World Academy of Science, Engineering and Technology
International Journal of Pharmacological and Pharmaceutical Sciences
Vol:17, No:10, 2023

Neurotoxic Effects Assessment of Metformin in Danio rerio

Authors : Gustavo Axel Elizalde-Velázquez

Abstract : Metformin is the first line of oral therapy to treat type II diabetes and is also employed as a treatment for other indications, such as polycystic ovary syndrome, cancer, and COVID-19. Recent data suggest it is the aspirin of the 21st century due to its antioxidant and anti-aging effects. However, increasingly current articles indicate its long-term consumption generates mitochondrial impairment. Up to date, it is known metformin increases the biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription, but further information related to brain damage after its consumption is missing. Bearing in mind the above, this work aimed to establish whether or not chronic exposure to metformin may alter swimming behavior and induce neurotoxicity in Danio rerio adults. For this purpose, 250 Danio rerio grown-ups were assigned to six tanks of 50 L of capacity. Four of the six systems contained 50 fish, while the remaining two had 25 fish (≈1 male:1 female ratio). Every system with 50 fish was allocated one of the three metformin treatment concentrations (1, 20, and 40 µg/L), with one system as the control treatment. Systems with 25 fish, on the other hand, were used as positive controls for acetylcholinesterase (10 µg/L of Atrazine) and oxidative stress (3 µg/L of Atrazine). After four months of exposure, a mean of 32 fish (S.D. ± 2) per group of MET treatment survived, which were used for the evaluation of behavior with the Novel Tank test. Moreover, after the behavioral assessment, we aimed to collect the blood and brains of all fish from all treatment groups. For blood collection, fish were anesthetized with an MS-222 solution (150 mg/L), while for brain gathering, fish were euthanized using the hypothermic shock method (2–4 °C). Blood was employed to determine CASP3 activity and the percentage of apoptotic cells with the TUNEL assay, and brains were used to evaluate acetylcholinesterase activity, oxidative damage, and gene expression. After chronic exposure, MET-exposed fish exhibited less swimming activity when compared to control fish. Moreover, compared with the control group, MET significantly inhibited the activity of AChE and induced oxidative damage in the brain of fish. Concerning gene expression, MET significantly upregulated the expression of Nrf1, Nrf2, BAX, p53, BACE1, APP, PSEN1, and downregulated CASP3 and CASP9. Although MET did not overexpress the CASP3 gene, we saw a meaningful rise in the activity of this enzyme in the blood of fish exposed to MET compared to the control group, which we then confirmed by a high number of apoptotic cells in the TUNEL assay. To the best of our understanding, this is the first study that delivers evidence of oxidative impairment, apoptosis, AChE alteration, and overexpression of B- amyloid-related genes in the brain of fish exposed to metformin.

Keywords : AChE inhibition, CASP3 activity, NovelTank test, oxidative damage, TUNEL assay
Conference Title : ICAPT 2023 : International Conference on Advances in Pharmacology and Toxicology
Conference Location : Tbilisi, Georgia
Conference Dates : October 02-03, 2023