Original Article

P2Y₆ purinergic receptor regulates steroid synthesis and proliferation of ovarian luteal cells

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Abstract: Aim: As an important messenger, uridine 5'-diphosphate (UDP) is involved in series of physiological and pathological processes through activating P2Y₆ purinergic receptor. However, the detailed function and possible mechanism of P2Y₆ in ovarian luteal cells remain unclear. Methods: Primary murine luteal cells were isolated and cultured. CCK-8 assay was employed to analyze the cell viability after P2Y₆ agonist (UDP) and P2Y₆ selective antagonist (MRS2578) treatment. Radioimmunoassay was used to assess the progesterone and estradiol production. The expression of three essential steroidogenic enzymes, including the p450 cholesterol side-chain cleavage enzyme (CYP11A), 3β-hydroxysteroid dehydrogenase (3β-HSD) and steroidogenic acute regulatory protein (StAR) were examined by Western blotting. We also examined the ERK1/2 phosphorylation level and the expression of steroidogenic factor 1 (SF1). Results: We found that P2Y₆ was highly expressed in murine luteal cells. UDP decreased the progesterone secretion and MRS2578 rescued the effect of UDP. Further studies showed that CYP11A, 3β-HSD and StAR were regulated by UDP. UDP treatment also decreased ERK1/2 phosphorylation, concomitant with decreased expression of SF1, while MRS2578 treatment relieved the effect of UDP. Conclusions: In conclusion, this study demonstrated for the first time that UDP/P2Y₆ purinergic signaling regulated progesterone secretion by inhibiting the expression of CYP11A, 3β-HSD and StAR in luteal cells. The ERK1/2 MAPK signaling and downstream SF1 may contribute to the process.

Keywords: P2Y₆, UDP, progesterone, luteal cell

Introduction

Nucleotide receptors, also known as P2 receptors, together with P1 receptor subfamily, form the purinergic receptor family [1]. P2 receptors consist of two classes of purinergic receptors. P2X receptors belong to cationic channels and P2Y receptors are G protein-coupled receptors (GPCR) [2]. In mammals, seven different P2X subunits (P2X₁-P2X₇) and eight P2Y subtypes have been identified [3]. Eight P2Y receptors are subdivided into two distinct clusters based on different coupled G proteins: G₁-coupled receptors (P2Y₁, 2, 4, 6, 11) and G₂-coupled receptors (P2Y₁₂, 13, 14) [4]. Among them, P2Y₆ is widely expressed in diverse tissues including placenta, spleen, thymus, intestine, leukocytes, heart, liver, blood vessels, ovary, and microglial and rat aorta, spleen, stomach, intestine, lung, dorsal root ganglia, spinal cord, ovary, etc [5-9]. Extensive expression of P2Y₆ indicates it may play numerous critical roles in diverse systems.

P2Y₆ is a uridine 5'-diphosphate (UDP) preferring receptor, as UDP derivatives have higher potential in P2Y₆ activation than corresponding 5'-triposphates [10, 11]. Accumulating data showed that UDP/P2Y₆ signaling played a vital role in immune response. P2Y₆ modulated IL-8 secretion from monocytes [12, 13]. UDP/P2Y₆ signaling prevented microglia phagocytosis of viable neurons [14]. As a danger signal, UDP and P2Y₆ were found to protect mice from virus infection by increasing IFN-beta production [15]. In osteoclasts, functional P2Y₆ receptors initiated NF-kB signaling to enhance osteoclasts survival, as a result of inflammation and mechanical stimulation [16]. What’s more, P2Y₆ triggered the pressure overloaded-induced cardiac fibrosis and mediated vascular inflammation [17, 18]. These studies indicate that UDP/P2Y₆ is
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involved in a comprehensive range of physiological and pathological functions in different tissues. In the ovary, various P2 receptors have been found and proved to play indispensable roles. P2X<sub>7</sub> receptor was specifically expressed on porcine ovarian thecal cells and murine luteal cells. Its activation induced calcium-dependent cell apoptosis and decreased cell proliferation [19, 20]. Recent study showed that the P2Y<sub>6</sub> receptor was expressed in ovarian thecal cells and its activation promoted cell proliferation via triggering ERK1/2 signaling pathway [21].

The corpus luteum is a temporary but dynamic endocrine gland and originates from remaining granulosa and theca cells of the ovulated follicle. The main function of corpus luteum is secreting large amounts of progesterone, which plays a central role in regulating estrous cycle and the establishment and maintenance of pregnancy [22]. Luteinization of ovulated follicle is the most sophisticated event among mammalian reproduction, including the formation, maintenance and regression. Multiple factors, including hormones, cytokines, immune cells and nerves tightly regulate these processes [23, 24]. In this study, we found that P2Y<sub>6</sub> was highly expressed in murine luteal cells. However, the physiological role of P2Y<sub>6</sub> receptor in luteal cells is not clear. We will explore the role of UDP/P2Y<sub>6</sub> signaling in murine luteal cells and possible mechanisms.

**Methods and materials**

Steroidogenic acute regulatory protein (Star; D10H12), phospho-p44/42 MAPK (Erk1/2) and DNase I, UDP, and MRS2578, a P2Y<sub>6</sub> receptor-selective antagonist, were purchased from Sigma (St. Louis, MO, USA). GoScript Reverse Transcription System (A5001) was from Promega (Madison, WI, USA). Trizol reagent was acquired from Invitrogen (Carlsbad, CA, USA). DNA polymerase was obtained from NEB (Ipswich, MA, USA). Cell counting kit-8 was purchased from Beyotime (Shanghai, China). Collagenase (Type I), DNase I, UDP, and MRS2578, a P2Y<sub>6</sub> receptor-selective antagonist, were ordered from Sigma (St. Louis, MO, USA). GoScript Reverse Transcription System (A5001) was from Promega (Madison, WI, USA). Trizol reagent was acquired from Invitrogen (Carlsbad, CA, USA). DNA polymerase was obtained from NEB (Ipswich, MA, USA). Cell counting kit-8 was purchased from Beyotime (Shanghai, China).

**Animals and treatments**

Immature Kunming mice (26 days old) were purchased from the Animal Facility of Nanchang University and housed under a temperature and light controlled conditions with free access to water and food. The experimental protocols were approved by the ethical committee of Nanchang University. The mice were injected intraperitoneally with 36 IU of pregnant mare's serum gonadotrophin (PMSG; NingBo Biological Technology, Zhejiang, China) to induce follicular maturation. 72 hours later, they were treated with 36 IU human chorionic gonadotropin (hCG; NingBo Biological Technology, Zhejiang, China) to induce ovulation and luteinization, as previously described, with a slightly modification [25]. Ovaries were collected 7 days after hCG administration.

**Luteal cell culture**

The isolation of luteal cells from luteinized ovaries was performed as described in previous studies with slight modification [20, 26]. Briefly, fat and capsule tissue was removed from the luteinized ovaries. After mechanical dissection,

| Table 1. Oligonucleotides used for reverse transcription PCR |
|----------------|-----------------|-----------------|-----------------|
| Gene       | Gene bank number | Sense and antisense primer                        | Product size (bp) |
| P2Y<sub>1</sub> | NM008772.5      | 5'-TGGCGTGGTGTAACCCCTCAAGTCTCGG-3'     | 557             |
| P2Y<sub>2</sub> | NM008773.4      | 5'-CTGCCAGGACCCGTGCTCCTTAATT-3'     | 341             |
| P2Y<sub>4</sub> | NM020621.4      | 5'-ACTGGAACCATAGGTGTCCTCTC-3'      | 558             |
| P2Y<sub>6</sub> | XM011241739.2   | 5'-AGCCCAACCATCTCTGCT-3'       | 322             |
| P2Y<sub>12</sub> | NM027571.3     | 5'-CCATGAGCCGTACCTCAG-3'       | 330             |
| P2Y<sub>13</sub> | NM0288008.3    | 5'-CTATGAGACGTATGTTGCTGAT-3'    | 378             |
| P2Y<sub>14</sub> | NM1332004.0     | 5'-CCCTGCTGTCGCCAAACAT-3'      | 336             |
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Figure 1. Expression profiles of P2Y purinergic receptors in murine luteal cells. Expression level of P2Y\textsubscript{1}, P2Y\textsubscript{2}, P2Y\textsubscript{4}, P2Y\textsubscript{6}, P2Y\textsubscript{12}, P2Y\textsubscript{13} and P2Y\textsubscript{14} receptors was examined by RT-PCR. Amplification products were electrophoresed on 2% agarose gel and visualized by GoldView staining. Left lane shows DNA markers. Amplicon length is indicated in base pairs (bp) on the top.

Ovaries were incubated in medium containing 1 mg/mL collagenase, 0.025% trypsin, and 0.02 mg/mL DNase I for 5 minutes at 37°C. The digested suspension was filtered through 75 μm strainers in order to remove debris and centrifuged at 500 g for 5 minutes. Following two washes, the cells were seeded in Dulbecco’s Modified Eagle Media: Nutrient Mixture F-12 (DMEM/F12) culture medium, supplemented with 5% fetal bovine serum (FBS), 100 IU/mL penicillin and 100 μg/mL streptomycin sulfate and cultured overnight for adhesion. After this period the cells were cultured only in fresh medium (Control) or in fresh medium with UDP, MRS2578 or UDP + MRS2578, as described below.

Cell viability assay

Luteal cells were digested with trypsin and seeded in 96-well plates at 5 × 10\textsuperscript{3} cells per well and incubated in fresh medium with 1 μM UDP, 10 μM UDP and 100 μM UDP or 1 nM MRS2578, 10 nM MRS2578, 100 nM MRS2578, 1 μM MRS2578 and 10 μM MRS2578 or 100 μM UDP, 1 μM MRS2578 and 100 μM UDP + 1 μM MRS2578. 48 hours later, cell viability assays were performed by using cell counting kit-8 (CCK-8). CCK-8 reagent (10 μl) was added to each well of 96-well plate and incubated for 2 hours. Then the absorbance at 450 nm of reduced WST-8 (2-(2-methoxy-4-nitrophenoxy)-3-(4-nitrophenyl)-5-(2,4-disulfo-phenyl)-2H-tetrazolium), was recorded using an enzyme-linked immunosorbent assay plate reader.

Hormone measurements

Luteal cells were cultured in fresh medium and treated with 100 μM UDP, 1 μM MRS2578 or 100 μM UDP + 1 μM MRS2578. After 48 hours, the supernatant of media was harvested and stored at -80°C. The progesterone and estradiol values were measured with a commercial radioimmunoassay kit at a commercial laboratory (Beijing Sino-uk institute of Biological Technology). The intra- and inter-assay coefficients of variation were less than 10%. The cross-reactivity with other peptides and steroid hormones in these kits did not exceed 4%. The sensitivity of the progesterone and estradiol were 0.25 ng/mL and 2 pg/mL, respectively.

Reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA was isolated from luteal cells using Trizol Reagent. 2 μg total RNA was used to synthesize cDNA by reverse transcriptase. The cDNA was used to amplify P2Y\textsubscript{1}, P2Y\textsubscript{2}, P2Y\textsubscript{4}, P2Y\textsubscript{6}, P2Y\textsubscript{12}, P2Y\textsubscript{13} and P2Y\textsubscript{14} fragments. PCR was performed in 25 μl reaction volume which contained template cDNA, 0.5 U Phusion High-Fidelity DNA Polymerase, 200 μM dNTPs, forward and reverse primers 1 μM, Phusion High-Fidelity buffer and nuclease-free water. Following denaturation at 98°C for 30 sec, amplification was carried out using 32 cycles of 98°C for 10 sec, 60°C for 20 sec and 72°C for 20 sec, finished at 72°C for 10 min. The sequences for specific primers were listed in Table 1. After amplification reactions, samples were run on 2% agarose gel, stained with GoldView and visualized by ChemiDoc XRS + Molecular Imager (Bio-Rad).

Western blotting

Luteal cells were lysed in radioimmune precipitation assay (RIPA) lysis buffer containing com-
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Figure 2. The influence of P2Y<sub>6</sub> purinergic signaling on murine luteal cells viability. A: Cell viability assay for cultured luteal cells with fresh medium (control), 1 μM UDP, 10 μM UDP and 100 μM UDP treatment after 48 hours of culture. B: Cell viability assay for cultured luteal cells with fresh medium (control), 1 nM MRS2578, 10 nM MRS2578, 100 nM MRS2578, 1 μM MRS2578 and 10 μM MRS2578 treatment after 48 hours of culture. C: Cell viability assay for cultured luteal cells with fresh medium (control), 100 μM UDP, 1 μM MRS2578 and 100 μM UDP + 1 μM MRS2578 treatment after 48 hours of culture. D: From a to d, primary luteal cells treated with fresh medium (control), 100 μM UDP, 1 μM MRS2578 and 100 μM UDP + 1 μM MRS2578 after 48 hours of culture. Bar graphs shown mean ± standard error of mean (S.E.M.) from three independent experiments. *P<0.05.

complete mini protease-inhibitor cocktail tablets (Roche, Mannheim, Germany). The total protein concentration in the supernatants was estimated by using a Bradford assay (Bio-Rad Laboratories, Hercules, CA, USA). Samples were electrophoresed under reducing conditions in 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gels and transferred to nitrocellulose membranes. The membrane was blocked with 5% skim milk and incubated overnight with primary antibody at 4°C. Then the membrane was washed with Tris-buffered saline with Tween-20 (TBST, pH 8.0) and incubated with horseradish peroxidase (HRP)-labelled secondary antibody for 1 h at room temperature. Enhanced chemiluminescence (ECL) Western blotting substrate was utilized to visualize the target bands and the intensity of the bands was quantified by densitometry (BIO-RAD Image Lab). The background was subtracted, then semi-quantitative examination of relative protein expression abundance was carried out by normalizing to the amount of β-actin. The following antibody dilutions were used: anti-StAR (1:1000), anti-3β-HSD (1:300), anti-CYP11A (1:400), anti-p-ERK1/2 (1:1000), anti-ERK1/2 (1:1000) anti-SF1 (1:400) and anti-β-actin (1:1500).

Statistical analysis

All statistical analyses were performed using GraphPad Prism v6.01 (GraphPad Software Inc., San Diego, CA, USA). Data are presented as the mean and standard error of the mean (S.E.M). One-way ANOVA followed by a least-significant-difference test was used for statistically comparisons among multiple groups. A p value less than 0.05 was deemed as statistically significant.

Results

P2Y<sub>6</sub> receptor was highly expressed in murine luteal cells

We examined the expression of seven P2Y receptor transcripts including G<sub>q</sub>-coupled P2-
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Y$_1$R, P2Y$_2$R, P2Y$_4$R and P2Y$_6$R, as well as G$_i$-coupled P2Y$_{12}$R, P2Y$_{13}$R and P2Y$_{14}$R [3]. RNA from luteal cells was reverse transcribed and then PCR was carried out with specific oligonucleotides (Table 1) for each receptor subtype. As shown in Figure 1, P2Y$_1$, P2Y$_2$, P2Y$_6$, P2Y$_{12}$, P2Y$_{13}$ and P2Y$_{14}$ receptors were expressed in murine luteal cells. Compared with other members of P2Y, P2Y$_6$ was highly expressed in murine luteal cells.

UDP increases the viability of murine luteal cells

To investigate the function of P2Y$_6$ receptor in luteal cells, we treated luteal cells with P2Y$_6$ receptor-selective agonist (UDP) and antagonist (MRS2578). CCK8 assay was performed to observe the luteal cell viability. As shown in Figure 2A, UDP increased the viability of luteal cell in a dose-dependent manner. However, different concentration of MRS2578 had no obvious effect on the luteal cell viability (Figure 2B). MRS2578 significantly blocked the effect of 100 μM UDP on luteal cell viability (Figure 2C). In the meanwhile, increased viable primary luteal cell number was observed after treated with 100 μM UDP (Figure 2D).

UDP inhibited progesterone secretion

To study the possible effect of P2Y$_6$ purinergic signaling on steroidogenesis, we cultured primary murine luteal cells and harvested the supernatant of media to examine the progesterone and estradiol. As shown in Figure 3A, UDP treatment decreased the progesterone secretion. MRS2578 had no obvious effect on progesterone secretion. The decreased progesterone level induced by UDP was rescued by MRS2578. Neither UDP nor MRS2578 treatment altered estradiol secretion (Figure 3B).

UDP decreased CYP11A, 3β-HSD and StAR expression

To investigate the possible mechanism of UDP on progesterone secretion, we examined the expression of steroidogenic-related enzymes including CYP11A, 3β-HSD and StAR by Western blot. CYP11A, 3β-HSD and StAR control the rate limiting steps during steroidogenesis [25]. β-actin was used as the internal reference for normalization. The results indicated that the expression of CYP11A, 3β-HSD and StAR was decreased after UDP treatment, as shown in Figure 4A-C, respectively. CYP11A, 3β-HSD and StAR had no obvious change after treated with MRS2578. 3β-HSD and StAR returned to normal level in UDP + MRS2578 group.

UDP inhibited the ERK1/2 MAPK signaling pathway

Accumulating evidences showed that UDP/P2Y$_6$ system performed their function mainly through ERK1/2 signaling pathway [21, 27]. We
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![Figure 4](image)

**Figure 4.** P2Y\textsubscript{6} purinergic signaling regulates steroidogenic enzymes in murine luteal cells. (A) CYP11A, (B) 3β-HSD and (C) StAR protein expression level in luteal cells after fresh medium (control), 100 μM UDP, 1 μM MRS2578 and 100 μM UDP + 1 μM MRS2578 treatment. (D) Representative Western blots of CYP11A, 3β-HSD, StAR and β-actin. β-actin serves as a loading control. Values represent the mean ± S.E.M. were from three independent experiments. *P<0.05. StAR, steroidogenic acute regulatory protein; 3β-HSD, 3β-hydroxysteroid dehydrogenase.

also examined the change of ERK1/2 signaling pathway by Western blot. As shown in Figure 5, compared with control group, UDP inhibited the p-ERK1/2 protein expression level. MRS2578 reserved the effect of UDP on phosphorylated ERK1/2 in murine luteal cells.

**Discussion**

The P2Y\textsubscript{6} purinergic receptor is wildly expressed innumerous cell types. It’s involved in massive physiological and pathological processes by regulating cell proliferation, survival, cytokines secretion, phagocytosis and etc [13, 16, 29, 30]. In the ovary, P2Y\textsubscript{6} signaling was demonstrated to regulate the theca cell proliferation [21]. Whereas, the role of P2Y\textsubscript{6} purinergic signaling in murine luteal cells has not yet been elucidated. In this study, we found that P2Y\textsubscript{6} receptor was highly expressed in murine luteal cells.

The main function of corpus luteum is to synthesis and secret steroid hormones, mainly progesterone. The progesterone is essential for...
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Figure 5. P2Y<sub>6</sub> purinergic signaling regulates ERK1/2 phosphorylation in murine luteal cells. (A) Western blotting detection of phosphorylated ERK1/2 after fresh medium (control), 100 μM UDP, 1 μM MRS2578 and 100 μM UDP + 1 μM MRS2578 treatment. B: Densitometric analysis results of phospho-ERK1/2 to total ERK1/2. Data are expressed as means ± S.E.M and bar graph in (B) is representative of three independent experiments. *P<0.05.

Figure 6. UDP/P2Y<sub>6</sub> signaling regulates SF1 in murine luteal cells. (A) Western blotting detection of SF1 after fresh medium (control), 100 μM UDP, 1 μM MRS2578 and 100 μM UDP + 1 μM MRS2578 treatment. (B) Densitometric analysis results of SF1 to β-actin. β-actin serves as a loading control. Total ERK1/2 serves as a loading control. Data are expressed as means ± S.E.M and bar graph in (B) is representative of three independent experiments. *P<0.05.

We found that UDP, an agonist of P2Y<sub>6</sub>, decreased the progesterone secretion and had no obvious effect on estradiol. To confirm the role of P2Y<sub>6</sub> purinergic signaling, MRS25678, a specific antagonist, was employed in this work. MRS2578 completely rescued the influence of UDP on progesterone secretion. These data implied that UDP/P2Y<sub>6</sub> signaling played a vital role in regulating progesterone synthesis in murine luteal cells.

Progesterone synthesis depends on three key enzymes including CYP11A, 3β-HSD and StAR. StAR mediates the translocation of intracellular cholesterol into inner membrane of mitochondria [32]. CYP11A, an inner membrane bound enzyme, cleaves the side-chain of cholesterol and converts it into pregnenolone [33]. 3β-HSD ultimately catalyses the reaction from pregnenolone to progesterone [34]. We show that the expression of CYP11A, 3β-HSD and StAR protein was inhibited after treatment with UDP. MRS2578 had no effect on these three key enzymes, but reversed the inhibition effect of UDP. These results suggested that UDP/P2Y<sub>6</sub> signaling affected progesterone secretion through regulating CYP11A, 3β-HSD and StAR.
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SF1 belongs to nuclear receptor 5A (NR5A) family and plays a pivotal role in the transcriptional regulation of P450scc, 3β-HSD and StAR [28]. Studies showed that ERK signaling influenced the steroid hormone synthesis through regulating SF1 [42, 43]. Our results showed that UDP decreased the SF1 expression. However, MRS2578 partially relieved the effect of UDP/P2Y<sub>6</sub> on SF1, indicating that SF1 was one possible mediator between p-ERK1/2 and steroidogenic enzymes.

Nucleotides are mainly intracellular distribution, however, they can also be released under either physiological or pathological conditions. Extracellular nucleotides mainly act as paracrine factors by binding P2 purinergic receptors on plasma membrane [29]. Massive studies showed that the purinergic signaling regulated the cellular physiology in different ovarian cells types including the oocytes, granulosa cells, theca cells, luteal cells and the ovarian surface epithelium [44]. In previous study, we reported that P2X<sub>7</sub> modulated the steroid synthesis and proliferation of murine luteal cells [20]. In this study, we showed that P2Y<sub>6</sub> regulated progesterone secretion by inhibiting CYP11A, 3β-HSD and StAR expression in murine luteal cells. The p-ERK1/2 and downstream transcription factor-SF1 were possible links between UDP and steroidogenesis (Figure 7). What’s more, we also presented that P2Y<sub>6</sub> participated in regulating proliferation of luteal cells, but the detailed mechanism needs further exploration.

In summary, this study demonstrated for the first time that UDP/P2Y<sub>6</sub> purinergic signaling regulated progesterone secretion by inhibiting the expression of CYP11A, 3β-HSD and StAR in luteal cells. The ERK1/2 signaling and downstream SF1 may contribute to the process. This study improved our understanding on the regul-
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Purinergic signaling plays a vital role in the corpus luteum. Luteal phase insufficiency is one of the major causes of female infertility. Nucleotides can be released from the sympathetic nerve ending and influence the function of corpus luteum. Therefore, exploring the function of purinergic signaling in luteal cells and purinergic abnormality in corpus luteum have implications for diagnosis and treatment for luteal phase insufficiency of luteal phase defect and other diseases related to corpus luteum development.

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Disclosure of conflict of interest

None.

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