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Topic: AS04 Neurons and Glia: Physiology and Inter-Cell Communication

MODULATION OF BRAIN CONNECTIVITY, STRUCTURE, NEURON AND GLIA, AND MOTOR FUNCTION BY SAFINAMIDE MULTIMODAL ACTIONS IN A PRE-CLINICAL MODEL OF PARKINSON'S DISEASE

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To date, no neuroprotective/disease-modifying strategy has been approved as a Parkinson's Disease (PD) therapy, because of the*'one-disease-one-target'* view that has been followed. New drug-based therapeutic routes, namely Safinamide, have been introduced as a promising multimodal drug combining dopaminergic and non-dopaminergic (neuroprotective) actions, representing a new potential alternative therapy to prevent or delay PD progression. Thus, the present work addressed Safinamide's impact on PD, relying on the possibility of potentiating dopaminergic neurons (DAn) survival by tackling cellular/molecular impairments responsible for its failure. Safinamide (10mg/kg) was given by oral gavage to a 6-OHDA preclinical rat model. DAn survival, neuroinflammation, and redox system homeostasis were assessed by histological and molecular analysis. Additionally, to overpass the selective blood-brain barrier (BBB) permeability, which reduces drug bioavailability reaching PD brain regions, we conducted magnetic resonance imaging (MRI)-guided focused ultrasound (FUS) to transiently open the BBB to precisely deliver Safinamide in PD-affected areas. Results revealed that Safinamide monotherapy was able to potentiate the densities of DAn and fibers, revealing a protective effect when compared to the untreated group. To understand possible pathways associated with this improvement, we found that Safinamide appears to be a modulator of the antioxidant and autophagy systems since an increase in the expression levels of DJ-1, SOD-1, and LC3B was observed when compared to the non-treated group. Furthermore, Safinamide presents a potential modulatory activity on neuroinflammation and astrogliosis, as a decrease in microglia (CD11b+) and astrocytic (GFAP+) cells number was observed when compared to 6-OHDA group. Additionally, the anatomical and functional MRI analysis exhibited connectivity and metabolite alterations. Collectively, these data demonstrate the promising therapeutic potential of Safinamide as a neuroprotection strategy for PD, which may open new therapeutic opportunities for individuals in prodromal stages, potentially delaying clinical manifestation in high-risk patients.

Declaration of Interest Statement: None

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GOLEXANOLONE IMPROVES PERIPHERAL INFLAMMATION, FATIGUE, LOCOMOTOR GAIT, MOTOR INCOORDINATION AND SHORT-TERM MEMORY IN RATS WITH CHOLESTASIS AND HEPATIC ENCEPHALOPATHY DUE TO BILE DUCT LIGATION

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Cholestasis may appear in patients with primary sclerosing cholangitis, primary biliary cholangitis, or drug-induced liver injury. Patients with cholestasis may show fatigue and other alterations that severely reduce their quality of life. Patients with liver disease may also show hepatic encephalopathy, with cognitive and motor impairment. Rats with bile-duct ligation (BDL) are a model both of cholestatic liver disease and of hepatic encephalopathy. There are no effective treatments for alterations such as fatigue or neurological impairment in liver diseases. Golexanolone, a GABAA receptor-modulating steroid antagonist, reduces GABAergic tone by reducing potentiation of GABAA receptors activation by neurosteroids. Golexanolone reduces peripheral inflammation and improves cognitive and motor function in rats with chronic hyperammonemia. The aims of this study were to assess if golexanolone treatment reduces peripheral inflammation and improves fatigue and cognitive and motor function in BDL rats. Rats were subjected to bile duct ligation. One week after surgery golexanolone was administered daily using intra-gastric probes. Fatigue was analyzed in the treadmill, motor coordination in the motorater, locomotor gait in the Catwalk, and short-term memory in the Y maze. These analyses were performed after 2-4 weeks of treatment with golexanolone. BDL increases the plasma levels of the pro-inflammatory interleukins TNFα, IL-6, IL-17 and IL-18. Golexanolone treatment reverses the increases in these interleukins. BDL induces fatigue in the rats, motor incoordination in the motorater test and alters locomotor gait analyzed in the Catwalk. Golexanolone reverses these changes. BDL impairs short-term memory in the Y maze. Golexanolone improves this impairment. Golexanolone reduces peripheral inflammation in BDL rats. This is associated with improvement in fatigue, locomotor gait and coordination, and short-term memory. Golexanolone may have beneficial effects to treat symptomatic alterations such as fatigue, and motor and cognitive impairment in patients with cholestatic liver disease, or hepatic encephalopathy.

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