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Original article

Vitamin D2 protects acute and repeated noise stress induced behavioral, biochemical, and histopathological alterations: Possible antioxidant effect

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ABSTRACT

Noise is an environmental stressor which causes distress and hearing loss in individuals residing in urban areas. Psychological deficits such as anxiety, depression, impaired memory and cognitive decline are caused by noise stress. Different vitamins have been used as a potential antioxidant for neuronal protection. In this study we investigate the anxiolytic, antidepressant and memory enhancing effect of vitamin D2 (Vit D2) following noise stress. Thirty-six albino rats were randomly divided into six groups. (i) Unstressed + corn oil (ii) Unstressed + Vit D2 (iii) Acute noise stress + corn oil (iv) Acute noise stress + Vit D2 (v) Repeated noise stress + corn oil (vi) Repeated noise stress + Vit D2**.** 600 IU/kg body weight of Vit D2 dosage was prepared in corn oil. Corn oil is used as vehicle and all the drugs administered via oral gavage till end of the experiment (day 16). Recorded sound of generator which was amplified by speakers and had 100 dB intensity was used as noise stress. Repeated stressed animals were exposed to noise (4-hrs) daily for 14 days, while acute stressed animals were exposed to noise (4-hrs) once after 14 days. Behavioral tests (elevated plus maze, light dark box, tail suspension test and Morris water maze) of all groups were performed after15 days treatment period. After behavioral tests rats received their last dosage and decapitated after 1-hr. Brain of all animals was removed and used for biochemical (oxidative stress biomarker, antioxidant enzymes and acetylcholinesterase) and histopathological estimations. Results show that Vit D2 decreased time spent in light box and open arm of light dark activity box and elevated plus maze test respectively (used for anxiety evaluation), decreased immobility time in tail suspension test (for depression) and improved cognitive ability evaluated by Morris water maze test in acute and repeated noise stressed rats. Furthermore, increased antioxidant enzymes activity, decreased lipid peroxidation and acetylcholinesterase activity were also observed in Vit D2 treated animals following acute and repeated noise stress. Normalization in histopathological studies was also observed in Vit D2 treated following acute and repeated noise stress. It is concluded that Vit D2 protects from noise stress induced behavioral, biochemical and histopathological impairment through its antioxidant potential.

1. Introduction

Stress is perceived as a threat and body responds to it accordingly (Osório et al., 2017). Different kinds of stressors have been used during experimental studies such as forced swimming, foot shock, restraint and noise (Jafari et al., 2017a; b). Noise is an environmental stressor which causes hearing loss and physiological alterations (Samad et al., 2020a,b). Acute stress is the short-term

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exposure (Rohleder, 2019) whereas repeated exposure to noise results in chronic stress (Mariotti, 2015). Previously in experimental studies, acute and chronic noise stress is involved in onset of neurological dysfunction such as anxiety and depression (Salehpour et al., 2018, Godoy et al., 2018). During noise stress, in locus coeruleus increased levels of corticotrophin releasing factor (CRF) stimulate tyrosine hydroxylase, an enzyme responsible for nor-epinephrine (NE) synthesis and thus increase the NE turnover (Wood and Valentino 2017) and excess release of catecholamine and glucocorticoids (stress hormones) (Jafari et al., 2017a). Reduction in serotonin transporter (SERT) expression in noise stress is reported earlier causes suppressed serotonergic release (Li et al., 2019). Lowered serotonergic and higher norepinephrine and dopaminergic levels seen in post-traumatic stress disorder (PTSD) impair memory and performance (Douma and de Kloet 2020). Low levels of serotonin results in anxiety, depressed mood, reduced resilience and cognitive dysfunction (Garcia-Garcia et al., 2018). Levels of acetylcholine significantly reduce when exposed to noise stress (Garcia-Garcia et al., 2018). Anxiety and depression are psychiatric disorders characterized by mania, social isolation, (Samad et al., 2018) disorganized cognition, hunger abnormalities and sleep-wake cycle, enhanced or ceased psychomotor activity, difficulty to take a decision and suicidal thoughts (Peres et al., 2017). Bed nucleus of the stria-terminalis (BNST) are mainly involved in anxiety like behaviors (Thomson 2019) while amygdala, hippocampus, and prefrontal cortex are involved in major depressive disorder (MDD) (Liu et al., 2018).

Noise stress results in increased reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Daiber et al., 2020). An imbalance between ROS and scavenging antioxidants results in OS characterized by elevated MDA levels which is the end product of lipid peroxidation and causes loss of enzymatic activity, and neurodegenerative diseases (Azman et al., 2018; Pizzino et al., 2017) such as Parkinson disease (PD), Alzheimer disease (AD), depression, and memory loss (Liu et al., 2016). Antioxidants prevent the oxidation of biomolecules by donating an electron to highly reactive free radicals, neutralizing and thus terminating the chain reactions. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH) (Wang et al., 2017). Antioxidants such as β-carotenes and Vit C protect against tumor, Vit E influence the immunity by improving HAP [humoral antibody protection] (Bernardo-Colón et al., 2018). Vit K protects oligodendrocytes against oxidative stress (OS) thus involves in neuronal protection and cell signaling (Singh and Devasahayam 2020).

Vitamin D (sunshine vitamin) is a fat-soluble steroidal hormone/vitamin (Aljohri et al., 2019). Vitamin D3 (Vit D3) and vitamin D2 (Vit D2) are its two types. Vit D2 also known as ergocalciferol is present in fungi and some plants such as cotton seed, wheat, mushrooms and lettuce. Ergosterol is the precursor compound when exposed to UV radiations gives Vit D2. In contrast to Vit D3, Vit D2 contains methyl group at C24 and a double bond between C22 and C23 (Omotosho 2019). Receptors of Vit D (both D2 and D3) are present in abundance in various brain regions (Chang and Lee 2019). It acts as neuroprotective agent (Wilson et al., 2017) via its antioxidant (Wimalawansa 2019) and anti-inflammatory (Giordano et al., 2017) potential. Vit D from skin or any dietary source enters in the body where it binds with Vit D binding proteins and albumin and then transported to liver where it is hydroxylated to 25-hydroxyvitamin D (25(OH) D) via action of 25-hydroxylases. The mitochondrial enzyme 25-hydroxyvitamin D (3)-1 alpha-hydroxylase (1 alpha-hydroxylase) plays an important role in calcium homeostasis by catalyzing synthesis of the active form of Vit D, 1,25-dihydroxyvitamin D(3), in the kidney. Active form of Vit D then transported to various target cells and tissues and transcriptional effects occur (Wilson et al., 2017). Vit D deficiency results in cognitive decline, loss of memory, psychotic illnesses such as anxiety and depression (Casseb et al., 2019). Recommended dose of Vit D for 51 to 70 years old is 600 IU/day and 800 IU/day for individuals over 70 years, while, 400 IU/day is recommended for children (Kimball and Holick, 2020).

Keeping in view the prevailing situation of various environmental stressors associated diseases/disorders due to Vit D insufficiency, the goal of our study is to examine the protective effects of Vit D2 following exposure to acute and repeated noise stress in rats. In the present study we examined the repeated administration of Vit D2 on acute and repeated noise stress induced behavioral, biochemical, and histopathological alterations in rats.

2. Materials and methods

2.1. Animals

36 Albino male rats were included in this study (obtained from Pharmacy Department of Bahauddin Zakariya University, Multan, Pakistan). Kept under natural 12-hr light/dark cycle in a cage roofed with wire lids and floor was covered with wood shavings. Temperature maintained at (22 ± 3 °C) with free access to standardized rodent food and tap water. Animal study was performed after getting approval from ethical committee of Department of Biochemistry, Bahauddin Zakariya University, Multan, Pakistan (Ref # D/356/2020/Biochem; Dated: February 6, 2020).

2.2. Chemicals and reagents

Vitamin D, Acetylthiocholine iodide, Sodium azide, Thiobarbituric acid (TBA), H_2O_2 stock solution, Nitroblue tetrazolium (NBT) and all chemical and reagent were purchased from Sigma Chemicals Co. (St. Louis, USA).

2.3. Drug preparation

Vit D2 was dissolved in corn oil and administered through gavage for two weeks every day at the same time (10:00–11:00 am), with selected dose of 600 IU/kg body weight of animal (Babu et al., 2014; El Agaty 2019). Vit D2 was kept safe in dark bottle and measured in dark as well.

2.4. Experimental design

Thirty-six male albino rats (weighed 170–200 g and 4–5 months by age) were randomly divided into 6 groups (n = 6 for each group). (i) Unstressed Corn oil (ii) Unstressed Vit D2 (iii) Acute noise stress + corn oil (iv) Acute noise stress + Vit D2 (v) Repeated noise stress + corn oil (vi) Repeated noise stress + Vit D2. From day 1 till the day of decapitation (day 16) animals of group (v) and (vi) were exposed to repeated noise stress for 4-hrs daily with pre-administration of corn oil and Vit D2 respectively. Group (iii) and (iv) were administered daily with corn oil and Vit D2 respectively while exposed to noise only once on 15th day for 4-hrs. Group (i) and (ii) were given corn oil and Vit D2 regularly during the whole experimental duration and are not exposed to noise stress (unstressed group). Corn oil is used as a vehicle. Vit D2 (600 IU/kg body weight) was dissolved in corn oil and administered orally. Animals were subjected to noise stress in a separate room. On 16th day, after noise stress, behavioral tests such as elevated plus maze (EPM) test, light dark box activity (L/D) test, tail suspension test (TST) and Morris water maze (MWM) test (acquisition, short term and long-term memory) were performed. Animals were kept in behavioral room 60 mins before starting the behavioral analysis so that they became familiar to the new environment. On day 17th

long term memory in MWM was performed. After behavioral test completion animals were anesthetized (Imran et al., 2020) and decapitated. Whole brains were collected and utilized for biochemical estimation (malondialdehyde, antioxidants enzymes, acetylcholinesterase activity) and histopathological studies.

2.5. Noise stress protocol

Sound of generator was recorded and amplified by speakers. Rats were exposed to noise by keeping speakers at the wire of the cage in a closed separate room. The intensity of noise was maintained at 100 dB and monitored by a sound level meter (Smart Tools co., Ltd., Japan; Range: 80–120 dB, Accuracy: ±1.3 dB (30 Hz) (Samad et al., 2020a,b).

2.6. Behavioral tests

2.6.1. Elevated plus maze (EPM-test)

EPM activity was an experimental tool to assess anxiety in rodents (Samad et al., 2020a,b,c). EPM apparatus is consists of four arms which were connected at the center and helped in the assessment of anxiety. To evaluate anxiety-like behavior, time spent in open arm was recorded for 5 min.

2.6.2. Light dark box (L/D) activity

To evaluate the anxiety profile in rodents L/D activity was used (Samad et al. 2020a). L/D apparatus is consists of 2 boxes, one is lighted while other one is darked. A small connectivity is present between the two boxes. Time spent in the light box was noted for 5 min to evaluate the anxiety in rats.

2.6.3. Tail suspension test (TST)

To evaluate the depression like behavior TST was performed (Salehpour et al., 2018). The apparatus consists of wooden box whose length was 54 cm and 30 cm wide. At the top of roof, a hook was placed at center and a distance of 350 mm was maintained between hook and floor of apparatus. Animal was suspended by its tail with an adhesive tape to hook of apparatus and was kept isolated visually and acoustically from nearest objects. To evaluate the depression like behavior, immobility time during TST was noted for 5 min.

2.6.4. Morris water maze test (MWM)

To evaluate the memory function in rodents, MWM test was used (Samad et al., 2018). A circular pool with cloudy water was used as maze that having hidden wooden platform. Training trails were given to animal to hint the hidden platform in the pool. MWM test consists of 3 phases' acquisition, short term memory (4-hrs after the training) and long term memory (24-hrs after the training). Each phase was last for 120 sec for each rat, escape latency or time to reach the platform was monitored in every phase.

2.7. Biochemical assays

2.7.1. Malondialdehyde (MDA)

MDA test was performed by previously reported method (Samad et al., 2019). A light pink colored solution was appeared when all the chemicals as reported previously were used for MDA estimation. The absorbance of the solution is read at 532 nm.

2.7.2. Superoxide dismutase (SOD)

The activity of SOD was assessed by the method of Samad et al. (2019; 2020b). For the test group tissue homogenate was treated with reported chemical while test tubes without tissue homogenate were used as control. The absorbance was noted at 570 nm and expressed as percent inhibition of SOD.

2.7.3. Catalase (CAT)

Method of Pari and Latha (2004) was used for evaluating the activity of catalase. Tissue homogenate was prepared in phosphate buffer (0.1 M). Reported chemicals with tissue homogenate were used for the analysis. The absorbance was recorded at 570 nm. The activity of CAT in tissue sample was expressed as μmoles of H_2O_2 consumed/min/mg protein.

2.7.4. Glutathione peroxidase (GPx)

GPx activity was evaluated by the method of Samad et al. (2019; 2020a b). The absorbance was measured at 420 nm. The activity of GPx in tissue sample was described as μmol/min/g.

2.7.5. Acetylcholinesterase (AChE)

The method of Ellman et al. (1961) was used to assess the AChE activity in given samples. The activity of AChE described as μmol/min/g.

2.8. Histopathology estimation

Brain sample was stored in 4% *para*-formaldehyde for histopathology analysis. Samples were mounted in petroleum wax and microtome was used to produce slices of 5 μm thickness. These slices were placed onto the labelled slides and stained using hematoxylin and eosin [H&E] dye. Thenmozhi et al. (2015) staining method was used. Stained slides were examined at 200X magnification using light microscope.

2.9. Statistical analysis

Data was analyzed by using SPSS software and expressed as mean ± standard deviation (n = 6). Tukey's test followed by two-way ANOVA was used to compare the various variables. Data was considered significant when $p < 0.05$.

3. Results

3.1. Impact of Vit D2 on noise stress induced anxiety evaluated through EPM

The effect of Vit D2 on acute and repeated noise stress induced anxiety, measured through EPM (Fig. 1). Data on time spent in open arm was evaluated by Two way ANOVA which showed signif-

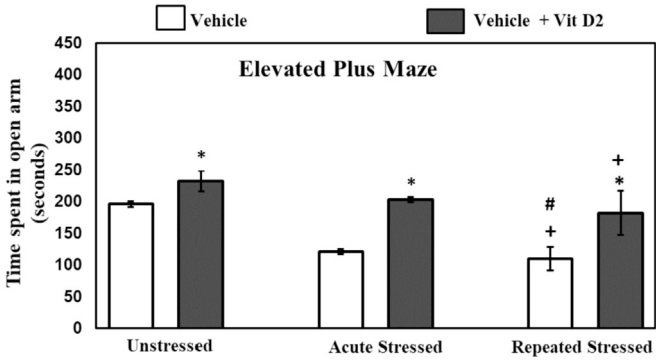

Fig. 1. Time spent in open arm in EPM in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group, #p < 0.05 vs acute stressed group.

icant effect of noise stress [$F_{(2,30)}$ = 32.36, p = 0.0001] and Vit D2 [$F_{(1,30)}$ = 48.68, p = 0.0001], while interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 0.889, p = 0.421] was not significant. Tukey's test showed that Vit D2 increased the time spent in open arm in unstressed, acute and repeated noise stressed animals. Time spent in open arm was smaller in Vit D2 treated repeated noise stressed than unstressed group. Repeated noise stressed animal treated with vehicle, exhibited smaller time spent in open arm than acute stressed and unstressed groups.

3.2. Impact of Vit D2 on noise stress induced anxiety evaluated through L/D

The effect of Vit D2 on acute and repeated noise stress induced anxiety, measured through L/D (Fig. 2). Data on time spent in light box was evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 124.52, p = 0.0001], Vit D2 [$F_{(1,30)}$ = 722.50, p = 0.0001], and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 26.98, p = 0.0001]. Tukey's test showed that Vit D2 increased the time spent in light box in unstressed, acute and repeated noise stressed animals. Time spent in light box was smaller in Vit D2 treated acute and repeated noise stressed than vehicle treated unstressed animal. In vehicle treated repeated noise stressed animal, time spent in light was smaller than unstressed and acute stressed animals.

3.3. Impact of Vit D2 on noise stress induced depression

The effect of Vit D2 on acute and repeated noise stress induced depression, measured through TST (Fig. 3). Data on immobility time was evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 701.56, p = 0.0001], Vit D2 [$F_{(1,30)}$ = 348.75, p = 0.0001], and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 114.50, p = 0.000.1]. Tukey's test showed that Vit D2 decreased the immobility time in unstressed, acute and repeated noise stressed animals. Vehicle treated repeated noise stressed animals exhibited increased immobility time than vehicle treated unstressed and acute noise stressed animals. Immobility time of repeated noise stressed in Vit D2 treated animals was greater than unstressed and acute noise stressed.

3.4. Impact of Vit D2 on noise stress induced memory impairment

The effect of Vit D2 on acute and repeated noise stress induced memory impairment, measured through MWM (Fig. 4). Data for acquisition was evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 60.44, p = 0.0001], Vit D2

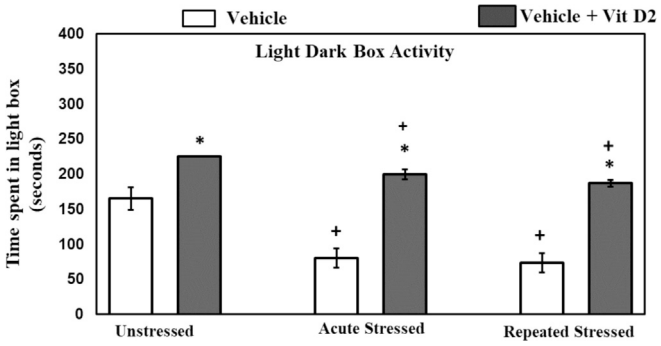

Fig. 2. Time spent in lightbox in L/D in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group.

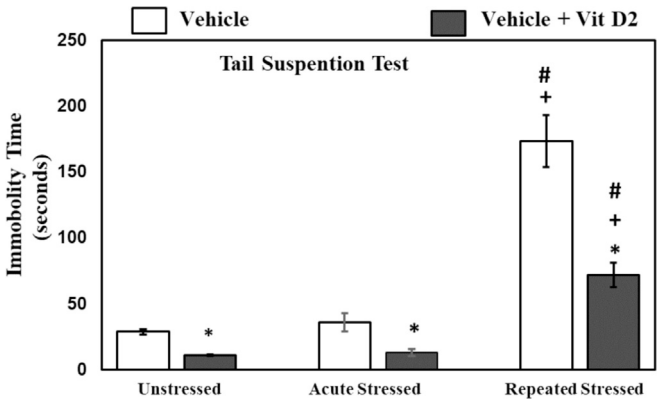

Fig. 3. Immobility time in TST in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group, #p < 0.05 vs acute stressed group.

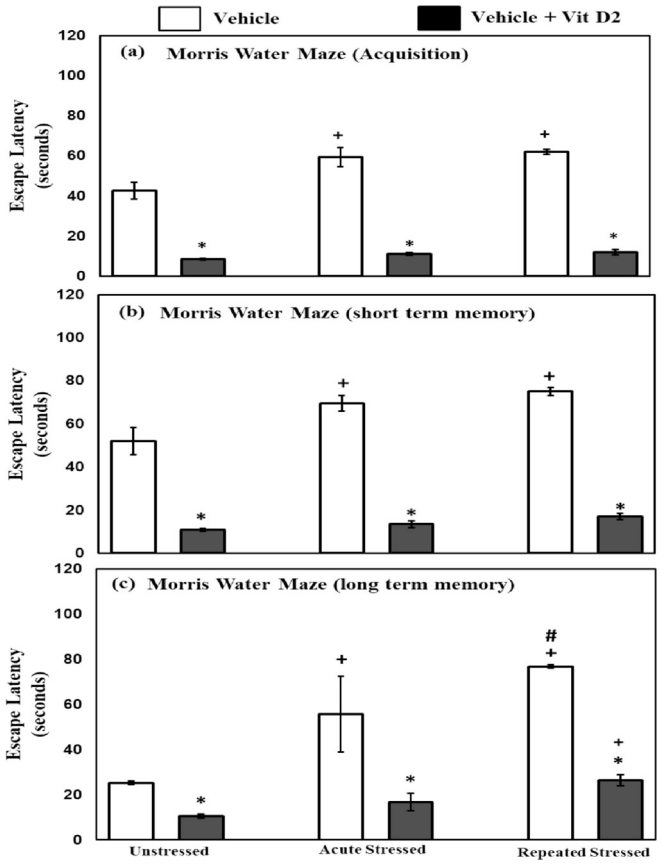

Fig. 4. Latency Escape in MWM during acquisition, short term and long term memory in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group, #p < 0.05 vs acute stressed group.

[$F_{(1,30)}$ = 2326.65, p = 0.0001], and interaction between noise stress and vit D2 [$F_{(2,30)}$ = 29.78, p = 0.0001]. Tukey's test showed that Vit D2 decreased the escape latency time in unstressed, acute noise stressed and repeated noise stressed animals. Acute and repeated noise stressed animal treated with vehicle, exhibited increased escape latency time than unstressed vehicle treated animals. Data for short term memory was evaluated by Two way ANOVA which

showed significant effect of noise stress [$F_{(2,30)}$ = 63.52, p = 0.0001], Vit D2 [$F_{(1,30)}$ = 2280.97, p = 0.0001] and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 23.92, p = 0.0001]. Tukey's test showed that Vit D2 decreased the escape latency time in unstressed, acute and repeated noise stressed animals. Acute and repeated noise stressed animal treated with vehicle, exhibited increased escape latency time than unstressed vehicle treated animals. Data for long term memory was evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 67.48, p = 0.0001], Vit D2 [$F_{(1,30)}$ = 213.05, p = 0.0001] and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 19.45, p = 0.00013]. Tukey's test showed that Vit D2 decreased the escape latency time in unstressed, acute and repeated noise stressed animals. Escape latency was increased in acute and repeated stressed vehicle treated animals than unstressed vehicle treated animals. Escape latency was also greater in repeated stressed vehicle treated than acute stressed vehicle treated animals. Repeated Vit D2 treated animals showed increased escape latency than unstressed Vit D2 treated animals.

3.5. Impact of Vit D2 on noise stress induced oxidative stress

The effect of Vit D2 on acute and repeated noise stress induced lipid peroxidation, measured through MDA content (Fig. 5). Data for MDA levels was evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 730.684, p = 0.004], Vit D2 [$F_{(1,30)}$ = 609.37, p = 0.000], and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 42.04, p = 0.000]. Tukey's test showed that Vit D2 decreased the lipid peroxidation in unstressed, acute and repeated noise stressed animals. Vehicle treated stressed animals exhibited increased lipid peroxidation than unstressed vehicle treated animals. Acute noise stressed vehicle treated animals exhibited increased MDA levels than acute noise stressed Vit D2 treated animals. MDA levels were increased in Vit D2 treated stressed animals than unstressed Vit D2 treated animals. Repeated noise stressed Vit D2 treated animals showed increased MDA levels than acute noise stressed Vit D2 treated animals.

3.6. Impact of Vit D2 on antioxidant enzymes following noise stress.

The effect of Vit D2 on antioxidant enzymes activities in acute and repeated noise stressed animals (Fig. 6). Data on SOD activity were evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 786.15, p = 0.0001], vit D2 [$F_{(1,30)}$ = 207.31, p = 0.0001], and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 2.18, p = 0.0001]. Tukey's test showed that

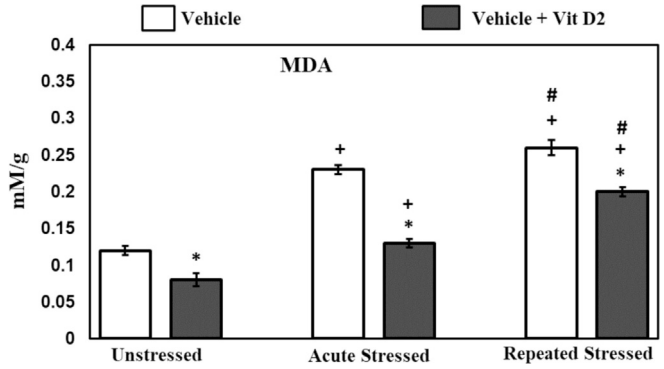

Fig. 5. Brain lipid peroxidation in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group, #p < 0.05 vs acute stressed group.

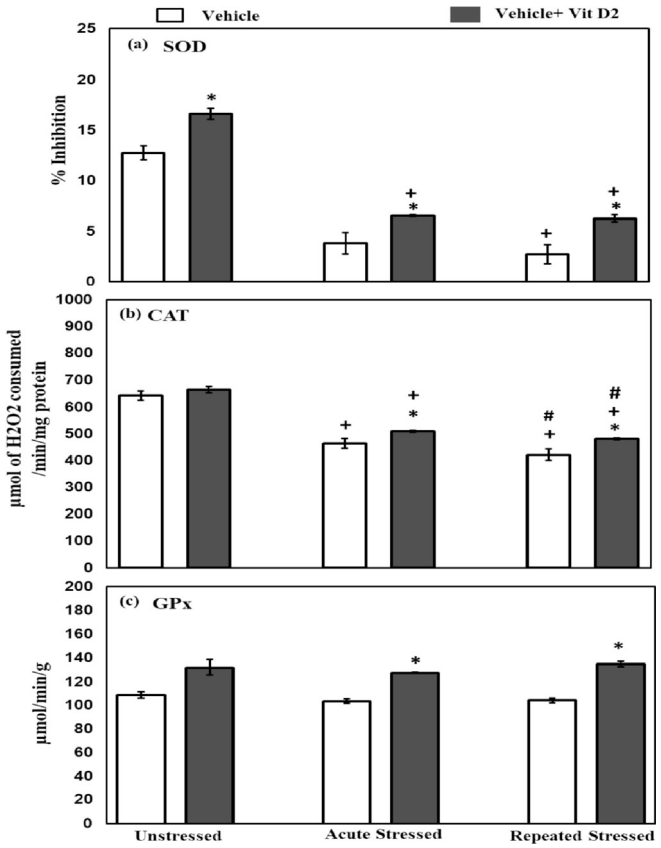

Fig. 6. Brain antioxidant enzymes SOD, CAT and GPx activities in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group, #p < 0.05 vs acute stressed group.

Vit D2 increased the SOD activity in unstressed, acute and repeated noise stressed animals. Acute and repeated noise stressed Vit D2 treated animals exhibited lowered activity of SOD than unstressed Vit D2 treated animals. Acute noise stressed vehicle treated animals showed lowered SOD activity than unstressed vehicle treated animals.

Data on CAT activity were evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 676.72, p = 0.0001], Vit D2 [$F_{(1,30)}$ = 78.70, p = 0.0001], and interaction between noise stress and vit D2 [$F_{(2,30)}$ = 5.55, p = 0.009]. Tukey's test showed that Vit D2 increased the CAT activity in acute and repeated noise stressed animals. Acute and repeated noise stressed Vit D2 treated animals exhibited decreased CAT levels than unstressed Vit D2 treated animals. Repeated noise stressed Vit D2 treated animals showed decreased CAT activity than acute noise stressed Vit D2 treated animals. Acute and repeated noise stressed vehicle treated animals showed decreased CAT activity than unstressed vehicle treated animals. The activity of CAT was lower in repeated stressed vehicle treated than acute stressed vehicle treated animals.

Data on GPx activity were evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 7.82, p = 0.002], Vit D2 [$F_{(1,30)}$ = 593.19, p = 0.0001], and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 4.93, p = 0.014]. Tukey's test showed that Vit D2 increased GPx activity in unstressed, acute and repeated noise stressed animals. Repeated noise stressed Vit D2 treated exhibited increased activity of GPx than acute noise stressed Vit D2 treated animals.

3.7. Impact of Vit D2 on AChE activity following noise stress.

The effect of Vit D2 on AChE activity in unstressed, acute and repeated noise stressed animals (Fig. 7). Data on AChE activity was evaluated by Two way ANOVA which showed significant effect of noise stress [$F_{(2,30)}$ = 562.44, p = 0.0001], Vit D2 [$F_{(1,30)}$ = 349.48, p = 0.0001], and interaction between noise stress and Vit D2 [$F_{(2,30)}$ = 24.87, p = 0.421]. Tukey's test showed that Vit D2 decreased the AChE activity in unstressed, acute and repeated noise stressed animals. AChE activity was increased in acute and repeated noise stressed Vit D2 treated than unstressed Vit D2 treated animals. Vehicle treated acute and repeated noise stressed treated animals exhibited increased AChE activity than unstressed animals. AChE activity was greater in chronic noise stressed Vit D2 treated than acute noise stressed Vit D2 treated animals.

3.8. Impact of Vit D2 on noise stress induced histopathological alterations

Fig. 8 shows the effect of Vit D2 on acute and repeated noise stress induced histopathological alterations. (8a) **Unstressed + corn oil**: Animals exhibited the presence of prominent neurons in cerebral cortex region. The granular layer was clear and at the periphery prominent basophilic Purkinje cells nuclear material was present. The molecular layer showed slight vacuolation and at a few places the glial cells population was increased. (8b) **Acute noise stress + corn oil**: Animals showed, decreased basophilic character of Purkinje cells nuclear material along with reduction in the neuronal structures in the cerebral cortical region. In cortical region there is an increase in vacuolation at a few places relatively dark stained pyknotic nuclei were present in the close proximity of neurons suggesting neuronal damage. (8c) **Repeated noise stress + corn oil**: Animals exhibited the decrease in basophilic characteristic of Purkinje cells nuclear material. The granular cell layer was not prominent. In the cerebral cortex vacuolation along with the presence of pyknotic nuclei in the close proximity of neurons indicate necrosis. (8d) **Unstressed + Vit D2**: Animals showed that the granular layer was intact and surrounded by prominent population of Purkinje cells. Neuronal cells population was prominent at few places. A slight increase in glial cells population was seen. (8e) **Acute noise stress + Vit D2**: Animals exhibited the absence of degenerative and inflammatory response in brain parenchyma as indicated by the prominent granular layer along with basophilic character of the Purkinje cells nuclear material. The neuronal population in the cortical region was prominent

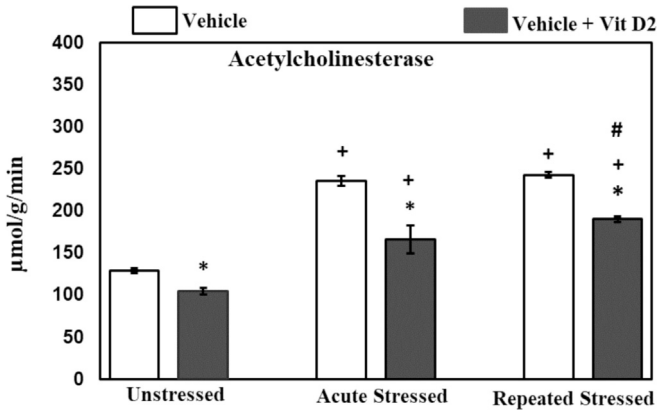

Fig. 7. Brain AChE activity in Vit D2 and vehicle treated acute and repeated noise stressed animals. Data expressed as mean ± S.D (n = 6). Two-way ANOVA statistics were applied. Significant variances were found via Tukey's-test, *p < 0.05 vs vehicle treated group, +p < 0.05 vs unstressed group, #p < 0.05 vs acute stressed group.

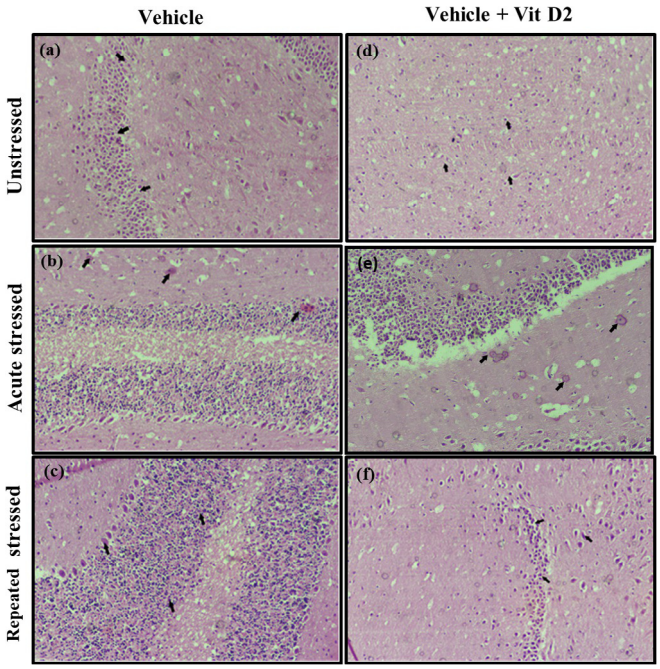

Fig. 8. Brain histopathological studies in Vit D2 and vehicle treated acute and repeated noise stressed animals.

however at few places in the cerebral cortex vacuolation was observed along with slight increase in glial cells population. (8f) **Repeated noise stress + Vit D2**: Vit D2 treated repeated stressed animals revealed the normal basophilic staining characteristic of Purkinje cells nuclear material suggesting the absence of degenerative changes. The overall brain tissues had normal appearance however at some places vacuolation was present.

4. Discussion

We are reporting for the first time the inhibitory effect of Vit D2 on acute and repeated noise stress induced behavioral, biochemical, and histopathological impairment in rats. This experimental study revealed that acute and repeated noise stress induced anxiety like behavior which were analyzed in EPM and L/D tests, reduced time spent in open arm and light box respectively. Acute and repeated noise stress instigated depression like behavior was analyzed by enhanced immobility time in TST. Cognitive function was measured by escape latency time in MWM test and it was observed that acute and repeated noise stress impaired memory function in the present study. Increased AChE activity is also associated with impaired memory in noise stressed animals. Noise stressed animals exhibited enhanced oxidative stress which were observed by elevated MDA levels and reduced antioxidant enzymes activities. Histopathological studies revealed that acute and repeated noise stress caused increased neuronal degeneration and vacuolation. Conversely, Vit D2 via its antioxidant potential resulted in anxiolytic, antidepressant and memory enhancement effects with normalization of histopathological alterations.

Noise pollution is one of the leading factors of neurological disorders. Noise stress cause hearing loss and induce cognitive decline (Haider et al., 2020). Acute and repeated noise stress results in over secretion of glucocorticoids due to HPA-axis hyper activation leading to cellular damage accompanying progressive degenerative effects in the hippocampus (Kent et al., 2017). Noise is well discussed environmental problem affecting a huge percent of world population. Adverse health issues arise due to noise annoyance

such as cardiovascular diseases, sleep disturbances and hypertension (Park et al., 2017). Anxiety is mainly related to fear and danger, arousal and vigilance while depression is associated with loss and grief. Yet they share same physiological and psychological morbidities (Eysenck and Fajkowska, 2018). Recent studies showed that children that are repeatedly exposed to noise develop behavioral deficits such as developing social anxiety and lack of confidence (Lim et al., 2018). Noise stress is related with neurobehavioral discrepancies and involve in onset of anxiety and depression (Beutel et al., 2016). In anxiety less, exploratory activity and avoidance of social contact is commonly seen (Sturman et al., 2018). Our results are consistent with previous studies. Anxious behaviors were observed via EPM and L/D and noise stressed (acute and chronic) rats spent less time in open arm (Fig. 1) and light box (Fig. 2).

Noise stress has annoyance association with depression (Beutel et al., 2016) and is supported by our findings as well. Enhanced immobility time taken by repeated noise stressed rats compared to unstressed and acute noise stressed rats during TST, suggests depressive-behavior (Fig. 3). Although immobility time was comparably greater in vehicle treated acute stressed group but appeared insignificant. Previous studies have stated that Vit D2 supplementation amends depression and anxiety like symptoms (Hoffmann et al., 2019). Clinical trial of depressed older (aged 60 years) patients with Vit D2 supplementation indicates its antidepressant potential (Alvin et al., 2019). Female rats having one or both ovaries surgically removed and treated with Vit D3 showed anxiolytic like effects in EPM and L/D tests (Fedotova 2019). Our results with Vit D2 are consistent with previous research work suggesting its anti-depressant and anti-anxiety effects. Vit D2 treated groups exhibit significantly lowered immobility activity in TST compared to their respective control group (Fig. 3). It is suggested that Vit D2 is involved in eradicating anxiety and depression like symptoms.

Repeated noise exposure results in free radicals generation resulting in lipid, protein and DNA peroxidation and inducing oxidative stress (OS) (Akefe et al., 2020). OS causes the stimulation of NADPH oxidase 2 (NOX-2) through protein-kinase C (PKC) and incite the $p47^{phox}$ phosphorylation in the brain, over-expression of inflammatory markers, amplified lipid peroxidation, reduced-regulation of neuronal nitric oxide synthase (nNOS) and depletion of antioxidant genes such as catalase (Cat) and forkhead box O3 (Foxo3) transcription factor. Such alterations provoke a neuroinflammatory phenotype with elevated cerebral OS (Daiber et al., 2020). High levels of MDA represent OS in acute and repeated stress (Ito et al., 2019). Our data is consistent with previous findings that acute and repeated noise stressed animal group exhibit significantly higher levels of MDA compared to unstressed control group. Repeated noise stressed group showed significantly higher MDA content compared to acute noise stressed exhibiting the adverse effects of repeated noise stress on brain (Fig. 5). Exposure to 100 dB noise, 1hr per day for 10 days can cause OS, increase MDA levels, and decrease SOD levels in rats (Mirmohammadi et al., 2020). Antioxidant enzyme SOD, CAT and GPx are involved in scavenging free radicals. SOD convert highly reactive super oxides into stable molecular oxygen moiety and water molecule along with CAT and GPx (Samad et al., 2020a; b). Antioxidant capacity of SOD, CAT and GPx was also seen to be considerably declined in acute and repeated noise stressed groups compared to unstressed group shown in Fig. 6 and is in agreement with previous studies as well (Daiber et al., 2020). Antioxidant response element (ARE) signaling pathway is the main regulatory system protecting cells against oxidative damage. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of the cellular response to OS (Yao et al., 2021). Vit D regulates redox signaling of mitochondria and modulates Nrf2 to play key role in cellular protection against OS (Wimalawansa, 2019) and by improving the action of glutathione in the cerebral cortex and striatum, antioxidant effect of Vit D2 potentiates (Shi et al., 2017). It decreases the MDA content and enhance the total antioxidant activity of SOD, GPx and CAT (Wimalawansa, 2019). Vit D2 treated group exhibits low levels of MDA (Fig. 5) and higher activities of SOD, CAT and GPx (Fig. 6) compared to their respective control group. We suggest that Vit D2 produces its antioxidant effects by upregulation of antioxidant enzymes.

Anxious and depressive behaviors often lead to cognitive decline. Recently reported studies suggest that Acute stress negatively impact the memory of individual and chronic stress alters neuronal plasticity and learning (Lukasik et al. 2019). Morris water maze is commonly used to test the cognitive abilities. Shorter escape latencies depict the retention of learning and memory. Our results show that noise stress produces drastic effects on acquisition-, short- and long-term memory as proved by previous researches as well (Jafari et al., 2017a; b). Fig. 4 shows the significantly increased escape latencies by acute and repeated noise stressed animals compared to unstressed animals explaining the fact that noise stress alters the memory, navigation and spatial learning abilities of animal. The repeated noise stressed rats considerably alter the long term, memory compared to acute stress. Acute and repeated stress intensify the impulsiveness of glutamatergic cells or abridged the inhibitory effect from GABAergic inhibitory interneurons leading to over activity of amygdala and significant loss of gray matter in the hippocampus. Hippocampus is crucial for the creation of a background memory. Proper hippocampal functioning mainly during memory development, rest on cholinergic responses (Hersman et al., 2019). Acetylcholine is a neurotransmitter which has impact on cognition. Reduced levels of acetylcholine result in dysfunctional memory and neuroplasticity. Acetylcholine esterase is a degradative enzyme for acetylcholine, which converts it into choline and acetic acid. Deterioration of central cholinergic-neurons damages memory, and enrichment of cholinergic-synapses develops cognitive practices (Maurer and Williams, 2017). Lateral olivocochlear (LOC) neurons release acetylcholine, which stimulates activity in auditory nerve fibers. Noise stress by enhancing the AChE activity indirectly lowers the acetylcholine concentration thus involve in hearing loss (Wu et al., 2020). Our findings proved that acute and repeated noise stress enhance the AChE activity compared to unstressed control group (Fig. 7). It is reported earlier that Vit D3 reduces the AChE activity and normalize the acetylcholine transmission in diabetic rats (Kumar et al., 2011). In our study we confirmed for the first time that Vit D2 also showed the same neurological effect as Vit D3. AChE activity decreases in Vit D2 treated acute and repeated noise stress compared to Vit D2 treated unstressed control group indicating that Vit D2 may enhance memory by reducing AChE activity and increasing the synaptic acetylcholine levels. Vit D2 is a plant-based source of Vit D and suitable for vegetarians as well. Mushrooms are rich source of ergosterol which is the precursor of Vit D2 and get activated when irradiated with UV light. Latest investigations have stated that Vit D2 is as effective as Vit D3 in sustaining circulatory concentration of 25-hydroxyvitamin D. Common malignancies, rickets; osteoporosis, diabetes, autoimmune diseases, and cardiovascular diseases were seen in patients deficient in Vit D (Wu et al., 2019). Our brain is rich in Vit D receptors since Vit D can cross the blood brain barrier hence involve in brain development. There is a potential association between Vit D and psychotic behaviors such as anxiety, depression and cognition (Cheng et al., 2020). Vit D is involved in neuron protection, reducing inflammation and has antioxidant potential. It promotes the neuronal growth in rat hippocampal cell cultures via production of nerve growth factor (NGF). It is also involved in regulation of gene expression of different neurotrans-

mitters such as acetylcholine, dopamine, serotonin and GABA. Visual memory and cognition specifically improved by Vit D (Sultan et al., 2020). Our data is consistent with previous research findings. Vit D2 treated animals readily navigate the platform and exhibit reduced escape latencies (Fig. 4), indicates improvement in memory.

It was reported that repeated noise stress causes reduction in hippocampal dendritic branches results in impaired neurogenesis (Huet-Bello et al., 2017). It also induces apoptosis in granule neurons of the dentate gyrus hence involves in neuronal death. Previous reported data showed that rats exposed to 100 dB noise stress for one week (30 min repeatedly for 3 times in a day) decrease the granular layer volume and granular cellular density in cerebellum along with decreased volume of Purkinje cells (Hosseini-Sharifabad and Sabahi, 2014). Another study reported the first day exposure of noise stress results in nuclear deviancy from the center and pervasive vacuole development which become intensified if the noise exposure persisted, consequently pyknotic nuclei were detected and auditory cortex injury occur (Su et al., 2017). Our data is consistent with previous work that acute noise stress exhibits cerebral cortex vacuolation at few places and in repeated noise stress decreases basophilic characteristic of Purkinje cells, granular cell layer and obscure medulla of the white matter indicating the noise stress induced neuroplasticity and neurodegeneration compared to vehicle treated group. Previously reported findings suggest that pre-administration of Vit D for 8 days enhances the glial cell line derived neurotropic factor (GDNF). The neural stem cells are involved in the proliferation and differentiation of Vit D receptor in the central nervous system (Farghali et al., 2020) hence crucially involved in neuroplasticity (Garcia et al., 2017). In Purkinje cells which are present in cerebral cortex, Vit D activating (CYP27B1) and catabolic (CYP24A1) enzymes are present which showed the involvement of Vit D in brain neurogenesis (Wagner and Hollis 2018). We are reporting for the first time the histopathological effect of Vit D2 specifically in context with noise stress. Vit D2 treated groups' exhibit typical cerebral cortex, prominent neuronal cell population and normal basophilic staining characteristic of Purkinje cells nuclear material suggesting the absence of degenerative changes in the brain. No evidence of congestion or presence of prominent inflammatory response in the brain parenchyma was observed except at few places the number of glial cells were increased.

5. Conclusion

The present study first time reports the antioxidant ability of Vit D2, thus diminishing the acute and chronic noise stress induced anxiety, depression and impaired cognition. Furthermore, the present study emphasizes the use of dietary sources rich in Vit D2 and/or supplementation of Vit D2 as an effective remedy for stress and associated disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors Contribution

NS conceived and design research. AI conducted experiments. II provided laboratory facility for the conduction of experiments, SAB done histopathological studies. FA, AFA, FS provided support for experiments. NS and AI wrote the manuscript. All author read and approved the manuscript.

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