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GABAergic Signalling in the Posterodorsal Medial Amygdala Mediates Psychological Stress-induced Suppression of the GnRH Pulse Generator in Female Mice

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Psychological stress is linked to infertility and reproductive dysfunction by suppressing the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator and pulsatile luteinising hormone (LH) secretion. The posterodorsal subnucleus of the medial amygdala (MePD) is a key upstream regulator of GnRH pulse generator activity and displays increased neuronal activation in response to psychological stressors. The MePD is primarily a GABAergic nucleus with a strong GABAergic projection to hypothalamic reproductive centres, however, their functional significance has not been determined. We hypothesis that MePD GABAergic signalling is a crucial mediator of psychological stress-induced suppression of pulsatile LH secretion. We used a chemogenetic approach to selectively silence MePD GABA neurones during psychological stress to determine the effect on pulsatile LH secretion. Female ovariectomised Vgat-cre mice (n=7) were virally infected to selectively express inhibitory hM4DGi-DREADDs in MePD GABA neurones. Mice were exposed to either predator odour (PO) or restraint stress and given an intraperitoneal injection of either saline or the DREADD chemical activator clozapine-N-oxide (CNO, 5mg/kg). Statistical significance was determined using a one-way ANOVA and post-hoc Tukey test. Data are presented as mean ± SEM and $p<0.05$ was considered significant. PO exposure significantly increased LH inter-pulse interval (IPI) in the saline

group (prestress: 19.05 ± 1.16 min vs. PO: 29.28 ± 3.16 min, $p<0.05$, n=7) and this effect was blocked by DREADD-mediated inhibition of MePD GABA neurones (prestress: 20.59 ± 1.12 min vs. PO: 21.31 ± 1.76 min, $p>0.05$, n=7). Restraint stress dramatically increased LH IPI in the saline group (prestress: 17.78 ± 1.02 min vs. restraint: 45.71 ± vs 5.50 min, $p<0.05$, n=7) and DREADD-mediated inhibition of MePD GABA neurones blocked this effect (prestress: 18.57 ± 1.97 min vs. restraint: 27.26 ± 4.02 min, $p>0.05$, n=7). Direct projections from the MePD to the GnRH pulse generator in the hypothalamic arcuate nucleus (ARC) have been identified, however, their phenotype is unknown. In this study, we optogenetically stimulated potential MePD GABAergic projection neurone terminals in the ARC and determined the effect on LH IPI. MePD GABA neurones in female Vgat-cre ovariectomised mice (n=6) were virally infected to express channelrhodopsin 2 protein and MePD GABAergic terminals in the ARC were selectively stimulated by blue light via a chronically implanted fibre-optic cannula in the ARC. Sustained optogenetic stimulation at 10 and 20Hz of MePD GABAergic terminals in the ARC dose-dependently suppressed pulsatile LH secretion (LH IPI; control: 23.34 ± 2.11 min vs. 10Hz: 38.08 ± 3.61 min; 20Hz: 56.67 ± 3.33 min, $p<0.05$, n=6). These findings confirm a functionally significant MePD GABAergic projection to the ARC and highlight the importance of GABA signalling in the MePD in mediating stress-induced suppression of reproductive function. Collectively, these findings provide novel insight into the amygdala neural circuitry underpinning stress-induced reproductive function.

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