PHYSICAL CHEMISTRY 2014

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on Fundamental and Applied Aspects of
Physical Chemistry

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ASSOCIATION OF FEMALE GONADAL HORMONES AND IMMUNITY IN DEPRESSION

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ABSTRACT

In this study, we examined the influence of immunity on depressive-like behavior in females in the context of gonadal hormones. We used neuroinflammatory model of depression elicited by lipopolysaccharide (LPS) administration on naïve and ovariectomozed (OVX) females and examined the effects of estradiol (E2) and/or progesterone (P4) replacement therapy on Wistar rat behavior. LPS induced depressive–like behavior in both naïve and OVX females. Our behavioral data indicated that E2 and P4 applied alone had opposite effects compared to the E2/P4 combination. The supplementation of both hormones attenuates detrimental effects of LPS-induced inflammation, particularly through stimulation of noradrenergic transmission. Overall immune challenge with LPS is able to induce depressive-like behavior either of naïve or ovariectomized females, particularly depending on ovarian hormones background.

INTRODUCTION

The vulnerability to depression in women is associated with the hormonal fluctuations during their life [1]. The negative symptomology associated with depression is greater in premenstrual and postpartum periods, as well as after menopause or oophorectomy, when women's 17β-estradiol (E2) levels are decreased [2]. Preclinical evidencealso points out that E2 affects depressive-like behavior. Reduced depressive-like behavior has been found in females during proestrous, when E2 levels are high, compared to females in diestrous, when E2 levels are low [3]. Within multifactorial origins of depression, chronic inflammation has received increasing attention.Elevated biomarkers of inflammation, cytokines and acute-phase proteins, have been found in depressed patients [4]. Also, it has been shown that gender is the risk factor for depression upon administration of some inflammatory stimuli [5]. To explore the interplay of female gonadal hormones and inflammation in the etiology of depression, we utilize neuroinflammatory model of depression elicited by lipopolysaccharide (LPS) administration on naïve and

ovarioctomozedfemales and examine the effects of E2 and/or progesterone (P4) replacement therapy on animal behavior.

EXPERIMENTAL

Naïve and ovariectomizedadult 3-month females were administered intraperitoneally with LPS (dose of 500μg/kg of body mass) and with 17 β-estradiol (E2) (10μg/kg) and with progesterone (P4) (4mg/kg). Both steroids were administered subcutaneously dissolved in sesame oil vehicle. Modified forced swim test (FST) was used to test depressive-like behavior. Data are presented as a mean ± SD and analyzed by Two and Three–way ANOVA. The statistical significance was accepted at $p<0.05$.

RESULTS AND DISCUSSION

The LPS treatment increased immobility in both naïve ($F=21.54$, $p<0.05$) and ovariectomized females (LPS x OVX interaction, $F=149.08$, $p<0.05$) (Figure 1), and decreased swimming in both naïve ($F=6.67$, $p<0.05$) and ovariectomized females (LPSxOVX interaction, $F=107.46$, $p<0.05$).

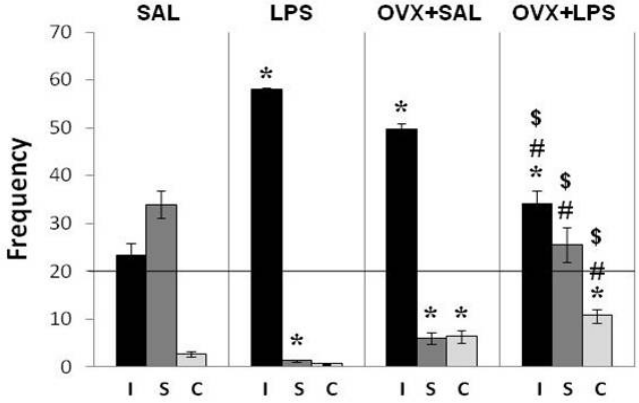

Figure1. Changes in swimming (S), climbing (C) and immobility(I) (frequency) in the FST in naïve and ovariectomized (OVX) female upon immune challenge. Naïve and ovariectomized females were assigned to the following groups: control (SAL-saline solution, n=14), LPS-group (n=14), ovariectomized females treated i.p. with saline (OVX+SAL, n=10) and ovariectomized females treated i.p. with LPS (OVX+LPS, n=10). Data and presented as mean ± SD, $p < 0.05$ (* vs SAL, $^{\#}$vs LPS, $^{\$}$vs OVX+SAL).

The climbing behavior was significantly affected both by ovariectomy (OVX, $F=67.09$, $p<0.05$) and upon LPS treatment of OVX females (LPSxOVX interaction, $F=14.67$, $p<0.05$). OVX females treated with

vehicle or LPS exhibited significantly increase in climbing compared to controls ($p<0.05$), to naïve females treated with SAL group ($p<0.05$) orLPS ($p<0.05$).

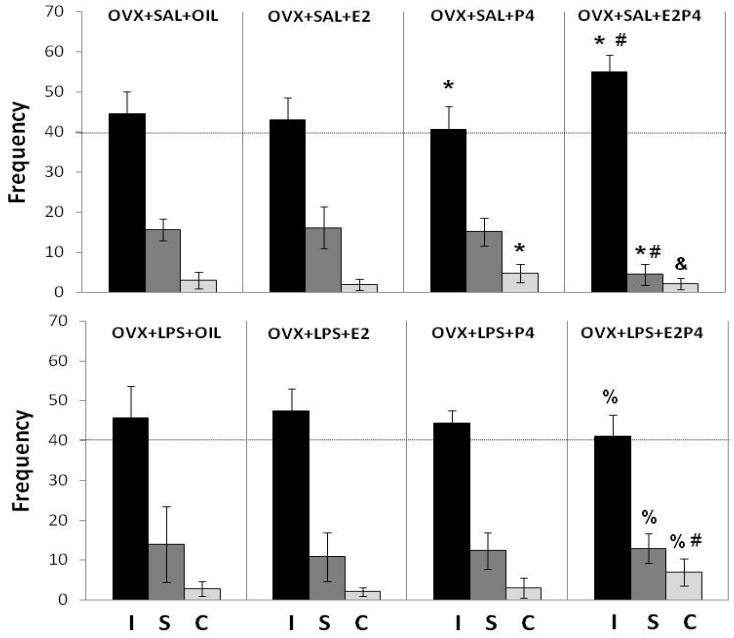

Figure 2: Changes in swimming (S), climbing (C) and immobility (I) (frequency) in FST in ovariectomized (OVX) female rats treated with saline (SAL), lipopolysaccharide (LPS), and hormones (solely E2 and P4 or in combination E2P4).Ovariectomized females were divided in eight experimental groups: ovariectomized-control-control group (OVX+SAL+OIL, n=8), ovariectomized-control-E2 group (OVX+SAL+E2, n=8), ovariectomized-control-P4 group (OVX+SAL+P4, n=8), ovariectomized-control-E2P4 group (OVX+SAL+E2P4, n=8), ovariectomized-LPS-control group (OVX+LPS+OIL, n=8), ovariectomized-LPS-E2 group (OVX+LPS+E2, n=8), ovariectomized-LPS-P4 group (OVX+LPS+P4, n=8) and ovariectomized-LPS-E2P4 group (OVX+LPS+E2P4, n=8).Data are presented as mean ± SD, $p < 0.05$ (* vs SAL+OIL, $^{\#}$E2P4 vs other groups, $^{\&}$ E2P4 vs P4, and $^{\%}$ LPS+E2P4 vs SAL+E2P4).

In Figure 2, P4 administration significantly decreased immobility ($F=14.59$, $p<0.05$) and in parallel increased climbing ($F=16.41$, $p<0.05$) of OVX females. Concomitant treatment with both E2 and P4 significantly increased

immobility (E2xP4 interaction, $F=57.81$, $p<0.05$) while decreased swimming (E2xP4 interaction, $F=48.71$, $p<0.05$) and climbing (E2xP4 interaction, $F=4.53$, $p<0.05$). The increase in immobility upon parallel E2 and P4 treatment of OVX rats was significantly higher in comparison to the control group and to the group treated solely with either E2 or P4 ($p<0.05$). Administration of E2 and P4 to OVX females significantly increased climbing compared to all other LPS groups (E2 x P4 interaction, $F=16.36$, $p<0.05$).Significant decrease in immobility (LPSxE2xP4 interaction, $F=40.78$, $p<0.05$) with concomitant increase in swimming (LPSxE2xP4 interaction, $F=22.25$, $p<0.05$) and climbing (LPSxE2xP4 interaction, $F=19.08$, $p<0.05$) was detected upon E2P4 treatment in LPS injected animals.

CONCLUSION

The current study demonstrates that immune challenge with LPS is able to induce depressive-like behavior either of naïve or ovariectomized females.Individual treatment with E2 or P4 of LPS injected OVX rats did not affect behavior profile. However, when LPS-injected animals were treated with both hormones we found a significant increase in climbing compared to other OVX-LPS-groups. These results indicated that supplementation of both ovarian hormones could attenuate the detrimental effects of LPS induced inflammation, particularly through stimulation of noradrenergic transmission.

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