Bilateral Stimulation of the Amygdala Treats the Anxiety Component of PTSD by Upregulation of the Neuro -peptide Y System

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Introduction

Post-traumatic stress disorder (PTSD) is one of the hallmark conditions of Soldiers returning from Operations Iraqi Freedom and Enduring Freedom, with as many as 20% of Soldiers affected. Approximately 30% of patients do not respond to conventional treatment, resulting in a significant unmet treatment need. The hallmark symptoms of PTSD are both avoidance and anxiety. Since amygdalar activity is increased in fear learning and PTSD, leading our group and others to hypothesize that amygdalar stimulation may attenuate PTSD-related symptoms. Prior studies showed decreased avoidance behavior with right amygdalar stimulation in a foot-shock paradigm. However, the underlying molecular mechanisms remain incompletely understood. Human and animal studies indicate an anxiolytic function for the neurotransmitter Neuropeptide Y (NPY) in PTSD patients and models of PTSD. We hypothesized that amygdalar stimulation would attenuate behavioral effects in the predator scent model of PTSD, and that effects would be mediated by NPY.

Methods

Anxiety Testing

Lewis rats (10-12 weeks) underwent exposure to feline urine. One week later, baseline behavioral testing on the elevated plus maze confirmed increased anxiety-related behavior. One day after testing, rats were stereotactically implanted with bilateral stimulating electrodes in the basolateral amygdalae. After one week of recovery, rats were stimulated 4 hours/day for 7 days (300mA, 120μs pulse width, 160Hz), and then were re-tested. After sacrifice, immunohistochemistry for amygdalar NPY, C-fos, and DAPI was performed.

Avoidance Testing

Lewis Rats (10-12 weeks) underwent a 4 day avoidance paradigm (Fig. 1). They were then implanted with bilateral basolateral amygdala electrodes and then stimulated for one week and re-tested for resoltuion of their avoidance behavior.

Figure 1

Avoidance Paradigm

Results

Bilateral stimulation resulted in increased mean time in the open arm of the elevated plus maze (87±16.8 vs 32±9.7 sec, $p<0.05$, $n=4$), indicating decreased anxiety, while rats undergoing sham stimulation showed no change (Figure 3). The time the animals spent in the previoulsy avoided space after stimulation trended toward statistical significance when compared to the non-stimulated rats (Figure 4). Immunohistochemistry showed increased NPY peptide levels in the amygdalae of stimulated rats (Figure 2) which trended toward a statistically significant increase (Figure 5).

Figure 3

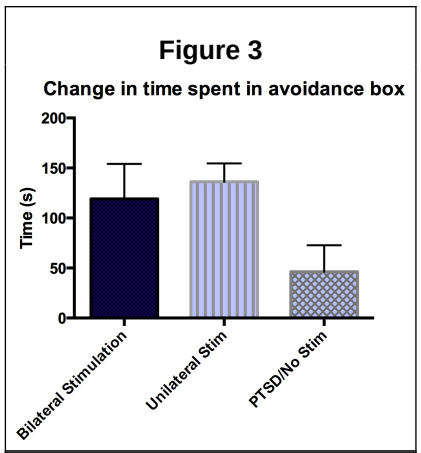


Figure 2

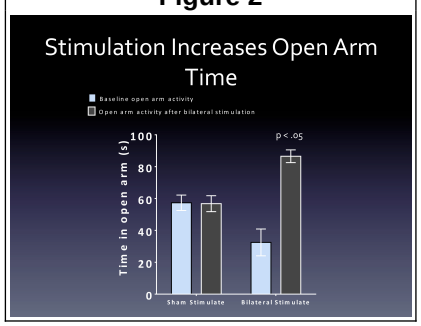
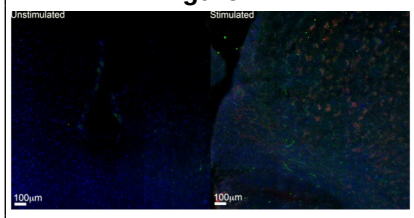
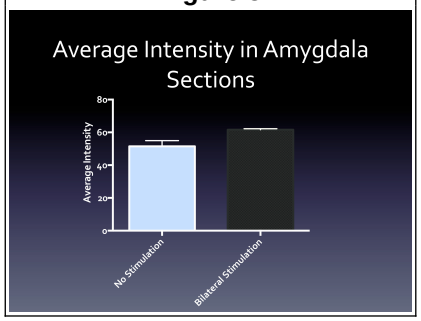


Figure 4



NPY Staining on Stimulated and Unstimulated Rats (green = NPY)

Figure 5



Conclusions

Bilateral amygdalae stimulation attenuated anxiety-like behavior in the predator scent model of PTSD while also decreasing avoidance. Treatment was correlated with increased amygdalar NPY. Amygdalar stimulation may alleviate PTSD symptoms, and these data provide the first evidence of a possible underlying molecular mechanism.

Learning Objectives

By the conclusion of this session participants should be able to: 1)Discuss the symptoms of PTSD, 2)Describe how amygdalar stimulation can drive the output of the basolateral nucleus and lead to decrased symptom expression, 3) Describe how stimulation of the amygdala can alleviate anxiety by increasing NPY expression

References

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