Restless Legs Syndrome and Histamine

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Restless legs syndrome (RLS) appears to have some mechanism creating a 'hyperarousal' phenomenon in such a way that despite producing profound chronic sleep loss there is no significant daytime sleepiness. Abnormal activation of the histamine system could contribute to this 'hyperarousal' and clinical patients have complained that sedating anti-histamines profoundly exacerbate their symptoms even when they are normally adequately treated with medications. We sought to evaluate the clinical response to an anti-histamine challenge and the autopsy status of the H2 and H3 receptors in the substantia nigra. The clinical response was assessed by the number of leg movements and the patient's report of leg discomfort during two suggested immobilization tests (SIT) at 15:45 and again at 18:00 on each of 3 consecutive days in the General Research Center. An intravenous (IV) dose of 0.25 mg diphenhydramine or 1.0 mg lorazepam or placebo was given about 90 minutes before each SIT test with the same medication given in a randomized double-blind fashion on each day, except placebo, which was always given on day 2. The day for the placebo was not known by any of the staff interacting with the patient during the study. Twelve RLS patients (8 females, 4 males) adequately treated with dopaminergic agents for RLS completed the study. All 12 reported significantly worse RLS symptoms and had dramatically more leg movements, as measured by the SIT, after diphenhydramine compared to after either lorazepam ($p<0.05$) or placebo ($p<0.01$). These responses were more dramatic than any reported for other drugs including dopamine antagonists.

We also examined histamine receptors in substantia nigra tissue obtained from the RLS Foundation's collection of RLS brains (6 females) and from age-matched controls (6 females) from the Harvard Brain Bank. In the nigra, histamine receptor 3 staining was more intense in 5 of the 6 RLS patients as compared to their age-

matched controls. Histamine receptor 2 staining followed a similar pattern: staining was more intense in RLS nigra 4 out of 6 times as compared to controls. The staining was primarily confined to the neuromelanin cells.

Thus it appears that histaminergic stimulation is needed to avoid RLS symptoms and that it has an abnormal regulation in RLS that may contribute to the hyperarousal observed with RLS. Histamine not only supports arousal but also modulates dopaminergic pathways. Abnormalities in the histaminergic system may, therefore, contribute not only to the hyperarousal but also to the development of the motor and sensory symptoms of RLS.