The Effect of Arginine Vasotocin and Prostaglandins on Oviposition in the Domestic Fowl (*Gallus domesticus*)

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Introduction

The oviposition in birds and the parturition in mammals appear to be similar phenomena although the underlying fundamental mechanisms are not fully understood. Since the high-producing domestic hen lays an egg almost daily, it is a convenient animal for the study of such mechanisms.

Arginine vasotocin (AVT) and prostaglandins (PGs) are reported to be concerned in the mechanism of oviposition in hens. TANAKA *et al.*^{1,2)} reported a decrease in the AVT content of the neurohypophysis which coincided with oviposition. DOUGLAS *et al.*³⁾ and STURKIE *et al.*^{4,5)} measured AVT in the blood of laying hens and found that the activity of the hormone increased during oviposition. This was later confirmed by NIEZGODA *et al.*⁶⁾ NAKADA *et al.*⁷⁾ reported that a surge in AVT occurred before ovulation of the first egg (C₁) of a clutch; later TANAKA *et al.*⁸⁾ demonstrated that the circulating hormone reached a peak 55 min before C₁ ovulation. Recently, TANAKA *et al.*⁹⁾ reported that immunoreactive AVT in the plasma of hens increased 5–6 min before oviposition, reached a peak during oviposition and decreased rapidly in the following 5–6 min. The surge in plasma AVT occurred at 48 min before C₁ ovulation.

It has been demonstrated that several PGs, particularly the E series, when injected directly into the hen uterus can induce premature oviposition¹⁰⁾. Several additional lines of evidence indicate that certain PGs play a functional role in the regulation of oviposition^{11,12,13,14)}. Administration of inhibitors of PG synthesis blocks the premature, as well as spontaneous, oviposition^{15,16)} and inhibits the response to vasotocin which has been implicated in the regulation of oviposition²⁾.

The shell gland contractility displays an increasing sensitivity to AVT^{17,18)} and PGE₁¹⁹⁾ as the time of expected oviposition approaches. An increase in the concentration of PGs in the hen uterus before oviposition has also been demonstrated²⁰⁾. HERTELENDY¹⁵⁾ and RZASA²⁰⁾ suggested that the uterine-stimulating activity of neurohypophysial peptides might be mediated through uterine PGs. Recently, RZASA²¹⁾ reported that uterine homogenate from laying hens not only produced PG but also responded to AVT stimulation by an increase in PG synthesis based on the bioassay determination.

The present study was conducted to examine the effect of AVT, PGE₂ and PGF_{2α} on oviposition of hens. In addition the effect of indomethacin, an inhibitor of PG synthesis, on AVT-induced premature oviposition and the effect of AVT on immunoreactive PGE₂ pro-

duction in the uterine homogenate of hens *in vitro* were examined.

Materials and Methods

Materials. Prostaglandin $F_{2\alpha}$ THAM salt (Pronalgon F, No. 327-7) was kindly supplied from Takeda Chemical Co. (Tokyo, Japan). PGE_2 (No. p-5640) and AVT (No. V-4252) were obtained from Sigma Chemical Co. (St Louis, Missouri, U.S.A.). Indomethacin (PEP 7180) was from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan).

PGE_2 solution (1 mg/ml) was prepared in 95% ethanol and kept in the freezer; dilutions were made in 0.9% NaCl immediately before use. Solution of $PGF_{2\alpha}$ THAM salt (5 mg/ml) was diluted with 0.9% NaCl. AVT was dissolved in 0.9% NaCl shortly before use. Indomethacin was suspended in sesame oil.

Animals. White Leghorn hens which had regular clutches of 5 and 6 consecutive eggs were used. The birds were kept in individual cages, were exposed to 14 h light/24 h and provided food and water *ad libitum*.

Experiments 1 and 2. Experiments were carried out to test the effects of AVT, PGE_2 and $PGF_{2\alpha}$, injected intravenously, on oviposition of the mid-clutch egg of hens. In experiment 1, the drugs were injected at 1-4 (hard-shell egg in uterus) or 15-19 h (soft-shell egg in uterus) before the expected time of oviposition. In experiment 2, AVT or saline (0.9%) was injected 1, 3, 6 or 9 h after the intramuscular injection of indomethacin (50 mg/bird). Indomethacin had been injected at 2-3 h before the expected time of oviposition. Before the start of Experiment 2, we confirmed that the intramuscular injection of sesame oil (1 ml/bird) has no effect on normal laying of egg in the hen. The response of the hen was regarded as positive when oviposition was induced within 15 min after the injection of PGE_2 , $PGF_{2\alpha}$ or AVT. All of the drugs used in the experiments 1 and 2 were injected at the volume of 1 ml.

Experiment 3. The effect of AVT on PGE_2 production in the uterine homogenates of hens was examined *in vitro*. Ten hens were killed at 1.5 h after the oviposition of mid-clutch eggs. The uterus (10 mg) of each hens was removed and homogenized in 20 ml of TCM 199 at 0°C. One ml aliquots of the uterine homogenate either alone or with AVT (0.1 or 1.0 μ g/ml), 50 μ g/ml indomethacin, or a combination of these compounds were incubated at 41°C for 90 min under a humidified atmosphere of 95% O_2 and 5% CO_2 . After the end of incubation, the tubes containing uterine homogenate were centrifuged at 2000 g for 30 min at 4°C and the supernatants were used for the extraction of PGs.

Extraction. The supernatant of the uterine homogenate was acidified to pH 3.5 by the addition of 0.1 N HCl. Small column packed with octadecasilyl silica (C_{18} SEP-PAK, Waters Associates, Milford, MA) was used to extract PGs from the supernatant. The column was attached to a plastic syringe and washed with 2 ml of methanol, followed by 2 ml of deionized water. The acidified supernatant was then applied to the column under a slight positive pressure in which the flow rate is less than 1 ml/3 min. The column was washed with 1 ml of deionized water. The column was then eluted with 1 ml of methanol and the elute was collected in polypropylene tube. The collected elute was dried at room temperature with gentle stream of N_2 gas. The recovery of labeled PGE_2 was 96% in this procedure.

Radioimmunoassay. (RIA). Prostaglandin E₂, ¹²⁵I-RIA kit (NEK-020) was obtained from New England Nuclear Company (Boston, MA). The solution of PGE₂ (100 ng/ml) in organic solvent (acetonitrile: H₂O=9:1, pH 5.0) was diluted immediately before use by assay buffer. PGE₂ standards consist of 0.1–25 pg/tube. The assay buffer consists of 0.9% NaCl, 0.01 M EDTA, 0.3% bovine γ -globulin (Fr. II), 0.005% Triton X-100 and 0.05% sodium azide in 50 mM phosphate buffer, pH 6.8.

The specific activity of ¹²⁵I-labeled PGE₂ was 2200 Ci/mmol.

The extracted and dried sample was reconstituted with an appropriate volume of the assay buffer. Duplicate 100 μ l aliquots of appropriate standards and samples were incubated at 4°C in borosilicate RIA tubes with 100 μ l of antiserum and 100 μ l of labeled PGE₂ (15000 cpm) for 24 h. Free and bound hormones were separated by adding 1 ml of precipitating solution (16% polyethylene glycol 6000 and 0.05% sodium azide in 50 mM phosphate buffer, pH 6.8). After centrifugation at 1000 g for 30 min, precipitate was counted on an autogamma counting system (Packard Model 800 C).

Cross reaction of the PGE₂ antiserum with other compounds was as follows: PGE₁, 3.7%; 1314 Dihydro-15-keto-PGE₂, 0.4%; PGA₂, 0.4%; PGF_{1 α} , 0.03%; Thromboxane B₂, 0.02% and exhibits less than 0.01% cross-reactivity with a number of other prostaglandins including PGF_{2 α} .

Intraassay coefficient of variation was 8.0% (N=5). The minimum detectable does defined as the mass corresponding to twice the standard deviation of the zero binding, the sensitivity of the system was 0.1 pg/tube. Uterine PGE₂ values were not corrected for recovery.

Statistical analysis. The data were analyzed by ANOVA using the procedure outline in SAS statistical package (BARR *et al.*²³). Means were separated using the Duncan option of the procedure^{23,24}.

Results

All three drugs (AVT, PGE₂ and PGF_{2 α}) induced premature oviposition within a few minutes when injected 1–4 h before the expected laying time (Table 1). AVT (0.1 μ g/bird) gave 100% (8/8) successful induction. In comparison, 2 μ g/bird of PGE₂ and 1 μ g/bird of PGF_{2 α} were needed to induce 100% successful induction. An equal volume of 0.9% saline (1 ml) was without effect.

AVT (0.1 μ g/bird) failed to cause premature oviposition when injection 15–19 h before the expected laying time (Table 2). AVT (0.5 μ g/bird) was needed to cause 80% (4/5) premature oviposition which was five-times greater does of AVT used than that injected 1–4 h before the expected laying time to cause 100% premature oviposition. PGE₂ (10 μ g/bird) and PGF_{2 α} (1 μ g/bird) caused only 25% (2/8) and 40% (2/5) premature oviposition when injected 15–19 h before the expected laying time, respectively.

The effect of indomethacin pretreatment (50 mg/bird) at 2–3 h before the expected laying time on AVT-induced premature oviposition is shown in Table 3. As shown in Table 1, AVT (0.1 μ g/bird) can cause 100% premature oviposition when injected 1–4 h before the expected laying time. AVT (0.1 μ g/bird) induced 71 (5/7), 100 (6/6), 38 (5/13) and 0%

Table 1. Induction of oviposition in the hen by i.v. injection of PGE₂, PGF_{2α} and AVT (Exp. 1)^a

Drug	Dose (μg/bird)	No. of test	No. of premature oviposition ^b	Average induction time (min) ^c
PGE ₂	0.1	3	1	9.1
	0.5	6	1	11.6
	1.0	7	5	6.8±2.3
	2.0	4	4	4.7±1.3
	10.0	3	3	1.7±0.3
PGF _{2α}	0.2	5	0	—
	1.0	6	6	7.8±4.4
	2.0	7	7	2.5±0.6
	20.0	4	4	2.7±0.9
AVT	0.05	5	2	4.9±0.8
	0.1	8	8	3.2±0.7
	0.5	4	4	2.2±0.7
Saline (0.9%)	—	5	0	—

^a Drug was injected 1-4 h before expected oviposition.^b The response of the hen was regarded as positive when oviposition was induced within 15 min after injection.^c Values are mean ± s. d.Table 2. Induction of oviposition in the hen by i.v. injection of PGE₂, PGF_{2α} and AVT (Exp. 1)^a

Drug	Dose (μg/bird)	No. of test	No. of premature oviposition ^b	Average induction time (min) ^c
PGE ₂	2.0	3	0	—
	5.0	3	0	—
	10.0	8	2	4.5±1.0
PGF _{2α}	1.0	5	2	5.0±3.0
	2.0	6	4	5.5±1.4
	10.0	7	4	3.1±0.4
AVT	0.1	5	0	—
	0.5	5	4	2.5±0.6
Saline (0.9%)	—	4	0	—

^a Drug was injected 15-19 h before expected oviposition.^b The response of the hen was regarded as positive when oviposition was induced within 15 min after injection.^c Values are mean ± s. d.

(0/8) premature oviposition when injected at 1, 3, 6 and 9 h after indomethacin treatment, respectively. AVT (0.5 μg/bird) induced 67 (4/6), 67 (4/6) and 78% (7/9) premature oviposition when injected at 1, 6, and 9 h after indomethacin treatment, respectively. An equal volume of saline (0.9% NaCl) was without effect. All hens which failed to cause

Table 3. Induction of oviposition in the hen by i.v. injection of AVT following to i.m. injection of indomethacin (Exp. 2)^a

Time after injection of indomethacin	Drug	Dose ($\mu\text{g}/\text{bird}$)	No. of test	No. of premature oviposition ^b	No. of delayed oviposition	Average induction time (min) ^c	Delayed oviposition (h)
1	AVT	0.1	7	5	2	3.1 ± 0.5	14-23
1	AVT	0.5	6	4	2	1.7 ± 0.4	15-23
3	AVT	0.1	6	6	0	4.0 ± 1.4	—
3	AVT	0.5	—	—	—	—	—
6	AVT	0.1	13	5	8	5.0 ± 0.6	12-21
6	AVT	0.5	6	4	2	3.5 ± 1.5	13-22
9	AVT	0.1	8	0	8	—	11-23
9	AVT	0.5	9	7	2	4.1 ± 0.8	21-22
1	Saline (0.9%)	—	8	0	8	—	12-20
3	Saline (0.9%)	—	8	0	8	—	12-20
6	Saline (0.9%)	—	5	0	5	—	13-23
9	Saline (0.9%)	—	5	0	5	—	12-23

^a Indomethacin (50 mg/bird) was injected intramuscularly 2-3 h before expected oviposition.^b The response of the hen was regarded as positive when oviposition was induced within 15 min after the injection of AVT.^c Values are mean $\pm$ s. d.Table 4. Effects of AVT and indomethacin (IND) on immunoreactive PGE₂ production in uterine homogenate of hens (exp. 3)

Treatment	n	Production of PGE ₂ /90 min (ng/g wet wt) ^a
Control	10	108 ± 16^c
AVT (0.1 $\mu\text{g}/\text{ml}$)	10	151 ± 23^b
AVT (0.1 $\mu\text{g}/\text{ml}$) + IND (50 $\mu\text{g}/\text{ml}$)	10	57 ± 8^d
IND (50 $\mu\text{g}/\text{ml}$)	10	52 ± 8^d
AVT (1.0 $\mu\text{g}/\text{ml}$)	5	182 ± 20^a
AVT (1.0 $\mu\text{g}/\text{ml}$) + IND (50 $\mu\text{g}/\text{ml}$)	5	62 ± 4^d

^a Values are mean $\pm$ s. d., Means with different superscripts are significantly different ($P < 0.05$).

premature oviposition laid eggs 11-23 h after the expected laying time.

Basal- and AVT-stimulated synthesis and the effect of indomethacin on PGE₂ production in the uterine homogenate of hens are shown in Table 4. AVT in the absence of indomethacin stimulated PGE₂ production significantly. Both the control PGE₂ production and the AVT-stimulated production in the uterine homogenates were suppressed by indomethacin.

Discussion

The effect of various PGs on the uterus and oviduct both *in vivo* and *in vitro* has been studied extensively in animals. HERTELENDY¹⁵⁾, HERTELENDY *et al.*¹⁰⁾ and RZASA²⁰⁾ examined

the effects of PGs in the avian species and they induced premature oviposition in the Japanese quail and in the domestic hen by the administration of PGs. The present result of PGE₂- and PGF_{2 α} -induced oviposition agree with those reports.

Several authors demonstrated that the injection of oxytocin, and especially its 8-arginine analog AVT, can induce premature oviposition in hens^{2,18,20}. The present result of the AVT-induced premature oviposition agrees with those reports.

All three drugs (PGE₂, PGF_{2 α} and AVT) used in the present study were more effective in inducing oviposition when a hard-shell egg was in the uterus than when a soft-shell egg was in the uterus. This indicates that the sensitivity of the uterus to AVT rises toward the time of normal oviposition¹⁸. The similar changes in the sensitivity of the uterus to PGE₂ and PGF_{2 α} were also observed as suggested to PGE₁¹⁹.

VANE *et al.*²⁵ first suggested that the uterine-stimulating activity of the neurohypophyseal hormone, oxytocin, might be mediated through uterine PG. HERTELENDY¹⁵ showed that oxytocin-induced parturition in the term pregnant rabbits could be blocked by indomethacin, an inhibitor of PG biosynthesis. Oxytocin-induced oviposition in the Japanese quail¹⁵ and AVT-promoted contractile activity of hen uterine strips²⁰ can also be suppressed with indomethacin. This suggests that endogenous PG production is involved in the uterotonic action of these neurohypophyseal hormone in bird. This was later confirmed by RZASA²¹ who reported that PG-releasing effect of AVT is not a secondary response to uterine contraction but represents a direct effect of AVT in hens.

The high incidence (100%) of exogenous AVT-induced premature oviposition at 3 h after indomethacin treatment could be due to the increased sensitivity of uterus to AVT since this is the time very close to the expected oviposition. However, even at this time the injection of saline (0.9% NaCl) was without effect and the egg was laid 12–20 h after the expected laying time. This indicates that either the endogenous AVT surge which is known to occur before oviposition^{3,4,5,6,9} failed to induce PG synthesis due to indomethacin treatment or the surge of AVT was blocked by indomethacin treatment.

AVT (0.1 μ g/bird) failed to induce premature oviposition when injected at 9 h after indomethacin treatment but high does (0.5 μ g/bird) of AVT induced 78% (7/9) premature oviposition. This should be due to the following reasons. (1) AVT-induced PG-synthesis is blocked completely at low dose (0.1 μ g/bird) of AVT-injected birds by indomethacin but high does (0.5 μ g/bird) of AVT overcomes the block of indomethacin to induce oviposition. (2) The decreased sensitivity of uterus to AVT because this is 6–7 h after the expected laying time.

However, alternative explanation remains that the efficacy of i. m. injection of indomethacin is influenced by the rate of absorption and delivery to the site of action, hence it showed the ability to block completely the low dose of AVT (0.1 μ g/bird) at 9 h but not at 1–3 h after injection.

Our present result would suggest that the sensitivity of hen uterus to AVT, PGE₂ and PGF_{2 α} increased as the time of oviposition approaches and that the AVT acts through the enhancement of PGE₂ production in the hen uterus. However, several questions are remained to be elucidated. Some of them are: (1) Whether or not indomethacin blocks endogenous

AVT surge under certain condition. (2) Whether or not PGs have a feedback mechanism to neurohypophysis to control AVT release. (3) What is controlling the sensitivity of uterus to AVT and PGs?

TANAKA *et al.*²⁶⁾ reported an ovarian oviposition-inducing factor (OOIF), which causes premature oviposition in the ruptured follicles of hens. Thus, an additional and comprehensive study is needed before the mechanism of oviposition is fully understood.

Summary

Arginine vasotocin (AVT), prostaglandin E₂ (PGE₂) and prostaglandin F_{2α} (PGF_{2α}) induced premature oviposition when injected 1–4 h (hard-shell egg in uterus) and 15–19 h (soft-shell egg in uterus) before the expected laying time.

These drugs were more effective in inducing oviposition when a hard-shell egg was in the uterus than when a soft-shell egg was in the uterus. AVT caused an increase in immunoreactive PGE₂ production when incubated with uterine homogenate.

The present results suggest that the sensitivity of the hen uterus to AVT, PGE₂ and PGF_{2α} increases as the time of oviposition approaches and that AVT acts through the enhancement of immunoreactive PGE₂ production in the uterine tissue of hens.

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アルギニン・バゾトシンとプロスタグランジンの 鶏の放卵に及ぼす影響

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アルギニン・バゾトシン (AVT) とプロスタグランジン (PG) は鶏の放卵機序に関与していることが知られているが, AVT と PG の放卵に及ぼす相互関係についての報告は少ない。本研究では, AVT, PGE_2 , $\text{PGF}_{2\alpha}$, の放卵に及ぼす効果, AVT による誘起放卵に対するインドメタシン (PG 合成阻害剤) 前処理の効果, ならびに子宮の PG 生合成に及ぼす AVT の効果を *in vitro* で検討した。

実験 I では, C₀ 卵の推定放卵前 1—4 時間の鶏に, 実験 II では, C₀ 卵の推定放卵前 15—19 時間の鶏に, AVT, PGE_2 , $\text{PGF}_{2\alpha}$ を静脈内投与し, 放卵に及ぼす効果を調べた。実験 III では, 推定放卵前 2—3 時間の鶏にインドメタシン (50 mg/bird) を筋肉内投与し, その後 1, 3, 6, 9 時間目に AVT を静脈内投与し, AVT の誘起放卵に及ぼすインドメタシンの効果を調べた。実験 IV では, 放卵後 1.5 時間目に子宮を取り出し, TCM 199 を加えてホモゲナイズ後, 無菌的に 95% O₂, 5% CO₂

下で 1.5 時間培養した。実験区には, AVT, インドメタシンを単独で, あるいは併用して添加して培養し, 無添加区を対照区とした。培養後生産された PGE_2 量を RIA にて測定した。

以上の実験より, AVT, PGE_2 , $\text{PGF}_{2\alpha}$ はいずれも推定放卵時刻に近い程, 放卵誘起効果が高いことがわかった。インドメタシン前処理 (推定放卵前 2—3 時間) は, すべての鶏において放卵を 11—23 時間遅延させ, インドメタシン前処理の鶏に AVT を投与すると推定放卵時刻に近い時間帯に投与する程, 放卵誘起効果が高かった。AVT を子宮のホモジネイトに添加して培養すると, PGE_2 の生産量が有意に増加した。

以上の結果より, 子宮の AVT, PGE_2 , $\text{PGF}_{2\alpha}$ に対する感受性は放卵時刻が近づくにつれて上昇すること, また AVT は子宮での PG 生合成を促進することにより放卵に関与していることが示唆された。

(家禽会誌, 22, 55~63, 1985)