Review

Biological Psychiatry

Pituitary Adenylate Cyclase Activating Polypeptide in Stress-Related Disorders: Data Convergence from Animal and Human Studies

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ABSTRACT

The maladaptive expression and function of several stress-associated hormones have been implicated in pathological stress and anxiety-related disorders. Among these, recent evidence has suggested that pituitary adenylate cyclase activating polypeptide (PACAP) has critical roles in central neurocircuits mediating stress-related emotional behaviors. We describe the PACAPergic systems, the data implicating PACAP in stress biology, and how altered PACAP expression and signaling may result in psychopathologies. We include our work implicating PACAP signaling within the bed nucleus of the stria terminalis in mediating the consequences of stressor exposure and relatedly, describe more recent studies suggesting that PACAP in the central nucleus of the amygdala may impact the emotional aspects of chronic pain states. In aggregate, these results are consistent with data suggesting that PACAP dysregulation is associated with posttraumatic stress disorder in humans.

Keywords: Amygdala, Anxiety, Bed nucleus of the stria terminalis, Fear, Pain, Parabrachial nucleus

http://dx.doi.org/10.1016/j.biopsych.2014.12.003

Several decades of research have implicated corticotropin-releasing hormone (CRH) as a critical stress-related peptide, since CRH in the hypothalamic paraventricular nucleus (PVN) plays a crucial role in regulating sympathetic and endocrine responses to stressor exposure [see (1–3) for review]. Moreover, extrahypothalamic CRH expression is high in many brain regions that respond to stressful stimuli, such as the central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), and locus coeruleus, and CRH activity in these structures has been argued to mediate behavioral responses to stressful stimuli (4). Overactive CRH activity has been associated with posttraumatic stress disorder (PTSD) and a single nucleotide polymorphism in the CRF1 receptor gene (rs12944712) has been associated with PTSD onset in traumatized pediatric patients (5). While CRH systems have received considerable attention in normal stress responses and stress-related psychopathology, recent evidence has implicated other peptides in these functions. Of these, pituitary adenylate cyclase activating polypeptide (PACAP) has emerged as a key regulator of stressor responding (6–9) that may be upstream of CRH in stress-related circuits (Figure 1), and PACAP dysregulation has been associated with PTSD [(10), see below].

PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE

PACAP was identified from hypothalamic extracts based on its ability to stimulate anterior pituitary adenylyl cyclase activity (11). From molecular and biochemical analyses, the alternative endoproteolytic processing of the PACAP precursor can generate bioactive α-amidated PACAP38 or PACAP27 (38 or 27 amino acids, respectively) but PACAP38 appears approximately 10-fold to 100-fold more abundant in most tissues including the central nervous system (CNS) (12,13). PACAP is highly conserved among species and as the peptide is expressed in primitive chordates, the peptide is phylogenetically very old and recognized as the ancestral molecule to the glucagon/secretin/vasoactive intestinal peptide (VIP) superfamily of peptides (14,15).

From PACAP isolation, the three G-protein coupled PACAP receptor subtypes were identified in rapid succession. The PAC1 receptors bind the two forms of PACAP with high affinity and selectivity; VPAC1 and VPAC2 receptors bind both PACAP and VIP with similar affinities (16). Uniquely, there are multiple isoforms of the PAC1 receptors from alternative splicing in domains corresponding to the N-terminal extracellular region (short variants) and the third cytoplasmic loop (Hip and/or Hop variants) that can potentially impact ligand binding and intracellular signaling, respectively (Figure 2). The various PACAP receptor subtypes are expressed in specific regions of the CNS (15,17,18) and the differential PAC1 receptor isoform transduction of Gαs and/or Gαq can variably engage adenylyl cyclase and phospholipase C, respectively, to activate signaling pathways resulting in enhanced calcium mobilization, membrane depolarization, action potential frequency, and neurotransmitter synthesis and release (16,19,20). These signaling mechanisms coupled with those following receptor internalization in signaling endosomes can also engage mitogen-activated protein kinase kinase/extracellular signal-regulated

ISSN: 0006-3223

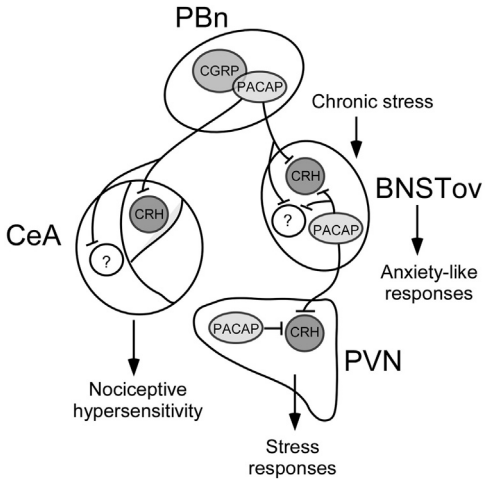

Figure 1. Schematic of proposed pituitary adenylate cyclase activating polypeptide (PACAP)–corticotropin-releasing hormone (CRH) interactions. Chronic stress increases endogenous PACAP expression and levels in the oval nucleus of the BNST (BNSTov), which may impact local CRH function to facilitate anxiety-related behaviors and produce long distance effects in the hypothalamic paraventricular nucleus (PVN) to mediate stress responses (54,60). Endogenous PVN PACAP signaling may also participate in chronic stress processes. Recently, PACAP and calcitonin gene related peptide (CGRP) have been shown to be co-localized in a large population of the lateral parabrachial nucleus (PBn) neurons that project not only to the BNSTov but also to the central nucleus of the amygdala (CeA), which may have significant roles in nociception hypersensitivity (62). In addition to CRH, the various PACAP-producing cells may also project to other yet unidentified neurons to affect behavior and hormonal stress responses.

kinase and phosphatidylinositol 3-kinase/Akt pathways, which appear important for trophic signaling during neurodevelopment, survival, repair, and regeneration following injury and neuroplasticity following physiological challenges (21). These trophic responses are further amplified by PACAP/PAC1 receptor abilities to enhance expression of other growth factor mechanisms including BDNF and tropomyosin receptor kinase B (22–24). While the neurotrophic and neuroplasticity functions of PACAP/PAC1 receptor signaling are important attributes under physiological adversities, the same mechanisms may participate in the development of pathological anxiety states associated with stressor exposure. Stressor exposure has been shown to enhance indices of neuroplasticity in anxiety-associated brain regions such as the BNST (25–28), and we have observed similar changes concurrent with increases in BNST PACAP signaling (May and Hammack, unpublished observation, 2010). But whether stress-induced BNST PACAP signaling drives the maladaptive neuroplasticity in the BNST leading to anxiety-related disorders remains to be investigated.

PACAP AND THE STRESS RESPONSE

PACAP and PACAP receptors have been identified in classical hypothalamic-pituitary-adrenal (HPA) and autonomic stress pathways. The roles of PACAP in stress have been reviewed recently and will only be discussed briefly here (7,8). PACAP-positive terminals can form synapses with hypothalamic PVN CRH-expressing neurons (29) and PACAP can

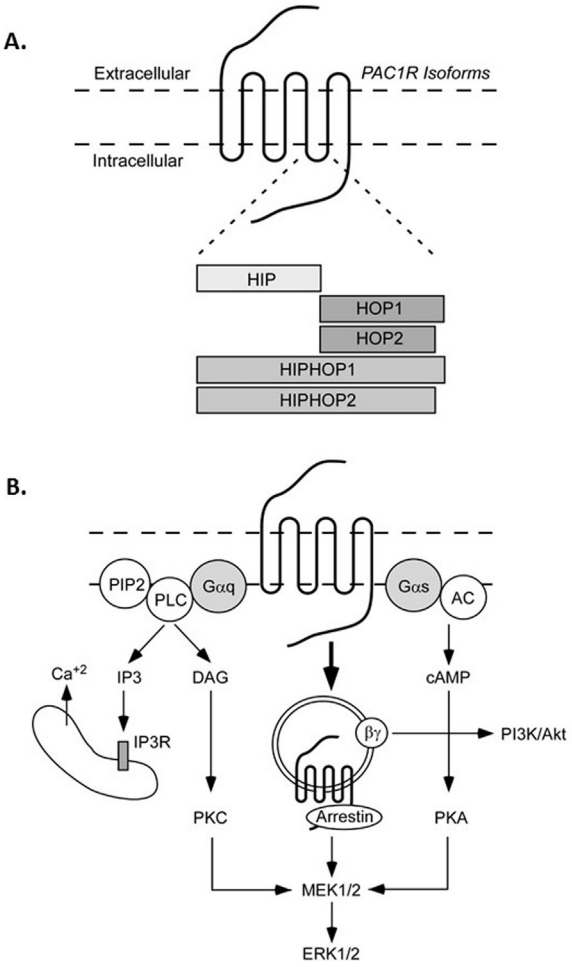

Figure 2. **(A)** G-protein-coupled PAC1 receptor isoforms within the third cytoplasmic loop. PAC1 receptors can be expressed in various isoforms depending on the absence or presence of two 84 base pair Hip and/or Hop cassettes encoding segments within the third cytoplasmic loop of the 7-transmembrane receptor (14–16,19–21). The PAC1 receptors can contain neither Hip nor Hop (null isoform), Hip, Hop1, Hop2 (shortened form of Hop1), HipHop1, and HipHop2; the principal forms in the central nervous system are the null and the Hop1 receptor isoforms. **(B)** PAC1 receptor signaling cascades. The various PAC1 receptor isoforms can be differentially coupled to Gαs and Gαq to initiate adenylate cyclase (AC) and phospholipase C (PLC) signaling cascades, respectively (16,19–21,23). In addition, as in other Class B G-protein-coupled receptors, the PAC1 receptor contains consensus Ser sequences in the intracellular cytoplasmic tail for high-affinity arrestin binding for endosome signaling following PAC1 receptor internalization. Arrestin molecules can serve as scaffolds for adaptor proteins and enzymes for extracellular signal-regulated kinase (ERK) pathway activation; in addition to downstream protein kinase A (PKA)/protein kinase C (PKC)-dependent signaling events, both PLC/PKC and AC/PKA pathways may also intersect with ERK signaling (19,96–98). The internalization of G-protein βγ subunits may result in other pathway activation including phosphatidylinositol 3-kinase (PI3K)/Akt (98). Ca^{+2}, calcium ion; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP3, inositol 1,4,5-triphosphate; MEK, mitogen-activated protein kinase kinase.

stimulate CRH production and secretion (30). In contrast to wild-type mice, PVN CRH messenger RNA (mRNA) is not upregulated following restraint in PACAP null animals (31), suggesting that PACAP signaling is upstream of CRH