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Prenatal stress-induced cognitive impairment and neuronal oxidative stress and its amelioration by resveratrol in neonate rats

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ABSTRACT

Prenatal stress induced neuronal damage in offspring is multi-factorial, including oxidative damage in developing brain. Resveratrol is known to exert its neuroprotective potentials by up regulating several antioxidant enzymes. Hence in the present study we tested antioxidant potential of resveratrol against prenatal stress induced neuronal damage in the hippocampus of offspring. Pregnant rats were subjected to restraint stress during early or late gestational period. Another sets of rats received resveratrol during entire gestational period along with early or late gestational stress. The cognitive function is assessed through passive avoidance test. At the end of the behavioural test (on 40th postnatal day), the offspring were sacrificed their brain homogenate was subjected to various antioxidants studies. Prenatal stress affected the memory retention capability with significant decrease in glutathione, glutathione reductase and superoxide dismutase activity in offspring brain. Administration of resveratrol during pregnancy reversed the prenatal stress-induced memory impairment and oxidative damage in the offspring who received prenatal stress during late gestation but not in early gestation. These results suggest that resveratrol treatment may be an effective strategy for preventing the brain oxidative damage and cognitive dysfunction associated with prenatal stress.

Keywords: prenatal stress, resveratrol, passive avoidance test, reduced glutathione, glutathione reductase, superoxide dismutase.

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INTRODUCTION

Resveratrol (3, 4', 5 trihydroxystilbene) is a naturally occurring phytoalexin present in high concentration in the skin and seeds of grapes [1]. Resveratrol exerts neuroprotective properties by up regulating several detoxifying enzymes, most of which are iron proteins [2]. Ates et al [3] demonstrates that resveratrol as a potent neuroprotective agent against diabetic induced oxidative damage in the brain. In an in vitro ischemia model resveratrol derivatives has reduced neuronal cell death and found to be neuroprotective [4]. Treatment of resveratrol immediately after traumatic brain injury reduces oxidative stress and lesion volume [5]. In addition resveratrol decreased anxiety and increased cortex/hippocampus dependent memory of animals subjected to blunt head trauma [6]. Studies further extending to the level of neurotransmitters claim that resveratrol protects dopaminergic neurons in midbrain slice culture from multiple insults [7]. Resveratrol is known to possess potent antioxidant activity [8] and it is generally assumed that its neuroprotective action is principally associated with this property [9,10].

Stress has effects on brain areas that play a critical role in learning and memory. Stress and adaptation to stress require numerous homeostatic adjustments such as hormones, neurotransmitters, oxidants, and other mediators. Among these factors, the balance between oxidants and antioxidants seems to play a critical role [11]. Using supplements of antioxidants has been an effective strategy for preventing stress-induced abnormality [11]. Retrospective studies on humans, and research on animals, suggest that prenatal stress can influence the physical, behavioural and cognitive outcomes of the offspring [12]. It is found that prenatal stress causes alterations of the hypothalamic–pituitary–adrenocortical axis and brain neurotransmitter systems in the offspring, increases anxiety and emotionality and decreases spatial learning and memory [13]. Studies have proven that prenatal restraint stress results in the offspring's cognitive impairment accompanied by a decrease in neuron numbers, and by increases in other parameters including nNOS expression, oxidative damage to mitochondrial DNA, and damage to the hippocampal antioxidant systems [14]. Resveratrol can cross the blood brain barrier [15] and placental barrier [16]. So we hypothesize that, resveratrol as it exerts potent antioxidant and neuroprotective features may minimize the stress effects in pregnant rats and also cross placental barrier to exert neuroprotective effect on developing brain.

Hence in the present study, we investigated the protective effect of resveratrol on prenatal stress-induced cognitive dysfunction in a prenatal restraint stress model in rats. In addition we also evaluated the effect of prenatal stress and resveratrol treatment on antioxidant defence system in neonatal rat brain.

MATERIALS AND METHODS

Animals and housing conditions

In-house bred male and female albino Wistar rats (3-4 months old) of weight 200-230gm were selected for the study. The rats were maintained in 12 hours light and dark cycle in temperature and humidity controlled environment. The rats were fed with standard food pellet and water *ad libitum*. Polypropylene cage with paddy husk as bedding materials

was used for housing the rats. Breeding and maintenance of the animals were done as per the guidelines of Government of India for use of Laboratory animals (Government of India notifies the rules for breeding and conducting animal experiments, proposed in the gazette of India Dec 15, 1998: which was reproduced in Ind. Journal of Pharmacol 31:92-95, 1999). Institutional Animal Ethics Committee (I.A.E.C) approval was obtained before the conduct of the study (IAEC/KMC/2010) and care was taken to handle the rats in humane manner.

Mating of rats and animal groups

Three female rats were allowed to mate with one fertile sexually active male rat for 4 hours per day (separate male rats for each group). At the end of 4 hours, female rats were separated and vaginal smears taken to detect the presence of sperm for the confirmation of pregnancy and the rats were designated as day 0 of pregnancy for further counting the days. The pregnant rats were housed individually in separate cages with proper label indicating the day of conception and randomly allocated into six groups of six each. One male and one female pups from each mother were considered for the study (n=12; six male and six female pups). All the mothers delivered at term (22-24th day of gestation). The offspring were raised by their biological mothers until weaning (21 days after birth). The number of offspring considered for neonatal parameters is in accordance with Holson & Pearce [17].

Stressing procedure

The pregnant rats were stressed (restraint stress) using a wire mesh restrainer [18] for three times daily for 45 minute. To prevent habituation of animals to the daily procedure, restraint periods were shifted randomly within certain time periods (08:00 AM–11:00 AM, 12:00 AM–3:00 PM, and 4:00 PM–7:00 PM). The wire mesh restrainer will have a wooden base and stainless steel wire mesh restrainer hinged to the base. A pad lock and latch will help to secure the rat in the restrainer. The restrainer with dimension 11 cm (L) x 6cm (B) x 6 cm (H) was used for rats with gestation day 1 to 10. Restrainer of 11cm (L) x 8 cm (B) x 8 cm (H) was used for rats with gestation day 11 to till delivery. This type of restrainer will only restrict the animal movement without any pain, discomfort or suffocation.

Animal groups

Group 1. (Control) The pups belonging to the pregnant rats who received only 0.5% carboxy methyl cellulose in a dose of 10ml/kg body weight (oral) throughout pregnancy.

Group 2. The pups belonging to the pregnant rats who received only resveratrol alone in a dose of 10mg/kg body weight (oral) throughout pregnancy.

Group 3. The pups belonging to the pregnant rats who received restrain stress from gestation day 1 to 10.

Group 4. The pups belonging to the pregnant rats who received restrain stress from gestation day 11 to till delivery.

Group 5. The pups belonging to the pregnant rats who received restrain stress from gestation day 1 to 10 and resveratrol (10mg/kg body weight, oral) throughout pregnancy.

Group 6. The pups belonging to the pregnant rats who received restrain stress from gestation day 11 to till delivery and resveratrol (10mg/kg body weight, oral) throughout pregnancy.

Resveratrol (Cat. no. 70675, Cayman chemicals, USA) was obtained from Pro Lab marketing, New Delhi, India. The dose of resveratrol considered in the present study is according to the earlier study by Kumar et al [19] and it was suspended with carboxy methyl cellulose.

Behavioural testing

Passive Avoidance test

To test the memory retention 30 days old rats were subjected to passive avoidance test [20]. The test determines the ability of a rat to remember a foot shock delivered 24 hr prior to the memory retention test. The apparatus used for this purpose was the digital passive avoidance apparatus (Techno, Lucknow, India). Passive avoidance apparatus consists of a wooden box with two compartments: (a) larger, bright compartment and (b) smaller, dark compartment equipped with grid floor, which is attached to a shock source. On the first day of test, rat was placed in the illuminated large compartment for exploration. The door between the two compartments remained open at this time. The rat was allowed to explore both compartments for 5 min. This is followed by three test trials of 5 min each. In each trial, fraction of time spent in each compartment was noted. At the end of 3rd test trial, as soon as the animal stepped into dark compartment, a foot shock was delivered through the grid floor (1.5mA. 1 sec). The rat was held additional 10sec, to allow the animal to form an association between the properties of the chamber and foot shock. It was then returned to its home cage. The memory retention test was done 24 hr after foot shock. The rat was placed in the bright compartment and the time taken (the step-through latency) for it to enter the dark compartment for the first time was recorded using a stop watch. A maximum of 300 sec were given for the rat to explore. Fraction of time spent in dark and bright compartment for each rat was noted.

Neurochemical measurements

Preparation of brain homogenate for measurement of oxidative stress

At the 40th postnatal day, six male and six female offspring were used for each group (n=12). The whole brain was removed rapidly and rinsed with 0.1M/L saline phosphate buffer (pH 7.4). Tissue was weighed and homogenized (1:10w/v) in 0.1M/L saline phosphate buffer. The homogenate was centrifuged at 10 000g for 20 min at 4°C and aliquots of supernatant were separated and used for following biochemical estimations.

Estimation of reduced Glutathione

Tissue reduced glutathione (GSH) concentration was estimated according to the method described by Ellman (21). One ml of supernatant was precipitated with 1ml of metaphosphoric acid and cold digested at 4ºC for 1h. The samples were centrifuged at

1,200g for 15min at 4ºC. To 1ml of this supernatant, 2.7ml of phosphate buffer and 0.2ml of 5, 5' dithio-bis (2-nitrobenzoic acid, DTNB) was added. The yellow color that developed was read immediately at 412nm using a Systronic-117 spectrophotometer. The values were expressed in mg/gm protein. The total protein concentration of tissues was measured by the method of Lowry et al [22].

Assay of Glutathione Reductase

The Glutathione Reductase (GSSG-Rd) activity was measured using the method originally described by Moron et al [23]. The reaction mixture consisted of 1.6ml of 0.067M potassium phosphate buffer (pH 6.6), 0.12ml of 0.06% NADPH, 0.12ml 1.15% GSSG, 0.1ml of enzyme source (supernatant) and water in a final volume of 2ml. All mixtures and solutions were prepared at room temperature. Control cuvettes then received 180µL of deionised water while sample cuvettes received 60µL of deionised water and 120 µL of GSSG solution. NADPH oxidation was followed for 5min and was recorded using a Systronic-117 spectrophotometer. The reduction of GSSG to GSH was determined indirectly by the measurement of the consumption of NADPH, as demonstrated by a decrease in absorbance at 340 nm as a function of time. The enzyme activity was calculated using extinction coefficient of chromophore ($1.36x10^4$ $(mol/l)^{-1}$ cm^{-1}) and expressed as nmol NADPH oxidized/min/mg protein. Protein content was determined by the method of Lowry et al [22] with bovine serum albumin as standard.

Assay of Superoxide Dismutatase activity

Superoxide dismutatase **(**SOD) activity was determined by the method of Marklund et al [24]. The reaction was perfomed in an mixture containing $5.6x10^{-5}$ M nitrobluetetrazolium (NBT), $1.17X10^{-6}$M riboflavin, $1x10^{-2}$M methionine in 0.05M potassium phosphate buffer, pH 7.8 with suitably diluted brain homogenate in a total volume of 3ml. Illumination of solution was carried out in an aluminium lined foil box fitted with an 15v fluorescent lamp. The solution taken in a beaker was kept in the box and illuminated exactly for 10min. Control without the enzyme source was prepared. The absorbance was measured spectrophotometrically with a Systronic-117 UV-Visible spectrophotometer at 560 nm. SOD activity was expressed as specific activity of the enzyme in units per mg protein (U/mg protein). Protein content was determined by the method of Lowry et al [22].

Quantification of cortisol concentrations in blood serum

Blood samples were taken between 8.00 and 10.00 AM to avoid circadian variations of serum cortisol concentrations. The animals were anesthetized individually in a glass jar containing saturated ether vapour and intracardiac blood was collected. Corticosterone was measured by using electro chemiluminescent method using an ECOBAS 411 automatic analyzer (Roche Diagnostics, U.S.A.) established at the Kasturba Medical College Laboratory, Mangalore, India. The concentration of cortisol was expressed in ng/ml serum.

Statistical analysis

Data were presented as the mean±SE. Statistical analysis for multiple comparisons was performed by one way analysis of variance (ANOVA) with Bonferroni's corrections. Comparison of data between male and female group was assessed by unpaired "t" test. *p* values < 0.05 were considered as significant.

RESULTS

There was no sexually dimorphic effect was observed in all the assessed parameters, hence mean values for both male and female were collapsed together. Restraint stress (both early and late) during pregnancy and resveratrol treatment do not have any significant effect on gestational length (p=0.077, F=2.231) and litter size (p=0.689, F=0.614). There was no mortality in any of the group till 21st postnatal day.

Passive avoidance test

There was no significant difference between the different treatment groups (prenatal stress, resveratrol and their combination) on the initial latency to enter the dark compartment, time spent in dark and bright compartments during the passive exploration test. Therefore any differences seen subsequently are a reflection of differences in the retrieval and are not related to the initial baseline activities. (Data not shown)

Latency to enter the dark compartment: During passive avoidance retention test, the offspring who received prenatal stress during early (group-3, p<0.001) and late (group-4, p<0.01) gestation took shorter time to enter the dark compartment compared to control offspring (group-1). Shorter latency indicates poor retrieval of learned behaviour. Prenatal resveratrol treatment reversed the cognitive impairment of the offspring who received late gestational stress (group-6 vs. group-4, p<0.001) but not in early gestational stress (group-5 vs. Group-3, p>0.05) by taking longer time to enter in to the dark compartment. (Figure 1A)

Time spent in bright compartment: On assessing total time spent in bright compartment of the passive avoidance apparatus during the retention test, it was found that prenatally stressed rats (group-3 & group-4) spent significantly less time in bright compartment compared to control (group-1, p<0.05) and prenatally resveratrol alone treated rats (group-2, p<0.001). Offspring who received prenatal stress during late gestation and resveratrol treatment spent significantly more time in bright compartment (group-6 vs. Group-4, p<0.001). (Figure 1B)

Time spent in dark compartment: On assessing total time spent in dark compartment of the passive avoidance apparatus during the retention test, it was found that prenatally stressed rats (group-3 & group-4) spent significantly more time in dark compartment compared to control (group-1, p<0.05) and prenatally resveratrol alone treated rats (group-2, p<0.001). Offspring who received prenatal stress during late gestation and resveratrol treatment spent significantly less time in dark compartment (group-6 vs. Group-4, p<0.001). (Figure 1C)

Reduced glutathione level in brain

Prenatal stress during early (group-3) and late gestation (group-4) caused a significant (p<0.001) depletion of GSH level in the brain compared to control (group-1). Offspring who received late gestational stress and resveratrol treatment (group-6) showed a significant (p<0.01) increase in GSH level when compared to prenatally stressed offspring (group-4). While, Offspring which received both prenatal stress during early gestation and resveratrol treatment (group-5) did not differ (p>0.05) from offspring received only prenatal stress during early gestation (group-3). No significant change in GSH level was observed in offspring whose mothers were treated with resveratrol alone (group-2). (Figure 2)

Glutathione reductase activity in brain

The activity of brain GSSG-Rd was significantly (p<0.001) decreased in prenatally stressed offspring (group-3 and group-4) compared to control (group-1). Resveratrol treatment significantly (p<0.01) elevated the GSSG-Rd activity in the offspring who received prenatal stress during late gestation but not in early gestation compared to prenatally stressed offspring. No significant change in GSSG-Rd activity was observed in offspring whose mothers were treated with resveratrol alone (group-2). (Figure 3)

Superoxide Dismutase activity in brain

The brain SOD activity was significantly decreased in the offspring who received stress during early (group-4, p<0.05) and late (group-4, p<0.01) gestation. But resveratrol treatment failed to restore the inhibited SOD activity in prenatally stressed offspring. No significant change in SOD activity was observed in offspring whose mothers were treated with resveratrol alone (group-2). (Figure 4)

Serum cortisol level

There is an increased serum cortisol level in the offspring of stressed mothers {group-3(p<0.01) and group-4(p<0.001)} compared to non-stressed control rat pups (group-1, indicates prenatal stress induced corticosterone secretion in the offspring. Offspring which received both prenatal stress and resveratrol treatment (group-5 and group-6) did not differ in serum cortisol level (p>0.05) from offspring received only prenatal stress (group-3 and group-4). (Figure 5)

DISCUSSION

Prenatal restraint stress has been reported to alter the development of the central nervous system in the fetus, and has long-term effects on the brain functions, including hormonal responses, neurotransmission and behaviour (14). In both animal experiments and human studies, offspring observed to be suffering from prenatal stress were found to have altered brain morphology, disturbances in the hypothalamo-pituitary–adrenal (HPA) axis, delayed in developmental reflexes, increased anxiety, reduced immune responses, depressive behaviour, and learning deficits [25]. The results of our present study also revealed that prenatal stress during early and late gestation showed an increased basal

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Figure 1

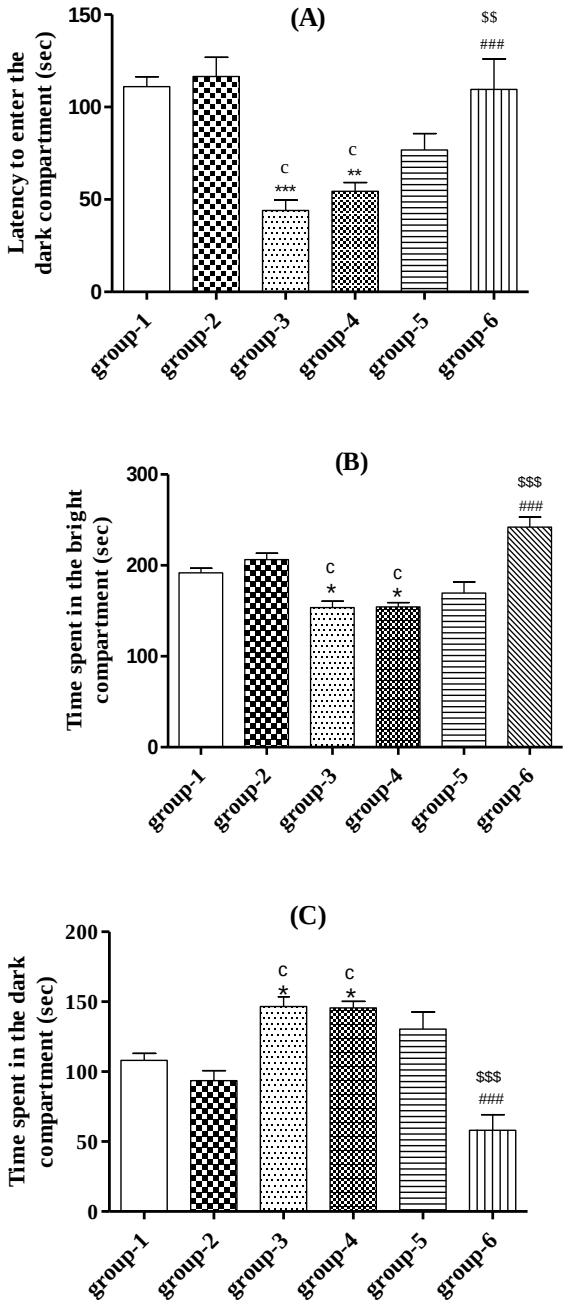

Figure 1. Effect of prenatal stress, resveartrol and their combinations on (A) latency to enter the dark compartment (B) time spent in the bright compartment and (C) time spent in the dark compartment in the passive avoidance apparatus during the retention test. Animal groups: Group-1: control, Group-2: pups received prenatal resveratrol during entire gestation period, Group-3: pups received prenatal stress during day 1 to 10, Group-4: pups received stress during day 11 till delivery, Group-5: pups received prenatal stress during day 1 to 10 and resveratrol during entire gestation period and Group-6: pups received prenatal stress during day 11 to till delivery and resveratrol during entire gestation period. For comparison with Group-1, *** p<0.001; **p<0.01; *p<0.05, for comparison with Group-2, ^{c} p<0.001, for comparison with Group-3, $^{###}$ p< 0.001 and for comparison with Group-4, $^{\$\$\$}$ p< 0.001; $^{\$\$}$p<0.01. (One way ANOVA, Bonferroni's test. Each data represents mean±SEM, n=12 per group).

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Figure 2.

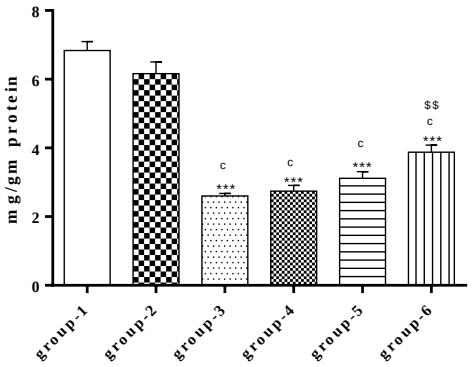

Figure 2. Brain reduced Glutathione level (mg/gm protein) in rats. Animal groups: Group-1: control, Group-2: pups received prenatal resveratrol during entire gestation period, Group-3: pups received prenatal stress during day 1 to 10, Group-4: pups received stress during day 11 till delivery, Group-5: pups received prenatal stress during day 1 to 10 and resveratrol during entire gestation period and Group-6: pups received prenatal stress during day 11 to till delivery and resveratrol during entire gestation period. For comparison with Group-1, *** p<0.001, for comparison with Group-2, [c] p<0.001, and for comparison with Group-4, [$$]p<0.01. (One way ANOVA, Bonferroni's test. Each data represents mean±SEM, n=12 per group).

Figure 3

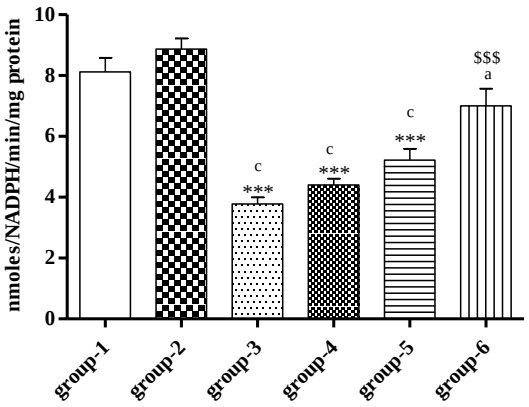

Figure 3. Brain Glutathione reductase activity (nmol NADPH oxidized/min/mg protein) in rats. Animal groups: Group-1: control, Group-2: pups received prenatal resveratrol during entire gestation period, Group-3: pups received prenatal stress during day 1 to 10, Group-4: pups received stress during day 11 till delivery, Group-5: pups received prenatal stress during day 1 to 10 and resveratrol during entire gestation period and Group-6: pups received prenatal stress during day 11 to till delivery and resveratrol during entire gestation period. For comparison with Group-1, *** p<0.001, for comparison with Group-2, [a] p<0.05; [c] p<0.001, and for comparison with Group-4, [$$$] p< 0.001. (One way ANOVA, Bonferroni's test. Each data represents mean±SEM, n=12 per group).

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Figure 4

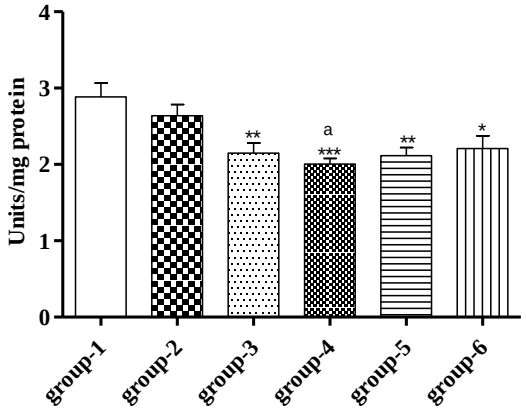
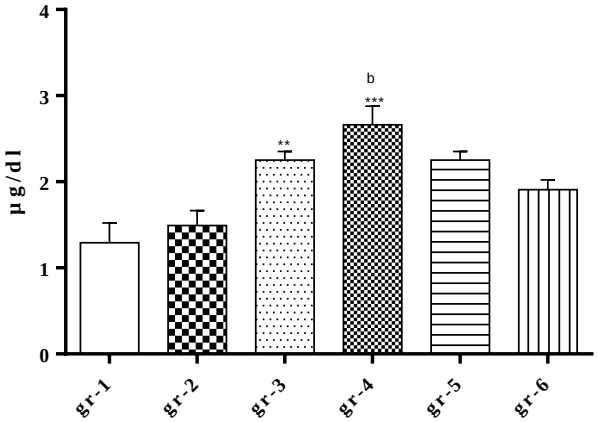


Figure 4. Brain Superoxide dismutase activity (U/mg protein) in rats. Animal groups: Group-1: control, Group-2: pups received prenatal resveratrol during entire gestation period, Group-3: pups received prenatal stress during day 1 to 10, Group-4: pups received stress during day 11 till delivery, Group-5: pups received prenatal stress during day 1 to 10 and resveratrol during entire gestation period and Group-6: pups received prenatal stress during day 11 to till delivery and resveratrol during entire gestation period. For comparison with Group-1, * p<0.05; ** p<0.01; *** p<0.001, and for comparison with Group-2, [a] p<0.05 (One way ANOVA, Bonferroni's test. Each data represents mean±SEM, n=12 per group).

Figure 5



Serum Cortisol level (µg/dl) in rats. Animal groups: Group-1: control, Group-2: pups received prenatal resveratrol during entire gestation period, Group-3: pups received prenatal stress during day 1 to 10, Group-4: pups received stress during day 11 till delivery, Group-5: pups received prenatal stress during day 1 to 10 and resveratrol during entire gestation period and Group-6: pups received prenatal stress during day 11 to till delivery and resveratrol during entire gestation period. For comparison with Group-1, * = *p*<0.001; ** = p<0. , for comparison with Group-2, [b] p<0.01 (One way ANOVA, Bonferroni's test. Each data represents mean±SEM, n=12 per group).**

cortisol secretion and impairs learning and memory abilities in offspring. The results of the present study are consistent with earlier reports [26,27]. The chronic maternal stress induced memory impairment, may be due to the influence of stress hormone on the developing brain. Exposures to excessive glucocorticoids during critical windows of neuroendocrine development have been reported to lead into cognitive deficits [28]. The possible involvement of oxidants and the relation to glucocorticoid hormones in stress has been proposed [11]. Increased glucocorticoids may cause increased activation of excitatory amino acid receptors and unregulated increases in intracellular Ca^{2+} concentrations, and consequently increased generation of oxidants and oxidative damage in the brain [14]. The excess production of reactive oxygen species (ROS), such as superoxide anion radical, hydroxyl radical, hydrogen peroxide, nitric oxide, and peroxynitrate, can oxidize key components of the cell including lipids, proteins, and nucleic acids [29]. Brain is more vulnerable to the damage of ROS than are other organs because brain is enriched in oxidizable polyunsaturated fatty acid and redox-active metals, but antioxidant molecules are low [30]. Hence we estimated various antioxidant systems in the offspring brain and we found prenatal stress during early and late gestation caused a significant decrease in GSH level, GSSG-Rd and SOD activity in offspring brain. Hence the prenatal stress-induced learning impairment may be mediated partly by oxidant production and suppressed antioxidant systems which cause oxidative damage to and loss of hippocampus neurons.

Stress and adaptation to stress require numerous homeostatic adjustments such as hormones, neurotransmitters, oxidants, and other mediators. Stress induced hormones, neurotransmitters, and oxidants all have beneficial effects that may become harmful if they are out of balance. Such imbalances and the over-interaction of these imbalances may ultimately cause increased oxidant generation in mitochondria, leading to oxidative damage to biomolecules (lipids, proteins, DNA, and RNA) and a decrease in antioxidant defences [11]. When these defense mechanisms become incompetent to scavenge free radicals, tissue damage begins. So, it is important to support endogenous defense mechanism by exogenous antioxidant agents.

Increasing evidence shows that cognitive dysfunction is related to neuronal oxidative damage in the hippocampus [31]. In addition, any exogenous antioxidant agents which are able to inhibit ROS generation, inhibit oxidative damage, may ultimately ameliorate cognitive dysfunction. Although mounting evidence convincingly demonstrates the neuroprotective and antioxidant activity of resveratrol in adult animals, but the efficacy of resveratrol against prenatal stress was not studied to the best of our knowledge. Hence in the present study, we evaluated the effect of resveratrol on prenatal stress-induced cognitive dysfunction and antioxidant defence system in neonatal rat brain. The results of our study demonstrated that prenatal resveratrol treatment not only enhances the learning and memory abilities but also enhanced the activity of antioxidant defense system in the offspring who received prenatal stress during late gestation but not in the offspring who received prenatal stress during early gestation. Most of the protective actions associated with resveratrol are due to its intrinsic radical scavenger properties, possibly by increasing the endogenous defensive capacity of the brain to combat oxidative stress. Resveratrol was also found to be a highly potent antioxidant that could inhibit free radical generation in brain and spinal cord [32]. It has been showed that it inhibits lipid peroxidation [33], and

prevents apoptotic cell death induced by oxidative stress [34]. It has been postulated that resveratrol could suppress mitochondria-induced production of ROS in rat brain [35], and protect DNA from oxidative damage in stroke-prone hypertensive rats [35] and could inhibit neuronal loss after ischemia/reperfusion injury in gerbils. Additionally, treatment with resveratrol decreased anxiety and increased cortex/hippocampus dependent memory of animals subjected to blunt head trauma (6). NADPH oxidase–dependent production of superoxide radical (O_2^-) has been identified as one of the major contributor to oxidative injury in the brain [36]. Resveratrol were shown to inhibit the activation of NADPH oxidase, mitogen-activated protein kinases and nuclear factor-kappaB (NF-κB) signalling pathways in microglia and thus prevents subsequent reactive oxygen species generation in different brain regions [37].

CONCLUSION

In conclusion, we found that maternal administration of resveratrol effectively prevented prenatal stress-induced cognitive dysfunction in offspring rats. We also found that resveratrol enhanced the antioxidant defense system against oxidative damage in offspring brain due to prenatal stress. These results suggest that, resveratrol prevents prenatal stress-induced cognitive impairment in offspring through decreasing ROS formation and oxidative damage, enhancing of the antioxidant defense system, and by protecting brain against oxidative injury. Based on the results of this study, we suggest that the beneficial effects of resveratrol can be explained, in part, by its antioxidant activity. Resveratrol treatment may be an effective strategy for preventing the brain oxidative damage and cognitive dysfunction associated with prenatal stress.

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