Department of Neuroscience
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General Summary

Our research projects have concerned neurodegenerative disorders caused by intracellular accumulation of abnormal proteins. We are also studying mouse models of neurodegenerative disorders and autopsy cases by means of standard morphologic analysis and molecular biological analysis.

Research Activities

Histopathological safety evaluation of transcranial low-frequency ultrasound in the brains of stroke-prone spontaneous hypertensive rats

The main goal in the treatment of acute ischemic stroke is prompt arterial recanalization. Thrombolysis with recombintant tissue plasminogen activator (rt-PA) is efficient in humans but has significant problems, including slow and incomplete recanalization, frequent bleeding complications, and a limited therapeutic window. Therefore, adjunctive therapies are needed to extend the reperfusion time window, to increase efficacy, and to reduce the side effects of rt-PA. Ultrasound insonation has recently attracted attention as an adjunctive therapy. Low-frequency ultrasound (<1 MHz) is, however, believed to be unsafe, and high-frequency ultrasound (2 MHz) is largely ineffective. The major objective of this study was to examine the safety of low-frequency ultrasound thrombolysis in stroke-prone spontaneous hypertensive rats. Low-frequency ultrasound with a spatial-peak temporal-average intensity (Ispta) in the brain of 0.14 W/cm^2 at 297.3 kHz and 268.4 kHz showed an increased rate of cortical necrosis. With ultrasound with an Ispta in the brain of 0 to 0.06 W/cm^2 at 489.6 kHz, the percentage of cases with hsp70-immunoreactive cells and the number of hsp70-immunoreactive cells were increased in rats treated with ultrasound with a higher Ispta in the brain.

Ubiquitin — small ubiquitin-like modifier — positive neuronal intranuclear aggregates formed by proteasome inhibitor: Relation with intranuclear domains

Treatment with a proteasome inhibitor (MG-132) of neuronal cells (SH-SY5Y) produces ubiquitin-positive cytoplasmic and intranuclear aggregates. We have previously reported that the intranuclear ubiquitinpositive aggregates are SUMOylated and associated with promyelocytic leukemia protein (PML) — positive nuclear bodies. The ubiquitin — small ubiquitin-like modifier (SUMO) — positive aggregates have protein components similar to those of intranuclear inclusions observed in polyglutamine diseases or neuronal intranuclear inclusion disease. We examined the relation between the intranuclear ubiquitin-SUMO — positive aggregates and nuclear domains, including

PML-positive nuclear bodies, Cajal bodies, splicing factor compartments, and nucleoli. After treatment with high doses of MG-132, small dot-like and larger, irregular ubiquitin-SUMO — positive aggregates appeared. With lower doses, small, dot-like aggregates appeared, although larger aggregates were rare. The small aggregates were colocalized with PML-positive nuclear bodies and were occasionally adjacent to coilin-positive Cajal bodies, suggesting that the small aggregates were linked to the nuclear body — Cajal body domains related to a small nuclear RNA gene locus. The larger aggregates were surrounded by fibrillarin-positive structures, indicating that the aggregates might be associated with the nucleolus.

Publications

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