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Vascular Resistance is Decreased in the Luteal Rat Ovary by a 20 Minute Continuous Infusion of Noradrenaline

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ABSTRACT

The effect of a 20 min continuous infusion of noradrenaline (2 nanomoles/min) on the blood flow and vascular resistance of 2-, 6- and 11-day-old corpora lutea from adult pseudopregnant rats was studied. Pseudopregnancy was induced by mating with vasectomized male rats. The blood flow of the corpus luteum and the remaining ovary was measured with the microsphere technique. The basal blood flow varied between the luteal ages studied and was highest at day 6 of pseudopregnancy. Noradrenaline induced a two-fold increase in the blood flow of the corpus luteum at the luteal ages studied. The vascular resistance (blood pressure/blood flow) decreased for all luteal ages, while the vascular resistance for kidney, spleen and diaphragm was unchanged. Antidiuretic hormone was found to markedly decrease the luteal blood flow and the vascular resistance remained increased. The effect of noradrenaline infusion on the luteal blood flow thus in contrast to other vasoactive substances is biphasic, with an initial vasoconstriction followed by vasodilatation.

INTRODUCTION

A catecholamine exposure is known to elicit acute vasoconstricion for vascular beds of many different organs (11). This also includes several ovarian preparations. Acute administration of catecholamines in vitro immediately or within a few minutes resulted in vasoconstriction as shown for the perfused rabbit ovary (18) and the perfused human ovary (24). Also, acute in vivo administration of noradrenaline resulted in vasoconstriction of the vascular bed, as shown for the ovine ovary near term (16) and the mid-luteal rat corpus luteum during pseudopregnancy (19). These acute effects are probably mediated by stimulation of α-receptors in ovarian blood vessels. However, β-receptors have also been detected in the ovary and the β-receptor concentration of rat corpora lutea is highest in the early luteal phase (15). A longer exposure to noradrenaline may alter an α-receptor response or may include stimulation of

β-adrenergic receptors. In the present study the effect of a 20 min continuous infusion of noradrenaline on vascular resistance of ovaries from early, mid and late luteal phase of the adult pseudopregnant rat, was studied. In comparison, a non-adrenergic vasoconstrictor of the ovarian vascular bed (25), the antidiuretic hormone (ADH), was infused for the same length of time.

METHODS

Animals

67 female rats of the Sprague-Dawley strain were purchased from ALAB (Sollentuna, Sweden) when 3-4 months of age. They were kept at the local animal house under controlled environmental conditions (20-23°C, 40-60% humidity) with the light period running between 0500 and 1900 hours. Rats were given free access to standard diet pellets (Type R 3 pellets from Ewos Ltd, Södertälje, Sweden) and tap water. The rats were allowed to acclimatize for 1-2 weeks before pseudopregnancy was induced.

Rat model

Female rats, 225-300 grams of body weight (3-4/cage), were mated with vasectomized sterile male rats (1/cage). Day 1 of pseudopregnancy was defined as the day when a vaginal plug was recovered. The copulatory stimulus is known to prolong the rat luteal phase (7). The length of pseudopregnancy in this study was 13±1 days (mean±SD), as judged from plasma steroids and vaginal smears. The animals were submitted to experiments on day 2, 6 and 11 of their first pseudopregnancy and corpora lutea of pseudopregnancy were designated as 2-, 6- and 11-day-old corpora lutea, respectively. After the microsphere infusion (see below), the rats were killed by an overdose of sodium pentobarbitone, the abdomen was opened and the ovaries were dissected free and trimmed. 2-, 6- and 11-day-old corpora lutea were identified and extirpated under a stereomicroscope. The corpora lutea of pseudopregnancy were distinguished from corpora lutea of earlier estrous cycles using the following criteria:

2-day-old corpora lutea: More loose structure, presence of a distinct vascular network around the ovulatory point, which usually could be discerned, and their slightly paler appearance. The mean wet weight of the corpus luteum was 0.84±0.04 mg (mean±SD). The number of corpora lutea per rat was for this study 13.6±0.04 (mean±SD).

6-day-old corpora lutea: Larger size and more reddish appearance (1.45±0.40 mg wet weight and 13.8±0.40 corpora lutea per rat).

11-day-old corpora lutea: Larger size, a slightly more reddish appearance and a few larger vessels over the surface (1.58±0.14 mg wet weight and 14.3±1.7 corpora lutea per rat).

The term "remaining ovary" is defined as the ovarian tissue left after extirpation of the corpora lutea of pseudopregnancy. The remaining ovary contains corpora lutea from earlier estrous cycles, follicles of different stages and stromal tissue. The main part of the tissue consists of stromal tissue and corpora lutea from earlier estrous cycles.

Induction of anaesthesia and surgical preparation

Anaesthesia was induced with an intraperitoneal injection of 15-20 mg of sodium pentobarbitone (Mebumal vet.^{R}, ACO, Sweden). 20 min after the injection rats reached surgical anaesthesia. The rats were placed in a supine position on a 40^{o}C thermostat-regulated heating pad, whereafter the surgical preparation of the rats commenced. Plastic catheters (purchased from Intramedic, Parsippany, New Jersey, USA with inner diameters of 0.3 and 0.6 mm, dimensions PE-10 and PE-50 respectively) were used to cannulate both axillary arteries (PE-10), the right carotid artery (PE-50) and the tail artery (PE-50). Catheters were pre-filled with a heparin solution (500 IU/ml saline) and a total of approximately 250 IU heparin per rat was infused. The left axillary arterial catheter was connected to a device for continuous arterial blood pressure recording (pressure transducer mod. 267A with amplifier mod. 311A, Sanborn Co., USA). The pressure transducer was placed at the heart level. The total time for surgery was approximately 30-40 min.

Treatment groups

After surgey, the rats were given continuous infusions of vehicle (0.1 mg ascorbic acid/ml saline), l-noradrenaline (Sigma Co., St Louis, USA) or antidiuretic hormone (ADH= Arg^{8}-vasopressin, Sigma Co.). The infusions were Operformed through the right axillary artery and according to the following schedule:

1. Continuous noradrenaline infusion.

2-, 6- or 11-day pseudopregnant rats were continuously infused with l-noradrenaline (20 µM) dissolved in vehicle at a rate of 0.1 ml/min and blood flow was measured at 20 min after the start of infusion (Fig. 1 and Table 1).

2. Discontinuous noradrenaline infusion.

6-days pseudopregnant rats were continuously infused with vehicle or l-noradrenaline (20 µM) at a rate of 0.1 ml/min for 20 min, whereafter noradrenaline infusion was stopped. Blood flow was measured at 5 min after discontinuing the infusion (Table 2).

3. Continuous ADH infusion.

6-days pseudopregnant rats were continuously infused with ADH (10 µM) at a rate of 0.1 ml/min and blood flow was measured at 20 min after the start of infusion (Table 3).

Control groups.

2-, 6- or 11-day pseudopregnant rats in the control groups received a 20 min continuous infusion of vehicle (0.1 ml/min) and blood flow was measured with radioactive microspheres either at 20 min after the start of infusion (group 1 and 3) or 5 min after the infusion was discontinued (group 2).

Measurement of regional blood flow and vascular resistance with radioactive microspheres

Blood flow was determined with radioactive microspheres (17). Microspheres labelled with ^{141}Cerium (15 ± 0.3 μm diameter, specific activity 10 mCi/g) from New England Nuclear Co, Boston, Mass, USA were vigorously shaken in a small glass bottle. 1 ml of microspheres suspended in saline (containing approx. 200,000 microspheres) was injected at 20 min after the start of vehicle, noradrenaline or ADH infusion, into the ascending aorta via the right carotid catheter. In one group the infusion of noradrenaline or vehicle was discontinued at 20 min and 1 ml of microsphere suspension was injected at 25 min after the start of vehicle or noradrenaline infusion. Microspheres were injected during 30 sec and the catheter was flushed with a small volume of saline immediately afterwards. A reference sample was aspirated from the tail artery at a constant rate (0.1 ml/min) from 15 sec before until 15 sec after the microsphere injection. Rats were killed with an overdose of sodium pentobarbitone. Corpora lutea of pseudopregnancy, remaining ovary, kidney, spleen and a piece of the diaphragm were extirpated, weighed and put into plastic vials for determination of γ-radiation from the main energy peak of ^{141}Ce (Rackgamma, LKB-Wallac, Sweden). Tissue blood flow in ml/min was calculated as:

$$\text{Blood flow} = Q_{ref} \times N_{org}/N_{ref},$$

where Q_{ref} = rate of withdrawal of the reference sample (ml/min), N_{org} = total radioactivity (cpm) of the organ and N_{ref} = total radioactivity (cpm) of the reference sample.

Vascular resistance (mm Hg/ml/100 g/min) was calculated according to the formula:

$$\text{Vascular resistance} = \text{MABP (mm Hg)}/\text{ blood flow (ml/100g/min)},$$

where MABP=mean arterial blood pressure (mm Hg) during microsphere infusion. Methodological studies on the luteal rabbit ovary (1) have shown that arterio-venous shunts of physiological significance do not exist, this being a

prerequisite for measurement of nutritive blood flow using microspheres. Furthermore, the indirect method, using microspheres for blood flow measurement, involves no direct manipulation of the ovary. This is an important factor, since manipulative procedures of the ovary has been shown to cause an increase in ovarian blood flow (6). Only rats with a stable MABP during microsphere infusion were included into this study. Side distribution of microspheres between paired organs was highly correlated (kidney 0.88, remaining ovary 0.97 and corpus luteum 0.84, all r_s-values significant ($p<0.001$). The precision of blood flow measurements was calculated at a 95% confidence level according to Buckberg *et al.*(3), with a minimum of 400 microspheres per sample counted.

Statistics

Values are presented as mean ± SEM, unless otherwise indicated. For vascular resistance mean ± SEM of the ratios 'mean arterial blood pressure/blood flow' for each rat are presented. For comparison between groups the Mann-Whitney U-test (22) was used. Correlation was calculated with Spearman's rank correlation coefficient (r_s). Differences between groups were considered significant for p-values of 0.05 or less.

RESULTS

Effect of a continuous noradrenaline infusion on luteal blood flow and vascular resistance at different days of pseudopregnancy

The blood flow of corpora lutea of pseudopregnancy measured directly at the end of vehicle and noradrenaline infusions is shown in Fig. 1 A and B. The blood flow of the corpora lutea of pseudopregnancy in rats receiving vehicle changed during pseudopregnancy and was significantly higher in 6-day-old corpora lutea as compared to 2- and 11-day-old corpora lutea ($p<0.05$). The MABP during microsphere injection at 20 min infusion of vehicle was 117 ± 5 mm Hg (mean ± SEM for 32 observations) and did not differ between the different days of pseudopregnancy tested. The MABP at the end of a 20 min infusion of noradrenaline (2 nanomoles/min) increased significantly ($p<0.05$) to 142 ± 5 mm Hg (mean± SEM of 20 observations). The vascular resistance in 6-day-old corpora lutea was significantly lower ($p<0.05$) than in 2- and 11-day-old corpora lutea, as shown in Fig. 1 C. A 20 min infusion of noradrenaline increased blood flow in 2-, 6- and 11-day-old corpora lutea ($p<0.05$), as shown in Fig. 1 A and B. The calculated vascular resistances of corpora lutea at the end of vehicle or noradrenaline infusion are shown in Fig. 1 C. Noradrenaline infusion decreased the luteal vascular resistance ($p<0.05$) for 2-, 6- and 11-day-old corpora lutea, when measured at 20 min of infusion.

Effect of a continuous noradrenaline infusion on blood flow and vascular resistance of the remaining ovary

The blood flow and the vascular resistance in the remaining ovary were also determined. As can be seen in Table 1 the blood flow of the remaining ovary determined at 20 min of infusion of vehicle did not change during pseudopregnancy. Also the vascular resistance of the remaining ovary was of the same magnitude for all days of pseudopregnancy tested. Infusion of noradrenaline for 20 min more than doubled the blood flow in the remaining

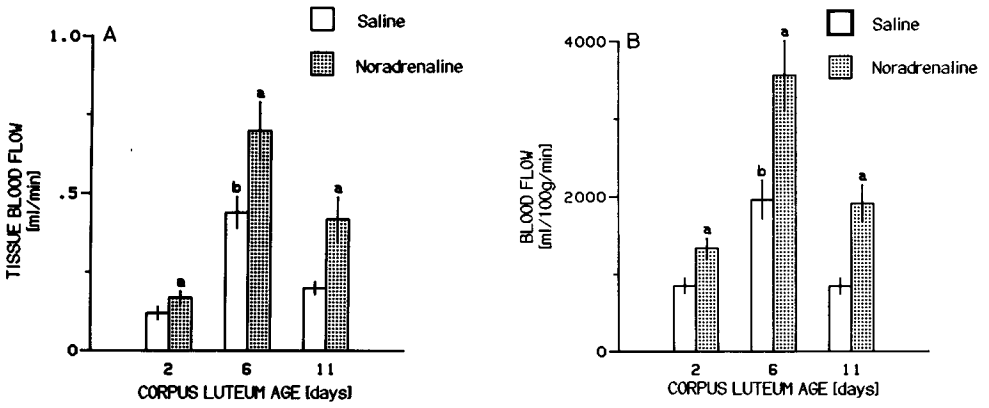
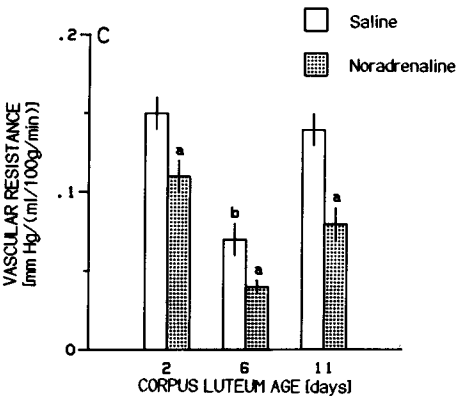


Fig. 1. Effect of a 20 min infusion of noradrenaline (2 nanomoles/min) on the tissue blood flow (A), blood flow (B) and vascular resistance (C) of the corpus luteum of the adult pseudopregnant rat. Pseudopregnancy was induced by mating with vasectomized male rats. The number of control rats were 10, 14 and 8 for day 2, 6 and 11 of pseudopregnancy, respectively and the number of noradrenaline-treated rats were 8, 8 and 4, resp. Values are given as mean±SEM.



a=p<0.05 versus vehicle-treated rats.
b=p<0.05 versus vehicle-treated rats of 2 and 11 days of pseudopregnancy.

ovary (Table 1). The vascular resistance of the remaining ovary was significantly decreased by the noradrenaline infusion (Table 1).

Effect of a continuous noradrenaline infusion on blood flow and vascular resistance of the kidney, spleen and diaphragm

As a comparison to the corpus luteum and the remaining ovary blood flows and vascular resistances were also determined in kidney, spleen and diaphragm (Table 1). A significant increase in blood flow was seen for the kidney and spleen at 20 min of noradrenaline infusion ($p<0.05$). The vascular resistances for these organs as well as the diaphragm were unchanged.

Table 1. Effect of a 20 min continuous noradrenaline infusion on the blood flows and vascular resistances of the remaining ovary, kidney, spleen and diaphragm in the adult pseudopregnant rat.

	Remaining ovary			Kidney	Spleen	Diaphragm
	Day of pseodopregnancy					
	2	6	11			
Tissue Blood Flow (ml/min):						
Vehicle	0.31±0.05	0.28±0.03	0.30±0.07			
Noradrenaline	0.73±0.15*	0.75±0.16*	0.51±0.06*			
Blood Flow (ml/100g/min):						
Vehicle	412± 56	459±37	409±86	525±25	165±14	56±5
Noradrenaline	1274±272*	1235±271*	1023±83*	629±38*	288±38*	63±6
Vascular resistance:						
Vehicle	0.30±0.03	0.29±0.03	0.32±0.08	0.24±0.01	0.82±0.08	2.35±0.19
Noradrenaline	0.18±0.06*	0.18±0.06*	0.16±0.02*	0.25±0.02	0.74±0.10	2.62±0.26

*=$P<0.05$ versus control as tested with the Mann-Whitney U-test.
Values are given as mean±SEM of the number of rats given for Fig. 1. Values of kidney, spleen and diaphragm represent mean±SEM for all luteal ages.

Effect of a discontinuous noradrenaline infusion on blood flow and vascular resistance of the corpus luteum and the remaining ovary

In order to test, whether the effect of noradrenaline on the vascular resistance of the ovary was sustained or transient, the noradrenaline infusion was stopped at 20 min after the start of infusion and blood flow measured 5 min later, in rats at day 6 of pseudopregnancy. Vascular resistances had almost returned to control levels and there was no significant difference between vehicle- and noradrenaline- infused rats when comparing vascular resistances and blood flows of either the corpora lutea of pseudopregnancy or the remaining ovary (Table 2).

Table 2. Effect of a discontinuous noradrenaline infusion on blood flows and vascular resistances of the remaining ovary, corpus luteum, kidney and spleen in the adult rat at day 6 of pseudopregnancy.

	Corpus luteum	Remaining ovary	Kidney	Spleen
Tissue blood flow (ml/min):				
Vehicle	0.35±0.12	0.31±0.11	8.3±1.3	2.0±0.6
Noradrenaline	0.38±0.08	0.28±0.06	11.4±2.8	2.4±0.4
Blood flow (ml/100g/min):				
Vehicle	1716±495	536±175	518±67	280±71
Noradrenaline	1722±295	487±93	681±112	302±52
Vascular resistance:				
Vehicle	0.086±0.016	0.36±0.14	0.25±0.04	0.52±0.10
Noradrenaline	0.084±0.009	0.31±0.06	0.22±0.05	0.48±0.07

Values are given as mean±SEM for n=4.
No significant difference between control and noradrenaline-treated rats were seen.

Effect of a continuous infusion of ADH on blood flow and vascular resistance of the corpus luteum and the remaining ovary

A continuous infusion of 1 nanomole ADH/min caused a significant increase in MABP at our experimental conditions (127±9 mm Hg in vehicle-infus ed rats and 147±9 mm Hg at 20 min of ADH infusion, n=3 and n=4 respectively, $p<0.05$). ADH dramatically decreased blood flows of 6-day-old corpora lutea of pseudopregnancy as well as of the remaining ovary. Vascular resistances were markedly increased (Table 3).

Table 3. Effect of 20 min continuous antidiuretic hormone infusion on blood flows and vascular resistances of corpus luteum, remaining ovary, kidney and spleen in the adult rat at day 6 of pseudopregnancy.

	Vehicle	ADH
Tissue blood flow (ml/min):		
Corpus luteum	0.42±0.15	0.03±0.00*
Remaining ovary	0.41±0.06	0.05±0.01*
Kidney	9.6±0.9	6.9±1.9
Spleen	1.20±0.27	0.83±0.15
Blood flow (ml/100g/min):		
Corpus luteum	2227±649	190±23*
Remaining ovary	608±116	109±20*
Kidney	575±52	384±72
Spleen	143±26	155±46
Vascular resistance:		
Corpus luteum	0.08±0.03	0.79±0.11*
Remaining ovary	0.23±0.03	1.47±0.30*
Kidney	0.23±0.03	0.41±0.08
Spleen	0.95±0.15	1.19±0.42

*=$p<0.05$ versus control as tested with the Mann Whitney's U-test.
Values are given as mean±SEM of 3 rats in the vehicle-infused group and 4 rats in the noradrenaline-infused group.

DISCUSSION

In the present study, we have shown that noradrenaline given during a 20 min infusion period, markedly decreases the vascular resistance of the ovary as a whole and also of the corpus luteum of pseudopregnancy in contrast to acute stimulation. This decrease in vascular resistance in combination with the increase in mean arterial blood pressure resulted in a marked increase in luteal as well as total ovarian blood flow. Such a decrease in vascular resistance was not seen in the other organs tested. The increase in blood flow of the remaining ovary is similar to the effect of LH, but noradrenaline is the first hormone demonstrated, that can increase the blood flow of the corpus luteum. The effect of LH/hCG on luteal blood flow is either inhibitory or none (13). The corpus luteum has also been shown to possess β-receptors although the degree of localization to blood vessels is not known. The luteal β-receptors are coupled to adenylate cyclase (15). Since a vasodilatation was seen both for the corpus luteum as well as the remaining ovary it is most likely that the initial α-effect gradually decreased leading to a dominance for a vasodilatory effect that may have been exerted via β-receptors. In favour of an effect of noradrenaline via adrenergic receptors is the fact that the non-adrenergic stimulator ADH had a vasoconstrictor effect throughout the infusion period.

The increase in blood flow of corpora lutea of pseudopregnancy by noradrenaline is due to an increased blood pressure as well as to a vasodilatation, since the MABP was increased and the luteal vascular resistance decreased. The mechanism behind the vasodilatation is at present unknown. Systemic infusion of noradrenaline can induce β-adrenergic mediated vasodilatation as has been claimed for many tissues (e.g. 8). For the ovary this may be the case, since one β_2-adrenergic agonist, fenoterol, has been shown to decrease vascular resistance of the perfused human ovary (24). Such effects, although induced by systemic infusion of noradrenaline, could be hypothesized to mimick a putative neuronal regulation of ovarian vasomotion. This explanation is, by no means unlikely, since nerve endings have been observed around ovarian blood vessels (4, 5). Furthermore, one report exists, where nerve stimulation changed ovarian blood flow (26). An alternative explanation to the vasodilatation, observed in the present study, may be that the vasodilatation is secondary to metabolic effects of noradrenaline. Noradrenaline as well as other β-adrenergic agonists can markedly increase the luteal production of cyclic AMP and progesterone during in vitro conditions (12, 20). Furthermore, stimulatory effects have been demonstrated on luteal cyclic AMP production after in vivo infusion of noradrenaline (14). Released cyclic AMP, prostaglandins, lactate as well as other metabolites could have elicited the vasodilatation. A direct effect of progesterone on luteal blood flow seems to exist (23), but progesterone is not

the sole factor, since Bruce *et al.* (2) did not find a correlation between ovarian blood flow and progesterone secretion in the pregnant rat. The observation that the blood flow of the corpus luteum of pseudopregnancy in control rats was higher at day 6 of pseudopregnancy than at day 2 or 11 is interesting, since the progesterone production and luteal blood flow is maximal at day 6 of pseudopregnancy (13). A maximal stimulation of the luteal adenylate cyclase (21) was seen during early luteal phase at a time when β-receptor concentration was maximal (15). Such an age dependent difference was not seen for noradrenaline-induced changes in luteal blood flow making metabolic vasodilatation of luteal vessels unlikely as an explanation to the increased blood flow by noradrenaline. It therefore seems most likely that if β-receptors are stimulated, they ar of a vascular origin.

Another possible mechanism behind the noradrenaline-induced vasodilatation is that the vasodilatation may be secondary to an initial vasoconstriction. An initial increase in vascular resistance is seen in many organs like the kidney and also in this type of corpus luteum (19). The initial increase in vascular resistance may have temporarily decreased the nutritive metabolic support of the corpus luteum and produced an accumulation of vasodilatory metabolites. Such an effect of noradrenaline infusion, with a rapid increase in α-receptor mediated vascular resistance followed by a vasodilatation, is an old finding e.g. for the intestine (9). The difference between the corpus luteum of pseudopregnancy and e.g. the kidney is that after a longer infusion period of noradrenaline the vascular resistance of the corpus luteum is decreased resulting in an increase of the blood flow to a level well above the control, while for the kidney the vascular resistance has returned to control levels. It is possible, that at still longer infusion times the vascular resistance may decrease in other organs as well, but the luteal vascular bed seems to be very sensitive to vasoactive substances, although with quite different effects. Our observation that an infusion of noradrenaline for 20 min apart from increasing luteal blood flow also increased the blood flow of the remaining ovary is of special interest, since a substantial amount of the remaining ovary consists of corpora lutea from earlier estrous cycles. These corpora lutea are believed to be non-functional, since in terms of progesterone production they are not active, but they do have a high blood flow (19). Thereby, our results may indicate that the increase in luteal blood flow is not secondary to an increase in luteal metabolism, but rather due to a direct dilatory effect of noradrenaline on ovarian blood vessels. However, the remaining ovary is a "multicompartment" tissue and to which extent the increased blood flow is pertainable to corpora lutea of earlier estrous cycles remains to be investigated.

Infusion of ADH for 20 min gave dramatical changes in luteal blood flow, with a 80-90% decrease in blood flow of the ovary and its luteal compartment, due to increased vascular resistance. The increase in vascular resistance for kidney and spleen was only moderate. Also, systemically administered angiotensin II has been reported to decrease ovarian blood flow (16). Thus, noradrenaline is the only vasoactive substance reported that can decrease ovarian and luteal vascular resistance resulting in an increased ovarian and luteal blood flow. Noradrenaline is a substance that can also stimulate steroidogenesis in the corpus luteum (12) in contrast to ADH, which has been reported to have no effect on luteal steroidogenesis (10).

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