World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Teratogenic, anti-angiogenic and biochemical effects of an atypical-antidepressant Tianeptine on chick embryo

Pinakin Shrikant Wagh, Kaushik Kumar Karandikar, Atharva Milan Mulye * and Tanmay Abhijit Kadle

Operon Research and Learning, Kothrud, Pune, MH 411038, India.

World Journal of Biology Pharmacy and Health Sciences, 2025, 21(03), 212-220

Publication history: Received on 26 January 2025; revised on 03 March 2025; accepted on 05 March 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.21.3.0240

Abstract

Tianeptine is an atypical antidepressant used to treat disorders like Major Depressive Disorder (MDD), anxiety, Parkinson's disease, Post-Traumatic Stress Disorder (PTSD), erectile dysfunction, asthma, and Irritable Bowel Syndrome (IBS). Tianeptine is not globally accepted in the treatment of MDD and anxiety as some countries have restricted its prescription or have revised the warning labels and stated its abuse potential. The aim of this study was to assess the potential teratogenic effect of Tianeptine on developing 3-4 day old *Gallus gallus domesticus* embryos. Treated embryos were divided into two groups based on dosage viz. 10ppm and 100ppm Tianeptine. The results of our study showed that Tianeptine induces mild to severe teratogenesis for the selected doses. Embryos treated with Tianeptine showed teratogenic defects like neural tube defects (NTDs), abnormal neurogenesis, anomalous lumbar flexure and torsion, formation of haematomas and ophthalmic defects. Tianeptine treatment also negatively affected angiogenesis by decreasing the vessel density, total vessel network length, total segments and total branching points of the blood vessels on the Yolk-sac membrane (YSM). Biochemical studies showed that Tianeptine treatment increased the total protein content, increased the Acetylcholinesterase (AChE) level and decreased the Alkaline Phosphatase (ALP) level in the treated embryos. This study sheds light on the potential detrimental effects Tianeptine may have on other embryonic models. More studies on atypical antidepressants like Tianeptine need to be carried out to assess its impact on embryonic development and developmentally regulated gene expression.

Keywords: Tianeptine; Atypical Antidepressant; Teratogenesis; Chick embryo; Yolk-sac membrane (YSM); Acetylcholinesterase (AChE); Alkaline Phosphatase (ALP)

1. Introduction

Tianeptine (7-[(3-Chloro-6-methyl-5,5-dioxo-11H-benzo[c] [2,1] benzothiazepin-11-yl) amino] heptanoic acid) is commercially sold under the brand names Stablon, Tatinol, and Coaxil[1]. It is an atypical antidepressant used to treat Major Depressive Disorder, anxiety, Parkinson's disease, Post-Traumatic Stress Disorder and panic disorder [2,3]. It is structurally similar to tricyclic antidepressants, but is no longer classified as a tricyclic antidepressant. It is also effective against asthma, erectile dysfunction and irritable bowel syndrome [2,4,5,6]. Tianeptine has been shown to have anxiolytic and antidepressant effects, without many sedative, anticholinergic and cardiovascular side-effects at therapeutic doses [7]. It is also an anticonvulsant, analgesic, and has even shown its use in the effective treatment of attention-deficit hyperactivity disorder (ADHD) [2,8,9]. Tianeptine has also been shown to counteract depression-induced cognitive dysfunction [10].

* Corresponding author: Atharva Milan Mulye

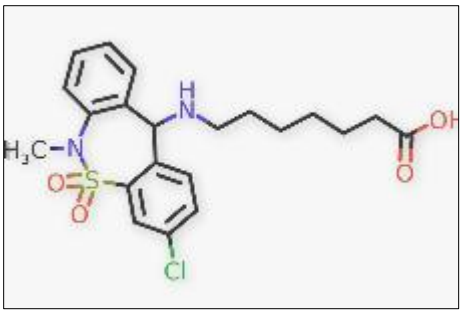

Figure 1 Molecular structure of Tianeptine [11]

The U.S. Food and Drug Administration (FDA) has not approved Tianeptine for any medical use and warned consumers about its exploitation as an opioid agonist used to induce euphoric high with a risk of overdose. As Tianeptine is a complete agonist of μ-opioid receptor and weak δ-opioid receptor agonist, it enhances mesolimbic release of dopamine. This leads to a euphoric effect if consumed in high doses, which can lead to exploitation as recreational "gas station" drug. It has high potential for abuse and dependence as it is readily available in pharmacies, convenience stores and independent vendors without prescription and even illegally on the internet [2].

The link between the modulation of glutamatergic functionality and antidepressant effect has been documented. Tianeptine is an atypical agonist of μ-opioid receptors, but does not show a significant effect on δ-opioid receptors and κ-opioid receptors [2,12]. It has demonstrated the ability to indirectly alter and inhibit glutamate receptors. Treatment of Tianeptine normalizes the stress-altered glutamatergic neurotransmission by acting as a NMDA receptor antagonist. This might protect against stress-induced structural or cellular changes in the brain. There is evidence that Tianeptine enhances the activity and sensitivity of the AMPA receptor by enabling phosphorylation of GluA1 subunit and increasing the traffic and synthesis of AMPA receptors towards the membrane [10].

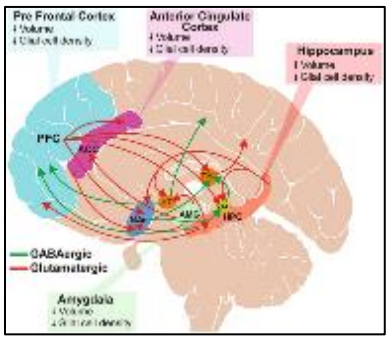

Figure 2 Distribution of GABAergic and glutamatergic neurons in the brain [13]

Tianeptine works well in mitigating the negative effects of stress on behaviour and physiology. It prevents acute stress from altering synaptic plasticity in the hippocampus and prefrontal cortex (PFC) and prevents chronic stress from causing morphological abnormalities in the hippocampus and amygdala. Furthermore, it has been discovered that Tianeptine has pro-cognitive benefits, improving learning and memory that are dependent on the hippocampal region while guarding against stress-related deficits in these functions [14].

Gallus gallus domesticus is a scientific model organism that plays a vital role in the fields of developmental biology, toxicology, reproductive biology, etc. *G. domesticus* has a well-distinguished body plan and it is also amenable to genetic and physiological modifications. It is sensitive to manipulations and has rapid response to treatment of xenobiotics and toxicants. Fertilized chicken eggs are affordable to purchase in bulk and are easy to culture in a laboratory environment [15]. There is about 60% similarity between the corresponding genes of *G. domesticus* and humans. This makes them a dependable organism to study and draw relevant conclusions [16].

The yolk-sac membrane (YSM) is a complex structure responsible for nutrient and gaseous exchange along with it being implicated in immune function by transfer of maternal antibodies to the embryo. It has a network of blood vessels that gives rise to the vasculature of the chick embryo and is a site of haematopoiesis till about day 15 of embryogenesis [17].

The chorioallantoic membrane (CAM) is a conventional model for angiogenesis, but the YSM is a cost-effective, simple and replicable assay to study the anti-angiogenic effect of external agents in the chick embryo [18].

Acetylcholinesterase is an enzyme found at neuromuscular junctions and is responsible for the hydrolysis of the neurotransmitter acetylcholine into acetic acid and choline [19]. It has also been shown to be involved in neuritogenesis, synaptogenesis, cell adhesion, activation of dopaminergic neurons, haematopoiesis and thrombopoiesis and amyloid fibre assembly [22].

Alkaline phosphatases are isoenzymes that catalyse the hydrolysis of extracellular organic phosphate esters. They are found primarily in liver and bone tissues, but they are also found throughout the body. Alkaline Phosphatases are involved in processes like calcification of cartilage, metabolism in the liver, normal skeletal development, nutrient absorption in the intestine, etc. [21, 22]

2. Materials and Methods

Fertilized and pre-incubated eggs of 72hrs (HH 20-21) [23] of *Gallus gallus domesticus* (White-Leghorn strain) were procured from Venkateshwara Hatcheries Pvt Ltd Pune. Eggs were cleaned with 70% ethanol, labelled and incubated in BOD incubator (REMI®) at 37.5 ℃ at 70-80% relative humidity (Rh). Working solution of Tianeptine (Stablon™, Servier India Pvt. Ltd.) of concentrations 10ppm (22.9µM) and 100ppm (229µM) were prepared using the stock solution and filter sterilized (0.22micron pore size, 25mm diameter) before treatment.

- **Teratogenesis:** Chick embryos were treated with Tianeptine (10ppm and 100ppm) by air-sac route (*in ovo*) window technique [24]. Eggs were sealed with Parafilm M and were incubated at 37.5 ℃ for 24 hours at 70-80% relative humidity. The embryos were harvested 24 hours later and transferred into sterile, chilled 1X PBS (pH 7.4) and were analysed for drug induced deformities.
- **YSM analysis:** Photographs of the YSM vasculature of the control and treated embryos were taken after opening the eggshell and were analysed using WimCAM (Wimasis) software [25].
- **Biochemical studies:** Control and treated embryos were harvested and homogenized (Potter-Elvehjem PTFE pestle) in sterile chilled 1X protein extraction buffer (PEB). Protein quantification in treated and control embryos was performed using Bradford's method [26]. Optical density (OD) was measured (Systronics µC colorimeter 115) at absorbance 595 nm for control and treated protein extracts. Enzyme assays for Alkaline Phosphatase (ALP) and Acetylcholinesterase (AChE) were performed using Meril Diagnostics AutoQuant 100 Amara- Alkaline phosphatase kit and AChE assay was performed using Delta Cholinesterase, Delta lab. Both the assays were analysed using HORIBA Yumizen, CA60 semi-automatic analyser.

3. Results

3.1. Teratogenesis and embryonic malformations

Our study showed that Tianeptine induces teratogenic defects in 3-4 day old (HH stage 20-21) *Gallus gallus domesticus* embryos for the selected doses. The embryos exhibited developmental anomalies, including neural tube defects (NTDs) alterations in neuromere morphogenesis, craniofacial abnormalities, haematoma in the heart, compression of antero-posterior axis, abnormal torsion and flexure throughout the embryonic axis, ophthalmic defects like absence of pigmentation, deformed lens and optic cup.

3.2. Degeneration of YSM vasculature:

Tianeptine treatment resulted in severe degeneration in the vessel density, total vessel network length, total branching points and total segments of the blood vessels on the YSM of 3-4 day old chick embryos as revealed by analysis using WimCAM software.

Figure 3 Control embryo HH 20-21

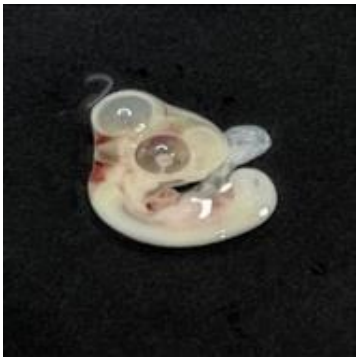

Figure 4 Control embryo HH 20-21

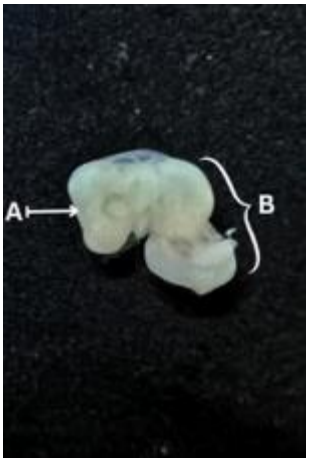

Figure 5 Tianeptine 10ppm HH 20-21

A: Brain vesicles severely malformed.

B: Severe torsion of the embryonic axis.

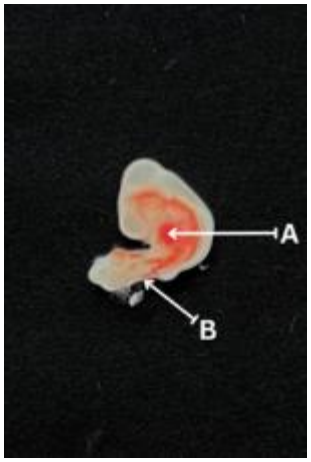

Figure 6 Tianeptine 10ppm HH 20-21

A: Severe haematoma in the heart.

B: Abnormal torsion of the embryonic axis.

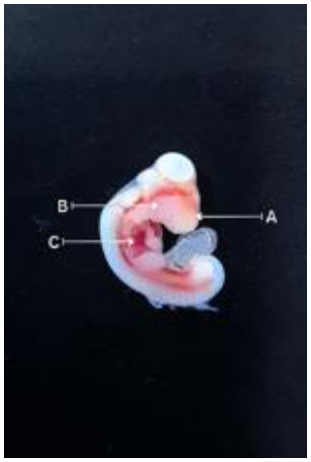

Figure 7 Tianeptine 100ppm HH 20-21

A: Enlargement of brain vesicles and craniofacial abnormalities.

B: Eye pigmentation absent, optic cup deformed.

C: Haemorrhaging in thoracic region

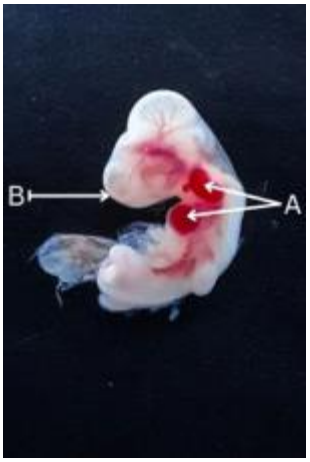

Figure 8 Tianeptine 100ppm HH 20-21

A: Haematomas in the heart and cervical region.

B: Enlargement of brain vesicles and craniofacial abnormalities.

Figure 9 Control YSM vasculature HH 20-21 Vessel density= 20.2%, Total vessel network length= 17446.6px, Total branching points=116, Total segments= 223.

Figure 10 Tianeptine 10ppm YSM vasculature HH 20-21. Vessel density= 6.3%, Total vessel network length= 7165.9px, Total branching points= 30, Total segments= 67.

Figure 11 Tianeptine 100ppm YSM vasculature HH 20-21. Vessel density= 7.2%, Total vessel network length= 6622.1px, Total branching points= 20 Total segments= 44.

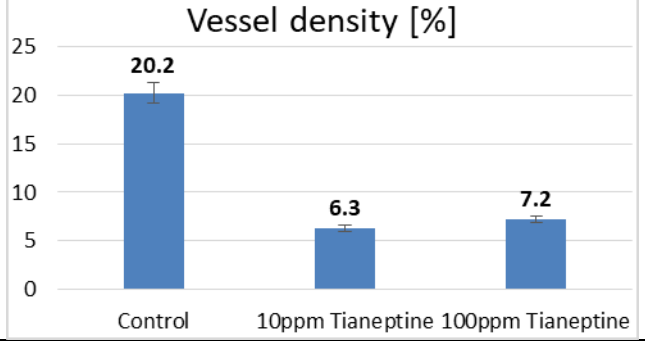

Figure 12 Vessel density of YSM in 3-4 day old chick embryos treated with 10ppm and 100ppm Tianeptine

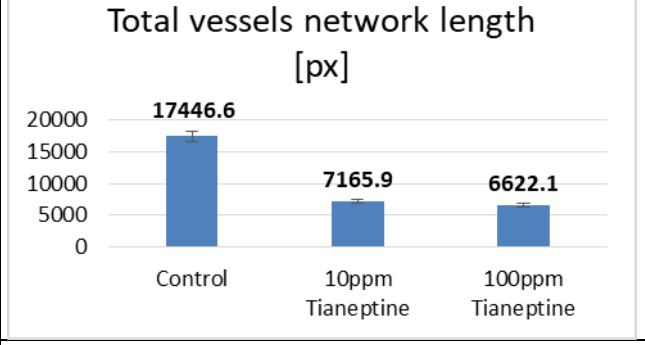

Figure 13 Total vessel network length of YSM in 3-4 day old chick embryos treated with 10ppm and 100ppm Tianeptine

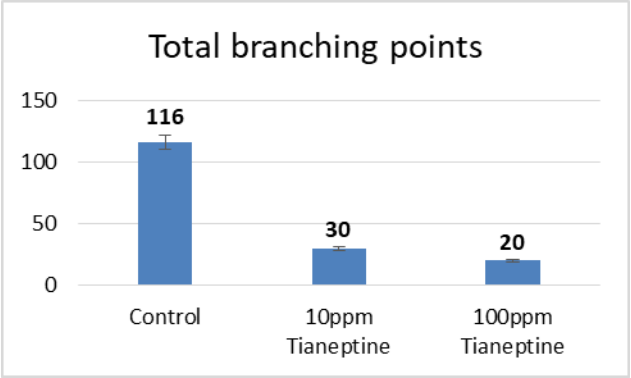

Figure 14 Total branching points of YSM in 3-4 day old chick embryos treated with 10ppm and 100ppm Tianeptine

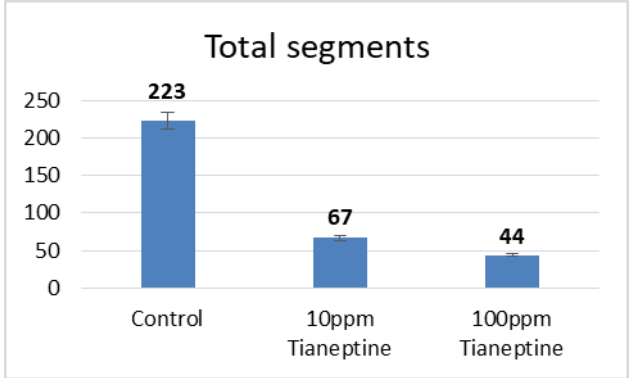

Figure 15 Total segments of YSM in 3-4 day old chick embryos treated with 10ppm and 100ppm Tianeptine

3.3. Biochemical studies

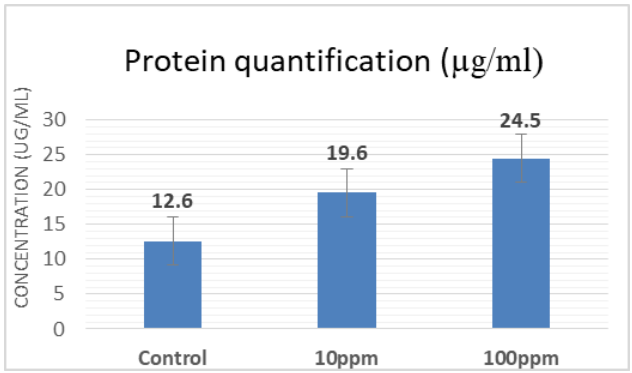

Figure 16 Protein quantification of 3-4 day old chick embryos treated with 10ppm and 100ppm Tianeptine by Bradford's method

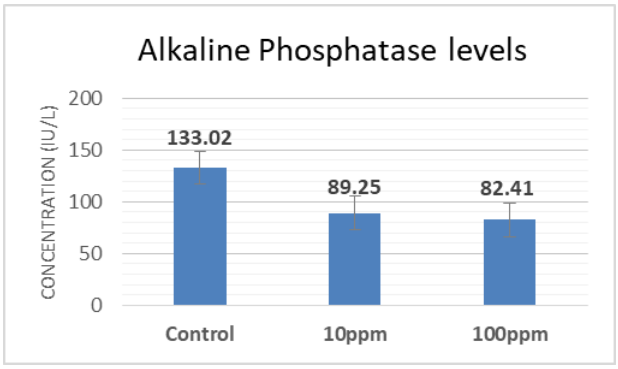

Figure 17 Alkaline Phosphatase levels of 3-4 day old chick embryos treated with 10ppm and 100ppm tianeptine

Biochemical studies revealed that Tianeptine treatment altered the total protein content and AChE and ALP levels of treated embryos as compared to control embryos. Total protein content was found to be increased in Tianeptine treated embryos (**10 ppm:19.6µg/ml and 100 ppm: 24.56µg/ml**) as compared to control embryos (**12.6 µg/ml**). Alkaline phosphatase levels in the control embryo were **133.02 IU/L** and they were found to be reduced in the treated embryos (**10 ppm: 89.25 IU/L and 100 ppm: 82.41 IU/L**). Tianeptine treated embryos showed an increase in Acetylcholinesterase levels at **10ppm: 178 IU/L** but the concentration did not increase significantly in **100 ppm:179 IU/L** while the level in the control embryo was **105 IU/L.**

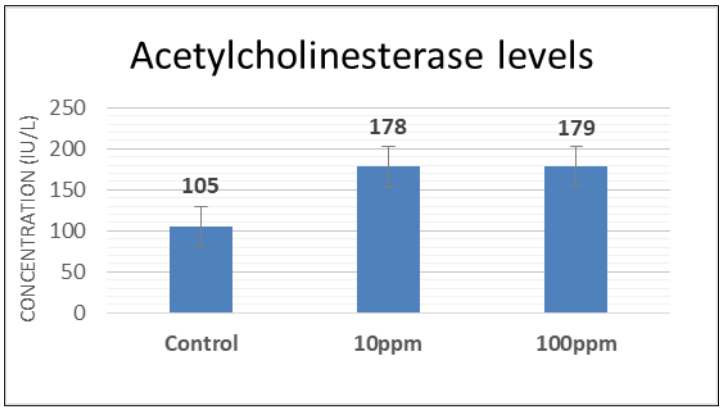

Figure 18 Acetylcholinesterase levels of 3-4 day old chick embryos treated with 10ppm and 100ppm tianeptine

4. Discussion

From the above studies it is apparent that Tianeptine concentrations of 10ppm and 100ppm are teratogenic to early stages of chick embryos (3-4 day old). Tianeptine showed neuroteratogenic activity as treated embryos showed abnormal neuromere morphogenesis, malformed brain vesicles and craniofacial defects. Along with this, the Tianeptine treated embryos showed ocular abnormalities like deformities in the optic cup and pigmentation anomalies. Biochemical studies revealed that Tianeptine elevated the total protein content (*10 ppm: 19.6µg/ml, 100 ppm: 24.56µg/ml*) as compared to control embryos (*12.6 µg/ml*). Similarly, Acetylcholinesterase levels (*10ppm: 178 IU/L*, *100 ppm: 179 IU/L)* were elevated with respect to the treated embryos (*105 IU/L)* while the level of Alkaline Phosphatase was found to be reduced (*10 ppm: 89.25 IU/L, 100 ppm: 82.41 IU/L*) as compared to *133.02 IU/L* in the control embryos. Both concentrations of Tianeptine-treated embryos resulted in marked degeneration of blood vessels as compared to the YSM vasculature of the control embryos, as seen by the decline in vessel density (%), total vessel network length, total branching points and total segments. This suggests that Tianeptine may have anti-angiogenic properties in early-stage chick embryos.

It is well established that most antidepressants cross the placental barrier and can also be passed through breast milk. Antidepressants taken during gestation or while breastfeeding can cause many complications like birth defects, withdrawal symptoms, neurodevelopmental concerns etc. in the foetus [27]. The results of this study may perhaps help to shed light on the potential correlation of prenatal exposure to antidepressants and teratogenicity in human foetuses. However, more studies on the effect of Tianeptine exposure on embryonic development in mammalian models need to be carried out to comment on the potential effect of Tianeptine in human foetuses and to assess if the benefits outweigh the risks of antidepressant prescription in depressed pregnant women.

Previous studies have shown that treatment of Tianeptine decreased the MMP-9 activity by regulating NF-κB expression. NF-κB is a transcription factor for the regulation of many genes like MMPs and it is activated by TNF-α [28]. There is a correlation of MMP inhibitors and anti-angiogenic effects by generation of angiogenesis inhibitors [29]. Microglial cells are derived from progenitors originating from the yolk sac [30]. As microglia are a major source of TNF-α [31], tianeptine-induced inhibition of MMPs may perhaps explain the anti-angiogenic effect observed in our study, but definitive evidence supporting this hypothesis needs to be investigated.

Tricyclic antidepressants have been found to cause hepatotoxicity which can induce change in Alkaline phosphatase levels [32]. Our observations show a consistent decrease in ALP level with respect to the dose of treatment. In contrast to our findings, a case study reporting a rare acute hepatotoxicity induced by Tianeptine showed elevated levels of ALP [33]. Another contrasting finding showed elevated ALP in rats (but still within normal range) [34]. In a study on ovariectomized rats showing elevated Bone-specific ALP (BAP) level, Tianeptine treatment reduced these elevated BAP level and inhibited subsequent osteoporosis [35]. Our findings show there is decrease in the level of Acetylcholinesterase (AChE) after treatment of Tianeptine. Previous studies found no significant change in the enzyme activity of AChE. However, a decrease in the acetylcholine level was found, suggesting that Tianeptine may affect the cholinergic system indirectly [36]. According to another documentation, Tianeptine did not show inhibitory effect on AChE or BuChE (Butyrylcholinesterase) based on IC_{50} values [37]

5. Conclusion

The consensus of this study was that Tianeptine induces teratogenic defects in early-stage (3-4 day old) chick embryos. The embryos treated with Tianeptine showed alterations in neuromorphogenesis, ophthalmic defects, abnormal torsion and flexure of the embryonic axis and degeneration of the YSM vasculature as seen by reduced vessel density, total vessel network length, total segments and total branching points. The treated embryos showed elevated total protein content and Acetylcholinesterase (AChE) levels while Alkaline phosphatase (ALP) levels were found to be decreased as compared with control embryos. More studies need to be done to understand the effect of Tianeptine on developmentally regulated gene expression and its interactions with neurotransmitters and their receptors in the Central Nervous System (CNS).

Compliance with ethical standards

Acknowledgments

We would like to extend our sincere gratitude to Operon Research and Learning, Pune for allowing us to conduct our research. We would also like to thank our colleagues, Aarushi Poyrekar, Riddhi Walimbe, Sayali Phatak and Anish Divekar for their assistance with the project.

Disclosure of conflict of interest

There is no conflict of interest to be disclosed.

References

[1] Tianeptine. In: Wikipedia [Internet]. 2025 [cited 2025 Feb 2]. Available from: https://en.wikipedia.org/w/index.php?title=Tianeptine&oldid=1271752766

[2] Edinoff AN, Sall S, Beckman SP, Koepnick AD, Gold LC, Jackson ED, et al. Tianeptine, an Antidepressant with Opioid Agonist Effects: Pharmacology and Abuse Potential, a Narrative Review. Pain Ther. 2023 Oct 1;12(5):1121–34.

[3] Levin OS. Coaxil (tianeptine) in the treatment of depression in Parkinson's disease. Neurosci Behav Physiol. 2007 May 1;37(4):419–24.

[4] Lechin, F., Van Der Dijs, B., Lechin, A.E. Treatment of bronchial asthma with tianeptine. Methods and Findings in Experimental and Clinical Pharmacology. 2004;26(9):697.

[5] El-Shafey H, Atteya A, Abu el-Magd S, Hassanein A, Fathy A, Shamloul R. Tianeptine Can Be Effective in Men with Depression and Erectile Dysfunction. The Journal of Sexual Medicine. 2006 Sep 1;3(5):910–7.

[6] Sohn W, Lee OY, Kwon JG, Park KS, Lim YJ, Kim TH, et al. Tianeptine vs amitriptyline for the treatment of irritable bowel syndrome with diarrhea: a multicenter, open-label, non-inferiority, randomized controlled study. Neurogastroenterology & Motility. 2012;24(9):860-e398.

[7] Lôo H, Deniker P. Position of tianeptine among antidepressive chemotherapies. Clin Neuropharmacol. 1988 Jan 1;11 Suppl 2:S97-102.

[8] Reeta KH, Prabhakar P, Gupta YK. Anticonvulsant activity of the antidepressant drug, tianeptine, against pentylenetetrazole-induced seizures mitigates cognitive impairment in rats. Behavioural Pharmacology. 2016 Oct;27(7):623.

[9] Niederhofer H. Tianeptine as a Slightly Effective Therapeutic Option for Attention-Deficit Hyperactivity Disorder. Neuropsychobiology. 2004 Mar 25;49(3):130–3.

[10] Alamo C, García-Garcia P, Lopez-Muñoz F, Zaragozá C. Tianeptina, un abordaje farmacológico atípico de la depresión. Revista de Psiquiatría y Salud Mental. 2019 Jul;12(3):170–86.

[11] TIANEPTINE [Internet]. [cited2025 Mar 5]. Available from: https://frontend.m.jchem.test.gsrs.ncats.io/ginas/app/ui/substances/366c3350-0072-408d-b7d8-7d4c1fbe4963

[12] Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MM, et al. The Behavioral Effects of the Antidepressant Tianeptine Require the Mu-Opioid Receptor. Neuropsychopharmacol. 2017 Sep;42(10):2052–63.

[13] Cutler AJ, Mattingly GW, Maletic V. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. Transl Psychiatry. 2023 Jun 26;13(1):1–16.

[14] Zoladz PR, Muñoz C, Diamond DM. Beneficial Effects of Tianeptine on Hippocampus-Dependent Long-Term Memory and Stress-Induced Alterations of Brain Structure and Function. Pharmaceuticals. 2010 Oct;3(10):3143–66.

[15] Bahr JM. The Chicken as a Model Organism. In: Conn PM, editor. Sourcebook of Models for Biomedical Research [Internet]. Totowa, NJ: Humana Press; 2008 [cited 2024 Oct 23]. p. 161–7. Available from: http://link.springer.com/10.1007/978-1-59745-285-4_18

[16] Researchers Compare Chicken, Human Genomes [Internet]. [cited 2024 Oct 24]. Available from: https://www.genome.gov/12514316/2004-release-researchers-compare-chicken-human-genomes

[17] Wong EA, Uni Z. Centennial Review: The chicken yolk sac is a multifunctional organ. Poultry Science. 2021 Mar 1;100(3):100821.

[18] As MN, Deshpande R, Kale VP, Bhonde RR, Datar SP. Establishment of an in ovo chick embryo yolk sac membrane (YSM) assay for pilot screening of potential angiogenic and anti-angiogenic agents. Cell Biology International. 2018 Nov;42(11):1474–83.

[19] Trang A, Khandhar PB. Physiology, Acetylcholinesterase. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2023. PMID: 30969557.

[20] Soreq H, Seidman S. Acetylcholinesterase — new roles for an old actor. Nat Rev Neurosci. 2001 Apr;2(4):294–302.

[21] Lowe D, Sanvictores T, Zubair M, et al. Alkaline Phosphatase. [Updated 2023 Oct 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459201/

[22] Habuchi H, Conrad HE, Glaser JH. Coordinate regulation of collagen and alkaline phosphatase levels in chick embryo chondrocytes. J Biol Chem. 1985 Oct 25;260(24):13029–34.

[23] Hamburger V, Hamilton HL. A series of normal stages in the development of the chick embryo. Developmental Dynamics. 1992 Dec;195(4):231–72.

[24] Farzaneh M, Attari F, Khoshnam SE, Mozdziak PE. The method of chicken whole embryo culture using the eggshell windowing, surrogate eggshell and ex ovo culture system. Br Poult Sci. 2018 Apr;59(2):240-244. doi: 10.1080/00071668.2017.1413234. Epub 2018 Jan 11. PMID: 29206486.

[25] Wimasis, 2016. WimCAM: CAM Assay Image Analysis Solution. Release 1.1. Available from: https://www.wimasis.com/en/products/2/WimCAM

[26] Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Analytical Biochemistry. 1976 May;72(1–2):248–54.

[27] Dubovicky M, Belovicova K, Csatlosova K, Bogi E. Risks of using SSRI / SNRI antidepressants during pregnancy and lactation. Interdisciplinary Toxicology. 2017 Sep 1;10(1):30–4.

[28] Jayasooriya RGPT, Dilshara MG, Choi YH, Moon SK, Kim WJ, Kim GY. Tianeptine sodium salt suppresses TNF-α-induced expression of matrix metalloproteinase-9 in human carcinoma cells via suppression of the PI3K/Akt-mediated NF-κB pathway. Environmental Toxicology and Pharmacology. 2014 Sep;38(2):502–9.

[29] Rundhaug JE. Matrix metalloproteinases and angiogenesis. J Cellular Mol Med. 2005 Apr;9(2):267–85.

[30] Alliot F, Godin I, Pessac B. Microglia derive from progenitors, originating from the yolk sac, and which proliferate in the brain. Developmental Brain Research. 1999 Nov;117(2):145–52.

[31] Welser-Alves JV, Milner R. Microglia are the major source of TNF-α and TGF-β1 in postnatal glial cultures; regulation by cytokines, lipopolysaccharide, and vitronectin. Neurochemistry International. 2013 Jul;63(1):47–53.

[32] Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-Induced Liver Injury: A Review for Clinicians. American Journal of Psychiatry [Internet]. https://psychiatryonline.org/doi/full/10.1176/appi.ajp.2013.13050709. American Psychiatric Publishing; 2014 Apr 1 [cited 2024 Jul 8];171(4):404–15. Available from: 10.1176/appi.ajp.2013.13050709

[33] Le Bricquir Y, Larrey D, Blanc P, Pageaux GP, Michel H. Tianeptine--an instance of drug-induced hepatotoxicity predicted by prospective experimental studies. J Hepatol. 1994 Nov;21(5):771-3. doi: 10.1016/s0168-8278(94)80237-8. PMID: 7890892.

[34] Salam NA, Naeem MA, Malik NS, Riaz M, Shahiq-Uz-Zaman, Masood-Ur-Rehman, et al. Exploring the potential of tianeptine matrix tablets: synthesis, physico-chemical characterization and acute toxicity studies. Pakistan Journal of Pharmaceutical Sciences. 2020 Jan 1;33(1):269–79.

[35] Alkhamees OA, Al-Roujayee AS, Abuohashish HM, Ahmed MM. Anti-osteoporotic effects of an antidepressant tianeptine on ovariectomized rats. Biomedicine & Pharmacotherapy. 2017 Mar;87:575–82.

[36] Bertorelli R, Amoroso D, Girotti P, Consolo S. Effect of tianeptine on the central cholinergic system: involvement of serotonin. Naunyn-Schmiedeberg's Arch Pharmacol. 1992 Mar 1;345(3):276–81.

[37] Ceschi MA, Da Costa JS, Lopes JPB, Câmara VS, Campo LF, Borges ACDA, et al. Novel series of tacrine-tianeptine hybrids: Synthesis, cholinesterase inhibitory activity, S100B secretion and a molecular modeling approach. European Journal of Medicinal Chemistry. 2016 Oct;121:758–72