

Increased Levels of Kynurenic Acid Lead to Changes in Fear Learning: Implications for PTSD

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New Hampshire Academy of Science - 2016

Kynurenic acid (KYNA) is an endogenous chemical produced in the brain and is the final product of the tryptophan metabolic process. KYNA acts as an antagonist of nicotinic acetylcholine receptors and also as an allosteric inhibitor of the glycine site on NMDA receptors. Both of these receptors are critically involved in the learning processes following environmental stimuli, including aversive stimuli related to fear and stress. Recent findings suggest that the concentration of KYNA may be elevated in persons with Post-Traumatic Stress Disorder (PTSD), who exhibit hyper reactivity in response to aversive stimuli and heightened fear behavior. This has led to the hypothesis that elevated levels of KYNA may lead to PTSD symptoms. To test this hypothesis we raised the levels of KYNA in rats by injecting them one time with L-KYN (a precursor of KYNA), which resulted in a significant increase in KYNA concentration. During the conditioning session that followed, rats received presentations of one auditory stimulus (10 second tone) paired with a mild foot shock (CS+, conditioned stimulus positive) and 3 minutes later, a second auditory stimulus (10 second white noise) that was not paired with shock (CS-, conditioned stimulus negative). During the subsequent test sessions, the rats were re-exposed to the two auditory stimuli, but no shock was delivered. The length of freezing (the absence of movement except for respiration) served as the measure of conditioned fear. This was assessed by observing the rats after the presentations of the stimuli. The results showed that the rats injected with L-KYN during training exhibited similar amount of fear (freezing behavior) in response to CS- when compared to the initial CS+, while the control rats froze more in response to the CS+ than to the CS-, as expected. The reaction of the KYNA-treated rats is characteristic of PTSD: inappropriately high levels of fear to neutral stimuli. This finding is consistent with our hypothesis that elevated levels of KYNA may lead to PTSD symptoms.