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Urocortin 3 Interaction with GABA and Glutamate in the Posterodorsal Subnucleus of The Medial Amygdala Mediates Suppression of GnRH Pulse Generator Frequency in Female Mice

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Stress exerts a profound impact on reproductive function and disrupts pulsatile luteinizing hormone (LH) secretion. The posterodorsal subnucleus of the medial amygdala (MePD) is an upstream modulator of the hypothalamus pituitary gonadal axis. Stress alters neuronal activity within the MePD, increasing the expression of Urocortin3 (Ucn3) while enhancing the inhibitory output from the MePD to key hypothalamic reproductive centres. Designer receptor exclusively activated by designer drugs (DREADDs) inhibition of MePD Ucn3 neurons prevents psychological stress-induced suppression of LH pulses in female mice. The neurochemical pathways in the MePD responsible for regulating the GnRH pulse generator in the presence of stress remain unknown. We investigate the neurotransmission involved in the neural circuitry responsible for the suppression of GnRH pulse generator activity by MePD Ucn3 neuronal activation. Ucn3-Cre-tdTomato female ovariectomised (OVX) mice were unilaterally injected with AAV-ChR2 and implanted with optofluid cannulae targeting the MePD. Firstly, we optically stimulated MePD Ucn3 neurons with blue light at 10 Hz, 10 mW and monitored the effect on LH pulses. Next, we combined optogenetic activation of MePD Ucn3 neurons with pharmacological antagonism of GABAA or GABAB receptors with bicuculline or CGP, respectively, and observed the effect on LH pulsatility. Finally, during optical activation of MePD Ucn3 neurons we administered a combination of NMDA and AMPA receptor antagonists, AP5 and CNQX respectively, and monitored the effect on pulsatile LH secretion. Optogenetic stimulation of MePD Ucn3 neurons suppressed pulsatile LH secretion compared to controls and administration of aCSF had no effect on LH pulse interval (MePD Ucn3 activation: 36.04 ± 2.49 vs. pre-treatment control period: 17.50 ± 0.67 vs control virus: 21.67 ± 1.67 min; mean ± SEM; $p<0.0001$; n=12). Intra-MePD infusion of bicuculline (BIC) or CGP during optogenetic stimulation of MePD Ucn3 neurons completely blocked the suppressive effect of MePD Ucn3 neuronal activation on LH pulsatility (MePD Ucn3 activation and BIC: 20.50 ± 2.03 vs. pre-treatment control period: 17.58 ± 0.75 min; MePD Ucn3 activation and CGP: 16.30 ± 0.63 vs. pre-treatment control period: 17.50 ± 0.77 min; n=7-10). Intra-MePD infusion of AP5 + CNQX during optogenetic stimulation of MePD Ucn3 neurons similarly completely blocked the suppressive effect of MePD Ucn3 neuronal activation on LH pulsatility (MePD Ucn3 activation and AP5 + CNQX: 19.58 ± 1.42 min; n=6). Our findings show for the first time that optogenetic stimulation of MePD Ucn3 neurons inhibits GnRH pulse generator activity via GABA and glutamate signalling within the MePD.

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