Roles for PACAP and the PAC1 receptor in anxiety-like behavior in female rats

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The goal of this project is to investigate the relationship between the ovarian hormone estrogen (E) in the modulation of pituitary adenylate cyclase-activating peptide (PACAP) and its cognate (PAC1) receptor expression and signaling in the bed nucleus of the stria terminalis (BNST) in female rats. Previously, our lab has shown that the PACAPergic system is implicated in facilitating stress-induced neuroplasticity in the BNST. Using quantitative polymerase chain reaction, we first examined the effect of E on the expression of PACAP-PAC1 messaging in various limbic and hypothalamic regions in the female rat brain. We found that physiological levels of E administered for a period of 7 days to ovarianectomized (OVX) female rats induced a significant elevation of PACAP mRNA in both the dorsal and ventral aspects of the lateral BNST and a significant elevation of PAC1 mRNA in the dorsal aspect of the lateral BNST. These findings suggest that, in the female rat brain, both PACAP and PAC1 expression is dynamically modulated via E within a brain region specifically associated with mediating stress mechanisms and anxiety-like behavior. The next behavioral experiment in this project will be to determine if intra-BNST bilateral infusion of PACAP is anxiogenic in female rats. We predict that intra-BNST bilateral infusion of PACAP will induce a dose-dependent increase in long-lasting anxiety-like behavior on the elevated plus-maze and hole-board test, which will be greater in OVX female rats replaced with a physiological dose of 17β-estradiol than in non-replaced

OVX female rats. These findings potentially implicate perturbations in PACAPergic system expression/signaling, modulated via E, in facilitating the neuroplasticity associated with stress mechanisms and anxiety-like behavior in female rats. Moreover, the sexual dimorphism of the BNST may be a casual factor in explaining the disproportionate prevalence of clinical pathologies in women that involve the dysregulation of stress- and emotional-response systems.