Using Pharmacogenetics to Determine the Role of the Orexin System in Panic-Associated Behavior and Physiology

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Background: Orexin is a neuropeptide that is exclusively synthesized in the perifornical hypothalamus, which is a brain region that when stimulated elicits panic-associated behavior in rodents. But what role does orexin play in this? In order to examine this relationship, one needs to stimulate the system. The solution to exciting only orexin neurons is to use DREADD technology: a virus under orexin promotor is used to express an excitatory designer Gq receptor that is only activated by a biologically inert designer drug (clozapine-N-oxide, CNO). Project goals: The goal of my project is two-fold: to utilize immunohistochemical techniques to validate that orexin plays a direct role in panic-associated responses observed by staining for c-Fos and orexin. The second goal was to see if DREADD technology is actually activating orexin neurons and also panic-associated brain regions with dense innervation from orexin neurons by staining for c-Fos and tyrosine and tryptophan hydroxylase (key mediators for panic). The two other region of the brain were the locus coeruleus and the dorsal raphe, which are known sites for panic and also receive dense input from orexin neurons. Results: There was a significant increase in c-Fos and orexin expression in the CNO treated rats compared to vehicle treated rats and a significant increase in both TH and TPH expression in both regions of the brain in CNO treated rats confirming that CNO treated rats have significantly increased cellular responses in orexin neurons and that CNO injection are activating other known sites for panic. Conclusion: Pharmacogenetic excitation of orexin neurons mobilizes an integrative panic response, which suggests that orexin could be a therapeutic target for treating aberrant panic.

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