AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 08, December 2022

THE EFFECT OF HIGH CONCENTRATION OF EXOGENOUS IODINE ON THE BRAIN OF PREGNANT MOTHER AND EMBRYOS RATS

Ghina H. Hussein[1], Alaa Tareq Shakir Alhassnawi[1] and Eyhab R. Al-Samawy[2]

Science Collage- Babylon University[1]

Medicine collage-AL Muthanna University[2]

Abstract

The study was investigated the effect of high concentration exogenous iodine on the thyroid transcription factors. **Methods** : The study was included 3 groups as following **Group (1):** Involved 20 adult female rats, animals in this group administered distilled water and served as control.**Group (2):** Involved 15 adult female rats, animals in this group treated group animals in low dose of iodine (0.06 mg) ,**Group (3):** Involved 15 adult female rats, animals in this group treated group animals in medium dose of iodine(0.18 mg), after 18 days of pregnancy the animals was sacrificed and the serum was collected to determination Rat Paired box protein (PAX-8), Rat Forkhead box protein E1(FOXE1), Rat Homeobox protein (Nkx-2.1) done by ELISA assay for the mother while the thyroid factors for embryo was determined after tissues disruption with glass Homogenizers for the thyroid gland, **the results** reported the mother brain parameters showed the highest ACh concentration was in 1.8 gm $86.18^{c}\pm1.02$ followed by in 0.06 gm ,the concentration was 66.5±1.03, while the lowest value recorded in control group however the highest BDNF concentration was in 1.8 gm $5.77^{b}\pm1.33$followed by in 0.06 gm was $3.86^{a}\pm0.15$, and the lowest value recorded in control group with significant at($p\leq0.05$) between studied groups. same findings in embryonic brain parameters which highest ACh concentration was in 1.8 gm $65.38^{c}\pm1.02$ followed by in 0.06 gm ,the concentration was $50.5^{b}\pm1.03$, however the highest BDNF concentration was in 1.8 gm $3.67^{b}\pm0.0883$ followed by in 0.06 gm was $1.96^{a}\pm0.0581$, and the lowest value recorded in control group in both groups with significant at($p\leq0.05$) between studied groups. **Conclusion**, the current study was found the parameters were involved directly with excess iodine taken , which all the parameter were evaluated with iodine doses in both pregnant mother and embryos rats.

Keywords: **Rat Paired box protein (PAX-8), Rat Forkhead box protein E1(FOXE1), Rat Homeobox protein (Nkx-2.1), pregnant mother and embryos rats, iodine**

Introduction iodine is a microelement that can be found as a dietary supplement, added to some foods, and naturally in others. Before being absorbed by the gastrointestinal tract, iodine from the meal is transformed into the iodide ion[1] Iodide enters the blood, is concentrated by the thyroid gland in the precise levels needed for the manufacture of thyroid hormone, and the majority of the residual quantity is eliminated in the urine [2].Iodine requirements may be inferred using median urinary iodine concentrations of 100 g/L, which equate to around 150 g of iodine consumption per day [3]. Iodine intakes are adequate as evidenced by median urinary iodine concentrations of 100-

199 g/L in children and adults, 150-249 g/L in pregnant women, and >100 g/L in lactating women [4]. thyroid metabolism of iodine As previously stated, the thyroid gland's production of TH is the primary physiological function of iodine [5]. NIS actively transports bloodstream iodide through the plasma membrane into the cytoplasm of thyrocytes by using the Na+/K+ -ATPase transporter's produced concentration gradient of Na+ as a propulsion source [6]. Several transporters, such as PENDRIN, ANO1, and CFTR, then carry iodide to the lumen of thyroid follicles [7].The quantity of iodine that our bodies require depends on a variety of conditions, including physiological changes like pregnancy. Acetylcholine (ACh) production is increased by the hormone thyrotrophicreleasing hormone (TRH) [8] according to one study, the amount of acetylcholine in the hippocampi of people with hypothyroidism had dramatically reduced. And that T4 treatment brought ACh levels back to normal [9]. Hypothyroidism can be brought on by a lack of iodine. can adversely impact the brain's capacity to produce ACh. influencing mood as well as cognition, memory, learning, and recall. Neurotransmitters in the brain are adversely impacted by inadequate iodine intake. It can lead to neurodegenerative disorders like Alzheimer's and Parkinson's as well as depression, mental fog, anxiety, learning, and memory issues [10 ;11]. It is unknown if autoimmune thyroiditis (AIT), which can be brought on by too much iodine, has any effects on neurodevelopmental processes in children. Due to the knowledge that brain-derived neurotrophic factor (BDNF) plays a significant role in neurodevelopment, we investigated the impact of experimental autoimmune thyroiditis (EAT) rats with varying iodine consumption on offspring brain development [12].The aim of this study was to investigate if there is a relation between the effect of of high concentration exogenous iodine on the brain in pregnant mother rat and embryos.

Material and Methods

Preparation iodine

Iodine powder by using of an electronic balance, the doses were dissolved in distal water every day over the experiment period. The solution was administered orally by gavage in a dose after conducting an experimental dose to measure the safety of the dose on one animal for 24 to 48 hr before use.

Lab animals laboratory rats with weights ranging 250-300 g and 8 weeks of life were used in the experiment. The animals were placed in the Animal House of the Biology department/ College of Science at the University of Babylon, with environmental conditions that include moderate temperature, a 12 hour dark and 12 hour light cycle. The animals were treated with the approval of the ethics committee at the department, where they were kept in meshed plastic cages containing sawdust; the pellets were fed (mix of corn, wheat and milk) and they drank tap water throughout the experiment. Housed in 45cm×27cm×16cm polypropylene cages and will be given food and water ad libitum. The animals were left to adapt for 14 days before starting the experiment, male added for 15 day, Checking the female every day for pregnancy by mucus ring **,** food intake **,** mothers weight , mortality rate of mothers**.**

This study was included 2 groups as following: **Group (1):** Involved 20 adult female rats, animals in this group administered distilled water and served as control.**Group (2):** Involved 15 adult

female rats, animals in this group treated group animals in low dose of iodine (0.06 mg) ,**Group (3):** Involved 15 adult female rats, animals in this group treated group animals in medium dose of iodine(0.18 mg).

Blood collection

After 18 days of pregnancy, all groups of animals were sacrificed. Three milliliters of blood were drawn from the antecubital vein using a G23 needle, and the remaining blood was allowed to clot in a gel test tube at room temperature. The serum was aspirated after centrifugation at 2500 cycles per minute for 15 minutes, divided into aliquots in epindroff tubes, and stored at -20C°.

Determination the brain parameters in mother and embryo

Rat Brain derived neurotrophic facor (BDNF) and Rat Acetylcholine (ACH**)** achieved by ELISA assay(Enzyme-linked immunosorbent assay) (Elisys Uno) and the concentration obtained according the standard curve figure (1,3)To determine thyroid factors in embryo done after tissues disruption with glass Homogenizers for the thyroid gland of embryo .

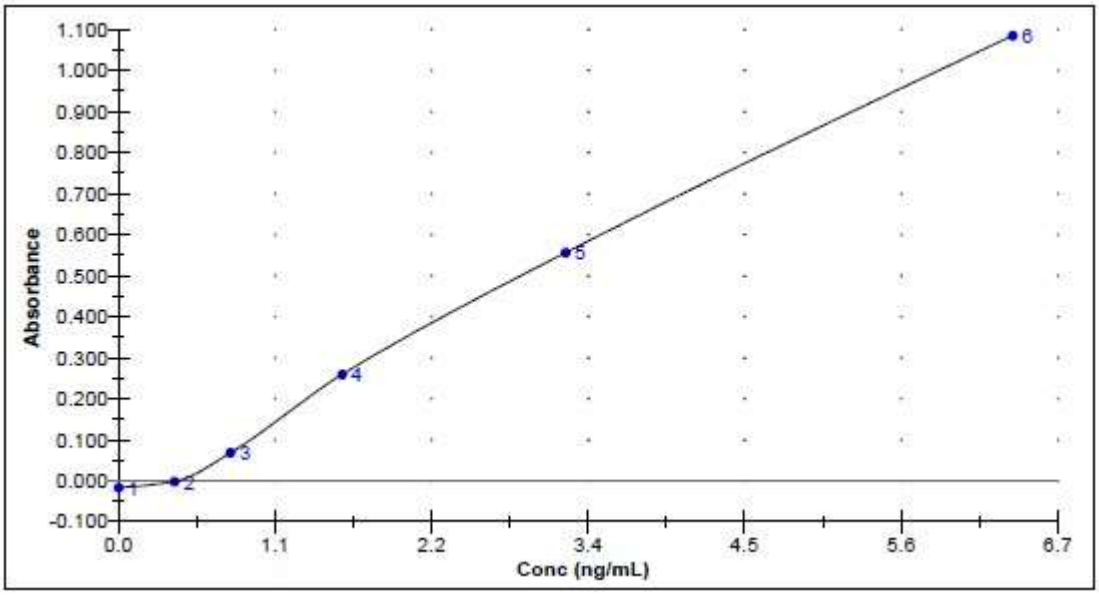

Figure 1. The standard curve of Rat Brain derived neurotrophic factor (BDNF).

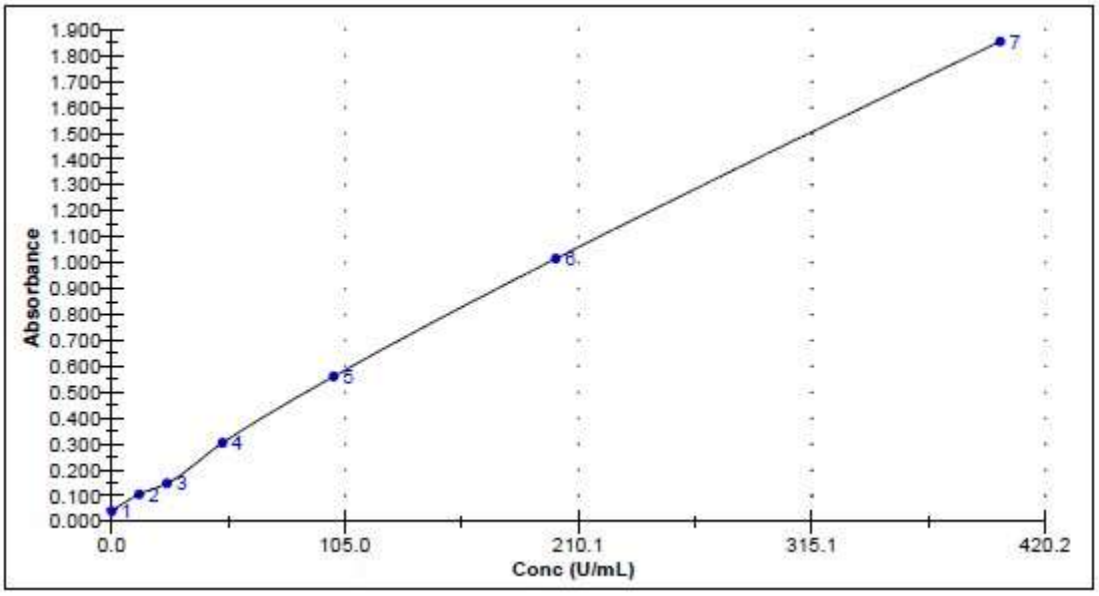

Figure 2. The standard curve of Rat Acetylcholine (ACH)

Statistical Evaluation Methods:

Data were analyzed using SPSS (Version 15), and statistical tests were carried out using a null hypothesis of no difference student t-test to determine the significance of difference. P-value and significance level were (0.05) and (0.01), respectively.

Results and Discussion

The embryonic brain parameters

The results showed the highest ACh concentration was in 1.8 gm $65.38^{c}\pm1.02$ followed by in 0.06 gm ,the concentration was $50.5^{b}\pm1.03$, while the lowest value recorded in control group $36.96^{a}\pm0.756$ with significant differences at($p\leq0.05$), however the highest BDNF concentration was in 1.8 gm $3.67^{b}\pm0.0883$ followed by in 0.06 gm was $1.96^{a}\pm0.0581$, and the lowest value recorded in control group $1.01^{a}\pm0.052$ with significant at($p\leq0.05$) between studied groups.

Table 1. The effect of different concentrations of exogenous iodine on the embryonic brain parameters

	Doses of Idoline(M±SE)				
Biomarker	Control	0.06 gm	1.8 gm	F-test	P-value
ACh	$36.96^{a}\pm0.756$	$50.5^{b}\pm1.03$	$65.38^{c}\pm1.02$	1657.39	0.0001
BDNF	$1.01^{a}\pm0.052$	$1.96^{a}\pm0.0581$	$3.67^{b}\pm0.0883$	1032.83	0.0001

Rat Brain derived neurotrophic factor (BDNF), Rat Acetylcholine (ACH)

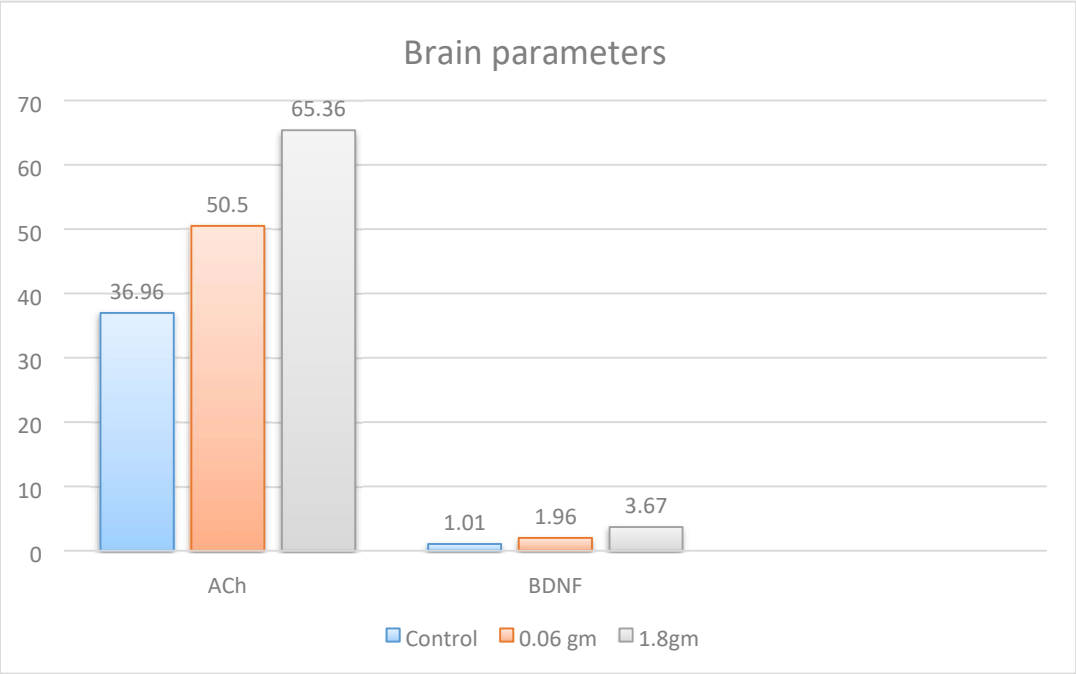

Figure 3. The effect of different concentrations of exogenous iodine on the embryonic brain parameters.

The Mother Brain Parameters

The results showed the highest ACh concentration was in 1.8 gm $86.18^{c}\pm1.02$ followed by in 0.06 gm ,the concentration was 66.5±1.03, while the lowest value recorded in control group $50.86^{a}\pm0.36$ with significant differences at($p\leq0.05$), however the highest BDNF concentration was in 1.8 gm $5.77^{b}\pm1.33$followed by in 0.06 gm was $3.86^{a}\pm0.15$, and the lowest value recorded in control group $2.11^{a}\pm1.05$with significant at($p\leq0.05$) between studied groups.

Table 2. The effect of different concentrations of exogenous iodine on the mother brain parameters

	Doses of Idoline(M±SE)				
Biomarker	Control	0.06 gm	1.8 gm	F-test	P-value
ACh	$50.86^{a}\pm0.36$	$66.5^{b}\pm1.03$	$86.18^{c}\pm1.02$	1657.39	0.0001
BDNF	$2.11^{a}\pm1.05$	$3.86^{a}\pm0.15$	$5.77^{b}\pm1.33$	1032.83	0.0001

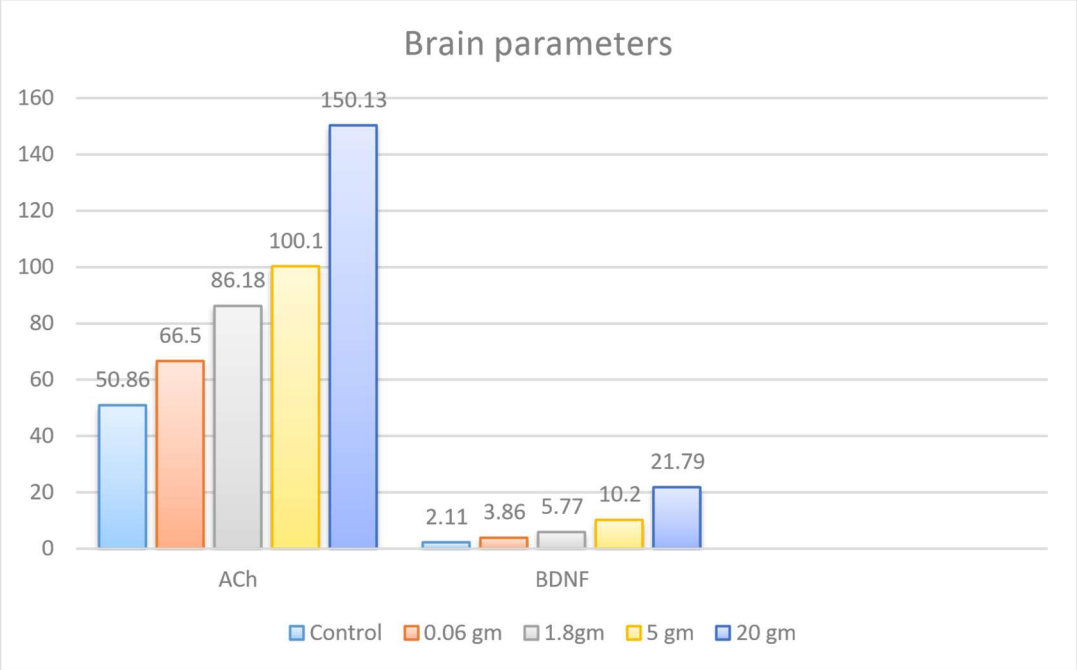

Figure 4. The effect of different concentrations of exogenous iodine on the mother brain parameters.

This results agreed with Jagadis et al.[13] that studied excess iodine on the rat primarily divided into two groups on the basis of the duration of treatment viz. 30 days group and 60 days group respectively and on the exposure of the dose of iodine was divided in to two sub-group, excess iodine exposed group (100HI) orally potassium iodide (KI) at the dose of 7 mg/Kg body weight and excessive iodine group (500HI) was gavaged orally KI at the dose of 35mg/Kg body weight and revealed result revel that those doses of excessive iodine causes a state of hypothyroidism as manifested by serum T3 serum T4 and TSH levels and thyroid morphology and also alters of cholinergic homeostasis in different areas of brain as revealed by acetylcholinesterase and Na+ -K+ ATPase activity An increase in AChE activity caused by excess iodine may lead to a reduction of clolinergic neurotransmission efficacy due to a decrease in Ach level in the synaptic cleft. Decreased Ach level in the synaptic cleft causes progressive cognitive impairment, especially in the young adult was suggested due to increase of synaptosomal membrane sphingomyelin. Increased AChE level participates in apoptosis by promoting or suppressing cell death[14].

For the supplementation of excess iodine there develops a biochemical state of hypothyroidism that in turn increased acetylcholinesterase activity markedly in cerebral cortex and hippocampus but not so much in the hypothalamus and cerebellum [13] Our findings supported by Zhang et al.,[15] sup investigated whether and how a 3-fold increase in the physiological dose of iodine in rat would affect brain development of their offspring female Wistar rats maintained on low-iodine grain were randomly assigned to three groups based on iodated water concentration: low iodine (LI, 1.2 μg/d), normal iodine (NI, 5–6 μg/d), and 3-fold high

iodine (3HI,15 16 µg/d) and found n PN7 the BDNF levels in the pups of the LI group were 58.84% that of the NI ($P < 0.01$) and the BDNF levels of the pups in the 3HI group were 83.5% that of the NI ($P < 0.05$). On PN45, the BDNF levels in the pups of the LI group were 59.78% that of the NI ($P < 0.01$), and the BDNF levels of the pups in the 3HI group were 88.8% that of the NI There is evidence that maternal thyroid hormones can cross the human placenta and act to modulate fetal development before the onset of the fetus's own thyroid hormone production [16] .Recent studies have reported that excess thyroid hormone could impair fetal brain development and affect the neurological outcome of rat offspring [17; 18].

Human studies depicting the effect of hypothyroidism on BDNF expression are very rare. Studies have shown improvement in symptoms like depression and lethargy which are commonly found in hypothyroid patients after treatment with antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and after hormone replacement therapy [19]. It has shown that thyroid hormone regulates 5HT neurotransmission by enhancing 5HT metabolism and 5HT receptor expression thyroid hormone modulates both 5HT and BDNF expression in the brain [20].

Conclusion

Depending on the obtained results , the current study was found the parameters were involved directly with excess iodine taken , which all the parameter were evaluated with iodine doses in both pregnant mother and embryos rats.

References

1- Patience, S. (2018). Iodine deficiency: Britain's hidden nutrition crisis. *Independent Nurse*, *2018*(6), 28-31.

2- Vought, R. L., & London, W. T. (1967). Iodine intake, excretion and thyroidal accumulation in healthy subjects. *The Journal of Clinical Endocrinology & Metabolism*, *27*(7), 913-919.

3- Institute of Medicine . *Academy of Sciences 2001 Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* National Academy Press; Washington, DC, USA: 2001.

4- World Health Organization.(2007) United Nations Children's Fund. International Council for the Control of Iodine Deficiency Disorders . *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination.* 3rd ed. World Health Organization; Geneva, Switzerland.

5- Zimmermann, M. B., Jooste, P. L., & Pandav, C. S. (2008). Iodinedeficiency disorders. *The Lancet*, *372*(9645), 1251-1262.

6- Wapnir, I. L., van de Rijn, M., Nowels, K., Amenta, P. S., Walton, K., Montgomery, K., ... & Carrasco, N. (2003). Immunohistochemical profile of the sodium/iodide symporter in thyroid, breast, and other carcinomas using high density tissue microarrays and conventional sections. *The Journal of Clinical Endocrinology & Metabolism*, *88*(4), 1880-1888.

7- Twyffels, L., Strickaert, A., Virreira, M., Massart, C., Van Sande, J., Wauquier, C., ... & Kruys, V. (2014). Anoctamin-1/TMEM16A is the major apical iodide channel of the thyrocyte. *American Journal of Physiology-Cell Physiology*, *307*(12), C1102-C1112.

8- Annerbo, S., & Lökk, J. (2013). A clinical review of the association of thyroid stimulating hormone and cognitive impairment. *International Scholarly Research Notices*, *2013*.

9- Wang, N., Cai, Y., Wang, F., Zeng, X., Jia, X., Tao, F., & Zhu, D. (2014). Effects of thyroxin and donepezil on hippocampal acetylcholine content and syntaxin-1 and munc-18 expression in adult rats with hypothyroidism. *Experimental and Therapeutic Medicine*, *7*(3), 529-536.

10- Zimmermann MB, Boelaert K. (2015).Iodine deficiency and thyroid disorders. The lancet Diabetes & endocrinology. Apr 1;3(4):286-95.

11- Salazar P, Cisternas P, Martinez M, Inestrosa NC.(2019). Hypothyroidism and cognitive disorders during development and adulthood: implications in the central nervous system. Molecular Neurobiology.;56(4):2952-63..

12- Jin, M., Zhou, Z., Zhang, L., Chen, Y., Liu, L., & Shen, H. (2022). Effects of Excessive Iodine on the BDNF-TrkB Signaling Pathway and Related Genes in Offspring of EAT Rats. *Biological Trace Element Research*, 1-10..

13- Jagadis Mandal, Arijit Chakraborty, Amar K Chandra (2016).Altered Acetylcholinesterase and Na + -K + ATPase Activities in Different Areas of Brain in Relation to Thyroid Gland Function and Morphology Under the Influence of Excess Iodine nternational Journal of Pharmaceutical and Clinical Research;8(12): 1564-1573.

14- Jiang, H., & Zhang, X. J. (2008). Acetylcholinesterase and apoptosis: a novel perspective for an old enzyme. *The FEBS journal*, *275*(4), 612-617.

15- Zhang, L., Teng, W., Liu, Y., Li, J., Mao, J., Fan, C., ... & Shan, Z. (2012). Effect of maternal excessive iodine intake on neurodevelopment and cognitive function in rat offspring. *BMC neuroscience*, *13*(1), 1-9.

16- Kilby, M. D. (2011). *The role of thyroid hormones in placental and fetal central nervous system development* (Doctoral dissertation, University of Birmingham).

17- Ahmed, O. M., Abd El-Tawab, S. M., & Ahmed, R. G. (2010). Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: I. The development of the thyroid hormones–neurotransmitters and adenosinergic system interactions. *International Journal of Developmental Neuroscience*, *28*(6), 437-454.

18- Chen, C., Zhou, Z., Zhong, M., Li, M., Yang, X., Zhang, Y., ... & Yu, Z. (2011). Excess thyroid hormone inhibits embryonic neural stem/progenitor cells proliferation and maintenance through STAT3 signalling pathway. *Neurotoxicity research*, *20*(1), 15-25.

19- Binder, D. K., & Scharfman, H. E. (2004). Brain-derived neurotrophic factor. *Growth factors (Chur, Switzerland)*, *22*(3), 123.

20- Madhusudhan, U., Kalpana, M., Singaravelu, V., Ganji, V., John, N., & Gaur, A. (2022). Brain-Derived Neurotrophic Factor-Mediated Cognitive Impairment in Hypothyroidism. *Cureus*, *14*(4).