Journal of the Medical Research Institute

JMRI, 2023; Vol. 44 No. 2: (42- 50)

Journal of the Medical Research Institute

Stress Response of Neurotransmitters and Micro-RNAs 34c and 7a in Serum and Hypothalamus of Rats after Exposure to Different Powers of Noise.

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ABSTRACT:

Noise pollution is considered a stressful biological factor which can be hazardous for the health. Noise stress stimulates the hypothalamus-pituitary-adrenal axis (HPA). Acute and chronic stress increase such stress hormones as epinephrine, norepinephrine and cortisol. The purpose of this research is to determine the neurotransmitter levels. (dopamine (DA), norepinephrine (NE), serotonin (5-HT)) and microRNA-7a and -34c in serum and hypothalamus tissue of rats exposed to different powers of noise. To achieve this aim, 40 adult albino male rats were grouped in to 4 groups (10 rats each). Group I (GI) represented the control group and the test groups (GII, GIII and GIV) were exposed to different powers of noise at 85 dB, 100 dB and 135 dB respectively for 4 hours/day from 7a.m - 11a.m. for 15 days. The results of the research indicated that noise exposure led to a significant increase in serum level of NE in the tested groups and also increase in the relative expression of microRNA-34c in hypothalamus tissue in (GIV) at 135 which can lead to activation of (fight-flight) response. Also led to significant reduction in levels of neurotransmitter DA in serum in the tested groups and reduction in neurotransmitter 5-HT levels in serum in (GIII) and (GIV) at 100 dB and 135 dB respectively and also reduction in the relative expression of microRNA-7a in hypothalamus tissue in (GIV) at 135dB. Noise exposure as a potent stressor caused a decrease in serum levels of neurotransmitters and a reduction in the relative expression of microRNA-7a in hypothalamus tissue that may lead to disorders in the function of HPA axis and the release of hormones.

Keywords: Noise Stress, Neurotransmitters, Hypothalamus, microRNA-7a, microRNA-34c.

1. INTRODUCTION

Noise is the unwanted and harmful levels of sound. Sound is a form of mechanical wave and is regarded as an essential instrument for communication [(1)].The best-known unit of sound evaluation is the decibel (dB) [(2)]. Hearing impairment due to noise may be caused by a one-time exposure to an extreme sound of impulses such as (gun fire) or by long-term exposure or steady state exposure to sound pressure levels more than 75-85 dB, e.g., in industrial settings [(3)]. Both acute and chronic noise stress at levels higher than 90 dB may be associated with a disorder in the brain's dopaminergic and serotonergic systems, which may result in anxiety and depression [(4)]. The World Health Organization (WHO) reports that sound levels of less than 70 dB are not detrimental to living things, regardless of how long or consistently they are exposed. Over eight hours of exposure to strong noise levels exceeding 85 dB may be detrimental.

The ability of the brain to cope and differentiate between several levels of noise in response to stress is explained by adaptive plasticity mediated through the hypothalamic-pituitary-adrenocortical axis (HPA) and sympathetic-adrenal-medullary axis (SAM) axis, as the modifications that occur in the function and structure are modulated by neurotransmitters and endocrine hormones interaction [(5)]. Noise exposure exerts its effect on HPA and the limbic system through the auditory system [(6)].The hypothalamus consists of a cluster of small crucial nuclei, which are distinct cell groupings that are often localized by tissue in the diencephalon, which is located directly beneath the thalamus [(7)].

The Noise exposure activates the HPA and SAM leading to increased adrenal gland secretions such as cortisol and catecholamines [(8-9)].Catecholamines are classified in to Norepinephrine (NE), epinephrine and dopamine (DA) [(10)]. Catecholamines are hormones and neurotransmitters that play a crucial role to the autonomic nervous system's mechanism that helps to preserve homeostasis [(11)].NE is formed in the brain in nuclei that are small but have powerful effects on other areas of the brain. NE reaches far higher levels in situations of stress increases excitement and alertness in the brain, stimulates resilience, improves memory development and retrieval, and focuses attention in the so-called fight-or-flight response [(12-13)].Chronic noise stress exposure induces the SAM system by sensitizing the cortex to the action of the corticotrophin releasing hormone and activates the cortex directly as well, and

Received:1-12-2023 Accepted: 15-12-2023
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triggers fight-or-flight response to respond to stress resulting in nervous, hormonal and vascular changes that have far-reaching effects (14-15).Dopamine controls cognition, memory, attention, emotional behavior, and also controls the hypothalamic pituitary endocrine system (16). Dopamine concentration changes under chronic stress results in loss of pleasure and lack of motivation (17).Serotonin (5-HT) participates in hypothalamic control of pituitary secretion, particularly in the regulation of adreno-corticotropin hormone (ACTH) (18). Under chronic stress changes in serotonin concentration occur in many brain regions (19).

MicroRNAs are important regulators for gene expression in mammals' brain, they are small non-coding (20-24 nucleotides) single stranded highly conserved RNAs [(20)]. They direct RNA induced silencing complex to complementary sites on mRNA targets, to repress the translational process and/or degrade the microRNA in the brain [(21)]. The brain expresses an estimated 70% of mammalian miRNAs, and defects in miRNA formation impair neuronal growth, efficiency. and lifespan [(22)]. Abnormal expression of miRNAs can lead to several neuropsychiatric disorders [(23)]. Stress cause alteration in microRNAs function and alter neurotransmission and gene regulation [(24)].Micro RNA-7a expressed in the rat arcuate nucleus and paraventricular nuclei at especially high levels [(25)]. MiR-7a is co-expressed in both invertebrate and vertebrate organisms and is thought to be a prototypical neuro-endocrine miRNA [(26)].Stress-related microRNA-34c, which rises in response to stress and reduces anxiety-like behavior, has resulted to a hypothesis that the hypothalamus's production of miR-34c may be a unique regulator of stress response[(27-28)]. The present work aimed to is to evaluate the neurotransmitter concentrations(DA, NE, and 5-HT) and microRNA-7a and -34c in serum and hypothalamus tissue of rats exposed to different powers of noise.

2. Materials and Methods

Experimental animals;

Animals used in the research are all wholesome adult male albino rats of the Wistar strain weighing 180-220 gram. The study included forty male albino rats. All animals were kept individually with a 12-hr. light-dark cycle and regulated room temperature (22 ± 2 ºC) with free access to standard rodent diet and tap water for at least one week before experimentation so that rodents could acclimate to their new surroundings.

Ethical statement;

The current protocol was approved by Alexandria University-Institutional Animal Care and Use Committee (AlexU-IACUC, Approval number: AU01222123111). All experiments fulfilled the guidelines of the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978) and the recommendations of Egypt's guide for the care and use of laboratory animals. Rats were kept as relaxed as possible throughout the experiment by following standard operating procedures and best practices for routine tasks, such as blood sampling, providing a steady supply of food and water, and cleaning the rats' cages at the same time. These actions can significantly enhance the welfare of the animals.

Experimental design;

Animals were split up into four groups (10 rats each), control group 1 (GI) and three test groups GII, GIII and GIV. Test groups were exposed to noise at 85 dB, 100 dB and 135 dB respectively. The rats in noise-exposed groups were kept in their anechoic chamber [(29)] in the room of experimental animal's laboratory for 15 days for 4 hours/day from 7 a.m. to 11 a.m. and were exposed to workplace noise by using computer-operated speakers' system. The level of noise was measured by a sound meter. At the same duration, the control group (GI) was housed in the exact same room without having the noise device turned on.

Biochemical investigations;

Immediately after noise exposure, the test groups (GII, GIII, and GIV) and control animals were sacrificed under deep anesthesia using Isoflurane to obtain blood and hypothalamus tissues. All the experimental procedures were carried out in the morning to avoid the influence of circulation fluctuation. Serum was separated by centrifugation and the hypothalamus tissue was dissected from the brain and stored at -80°C.

Determination of serotonin (5HT) and dopamine levels in serum:

As indicated in the modification of the methodology of Schlumpf et al, [(30)] this methodology is based on extraction of monoamines by acidified butane treatment of the extract with a sensitive indicator o-phthaldialdehyde (OPT) 20 mg% will form fluorescent compound with serotonin which was measured at excitation wavelength of 360 nm and emission wavelength of 470 nm in the Spectro-fluorophotometer. Treatment of another portion of the extract with iodine in a weak acid medium result in reaction products which isomerize in alkaline medium in the Spectro-fluorophotometer at excitation wavelength of 330 nm and emission wavelength of 375 nm to measure dopamine.

Determination of Norepinephrine:

The concentration of NE in serum samples was determined by using a specific rat ELISA kit (life Span Bioscience USA) in compliance with the manufacturer's recommendations [(30)]. Using Lowry's technique, the total protein concentration was calculated.

Gene expression analysis;

Thirty mg of the hypothalamus tissues were used for total RNA and miRNA extraction using the miRNeasy Mini Kit (Qiagen, Germany) according to the manufacturer's instructions and the concentration and integrity of extracted RNA were checked using nanodrop. The reverse transcription of the extracted RNA was performed using Reverse transcription (RT) by TOPscript™ RT DryMIX kit (dT18/dN6 plus) (Enzynomics, Korea) according to the manufacturer's instructions. Using the QuantiNovaTM SYBR® Green PCR Kit (Qiagen, Germany) and CFX MaestroTM Software (Bio-Rad, USA), the tissue expression of miR-34c and miR-7a was quantified in the cDNA. The conditions for the quantitative PCR amplification were set up as an initial denaturation at 95 °C for 10 min, followed by 45 cycles of PCR for amplification: denaturation at 95 °C for 20 s, annealing at 55 °C for 20 s, and extension at 70 °C for 15 s. The housekeeping gene SNORD68 was used as a reference gene for miRNAs, and the relative change in miRNA expression in samples was calculated using the $2^{-\Delta\Delta Ct}$ method.

3. RESULTS

Serum Serotonin Levels (µg/ml)

The presented data indicated a statistically significant reduction in serum serotonin levels in GIII and GIV in contrast to the control group and there is also a statistically significant decrease in serum serotonin levels in GIII and GIV when compared to GII. Moreover, there was a statistically insignificant reduction in serum serotonin levels in GII when in contrast to the control group GI, also there was a statistically insignificant decrease in serum serotonin levels between GII & GIII and between GIII &GIV**(Figure1)**

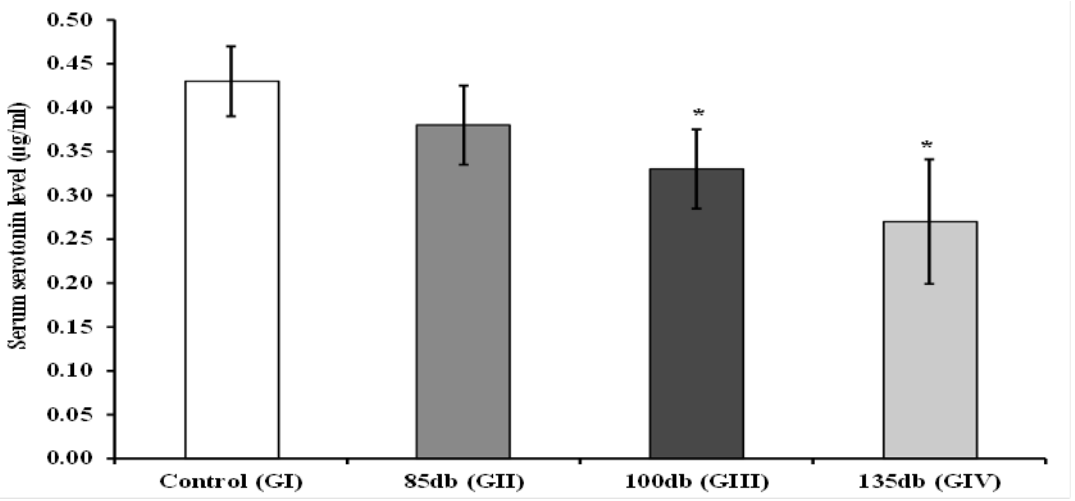

Figure (1):Serum serotonin levels (µg/ml) in the control rats and rats exposed to different powers of noise. Data are presented as mean ± SD and n = 10. *: Statistically significant compared with control group at $p \leq 0.05$ by ANOVA test, followed by Post Hoc Test (Tukey)

Serum Dopamine Levels (µg/ml)

The current research data showed a statistically significant reduction in dopamine levels in the serum of tested groups as in contrast to the control group. Also, there was a statistically significant reduction in serum dopamine levels in GIII and GIV in contrast to GII, and a statistically significant decrease in its serum levels in group GIV in contrast to GIII. On the other hand, the data showed a statistically insignificant reduction in serum dopamine levels between GIII and GIV. (**Figure 2**)

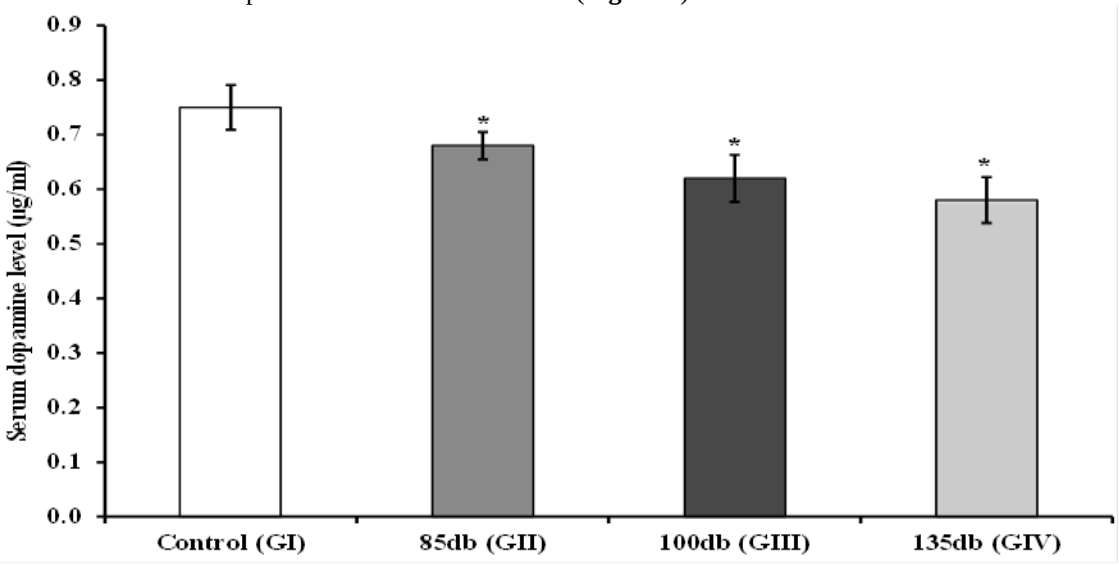

Figure (2): Serum dopamine (µg/ml) in the control rats and rats exposed to different powers of noise. Data are presented as mean ± SD and n = 10. *: Statistically significant compared with control group at $p \leq 0.05$ by ANOVA test, followed by Post Hoc Test (Tukey)

Serum Norepinephrine Levels (pg/ml)

The data indicated a statistically significant increase in serum norepinephrine levels in the tested groups in contrast to the control. There was a statistically significant increase in serum norepinephrine levels in GIII and GIV in contrast to GII and a statistically significant increase in its serum levels in GIV in contrast to GIII. (**Figure 3**).

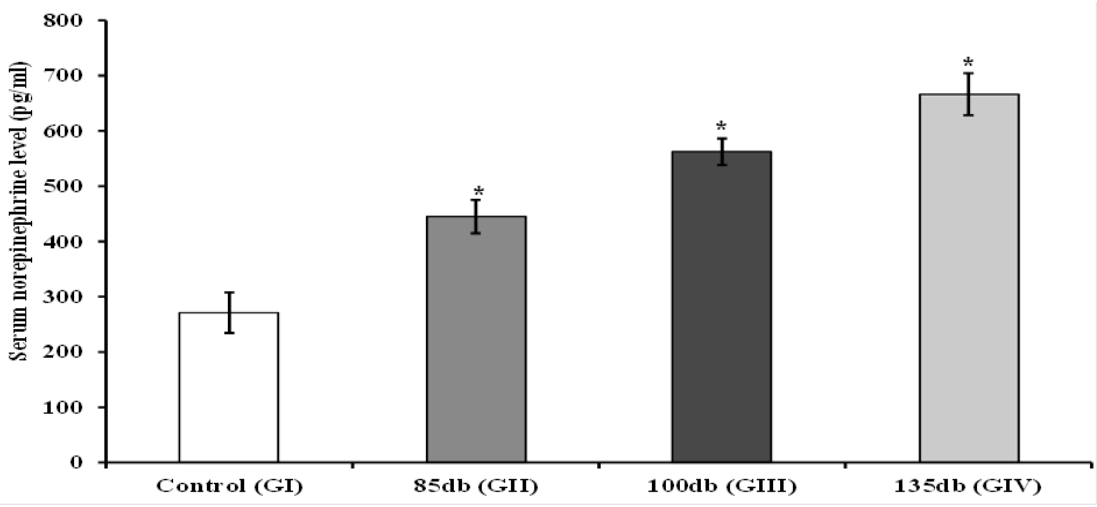

Figure (3): Serum Norepinephrine levels (pg/ml) in the control rats and rats exposed to different powers of noise. Data are presented as mean ± SD and n = 10. *: Statistically significant compared with control group at $p \leq 0.05$ by ANOVA test, followed by Post Hoc Test (Tukey)

Relative Expression of Hypothalamus miR-34c

The current study indicated a statistically significant increase (Upregulation) in relative expression of miR-34c in hypothalamus tissues between GIV and the control group GI. On the other hand, there was a statistically insignificant increase in the relative expression ofmiR-34c inhypothalamustissues of GII and GIII in contrast to the control group GI. Also, there was a statistically insignificant increase in the relative expression of miR-34c between GII & GIII. (**Figure 4**)

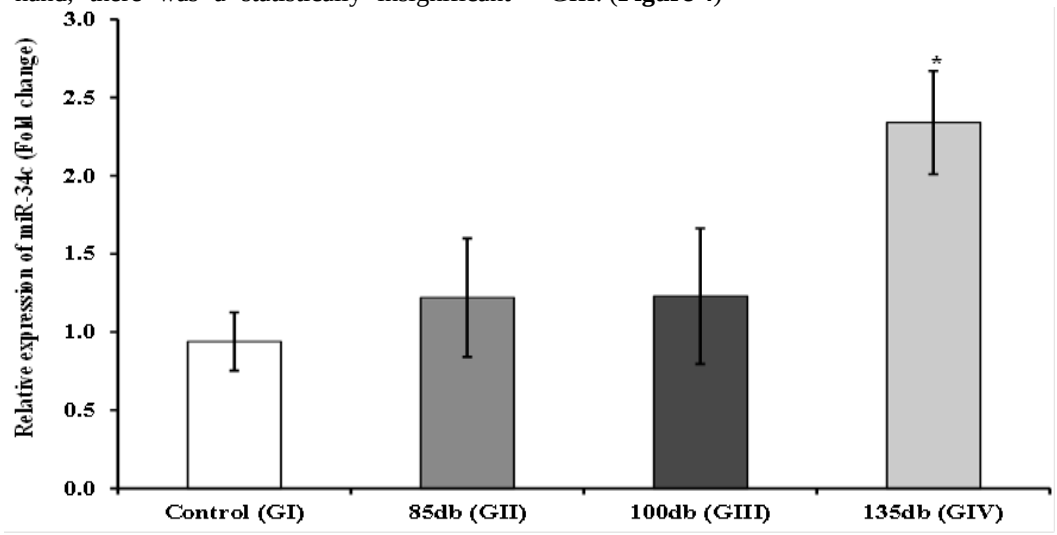

Figure (4): Relative expression of miR-34c in the control rats and rats exposed to different powers of noise. Data are presented as mean ± SD and n = 10. *: Statistically significant compared with control group at $p \leq 0.05$ by ANOVA test, followed by Post Hoc Test (Tukey)

Relative Expression of Hypothalamus miR-7a

There was a statistically significant decrease (Downregulation) in relative expression of miR-7a inhypothalamus tissues of GIV compared to the control group GI. The data indicated a statistically insignificant decrease in the relative expression of miR-7a in hypothalamus tissues of GII and GIII in contrast to the control group GI, also this was observed between GII, GIII and GIV. (**Figure 5**).

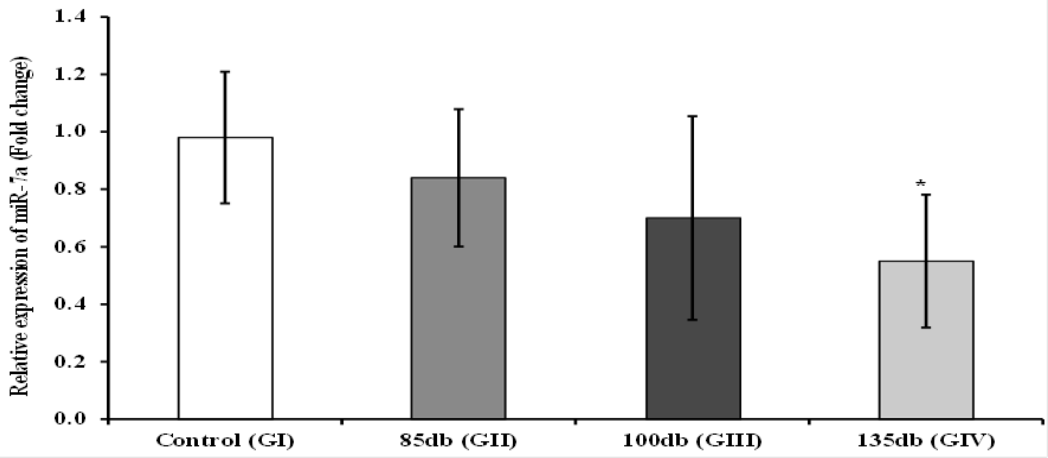

Figure (5): Relative expression of miR-7a in the control rats and rats exposed to different powers of noise. Data are presented as mean ± SD and n = 10. *: Statistically significant compared with control group at $p \leq 0.05$ by ANOVA test, followed by Post Hoc Test (Tukey)

Correlation Studies

The correlation studies between hypothalamic expression of microRNA-7a or microRNA-34c and serum neurotransmittersshowed that: microRNA-7a significantlyand negatively correlated with serum level of NE ($p < 0.001$, $r = -0.378$, **Figure 6A**). on the other hand, microRNA-34c showed positive correlation with serum NE ($r = 0.662$, $p < 0.001$, **Figure 6B**) and significant negative correlation with serum dopamine ($r=-0.520$, $p = 0.003$, **Figure 6C**) and serotonin ($r=-0.425$, $p=0.019$, **Figure 6D**).

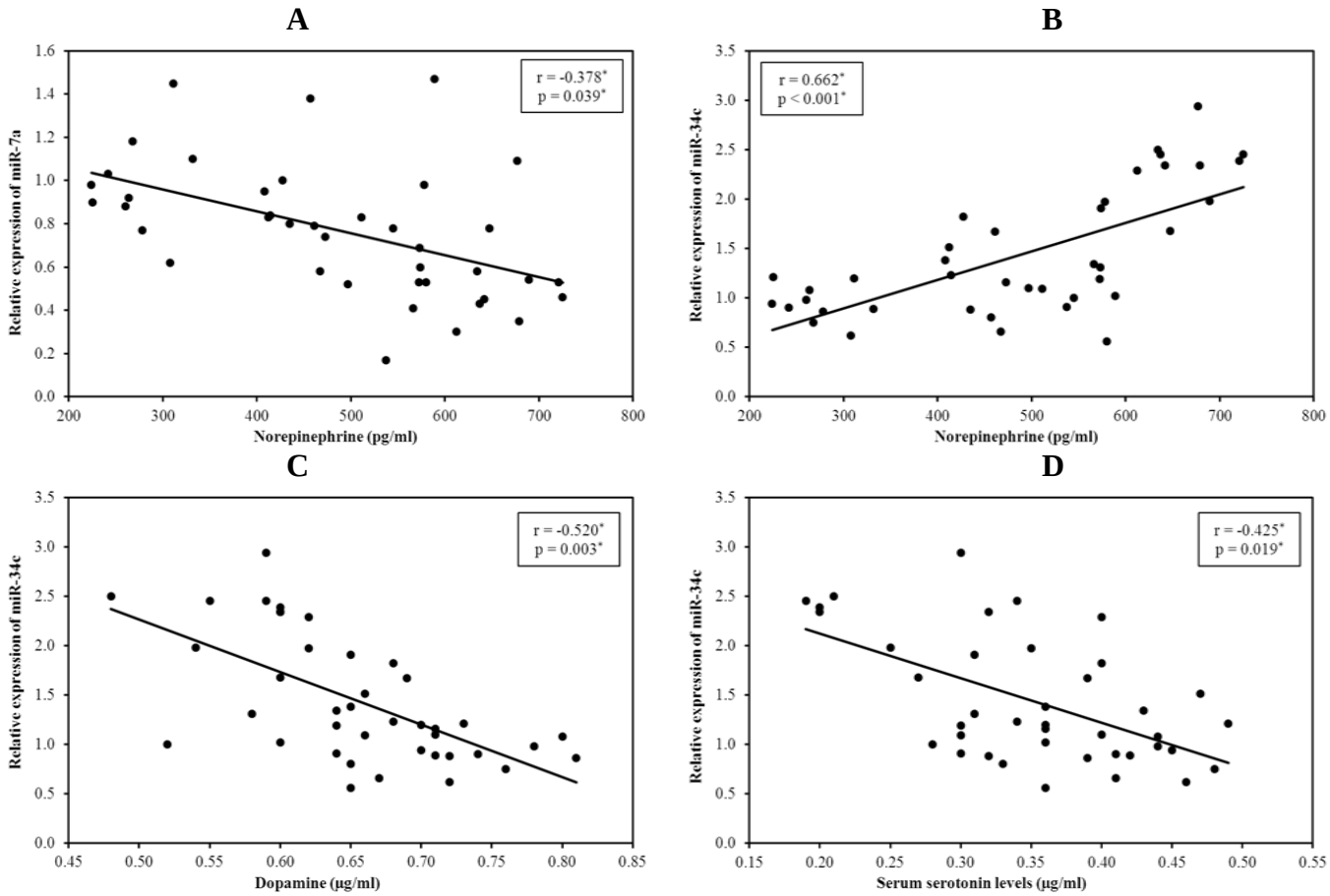

Figure (6): Correlation between hypothalamic expression of microRNA-7a or microRNA-34c and serum neurotransmitters.

4. Discussion

Noise increase stress hormone such as epinephrine, norepinephrine and cortisol as it is a stressful biological factor that stimulates HPA and hypothalamus gonadal adrenal axis (HGA) which are closely regulated in regulating reproduction [(31)]. As the HPA axis can modulate the responsiveness of the auditory system and be activated by acoustic stress, noise can trigger physiological stress [(32-33)]. The effects of noise stress are subtle and gradual rather than abrupt and disastrous. Noise-induced sickness may result from interactions between physiological systems that battle noise and mechanisms that cause noise stress[(34)].

After receiving multiple signals from various brain regions, the hypothalamus releases hormones that either release or inhibit the function of the thyroid, adrenal glands, or reproductive organs. These hormones then act on the pituitary gland to regulate development, fluid balance, and milk production [(35)]. Severe stressful situations such as noise pollution are in charge of the etiopathogenesis of many psychosomatic illnesses. Different physiological mediators work together to regulate homeostasis by communicating with receptors located at distinct physiological levels and the neurotransmitter's functional identity under extreme stress. There are numerous processes that take place in between a stressful input and the body's ensuing reactions. Both the central and autonomic nervous systems are involved in a range of neurochemical reactions throughout these activities [(36)]. The result of the present research showed that noise exposure for four hours per day for 15 days at increasing intensities of 85 dB, 100 dB and 135 dB caused significant reduction in the levels of serum dopamine and serotonin in contrast to the control group. These changes might cause dysregulated day-night rhythm, lack of reward feelings, disturbed eating, sex and disturbed cognitive functions. These adverse effects of noise exposure were observed in a study by Bao and Swaab[(37)]. Rats subjected to noise for 30 days showed a drop in brain biogenic amines, according to another study [(38)]. Chronic and acute noise stress exposure exceeding 90 dB is linked to dopaminergic and serotonergic system imbalances in the brain, which can lead to anxiety and depression. Also, after chronic noise exposure above 100 dB, despair longer immobility activity, reduced muscle movement and exhaustion were observed due to changes in dopamine and serotonin concentrations in rats' model [(39)].Chronic stress was found to influence the distribution of serotonin in the brain and can also alter the body temperature regulated by the medial preoptic area of the hypothalamus (mPOA) as the exposure to chronic stress decreases serotonin in the mPOA region contributing to long-lasting thermoregulatory malfunction [(40)].

The result of the present research showed that noise exposure caused significant increase in serum NE levels compared to the control group. NE affects how an organism reacts to stress as it increases the brain's capability to cope with stress. It was found that chronic noise exposure leads to trigger the "fight or flight" responses by disrupting the homeostasis by dysregulating the APA axis and SAM axis [(41)]. Adrenal gland activation allows epinephrine to be released, and NE allows the body to elevate its heart rate, blood pressure and The rate of breathing [(42)].The stimulation of HPA axis with the plasma glucocorticoid levels that serves as the end point of that activation is considered as the hallmark of stress also the release of brain NE considered as the hallmark of stress as it is induced by many of the same challenges in parallel with the HPA axis [(43)]. NE is a crucial neurotransmitter that is involved in signaling stress. It was reported that stressors from multiple causes stimulate the noradrenergic brain system, leading to increased release of NE from the terminal region of noradrenergic nerves, leading to a decrease in NE levels in the brain [(44)].Chronic stress exposure was found to cause an inverse relationship between NE and dopamine levels, tumor growth in rats, and reduced serotonin in the rat hypothalamus but not the mouse hypothalamus. This is because stress causes distinct changes in brain monoaminergic neurotransmission that vary depending on the species of rodent and mouse. This could result in various stress-induced consequences on the body's ability to reproduce, grow, build immunity, and become detoxicated[(45)].

MicroRNAs are widely expressed in neurons in brain and defenders of cellular homeostasis together with transcription factors and protein partners, control stress responses Also they function as regulators biological mechanisms such as atherosclerosis and glucose metabolism [(46-47)].The relation between relative expression of MicroRNA-7a and noise pollution was first studied here in, observing that when rats were exposed to noise stress 135 dB for 4 hours/day for 15 days, there was a significant reduction in miR-7a relative expression in the hypothalamus tissue. In order to provide an appropriate response, the hypothalamus integrates signals from other brain regions as well as environmental, hormonal, and neuronal signals from the periphery. Xu Y. *et al* indicated that stress and the ensuing hyperactivity of the HPA axis in the hypothalamus may be the most important etiological risk factor for the onset of depression. Additionally, altered hypothalamic miRNAs during stress have been observed[(48)].

The significant role of microRNA-7a in the regulation of neurotransmitters is evident in the present research by correlation study which indicated negative correlation between microRNA-7a and serum level of NE. MicroRNA-7 familyare highly conserved in pituitary gland, hypothalamus and pancreatic cells [(49)]. In secondary ischemic brain damage, it was found that miRNA-7 level reduced after cerebral ischemia· Reduced abundance of miRNA-7 in cancer and Parkinson disease contribute to the neuro degeneration that appear in the disease, so it was reported that miRNA-7 ameliorates cellular stress [(50)].microRNA-34 is another important microRNA in CNS, three groups of the MicroRNA-34 family are miRNA-34a, miRNA-34b, and miRNA-34c. Due to their synergistic effect with the tumor suppressor p53, they are dysregulated and considered as a tumor suppressive miRNA under stress such as cancer. MiRNA-34a has a special transcript and is located in chromosome 1p36.22, while the other two miRNA-34b and miRNA-34c have a similar transcript located in chromosome 11q23.11.11[(51)]. In response to cellular stress, the transcription factor p53 activates the miRNA-34 family genes [(52)].The result of the present research showed that noise exposure for 4 hours/day for 15 days at increasing intensities of 85 dB, 100 dB and 135 dB caused significant increase in

the relative expression of miRNA-34c in the hypothalamus tissue in the group exposed to 135 dB of rats compared to the control group. Researchers found that miR-34c increases under chronic stress [(53)]. It was suggested a role of miRNA-34a and miRNA-34c in antibiotic-induced autotoxicity in dose dependent manner in cochlear cells [(54)]. The primary factor contributing to age-related hearing loss, or the progressive loss of hearing that comes with aging, is the deterioration of the organ of caused by alterations of miRNA-29 and miRNA-34 families. These miRNAs control pro-apoptotic pathways, as miR-34 exhibits a significant stimulator in mice during ageing to increase cochlea, auditory cortex and plasma[(55)]. The microRNA-34c has important role in the regulation of neurotransmitters as indicated by negative correlation between microRNA-34c expression and serum level of serotonin and dopamine and positive correlation with NE[(56)].

5. Conclusion

Noise exposure is a powerfulCNS stressor caused a reduction in serum levels of serotonin and dopamine and caused marked elevation of NE. It also suppressed the relative expression of microRNA-7a and induced the expression of microRNA-34c in hypothalamus tissue. These may dysregulate the function of HPA axis and the release of hormones.

Data availability; All data available upon your request to the corresponding author.

6. References

1. Thammarong Eadkhong. (2023). Mechanical wave: sound resonance Lab 1 Intermediate Physics lab @ WU: PHC-200 Intermediate Physics Laboratory. Wu-eLearning, 23(1), 1-8.
2. Pantawane, R. N., Maske, K. V., & Kawade, N. S. (2017). Effects of noise pollution on human health. International advanced research journal in science, engineering and technology, 4(3), 33-35.
3. Zbysińska, M., & Lachowska, M. (2020). Hearing damage caused by noise in classical musicians. Pol otorhino rev., 9(2), 41-53.
4. Salehpour, F., Mahmoudi, J., & Eyvazzadeh, N. (2018). Effects of acute and chronic noise stress on depressive-and anxiety-like behaviors in mice. Journal of Experimental and Clinical Neurosciences, 5(1), 1-6.
5. Jafari, M.J., Khosrowabadi, R., Khodakarim, S., &Mohammadian F. (2019). The Effect of Noise Exposure on Cognitive Performance and Brain Activity Patterns. Open Access Maced J Med Sci., 7(17), 2924-2931.
6. Mcewen,B,S, Gray, J.D., Nasca,C., (2015). Redefining neuroendocrinology stress, sex and cognitive and emotional regulation. Journal of Endocrinology., 2(226), 67-83.
7. Tousson, E., Ibrahim, W., Arafa, N., & Akela, M. A. (2012). Histopathological Changes in Rat Hypothalamus After Propylthiouracil Induced Hypothyroidism and The Protective Role of Folic Acid. Journal of Neurological Sciences, 29(4),705-713.
8. Myers, B., & Greenwood-Van Meerveld, B. (2012). Differential involvement of amygdala corticosteroid receptors in visceral hyperalgesia following acute or repeated stress. American Journal of Physiology-Gastrointestinal and Liver Physiology, 302(2), G260-G266.
9. Eraslan, E., Akyazi, I., Ergül-Ekiz, E., & Matur, E. (2015). Noise stress-induced changes in mRNA levels of corticotropin-releasing hormone family molecules and glucocorticoid receptors in the rat brain. Folia biologica, 61(2), 66-73.
10. Kruk, J., Kotarska, K., & Aboul-Enein, B. H. (2020). Physical exercise and catecholamines response: benefits and health risk: possible mechanisms. Free Radical Research, 54(2-3), 105-125.
11. Jack, C. (2019). Biogenic Amine Neurotransmitters In: An Electronic Textbook for the Neurosciences.Availablefrom:https://nba.uth.tmc.edu/neuroscience/m/s1/chapter12.html. [Accessed in: Feb, 2020].
12. Wang, X., Li, J., Dong, G., & Yue, J. (2014). The endogenous substrates of brain CYP2D. European Journal of Pharmacology, 724, 211-218.
13. Broadley, K. J. (2010). The vascular effects of trace amines and amphetamines. Pharmacology & therapeutics, 125(3), 363-375.
14. Harvard Health Publishing. (2020). Understanding the stress response. Retrieved November22, 2021, from https://www.health.harvard.edu/stayinghealthy/understanding-the-stress-response.
15. Otten, W., Kanitz, E., Puppe, B., Tuchscherer, M., Brüssow, K. P., Nürnberg, G., et al. (2004). Acute and long-term effects of chronic intermittent noise stress on hypothalamic-pituitary-adrenocortical and sympatho-adrenomedullary axis in pigs. Animal Science, 78(2), 271-283.
16. Ironside, M., Kumar, P., Kang, M.-S. &Pizzagalli, D. A. (2018) Brain mechanisms mediating effects of stress on reward sensitivity. Curr. Opin. Behav. Sci, 10(22), 106-113.
17. Baik, J. (2020). Stress and the dopaminergic reward system. Experimental & Molecular Medicine, 52, 1879-1890.
18. Ogłodek, E.A., (2022). Changes in the Serum Concentration Levels of Serotonin, Tryptophan and Cortisol among Stress-Resilient and Stress-Susceptible Individuals after Experiencing Traumatic Stress. Int. J. Environ. Res. Public Health, 19,1-12.
19. rice, C.M., Feduccia, A.A., DeBonis, K., (2022). Effects of Selective Serotonin Reuptake Inhibitor Use on 3,4-Methylenedioxymethamphetamine-Assisted Therapy for

Posttraumatic Stress Disorder: A Review of the Evidence, Neurobiological Plausibility, and Clinical Significance. J. Clin. Psychopharmacology, 42, 464–469.

20. Thomas, K. T., Gross, C., & Bassell, G. J. (2018). MicroRNAs sculpt neuronal communication in a tight balance that is lost in neurological disease. Frontiers in molecular neuroscience, 11, 455.
21. Ratti, M., Lampis, A., Ghidini, M., Salati, M., Mirchev, M.,Valeri, N., et al. (2020). MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside. Target Oncol., 15(3), 261–278.
22. Woldemichael, B. T., Jawaid, A., Kremer, E. A., Gaur, N., Krol, J., Marchais, A., &Mansuy, I. M. (2016). The microRNA cluster miR-183/96/182 contributes to long-term memory in a protein phosphatase 1-dependent manner. Nature communications, 7(1), 1-11.
23. Park, J., Lee, J., Choi, K., & Kang, H. J., (2020). Regulation of behavioral response to stress by microRNA-690. Molecular Brain, 14(7), 1-4.
24. Rinaldi, A., Vincenti, S., De, Vito F., Bozzoni, I., Oliverio, A., Presutti, C., et al. (2010). Stress induces region specific alterations in microRNAs expression in mice. Behav Brain Res., 208(1), 265–9.
25. Amar, L., Benoît, C., Beaumont, G., Vacher, C.-M., Crepin, D., Taouis, M. et al. (2012). MicroRNA expression profiling of hypothalamic arcuate and paraventricular nuclei from single rats using Illumina sequencing technology. Journal of neuroscience methods, 209(1), 134-143.
26. Kredo-Russo, S., Ness, A., Mandelbaum, A. D., Walker, M. D., & Hornstein, E. (2012). Regulation of pancreatic microRNA-7 expression. Experimental diabetes research, vol.2012, Article ID 695214, 7 pages.
27. Haramati, S., Navon, I., Issler, O., Ezra-Nevo, G., Gil, S., Zwang, R., et al. (2011). MicroRNA as repressors of stress-induced anxiety: the case of amygdalar miR-34. Journal of Neuroscience, 31(40), 14191-14203.
28. Li, C., Liu, Y., Liu, D., Jiang, H., & Pan, F. (2016). Dynamic alterations of miR-34c expression in the hypothalamus of male rats after early adolescent traumatic stress. Neural plasticity, Vol. (2016), 5249893, 8 pages.
29. Mohamed, M. A. (2016). Bio-effects of aircraft noise and antioxidant activity of omega3 on mice brain. International Journal of Biomedical Engineering and Science, 3(3), 9-21.
30. Schlumpf, M., Lichtensteiger, W., Langemann, H., Waser, P. G., & Hefti, F. (1974). A fluorometric micro method for the simultaneous determination of serotonin, noradrenaline and dopamine in milligram amounts of brain tissue. Biochemical pharmacology, 23(17), 2437-2446.
31. Qassemian, A., Jahromi, M. K., Salesi, M., & Jahromi, B. N. (2019). Swimming modifies the effect of noise stress on the HPG axis of male rats. Hormones, 18(4), 417-422.
32. Graham, C. E., Basappa, J., & Vetter, D. E. (2010). A corticotropin-releasing factor system expressed in the cochlea modulates hearing sensitivity and protects against noise-induced hearing loss. Neurobiology of disease, 38(2), 246-258.
33. Le, T. N., Straatman, L. V., Lea, J., & Westerberg, B. (2017). Current insights in noise-induced hearing loss: a literature review of the underlying mechanism, pathophysiology, asymmetry, and management options. Journal of Otolaryngology-Head & Neck Surgery, 46(1), 41-46.
34. Samson, J., Sheeladevi, R., Ravindran, R., & Senthilvelan, M. (2007). Stress response in rat brain after different durations of noise exposure. Neuroscience research, 57(1), 143-147.
35. Cocco, C., Brancia, C., Corda, G., & Ferri, G.-L. (2017). The Hypothalamic–Pituitary Axis and Autoantibody Related Disorders. International journal of molecular sciences, 18(11), 2322, 13 pages.
36. Malathi, S. (2016). Restoration of memory and acetyl cholinesterase activity by micheliachampaca in chronically noise stressed wistar albino rats. Asian Journal of Pharmaceutical and Clinical Research, 9(6), 210-214.
37. Bao, A.-M., & Swaab, D. F. (2019). The human hypothalamus in mood disorders: the HPA axis in the center. International brain research organization reports, 6, 45-53.
38. Salehpour, F., Mahmoudi, J., & Eyvazzadeh, N. (2018). Effects of acute and chronic noise stress on depressive-and anxiety-like behaviors in mice. Journal of Experimental and Clinical Neurosciences, 5(1), 1-6.
39. Farzad, S., Javad M., Nazila, E., (2018). Effects of Acute and Chronic Noise Stress on Depressive- and Anxiety-like Behaviors in Mice. J Exp Clin Neurosci., 5(1), 1-6
40. Di, G., & He, L. (2013). Behavioral and plasma monoamine responses to high-speed railway noise stress in mice. Noise and Health, 15(65), 217-23.
41. Walker, E. D., Brammer, A., Cherniack, M. G., Laden, F., & Cavallari, J. M. (2016). Cardiovascular and stress responses to short-term noise exposures—A panel study in healthy males. Environmental research, 150, 391-397.
42. Wadhwa, S., & Thakar, A. (2017). A Qualitative Study on Workplace Stress: Fight or Flight Response. International journal of engineering and management research, 7(3), 57-61.
43. Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R. et al. (2016). Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Comprehensive Physiology, 6(2), 603-621.

44. Schmidt, K. T., Makhijani, V. H., Boyt, K. M., Cogan, E. S., Pati, D., Pina, M. M. et al. (2018). Stress-induced alterations of norepinephrine release in the bed nucleus of the stria terminalis of mice. ACS Chemical Neuroscience, 10(4), 1908-1914.
45. Wardhana, M., Windari, M., Puspasari, N., Suryawati, P. (2019). Role of Serotonin and Dopamine in Psoriasis: A Case-Control Study. Macedonian Journal of Medical Sciences, 7(7), 1138-1142.
46. Chen, L. B., An, Z., Zheng, H. K., Wang, X. P., Shan, R. T., Mao, C. Y., et al. (2020). MicroRNA-34c suppresses proliferation of vascular smooth muscle cell via modulating high mobility group box protein 1. Journal of Clinical Laboratory Analysis, 34(1), e23293, 8 pages.
47. Marta O., Anna Kotowska-Zimmer., Wlodzimierz K., (2018). Stress-induced changes in miRNA biogenesis and functioning. Cell. Mol. Life Sci., (75), 177–191.
48. Ya-Yun Xu, Qian-HuiXia, Qing-Rong Xia,Xu-Lai Zhang and Jun Liang. (2019). MicroRNA-Based Biomarkers in the Diagnosis and Monitoring of Therapeutic Response inPatients with Depression. Neuropsychiatric Disease and Treatment, (15), 3583–3597.
49. Latreille, M., Hausser, J., Stützer, I., Zhang, Q., Hastoy, B., Gargani, S. et al. (2014). MicroRNA-7a regulates pancreatic β cell function. The Journal of clinical investigation, 124(6), 2722-2735.
50. Lee, H. J., Palkovits, M., & Young, W. S. (2006). miR-7b, a microRNA up-regulated in the hypothalamus after chronic hyperosmolar stimulation, inhibits Fos translation. Proceedings of the National Academy of Sciences, 103(42), 15669-15674.
51. Zhang, L., Liao, Y., & Tang, L. (2019). MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. Journal of experimental & clinical cancer research: CR, 38(1), 53.
52. Li-Bo Chen, Zhe An, Hai-Kuo Zheng, Xin-Peng Wang, Rui-Ting Shan, Cui-Ying Mao, et al. (2020). MicroRNA-34c suppresses proliferation of vascular smooth muscle cell via modulating high mobility group box protein. J Clin Lab Anal., 23293, 1 - 8.
53. Huang, Y., Liu, X., Liao, Y., Liao, Y., Zou, D., Wei, X.et al. (2018). Role of miR-34c in the cognitive function of epileptic rats induced by pentylenetetrazol. Molecular medicine reports, 17(3), 4173-4180.
54. Jami, M.-S., Pal, R., Hoedt, E., Neubert, T. A., Larsen, J. P., & Møller, S. G. (2014). Proteome analysis reveals roles of L-DOPA in response to oxidative stress in neurons. BMC Neuroscience, 15(1), 15-93.
55. Pang, J., Xiong, H., Yang, H., Ou, Y., Xu, Y., Huang, Q., et al. (2016). Circulating miR-34a levels correlate with age-related hearing loss in mice and humans. Experimental Gerontology, 76, 58-67.
56. Chuting Li, Yuan Liu, Dexiang Liu, Hong Jiang, and Fang Pan. (2016). Dynamic Alterations of miR-34c Expression in the Hypothalamus of Male Rats after Early Adolescent Traumatic stress. Neural plasticity, 5249893, 8 pages.