Development of Astroglia-targeted Neuroprotective Drugs

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Abstract

Astroglial dysfunction has been observed in the patients of Parkinson's disease and ALS who desire neuroprotective drugs. We found some astroglial molecules to exert neuroprotective effects by promotion of astroglial proliferation and by activation of its anti-oxidative system (Asanuma et al., Ann. Neurol., 67: 239-249, 2010). Furthermore, we revealed that induction and secretion of metallothionein and glutathione specifically in/from reactive astroglia protect dopaminergic neurons from oxidative stress (Miyazaki et al., GLIA, 59: 435-451, 2011). We are planning to screen or develop astroglia-targeted neuroprotective drugs which activate those astroglial molecules using already established screening methods. Screening of drugs already released as medicines for other diseases can accelerate clinical use of the drug. This study would promote development of new neuroprotective drugs or techniques not only for Parkinson's disease and ALS but also for other neurological disorders. (Oral Presentation, April 27, 14:50-15:20)

Neuro-astroglia interaction in glutathione (GSH) synthesis and metallothionein (MT) induction against oxidative stress
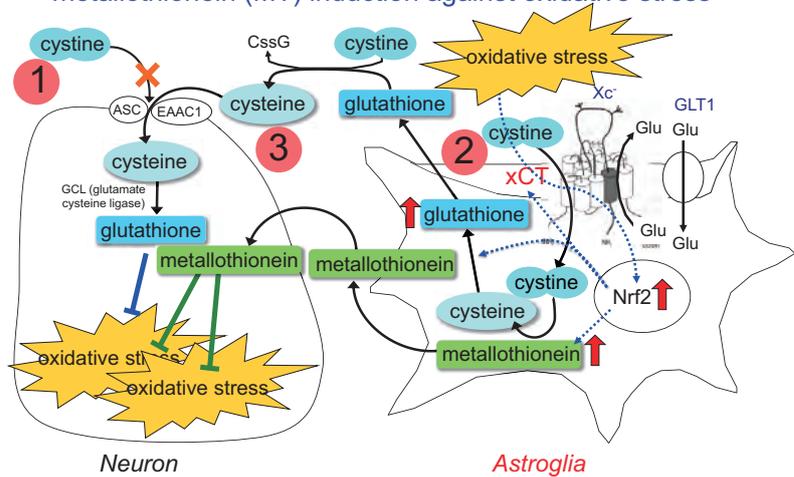

1. Neurons express less transporting system of cystine, oxidized form of cysteine as substrate for glutathione (GSH) synthesis.

2. Astroglia surrounding neurons can uptake cystine via cystine/Glu exchange transporter (xCT), synthesize GSH and release it.

3. Cysteine is enzymatically/nonenzymatically converted from GSH can be rapidly uptaken into neurons for GSH synthesis in neurons.

GSH synthesis in neurons is dependent on the cystine uptake, GSH synthesis and secretion in/from astroglia.

Metallothionein (MT) induction and GSH synthesis in astroglia and their release protects neurons against oxidative stress.
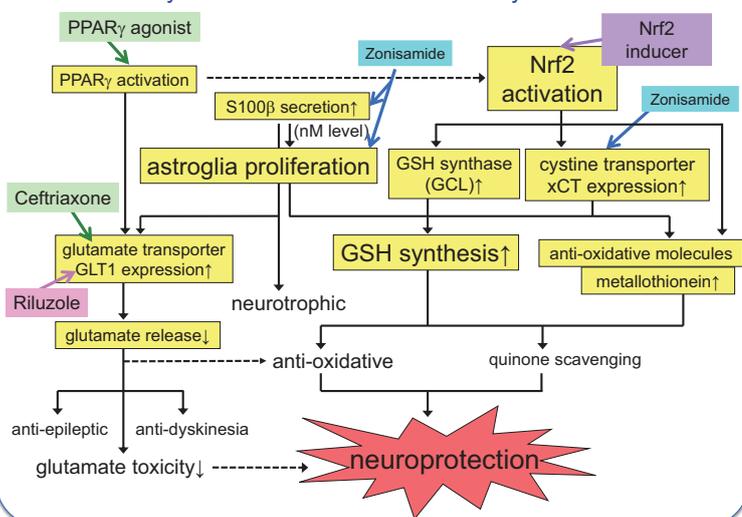
Striatum in the model of Parkinson's disease
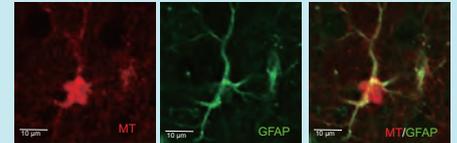
Strong antioxidant MT expressed specifically in reactive astroglia in the striatum of parkinsonian model.

Miyazaki et al., GLIA, 59: 435-451, 2011.

Astroglial target molecules to exert neuroprotective effects by promotion of astroglial proliferation and by activation of its anti-oxidative system

Development of new neuroprotective drugs or techniques which activate astroglial anti-oxidative molecules

candidate drugs/agents for screening

screening
 by astroglia proliferating effects
 by effects on astroglial molecules
 of anti-oxidative sysytem

candidate neuroprotective drugs/agents

neuron-astroglia co-culture system

apply to animal model of neurological disorders

development astroglia-targeted neuroprotective drugs

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