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Chronic, predictable stress during adolescence increases resilience in female mice via α4δ GABAA receptors

Many experiments investigating stress during adolescence focus on its negative effects, while few explore its benefits during this critical period. Those that do have conflicting results and lack mechanistic explanations. The goal of this study was to explore the effect of chronic, predictable stress during the pubertal period in female mice on measures of anxiety and depression. Mice were restrained for 2 hours/day over 2 weeks, beginning at the onset of puberty (assessed by vaginal opening). They were then tested with the elevated plus maze (EPM) and forced swim test (FST) to assess anxiety and depression, respectively. Restrained mice were significantly less immobile in the FST compared to controls (R: 37% ± 0.04, C: 56% ± 0.04, $t(26)= 3.6$, $p= 0.001$), suggesting development of resilience to depressive behavior.

Allopregnanolone (THP), a neurosteriod that is a metabolite of progesterone, decreases during puberty and is released in the brain during stress. Therefore, its importance to the mechanism of observed resiliency was examined. Restrained mice were administered finasteride, which blocks the production of THP, daily for 2 weeks. This increased immobile time to that of unrestrained mice (vehicle: 36% ± 0.08, finasteride: 55% ± 0.04), implicating THP's importance in developing resiliency. THP binds to GABAA receptors (GABARs), typically increasing inhibition and reducing anxiety. It is especially potent at an extrasynaptic GABAR isoform, α4δ. To explore this receptor's role in building resilience, α4 knockout (KO) mice were studied. There were no differences in the FST (C: 62% ± 0.04, R: 60% ± 0.04, $t(13)= -0.08$, $p=0.94$) and restrained α4 KO mice spent less time in the open arms of the EPM (C: 35.3% ± 0.08, R: 23.8% ± 0.04, $t(18)= 2.5$, $p=0.02$), indicating higher anxiety. Altogether, results indicate that chronic, predictable stress during puberty prevents anxious and depressive behaviors in female mice, likely through a mechanism involving THP and α4δ GABARs.