

Animal Model Explains the Origins of the Cranial Dystonia Benign Essential Blepharospasm

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The (Clinical) Workshop that BEBRF sponsored in Bethesda, MD a few years ago completely reorganized my thinking about the causes of benign essential blepharospasm. We now have an animal model of blepharospasm that was based on our ideas about how blepharospasm might arise in humans (included in the following article). We have even started some promising drug treatments that appear to eliminate reflex blepharospasm in our rat model of reflex blepharospasm in Parkinson's Disease.

Modeling two brain changes which we believe cause benign essential blepharospasm (BEB) in humans, Drs. EJ. Schicatano, M.D. Basso and I recently reported producing blepharospasm in rats (Animal Model Explains the Origins of the Cranial Dystonia Benign Essential Blepharospasm, *I. Neurophysiol.* 77:2842-2846, 1997). We hypothesize that two typical characteristics of human BEB, that people are at least 50 when it first appears and the presence of "dry eye," illustrate the two prerequisites of developing BEB. We identified the first requirement, the "permissive condition," in our studies of reflex blepharospasm. Our studies of "dry eye" identified the second prerequisite, the "initiating condition."

While investigating the reflex blepharospasm caused by Parkinson's disease, we found that a catastrophic loss of a specific brain chemical, dopamine, caused the region of the brain that regulates reflex blinking, the trigeminal complex, to be overly sensitive to blink evoking stimuli. This increased sensitivity did not cause the spontaneous spasms of lid closure associated with BEB, but touching the eyelid during an eye exam caused prolonged spasms of lid closure. While nowhere near as complete as the loss with Parkinson's disease, everyone loses some dopamine containing brain cells with normal aging. My studies with Dr. K. R. Peshori showed that this normal dopamine loss significantly increased the sensitivity of the trigeminal complex in people over 55 years

of age. We reasoned that people who may develop BEB lose dopamine, or the neurons that manufacture dopamine, more rapidly than the average person but less rapidly than a person who will get Parkinson's disease. This excessive dopamine loss creates a "permissive condition" in the trigeminal complex. To mimic this "permissive condition" in rats, we destroyed a small number of neurons in the brain that manufacture dopamine.

One of the triggers for the "initiating condition" may be the development of "dry eye." My colleagues and I found that the nervous system responds to chronic eye irritation by producing extra blinks each time the person needs to blink. This pattern of extra blinks results from changes occurring in the trigeminal complex. Normally this pattern of blinking is adaptive because the extra blinks improve eye wetting. In people with a "permissive condition" in the trigeminal complex, however, we believe that this normally useful pattern of extra blinks grows out of control to become BEB. Thus, "dry eye" provides the "initiating condition" for BEB. We produce the "initiating condition" in rats by slightly weakening the lid closing muscle to create "dry eye." When we combine the "permissive condition," a loss of dopamine neurons, with the "initiating condition," dry eye, rats rapidly develop spontaneous spasms of lid closure similar to those seen in human BEB. Just as in humans, neither the "permissive condition" nor the "initiating condition" produce BEB by themselves. The two conditions must occur together and in the proper order. We hope that our animal model of blepharospasm provides researchers with an approach for creating new treatments that may reduce the severity or prevent the development of benign essential blepharospasm.

Published on the BEBRF Blepharospasm Web site July 12, 1997

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