PHYSICAL CHEMISTRY 2012

11th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

Under the auspices of the
University of Belgrade

Proceedings

The Conference is dedicated to
Professor Ivan Draganić

September 24-28, 2012
Belgrade, Serbia

ISBN 978-86-82475-27-9 ***Volume*** **1**
ISBN 978-86-82475-28-6 ***Volume*** **II**

Title: PHYSICAL CHEMISTRY 2012 (Proceedings)
Editors: S. Anić and Ž. Čupić
Published by: Society of Physical Chemists of Serbia, Studenski trg 12-16, 11158, Belgrade, Serbia
Publisher: Society of Physical Chemists of Serbia
For Publisher: S. Anić, President of Society of Physical Chemists of Serbia
Printed by: "Jovan" Priting and Publishing Company; 200 Copies;
Number of pages: 6+ 497; **Format**: B5; Printing finished in September 2012.

Text and Layout: "Jovan"

200- *Coppy printing*

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F-09-P

CHRONIC STRESS AND CONCOMITANT FLUOXETINE TREATMENT EXERT GENDER-SPECIFIC EFFECTS ON BEHAVIOR AND HIPPOCAMPAL CDK5 SIGNALING IN WISTAR RATS

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Abstract

Depression is one of the most pervasive and debilitating stress-related psychiatric diseases worldwide. Cyclin-dependent kinase 5 (Cdk5) is of particular importance for normal adult brain functioning and has recently been associated with anxiety and depressive disorders. In the present study, we investigated how alterations in depressive-like behavior are accompanied by the changes in hippocampal Cdk5/p35/p25 signaling in female and male Wistar rats exposed to chronic psychosocial isolation (CPSI) and concomitant antidepressant fluoxetine (FLU) treatment. Our results showed that CPSI induced different behavioral responses in female and male rats which were accompanied by dissimilarities in Cdk5/p35/p25 signaling. The effect of concomitant FLU treatment was also gender-specific regarding behavioral responses and Cdk5 levels, but gender-independent regarding p35 levels, which was accompanied with normalization of female and male rat behavior.

Introduction

Stress-related disorders, with depression among the leading ones, are becoming major burden of disease and disability in society worldwide. Animal models of psychosocial isolation are of particular importance, since they appear to be relevant to certain subtypes of human depression [1].

Cyclin-dependent kinase 5 (Cdk5) exerts high activity in the brain and is essential for neuronal synaptogenesis and survival [2]. Cdk5 is activated by neuronal-specific proteins p35 and p25 (C-terminal fragment of p35) through direct binding. The protein p25 has a substantially longer half-life than p35, causes prolonged activation of Cdk5 and is considered to be neurotoxic [2]. Increased activity of Cdk5 in hippocampus has been recently associated with anxiety and depressive-like behavior, suggesting that Cdk5 could be an important target for treatment of emotional disorders [3].

In the present study, we investigated how behavioral changes are accompanied by alterations in hippocampal Cdk5/p35/p25 signaling in female and male Wistar rats exposed to chronic psychosocial isolation (CPSI) and concomitantly treated with the antidepressant fluoxetine (FLU).

Experimental

Adult female and male Wistar rats were divided into four groups: (I) naive rats vehicle treated for 21 days, (II) naive rats FLU treated for 21 days, (III) rats exposed to 21-day CPSI followed by vehicle treatment for 21 days under the same stress conditions and (IV) 21-day CPSI followed by FLU treatment for 21 days under the same stress conditions. FLU dissolved in water was administered intraperitoneally at daily base (at 9 a.m.) with dose of 5 mg/kg of body mass. After the treatments, rats from each group were devided in two sets, one for evaluation of molecular parameters and the other one for testing the behavior. The depressive-like behavior was assesed by the forced swimming test (FST), in which the immobility time during a single 5 min session was used as its relevant measure. The other set of rats was sacrificed, their hippocampi were removed and used for preparation of cytosolic fractions and molecular analyses. The proteins of interest, Cdk5, p35 and p25, were detected using Western blot technique with β-actin as a loading control. Data were analyzed by two-way ANOVA followed by post-hoc Tukey test for examining the effects of CPSI and FLU, or by three-way ANOVA followed by post-hoc Tukey test for examining the effect of gender.

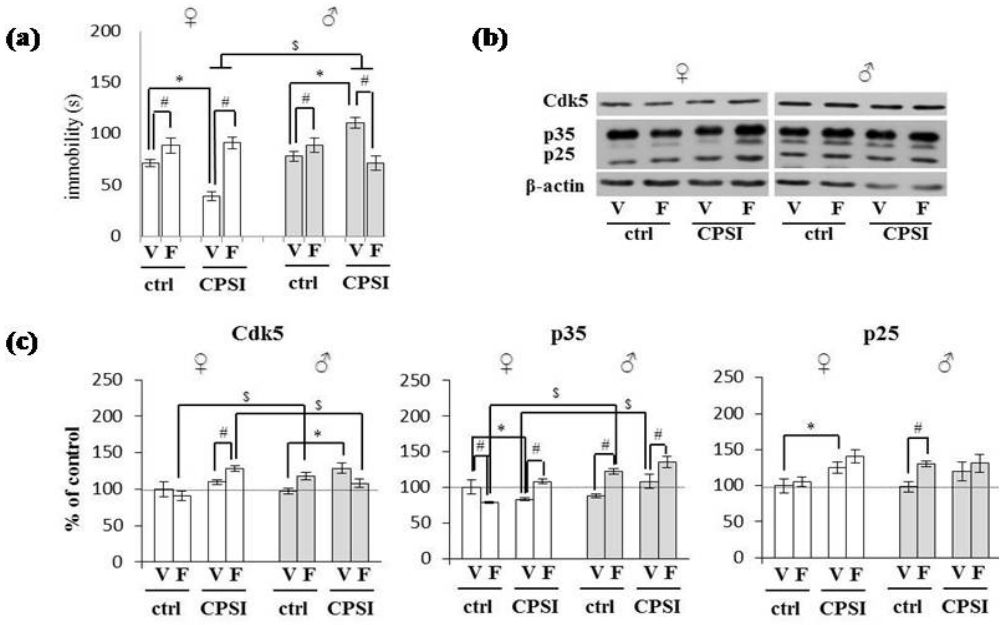

Figure 1. The immobility time in FST (a), representative Western blots (b) and levels of hippocampal cytosolic Cdk5, p35 and p25 (c) in vehicle (V) and FLU (F) treated control (ctrl) and CPSI rats. Data are presented as mean ± SEM (* ctrl *vs.* CPSI, $p<0.05$; # V *vs.* F, $p<0.05$, $ females *vs.* males, $p<0.05$).

Results and discussion

Our results showed that FLU treatment normalized depressive-like behavior in rats of both genders, although its effects were opposite in females and males (Figure 1a; gender x CPSI interaction $F=13.93$, $p<0.05$; gender x CPSI x FLU interaction

F=28.45, $p<0.05$). Namely, in accordance with our previous studies [4], CPSI increased immobility time in FST in males, ($F=4.68$; $p<0.05$) and the concomitant FLU treatment reduced it ($F=26.54$; $p<0.05$). Contrary to that, in females, CPSI decreased their immobility time in FST ($F=12.52$; $p<0.05$), while concomitant FLU treatment normalized it ($F=8.14$; $p<0.05$).

CPSI and concomitant FLU treatment also affected hippocampal Cdk5/p35/p25 signaling in a gender-specific manner (Figure 1b, 1c; Cdk5: gender x CPSI x FLU interaction $F=25.13$, $p<0.05$; p35: gender x CPSI interaction $F=5.8$, $p<0.05$). Increased depressive-like behavior in CPSI male rats was associated with increased levels of Cdk5 ($F=5.75$, $p<0.05$) and slight elevation of its activator p35, consistent with previous study [3]. The concomitant FLU treatment, that reduced depressive-like behavior, also slightly decreased Cdk5 levels, but increased the levels of its activator p35 ($F=2.13$; $p<0.05$). On the other hand, in females, the reduced immobility in FST by CPSI was associated with decrease in p35 ($F=3.18$; $p<0.05$), but increase in p25 ($F=23.72$; $p<0.05$), a more potent activator of Cdk5 regarded to be neurotoxic [2]. The normalization of female behavior by concomitant FLU treatment co-occurred with elevation of Cdk5 ($F=4.36$; $p<0.05$) and p35 levels ($F=88.5$; $p<0.05$). Our results suggest that although FLU treatment of CPSI rats exerted some gender-unspecific effects (increase in p35), FLU gender-specific effects on Cdk5 levels are at least partly responsible, for normalization of rats behavior in FST in both genders affecting it in opposite ways.

Conclusion

CPSI caused divergent behavioral responses in female *vs.* male rats which was accompanied with dissimilar alterations in hippocampal Cdk5/p35/p25 signaling in both genders. The effect of concomitant FLU treatment on CPSI rats was also gender-specific regarding the behavioral responses and Cdk5 levels, but gender-independent regarding the p35 increase, which was accompanied with normalization of female and male rat behavior.

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CIP Volume I

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

544(082)
621.35(082)
66.017/.018(082)

MEĐUNARODNA konferencija iz fundamentalne i primenjene fizičke hemije (11 ; 2012 ; Beograd)
Physical Chemistry 2012 : proceedings. #Vol. #1 / 11th International Conference on Fundamental and Applied Aspects of Physical Chemistry, September 24-28, 2012, Belgrade ; [editors S.[Slobodan] Anić and Ž.[Željko] Čupić ; organized by Society of Physical Chemists of Serbia ... et al.]. - Belgrade : Society of Physical Chemists of Serbia, 2012 (Belgrade : Jovan). - VI, 498 str. : ilustr. ; 24 cm

"The Conference is dedicated to Professor Ivan Draganić" --> nasl. str. - Tiraž 200. - Bibliografija uz svaki rad.

ISBN 978-86-82475-27-9
1. Društvo fizikohemičara Srbije (Beograd)
a) Физичка хемија - Зборници b) Електрохемијско инжењерство - Зборници c) Наука о материјалима - Зборници
COBISS.SR-ID 193432332