September 1997 (Volume 38, Number 3)

Kainate-Induced DNA Damage and P53 Immunoreactivity in the Rat Hippocampus: Protection with Melatonin

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Aim. To characterize the temporal pattern of kainate-induced markers of apoptotic neuronal death in the rat hippocampus, and to evaluate the effect of the pineal hormone, melatonin, upon these markers.

Method. Epilepsy-like seizures were induced in male Wistar rats by intraperitoneal injection of a glutamate receptor agonist, kainate (10 mg/kg). Melatonin (4 x 2.5 mg/kg) or its vehicle were injected 20 min prior to kainate, immediately after kainate, and one and two hours after kainate injection. Rats were sacrificed at different times after kainate injection (three hours to three days). The markers of apoptosis we assayed using a quantitative computer-assisted imaging included DNA damage (TUNEL assay) and p53 immunostaining. Necrotic injury was assessed using a quantitative assay of the loss of Nissl staining.

Results. The TUNEL assay revealed DNA damage as early as three hours after kainate. This damage increased further by 24 hours, and then remained stable for the next two days. The p53 immunostaining was first positive 24 hours after kainate. Melatonin reduced the appearance of both the early DNA damage, the late p53 up-regulation, and the loss of Nissl staining.

Conclusion. Kainate-triggered, epilepsy-like seizures lead to neuronal loss which is, in part, due to an apoptosis-like process involving DNA damage and p53 up-regulation. Melatonin injections are capable of halting this process and rescuing neurons. Melatonin could be considered for the treatment of excitotoxicity-associate neurodegeneration, whereas melatonin deficiency, normally occurring in aging, might be involved in the pathophysiology of aging-associated neurodegenerative disorders.

Key words: *apoptosis; hippocampus; kainic acid; melatonin*

Received: April 2, 1997
Accepted: May 2, 1997

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