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Research Article
Effect of Resveratrol on Neurotrophic Factors and Depression-Like Behavior in a Rat Model of Male Hypogonadism

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Abstract

Background and Objective: Male hypogonadism is associated with depression. Hippocampal neurogenesis is reduced in depression. Resveratrol is a phytoalexin with antioxidant properties. This study aimed to investigate the effects of resveratrol on Brain-Derived Neurotrophic Factor (BDNF) and neurotrophin3 (NT3) levels in the hippocampus and prefrontal cortex and Depressive-like behaviours in rats with surgical hypogonadism. **Materials and Methods:** Forty Wistar-Kyoto male rats were divided into four groups (10 rats each): control (sham), Control+resveratrol, orchidectomy and orchidectomy+resveratrol groups. Forced Swimming Test (FST) and sucrose intake were performed. Hippocampal and prefrontal cortical levels of BDNF, NT3, 5-hydroxytryptamine, dopamine, norepinephrine, malondialdehyde and reduced glutathione (GSH) and serum corticosterone level were detected. **Results:** Orchidectomy decreased Latency of Attempt of Escape (LAE), sucrose intake and BDNF, NT3, 5-hydroxytryptamine, dopamine, norepinephrine and GSH and increased malondialdehyde, corticosterone and Behavioural Immobility (BI). Resveratrol increased LAE, sucrose intake, BDNF, NT3, 5-hydroxytryptamine, dopamine, norepinephrine and GSH and decreased malondialdehyde, corticosterone and BI. **Conclusion:** RES improves Depressive-like behaviours through increasing BDNF and NT3, ameliorating oxidative stress and reducing corticosterone in a rat model of hypogonadism.

Key words: Hypogonadism, BDNF, oxidative stress, corticosterone, resveratrol, malondialdehyde, dopamine

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Depression is a heterogeneous condition including complex cognitive and emotional processes which are difficult to model in animals[1]. Most models of depression use chronic exposure to stress or administration of glucocorticoids as a means of generating the disrupted neuroendocrine function, as well as the neurophysiological and behavioural phenotypes[2]. In the present work, we aimed to investigate the effects of surgical hypogonadism on the development of Depressive-like behaviour in an animal model of depression. Studying the behavioural and rewarding alterations and the underlying physiological mechanisms in animal models of depression may be useful in obtaining more insight into human depression[3].

Gonadal hormones may play an important role in mediating the presentation and progression of depression[4]. Previous studies showed that there is a great association between male hypogonadism and depressive manifestations[4-6]. Besides, the incidence of depression-spectrum disorders is increased in young and older men with lower levels of testosterone[7] and androgen replacement therapy can be effective in the treatment of depression in hypogonadal men[8]. Accordingly, the development of extant depressive disorders could be impeded or ameliorated with the antidepressant properties of androgens[2].

Neurogenesis is the formation of new neurons in the brain tissue. Normally the hippocampus is the major site for neurogenesis under the effect of several neurotrophic factors. The most prevalent neurotrophic factor is Brain-Derived Neurotrophic Factor (BDNF). BDNF is a protein that plays an important role in stimulating the growth of new brain cells and the performance of existing neurons. It is best defined as the brain's growth hormone. Several factors affect the expression of BDNF like exercise, sleep, ageing as well as dietary habits[9].

Resveratrol (RES) is a phytoalexin having anti-oxidant actions. It is found in a wide variety of foods particularly red wine and grape. During the last decade, RES has been shown to possess a wide spectrum of pharmacologic properties such as anti-inflammatory, antioxidant, anticarcinogenic, anti-ageing, neuroprotective and cardioprotective effects[10]. RES has also been implicated as a neuroprotective agent with the ability to increase neurogenesis, most notably in reducing Alzheimer's disease progression[11]. Besides, RES is reported to reduce fatigue[12], improve sleep quality[13] and ameliorate depression and anxiety[14].

Several reports previously indicated the hazardous psychological and neurological complications of antidepressants[15]. We hypothesized that RES could ameliorate Depressive-like behaviours induced by hypogonadism in rats.

Therefore, the current work aimed to investigate the effects of surgical hypogonadism on neurotrophic factors (BDNF and neurotrophin 3 in hippocampus and prefrontal cortex) and Depressive-like behaviours in rats. Besides, the effects of RES on Depressive-like behaviours and levels of BDNF, NT3, 5-hydroxytryptamine (5-HT), dopamine, norepinephrine and oxidative stress markers in the hippocampus and prefrontal cortex in rats with hypogonadism were examined.

MATERIALS AND METHODS

Study area: Part of this study was carried out in the College of Medicine, King Khalid University, Abha, Saudi Arabia and the other part was carried out in the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman from April-December, 2020.

Chemicals: RES, carboxymethyl cellulose and sodium pentobarbital were purchased from Sigma (St. Louis, Mo., USA).

Animals: Forty adult healthy Wistar-Kyoto male rats (14 weeks/300±25 g) were provided and housed in the animal facility department of Sultan Qaboos University (SQU), Muscat, Oman. During the 1 week adaption period and through all the experimental procedures, all rats were housed at 23±1°C, 50-60% humidity and 12/12 hrs a day/dark cycle. All animals were allowed free access to food and tap water. All procedures were conducted after the approval of the medical research and animal use ethical committee of SQU (SQU/AEC/2017-18/8). The procedures followed were under the standards outlined in the eighth edition of "Guide for the Care and Use of Laboratory Animals.

Experimental model of orchidectomy (ORCD): Bilateral orchidectomy was performed as described by our group and others[16]. Briefly, the rats were anaesthetized with intraperitoneal (i.p.) injection of sodium pentobarbital (60 mg kg^{-1}). At the time of the surgery, the eyes of the anaesthetized rats were wet by gel omit and the temperature was continuously monitored by a thermal anal probe. Each rat was placed in a supine position on a heating table and a small

surgical incision was made in the centre of the scrotum to expose both testicles. Then, the ductus deferens and all attached blood vessels were isolated and lighted and both the testicle and epididymis were removed. After this, the incision was then closed and sutured. The povidone-iodine solution was applied at the incision site and all rats were returned to their cages and monitored for wound healing and infections.

Experimental design: Rats were divided into four groups of ten rats each. The control sham group underwent a similar surgical procedure that is used to induce ORCD but without any ligation of the arteries or veins or removal of the testicle and epididymis. The control+RES-treated (Control+RES) group underwent a similar sham procedure as in the control group but were then treated with RES as explained below. The ORCD-induced group underwent a bilateral ORCD surgical procedure as described above. The ORCD+RES-treated group underwent a bilateral ORCD surgical procedure and then treated with RES. RES was purchased from Sigma (St. Louis, Mo., USA), dissolved in 0.5% carboxymethyl cellulose and given orally by orogastric gavage in a dose of 40 mg kg^{-1} b.wt., daily[17] for 90 days. The same volume of carboxymethyl cellulose was applied as a vehicle and administered to rats in the control and ORCD-induced groups.

Sucrose intake: In the present study, we used a sucrose test to assess anhedonia. Sucrose intake (1% sucrose solution) was measured once a week, on separate days (on days 0, 15, 30, 45, 60, 75 and 90), during a 1 hr window after 4 hrs of food and water deprivation. Consumption was measured by comparing bottle weight before and after the 1 hr window. The food and water deprivation period preceding sucrose intake measurement may be considered as further stress. However, control rats were also exposed to food and water deprivation, as a part of the test[18].

Forced Swimming Test (FST): At the end of the experiment, the depressive behaviour was evaluated in all animals using the modified method of Porsolt[19]. This procedure consists of exposing an animal to a situation of inescapable stress, in which the rat is forced to swim. After an initial period of vigorous swimming activity in the direction of the tank border (Latency of the Attempt of Escape), the animal reduces the intensity of the movements, just producing the necessary movements to maintain its head out of the water. This answer was classified as behavioural immobility, indicating a possible state of despair of the animal when it realizes that there is no escape. The rats were placed individually in a cylindrical tank (100 cm diameter × 60 cm height) whose level of water does not allow the animal to lean on the floor, nor arise by the border. The temperature of the water was maintained at 25°C. The animals were submitted to the forced swimming for 15 min (pre-test). After 15 min of forced swimming, each animal was gently dried and then returned to their cages. Twenty-four hours after the pre-test, all the animals were put back inside of the tank. The individual behavioural evaluation was accomplished and quantified during 5 min of forced swimming. The behavioural parameters as Latency of the Attempt of Escape (LAE) and Behavioral Immobility (BI) were quantified in seconds (s). Then the animals were removed from the water and gently dried and placed back into their cages.

Sampling protocol

Blood samples: At the end of the experimental period, all rats were anaesthetized again by sodium pentobarbital (60 mg kg^{-1}, i.p). These blood samples were collected without anticoagulant, left for 10 min and then centrifuged for 10 min at 3,000 r min^{-1} to obtain serum, which was stored at -20°C until further biochemical analysis for determination of serum corticosterone level.

Tissue samples: Brain tissue preparation: The whole brain was quickly removed and washed in 0.9% cold saline. The prefrontal cortex and hippocampus were carefully dissected and homogenized. The homogenates were centrifuged at 10,000 g for 15 min at 4°C and the supernatant was kept at were stored at -80°C until used for determination of BDNF, neurotrophin 3 (NT 3), 5-HT, dopamine, norepinephrine, malondialdehyde (MDA) and reduced glutathione (GSH) levels.

Biochemical investigations

Estimation of BDNF, NT 3, 5-HT, dopamine and norepinephrine in prefrontal cortex and hippocampus: ELISA assay kits were used for the determination of BDNF (catalog number: MBS2700741, MyBioSource, USA), NT 3 (catalog number: MBS2701228, MyBioSource, USA), 5-HT (Catalog No: MBS725497, MyBioSource, USA), dopamine (Catalog No: MBS701755, MyBioSource, USA) and norepinephrine (Catalog No: MBS1600150, MyBioSource, USA) levels according to the manufacturer's instructions.

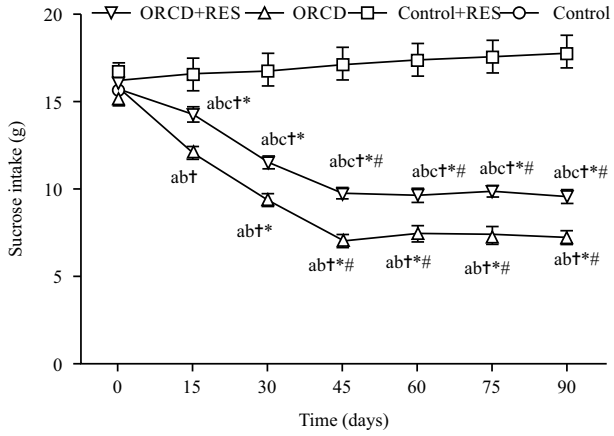
Estimation of MDA and GSH in prefrontal cortex and hippocampus: ELISA assay kits were used for the determination of MDA (catalog number: MBS738685, MyBioSource, USA), GSH (catalog number: MBS724319, MyBioSource, USA) levels according to the manufacturer's instructions.

Estimation of serum corticosterone: ELISA assay kits were used for the determination of serum corticosterone level (Catalog No: MBS747052, MyBioSource, USA) according to the manufacturer's instructions.

Statistical analysis: The data were expressed as mean±standard deviation (SD). Data were processed and analysed using the SPSS version 10.0 (SPSS, Inc., Chicago, Ill., USA). For analysis of sucrose intake, two-way ANOVA was done followed by Tukey's multiple comparison test. For analysis of serum corticosterone, as well as hippocampal and cortical BDNF, NT 3, 5-HT, dopamine, norepinephrine, MDA and GSH levels, one-way ANOVA was done followed by Tukey's post hoc test. Results were considered significant if $p \leq 0.05$.

RESULTS

Sucrose intake: The changes in sucrose intake in control, control+RES, ORCD and ORCD+RES groups are shown in Fig. 1. On day 0 of the experiment, there was no significant difference in sucrose intake among the different groups ($p>0.05$). No significant changes were observed in sucrose intake in normal rats with RES administration ($p>0.05$). ORCD induced a significant decrease in sucrose intake as compared with the normal control group ($p<0.05$). RES caused a significant increase in sucrose consumption in ORCD rats ($p<0.05$) in comparison with the untreated ORCD group, but the level was still significantly lower than that of control and control+RES groups (Fig. 1). Tests of main effects for the period of the experiment (day 0-90) showed statistically



ANOVA table	SS	DF	MS	F (DFn, DFd)	p-value
Interaction	591.9	18	32.89	F (18, 196) = 75.79	p<0.0001
Row factor	281.5	6	46.91	F (6, 196) = 108.1	p<0.0001
Column factor	2562	3	854.1	F (3, 196) = 1968	p<0.0001

Fig. 1: Sucrose intake (g) in control and orchidectomized rats either untreated or resveratrol treated

Data are expressed as Mean±SD of 10 rats in each group. RES: Resveratrol, ORCD: Orchidectomy. a: Significant ($p<0.05$) versus control, b: Significant ($p<0.05$) versus control+RES group, c: Significant ($p<0.05$) versus ORCD group, † Significant ($p<0.05$) versus their baseline (day 0), *Significant ($p<0.05$) versus day 15, #Significant ($p<0.05$) versus day 30

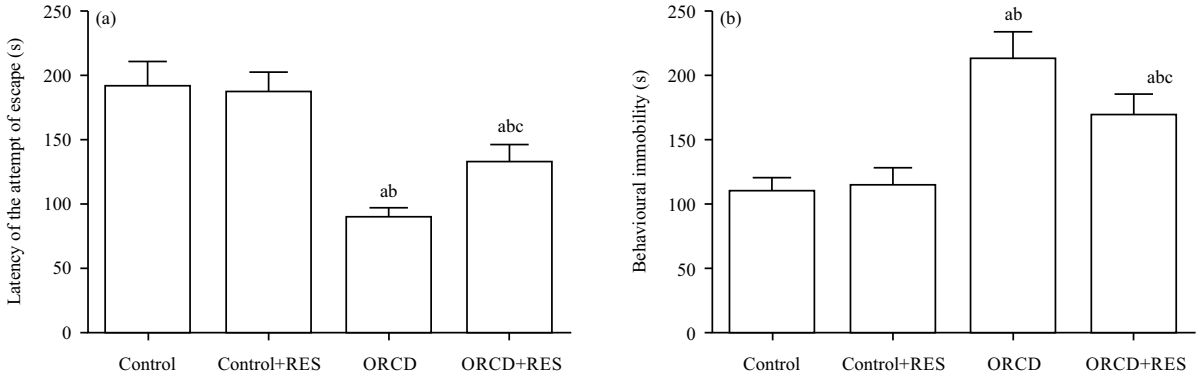


Fig. 2(a-b): (a) Latency of the attempt of escape (LAE) and (b) Behavioural Immobility (BI) in control and orchidectomized rats either untreated or resveratrol treated

Data are expressed as Mean±SD of 10 rats in each group. Cont: Control, RES: Resveratrol, ORCD: Orchidectomy, a: Significant ($p<0.05$) versus control group, b: Significant ($p<0.05$) versus control+RES group, c: Significant ($p<0.05$) versus ORCD group

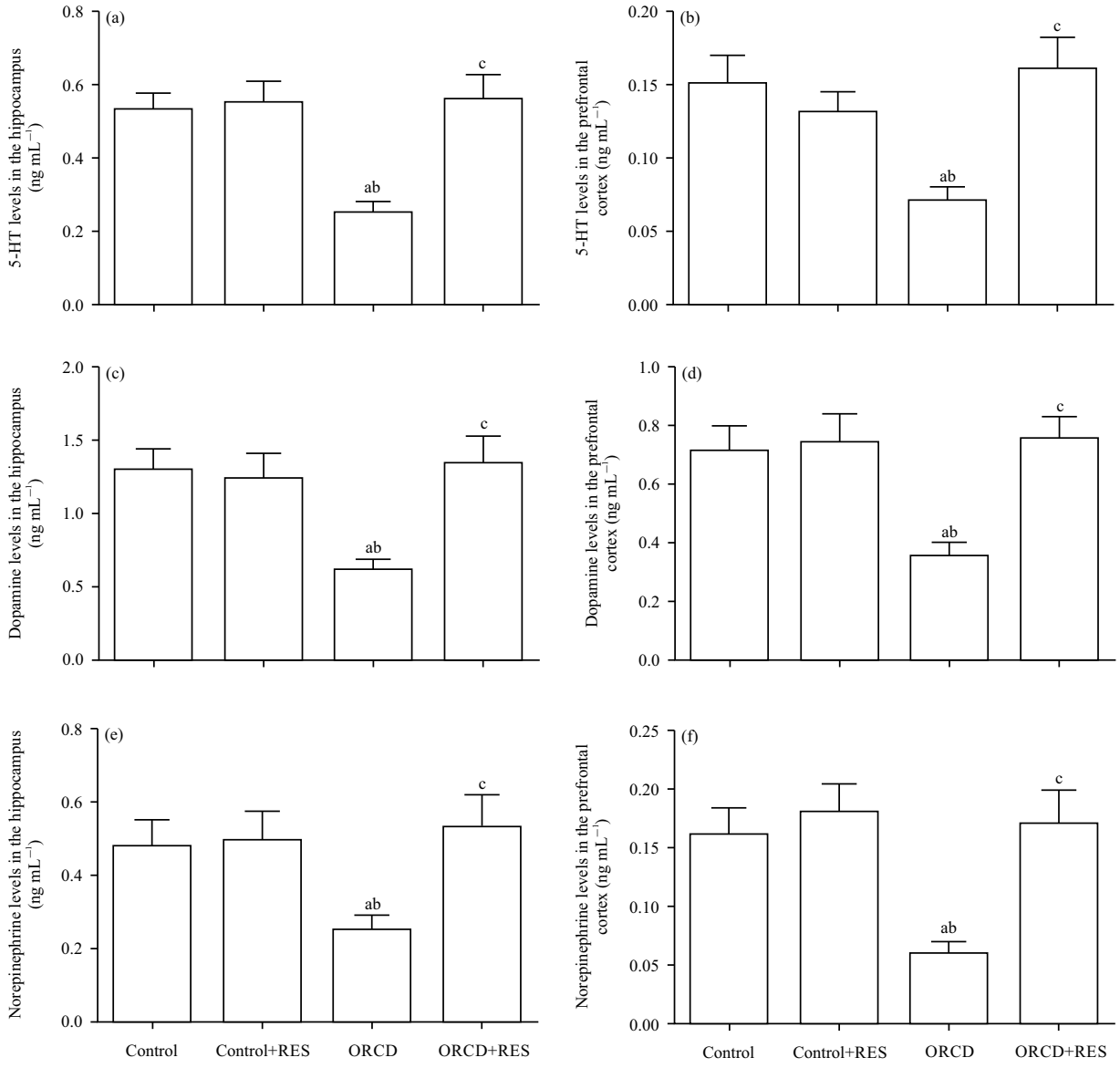


Fig. 3(a-f): (a-b) 5-HT, (c-d) Dopamine and (e-f) Norepinephrine levels in the hippocampus and prefrontal cortex of control and orchidectomized rats either untreated or resveratrol treated

Data are expressed as Mean ± SD of 10 rats in each group. Cont: Control, 5-HT: 5-hydroxytryptamine, RES: Resveratrol, ORCD: Orchidectomy. a: Significant ($p<0.05$) versus control group, b: Significant ($p<0.05$) versus control+RES group, c: Significant ($p<0.05$) versus ORCD group

significant differences among the four groups of animals (control, control+RES, ORCD and ORCD+RES) ($p<0.0001$). There was a significant interaction between group and day ($p<0.0001$).

FST: The behavioural parameters during the FST as LAE and BI were evaluated (Fig. 2a-b). LAE of the ORCD group was significantly smaller ($p<0.05$) while BI was larger ($p<0.05$) when compared with the control group. While RES had no significant effect on LAE and BI in control animals ($p>0.05$), it caused a significant increase in LAE and decrease in BI in ORCD rats ($p<0.05$) in comparison with the untreated ORCD group but the levels were still significantly different as compared to control and control+RES groups (Fig. 2a-b).

5-HT, dopamine and norepinephrine levels: Levels of 5-HT, dopamine and norepinephrine in the hippocampus and prefrontal cortex of control, control+RES, ORCD and

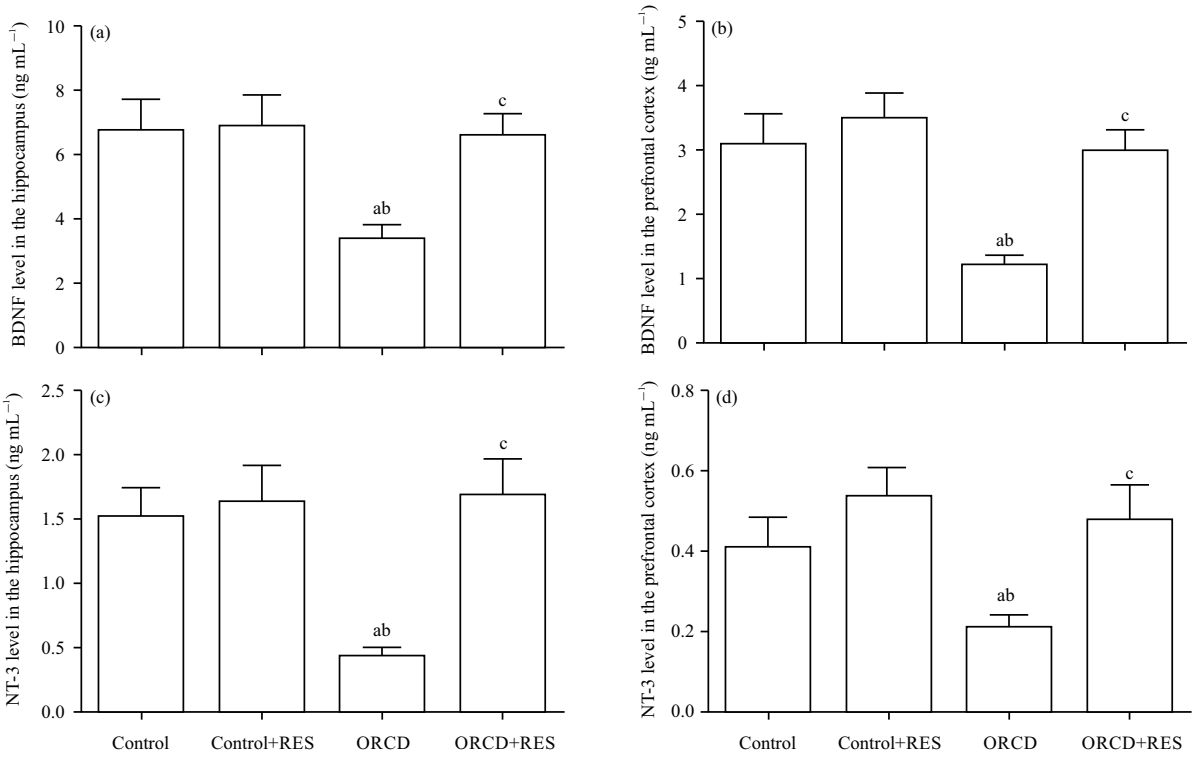


Fig. 4(a-d): (a-b) BDNF and (c-d) NT3 levels in the hippocampus and prefrontal cortex of control and orchidectomized rats either untreated or resveratrol treated

Data are expressed as Mean±SD of 10 rats in each group. BDNF: Brain-derived neurotrophic factor, NT 3: Neurotrophic factor, Cont: Control, RES: Resveratrol, ORCD: Orchidectomy, a: Significant (p<0.05) versus control group, b: Significant (p<0.05) versus control+RES group, c: Significant (p<0.05) versus ORCD group

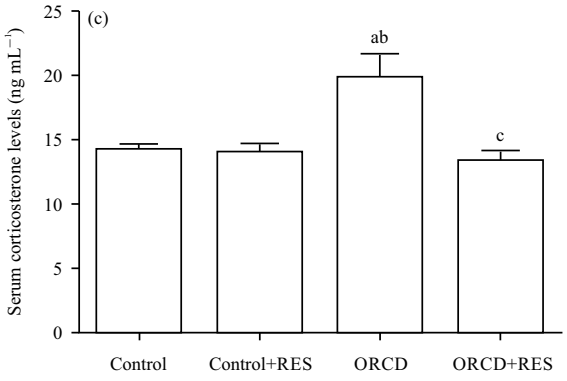


Fig. 5: Serum corticosterone levels in control and orchidectomized rats either untreated or resveratrol treated

Data are expressed as Mean±SD of 10 rats in each group. Cont: Control, RES: Resveratrol, ORCD: Orchidectomy. a: Significant (p<0.05) versus control group, b: Significant (p<0.05) versus control+RES group, c: Significant (p<0.05) versus ORCD group

ORCD+RES groups are shown in Fig. 3a-f. No changes in levels of 5-HT, dopamine and norepinephrine were detected in control rats with RES treatment (p>0.05). ORCD caused a significant decrease in levels of 5-HT dopamine and norepinephrine (p<0.05) in comparison with the control group. Administration of RES to ORCD rats caused a significant increase in levels of 5-HT dopamine and norepinephrine (p<0.05) in comparison with the untreated ORCD group.

BDNF and NT3 levels: Hippocampal and prefrontal cortical levels of BDNF and NT3 in control, control+RES, ORCD and ORCD+RES groups are shown in Fig. 4a-d. ORCD caused a significant decrease in levels of BDNF and NT3 in comparison with a control group (p<0.05). While RES caused no changes in levels of BDNF and NT3 in control rats, a significant increase in their levels was detected in ORCD rats treated with RES.

Serum corticosterone levels: Serum levels of corticosterone in control, control+RES, ORCD and ORCD+RES groups are shown in Fig. 5. ORCD caused a significant increase in serum levels of corticosterone in comparison with the control group (p<0.05). While RES caused no changes in serum levels of corticosterone in control rats, a significant decrease in their levels was detected in ORCD rats treated with RES.

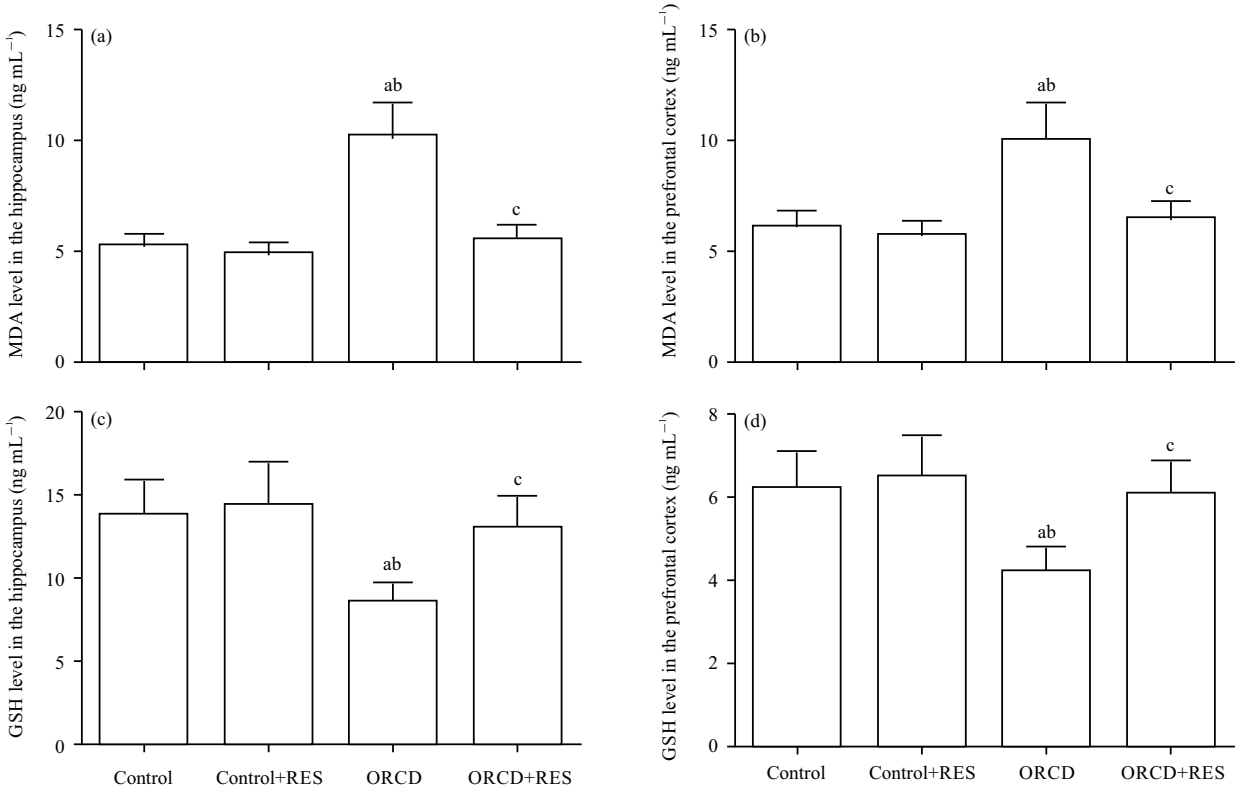


Fig. 6(a-d): (a-b) MDA and (c-d) GSH levels in the hippocampus and prefrontal cortex of control and orchidectomized rats either untreated or resveratrol treated

Data are expressed as Mean±SD of 10 rats in each group. Cont: Control, RES: Resveratrol, ORCD: Orchidectomy, a: Significant ($p<0.05$) versus control group, b: Significant ($p<0.05$) versus control+RES group, c: Significant ($p<0.05$) versus ORCD group

MDA and GSH levels: Levels of MDA and GSH in the hippocampus and prefrontal cortex of control, control+RES, ORCD and ORCD+RES groups are shown in Fig. 6a-d. No changes in levels of MDA and GSH were detected in control rats treated with RES ($p>0.05$). ORCD caused a significant increase in MDA and a decrease in GSH levels ($p<0.05$) in comparison with the control group. Administration of RES to ORCD rats caused a significant increase in GSH and decrease in MDA levels ($p<0.05$) in comparison with the untreated ORCD group.

DISCUSSION

This study was planned to investigate the antidepressant effect of RES in a rat model of surgical hypogonadism. The main findings of the current work were; 1-Gonadectomy in male rats induced Depressive-like behaviours and decreased neurotrophic factors (BDNF and NT3), 2-Administration of RES to gonadectomized male rats improved these Depressive-like behaviours through increasing neurotrophic factors (BDNF and NT3), ameliorating oxidative stress and reducing corticosterone.

Previous studies showed there is a great association between male hypogonadism and depressive manifestations[2,4-6]. Castrated rats were reported to be more susceptible to developing Depressive-like behaviours[2]. Besides, the incidence of depression-spectrum disorders is increased in young and older men with lower levels of testosterone[7]. Hypogonadal men with depression could be effectively treated with androgen replacement therapy[8]. In agreement with these studies, the results of FST in our work showed decreased LAE and increased BI in orchidectomized rats in comparison with control animals suggesting the development of Depressive-like behaviours. Besides, sucrose intake was significantly decreased in gonadectomised male rats indicating anhedonia, which is a core symptom of depression[18,20].

The decline in reward-seeking behaviour associated with depression is reversed with RES as evidenced by an increase in sucrose intake in depressed animals receiving RES[14,21]. Besides,

RES decreased immobility time in depressed animals[21]. Inconsistent with these studies, our results showed that administration of RES to orchidectomized Depressive-like animals caused a significant increase in LAE and a decrease in BI in FST as well as an increase in sucrose intake when compared with untreated orchidectomized rats suggesting an improvement of Depressive-like behaviours.

The monoamine hypothesis of depression reported that the brain depletion of norepinephrine, serotonin, and/or dopamine might explain the aetiology and pathogenesis of depression[22]. The results of the current work demonstrated a significant decrease in 5-HT, dopamine and norepinephrine levels in the hippocampus and prefrontal cortex of castrated rats suggesting the development of depression. Administration of RES to those castrated Depressive-like rats caused a significant elevation of these transmitters to the control values. These results were in agreement with those of the previous studies[23]. In an earlier study, it was reported that RES administration to depressed rats caused a significant increase in the dopamine, norepinephrine and 5-HT levels in different regions of the brain, which coincides with the monoamine hypothesis[24]. Moreover, treatment of rodents with RES has been shown to increase dopamine in the frontal cortex and striatum, norepinephrine in the frontal cortex and hippocampus and serotonin in the frontal cortex, hippocampus and striatum[25,26]. Also, the enzymes monoamine oxidase A and B, which reduce neurotransmitter levels through oxidative deamination, is reduced by RES in mice[26,27]. These outcomes reveal that RES may decrease Depressive-like behaviours in mice via the noradrenergic and serotonergic systems[26].

BDNF is a member of the neurotrophin family, a family of structurally related growth factors that, in mammals, also includes nerve growth factor (NGF), NT3 and NT4/5. BDNF and other neurotrophins are essential for the development and maintenance of the nervous system including regulation of neurogenesis, neuroplasticity and cell survival, learning mobility, behaviour and memory[28,29]. It was reported that some diseases such as Alzheimer's and depression are associated with a reduction in BDNF levels[30]. Also, an earlier study demonstrated that the levels of BDNF are lower in depressed individuals and that antidepressants increase BDNF levels[31]. Testosterone may also influence adult neurogenesis by increasing the levels of BDNF within the brain[32-34]. The results of the present work demonstrated that BDNF and NT3 levels in the hippocampus and prefrontal cortex were significantly decreased in castrated rats when compared with control animals suggesting a reduction of neurogenesis and indicating that testicular hormones modulate these factors. Our results were in agreement with those of previous studies which showed a significant reduction in the expression of hippocampal BDNF in gonadectomized rats[33]. Also, gonadectomy in male rats was reported to cause a reduction in BDNF expression levels in motor neurons of the spinal cord[34]. The gonadectomy-induced reduction of neurogenesis indicates that testicular hormones modulate this neurotrophic factors[2].

Treatment of castrated rats with RES resulted in a significant increase in BDNF and NT3 which indicates improvement of neurogenesis. These results were under those of previous studies which showed that administration of RES to rodents increases BDNF levels in various brain regions, including the hippocampus, prefrontal cortex and amygdala[21]. Moreover, acute and chronic RES treatment increased BDNF in the hippocampus of the rat model of depression[35].

Several studies showed that plasma and serum cortisol are higher in individuals with major depression[36]. In agreement with these studies, the results of the current study showed a significant increase in serum corticosterone in orchidectomized rats when compared with control animals suggesting that the development of depression in those castrated rats. In some animal models of depression, RES reduced the rise in serum and plasma levels of corticosterone[14,31]. Ali *et al.*[31] reported that administration of RES to corticosterone-treated mice significantly reduced the high serum corticosterone levels[31]. Also, mice induced with stress had lower serum corticosterone after 21 days of RES treatment than vehicle mice[37]. In a rat model of subclinical hypothyroidism-induced depression, RES reduced plasma corticosterone levels and depressive behaviours[14]. Inconsistent with these studies, our results demonstrated that RES significantly decreased serum corticosterone level in orchidectomized rats as compared to untreated orchidectomized animals suggesting that RES ameliorates depression in those rats.

The current study showed the development of oxidative stress in the hippocampus and prefrontal cortex after orchidectomy as demonstrated by the significant increase in MDA and the significant decrease in GSH. Our results are in agreement with several studies which showed that oxidative stress is a contributing factor in the pathogenesis of depression to the extent that antioxidants have been suggested as neuroprotectors against depression[38]. Moreover, oxidative stress may represent the mechanism underlying the neurodegeneration observed in depression[39]. Following these findings, our results showed that RES caused a significant decrease in MDA and an increase in GSH in the prefrontal cortex and hippocampus of orchidectomy-induced depression

in rats indicating improvement of the oxidative stress which may contribute to the alleviating effect of RES on depression in those rats.

CONCLUSION

Gonadectomy in male rats decreased neurotrophic factors (BDNF and NT3) and induced Depressive-like behaviours as evidenced by decreased sucrose intake and LAE and increased BI. Treatment of gonadectomized male rats with RES improves the Depressive-like behaviours, as shown by increased sucrose intake and LAE and decreased BI, through increasing BDNF and NT3, ameliorating oxidative stress and reducing corticosterone in this rat model of hypogonadism-induced depression.

SIGNIFICANCE STATEMENT

This study revealed the importance of RES in improving the depression induced by hypogonadism in rats. It showed that RES had a significant antidepressant effect through increasing the neurotrophic factors, decreasing the oxidative stress and lowering the corticosterone level. This study will shed light on researchers and psychologists to identify the importance of RES in the treatment of depression.

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