

Dopamine-Induced Apoptosis: Role of Nuclear Transcription Factor- κ B Relevance to Parkinson's Disease

Tiffany Ludka

James Krueger
Ping Taishi

Department of Veterinary and Comparative Anatomy, Pharmacology, and Physiology
Washington State University, College of Veterinary Medicine, Pullman WA.

Approximately 1 million people in the United States are affected with Parkinson's disease (PD). PD is a neurodegenerative disease marked by tremors, rigidity, and poor balance. The movement disorders seen in PD appear to be caused by degeneration of dopaminergic neurons in the substantia nigra area of the brain. This degeneration is thought to be caused by dopamine-induced apoptosis.

Human patients with PD are commonly afflicted with excessive daytime sleepiness (EDS) that appears to be unrelated to any certain medication. The sufferers tend to be older and have more advanced disease. The EDS may stem from an interrupted rapid eye movement sleep (REMS) pattern. Of PD patients, 25% suffer from REMS behavior disorder (RBD). The characteristics of RBD include loss of normal skeletal muscle atonia during REMS, prominent motor activity, and dreams. Some PD patients have reported a lessening of PD symptoms in the morning for ~30 min. to 1 hour after waking. This has been termed sleep benefit (SB). PD patients with young onset are more likely to show SB, and the longer a patient has had PD, the more likely they are to show SB.

Lewy bodies are an important hallmark of PD in humans. They are cellular deposits found in surviving dopaminergic neurons of post-mortem PD affected brains. Lewy bodies are composed of α -synuclein, and may be related to apoptosis.

Inhibition of nuclear transcription factor- κ B (NF- κ B) has been shown to inhibit spontaneous and interleukin- 1β -induced sleep. It is thought that NF- κ B is involved in dopamine-induced apoptosis. When NF- κ B is activated it moves to the nucleus of the cell. A cell-permeable NF- κ B inhibitor peptide inhibits translocation of NF- κ B into the nucleus. It is thought that it does this by competing with NF- κ B complexes for the cellular machinery responsible for nuclear translocation of NF- κ B. There are conflicting reports about NF- κ B and apoptosis. Panet, 2001, claims it induces activation of dopamine-induced apoptosis in PC12 cells. Lee, 2001, claims it inhibits activation in PC12 cells. There may be multiple reasons for this difference. The two studies used different types of NF- κ B inhibitors. Also, Panet added dopamine, whereas Lee used auto-oxidized dopamine.

The pesticide rotenone has been linked to Parkinson-like symptoms in rats. In rats treated with rotenone, dopamine-producing cells that survived had cellular deposits called Lewy bodies. Other toxins that appear to produce parkinsonism, e.g. MPTP, do not produce Lewy bodies. It has not been tested to see if NF- κ B has an effect in rotenone-induced parkinsonism.

In the proposed study, we will determine if rotenone acts through NF- κ B to induce apoptosis in dopaminergic neurons. We will inject rats with rotenone to induce PD and determine what affect that has on sleep and if NF- κ B has the same effect *in vivo* as it does in the cultured cells. We will also determine the effect of a NF- κ B injection on the rat sleep cycle.