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The functional heterogeneity of PACAP: Stress, learning, and pathology

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Abstract

Pituitary adenylate cyclase-activating peptide (PACAP) is a highly conserved and widely expressed neuropeptide that has emerged as a key regulator of multiple neural and behavioral processes. PACAP systems, including the various PACAP receptor subtypes, have been implicated in neural circuits of learning and memory, stress, emotion, feeding, and pain. Dysregulation within these PACAP systems may play key roles in the etiology of pathological states associated with these circuits, and PACAP function has been implicated in stress-related psychopathology, feeding and metabolic disorders, and migraine. Accordingly, central PACAP systems may represent important therapeutic targets; however, substantial heterogeneity in PACAP systems related to the distribution of multiple PACAP isoforms across multiple brain regions, as well as multiple receptor subtypes with several isoforms, signaling pathways, and brain distributions, provides both challenges and opportunities for the development of new clinically-relevant strategies to target the PACAP system in health and disease. Here we review the heterogeneity of central

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PACAP systems, as well as the data implicating PACAP systems in clinically-relevant behavioral processes, with a particular focus on the considerable evidence implicating a role of PACAP in stress responding and learning and memory. We also review data suggesting that there are sex differences in PACAP function and its interactions with sex hormones. Finally, we discuss both the challenges and promise of harnessing the PACAP system in the development of new therapeutic avenues and highlight PACAP systems for their critical role in health and disease.

Keywords

PACAP; learning; memory; stress; PAC1R

Introduction

Since its original isolation in 1989 from ovine hypothalamus, based on the ability to stimulate adenylate cyclase in cells of the anterior pituitary, pituitary adenylate cyclase-activating peptide (PACAP) has emerged as a critical regulator of neuronal activity in a variety of cell types and tissues. This neuropeptide exists either in a 27 or 38 amino acid form, based on alternate processing of the precursor protein prepro-PACAP (Arimura, 1998; Li *et al.*, 1999). While both PACAP-27 and PACAP-38 are widely distributed in the brain and body, PACAP-38 is the more abundant peptide in the central nervous system (CNS) (Arimura *et al.*, 1991; Hannibal *et al.*, 1995; Miyata *et al.*, 1990) although, as discussed below, both PACAP isoforms may regulate CNS activity, depending on the region (Gargiulo *et al.*, 2021).

A highly conserved neuropeptide, PACAP is recognized as a member of the glucagon/secretin/vasoactive intestinal peptide (VIP) family of peptides (Sherwood *et al.*, 2000; Vaudry *et al.*, 2009). Both PACAP and VIP bind with similar affinities to two common G-protein coupled receptors, VPAC1 and VPAC2, but PACAP also binds with high affinity to PACAP-specific PAC1 receptors. Multiple PAC1 isoforms may be expressed based on alternate splicing in the N-terminal extracellular region or in third cytoplasmic loop, and differences in these variants can potentially lead to differences both in ligand binding and the consequent signaling pathways activated, as discussed in more detail below. These high levels of heterogeneity in PACAP systems contribute to a diversity of functions and mechanisms by which PACAP may regulate CNS activity and behavior.

Due to the ubiquitous nature of the peptide, PACAP systems have been implicated in numerous physiological and behavioral functions. Hence, the development of multiple PACAP or PAC1 receptor null mice lines has demonstrated that they have hyperactive psychomotor behavior, poor fertility, circadian rhythm irregularities, and abnormalities in glucose/lipid homeostasis (Colwell *et al.*, 2003; Gray *et al.*, 2001; Hashimoto *et al.*, 2001; Jamen *et al.*, 2000a). Furthermore, PACAP null mice appear to have high early postnatal mortality, which may be related to acute thermosensitivity and apnea (Gray *et al.*, 2002). Importantly, PACAP, its related peptides, and its receptors are widely distributed throughout the nervous system, where high expression levels of PACAP and/or PACAP-associated receptors are observed in many brain regions associated with learning and

memory, addiction, stress responding, and emotional processing (Hashimoto *et al.*, 1996; Jaworski and Proctor, 2000; Zhang *et al.*, 2021). Expression levels of PACAP and the PAC1 receptor in the brain also suggest that the neuropeptide plays a role in regulating glutamatergic and GABAergic neurotransmission throughout the brain (Zhang *et al.*, 2021). Accordingly, PACAP null mice also demonstrate deficits in some learning tasks (Otto *et al.*, 2001a), reduced anxiety-like behavior (Ishihama *et al.*, 2010), and blunted stress responses (Lehmann *et al.*, 2013). Conversely, activation of central PACAP systems in mice and rats has been shown to produce the opposite effects on many of these same tasks (Donahue *et al.*, 2016; Hammack *et al.*, 2009; Iemolo *et al.*, 2016). Following these initial observations in PACAP null mice, over the next two decades several groups have clarified discrete central PACAP circuits that regulate these complex behavioral processes.

Convergence between the animal models and animal models and human clinical data has suggested that dysregulation in PACAP systems may play key roles across many behavioral processes that relate to several clinical disorders, suggesting that PACAP may represent an important target in their treatment. Moreover, substantial heterogeneity in PACAP systems may allow for the development of strategies that better target mechanisms of pathology while reducing off-target actions and subsequent side effects. In this review, we discuss the functional heterogeneity in PACAP systems, with a focus on psychopathology, and discuss how PACAP systems may be clinically targeted in the treatment of disorders related to these specific behavioral and physiological functions.

Heterogeneity of PACAP

The PACAP precursor, prepro-PACAP, is well-conserved across species, having been characterized in flies (Feany and Quinn, 1995), teleost fish (Parker *et al.*, 1993), mice (Okazaki *et al.*, 1995), rats (Ogi *et al.*, 1990), sheep (Kimura *et al.*, 1990), and humans (Ohkubo *et al.*, 1992), among others. Soma in the brain that contain PACAP are relatively restricted to select regions of the limbic system and brainstem, with the most prominent clustering of $PACAP^+$ cells being within the hypothalamus (Das *et al.*, 2007; Kivipelto *et al.*, 1992; Köves *et al.*, 1990; Nagashima *et al.*, 2022; Piggins *et al.*, 1996). Other $PACAP^+$ cells can be found in the midline thalamus (Gupta *et al.*, 2018; Skoglösa *et al.*, 1999), bed nucleus of the stria terminalis (BNST) (Köves *et al.*, 1991), hippocampal formation (Köves *et al.*, 1991; Murase *et al.*, 1995), prefrontal cortex (Köves *et al.*, 1991), areas of the brainstem (Das *et al.*, 2007; Légrádi *et al.*, 1994), and the cerebellum (Nielsen *et al.*, 1998). In addition to the brain regions that contain $PACAP^+$ soma (Hannibal, 2002; Köves *et al.*, 1991; Köves *et al.*, 1990; Légrádi *et al.*, 1994), $PACAP^+$ fibers and peptide levels have also been detected in the amygdala, nucleus accumbens, ventral tegmental area, locus coeruleus, dorsal raphe, lateral and medial septal nucleus, diagonal band, and central gray (Kozicz and Arimura, 2002; Masuo *et al.*, 1993; Piggins *et al.*, 1996). Thus, the PACAP system appears to be similar across species and to be particularly active in the limbic system.

One point of heterogeneity in the PACAP system is the diversity of the PACAP peptides. Through the different prohormone processing enzymes in the brain, SPC3 (also called PC1, PC3, or BDP) or SPC2 (also called PC2 or RPC2), prepro-PACAP can be processed into mature, bioactive PACAP-38 or PACAP-27, respectively (Li *et al.*, 1999). The prohormone

processing enzymes themselves have complementary distributions in the brain. For example, in the rat, SPC3 is found at high levels in the hippocampus, while SPC2 is at high levels in the paraventricular nucleus of the thalamus, and both SPC3 and SPC2 are at high levels in the paraventricular nucleus of the hypothalamus (Birch *et al.*, 1994). Notably, across the brain, the concentration of PACAP-38 is approximately eight times greater than that of PACAP-27 (Arimura *et al.*, 1991; Hannibal *et al.*, 1995; Miyata *et al.*, 1990). The existence of two peptide isoforms becomes meaningful considering their different binding affinities for their various receptors (discussed below), which is likely responsible for their divergent behavioral and physiological effects. For example, although PACAP-38 and PACAP-27 both suppress standard chow intake following systemic injection (Vu *et al.*, 2015). PACAP-38 but not PACAP-27 reduces time in the light chamber of a light-dark box following accumbal injection (Gargiulo *et al.*, 2021). PACAP-27 enhances the preovulatory luteinizing hormone surge while PACAP-38 instead prevents it following intracerebroventricular injection (Kántora *et al.*, 2000). This evidence further indicates the additional need to understand the roles of different subtypes of PACAP in behavioral functions.

While only recently gaining significant attention, sex-related differences in PACAP levels are another point of heterogeneity in the PACAP system (see Sex Differences in PACAP Function). Levels of PACAP in the hypothalamus of the rat have not been found to differ between males and females (Iwasa *et al.*, 2016; Kiss *et al.*, 2007; Mosca *et al.*, 2015); however, female mice and rats have been found to have greater gene expression of PACAP and more $PACAP^{+}$ cells than males in the paraventricular nucleus of the thalamus (Curtis *et al.*, 2023). Female rats also have higher mRNA levels of the PACAP type 1 receptor than males in the prefrontal cortex, and this fluctuates across the estrous cycle (Kirry *et al.*, 2018). These findings present a novel avenue for exploration of an already complex peptide system.

Taken together, PACAP has heterogeneity in distribution and function via the CNS. Understanding the precise mechanisms through which this neuropeptide regulates these functions could be key to unlocking its potential as a therapeutic target. Given that PACAP acts through various receptors subtypes, it is first important to understand its functions through these receptors.

Heterogeneity of the PACAP Receptors

Receptors for PACAP are class B1 G protein-coupled receptors (Lu *et al.*, 2022), and include not only the PACAP type 1 receptor (PAC1R), but also the PACAP type II receptors, VIP type 1 (VPAC1R) and VIP type 2 (VPAC2R) (Ishihara *et al.*, 1992; Lutz *et al.*, 1993; Pisegna and Wank, 1993). The binding affinity of PAC1 and VIP receptors for PACAP is roughly comparable ($K_d \approx 0.5$ nM vs $K_d \approx 1.0$ nM), as is the binding affinity of the VIP receptors for PACAP and VIP ($K_d \approx 1.0$ nM); however, the PAC1R binds PACAP with one thousand-fold greater affinity than VIP ($K_d \approx 0.5$ nM vs $K_d > 500$ nM) (Harmar *et al.*, 2012; Vaudry *et al.*, 2009; Zhou *et al.*, 2000). While PACAP-38 binds to PAC1R and VPAC2R with slightly higher affinity than PACAP-27, PACAP-27 binds to VPAC1R with slightly higher affinity than PACAP-38 (Ramos-Álvarez *et al.*, 2015). For all three receptors, stimulation is known to regulate the production of cyclic adenosine monophosphate (cAMP)

through G_s proteins, but it has also been shown to activate phospholipase C (PLC) and intracellular calcium mobilization through G_q and G_i proteins (Holighaus *et al.*, 2011; Lu *et al.*, 2022; MacKenzie *et al.*, 2001; Pisegna and Wank, 1993; Van Rampelbergh *et al.*, 1997). In addition, PACAP can promote PAC1 internalization independent of G-protein mechanisms (Parsons and May, 2019), and endosomal signaling can mediate some of the physiological (Johnson *et al.*, 2020b; Parsons and May, 2019) and behavioral (Missig *et al.*, 2014) consequences of PAC1 activation, particularly those that may be long-lasting. PAC1 signaling can be associated with the long-lasting activation of extracellular-signal regulated kinase (ERK)1/2 signaling, which is particularly dependent on PAC1 interactions with β-arrestin2, although interactions between multiple β-arrestin isoforms and PAC1 receptors may help to regulate PAC1 signaling (Shintani *et al.*, 2018). Moreover, these effects of PAC1 signaling may also regulate surface expression of other receptors subtypes, such as 5-HT2A receptors (Hayata-Takano *et al.*, 2021). This means that PACAP receptor binding can induce several different types of intracellular signaling, which may be differentiated in a multitude of cellular actions and with different temporal profiles.

Compared to VPAC1R and VPAC2R, PAC1R is more widely and densely expressed in the brain (Basille *et al.*, 2000). Gene expression for the PAC1 receptor can be found in the hypothalamus, midline thalamus, BNST, hippocampus, cingulate cortex, cerebellum, amygdala, nucleus accumbens, locus coeruleus, dorsal raphe, lateral septal nucleus, and central gray (Hashimoto *et al.*, 2006; Shioda *et al.*, 1997), largely the same regions where PACAP fibers have been detected. These PAC1Rs are predominantly, but not exclusively, postsynaptic (Vaudry *et al.*, 2009). The VPAC1Rs and VPAC2Rs overlap in their distribution with the PAC1Rs; gene expression and receptor binding for VPAC1R is found in the hypothalamus, BNST, hippocampus, cortex, cerebellum, and amygdala, and VPAC2R is additionally found in the thalamus, nucleus accumbens, caudate-putamen, and lateral septal nucleus (Joo *et al.*, 2004; Vertongen *et al.*, 1997). PAC1R binding may induce opposing behavioral effects to those of VPAC1R and VPAC2R binding (Rudecki and Gray, 2016). The overlap in expression between the different receptor types may allow for tighter regulation of behavioral effects, based on the timing and level of PACAP release.

In addition to the three receptors for PACAP, another point of heterogeneity is variants of these receptors, which arise from alternative splicing of the genes. In the rat, most of the differences in the PAC1R occur in the third intracellular loop, and are characterized by the absence (null variant) or presence of either one or two different insertions at the C-terminal end of the loop, which are 28 amino acid cassettes (hip or hop1 variant) or a 27 amino acid cassette (hop2 variant), that can be included together to form hiphop (Holighaus *et al.*, 2011; Vaudry *et al.*, 2009). In the mouse, both the null (short) and hop variants of the PAC1R have been identified (https://www.ncbi.nlm.nih.gov/gene/11517). While all variants of the PAC1R are G_s-coupled, the null and hop1 variants are also strongly G_q coupled (Holighaus *et al.*, 2011), and the presence of the hip cassette impairs stimulation of cAMP and abolishes stimulation of phospholipase C (Zhou *et al.*, 2000). Thus, PACAP can also act at any of several receptor variants, contributing to the heterogeneity of signaling and possible functional consequences of PACAP receptor binding. Next, we explore the mechanisms through which PACAP regulates functional outcomes associated with stress and aversive learning.

PACAP Regulates Stress Signaling Pathways

Circulating throughout the brain and periphery, PACAP is well positioned to regulate both central and peripheral responses to stress. Following exposure to a stressor, the hypothalamic-pituitary-adrenal (HPA) axis initiates a cascade of neuroendocrine pathways that alter several physiological processes, including autonomic function and immune processes, to maintain homeostasis. Critically, PACAP exerts a major regulatory role in coordinating the acute and sustained activity of this HPA circuit; these functions have been thoroughly explored in a number of publications (Boucher *et al.*, 2021; Denes *et al.*, 2019; Hammack and May, 2015; Hashimoto *et al.*, 2011; King *et al.*, 2017; Lutfy and Shankar, 2019; Mustafa, 2013; Nussdorfer and Malendowicz, 1998; Stroth *et al.*, 2011a). Briefly, PACAP is necessary for the release of adrenocorticotropic hormone (ACTH), corticosterone (CORT), and corticotropic-releasing hormone (CRH) (Agarwal *et al.*, 2005; Lehmann *et al.*, 2013; Stroth and Eiden, 2010; Stroth *et al.*, 2011b; Tsukiyama *et al.*, 2011). Additionally, in PACAP-deficient mice, stress-induced activation of limbic brain regions is impaired, including the amygdala, BNST, hippocampus, paraventricular nucleus of the hypothalamus, dorsal raphe nucleus, and periaqueductal gray (Gaszner *et al.*, 2012; Kormos *et al.*, 2016). Thus, by controlling the release of stress hormones as well as the activation of stress-related brain regions, PACAP plays a major role in stimulating the stress response.

In addition to its role in initiating responses to stress and activating stress-related brain regions, PACAP critically modulates stress-induced behaviors. In the BNST, PACAP is necessary and sufficient for the induction of anxiety-related exploratory behavior and may also facilitate reward seeking behaviors, particularly in response to stress (Ferragud *et al.*, 2021; Hammack *et al.*, 2009; Jovanovic *et al.*, 2013; Maita *et al.*, 2022; Miles *et al.*, 2019; Miles *et al.*, 2018; Roman *et al.*, 2014). PACAP may also alter stress-related reward learning and drug seeking by altering activity of the nucleus accumbens and paraventricular nucleus of the thalamus (Curtis *et al.*, 2020; Gargiulo *et al.*, 2021; Pirino and Barson, 2021). In the amygdala, PACAP may have distinct functions when acting in different subnuclei. In the central amygdala, PACAP facilitates the encoding and consolidation of fear memories and enhances anxiety-like behaviors induced by footshock, restraint, pain, and social defeat stress (Iemolo *et al.*, 2016; Legradi *et al.*, 2007; Meloni *et al.*, 2019; Missig *et al.*, 2014; Seiglie *et al.*, 2022; Varodayan *et al.*, 2020). Conversely, while PACAP does not alter neuronal excitability of central amygdala neurons, PACAP potentiates neuronal signaling in the basolateral amygdala, where it also acts to modulate different aspects of fear memories, such as fear learning, fear memory consolidation, and fear extinction, in a PAC1-dependent manner (Andero *et al.*, 2014; Cho *et al.*, 2012; Rajbhandari *et al.*, 2021; Velasco et al., 2022). In the hippocampus, PACAP is also vital for regulating neuronal activity in response to stress. PACAP projections from hilar mossy cells to dentate gyrus granule cells potentiate excitatory activity and initiate secondary messenger signaling, and this modulation of hippocampal dentate gyrus activity may contribute to altered fear extinction (Ciranna and Cavallaro, 2003; Condro *et al.*, 2016; Johnson *et al.*, 2020a; Johnson *et al.*, 2020b; Kondo *et al.*, 1997; Macdonald *et al.*, 2005; Pecoraro *et al.*, 2017; Roberto and Brunelli, 2000). Finally, in the prefrontal cortex, PACAP, which is mainly expressed in glutamatergic pyramidal neurons, is necessary for cued fear learning, facilitates behavioral

despair and anxiety-like behaviors, and contributes to the sustained response to social defeat stress (Ago *et al.*, 2017; Kirry *et al.*, 2018; Lehmann *et al.*, 2013; Martelle *et al.*, 2021). Overall, PACAP is widely expressed throughout the brain and demonstrably regulates numerous behaviors in response to stress. These actions may functionally overlap in the brain, and reciprocal PACAPergic connections between these and other brain regions may strongly regulate stress-induced behaviors.

Finally, PACAP is a vital regulatory neuropeptide for stimulating the sympathetic nervous system. For instance, PACAP is widely expressed throughout the sympathoadrenomedullary system, such as in neurons along the brainstem, spinal cord, and in the adrenal glands (Das *et al.*, 2007; Farnham *et al.*, 2008; Holgert *et al.*, 1996; Kumar *et al.*, 2010; Nogi *et al.*, 1997). Expression of PAC1 is high in the locus coeruleus, a brain region critical for the fight-flight-freeze response and modulation of metabolic functions in the periphery in response to stress (Duesman *et al.*, 2022). Following psychological stress, PACAP plays a key role in the synthesis of adrenaline and the release of catecholamines from the adrenal glands (Stroth and Eiden, 2010; Tönshoff *et al.*, 1997). When PACAP is released into the sympathetic nervous system, it suppresses the parasympathetic nervous system, indicating the importance of the neuropeptide in activating an active stress response (Tanida *et al.*, 2010). PACAP can also stimulate sympathetic nervous system activity following exposure to several other stressors, including hypoglycemic stress and cold stress (Gray *et al.*, 2002; Hamelink *et al.*, 2002); additionally, it plays neuroprotective and anti-inflammatory roles in the brain and body in response to oxidative stress (see Horvath *et al.*, 2019 and Sadanandan *et al.*, 2021 for a more thorough review). Moreover, PACAP expression is high in parasympathetic pathways, including the vagal ganglion (Kupari *et al.*, 2019). To our knowledge, understanding the role of this neuropeptide in modulating stress pathways via parasympathetic modulation has not yet been conducted but warrants further studies. Thus, by coordinating signaling in the HPA axis, activating key brain regions, and stimulating the sympathetic nervous system, PACAP plays a critical role in activating and sustaining central and peripheral responses to stress and therefore may be a key target for clinical treatments of stress-related psychopathology.

PACAP Promotes Aversive Learning

In addition to regulating the behavioral and physiological responses to stressors, PACAP contributes to the long-term encoding of aversive experience in memory. Genetic deletion of PAC1R either globally or in the forebrain produces mild to severe impairments in contextual fear conditioning, an associative paradigm in which subjects learn to associate the spatial configuration of environmental cues with a footshock. In contrast, navigational learning in the Morris water maze and social transmission of food preference is unaffected by loss of PAC1R (Otto *et al.*, 2001a; Otto *et al.*, 2001b; Sauvage *et al.*, 2000). Mice with genetic deletion of the PACAP peptide also showed impaired contextual fear memory as well as deficits in novel object recognition (Takuma *et al.*, 2014). These studies implicate PACAP in aversive learning, and while the memory deficits in genetically modified mice are confounded somewhat by the role of PACAP in neural development and HPA axis regulation (Ishihama *et al.*, 2010; Takuma *et al.*, 2014; Hashimoto, 2006), direct manipulation of PACAP signaling in adult rats also supports a role for PACAP in aversive learning

and memory. Consolidation of contextual fear memory in males is impaired when the PAC1R antagonist, PACAP6–38, is injected i.c.v. or directly into the dorsal hippocampus or amygdala after training (Sacchetti *et al.*, 2001; Schmidt *et al.*, 2015). Conversely, consolidation is enhanced, or at high doses even impaired, when PACAP is injected in these regions (Meloni *et al.*, 2018; Meloni *et al.*, 2016; Schmidt *et al.*, 2015). In the prefrontal cortex, blocking endogenous PACAP signaling impairs the formation of trace fear memory, a form of cued fear learning dependent on episodic memory systems, while sparing working memory in a spatial alternation task (Kirry *et al.*, 2018). These effects are observed in females, but not males. In the amygdala, viral-mediated deletion of PAC1R in the medial intercalated cells, a region involved in the suppression of fear following extinction (Duvarci and Pare, 2014), results in increased fear generalization and impaired extinction in males but not females (Rajbhandari *et al.*, 2021). Females show a reduced asymptotic level of fear during acquisition. Collectively, these studies reveal that PACAP exerts sex- and region-specific modulation of fear-related memories, and may provide insight into the genetic link between PAC1R and post-traumatic stress disorder (PTSD) in women (Ressler *et al.*, 2011). The risk allele is associated with enhanced startle to threat-related cues in adults (Jovanovic *et al.*, 2013; Ressler *et al.*, 2011) and in children one year after conditioning Jovanovic *et al.*, 2020; Velasco *et al.*, 2022). Impaired fear and safety discrimination and altered hippocampal and amygdala reactivity in fear conditioning are also observed in women with the risk allele (Ressler et al., 2011; Stevens *et al.*, 2014).

The mechanisms by which PACAP promotes synaptic plasticity and long-term memory for aversive events may be region-specific. CREB-mediated gene transcription downstream of adenylate cyclase/cAMP signaling is necessary for the formation of long-term memories (Asok *et al.*, 2019; Kandel *et al.*, 2014), and PACAP is a potent activator of these signaling cascades. In the dentate gyrus, for example, PACAP-PAC1R signaling drives CREB-mediated transcription and promotes excitability of dentate gyrus granule cells (Johnson *et al.*, 2019; Johnson *et al.*, 2020a; Johnson *et al.*, 2020b). Mossy fiber long-term potentiation (LTP), a cellular correlate of learning and memory, is impaired in mice lacking PACAP or PAC1R (Matsuyama *et al.*, 2003; Otto *et al.*, 2001b). In the central nucleus of the amygdala, the expression of the plasticity-related protein Arc following fear conditioning is enhanced by central administration of PACAP (Meloni et al., 2018). Arc is a key regulator of synaptic plasticity and PACAP may modulate its expression via PKA signaling (Nikolaienko et al., 2018; Bloomer et al., 2008; Shepherd and Bear, 2011). Moreover, PACAP-mediated changes in AMPA and NMDA signaling in the hippocampus and amygdala promote long-lasting effects onsynaptic efficacy that may support the acquisition and extinction of fear memories (Ciranna and Cavallaro, 2003; Cho et al., 2012; Varodayan et al., 2019; Costa *et al.*, 2009; Condro *et al.*, 2016; Johnson *et al.*, 2020a; Johnson *et al.*, 2020b; Kondo *et al.*, 1997; Macdonald *et al.*, 2005; Pecoraro *et al.*, 2017; Roberto and Brunelli, 2000; Roberto *et al.*, 2001; Yaka *et al.*, 2003). The mechanisms by which PACAP contributes to plasticity and memory in cortex and other systems remains to be determined.

In summary, PACAP not only facilitates the central and peripheral response to environmental stressors, but also influences the long-lasting memory of stressful situations. Vulnerabilities in PACAP signaling may thus contribute to pathological fear in PTSD

through intersecting roles in aversive learning and stress signaling in response to traumatic events.

Sex Differences in PACAP Function

While many of the initial studies of PACAP expression and function were conducted in male animals, increasing awareness has been paid to the distinct biological activities of PACAP in females, as evidenced by a growing number of studies documenting sex-specific aspects of PACAP signaling and function. Perhaps one of the most well-known sex differences in PACAP function is its role in mediating susceptibility to PTSD in women, but not men. In 2011, Ressler and colleagues found that the PACAP pathway is implicated in human psychological stress responses in a sex-specific manner (Ressler *et al.*, 2011). In female but not male subjects, high PACAP-38 peptide blood levels significantly predicted PTSD symptoms. Moreover, a single nucleotide polymorphism (SNP) (rs2267735), which replaces a G allele with a C allele in a putative estrogen response element within the PAC1R gene, was significantly associated with PTSD symptoms and heightened physiological fear responses in females, but not males. These results have since been replicated in numerous other studies (Almli *et al.*, 2013; Lind *et al.*, 2017; Stevens *et al.*, 2014; Uddin *et al.*, 2013; Wang *et al.*, 2013). Follow-up investigation suggests that this SNP may alter the reactivity of PACAP-PAC1R signaling in response to circulating levels of estrogen, leading to impaired fear and stress responses in female, but not male individuals (Ramikie and Ressler, 2016; Velasco *et al.*, 2022).

The interactions of PACAP with estrogen have also been documented in independent investigations. For instance, in rodent models, estrogen may modulate the pro-anorectic effect of PACAP in the BNST (Kocho-Schellenberg *et al.*, 2014). Interestingly, when PACAP is infused into the BNST, prior exposure to chronic variable stress enhances the startle response in intact female but not male rats, indicating that gonadal hormone levels may play a role in altering PACAP-mediated responses to stress, particularly in the BNST (King *et al.*, 2017). Beyond the BNST, PACAP expression has been shown to differ in a number of stress-related brain and peripheral regions, such as the adrenal glands and superior cervical ganglia, and PACAP expression in the hypothalamus and brainstem is differentially altered by exposure to stress in a sexually dimorphic manner (Kiss *et al.*, 2007; Mosca *et al.*, 2015). Moreover, PACAP expression in the middle and posterior subregions of the PVT are at baseline higher in females than in males; this sexually dimorphic PACAP expression may have further implications for sex differences in addictive and affective behaviors (Curtis *et al.*, 2023). Thus, sex-specific differences in the PACAP system, both at baseline and in response to stress, likely have functional consequences that contribute to sex differences in behavior and disease.

Finally, PACAP has also been implicated in the regulation of the female reproductive system and during pregnancy (Koppan *et al.*, 2022). In the CNS, PACAP is strongly expressed in various hypothalamic nuclei, where it can influence the release of a number of hormones, including oxytocin, vasopressin, luteinizing hormone (LH), and follicle stimulating hormone (FSH) (Dow *et al.*, 1994; Jolivel *et al.*, 2009; Lutz-Bucher *et al.*, 1996; Murase *et al.*, 1995; Murase *et al.*, 1993; Nomura *et al.*, 1999; Palkovits *et al.*, 1995; Petersen *et al.*, 1996; Yon

et al., 2001). Interestingly, the effects of PACAP on gonadotropin release in female mice may vary depending on age, time of day, and phase of the estrous cycle (Heinzlmann *et al.*, 2008; Köves *et al.*, 1998; Moore *et al.*, 2005). In the periphery, PACAP is strongly expressed in the ovaries, uterus, and placenta where it has been suggested to contribute to follicular development, oogenesis, and vasodilation in the uterus and placenta (Barberi *et al.*, 2007; Gräs *et al.*, 1996; Gräs *et al.*, 2005; Lee *et al.*, 1999; Park *et al.*, 2001; Scaldaferri *et al.*, 2000; Steenstrup *et al.*, 1996; Vaccari *et al.*, 2006). When PACAP or PAC1R is genetically deleted, female mice exhibit reduced fertility, disrupted maternal behaviors, and, in some studies, delayed estrous cycles (Hashimoto *et al.*, 2006; Isaac and Sherwood, 2008; Jamen *et al.*, 2000b; Lajko *et al.*, 2018; Shintani *et al.*, 2002). In women, levels of PACAP in human follicular fluid may influence the success of egg retrieval during in vitro fertilization (IVF), further suggesting that PACAP contributes to the female reproductive system (Brubel *et al.*, 2011; Koppan *et al.*, 2012). Further investigation is necessary to elucidate the sex-specific expression, signaling, and functions of PACAP, particularly in clinical populations.

Clinical Relevance of PACAP/PAC1 Systems in Health and Disease

Due to its neuromodulatory role in regulating the stress response and aversive learning, vulnerabilities in PACAP signaling are implicated in a variety of disorders. The behavioral, autonomic, and immune functions of PACAP and its receptor systems provide numerous opportunities to develop novel therapeutic treatments for such disorders. Consistent with evidence implicating PACAP dysregulation in stress responding and emotional processing, in 2011 Ressler *et al.* reported that high blood levels of PACAP and a single nucleotide polymorphism (SNP) in the PAC1R gene are correlated with PTSD symptom severity, especially in women with PTSD (Ressler *et al.*, 2011). This is especially relevant, as women with the PTSD PAC1R risk genotype show an impairment in fear extinction (Velasco *et al.*, 2022). Methylation of the PAC1R gene is also associated with symptoms of PTSD in both men and women (Ressler *et al.*, 2011). These associations in the 2011 study were subsequently tested again in several populations with mixed results (Almli *et al.*, 2013; Chang *et al.*, 2012; Jovanovic *et al.*, 2013; Uddin *et al.*, 2013; Wang *et al.*, 2013), and the SNP was located to a predicted estrogen response element (ERE) where it may regulate the binding of estradiol (E2) (Mercer *et al.*, 2016). Other reports have suggested that PACAP contributes to the pathology of schizophrenia, substance abuse disorder, major depressive disorder, and generalized anxiety disorder (Cooper *et al.*, 2013; Hashimoto *et al.*, 2007; Hashimoto *et al.*, 2010; Ishiguro *et al.*, 2001; Marquez *et al.*, 2009; Miles *et al.*, 2018; Ross *et al.*, 2020; Tseng *et al.*, 2019). Thus, the demonstrated role of PACAP in a number of psychiatric disorders suggests that targeting this neuropeptide may provide novel, effective interventions for both the treatment and prevention of such diseases.

As a member of the glucagon family of neuropeptides, PACAP has also been studied for its central control of digestive processes and feeding behaviors. Specifically, the role of PACAP in anorectic functions indicates that this neuropeptide could indirectly modulate processes in the CNS, by influencing the gut, and directly in the brain (Karpiesiuk and Palus, 2021; Reglodi *et al.*, 2018; Sekar *et al.*, 2017). Expression of PACAP and its receptors has previously been identified in the gastrointestinal tract (Sekar *et al.*, 2017), where the neuropeptide has been shown to: 1) regulate gastric secretion and emptying through

interactions with neuroendocrine cells (Håkanson *et al.*, 2001; Sandvik *et al.*, 2001), 2) modulate blood flow via PAC1 receptors (Naruse *et al.*, 1996), 3) stimulate cell proliferation and differentiation (Läuffer *et al.*, 2001; Oh *et al.*, 2005), and 4) regulate intestinal motility (Chang *et al.*, 1996; Chang *et al.*, 1998; Costa *et al.*, 2021; Cox, 1992; Fuchs *et al.*, 1996; Racké *et al.*, 1996). Centrally, PACAP administration has been shown to induce hypophagia and increase production of other hormones such as leptin, suggesting that it has a role in modulating energy homeostasis, appetite, and satiety (Iemolo *et al.*, 2015; Kocho-Schellenberg *et al.*, 2014; Nagashima *et al.*, 2022; Sekar *et al.*, 2017, Tomimoto *et al.*, 2008). Thus, novel therapies targeting PACAP may have a beneficial effect in treating disorders related to feeding or metabolism, such as anorexia, binge eating disorder, and diabetes (Nakata and Yada, 2004; Yada *et al.*, 2000).

In addition to anxiety and eating disorders, PACAP has been implicated in the pathogenesis of migraine and headache (Christensen *et al.*, 2022; Vécsei *et al.*, 2014). Infusion of PACAP-38 in human volunteers has been shown in several studies to induce migraine attacks (Amin *et al.*, 2014a; Ghanizada *et al.*, 2020; Vollesen *et al.*, 2019; Wienholtz *et al.*, 2021). While the mechanism of this effect is not fully determined, it is hypothesized that the role of PACAP in mediating vasodilation contributes to the onset of pain. Indeed, PACAP receptors are expressed throughout meningeal and arteries (Chan *et al.*, 2011; Knutsson and Edvinsson, 2002), and administration of a vasoconstrictor prior to PACAP-38 infusion reduces the probability of migraine onset (Amin *et al.*, 2013). Additionally, magnetic resonance angiography imaging indicates that there is significant vasodilation of the medial meningeal artery shortly after infusion and prior to the onset of migraine attack (Amin *et al.*, 2012; Amin *et al.*, 2014b; Ghanizada *et al.*, 2019). Therefore, because of its proposed role in headache pathophysiology, therapies targeting PACAP or its receptors may have a profoundly therapeutic role for preventing or treating headache and migraine pathologies. Regarding biomarker development targeting the PACAPergic system, a phase 2 randomized controlled trial for migraine using an antibody against the PAC1 R did not yield positive benefits (Ashina *et al.*, 2021). For neuropathic pain, a PAC1R antagonist has also been developed but is still undergoing further testing (Martin *et al.*, 2005; Takasaki *et al.*, 2020; Takasaki *et al.*, 2018).

Despite the strong therapeutic potential for targeting the PACAP system to better treat and prevent a variety of diseases, there are currently no available PACAP-based therapies. Although the parallel behavioral and physiological functions of PACAP make it an ideal candidate for modulating a range of diseases, it can also complicate the development of PACAPergic systemic therapeutics. Thus, developing a more complete and nuanced understanding of the structures and functions of PACAP as well as its receptors is critical for advancing drug development.

Challenges of Harnessing the PACAP System for Developing Therapeutics

Given the heterogeneity of the PACAP system, both in terms of its functional effects and its signaling profile, there are significant challenges for harnessing this system with pharmacotherapeutics. Thanks to recent advances in cryo-electron microscopy, however, there are now models of the PAC1R, VPAC1R, and VPAC2R that are of sufficient quality

to allow for drug discovery (Kobayashi *et al.*, 2020; Langer *et al.*, 2022; Liang *et al.*, 2020; Wang *et al.*, 2020, Xu *et al.*, 2022). Ligands can now be developed that are receptor-selective. Biased ligands can be developed that favor specific confirmations of the receptors, to activate only some of the signaling pathways (Langer *et al.*, 2022; Martin *et al.*, 2005; Takasaki *et al.*, 2020; Takasaki *et al.*, 2018). Ligands can also be developed to favor specific receptor splice variants, which each have their own signaling properties. One challenge will be to target specific receptors or splice variants in specific brain regions or networks, to accomplish the therapeutic goal with minimal off-target effects. This will require comprehensive mapping of the receptors and receptor variants, which can now be accomplished through whole brain tissue mapping. Although significant resources across multiple laboratories are needed to accomplish this, the field now has the capabilities to finely delineate these aspects of the PACAP system, allowing for incredibly precise manipulation of a highly pleiotropic system.

As consistently demonstrated, PACAP is an important regulatory neuropeptide for modulating the brain and body at the molecular, cellular, systems, and behavioral level. However, important questions remain that will need careful study and experimentation. While PACAP is highly conserved, it remains to be seen whether the expression and functions of PACAP are similar or divergent in different species; this consideration will be necessary for developing PACAP-based therapeutics to treat stress-related disorders. Determining the main points of synthesis and release of PACAP in the central and peripheral nervous system will also be important for investigating how PACAP may be targeted for disease intervention in a global or local manner. Further investigation is also needed to examine the temporal resolution of PACAP circulation and degradation. For instance, pharmacological agents either prolonging or accelerating the synthesis and/or degradation of PACAP could be viable lead targets for developing PACAP-related therapeutic agents. Finally, although PACAP is certainly a critical neuropeptide in the brain and body, its interactions with other neuropeptides and neurotransmitters must also be considered. Thus, determining how PACAP interacts with these other neuroactive agents will provide a more complete and nuanced understanding of the neuropeptide.

Conclusion

In sum, PACAP exerts diverse and critical functions in mediating a variety of central and peripheral processes. The versatility of the neuropeptide creates promising avenues for developing novel therapeutics for a number of disease conditions, including affective, fear, eating, energy metabolism, and pain disorders. However, the pleiotropic nature of PACAP signaling also introduces challenges for developing specific and effective therapeutics. Therefore, further study and investment in the basic and translational potential of PACAP and PACAPergic interventions is necessary to enhance our understanding of the neuropeptide and improve ongoing efforts to improve health outcomes.

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Highlights

- The neuropeptide PACAP regulates many biological and behavioral processes
- Targeting PACAP could innovate treatment for a variety of disorders
- Heterogeneity in PACAP signaling poses challenges for therapeutic development
- Nonetheless, harnessing the PACAP system may be a powerful strategy against disease

Table 1.

Clinical relevance of PACAP/PAC1 in disease.

Disease Indication	Species	Reference
Psychiatric Disorders		
Post-traumatic stress disorder	Human	Ressler *et al.*, 2011
	Rat	
Post-traumatic stress disorder	Human	Chang *et al.*, 2012
Post-traumatic stress disorder	Human	Jonanovic *et al.*, 2012
Post-traumatic stress disorder	Human	Uddin *et al.*, 2013
Major depressive disorder		
Post-traumatic stress disorder	Human	Wang *et al.*, 2013
Post-traumatic stress disorder	Human	Almli *et al.*, 2014
Post-traumatic stress disorder	Mouse	Mercer *et al.*, 2016
General anxiety disorder	Human	Cooper *et al.*, 2013
General anxiety disorder	Human	Ross *et al.*, 2020
Major depressive disorder	Human	Hashimoto *et al.*, 2010
Schizophrenia	Human	Hashimoto *et al.*, 2007
	Mouse	
Schizophrenia	Human	Ishiguro *et al.*, 2001
Bipolar disorder		
Substance abuse disorder	Rat	Miles *et al.*, 2018
Substance abuse disorder	Mouse	Tseng *et al.*, 2019
Substance abuse disorder	Mouse	Marquez *et al.*, 2009
Feeding and Energy Metabolism		
Anorexia	Rat	Iemolo *et al.*, 2015
Anorexia	Rat	Kocho-Schellenberg *et al.*, 2014
Anorexia	Mouse	Nagashima *et al.*, 2022
Type 2 diabetes		
Glucose intolerance	Rat	Yada *et al.*, 2000
	Mouse	
Obesity	Mouse	Tomimoto *et al.*, 2008
Pain		
Migraine	Human	Amin, *et al.*, 2014
Headache	Human	Ghanizada *et al.*, 2020
Migraine	Human	Ghanizada *et al.*, 2020
Migraine	Human	Vollesen *et al.*, 2019
Migraine	Human	Wienholtz *et al.*, 2021
Headache	Human	Amin *et al.*, 2012
Migraine	Human	Ashina *et al.*, 2021
Neuropathic pain	Mouse	Takasaki *et al.*, 2020

Disease Indication	Species	Reference
Inflammatory pain	Mouse	Takasaki *et al.*, 2019
Reproductive Disorders		
Decreased fertility	Mouse	Isaac & Sherwood, 2008
Decreased fertility	Mouse	Jamen *et al.*, 2000
Decreased fertility	Mouse	Shintani *et al.*, 2002