ISP-35-1  The suppressive effect of immune stress on LH secretion is absent in the early neonatal period in rats

Tokushima University
Munkhsaikhan Munkhzzaya, Toshiya Matsuzaki, Takeshi Iwasa, Altankhuu Tungalagsuvd, Mayila Yiliyasi, Minoru Irahara

[Objective] Some physiological functions display weak responses to stress in the early neonatal period: i.e., they exhibit stress hyporesponsese periods (SHRP). In this study, we evaluated whether gonadotropin regulatory factors exhibit SHRP in rats. [Methods] Rats were intraperitoneally injected with lipopolysaccharide (100 µg/kg) (LPS group) or saline (control group) on postnatal day (PND) 5, 10, 15 or 25. The serum LH concentrations and hypothalamic mRNA levels of pro-inflammatory cytokines were measured at 2 h after the injection. [Results] The serum LH concentration of the LPS group was lower than that of the control group at PND25 in both sexes, but such difference was not seen at PND5, 10, or 15 in either sex. In both sexes, the TNFα and IL-6 mRNA expression levels of the LPS group were higher than those of the control group at PND25, but not at PND5 or 10. The IL-1β mRNA expression level of the LPS group was higher than that of the control group at all time points. [Conclusion] These findings suggest that gonadotropin regulatory factors exhibit SHRP. The HPG might become responsive to immune stress between PND15 and 25, which could be related to enhanced hypothalamic cytokine expression. The avoidance of infectious stress during the early neonatal period might be important for normal development of the HPG axis.

ISP-35-2  Difference in myeloperoxidase between women with and without amenorrhea

Kanazawa Medical University
Takeo Shibata, Jinichi Sakamoto, Yasuhiro Osaka, Natsuko Neyatani, Hiroaki Takagi, Toshiyuki Sasagawa

[Objective] Myeloperoxidase is one of the enzymes derived from neutrophil, and produces reactive oxygen species to kill bacteria. Myeloperoxidase activity in female reproductive cycle was investigated to know association between inflammation and ovulation. [Methods] Blood samples were collected from 71 women aged 40 or younger to examine myeloperoxidase activity in neutrophil. The samples were from the women with (1) amenorrhea (amenorrhea group) and (2) with normal menstrual cycle (normal group) in state of (i) menstrual: (ii) early follicular: (iii) late follicular: (iv) ovulatory: and (v) luteal phase. This study was conducted using a stock data of myeloperoxidase in blood samples in the clinical laboratory after being approved by the Ethics Review Board in our institute. [Results] Myeloperoxidase index in normal group was 3.8±3.5 (SD), and that was about 7.0 fold higher than that of amenorrhea group (-0.6±6.4) (P=0.025, Welch’s t-test). Myeloperoxidase was the highest in the ovulatory phase (5.1±2.8), but it did not significantly differ to those of other phases within normal group (P=0.352, ANOVA). [Conclusion] Myeloperoxidase activity in neutrophil was highest in the ovulatory phase, suggesting that presence of inflammation is important in ovulation, although further research is needed to clarify it.

ISP-35-3  PAI-1 in granulosa cells is suppressed directly by statin and indirectly by suppressing TGF-β and TNF-α in mononuclear cells by insulin sensitizing drugs: a new therapy for PCOS

University of Toyama1, The University of Tokyo2, University of Nagoya3
Osamu Yoshino1, Ikumi Akiyama2, Akira Iwase2, Yutaka Osuga2, Shigeru Saito1

[Objective] Plasminogen activator inhibitor (PAI)-1 is elevated with polycystic ovary syndrome (PCOS). The regulation of PAI-1 in granulosa cells (GC) was examined using human GC cell line (HGrCl). [Methods] the protocol was approved by the institute. Ovarian sections were used for immunohistochemistry. Peritoneal fluid mononuclear cells (PFMC) were obtained from ovarian tumor patients. HGrCl were cultured with TGF-β (1 ng/ml) and/or TNF-α (5 ng/ml), and PFMC were treated with LPS (1 µg/ml) with insulin-sensitizing drugs (metformin, pioglitazone, and rosiglitazone). The mRNA levels were measured by quantitative PCR. PAI-1 activity in HGrCl supernatant was measured. [Results] Little expression of PAI-1 in GC in normal ovaries whereas GC of PCOS exhibited distinct expression in vivo. In HGrCl, with TGF-β or TNF-α, PAI-1 mRNA levels were 10-fold or 5-fold higher than control, respectively (P<0.01). PAI-1 activity had same tendency as mRNA levels. Simultaneous stimuli of TGF-β and TNF-α induced PAI-1 levels synergistically, which was suppressed with p38 MAPK inhibitor, ALK-5 inhibitor or simvastatin (P<0.01). Insulin sensitizing drugs suppressed LPS-induced TGF-β and TNF-α mRNA levels in PFMC (P<0.01). [Conclusion] We firstly found statin and insulin sensitizing agents provide a therapy for PCOS by down regulation of PAI-1 in GC and down regulation of TGF-β and TNF-α in PFMC, respectively.