CELECOXIB AS A NEUROPROTECTIVE AGENT IN CHRONIC CEREBRAL HYPOPERFUSION-INDUCED NEURODEGENERATION IN RATS

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Objectives: Reduced cerebral blood flow (CBF) has been associated with neurodegenerative disorders. Since neuroinflammation is thought to play a significant role in chronic degenerative neurological disorders like Alzheimer's disease, the present study was planned to assess the neuroprotective role of celecoxib in Alzheimer's model of rats (2VO).

Methods: Experimentally, a condition of chronic cerebral hypoperfusion due to reduced CBF can be induced by permanent bilateral occlusion of common carotid arteries (2VO) in rats. After 1 week of acclimatization, fifteen Sprague Dawley rats weighing 200–250 g were equally divided into three groups. Group A served as sham control, Group B = 2VO, and Group C = 2VO + celecoxib daily with celecoxib 50 mg/kg, orally following 2VO. On 6th week, all the rats were euthanized and the hippocampus were isolated. Viable neuronal cells in the hippocampal CA-1 region were counted and hippocampal COX-2 expression and prostaglandin E2 (PGE2) levels were estimated.

Results: There was a significant difference in neuronal cell death, increase in COX-2 mRNA expression and PGE-2 levels in 2VO group as compared to sham control group. In celecoxib-treated 2VO-C rats, the viable neuronal cell count of the hippocampus CA-1 region was significantly higher as compared to the untreated 2VO group. The hippocampal COX-2 mRNA expression and hippocampal PGE-2 levels were found to be significantly lower in the celecoxib-treated 2VO rats compared to untreated 2VO rats.

Conclusions: The results indicate that celecoxib could be successfully used in the management of Alzheimer's disease. No conflict of interest.

FERROUS CITRATE INDUCED OXIDATIVE INJURY TO RAT NIGROSTRIAL SYSTEM - IN VIVO RELEVANCE TO PARKINSON'S DISEASE MODEL

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Objectives: The present study was undertaken to investigate the effect of intratrial infusion of ferrous citrate on tetrahydrobiopterin (BH4) and GTP-CH turnover in rat nigrostriatal system.

Methods: Ferrous citrate solution (8 mmole) was infused through microdialysis probe at the rate of 0.8 μL/min to the right substantia nigra using stereotactic coordinates: AP: 3.2 mm, L: 2.1 mm and V: 2.0 mm. Animals were decapitated at different time intervals, 0 hr, 12 hr, 24 hr, 48 hr, 96 hr, and 1 week using guillotine. The corpus striatum was analyzed using liquid chromatography tandem mass spectrophotometry and Real time PCR techniques.

Results: The results showed that intraparenchymal ferrous citrate infusion caused significant increase in BH4 levels during 12 to 24 hr after stereotactic procedure and subsequently led to severe depletion of BH4 levels measured during 24 hr to 1 week due to auto-oxidation of overloaded BH4 produced in response to ferrous citrate injection after 12 hr of surgery. The oxidative injury to nigrostriatal system in response to ferrous citrate injection was confirmed by measuring the expression levels of GTP-CH during 12 hr to 1 week, which was found to be in increasing order in response to oxidative damage in nigrostriatal system. Conclusions: In conclusion, intraparenchymal infusion of ferrous citrate provides good animal model for studying oxidative stress and Parkinson's disease, which is in vivo relevance to Parkinson's disease. No conflict of interest.

THE OLIGOMER MODULATOR ANLE138B INHIBITS DISEASE PROGRESSION IN A MOUSE MODEL OF PARKINSON'S DISEASE EVEN WITH LATE TREATMENT STARTED AROUND CLINICAL DISEASE ONSET

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Objectives: Parkinson's disease (PD) is characterized by the deposition of aggregated α-synuclein (αSyn). Recent evidences suggest that oligomers formed in the aggregation process constitute the main toxic species causing neurodegeneration. Recently, we demonstrated that the novel oligomer modulator anle138b blocked formation and accumulation of αSyn oligomers, reduced disease-associated motor deficits and led to prolonged disease-free survival in mouse models of PD. However, so far it has not been investigated if anle138b is also effective when treatment is started when signs of disease become detectable.

Methods: The disease modifying effect of anle138b, a novel compound derived from a systematic drug-discovery project, was tested in a transgenic PD mouse model based on neuronal expression of human A30P-αSyn. Anle138b was given orally twice daily. Disease onset was monitored by measurements of rota-rod performance.

Results: In control mice, deposits of αSyn in the brainstem and fluctuations of rota-rod performance (e.g. disease onset) became apparent around the 50th week of life. Thus, oral treatment with anle138b was administered starting from this age. Anle138b-treated mice showed a significantly prolonged disease-free and overall survival. The effect size was comparable to previous results obtained with early start of treatment at 8 weeks of age.

Conclusions: The oligomer modulator anle138b has a strong effect on disease progression and survival also after disease onset, which is a key prerequisite for disease-modifying therapy in PD patients.

Reference

CLINICAL SIGNIFICANCE OF METALLOTHIONEINS IN PARKINSON'S DISEASE

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Objectives: Metallothioneins (MTs) are cysteine-rich, zinc-binding proteins that are induced by metal nanoparticles (NPs). MTs provide neuroprotection as antioxidant, anti-inflammatory, and anti-apoptotic agents by augmenting zinc-mediated transcriptional regulation of genes involved in cell proliferation and differentiation. Liposome-encapsulated MT1 promoter has been used to induce anti-apoptotic genes.

We discovered therapeutic potential of MTs in inhibiting Charnomy body (CB) formation and α-synucleinopathies for effective treatment of Parkinson's disease (PD).

Methods: We employed MTs gene manipulated cultured cells and animals, digital fluorescence imaging, E.M., ICP-MS, microPET imaging, and molecular neurological procedures to discover that MTs enhance Ubiquitination (NADH)-Oxidoreductase (complex-1), a rate-limiting enzyme involved in oxidative phosphorylation.

Results: C8Es are electron-dense multi-laminar structures formed by mitochondrial degeneration due to free radical overproduction. MTs as free radical scavengers inhibit CB formation and α-synucleinopathies before Lewy body formation. Selegiline also inhibits α-synuclein nitrillation, implicated in Lewy body formation. Furthermore, it inhibits 1-methyl-4-phenylpyridinium and 3-morpholinosydnonimine apoptosis in SK-N-SH and mesencephalic fetal stem cells.

Conclusions: (i) CB and α-Synuclein Index (SI) may be used as sensitive PD biomarkers; (ii) MTs transcytotic fetal stem cells may be transplanted in the striatal region of weaver mice exhibiting neurodegeneration and Parkinsonism; (iii) MTs may facilitate theranostic potential of NPs-labeled cells as therapeutic agents in PD; (iv) MTs could facilitate the synthesis, characterization, and functionalization of NPs for theranostic applications of PD and related disorders.

Reference

DOS THE LRRK2*R144G PD MUTATION MODULATE THE IMMUNE REACTION IN THE BRAIN?

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Objectives: Missense mutations in LRRK2 gene cause late-onset Parkinson's disease (PD) with clinical and pathological phenotypes similar to idiopathic Parkinson's disease (PD) and a familial carrier rate of 27–50% in patients. LRRK2 is a serine/threonine kinase that, through its C-terminal death domain (CTDD), modulates the expression of the transcription factor Nkx2.5 and the death receptor TRAIL.

Methods: To test the hypothesis that LRRK2*R144G mutation modulates the immune reaction in the brain, we performed a comparative analysis of immune-related cell surface markers (ICSM) and cytokines in human primary fetal brain cells (HFBC) from LRRK2*R144G–/– and LRRK2*R144G+/– individuals.