

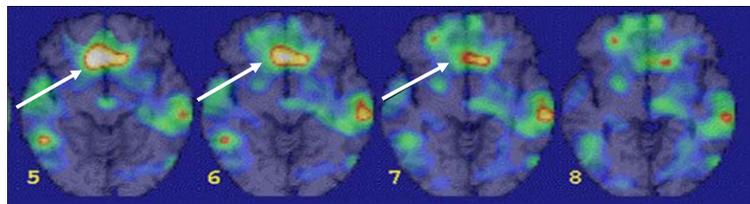


Preclinical Development of The Protein Kinase C Inhibitor, Chelerythrine, for the Treatment of PTSD



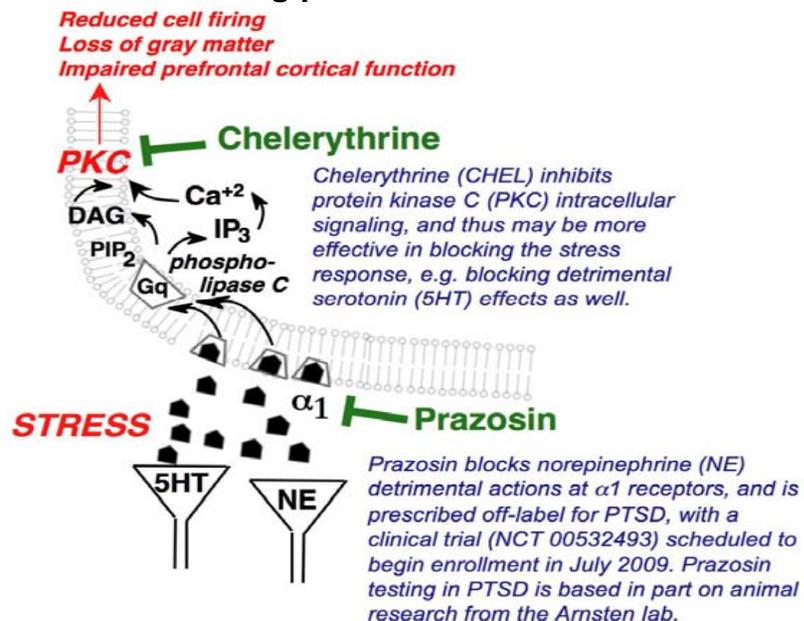
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The prefrontal cortex is the brain region most consistently afflicted in subjects with PTSD

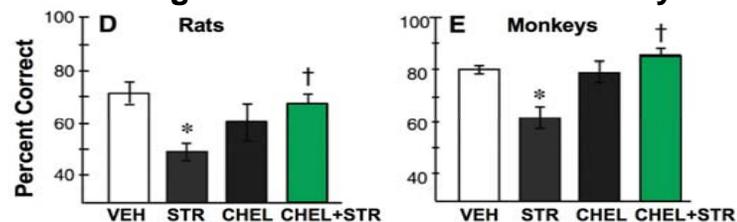


Loss of prefrontal cortical function is a consistent feature of PTSD. Prefrontal dysfunction likely contributes to symptoms such as flashbacks, intrusive memories and impaired regulation of emotion. This picture from Bremner, 2007 (*Neuroimaging Clin N Am* 17:523) shows reduced medial prefrontal activity (white arrows) in combat veterans with PTSD as they viewed and listened to traumatic, combat-related stimuli.

Chelerythrine protects prefrontal cortex by inhibiting protein kinase C

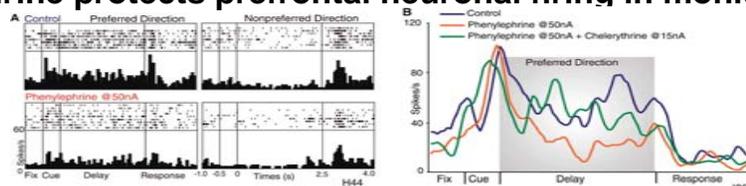


Chelerythrine protects prefrontal cognition from stress following oral administration in monkeys



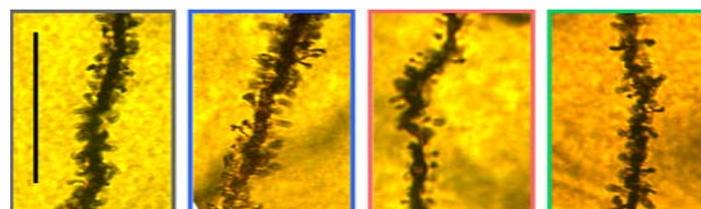
Acute treatment with CHEL significantly protects prefrontal function from the effects of acute, pharmacological stress (Birbaum et al. *Science* 306:882, 2004). In rats, injections of 0.3 μ g CHEL directly into the prefrontal cortex protected cognitive performance from acute stress exposure. In monkeys, oral treatment with 0.03 mg/kg CHEL significantly protected cognitive performance from acute stress, encouraging use in humans.

Chelerythrine protects prefrontal neuronal firing in monkeys



The NE α_1 agonist, phenylephrine, suppressed memory-related neuronal firing when applied by iontophoresis onto prefrontal neurons in monkeys performing a spatial working memory task (see Delay period in Figures A and B). Firing was restored by co-iontophoresis of CHEL (Figure B, green trace). From Birbaum et al. *Science* 306:882, 2004.

Chelerythrine protects prefrontal gray matter from chronic stress



Exposure to chronic stress (6 hrs/day of restraint stress for 21 days) significantly decreases dendritic spine density in the rat prefrontal cortex and produces marked loss of prefrontal cognitive function. Daily treatment with CHEL (1.0 mg/kg, s.c.) significantly protected dendritic spines and cognitive performance from the detrimental effects of chronic stress. Spine density significantly correlated with cognitive abilities, emphasizing the importance of protecting prefrontal gray matter. From Hains et al, in press, *Proc Nat Acad Sci USA*.

Chelerythrine has strong, preliminary preclinical safety data, encouraging translation to humans