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News & Comments

Metformin (MET) Mitigates the Toxic Effect of Chemotherapy (CMF)

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The global cancer burden is growing, with around 90 million people living with cancer. Up to 75% of chemotherapy patients experience cognitive impairment, which continues in percent of cancer survivors.

Chemo brain is still a clinical challenge, with few treatment options for the neurotoxicity generated by chemotherapy. CMF chemotherapy (a combination of cyclophosphamide [CYP], methotrexate [MTX], and 5-fluorouracil [5-FU], a standard breast cancer treatment) intraperitoneally (i.p.) affected learning and memory in rats. Furthermore, in both in vitro and in vivo models, CYP has been demonstrated to promote cytotoxicity, ultimately leading to apoptosis. Chemo brain's mechanisms aren't completely known. Chemotherapy-induced hepatotoxicity, nephrotoxicity, and neurotoxicity have all been suggested as possible mechanisms.

MET has been shown to stimulate AMP-activated Protein Kinase (AMPK), which may influence the actions of other proteins including mTOR and Protein Kinase B. (PKB, also known as Akt). Increased trafficking of the glucose transporter to the cell surface is caused by AMPK activation, and it is implicated in the cellular uptake of glucose to lower blood glucose levels. Activation of AMPK, on the other hand, causes mTOR to become inactive. MET may have a protective impact during chemotherapy, according to previous research. However, to the best of the authors' knowledge, no research has been done on the effect of MET on the side effects of CMF treatment, such as cognitive impairment.

This research project was conducted in September-November 2020 at the Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Kingdom of Saudi Arabia. Forty male rats (10-12 weeks old; 200-250 g body weight) were kept in a pathogen-free environment with a 12 hrs light/dark cycle (lights turned on at 6:00 a.m.). During the two-week trial period, the rats had unlimited access to food and drink. The animals were separated into four groups, each with ten individuals. Weekly i.p. injections of saline were given to the control group. The device was set down on the ground. To achieve even light distribution, the light was delivered from above. The animals were given 15 min to freely explore two arms during the training period. The animals were allowed to explore the entire maze, including the novel arm, during the test period.

The antidiabetic drug MET was tested in an albino rat model for its ability to protect against toxicity and memory impairment caused by the CMF chemotherapeutic treatment [CYP (50 mg kg^{-1}), MTX (2

mg kg^{-1}), and 5-FU (50 mg kg^{-1})].

By managing blood glucose levels, MET has been shown to improve the quality of life of diabetic patients. It also lowers the chances of developing Alzheimer's disease.

Furthermore, earlier research has shown that MET may lessen the toxic effects of chemotherapy, increasing survival rates, decreasing cardiotoxicity, and improving cognitive impairment caused by chemotherapy. It was hypothesized in this study that MET could alleviate cognitive impairment induced by CMF treatment and increase the survival rate of those who were treated. Another advantage is that the rats used were all of the same strain and age, and all of the experiments were carried out simultaneously across the research groups to prevent confounding influences. It's also worth noting that the rats in this study were cancer-free, thus the effects seen are most likely the product of the MET and CMF treatments rather than cancer itself.

In the early stages of CMF treatment, MET reduced the toxic effects of CMF and boosted survival rates, but it did not completely reverse mortality and had no effect on body weight. The cognitive abnormalities generated by CMF treatment were not improved by MET treatment. According to the EPM test, MET coupled with CMF can further decrease memory performance. When compared to CMF-treated animals and controls, CMF+MET-treated rats had considerably higher levels of IL-6 in the brain, indicating enhanced neuro-inflammation.

JOURNAL REFERENCE

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KEYWORDS

Metformine, CMF chemotherapy, AMP-activated Protein Kinase, mTOR, Protein Kinase B, side effects of CMF treatment