

Protective Effects of Dimebon on the Tumor Necrosis Factor Alpha-induced Disorders of Lipids in Mice Brain

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Dimebon (Dimebolin) is an antihistamine drug which has been used clinically in Russia since 1983. Recently Dimebolin has attracted renewed interest after being shown to have positive effects on persons suffering from Alzheimer's disease. Animal studies have shown that dimebon operates through multiple mechanisms of action, both blocking the action of neurotoxic beta-amyloid proteins and inhibiting L-type calcium channels, modulating the action of AMPA and NMDA glutamate receptors, and may exert a neuroprotective effect by blocking cytotoxic signals induced by proinflammatory cytokines such as TNF-alpha, which are believed to play a central role in Alzheimer's disease. Inflammatory response induced by TNF-alpha suggests that this cytokine affects the phospholipid metabolism and subsequent production of eicosanoids, ceramide, and ROS that may potentiate brain injury.

Methods: This study included 65 male mice (weight: 20 ± 2 g, average \pm SD). TNF-alpha (10mg/kg per mouse), dimebon (0,2 mg/kg) and their combination were injected to mice interperitoneally. Changes in level of phospholipids molecular species (phosphatidylcholine, lysophosphatidylcholine, phosphatidylethanolamine, sphingomyelin) and galactosylceramide in hippocampus, cerebellum and cerebral cortex within 30 min, 2, 4 and 24 hours after injection were detected by chromatomass-spectrometry.

Results: Maximal changes in phospholipids and galactosylceramides contents of different molecular species after single TNF-alpha administration were found in the hippocampus, and were less expressed in the cerebral cortex and cerebellum after 24 hours. Dimebon itself did not induce changes in lipids spectrum in brain sections, but protected lipids against disorders induced by TNF-alpha in mice brain.

Conclusions: Modern strategies in the search of new therapeutic approaches are based on the multitarget properties of new drugs. According to our results TNF-alpha may serve as a new target for dimebon. Dimebon preventing lipids disorders in brain induced by TNF-alpha might have a positive anti-inflammatory effects, preventing the negative response of nerve cells to the pathological process.