# Neuropathology of RLS and its treatment

Yuan-Yang Lai

There are two states of sleep, slow wave sleep (SWS), and rapid-eye-movement (REM) sleep. Muscle activity is low and quiescent in SWS and muscles relax completely, a phenomenon called "atonia", in REM sleep. The brain controls muscle activity in wake and in sleep. Thus, dysfunction of the brain causes excessive muscle activity, such as tremor and periodic leg movements (PLM). PLM has been reported in RLS and REM sleep behavior disorder (RBD) patients. Our muscles completely relax in REM sleep, that's why we are unable to act out our dreams, which occur during REM sleep. RBD is an abnormal behavior, and includes talking, yelling, kicking, and jumping, that appears to correlate with dream report. RBD patients may cause injury to themselves and to their bed partners. Atonia in REM sleep can prevent such destructive motor behaviors and has obvious beneficial value.

I have been working on motor systems since I was a graduate student in Texas. I studied RBD in my earlier research work. One of the techniques I used is "neurotoxic lesion", in which a drug is injected into a specific brain region that kills brain cells in that area. My first attempt was to kill cells in the area near the substantia nigra (SN), the largest dopamine producing area of the brain, to develop an animal model of RBD. I noticed that some animals with lesions express RBD activity, but others did not. Instead, these non-RBD animals displayed PLM in wake and in sleep, symptoms very much like those seen in RLS patients. I also noticed that in RLS animals brain cells killed by the drug are in the SN. Based on those studies, I received my first grant from the RLS Foundation and a 4-year grant from the National Institutes of Health (NIH) in 2003.

Although dopamine drugs are very effective in the treatment of RLS, patients develop augmentation after long term use. Other drugs, such as Neurontin and oxycodone, also produce adverse side effects. Thus, an animal model would greatly facilitate screening possible drugs for treating RLS. An animal model is also critical for the identification of specific brain regions, circuits, and brain chemicals involved in RLS. My research goals are to develop a suitable animal model and test potential drugs to treat RLS in this model, with the aim of identifying alternate treatments for RLS patients.

RLS affects as much as 10% of the population. The prevalence of RLS in iron deficient (ID) anemia patients is even greater, at 40%. Therefore, I examined whether ID rats display RLS symptoms. Similar to human patients, ID rats show PLM in wake and in sleep. Their symptoms improved with dopamine drug treatment, similar to RLS patients. I then tested a potential drug, histamine H3 receptor (H3R) antagonist, in ID rats and found that the drug improves PLM. These studies have been supported by the RLS Foundation.

In 75% of RLS patients, there is no sign of anemia. The aims of my current NIH supported project are to 1) develop another animal model of RLS, 2) test the H3R antagonist in this model, and 3) determine other brain regions and chemicals that may cause RLS . In my early studies, I found that 1) destruction of part of the basal ganglia causes RLS, 2) H3R antagonist drug also improves PLM in basal ganglia lesioned rats, just as it did in ID rats, 3) abnormal amount of H3R is found in the basal ganglia of ID rats, and 4) abnormal activity of the inferior colliculus, an area involved in auditory response, and SN causes RLS.

Thus far, I have only used male rats in my studies, however, more than 70% of RLS patients are women. Therefore, I wanted to find out the reason for the gender difference in the generation of RLS. I applied for and received additional funds for one-year from NIH in 2015 to carry out this project. Results from this study are still pending.

I have successfully developed 2 animal models of RLS. I have tested the H3R antagonist drug and found it to be effective in treating RLS in both animal models. I hope this drug will soon be used in clinical trials. It will benefit millions of RLS patients if clinical tests show that H3R drugs improve PLM and sleep in patients.

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