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Luteinizing Hormone and Ovarian Responses of Early Postpartum Debouillet Ewes Treated with Cyproheptadine and(or) Melatonin^{1,2}

R. T. Kridli³ and D. M. Hallford

Department of Animal and Range Sciences, New Mexico State University, Las Cruces 88003

ABSTRACT: Two trials were conducted to evaluate the effects of cyproheptadine (serotonin receptor antagonist, Trial 1) along with administering melatonin (Trial 2) to early postpartum (PP) ewes on LH profiles and follicular development. In Trial 1, 12 mature ewes received either control (CON) or cyproheptadine (CYP) treatments (six ewes/treatment). Beginning on d 5 PP, each ewe received i.v. either 0 (vehicle) or .1 mg of CYP/kg BW twice daily for 5 d. Cyproheptadine tended to stimulate ($P < .10$) release of LH on d 5 PP (1.3 and $.8 \pm .2$ ng LH/mL for CYP-treated and CON ewes, respectively) with a similar trend ($P < .10$) of LH release occurring on d 9. Cyproheptadine also had a positive effect on follicular

development, but no luteal activity was detected. In Trial 2, 16 mature ewes received CON, i.v. CYP (.1 mg/kg BW twice daily), i.m. melatonin (MEL, 5 mg-ewe⁻¹.d⁻¹), or CYP+MEL. Treatments were administered from d 5 through 14 PP. Cyproheptadine tended to increase ($P < .10$) LH pulsatility on d 5 and 14, but MEL had no effect ($P > .20$). Follicular development was not affected ($P > .40$) by CYP or MEL treatments. Neither MEL nor CYP affected progesterone ($P > .60$). Cyproheptadine tended to increase LH concentration and pulse frequency in early PP ewes, but MEL had no effect on LH profiles. Both treatments failed to initiate ovarian cyclicity in early PP ewes.

Key Words: Anestrus, Serotonin, Melatonin, Reproduction, Sheep

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Introduction

During seasonal anestrus, estradiol inhibits LH secretion by decreasing GnRH pulsatility (Karsch et al., 1993). This inhibition of LH is thought to be mediated by photoperiod (Turek and Campbell, 1979). Bittman and Karsch (1984) suggested that this effect of photoperiod is mediated by pineal production of melatonin (MEL). Administration of MEL to ewes can extend the duration of the breeding season in the spring (Nett and Niswender, 1982). Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter thought to be involved in LH release. Serotonin regulation of LH release is mediated via

5-HT₂ receptor (Tanaka et al., 1993). Serotonin stimulates LH release when administered in large dosages and inhibits LH release when administered at low dosages (Deaver and Daily, 1982). Cyproheptadine (CYP), a 5-HT₂ receptor antagonist, increased LH concentration and pulsatility in ovariectomized, estradiol-treated ewes (Le Corre and Chemineau, 1993). The objective of these trials was to examine effects on LH of mimicking in postpartum ewes what occurs during the breeding season (i.e., low serotonin and high melatonin concentration) through antagonizing serotonin and administering melatonin.

Materials and Methods

During both trials, sheep were maintained at ambient temperature and had free access to water, shade, salt, and trace mineral blocks. Ewes received 3.2 kg of alfalfa pellet (18% CP) and .23 kg of corn-ewe⁻¹.d⁻¹ for 60 d postpartum (PP) in both trials. Cyproheptadine hydrochloride sesquihydrate (99%; Aldrich Chemical Company, Milwaukee, WI) was used in both trials and was prepared daily to be administered i.v. at .1 mg/kg BW twice daily. This dosage of CYP was selected because previous research by Le Corre and Chemineau (1993) showed that .1

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³Current address: Jordan University of Science and Technology, Irbid, Jordan.

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mg of CYP/kg of BW initiated the greatest LH response compared with other dosages tested (.25, .6, and 1.5 mg/kg BW). Cyproheptadine was suspended in a 1:13 solution of ethanol:propylene glycol. A weighed amount of CYP was dissolved in ethanol and then suspended in propylene glycol to yield a final concentration of 7 mg of CYP/mL of solution. This solution was stored at room temperature in amber bottles to prevent photodegradation.

Trial 1. Twelve mature Debouillet ewes (average BW = 75 kg) were assigned randomly by age to one of two treatments in a completely random design 4 d following parturition. Ewe and lamb BW were obtained on d 4, 10, 20, and 30 PP (d 0 = parturition). Treatments consisted of i.v. injection of either 0 (vehicle; CON; $n = 6$) or .1 mg CYP/kg BW ($n = 6$) at 0700 and 1600 daily for 5 d beginning on d 5 PP.

Blood samples were collected via jugular venipuncture from each ewe on alternate days from d 4 through 40 PP. Serum progesterone (P_4) was quantified in these samples as a marker of luteal activity. In addition, on the first and last days of treatment (d 5 and 9), blood samples were collected frequently. On these days, ewes were fed at 0600 and allowed 1 h to eat. Starting at 0700, blood was collected at 15-min intervals for 3 h before and 3 h after the CYP injection. Luteinizing hormone was quantified in these samples.

On d 11 PP, midventral laparotomy was performed on each ewe (Noordsy, 1989). Ovarian dimensions (length, width, and depth) were measured, follicles on each ovary were counted and classified as either greater than or less than 3 mm in diameter, and the diameter of the largest follicle on each ovary was measured. Ewes were then returned to the pen with their lambs.

On d 13 PP, another intensive blood collection was conducted. Three ewes from each treatment were selected to receive a GnRH challenge. Ewes were fed 1 h before sampling was initiated. The first sample was collected at 0700, after which ewes were injected (i.m.) with 50 μ g of GnRH (Cystorelin, Sanofi Animal Health, Overland, KS). Blood samples were collected at 15-min intervals for 4 h following the GnRH challenge. All blood samples were collected into sterile serum separator tubes and allowed to clot at room temperature for 30 min before serum was separated by centrifugation at $1,500 \times g$ for 15 min at 4°C. Serum was poured into plastic vials and stored at -20°C until it was analyzed for LH.

Trial 2. Sixteen mature Debouillet ewes (average BW = 75 kg) were randomly assigned to treatments (four ewes/treatment) in a 2×2 factorial arrangement 4 d following parturition. Treatments were control (2 mL of safflower oil, 1 mL of CYP vehicle [described earlier]), CYP (no melatonin), melatonin (no CYP), and CYP plus melatonin. Ewe and lamb BW were recorded on d 4, 15, 25, and 35 PP.

Ewes were treated with CYP and/or MEL for 10 d starting on d 5 PP. Ewes assigned to CYP treatment received an i.v. injection of either 0 (vehicle) or .1 mg of CYP/kg BW at 0700 and 1600 daily for 10 d. Ewes assigned to MEL treatment received an i.m. injection of either 0 (safflower oil) or 5 mg MEL/d. Melatonin treatment was administered at 1600 daily for 10 d. Melatonin (Sigma, St. Louis, MO) treatment was prepared by suspending the material in safflower oil to yield a concentration of 2.5 mg/mL. This dosage of melatonin was selected because Perez-Eguia and Hallford (1994) found it effective in increasing nighttime serum melatonin concentration.

Frequent blood samples were collected (jugular venipuncture) on the first (d 5) and last (d 14) days of treatment. On both days, sheep were fed 1 h before sampling was initiated. Samples were collected at 15-min intervals for 2 h, after which CYP was administered at 0900, and then samples were collected for 4 h at 15-min intervals. Additional samples were obtained every 3rd d from d 4 through d 40 PP to monitor luteal activity. All blood samples were collected and processed as described for Trial 1. On d 15 PP, all ewes were laparotomized. Reproductive tracts were exteriorized and data were collected as described for Trial 1.

Serum LH (Hoefler and Hallford, 1987) was quantified by RIA using NIDDK anti-oLH-1, oLH-25 (reference preparation), and oLH-I₃ (iodination). Within-assay CV for LH were 9.4 and 12% for Trials 1 and 2, respectively. Serum P_4 was quantified using a commercially available kit (Diagnostic Products, Los Angeles, CA) with modifications reported by Schneider and Hallford (1996). Within-assay CV for P_4 were 6.1, 3, and 8.2 in Trial 1 and 17, 15.5, and 5.7% in Trial 2. Interassay CV was 4% in Trial 1 and 14% in Trial 2.

Animal BW, ovarian, and follicular data were analyzed by analysis of variance for a completely random design (Steel and Torrie, 1980). Serum hormone profiles were analyzed by split-plot analysis of variance for repeated measures on animals (Gill and Hafs, 1971). In the first trial, treatment (CYP) effects were included in the main plot and animal within CYP was used as the error term. Time and the treatment \times time interaction were included in the subplot. In the second trial, hormone profiles were also analyzed by split-plot analysis of variance. Cyproheptadine, MEL, and CYP \times MEL were tested in the main plot using animal within CYP \times MEL as the error term. Time and treatment(s) \times time interactions were tested in the subplot. Serum LH following GnRH challenge was analyzed by split-plot analysis of variance, and area under the curve was calculated with the trapezoidal summation method. Cluster analysis was used to estimate LH pulsatility (Veldhuis and Johnson, 1986). All analyses were computed using the GLM procedures of SAS (1989).

Table 1. Serum luteinizing hormone (LH) in ewes treated with cyproheptadine (CYP) during the early postpartum period in Trial 1^{a,b}

Item	Treatment		SE ^c
	CON	CYP	
Day 5			
Before treatment			
LH, ng/mL ^d	.73	.71	.1
LH pulses/3 h, no. ^{de}	2.00	2.33	.4
After treatment			
LH, ng/mL ^f	.73	.94	.1
LH pulses/3 h, no. ^{de}	1.00	1.16	.4
Day 9			
Before treatment			
LH, ng/mL ^d	.77	.76	.1
LH pulses/3 h, no. ^{de}	2.00	2.16	.4
After treatment			
LH, ng/mL ^d	.74	.86	.1
LH pulses/3 h, no. ^{de}	.50	.33	.33

^aSix ewes/treatment. Ewes were treated i.v. with either cyproheptadine (CYP; .1 mg/kg BW) or vehicle (CON; 1:13 ethanol:propylene glycol) twice daily for 5 d starting on d 5 postpartum. Ewes were bled every 15 min for 3 h before and 3 h after CYP injection.

^bNo treatment × time interactions were detected on either day ($P > .15$).

^cSE = standard error.

^dRow values do not differ ($P > .35$).

^eDetermined by Cluster analysis.

^fRow values differ ($P < .10$).

Results

Trial 1. Ewes were weighed on d 4 PP (d 5 was the beginning of treatment). Ewes receiving CYP weighed (mean ± SE) 78.0 ± 7.2 kg and CON ewes weighed 73.9 ± 7.2 kg ($P > .40$). On d 10, 20, and 30 PP, CON and CYP-treated ewes continued to lose a similar amount of BW as expected for the first 30 d of lactation. On d 30, CYP-treated and CON ewes weighed the same ($P > .20$). Lamb growth rates were not affected ($P > .40$) by maternal treatment; lambs in both groups gained the same amount of BW.

Ewes were intensively sampled on the first and last days of treatment (d 5 and 9 PP). Treatment × sampling time interactions were not detected ($P > .15$) on d 5 or 9. Before treatment on d 5, LH concentration was the same ($P > .80$) in control (.73 ± .1 ng LH/mL) and CYP-treated (.71 ± .1 ng LH/mL) ewes (Table 1). One hour following treatment, ewes treated with CYP had 1.25 ± .2 ng LH/mL, compared with .75 ± .2 ng LH/mL for controls ($P = .07$). Likewise, LH values pooled over the 3-h posttreatment period tended ($P < .10$) to be greater in CYP-treated ewes (.94 ± .1 ng/mL) than in controls (.73 ± .1 ng/mL). On d 9 PP (Table 1), pretreatment serum LH concentrations were similar ($P > .90$) in control and CYP-treated ewes. Although posttreatment LH concentration was similar ($P > .30$) in control (.74 ± .1 ng/mL) and CYP-treated (.86 ± .1 ng/mL) ewes, the numerical increase in ewes receiving CYP was similar to that observed on d 5. Cluster analysis revealed no

LH pulse differences ($P > .50$) between treatments on d 5 and 9 PP.

No treatment × time interactions were detected ($P > .90$) following GnRH on d 13 PP. Serum LH in response to GnRH was similar ($P > .40$) in control (6.7 ± 1.8 ng/mL) and CYP-treated (8.9 ± 1.8 ng/mL) ewes. Area under the LH curve for controls was 1,692 ± 461 units compared with 2,267 ± 461 units for CYP-treated ewes ($P > .40$).

Ovarian data are presented in Table 2. Ewes treated with CYP tended to have greater ($P < .10$) total ovarian volume, more ($P < .10$) follicles greater than 3 mm in diameter, and diameter of the largest follicle was greater ($P < .05$) than in CON ewes.

Progesterone analysis indicated that GnRH administration resulted in luteinized follicles in three CON and two CYP-treated ewes. This was evident by the rise in serum P₄ (greater than 1 ng/mL) on d 16 PP (3 d after the GnRH challenge), which lasted throughout the entire bleeding period (d 40 PP). The remainder of the ewes showed no luteal activity; P₄ concentration remained less than 1 ng/mL.

Trial 2. Results obtained in Trial 1 indicated potential effects of CYP on LH profiles and follicular development. Longer treatment and sampling times were therefore used in Trial 2 in an attempt to enhance these differences. No CYP × MEL interactions were detected for BW ($P > .20$). On d 4 PP, ewes assigned to receive MEL weighed 70.3 ± 2.9 kg, and CON ewes weighed 72.3 ± 2.9 kg ($P > .60$). On d 15, 25, and 35 PP, BW of MEL-treated and CON ewes were similar ($P > .90$). Control and CYP-treated ewes

Table 2. Ovarian responses of ewes treated with cyproheptadine (CYP) and(or) melatonin (MEL) during the early postpartum period

Item	Trial 1 ^a				SE ^b
	CYP, mg/kg BW				
	0	.1			
Ovarian volume, cm ^{3c}	3.4	6.1			1.0
Follicles > 3 mm, no. ^c	3.0	6.0			1.2
Largest follicle, mm ^d	4.5	7.7			.8

Item	Trial 2 ^e				SE ^b
	CYP, mg/kg BW ^f		MEL mg/d ^d		
	0	.1	0	5	
Ovarian volume, cm ^{3h}	6.1	5.4	5.7	5.7	.7
Follicles > 3 mm, no ^h	3.2	4.1	3.5	3.9	.8
Largest follicle, mm ^h	6.0	6.6	5.9	6.8	.9

^aSix ewes/treatment. Ewes were treated i.v. with either cyproheptadine (CYP; .1 mg/kg BW) or vehicle (CON; 1:13 ethanol:propylene glycol) twice daily for 5 d starting on d 5 postpartum. Midventral laparotomy was performed on each ewe on d 11 postpartum.

^bSE = standard error.

^cRow values differ ($P < .10$).

^dRow values differ ($P < .05$).

^e2 × 2 factorial (four ewes/treatment). No CYP × MEL interactions were detected ($P > .50$). Main effect treatment means are presented. Midventral laparotomy was performed on d 15 postpartum.

^fCYP was administered i.v. at 0700 and 1600 daily for 10 d beginning on d 5 postpartum.

^gMEL was administered i.m. daily at 1600 for 10 d beginning on d 5 postpartum. First MEL administration was after bleeding on d 5.

^hRow values within main effect treatment do not differ ($P > .40$).

weighed the same ($P > .40$) on d 4 PP (69.7 and 72.9 ± 3.0 kg, respectively), and they continued to lose a similar amount of BW during the first 35 d of lactation, reaching 67.7 and 67.9 ± 2.6 kg for CON and CYP-treated ewes, respectively ($P > .90$). Likewise, lamb BW was unaffected ($P > .40$) by maternal treatment.

On the 1st d of treatment (d 5 PP), ewes received MEL after the intensive bleeding regimen was conducted. The only experimental factor affecting serum LH profiles on d 5 was CYP. Serum LH concentrations for CON and CYP-treated ewes are presented in Table 3. During the 2-h sampling period before treatment on d 5, CON and CYP-treated ewes had similar ($P > .30$) serum LH concentrations. Following treatment on d 5, CON ewes had .78 ± .1 ng LH/mL compared with .96 ± .1 ng LH/mL for CYP-treated ewes ($P < .05$). No CYP × MEL interactions were detected ($P > .50$) on d 14 for serum LH concentration; therefore, data are presented in the form of main effect treatment means (Table 3). Melatonin treatment did not increase LH concentration before ($P > .10$) or after ($P > .90$) treatment on d 14. Before treatment on d 14, CYP-treated ewes had .95 ± .1 ng LH/mL compared with .72 ± .1 ng LH/mL for CON ewes ($P < .05$). Following CYP treatment on d 14, CYP-treated ewes had numerically greater serum LH ($P = .14$) than did controls (1.01 and .91 ± .1 ng LH/mL for CYP-treated and CON ewes, respectively).

No difference ($P > .90$) in LH pulses was observed before treatment on d 5; however, after treatment, CYP-treated ewes had more ($P < .10$) LH pulses than

did CON ewes (.9 and .3 ± .2 pulses·ewe⁻¹·4 h⁻¹, respectively). No effects of MEL on LH pulses were detected ($P > .40$) before treatment on d 14; however, after treatment, MEL-treated ewes had fewer ($P < .05$) LH pulses than CON ewes (.5 and 1.3 ± .2 pulses·ewe⁻¹·4 h⁻¹, respectively). Cyproheptadine-treated ewes had .4 ± .1 pulses·ewe⁻¹·2 h⁻¹ before treatment on d 14 compared with 0 pulses·ewe⁻¹·2 h⁻¹ for the controls ($P < .10$). This difference was not observed after treatment on d 14 ($P > .30$).

No CYP × MEL interactions were detected ($P > .30$) with respect to ovarian and follicular data. Ovarian and follicular data are presented in Table 2 in the form of main effect treatment means. Total ovarian volume was not affected by the MEL treatment ($P > .90$). Treatment with MEL did not influence ($P > .70$) the number of follicles greater than 3 mm in diameter, nor did it influence ($P > .50$) size (diameter) of the largest follicle present on d 15 PP. Similarly, CYP treatment did not affect ($P > .40$) ovarian volume, number of follicles greater than 3 mm in diameter, or diameter of the largest follicle. Serum samples collected every 3rd d between d 4 and 40 PP were analyzed for P₄ to monitor luteal activity. Analysis of P₄ indicated no luteal activity in any of the ewes (all values were ≤ 1 ng P₄/mL).

Discussion

Weight results from both trials show that antagonizing serotonin through CYP administration had no adverse effect on BW of ewes or their lambs.

Table 3. Serum luteinizing hormone (LH) profiles of early postpartum ewes treated with cyproheptadine (CYP) and/or melatonin (MEL) in Trial 2^a

Item	CYP, mg/kg BW ^b		MEL mg/d ^c		SE ^d
	0	.1	0	5	
Day 5					
Before treatment					
LH, ng/mL ^e	.76	.86			.1
LH pulses/2 h, no. ^{ef}	.38	.38			.2
After treatment					
LH, ng/mL	.78 ^g	.96 ^g			.1
LH pulses/4 h, no. ^f	.25 ^h	.88 ^h			.2
Day 14					
Before treatment					
LH, ng/mL	.72 ^g	.95 ^g	.76 ^e	.92 ^e	.1
LH pulses/2 h, no. ^f	0. ^h	.38 ^h	.13 ^e	.25 ^e	.1
After treatment					
LH, ng/mL	.91 ^e	1.01 ^e	1.00 ^e	1.01 ^e	.1
LH pulses/4 h, no. ^f	.75 ^e	1.00 ^e	1.25 ^g	.50 ^g	.2

^a2 × 2 factorial (four ewes/treatment). No CYP × MEL interactions were detected ($P > .80$). Main effect treatment means are presented. Serum was collected at 15-min intervals for 2 h before and 4 h after the morning CYP treatment.

^bCYP was administered i.v. at 0700 and 1600 daily for 10 d beginning on d 5 postpartum.

^cMEL was administered i.m. daily at 1600 for 10 d beginning on d 5 postpartum. First MEL administration was after bleeding on d 5.

^dSE = standard error.

^eRow values within main effect treatment do not differ ($P > .15$).

^fDetermined by cluster analysis.

^gRow values within main effect treatment differ ($P < .05$).

^hRow values within main effect treatment differ ($P < .10$).

Serotonin may be the message used by cholecystokinin to regulate feed intake (Esfahani et al., 1995). The 5-HT_{1A} receptor is thought to mediate this action of serotonin in rats (Voigt et al., 1995). Cyproheptadine probably did not influence BW because it antagonizes the 5-HT₂ receptor subtype.

Administering 5 mg of MEL/d to early PP ewes did not seem to influence ewe or lamb BW. These results agree with those reported by Turner and Hallford (1993), who observed no effect of exogenous MEL on BW of ewes. Moreover, Perez-Eguia and Hallford (1994) reported no effects of a similar dosage of MEL on BW of ewe lambs before a breeding season.

Serum MEL was not quantified in the present experiments because sufficient data (Turner and Hallford, 1993; Perez-Eguia and Hallford, 1994) from our laboratory indicate that i.m. MEL administration increases serum MEL of sheep for 3 to 6 h after administration. Melatonin administration did not affect LH release during the early PP period. Perez-Eguia and Hallford (1994) did not detect an effect of exogenous MEL on serum LH concentration in ewe lambs. Cyproheptadine administration tended to increase serum LH concentration immediately after treatment. During the first trial, LH concentration on the last day of treatment (d 9) was similar between CYP-treated and CON ewes. During the second trial, LH concentration on the last day of treatment (d 14) was greater ($P < .05$) in CYP-treated than in CON ewes before treatment and remained numerically

greater ($P > .15$) after treatment. Extending CYP treatment through d 14 PP seemed to maintain the stimulation of LH release as indicated by greater LH concentration and a trend for greater pulsatility before CYP treatment on d 14. These results agree with Le Corre and Chemineau (1993), who reported that mean LH concentration increased from $.41 \pm .1$ to $1.10 \pm .2$ ng/mL following CYP administration at .1 mg/kg BW. Even though CYP has a greater affinity for the 5-HT₁ histamine receptor than the 5-HT₂ serotonin receptor (Janssen, 1983), these effects on LH are thought to be caused by antagonizing the 5-HT₂ receptor. This concept is supported by Alexander et al. (1994), who concluded that the 5-HT₁ antagonist diphenhydramine did not have consistent effects on LH throughout the year, which indicates that histamine may not be a direct modulator of GnRH release.

Following GnRH challenge, serum LH was numerically, but not statistically, greater in ewes receiving CYP than in controls. These results agree with findings of Meyer and Goodman (1986), who reported that antagonizing dopaminergic or α -adrenergic neurons did not affect LH release in response to GnRH challenge when compared with control ewes. This finding may indicate that the effect of serotonin is exerted at the level of the hypothalamus and not the pituitary gland.

During the first trial, CYP seemed to stimulate follicular development. During the second trial, neither MEL nor CYP affected follicular development.

The rise in LH concentration and pulsatility may not have been great enough to stimulate follicular development during the early PP period. Alternatively, the 5 d longer period in the second trial may have allowed time for follicular development to progress in control ewes to that observed in CYP-treated ewes, thereby possibly masking early effects of CYP.

Previous studies on the effect of serotonin on LH secretion are contradictory. The present study, among a few others, indicates that 5-HT plays a negative role in regulating LH release. According to Mondragon et al. (1986), the mechanism by which 5-HT regulates LH release may be by exerting an effect on the hypothalamus reducing the firing of GnRH producing neurons, thus reducing LH pulse frequency. Another possibility for regulation of LH release by 5-HT is that infusion of 5-HT may increase the concentration of other neurotransmitters that, like dopamine, have been found to inhibit LH secretion (Deaver and Daily, 1982). Further research is needed to detect the specific site of action of serotonin along with studying other factors with which serotonin may be interacting.

Implications

Treatment of spring-lambing ewes during the early postpartum period with the serotonin receptor antagonist cyproheptadine slightly increased luteinizing hormone concentrations, but melatonin administrations did not influence luteinizing hormone secretion. Although results of the first trial suggested that cyproheptadine stimulated follicular development, data from the second trial indicated no improvement in ovarian volume or follicle size. Neither cyproheptadine nor melatonin was able to override the seasonal effect on luteinizing hormone secretory patterns in early postpartum seasonally anestrous ewes.

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