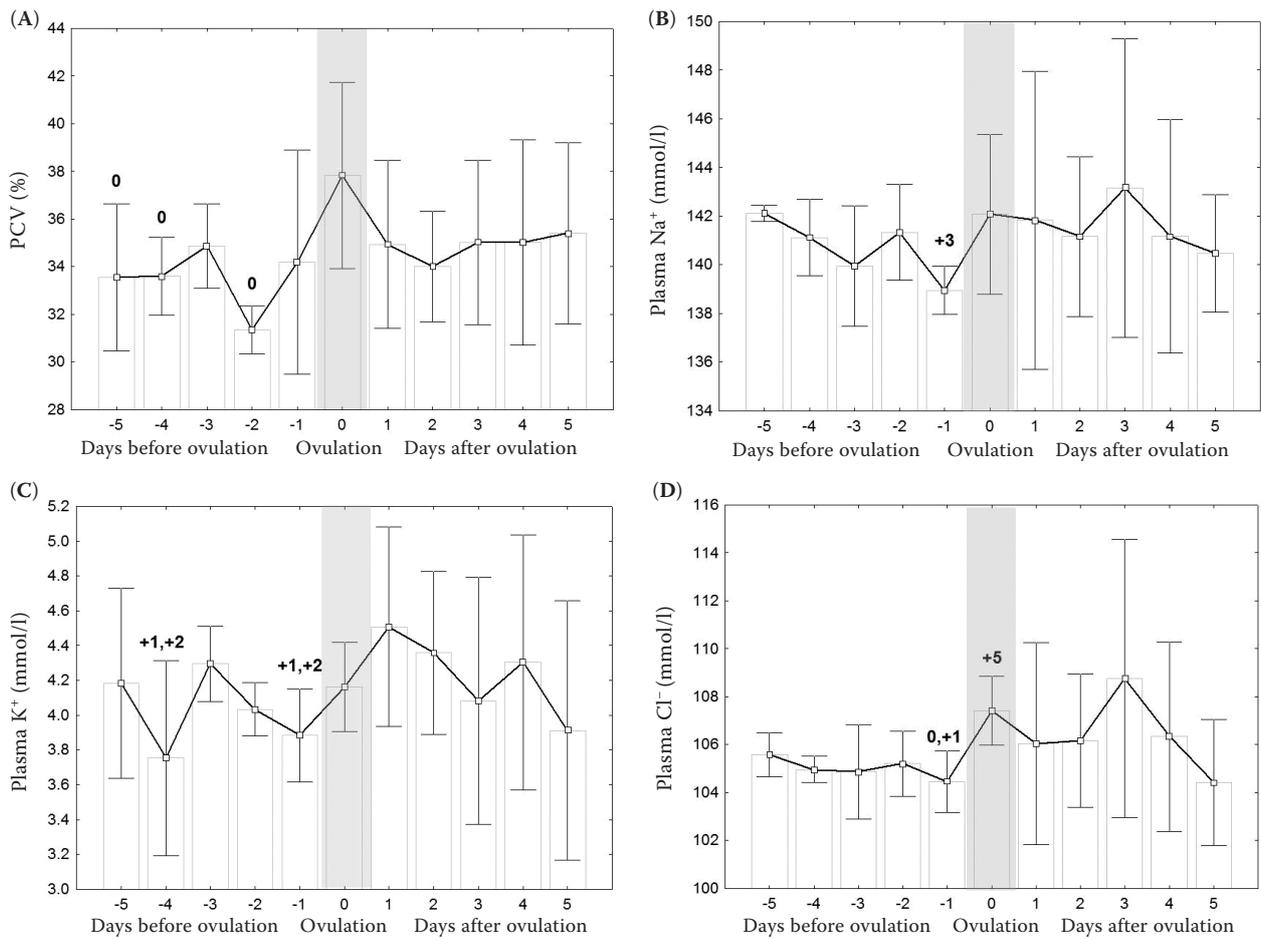


Figure 2. Packed cell volume (PCV) (A) and plasma concentrations of sodium (Na<sup>+</sup>) (B), potassium (K<sup>+</sup>) (C), and chloride (Cl<sup>-</sup>) (D) in mares before ovulation (from day -5 to day -1), on the day of ovulation (day 0), and after ovulation (from day +1 to day +5) (numbers indicate the days between which significant differences were found);  $P < 0.05$

the maximum values on days +1 and +2 ( $4.51 \pm 0.57$  mmol/l) (Figure 2).

Correlations between the components of the RAAS, DPF, PCV, and electrolytes before and after ovulation are presented in Tables 1 and 2, respectively.

## DISCUSSION

The present research evaluates the changes in the RAAS in mares around ovulation, as well as the relationships between these hormones and

Table 1. Coefficients of correlation between the diameter of preovulatory follicle (DPF), concentrations of renin (REN), angiotensin (ANG), aldosterone (ALD), packed cell volume (PCV), and electrolytes before ovulation in mares

	DPF	REN	ANG	ALD	PCV	Na <sup>+</sup>	K <sup>+</sup>
REN	<b>0.740*</b>						
ANG	0.370	0.360					
ALD	<b>0.800*</b>	<b>0.760*</b>	<b>-0.660*</b>				
PCV	0.190	0.370	0.010	0.350			
Na <sup>+</sup>	-0.090	-0.020	0.000	-0.070	-0.060		
K <sup>+</sup>	-0.040	0.000	-0.300	-0.010	0.250	0.280	
Cl <sup>-</sup>	0.210	0.320	0.040	0.266	0.470	<b>0.740*</b>	0.430

\*significant correlations in bold;  $P < 0.05$

Table 2. Coefficients of correlation between concentrations of renin (RE), angiotensin (ANG), aldosterone (ALD), packed cell volume (PCV), and electrolytes after ovulation in mares

	ANG	ALD	PCV	Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>
REN	-0.330	0.370	0.040	-0.060	0.030	-0.100
ANG		<b>-0.660*</b>	-0.070	0.060	0.270	0.130
ALD			0.020	-0.130	-0.130	-0.200
PCV				-0.150	-0.020	-0.260
Na <sup>+</sup>					0.090	<b>0.870*</b>
K <sup>+</sup>						0.090

\*significant correlations in bold;  $P < 0.05$

electrolytes, PCV, and DPF. The main findings were: (1) There was a progressive increase in plasma REN before ovulation, with the highest values on the day of ovulation; (2) Plasma ANG concentrations showed mild variations before ovulation, but experienced a sharp and progressive decrease after ovulation; (3) Plasma ALD concentrations increased progressively from day -5 to day +5; (4) A significant increase in PCV was found on the day of ovulation; and (5) DPF was positively correlated with REN and ALD concentrations, but not with ANG concentrations.

Our mean plasma REN and ANG concentrations were lower compared to the values reported for mares of the same breed during pregnancy, using the same analytical techniques (Satue and Domingo 2011; Satue et al. 2011). Therefore, although an activation of the RAAS happened around ovulation, pregnancy induced a greater activation. Our study demonstrates that the mares showed an increase in plasma REN and ALD concentrations before ovulation and an increase in plasma ALD concentrations after ovulation. A post-ovulatory increase in ALD has also been described in women (Sealey et al. 1994; Szmuiłowicz et al. 2006), after a rise in plasma REN and ANG because of the natriuretic effect of progesterone (Chidambaram et al. 2002; Szmuiłowicz et al. 2006).

A progressive increase in plasma REN concentrations before ovulation also happens in women (Kaulhausen et al. 1978; Loret de Mola et al. 1999), rats (De Vito et al. 1989), and baboons (Harewood et al. 1996). It has been attributed to the release of LH or to the stimulating effect of human chorionic gonadotropin (hCG). Therefore, there exists a tight control of the gonadotropins on REN synthesis and

release during the pre-ovulatory period (Loret de Mola et al. 1999). In fact, around ovulation, simultaneous peaks of LH, follicle-stimulating hormone (FSH), and prorenin have been described (Sealey et al. 1986), and prorenin is the precursor of active REN. In a previous study, we found significant correlations between estradiol (E2) and REN concentrations ( $r = 0.730$ ) (Satue et al. 2012), and that might be another explanation for increased REN concentrations at the time of ovulation. Similarly, Sealey et al. (1994) documented simultaneous increases of plasma REN and E2 during ovarian stimulation in women. Another explanation of the rise in REN concentrations could be a mild hypovolemia associated with interstitial fluid in abdominal cavity during ovulation, as reported in baboons (Harewood et al. 1996).

REN is released after renal nerve stimulation via increased sympathetic drive, changes in renal blood flow, and pressure associated with juxtaglomerular function, and changes in Na<sup>+</sup> and Cl<sup>-</sup> concentrations at the renal juxtaglomerular apparatus (Munos et al. 2010). However, in the present study, correlations between REN and electrolyte concentrations were low. In the same way, Roussel et al. (1983) described cyclic patterns of plasma Na<sup>+</sup> and ALD concentrations in cows, but without significant correlations with the RAAS.

After ovulation, the sharp decrease in plasma REN concentrations was followed by a slight but non-significant increase from day +3. This evolution agrees with data reported for women (Chidambaram et al. 2002). Ounis-Skali et al. (2006) suggested that the corpus luteum is an important source of REN, revealing a direct relationship between progesterone and REN after ovulation. Two recent studies in Spanish mares demonstrated low correlations between progesterone and REN ( $r = 0.220$ ) (Satue et al. 2012, 2014), indicating that factors other than progesterone might be considered in order to explain the increase of REN in the first days after ovulation.

The increase in ANG concentrations observed in sows (Sundsford and Aakvaag 1973) and rats (De Vito et al. 1987) after ovulation was not confirmed in our study. ANG concentrations in women after ovulation were almost the double of the values found before ovulation (Chidambaram et al. 2002; Ounis-Skali et al. 2006; Szmuiłowicz et al. 2006). These modifications have been linked in women with a modulation of the ovarian blood vessels

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during oocyte maturation (Sealey et al. 1994). In the mares, however, a progressive decrease in ANG was observed after ovulation. The reasons for these discrepancies are unknown, but differences between species should be considered.

ALD concentrations in women before ovulation have been reported to be higher (Sundsford and Aakvaag 1973) or similar to those found in the early post-ovulation period (Katz and Romfh 1972). In our mares, the progressive increase of ALD during the study might be explained partially by the increase of plasma REN before ovulation. However, a negative correlation between plasma ANG and ALD concentrations was found after ovulation. These data could reflex a dissociation between ANG and ALD. In this case, the synthesis of ALD might have occurred via other pathways independent from the activation of the RAAS after ovulation in the mare, as has been suggested for women (Szmuiłowicz et al. 2006). Because of this dissociation, REN decreased and ALD continued to rise.

In other species, the RAAS regulates development and growth of antral follicles. Receptors AT1 and AT2 for ANG have been found in the granulosa cells of the antral follicles and in the primordial primary and secondary follicles of sows (Shuttleworth et al. 2002). Administration of an ANG inhibitor in cows avoided the growth of the predominant follicle, and decreased the concentrations of E2 (Ferreira et al. 2011). Similarly, in women subjected to ovaric stimulation with human menopausal gonadotropin (HMG), concentrations of ANG were positively correlated with E2 and DPF (Jarry et al. 1988). In the current study, correlations between DPF and ANG concentrations were weak. However, correlations between DPF and REN and ALD concentrations were significant. These results might indicate that plasma ANG concentrations do not exert a significant effect on the development of the ovarian follicle or alternatively, some antagonist peptides of this hormone might be produced before ovulation in mares, as hypothesized by Montesinos et al. (2012).

Plasma electrolytes and PCV changes were not the main indicators of the RAAS modifications in the mares around ovulation, even though these parameters might experience simultaneous changes. A closer relationship between PCV, electrolytes, and the RAAS has been reported in pregnant mares. An increased activity of the RAAS led to a progressive decrease in PCV associated with an expansion of plasma volume (Bazzano et al.

2014). Our lack of significant variations of Na<sup>+</sup> concentrations around ovulation did not agree with the data described for women. Several authors (Chidambaram et al. 2002; Ounis-Skali et al. 2006; Lanje et al. 2010) found an increase in Na<sup>+</sup> concentrations at the time of ovulation, which was attributed to the antagonist effects of progesterone and ALD and their competition for binding to the same receptors (Chidambaram et al. 2002; Ounis-Skali et al. 2006; Lanje et al. 2010). The rise in ALD concentrations also resulted in decreased Na<sup>+</sup> concentrations in pregnant mares (Bazzano et al. 2016). Consequently, the reasons for the activation of the RAAS during ovulation and during pregnancy are clearly different.

## CONCLUSION

This study demonstrates that there is an activation of the RAAS around the time of ovulation in the mare, indicated by the increased plasma REN and ALD concentrations. Electrolyte alterations do not appear to be involved in this activation. After ovulation, the rapid decrease in plasma REN and ANG concentrations might indicate a modulation of the previously activated RAAS, even though plasma ALD concentrations increased during this period, suggesting a dissociation of the components of this system. The correlations between REN and ALD and the diameter of the predominant follicle during the last 5 days before ovulation might indicate that these hormones promote follicular growth or, alternatively, these parameters followed a parallel evolution.

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