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AGE-DEPENDENT AND BRAIN REGION-SPECIFIC RESPONSES TO COLD STRESS: MODULATION BY TRANS-RESVERATROL AND GRAPE SEED PROANTHOCYANIDINS IN WISTAR RATS.

Physiology

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ABSTRACT

Cold stress can disturb redox homeostasis in nervous tissue, but age-dependent differences in this response and the protective effects of natural polyphenols remain insufficiently understood. This study investigated age-related oxidative responses to repeated cold exposure and evaluated the effects of trans-resveratrol (RES) and grape seed proanthocyanidin extract (GSPE) in male Wistar rats aged 3, 6, and 12 months. Animals were assigned to control, cold stress (CS), CS+RES, CS+GSPE, and CS+RES+GSPE groups (n=6/group). Cold-stressed animals were exposed to 5 ± 0.5 °C for 6 h/day for 15 consecutive days, with RES and GSPE administered orally. Lipid peroxidation and antioxidant status were assessed in the cerebral cortex and hippocampus by measuring MDA, MnSOD, catalase, GST, GPx, and reduced glutathione (GSH). Cold exposure produced marked age- and tissue-dependent oxidative alterations. MDA increased substantially in both brain regions, with the greatest response generally observed in 3-month-old rats. The hippocampus showed pronounced lipid peroxidation with distinct antioxidant responses. SOD, catalase, GST, GPx, and GSH showed variable changes across age groups and brain regions, indicating differential responses to cold stress. RES and GSPE reduced cold-induced lipid peroxidation and modified antioxidant defence. Combined treatment produced the most consistent reduction in MDA and enhanced selected antioxidant parameters, although its effects were not uniformly greater across all biomarkers, ages, or tissues. Overall, the findings demonstrate that age and brain region influence the biochemical response to repeated cold stress, while RES and GSPE can attenuate cold-induced oxidative alterations and support neural redox homeostasis.

KEYWORDS

Cold stress; Age-dependent oxidative stress; Cerebral cortex; Hippocampus; trans-Resveratrol; Grape seed proanthocyanidins.

INTRODUCTION:

Environmental stress can disturb physiological homeostasis and influence the structure and function of the nervous system [1] (El Marzouki. et al. 2021). Among environmental stressors, low temperature or cold stress has received comparatively less attention despite its potential effects on neural function. Cold exposure activates thermoregulatory, sympathetic and hypothalamic–pituitary–adrenal responses that are initially adaptive but may become detrimental when exposure is prolonged or repeated. Increased metabolic demand during cold stress can enhance reactive oxygen species (ROS) generation and disturb cellular redox balance [2] (Kaushik et al. 2003). The brain is particularly vulnerable to oxidative injury because of its high metabolic activity, high oxygen requirement and abundance of polyunsaturated fatty acids [3] (Alva et al. 2013). Excessive ROS can pro-mote lipid peroxidation and impair cellular components, while dep-letion or alteration of endogenous antioxidant defence may further increase neuronal susceptibility to oxidative damage [2] (Kaushik et al. 2003).

Age is an important factor that may modify the response of nervous tissue to environmental stress. Age-related changes in cellular metabolism, antioxidant capacity and redox homeostasis may alter the ability of neural tissue to cope with additional oxidative challenges [4] (Zhang et al. 2015). The cerebral cortex and hippocampus are particularly relevant in this context because of their high metabolic requirements and roles in cognitive and neural functions [2] (Kaushik et al. 2003). However, the extent to which age influences cold stress-induced oxidative alterations in these brain regions remains insufficiently characterized. Comparative assessment of young adult, mature adult and middle-aged animals may therefore provide useful information about age-related differences in neural vulnerability and adaptive capacity. Such information is also relevant for understanding why individuals at different stages of life may respond differently to environmental cold exposure.

Natural polyphenols have received considerable attention as potential agents for limiting oxidative injury. trans-Resveratrol, a biologically active stilbene polyphenol, possesses antioxidant and cellular protective properties and may enhance endogenous defence against oxidative stress [5, 6] ((Jha, 2025; Ren et al. 2025). Grape seed proanthocyanidin extract (GSPE) is rich in proanthocyanidins with strong antioxidant activity and has demonstrated protective effects against oxidative damage in several experimental systems [7] (Mansouri et al. 2015). Both compounds may act through multiple mechanisms involving direct control of reactive species and modulation of endogenous antioxidant defences. However, their protective effects against repeated cold stress-induced oxidative alterations in brain tissue, particularly across different age groups, remain inadequately explored. Whether combined administration provides greater protection than individual treatment is also an important question.

Therefore, the present study was designed to investigate age-dependent oxidative responses to repeated cold stress and the potential neuroprotective effects of trans-resveratrol and GSPE in male Wistar rats**.** Young adult (3 months), mature adult (6 months) and middle-aged (12 months) animals were exposed to cold stress at 5 ± 0.5 °C for 6 h daily for 15 consecutive days. Oxidative damage and antioxidant status were evaluated in the cerebral cortex and hippocampus using lipid peroxidation, MnSOD, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione as biochemical indicators. The study further evaluated individual and combined treatment with trans-resveratrol and GSPE. This approach was intended to determine whether susceptibility to cold-induced oxidative damage varies with age and whether polyphenolic intervention can attenuate these alterations. The findings may provide experimental insight into the interaction between age, environmental cold stress and antioxidant neuroprotection and establish a basis for further investigation of natural polyphenols in stress-related neural injury.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Grape seed proanthocyanidin extract (GSPE; standardized to ≥95% proanthocyanidins) derived from *Vitis vinifera* L. was obtained from Inlife Group, India. The biologically active trans-isomer of resveratrol (RES; ≥95% purity), derived from *Polygonum cuspidatum* extract, was procured from Decode Age, Bengaluru, India. All other analytical-grade chemicals and reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA).

2.2 Experimental Animals and Ethical Approval

Male Wistar rats (*Rattus norvegicus*) belonging to three age groups—3 months (young adult), 6 months (mature adult), and 12 months (middle-aged)—were obtained from Sri Sai Biosciences, Bengaluru, India (CCSEA Reg. No. 2271/PO/Bt/S). Animals were acclimatized for one week before experimentation and maintained under controlled laboratory conditions with a 12:12 h light/dark cycle, temperature of 22 ± 2 °C and relative humidity of 55–65%. Standard rodent pellet diet and tap water were provided *ad libitum*. All experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC Approval No. 402/GO/Re/01/CPCSEA/003) and conducted in accordance with the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Government of India.

2.3 Experimental Design and Treatment

Animals within each age group were randomly assigned to five groups, with six rats in each group (n = 6). Treatments were administered once

daily by oral gavage using 0.9% physiological saline as the vehicle. The experimental groups were:

1. **Control (CON):** Animals maintained under standard laboratory conditions without cold exposure or treatment.
2. **Cold stress (CS):** Animals exposed to the cold-stress protocol without treatment.
3. **CS + RES:** Animals exposed to cold stress and administered trans-resveratrol at 75 mg/kg body weight/day.
4. **CS + GSPE:** Animals exposed to cold stress and administered GSPE at 75 mg/kg body weight/day.
5. **CS + RES + GSPE:** Animals exposed to cold stress and administered trans-resveratrol and GSPE at 50 mg/kg body weight/day each.

All treatments were administered throughout the 15-day experimental period. The selected treatment doses were based on the experimental design and preliminary observations.

2.4 Cold-Stress Exposure

Cold stress was induced using a precision-controlled biochemical oxygen demand (BOD) incubator (Colton, India) maintained at 5 ± 0.5 °C. Rats were housed individually in standard polypropylene cages containing minimal bedding and no nesting material to minimize behavioural thermoregulation. Food and water were available *ad libitum* during exposure. Animals were subjected to cold exposure for 6 h/day for 15 consecutive days. Treatments were administered orally 30 min before each daily cold exposure.

2.5 Brain Tissue Collection

At the end of the experimental period, animals were euthanized according to the approved institutional protocol. The brain was rapidly removed and placed on an ice-cold surface. The cerebral cortex and hippocampus were carefully dissected, cleared of adhering blood and rinsed with ice-cold phosphate-buffered saline (PBS; pH 7.4). The tissues were immediately frozen in liquid nitrogen and stored at −80 °C until biochemical analysis.

2.6 Preparation of Tissue Homogenates

Brain tissues were homogenized as required for individual biochemical assays using appropriate ice-cold buffer conditions. Homogenates were processed under chilled conditions to minimize post-excision oxidative changes. Protein concentration was determined using the appropriate standard method, and enzyme activities were expressed relative to tissue protein content where applicable.

2.7 Assessment of Oxidative Stress and Antioxidant Defence

2.7.1 Lipid Peroxidation

Lipid peroxidation was estimated as malondialdehyde (MDA) formation using the thiobarbituric acid reactive substances method described by Niehaus and Samuelsson [8] (1968). Briefly, tissue homogenate was reacted with a TCA–TBA–HCl reagent and heated in a boiling water bath. After cooling and centrifugation, absorbance was measured at 535 nm. MDA concentration was calculated using an extinction coefficient of 1.56×10^5 M^{-1} cm^{-1} and expressed as µmol MDA/g wet tissue.

2.7.2 Antioxidant Enzymes

MnSOD activity was determined according to Misra and Fridovich [9] (1972), based on inhibition of epinephrine auto-oxidation under alkaline conditions. The change in absorbance was monitored at 480 nm. Enzyme activity was expressed as U/mg protein.

Catalase activity was estimated according to Aebi [10] (1984) by measuring the decomposition of hydrogen peroxide. The decrease in absorbance was monitored at 240 nm, and activity was expressed as µmol H_2O_2 decomposed/min/mg protein.

Glutathione peroxidase (GPx) activity was determined following Lawrence and Burk [11] (1976). The assay was based on the oxidation of NADPH in a coupled reaction system, and the change in absorbance was monitored at 340 nm. Activity was expressed as nmol NADPH oxidized/min/mg protein.

Glutathione-S-transferase (GST) activity was measured according to Habig et al. [12] (1974), using 1-chloro-2,4-dinitrobenzene (CDNB) as the substrate. Formation of the glutathione–CDNB conjugate was monitored at 340 nm, and activity was expressed as µmol conjugate formed/min/mg protein.

2.7.3 Reduced Glutathione

Reduced glutathione (GSH) content was estimated using the method of Ellman [13] (1959). Tissue homogenate was reacted with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), and the resulting yellow-colored product was measured at 412 nm. GSH concentration was calculated using an extinction coefficient of 13.6 mM^{-1} cm^{-1} and expressed relative to wet tissue weight.

2.8 Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical comparisons were performed using an appropriate factorial statistical model to assess the effects of age, cold stress and treatment, followed by a suitable post-hoc multiple-comparison test where applicable. Statistical significance was considered at $P < 0.05$. The statistical analysis was performed using appropriate statistical software.

3. RESULTS

3.1. Cold stress increased lipid peroxidation and altered SOD activity

Cold exposure produced a marked increase in lipid peroxidation in both the cerebral cortex and hippocampus (Fig. A-B). The increase in MDA was greatest in 3-month-old rats. In the cortex, MDA increased approximately 18-fold in 3-month-old rats, 12-fold in 6-month-old rats and 3–4-fold in 12-month-old rats compared with the respective controls. A similar age-related pattern was observed in the hippocampus, where MDA increased approximately 8-fold, 13-fold and 3–4-fold in the 3-, 6- and 12-month groups, respectively. Thus, although cold stress increased lipid peroxidation at all ages, the magnitude of the response was greater in younger animals, particularly in the cortex, while the hippocampus showed substantial oxidative damage in both young and mature animals.

GSPE and RES reduced the cold-induced increase in MDA in both brain regions. The reduction was generally greater with the combined treatment. In the cortex, combined GSPE + RES treatment reduced MDA to approximately 0.02–0.03 µmol/g tissue across the age groups. In the hippocampus, the combined treatment similarly reduced MDA toward control values. These findings indicate that both individual treatments attenuated cold-induced lipid peroxidation, with the combined treatment showing the strongest overall effect.

SOD activity showed a contrasting and age-dependent response (Fig. C-D). In 3-month-old rats, cold stress reduced SOD activity in both the cortex and hippocampus to approximately 0.014–0.015 U/mg protein compared with the corresponding controls. In contrast, cold stress increased SOD activity in 6- and 12-month-old rats. In the cortex, activity increased from approximately 0.010 to 0.030 U/mg protein in 6-month-old rats and from approximately 0.019 to 0.029 U/mg protein in 12-month-old rats. A similar increase was observed in the hippocampus of these age groups.

GSPE and RES increased SOD activity in most cold-stressed groups. The combined treatment produced a particularly marked response in 3-month-old animals, whereas the response in older animals varied according to brain region. These results indicate that the SOD response to cold stress was strongly dependent on both age and tissue.

3.2. Catalase and GST showed distinct tissue- and age-dependent responses

Catalase activity showed marked differences between the cortex and hippocampus (Fig. E-F). In the cortex, cold stress produced a pronounced increase in CAT activity in 6-month-old rats, reaching approximately 0.78 µmol H_2 O_2/min/mg protein compared with approximately 0.42 in controls. In contrast, CAT activity decreased in 12-month-old cold-stressed animals and showed only a modest change in 3-month-old rats. In the hippocampus, cold stress generally reduced CAT activity across the age groups. The decrease was most evident in 12-month-old animals.

GSPE, RES and their combined treatment produced variable changes in CAT activity. In general, treatment shifted CAT activity toward the corresponding control range, although the response differed between cortex and hippocampus. The combined treatment did not produce a uniform increase in CAT activity across all age groups.

GST activity also showed distinct responses according to age and brain region (Fig. G-H). In the cortex, cold stress increased GST activity markedly in 3-month-old rats, from approximately 2.0 to 3.6 µmol conjugate/min/mg protein. In 6-month-old rats, cold stress produced a

lower GST activity than the control, whereas in 12-month-old rats' activity increased to approximately 4.2 µmol/min/mg protein.

In the hippocampus, the largest response to cold stress occurred in 3-month-old rats, where GST activity increased from approximately 2.2 to 5.3 µmol/min/mg protein. The response was much smaller in the 6- and 12-month groups. Treatment with GSPE or RES modified GST activity in both tissues, but the direction and magnitude of the response varied with age. Combined treatment produced relatively high GST activity in the cortex of 6-month-old rats and maintained activity close to the control range in the older groups.

3.3. GPx activity showed greater treatment-related changes in mature and middle-aged animals

GPx activity showed clear differences between age groups and brain regions (Fig. I-J). In the cortex of 3-month-old rats, cold stress produced only a modest increase in GPx activity. In contrast, cold stress reduced GPx activity in 6- and 12-month-old rats compared with their respective controls. Treatment with GSPE or RES markedly increased cortical GPx activity in the 6- and 12-month groups. The activity reached approximately 4–5 µmol NADPH oxidized/min/mg protein in these treated groups, compared with approximately 2–3 µmol/min/mg protein in the corresponding controls. Combined treatment also maintained high GPx activity.

The hippocampal response was different. In 3-month-old rats, cold stress increased GPx activity, whereas GSPE reduced it and RES produced a smaller response. In 6-month-old rats, GSPE and RES markedly increased GPx activity compared with cold stress alone. The increase was particularly evident with RES. In 12-month-old rats, GSPE produced the highest GPx activity, followed by RES and the combined treatment. Thus, the strongest treatment-associated increases in GPx were observed mainly in mature and middle-aged animals.

3.4. Reduced glutathione showed different patterns in cortex and hippocampus

GSH levels showed clear tissue- and age-dependent variation (Fig. K-L). In the cortex, cold stress produced little change in 3-month-old rats but increased GSH in 6- and 12-month-old animals. The increase was most evident in 6-month-old rats. However, GSPE and RES treatment reduced cortical GSH in the 6-month group, while the combined treatment maintained a value closer to the control level. In 12-month-old rats, treatment largely maintained GSH within the control range.

The hippocampus showed a different pattern. In 3-month-old rats, cold stress produced a modest reduction in GSH, whereas RES increased GSH to approximately 4.4 µmol/g tissue. In 6-month-old rats, the changes were relatively small, although the combined treatment produced a moderate increase. In 12-month-old rats, combined GSPE + RES treatment produced the highest hippocampal GSH level, reaching approximately 5.0 µmol/g tissue compared with approximately 3.6 µmol/g tissue in controls.

3.5. Overall age- and tissue-dependent response to cold stress

Overall, the results demonstrate that repeated cold exposure produced substantial oxidative alterations in both the cerebral cortex and hippocampus, but the pattern differed with age and brain region. Lipid peroxidation showed the clearest response to cold stress, with the greatest increases generally occurring in the younger animals. The hippocampus showed particularly pronounced oxidative changes despite differences in its antioxidant response.

The antioxidant enzymes did not show a uniform response to cold exposure. SOD, CAT, GST and GPx displayed age- and tissue-specific increases or decreases, suggesting that different components of the antioxidant system responded differently to the same cold exposure. The cortex showed prominent changes in CAT, GST and GPx, whereas the hippocampus showed marked changes in SOD, GST and GSH.

Treatment with GSPE and RES generally reduced lipid peroxidation and modified antioxidant defence. The combined treatment produced the most consistent reduction in MDA and strong increases in several antioxidant parameters. However, the combination was not uniformly superior for every biomarker, age group or brain region. The results therefore indicate that the protective response to GSPE and RES is dependent on both age and neural tissue.

4. DISCUSSION

Cold exposure is an important environmental stress that can disturb redox homeostasis in nervous tissue. In the present study, repeated exposure to 5 ± 0.5 °C for 6 h/day for 15 days produced clear oxidative alterations in both the cerebral cortex and hippocampus. The most consistent response was an increase in lipid peroxidation, indicating enhanced membrane oxidative damage. The magnitude of this response varied with age and brain region, with younger animals generally showing a greater increase in MDA. The hippocampus also showed substantial lipid peroxidation, suggesting that this region is particularly sensitive to cold-induced oxidative challenge. These findings indicate that the response to cold stress is not uniform throughout the brain and may depend on the physiological state of the animal.

The antioxidant enzymes showed a more complex pattern than lipid peroxidation. Cold exposure increased or decreased SOD, CAT, GST and GPx depending on age and tissue. The increase in some enzymes, particularly in mature animals, may represent an adaptive response to increased oxidative demand. In contrast, reductions in SOD or GPx in some cold-stressed groups may indicate inadequate antioxidant capacity under the imposed stress. Changes in GSH further support an age- and tissue-dependent alteration of redox homeostasis. The different responses of cortex and hippocampus suggest that individual brain regions may have different capacities to adapt to repeated cold expo-sure. Importantly, the present findings do not establish whether these enzymatic changes are protective adaptations or consequences of oxidative injury; they simply demonstrate that cold stress alters several components of the antioxidant system.

Treatment with trans-resveratrol and GSPE generally reduced cold stress-associated lipid peroxidation and modified antioxidant defence [14] (Adhikary et al. 2025). The reduction in MDA was particularly evident with the combined treatment, which brought lipid peroxidation closer to control levels in several groups. Both compounds also increased selected antioxidant parameters, although the response depended on age and brain region. These findings suggest that trans-resveratrol and GSPE can attenuate biochemical consequences of cold-induced oxidative stress [15] (Mim et al.2026). The effects of the two compounds were not, however, uniformly greater when combined for every marker and age group. Therefore, the present data support an enhanced protective effect of the combination for selected parameters, but do not provide sufficient evidence to claim pharmacological synergy. The different responses of GSH and antioxidant enzymes also indicate that antioxidant protection may involve modulation of endogenous defence rather than simply direct scavenging of reactive species.

An important observation of the present study is the age-dependent nature of the response. The relatively large increase in lipid peroxidation in younger rats suggests greater oxidative sensitivity to the present cold-stress regimen [16] (Xiao, 2015). In contrast, mature and middle-aged animals showed stronger changes in several antioxidant enzymes, which may indicate differences in adaptive antioxidant responses. However, the present design cannot determine whether these differences reflect developmental changes in antioxidant capacity, metabolic adaptation, or other age-related physiological factors. The study therefore provides evidence for age-dependent redox responses, rather than establishing a single progressive increase in cold-induced vulnerability with age.

4.1 Limitations of the Study

Several limitations should be considered. First, the study used only male Wistar rats; therefore, the findings cannot be directly extrapolated to females or to other species. Second, only three age groups were examined, and the 12-month group represents middle-aged rather than aged animals. Third, a single cold-exposure condition and duration were used. Consequently, the study cannot establish dose- or duration-dependent effects of cold stress. Fourth, the investigation was restricted to biochemical markers of oxidative stress and antioxidant defence. Histopathological changes, neuronal apoptosis, mitochondrial function, inflammatory mediators, neurotransmitters and behavioural or cognitive outcomes were not evaluated. Therefore, the present results demonstrate biochemical evidence of oxidative stress and its attenuation, but do not by themselves establish structural or functional neuroprotection. Finally, although the combined treatment produced stronger effects for several parameters, formal synergy analysis was not performed; hence, synergistic interaction between trans-resveratrol and GSPE cannot be conclusively claimed.

4.2 CONCLUSION

Repeated cold exposure produced significant oxidative alterations in the cerebral cortex and hippocampus of Wistar rats, with responses varying according to age and brain region. Increased lipid peroxidation was the most consistent indicator of cold-induced oxidative stress,

while SOD, CAT, GST, GPx and GSH showed tissue- and age-dependent changes. Trans-resveratrol and GSPE attenuated several of these alterations, and their combined administration produced particularly strong reductions in lipid peroxidation and improvements in selected antioxidant parameters. Overall, the findings indicate that age influences the biochemical response of nervous tissue to cold stress and modifies its response to polyphenolic intervention. Further studies incorporating histological, molecular, mitochondrial and behavioural endpoints are required to determine whether these biochemical effects translate into meaningful functional neuroprotection.

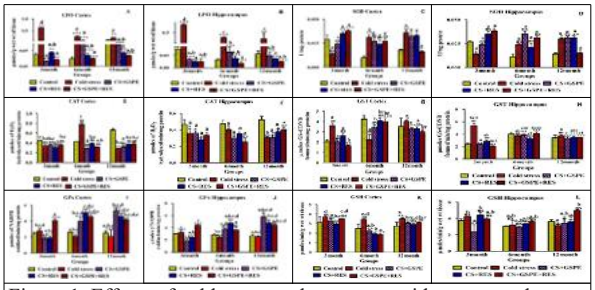

Figure 1. Effects of cold stress and treatment with grape seed proanthocyanidin extract (GSPE) and resveratrol (RES) on oxidative stress and antioxidant defense markers in the cortex and hippocampus. Changes in LPO levels in the cortex (A) and hippocampus (B); Changes in SOD activity in the cortex (C) and hippocampus (D); Changes in CAT activity in the cortex (E) and hippocampus (F); Changes in GST activity in the cortex (G) and hippocampus (H); Changes in GPx activity in the cortex (I) and hippocampus (J); and Changes in GSH levels in the cortex (K) and hippocampus (L). Data are expressed as mean ± SEM (n = 6). Experimental groups were Control, CS, CS + GSPE, CS + RES, and CS + GSPE + RES. Data were analyzed by two-way ANOVA followed by Tukey's multiple-comparison test. Different lowercase letters indicate significant differences among groups ($p < 0.05$), whereas asterisks indicate significant differences versus age-matched controls (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; ns, not significant).

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Conflict Of Interest: The authors report no financial or any other conflicts of interest in this work.

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