Introduction: Depressive disorders belong to the most frequent diseases worldwide showing a lifetime prevalence of up to 20%. The traditional focus on a prominent participation of the central serotonergic and noradrenergic systems in the mechanisms of depression is generally accepted. However, recent evidences suggest that the dysfunction of the central dopaminergic (DA) pathways may be a critical component of the neurobiological basis of depression [1]. On the other hand, androgens have powerful effects beyond their role in reproduction and sexual behavior. Androgens have been suggested to affect several psychiatric and neurodegenerative diseases including anxiety, depression, schizophrenia, and Alzheimer’s disease [2]. On the other hand, DA also can influence gonadal hormonal system [3]. Thus, such close interactions between gonadal hormonal and dopaminergic neurotransmitter systems then it is of interest to elucidate the involvement of D1 receptors in depression-like state under conditions of androgen deficiency, that is, under such critical conditions that are contributed to produce the profound mood impairments in males.

Aim: The aim of this work was to study the effects of administration of D1 receptor agonist SKF-38393 and D1 receptor antagonist SCH-23390 injected chronically for 14 days alone or in combination with low dose of testosterone propionate (TP) on depression-like behavior in adult gonadectomized (GDX) rats.

Methods: Gonadectomy was performed under ethyl ether anesthesia. GDX animals were allowed to have 14 days for postoperative recovery before administration of drugs. After two weeks, all GDX rats were randomly assigned to each of the experimental groups and subjected to treatments and behavioral tests. D1 receptor agonist SKF-38393 and D1 receptor antagonist SCH-23390 were dissolved in sterile saline (0.9%). The testosterone propionate (TP) was dissolved in sterile sesame oil. All solutions were freshly prepared before each experimental series. Drugs were administered during 14 days after postoperative period following gonadectomy. The two control groups were constituted of intact rats treated with SKF-38393 (0.1 mg/kg, i.p.) daily; intact rats treated with TP (1.0 mg/rat, s.c.) daily; GDX rats with SKF-38393 daily; GDX rats treated with TP in the same dose which was given to GDX; GDX rats injected with SKF-38393 daily; GDX females in combination with TP in GDX males resulted in potentiated antidepressant-like effect (p<.05, ANOVA). SKF-38393 in GDX male rats profoundly increased immobility time compared to the control intact and GDX groups. On the contrary, co-administration of SKF-38393 and TP in GDX rats completely blocked negative effect of SKF-38393 on immobility time as compared to the control GDX rats and GDX rats treated with TP (p<.05, ANOVA).

Results: Forced swimming test Gonadectomy significantly decreased immobility time as compared to the intact group (p<.05, ANOVA). TP reduced immobility time to some extent in GDX rats as compared to the control GDX rats (p<.05, ANOVA), indicating that TP in a low dose is an antidepressant. SCH-2339 alone significantly decreased immobility time in GDX rats as compared to control GDX rats (p<.05, ANOVA). Chronic SCH-23390 administration in a combination with TP in GDX males resulted in potentiated antidepressant-like effect (p<.05, ANOVA). SKF-38393 in GDX male rats profoundly increased immobility time as compared to the control intact and GDX groups. On the contrary, co-administration of SKF-38393 and TP in GDX rats completely blocked the prodepressant-like effect of SKF-38393 in immobility time as compared to the control GDX rats and GDX rats treated with TP (p<.05, ANOVA).

Hormonal assay SCH-23390 increased T level, but decreased LH level in the blood of GDX and GDX rats treated with TP as compared to the control GDX and GDX rats treated with TP (p<.05, ANOVA). SKF-38393 failed to induce changes in hormones concentration of intact and GDX males, however, increased LH level and reduced T level in GDX rats administered with TP as compared to the GDX rats received only TP (p<.05, ANOVA).

Conclusion: The D1 receptor agonist SCH-23390 administered alone or in a combination with a low dose of testosterone propionate resulted in an antidepressant-like effect in GDX rats. Repeated treatment with SCH-23390 and a low dose of TP profoundly enhanced antidepressant-like effects the single substances exert per se. The D1 receptor agonist SKF-38393 markedly impaired the depression-like behavior of GDX rats in the forced swimming test, inducing prodepressant-like effect. In addition, SKF-38393 in combination with TP completely blocked the prodepressant-like effect of SKF-38393 in GDX rats. Further research is needed to elucidate the detailed mechanisms by which SCH-23390 and TP exert synergic effect and affect the dopaminergic system.

References:
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Blockade of D1 dopaminergic receptors corrects depression-like behaviour in gonadectomised rats treated with a low dose of testosterone

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Statement on the purpose of the study: Depressive disorders belong to the most frequent diseases worldwide showing a lifetime prevalence of up to 20%. The traditional focus on a prominent participation of the central serotonergic and noradrenergic systems in the mechanisms of depression is generally accepted. However, recent evidences suggest that the dysfunction of the central dopaminergic pathways may be a critical component of the neurobiological basis of depression [1]. On the other hand, both basic and clinical reports showing that gonadal hormones are involved in the modulation of depression [2]. Meanwhile, there is increasing evidence that androgens may alter neuronal excitability via interaction with different types of neurotransmitter membrane receptors [3].

The present work was devoted to the comparative analysis of the behavioral and hormonal status in the gonadectomized (GDX) male rat of middle age chronically treated with high-selective agonist of D1 dopaminergic receptors agonist – SKF-38393 or antagonist D1-dopaminergic receptors – SCH-23390 alone or in a combination with low dose of testosterone propionate.

Methods: Two weeks after surgery, GDX male rats of 3–4 months age began 14 days of treatment with the vehicle, a low dose of testosterone propionate (1.0mg/kg, s.c.), D1-like dopaminergic agonist, SKF-38393 (0.1mg/kg, i.p.), D1-dopaminergic antagonist, SCH-23390 (0.1mg/kg, i.p.), SKF-38393 plus testosterone propionate or SCH-23390 plus testosterone propionate (TP). The animals were then tested in the forced swimming test (FST) and the open field test (OFT). The measurement of lutropine (LH) and testosterone (T) in the blood samples was performed by ELISA. Statistical processing of the received data was carried out with use of one-way ANOVA and post-hoc test at p<0.05.

Results: Repeated TP administration in a low dose GDX males significantly reduced immobility time compared to the control GDX rats, indicating that TP in a low dose is an antidepressant. The D1 receptor antagonist SCH-23390 significantly decreased immobility time compared to the control GDX males (p<0.05). Combined administration of SCH-23390 with TP to the GDX males resulted in a decrease of immobility behavior (post hoc versus control GDX rats, p<0.05). The D1 receptor agonist, SKF-38393 in GDX male rats profoundly increased immobility time compared to the control group (p<0.05). On the contrary, co-administration of SKF-38393 and TP in GDX rats completely blocked negative effect of SKF-38393 on immobility time in the FST. Also, SCH-23390 in combination with low dose of TP significantly increased T levels, but decreased LH levels in the blood serum of GDX male rats as compared to the control group (p<0.05).

Conclusions: The results of this study demonstrate that SCH-23390 and its combination with testosterone propionate in GDX rats interact to exert antidepressant-like action and that each of these drugs can improve effect of the other drug. Moreover, it provides additional evidence to support the role of dopaminergic mechanism in depression-like behavior after prenatal stress, and contributes to the better understanding of the complex interaction between androgens and dopamine neurotransmitter systems.

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Disclosure statement: This work was supported by RFBR grant 14–04–00795.

Citation: Eur Neuropsychopharmacol. 2014;24(Suppl 2):S363

Keywords
- Behavioural pharmacology
- Dopamine
- Depression: basic