ADIPONECTIN (APN), a hormone secreted by white adipose tissue (WAT), plays an important role in energy homeostasis as it is involved in the regulation of glucose and fatty acid metabolism in peripheral and central tissues, such as the liver, muscles, and hypothalamus [1-4]. There are two types of APN receptor, AdipoR1 and AdipoR2, and they are expressed in various tissues. In peripheral tissues, AdipoR1 is abundantly expressed in muscles, while AdipoR2 predominates in the liver [5]. In addition, APN acts as a major protective factor against metabolic and cardiovascular conditions associated with obesity in peripheral tissues [6]. As for central tissues, in rats AdipoR1 is ubiquitously expressed in the brain, whereas AdipoR2 expression is limited to specific regions such as the hypothalamus [1]. Furthermore, APN stimulates food intake and decreased energy expenditure via AMP-activated protein kinase (AMPK) in the hypothalamus [4].

It has also been established that APN plays an important role in the regulation of chronic tissue inflammation [7]. In addition, several studies have shown that APN acts as a protective factor against acute inflammatory conditions, such as sepsis; however, the results of these studies are slightly controversial. Critically ill patients exhibit lower serum APN levels than healthy individuals, and an inverse correlation between serum APN and C-reactive protein levels has been detected in critically ill patients [8]. On the other hand, increased serum APN levels are associated with mortality in patients that suffer respiratory failure [9]. In polymicrobial- or lipopolysaccharide (LPS)-induced septic conditions, APN knockout (KO) and obese APN-deficient rodents display significantly higher mortality rates than wild-type (WT) controls [10-13]. Similarly, it was found that polymicrobial-induced sepsis caused worse hepatic injuries in APN KO mice than in the WT
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controls [14]. Furthermore, it has been reported that APN attenuates the production of inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 [15, 16], and that APN prevents LPS-induced hepatic injury by inhibiting the synthesis of TNF-α [17]. Taking these results together, it is suggested that APN protects against sepsis- and critical illness-induced mortality and tissue injury by attenuating inflammatory cytokine production.

As noted above, the pathophysiological roles of APN in inflammatory responses have gradually been elucidated. Although some studies have detected alterations in endogenous APN and AdipoR expression levels under septic conditions, the results of these studies are contradictory. For example, whilst some reports have shown that serum APN levels are decreased by LPS- or cecal ligation and puncture (CLP)-induced sepsis in WT mice and rats [10, 11, 18], another study found that the serum APN level was not affected by CLP-induced sepsis in WT mice [12]. In addition, the injection of a septic dose of LPS into lean male rats did not affect their visceral WAT APN mRNA expression. The same study reported that the injection of LPS resulted in the downregulation of hepatic AdipoR2, but not AdipoR1, mRNA expression; however, to the best of our knowledge this is the only report to describe this finding [11]. Male rodents were used as experimental models in these studies, and the changes in the APN and AdipoR expression levels of female rats induced under septic conditions have not been evaluated. Furthermore, the changes in hypothalamic AdipoR and subcutaneous APN mRNA levels induced under septic conditions also remain to be investigated. As it has been suggested that basal adiponectin levels exhibit a certain degree of sexual dimorphism [19], we speculate that the changes in the expression levels of adiponectin and its receptors induced in response to acute inflammatory conditions might also differ between the sexes.

Accordingly, the present study evaluated the changes in APN and AdipoR expression at the peripheral and central levels; i.e., their serum, WAT, hepatic, and hypothalamic levels, under LPS-induced septic conditions in female rats. Both gonadal-intact and ovariectomized (OVX) rats were used because it has been suggested that gonadal steroids might affect the serum APN levels of female rodents [19, 20]. In addition, as APN has been reported to suppress the serum and hepatic concentrations of IL-6 and TNF-α, their serum, hepatic, and hypothalamic levels were also measured. The LPS-induced changes of APN and AdipoR at serum, WAT and liver were also evaluated in male rats because the changing patterns of these factors were different between OVX and gonadal-intact female rats.

Materials and Methods

Animals and treatments

Sprague–Dawley rats (Charles River Japan, Tokyo, Japan) were purchased and housed in a room under controlled light (12 h light:12 h darkness; lights on at 0800 and off at 2000) and temperature (24°C) conditions. In total, 58 rats (45 females and 13 males) were used in this study. All animal experiments were conducted in accordance with the ethical standards of the institutional Animal Care and Use Committee of the University of Tokushima. All surgical procedures were carried out under sodium pentobarbital-induced anesthesia (60–80 mg/kg; intraperitoneal, i.p.). At 10 weeks of age, 23 female rats were ovariectomized bilaterally (OVX), and 22 females underwent sham surgery (Sham). After 6–7 weeks’ recovery, the female rats were considered to be ready for the study. In separate experiment, gonadal intact male rats at 14 weeks of age were used. Immune stress was induced via the i.p. injection of a septic dose (5 mg/kg) of LPS (0111:B4; Sigma, St. Louis, MO, USA). The LPS was dissolved in sterile saline, and the injection volume did not exceed 0.3 ml. The rats were housed individually for several days to allow them to acclimate to their conditions before they were used in each experiment.

Effects of LPS injection on the circulating levels of adiponectin and cytokines in female rats

The rats in the Sham and OVX groups were subdivided into LPS (5 mg/kg)-injected and saline-injected groups. In the LPS-injected groups, tissue samples were collected at 6 h and 24 h after the LPS injection. These time-points for sampling were determined according to the BT profile, which was initiated 6 h after LPS injection, and then the plateau phase was continued until 36 h after LPS injection under same experimental protocol [28]. In addition, our previous studies indicated that responses of some central and/or peripheral inflammatory factors to high-dose LPS would peak around 6 to 12 h after injection [29].

The data for the saline-injected groups are shown
as the data for 0 h. The rats were deeply anesthetized with sodium pentobarbital, and their blood was taken from the left cardiac ventricle. Then, the rats were perfused with phosphate buffered saline via the left cardiac ventricle. The whole brain, visceral (parametrial) and subcutaneous (inguinal) WAT, and liver were collected after the perfusion procedure. Serum was obtained by centrifugation and stored at −20°C. The brain tissue and parametrial WAT were stored at −80°C and used for the subsequent experiments. The serum levels of adiponectin, TNF-α, and IL-6 were measured in duplicate using enzyme-linked immunosorbent assays (ELISA) (R&D Systems, Minneapolis, MN, USA).

Effects of LPS injection on the mRNA expression levels of adiponectin, adiponectin receptors, and cytokines in the hypothalamus, white adipose tissue, and liver in female rats

The whole brain, visceral and subcutaneous WAT, and liver were collected as described above. Hypothalamic explants were dissected from the frozen brain tissue using the following method. Brain sections were dissected via an anterior coronal cut at 2 mm anterior from the optic chiasm and a posterior coronal cut at the posterior border of the mammillary bodies. Subsequently, these tissue blocks were subjected to two parasagittal cuts along the hypothalamic fissures and a dorsal cut at 2.5 mm from the ventral surface. Total RNA was isolated from the hypothalamus and WAT using a TRIzol reagent kit (Invitrogen, Carlsbad, CA, USA) and an RNeasy mini kit (Qiagen, Hilden, Germany). cDNA was synthesized with oligo (deoxypthymidine) primers at 50°C using the SuperScript III first-strand synthesis system for the real-time polymerase chain reaction (RT-PCR) (Invitrogen). Real-time PCR analysis was performed using the StepOnePlus™ real-time PCR system (PE Applied Biosystems, Foster City, CA, USA) and SYBR green. Standard curves, which were generated by serially diluting an abundant sample 4 times, were used for the relative quantification of the expression levels of adiponectin (WAT), AdipoR1 and AdipoR2 (hypothalamus and liver), and TNF-α and IL-6 (hypothalamus and liver). Each expression level was normalized to the mRNA expression level of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) or 18s RNA. The mean expression level of each molecule at 0 h (saline-injected group) in the Sham group was defined as 1.0. Dissociation curve analysis was also performed for each gene at the end of the PCR. Each amplicon generated a single peak. The forward and reverse primers used were as follows: adiponectin (forward: 5’ – GGG AGA CGC AGG TGT TCT TG - 3’, reverse: 5’ – CGC TGA ATG CTG AGT AGA ACA TG - 3’); AdipoR1 (forward: 5’ – CTT CTA CTG CTC CCC ACA GC - 3’, reverse: 5’ – GAC AAA GCC CTC AGC GAT AG - 3’); AdipoR2 (forward: 5’ – ATG TTT GCC ACC CCT CAG TA - 3’, reverse: 5’ – AGC CTA TCT GCC CTA TGG T - 3’); TNF-α (forward: 5’ - AGC CCT GGT ATG AGC CCA TGT A - 3’, reverse: 5’ - CCG GAC TCC GTG ATG TCT AAG T - 3’); IL-6 (forward: 5’ - GCC ACC CCT CAG TAC ACC A - 3’, reverse: 5’ - GAT GTG GAT TTG CCT TCT CCT TCC ACC CCC AAC AAC TTG TC - 3’); GAPDH (forward: 5’ - GAC GGA CCA GAG CGA AAG C - 3’, reverse: 5’ - CGC TCC TGG AAG ATG GTG ATG AGC TCA AGG TCT CAG TGC TC - 3’, forward: 5’ - TTT GGT TTT GGT TCT TCT AGG GTT CTT CCT CTT CCT TAG CC - 3’); GADPH (forward: 5’ - ATG GCA CAG TCA AGG CTG AGA - 3’, reverse: 5’ - GTC TCC TGG AGG AGT GTG ATG AT - 3’); and 18s RNA (forward: 5’ - GAC GGA CCA GAG CGA AAG C - 3’, reverse: 5’ - AAC CTC CGA CCT TGG TAC CGA AGG AAG C - 3’).

Effects of LPS injection on the mRNA expression levels of adiponectin, adiponectin receptors, and cytokines in the hypothalamus, white adipose tissue, and liver in male rats

The serum, visceral and subcutaneous WAT, and liver were collected as described above. Serum adiponectin levels, adiponectin mRNA levels in WAT, and hepatic AdipoR1 and AdipoR2 mRNA levels were measured as noted above.

Statistical Analyses

Data analysis was performed using one-way ANOVA (for intra-group comparisons) followed by Dunnett’s test. The Student’s unpaired t-test or the Mann-Whitney U-test were used to confirm the significance of differences between the Sham and OVX groups. Differences were considered significant when \( P < 0.05 \). Data are expressed as mean ± SEM values.
Results

Effects of LPS injection on the circulating levels of adiponectin and cytokines in female rats

The rats in the OVX group (352.4 ± 3.2 g) were significantly heavier than those in the Sham group (306.2 ± 4.3 g). In addition, the uterine weight of the OVX group (197.0 ± 19.0 mg) was significantly lower than that of the Sham group (594.1 ± 33.3 mg), indicating that the OVX surgery successfully reduced the OVX rats’ estrogen levels. The injection of LPS did not affect the serum adiponectin levels of the Sham (one-way ANOVA; *P* = 0.15, F (3,52) = 1.45) or OVX group (one-way ANOVA; *P* = 0.15, F (3,47) = 2.11) (Fig. 1). However, the serum adiponectin levels of the OVX group were significantly higher than those of the Sham group at all time points (0 h (saline), 6 h, and 24 h after the LPS injection). The serum TNF-α and IL-6 levels detected at 0 h and 24 h after the LPS injection were below the sensitivity levels of the ELISA kits in both groups. However, the TNF-α, but not the IL-6, levels of the Sham group were significantly higher than those of the OVX group at 6 h after the LPS injection.

Effects of LPS injection on adiponectin mRNA expression in white adipose tissue in female rats

LPS injection increased adiponectin mRNA expression in visceral WAT in both the Sham (one-way ANOVA; *P* = 0.02, F (3,49) = 5.06) and OVX groups (one-way ANOVA; *P* < 0.01, F (3,47) = 15.3) (Fig. 2), but the visceral WAT adiponectin mRNA levels of the two groups did not differ significantly at any time point.

In addition, LPS injection increased adiponectin mRNA expression in subcutaneous WAT in the OVX group (one-way ANOVA; *P* < 0.01, F (3,47) = 12.7), but not the Sham group. Furthermore, the OVX rats exhibited significantly higher subcutaneous WAT adiponectin mRNA levels than the Sham group at 6 h and 24 h after the injection of LPS.

Effects of LPS injection on the hypothalamic mRNA expression levels of adiponectin receptors and cytokines in female rats

LPS injection did not affect the hypothalamic AdipoR1 mRNA levels of the Sham (one-way ANOVA; *P* = 0.11, F (3,49) = 2.51) or OVX group (one-way ANOVA; *P* = 0.45, F (3,47) = 0.83) (Fig. 3). On the other hand, LPS injection did increase hypothalamic AdipoR2 mRNA expression in both the Sham (one-way ANOVA; *P* < 0.01, F (3,49) = 7.33) and OVX groups (one-way ANOVA; *P* < 0.01, F (3,47) = 10.9). The hypothalamic AdipoR1 and AdipoR2 mRNA levels of the two groups did not differ significantly at any time point. In both the Sham and OVX groups, the hypothalamic TNF-α and IL-6 mRNA levels detected at 6 h after the LPS injection were significantly higher than those observed at 0 h in the corresponding group. In addition, the hypothalamic TNF-α and IL-6 mRNA levels of the Sham group were significantly higher than those of the OVX group at 24 h after the injection of LPS.

Effects of LPS injection on the hepatic mRNA expression levels of adiponectin receptors and cytokines in female rats

LPS injection altered hepatic AdipoR1 mRNA expression in the OVX (one-way ANOVA; *P* < 0.01, F (3,47) = 14.1) group, but not the Sham group (one-way ANOVA; *P* = 0.07, F (3,49) = 3.12) (Fig. 4). Namely, the hepatic AdipoR1 mRNA level of the OVX group was significantly higher at 6 h after the LPS injection than at 0 h. As for the hepatic AdipoR2 mRNA level, it was decreased by LPS injection in both the Sham (one-way ANOVA; *P* < 0.01, F (3,49) = 28.8) and OVX groups (one-way ANOVA; *P* < 0.01, F (3,49) = 11.6). However, the hepatic AdipoR2 mRNA levels of the two groups did not differ significantly at any time point. LPS injection resulted in increased hepatic TNF-α and IL-6 mRNA levels in both the Sham (TNF-α: one-way ANOVA; *P* < 0.01, F (3,49) = 59.2, IL-6: one-way ANOVA; *P* < 0.01, F (3,49) = 34.1) and OVX groups (TNF-α: one-way ANOVA; *P* < 0.01, F (3,49) = 65.2, IL-6: one-way ANOVA; *P* < 0.01, F (3,49) = 14.4). Both the TNF-α and IL-6 mRNA levels of the Sham group were significantly higher than those of the OVX group at 6 h and 24 h after the LPS injection. Changes of adiponectin and its receptors in serum, adipose tissue, hypothalamus and liver under endotoxemia are summarized in Table 1.

Effects of LPS injection on the mRNA expression levels of adiponectin, adiponectin receptors, and cytokines in the hypothalamus, white adipose tissue, and liver in male rats

The injection of LPS did not affect the serum adiponectin levels. LPS injection decreased adiponectin mRNA expression in visceral WAT, but not in the subcutaneous WAT in male rats (Fig. 5). In addition, LPS injection decreased hepatic AdipoR2 mRNA expres-
Effects of endotoxemia on adiponectin system

Fig. 1 Serum adiponectin levels before (0 h) and at 6 h or 24 h after the injection of LPS (5 mg/kg) and serum TNF-α and IL-6 levels at 6 h after the injection of LPS (n = 5-10) in the Sham and OVX groups. Data are presented as mean ± SEM values. * P < 0.05. UD: undetectable.

Fig. 2 Adiponectin mRNA levels in visceral and subcutaneous fat before (0 h) and at 6 h or 24 h after the injection of LPS (5 mg/kg) (n = 5-10) in the Sham and OVX groups. The values are expressed as ratios relative to the mRNA level observed at 0 h in the Sham group. Data are presented as mean ± SEM values. ** P < 0.01, †† P < 0.01 vs. the value observed at 0 h for the corresponding group.

Fig. 3 Hypothalamic AdipoR1, AdipoR2, TNF-α, and IL-6 mRNA levels before (0 h) and at 6 h or 24 h after the injection of LPS (5 mg/kg) (n = 5-10) in the Sham and OVX groups. Values are expressed as ratios relative to the mRNA level observed at 0 h in the Sham group. Data are presented as mean ± SEM values. * P < 0.05, †† P < 0.01 vs. the value observed at 0 h for the corresponding group.
Table 1  Summary of changes in adiponectin and its receptors under endotoxemia

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↓, Decrease; ↑, increase; →, no change; APN, adiponectin

Fig. 4  Hepatic AdipoR1, AdipoR2, TNF-α, and IL-6 mRNA levels before (0 h) and at 6 h or 24 h after the injection of LPS (5 mg/kg) (n = 5-10) in the Sham and O VX groups. The values are expressed as ratios relative to the mRNA level observed at 0 h in the Sham group. Data are presented as mean ± SEM values. * P < 0.05, † † P < 0.01 vs. the value observed at 0 h for the corresponding group.

Fig. 5  Serum adiponectin levels, adiponectin mRNA levels in visceral and subcutaneous fat, and hepatic AdipoR1 and AdipoR2 mRNA levels in saline-injected (n = 6) and LPS-injected (5 mg/kg, 6 h after injection) (n = 7) male rats. The values of mRNA are expressed as ratios relative to the mRNA level observed at 0 h. Data are presented as mean ± SEM values. * P < 0.05.
sion. On the other hand, LPS injection did not alter hepatic AdipoR1 mRNA expression.

Discussion

Although it has been reported that APN plays pivotal roles in the regulation of acute inflammatory responses [8-17], the changes in the expression levels of endogenous APN and AdipoR during such conditions have not been fully elucidated, especially in females. Therefore, the present study mainly focused on the effects of LPS-induced sepsis on APN and AdipoR expression in peripheral and central tissues in female rats. As a result, we found that female rats exhibited different changes in their APN and AdipoR expression levels in response to LPS injection compared with those reported for males. We also found that the changes in AdipoR2 mRNA expression observed after the injection of LPS differed between the liver and hypothalamus; i.e., AdipoR2 mRNA expression was decreased in the liver and increased in the hypothalamus. Furthermore, differences were detected in the basal APN level and the changes in APN, AdipoR, and cytokine mRNA expression induced by LPS injection between gonadal-intact and OVX rats.

In the present study, the serum APN level was not affected by LPS injection in either the gonadal-intact (Sham) or OVX rats, while the APN mRNA levels of visceral WAT increased after the injection of LPS in both the Sham and OVX rats. We speculate that up-regulation of APN mRNA in WAT might be one of the protective responses that preserves the serum APN level to prevent the tissue injury under LPS-induced septic condition. We also speculate that more serious condition, for example CLP or higher dose LPS injection, would disrupt this system and decrease the serum leptin levels. Some of these results were not consistent with the findings reported for male rodents in present and/or previous studies. In present study, APN mRNA level was decreased by LPS injection, whereas serum APN level was not changed by LPS injection at 6 h after injection in male rats. Uji et al. demonstrated that the serum APN level was decreased at 16 to 24 h after CLP in male mice [10], whereas Kaplan et al. did not detect any change in the APN level using the same experimental model [12]. Sakai et al. also found that the serum APN level was decreased by LPS injection at 6 h after injection in male rats [11]. Taken together, these findings indicate that there is no sexual dimorphism in the sensitivity of hepatic AdipoR2 expression to sepsis. Several studies have suggested that APN plays a protective role against septic, alcoholic, and non-alcoholic-induced liver injury and inflammation. For example, APN suppresses hepatic TNF-α production and alleviates steatosis in mice with fatty liver disease [21]. APN was also found to improve the liver injuries induced by injections of LPS and D-galactosamine in mice [17], and APN-KO mice exhibited worse liver injuries than WT mice under CLP-induced septic conditions [14]. As AdipoR2, but not AdipoR1, is predominantly expressed in the liver [5], the protective role of APN against liver injury might be mainly mediated via AdipoR2. Thus, reductions in AdipoR2 expression might affect the progression of liver inflammation and injury in both female and male rats; however, further studies will be necessary to confirm this.

In the present study, LPS injection increased hypothalamic AdipoR2 mRNA expression in both the Sham and OVX rats, whereas hypothalamic AdipoR1 expression...
sion was not affected in either group. Interestingly, the change in AdipoR2 expression observed in the hypothalamus was completely opposite to that seen in the liver. It has been reported that the roles of APN in regulating metabolic processes and food consumption differ between central and peripheral tissues. In peripheral tissues, APN stimulates fatty acid oxidation and enhances insulin sensitivity through AMPK, while in the hypothalamus it stimulates food intake and decreased energy expenditure through AMPK [4, 22]. A recent report has shown that both AdipoR1 and AdipoR2 are expressed on hypothalamic appetite-regulating neurons; i.e., neuropeptide Y and proopiomelanocortin neurons [2]. Under septic conditions, many factors, e.g., inflammatory cytokines and leptin, act on the hypothalamus to reduce appetite and stimulate febrile responses [23-25]. Such factors also suppress the actions of certain orexigenic molecules, e.g., ghrelin, under LPS-induced immune stress conditions in order to reduce feeding behavior [26]. Although these alterations are important for producing appropriate immune reactions, excess appetite loss can weaken the individual concerned and can even result in death. Thus, we speculate that increased hypothalamic AdipoR expression might be involved in stimulating appetite and maintaining energy storage, even under septic conditions.

Interestingly, the basal expression levels of APN, AdipoR, and cytokines as well as the changes in the expression levels of these molecules induced in response to LPS injection differed between the Sham and OVX rats. First, the serum APN levels of the Sham rats were lower than those of the OVX rats under both the basal and LPS-induced sepsis conditions. The high basal APN level observed in the OVX rats is in agreement with the results of a previous study in which it was demonstrated that the serum APN levels of female rats were increased after OVX and that these changes could be reversed by estradiol replacement [20]. In the present study, the difference in serum APN levels between the Sham and OVX rats was maintained even under septic conditions. Secondly, in the Sham rats the APN mRNA level of subcutaneous WAT was not affected by the injection of LPS while in the OVX rats it was markedly increased by LPS injection, resulting in the OVX rats exhibiting significantly higher subcutaneous WAT APN mRNA levels than the Sham rats after the LPS injection. Although we could not clarify the precise mechanism through which the sensitivity of subcutaneous WAT APN expression to sepsis was affected by OVX, we speculate that changes in the gonadal hormonal milieu and/or obesity, which is induced by estrogen deficiency, might be involved. Thirdly, the changes in AdipoR and cytokine expression induced by the injection of LPS differed slightly between the Sham and OVX rats. As noted above, the hypothalamic AdipoR2 mRNA levels of both the Sham and OVX groups were increased at 6 h after the injection of LPS. Although upregulated AdipoR2 mRNA expression was observed until 24 h after the injection of LPS in the OVX group, no such change was observed in the Sham group. In addition, upregulated hepatic AdipoR1 mRNA expression was observed in the OVX rats, but not the Sham rats. With respect to cytokines, the OVX rats exhibited significantly lower serum TNF-α levels at 6 h after the injection of LPS compared with the Sham rats, which was also the case for the hypothalamic IL-6 and TNF-α mRNA levels observed at 24 h after the injection of LPS. It has been reported that APN attenuates the systemic and local production of inflammatory cytokines, such as TNF-α and IL-6 [15, 16], and that these actions of APN prevent LPS-induced hepatic injury [17]. Sakai et al. reported that diet-induced obese rats, which exhibit lower serum APN and liver AdipoR2 mRNA levels, are more susceptible to hepatic injury under LPS-induced septic conditions [11]. Their data indicate that both APN and AdipoR play important roles in preventing excessive cytokine production and subsequent tissue injury [11]. Therefore, it is possible that higher serum APN levels and the prolonged upregulation of AdipoR mRNA expression might underlie the differences in hypothalamic and hepatic cytokine levels observed between the Sham and OVX rats in the present study.

In summary, the results of this study indicate that the changes in APN and AdipoR expression induced in response to LPS-induced sepsis in female rats differ from those observed in males. In addition, the response patterns of AdipoR2 expression to LPS injection differed between the liver and hypothalamus. Furthermore, the serum basal level and the response patterns of APN, AdipoR, and cytokine expression varied between gonadal-intact rats and ovariectomized rats. Our findings indicate that APN and AdipoR play roles in modulating inflammation under septic conditions in female rats and that the upregulation of APN and AdipoR expression might be involved in the attenuation of LPS-induced cytokine production in ovariectomized rats.
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References


