**PACAP and PAC1 receptor signaling in chronic stress responses: Implications for anxiety-related disorders**

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**Abstract**

Stressor exposure initiates multiple central and peripheral response systems aimed at restoring homeostasis. However, exposure to repeated or chronic stress has been shown to dysregulate normal stress circuits, leading to maladaptive physiological and behavioral responses that then manifest as behavioral disorders. Anxiety disorders are among the most common mental illnesses globally, with healthcare costs surpassing those of cardiovascular disease, cancer, and diabetes. Despite this large burden, little is known about the causal and mechanistic underpinnings of the disease. Here, we utilize a rodent model of chronic stress to elucidate the function of specific peptides in stress-induced anxiety related behaviors. The bed nucleus of the stria terminalis (BNST) is an important site mediating anxiety-like responses and chronic stressor exposure induces a number of changes within this region. We have previously shown that repeated variate stress increases both pituitary adenylate cyclase activating polypeptide (PACAP) and PAC1 receptor transcript expression selectively within the oval nucleus of the BNST. Our recent studies show that acute injection of PACAP into the BNST mimics many of the consequences of repeated stressor exposure including increases in anxiety-like behavior, decreased food intake and weight loss, and increased circulating stress hormone levels. Importantly, blocking BNST PACAP signaling by continuous infusion of the receptor antagonist PACAP(6-38) into the BNST during the week of repeated variate stress can attenuate anxiety-like behavior and blunt the accompanying weight changes typically observed after stressor exposure. As PACAP binds PAC1 and VPAC receptors (VPAC1 and VPAC2) with high affinity, the selectivity of the PAC1 receptor-mediated responses in stress-induced anxiety-like behavior is unclear. We now show that single infusions of the PAC1 receptor-selective agonist, maxadilan, into the BNST are able to produce effects similar to PACAP injection. These data are consistent with recent associations of PACAP/PAC1 receptor dysregulation in human post-traumatic stress disorder, and these results in aggregate suggest that BNST PACAP/PAC1 expression and signaling mechanisms may be novel therapeutic targets for stress-related behavioral abnormalities.