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New perspectives on vasoactive intestinal polypeptide as a widespread modulator of social behavior

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In terms of reproductive and social functions, vasoactive intestinal polypeptide (VIP) is best known as a major regulator of prolactin secretion in vertebrates and hence, as an essential contributor to parental care. However, VIP and its cognate VPAC receptors are distributed throughout the social behavior network in the brain, suggesting that VIP circuits may play important roles in a variety of behaviors. With the exception of VIP neuronal populations in the suprachiasmatic nucleus and tuberal hypothalamus (which regulate circadian rhythms and prolactin secretion, respectively), we have known very little about the functional properties of VIP circuits until recently. The present review highlights new roles for VIP signaling in avian social behaviors such as affiliation, gregariousness, pair bonding and aggression, and discusses recent advances in VIP's role as a regulator of biological rhythms, including the potential timing of ovulation, photoperiodic response and seasonal migration.

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Introduction

Vasoactive intestinal polypeptide (VIP) is a neuropeptide that is produced and released by numerous hypothalamic and extrahypothalamic cell groups and is perhaps best known as a major releasing factor of prolactin (PRL) from the pituitary in both birds [1] and mammals [2]. Because PRL regulates many reproductive and parental behaviors, such as egg incubation in bantam hens and turkeys [3,4], parental regurgitation and feeding in ring doves [5], lactation in mammals [6] and chick-rearing in native Thai hens [7], VIP has been assumed to play an important role in reproductive behaviors. Indeed, VIP-immunization blocks VIP-induced increases in plasma PRL levels, reducing nesting activity in turkeys [3] and increasing nest desertion in incubating bantam hens [4]. This immunization can be either passive, through injections of anti-chicken VIP serum [4], or active, whereby synthetic chicken VIP is conjugated to keyhole limpet hemocyanin (KLH) for injections [8]. In the latter case, KLH serves as a carrier protein for VIP that enables a robust immune response in the form of antibody production. Furthermore, changes in VIP within the portal blood, as well as VIP expression and immunoreactivity in hypothalamic regions, such as the infundibular nucleus (INF) and median eminence, closely mirror changes in plasma PRL levels across the reproductive cycle and different stages of parental care [7,9–11]. Interestingly, VIP's stimulation of PRL release from the pituitary in turkeys appears to be regulated via dopamine (DA) and its receptors [12,13], and changes in hypothalamic VIP are associated with changes in tyrosine hydroxylase-immunolabeling during incubation and nest deprivation in native Thai hens [14], suggesting that DA may modulate the VIP/PRL signaling cascade in certain avian species.

VIP's other well-known role is as a regulator of circadian rhythms in mammals [15,16•], mediated by GABAergic cells that contain VIP within the ventral core of the suprachiasmatic nucleus (SCN), the brain's main pacemaker nucleus. These core cells are retinorecipient cells that sense and respond to light [17] and mediate the phase shifting of activity rhythms [18,19]. VIP's effects can be mediated by VPAC receptors ($VPAC_1$ and $VPAC_2$), which bind both VIP and pituitary adenylate cyclase activating peptide (PCAP) [20]. However, PCAP also acts through the PACAP receptor, PAC_1, and binds to this receptor with high affinity, as compared to VIP, which binds PAC_1 with low affinity [20,21]. In animals lacking VIP or $VPAC_2$ (one of the VIP receptors), circadian rhythms of rest/activity are disrupted and the circadian system shows deficits in response to photic stimuli [22–24]. In tissue slices lacking the $VPAC_2$ receptor gene, both molecular timekeeping within individual SCN cells and spontaneous synchronization between SCN cells, is lost [25]. Thus, VIP signaling plays very important roles in the generation, maintenance and synchronization of circadian rhythms (for reviews see [15,16•]) and is likely at the top of a hierarchy of paracrine signals that control SCN molecular pacemaking [26•].

In addition to the hypothalamic INF and SCN, VIP elements (i.e. cells, fibers and receptors) are present in virtually every brain area that is known to be important for social behavior [27–30], including core nodes of the brain's 'social behavior network' [31,32], which include

the preoptic area (POA), anterior hypothalamus (AH), ventromedial hypothalamus (VMH), medial extended amygdala (medial amygdala, MeA, and medial bed nucleus of the stria terminalis, BSTm), midbrain central gray, ventral tegmental area (VTA) and lateral septum (LS). However, until recently, VIP's role in the social behaviors affiliated with this network remained largely unexplored. In the present review, we highlight research conducted within the last 3 years that describes new roles for VIP signaling in avian social behaviors such as aggression, affiliation, gregariousness, pair bonding and nesting, as well as recent advances in VIP's role as a regulator of reproductive and seasonal rhythms in both mammals and birds.

The role of VIP in grouping behavior, affiliation and pair bonding

Cross-species comparisons of VIP circuitry provided the first insight that VIP signaling may modulate grouping preferences and affiliative behavior in birds. VPAC receptors are found at higher densities within the subpallial LS and BSTm of year-round gregarious finch species relative to territorial species [27] and VIP innervation of the BSTm and PVN is greater in sparrow species that flock during the winter compared to species that do not winter flock [33••].

Given these links of increased VIP elements to flocking, and the well documented role of the BSTm and LS in grouping behavior and social affiliation, particularly with regards to nonapeptide circuitry [34], we hypothesized that activation of VPAC receptors promotes social contact and preference for larger groups, as well as pair bonding in the monogamous and highly gregarious zebra finch (*Taeniopygia guttata*). Indeed, central antagonism of VPAC receptors using a selective VPAC receptor antagonist (neurotensin6-11-mouseVIP7-28) that is known to block VIP stimulation of cyclic AMP production in chick brain slices without blocking PAC1 receptors [35], significantly impacts many affiliative behaviors (Figure 1). When exposed to a group choice apparatus that allows zebra finches to affiliate with either 2 or 10 unfamiliar conspecifics (Figure 1a), VPAC antagonism significantly decreases the amount of time subjects spend in social contact with either group, compared to control infusions, but only in the first trial when animals are tested in a novel social environment (Figure 1b). The antagonist has no effect in the second trial (Figure 1b), in subsequent novel-familiar conspecific choice tests in the same apparatus or in behavioral tests of general anxiety, suggesting that endogenous VIP signaling specifically promotes social contact in response to contextual novelty [36••]. This finding complements studies in mice where reduction of VIP signaling *in utero* leads to deficits in social approach and sociability in adolescent and adult offspring [37,38].

VPAC receptor antagonism also impacts gregariousness in zebra finches, with sex-specific and site-specific effects [36••]. Intracerebroventricular (ICV) antagonist infusions tend to reduce gregariousness (i.e. preferences for the larger of two groups) in females but increase gregariousness in males (Figure 1c). Since we have not observed sex differences in VIP binding densities for the BSTm and subpallial LS [27], areas likely impacted by the ICV infusions, we speculate that the sex difference in gregariousness may arise from sex differences in VIP innervation and/or sex-specific VIP neuronal activation. Interestingly, the sex-specific modulation of gregariousness by the nonapeptides [39–41] is now known to be associated with sex-specific activation of oxytocin (OT) or vasopressin (VP) cells following social stimuli exposure [42]. We further speculate that the sex-specific modulation of gregariousness by VIP could arise from an interaction with OT and/or VP, acting together to regulate behavior. Importantly, ICV infusions of VIP in rats increases plasma OT and VP [43], likely by means of the hypothalamo-neurohypophyseal system [44], suggesting that VIP may serve as a releasing factor for these hormones.

In contrast to ICV infusions, antagonism in the medial telencephalon reduces gregariousness in both sexes (Figure 1d). Together, these results suggest that gregariousness is modulated via VPAC activation in both the medial nidopallium and in one or more sites likely impacted by ICV infusions, such as the BSTm and LS.

Chronic VPAC receptor antagonism also significantly impairs zebra finches ability to pair bond. When tested in a colony environment (Figure 1e), zebra finches receiving chronic ICV infusions of the VPAC receptor antagonist took longer to form a pair bond [45•], were paired for fewer observation sessions [45•] and were less likely to be paired in the final observation session (Figure 1f). We hypothesize that VIP's sites of action likely include brain areas that are known to be important for the establishment of pair bonding in prairie voles [46], including the LS, VTA, nucleus accumbens (NAcc), and ventral pallidum. These proposed sites of VIP action are based on VIP's association with the mesolimbic dopamine system (for discussion, see [45•]), including a strong expression of VIP mRNA in the VTA [29], a high density of ^{125}I-VIP binding sites in the NAcc [27], and increased ^{125}I-VIP binding sites in the LS of gregarious zebra finches [27]. Based on this association of VIP elements with the mesolimbic dopamine system, we hypothesize that VIP and dopamine may interact to mediate behaviors characterized by incentive motivation. VIP may also interact with the nonapeptides as they are also found within the SBN and are known to modulate affiliative behavior and/or pair bonding [34,39,40,47].

VIP's role in modulating aggression

A role for VIP in aggressive behavior was first suggested by field and laboratory studies modulating central VIP in finches and sparrows in the late 1990s. Whereas VIP