REVIEW

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# Updating the picture of layer 2/3 VIP-expressing interneuron function in the mouse cerebral cortex

**Anna Posłuszny**

*Laboratory of Visual Neurobiology, Nencki Institute of Experimental Biology PAS, Warsaw, Poland,*
*Email: a.posluszny@nencki.edu.pl*

For years, interneurons expressing vasoactive intestinal peptide (VIP) interneurons and their function within the neocortex have been shrouded in mystery. Their relatively small size and minimal representation in the cortex have made investigation difficult. Due to their service role performed in co-operation with glia and blood vessels to supply energy during neuronal activation in the brain, the contribution of VIP interneurons to local neuronal circuit function was not appreciated. VIP interneurons in the neocortex account for roughly 12% of all interneurons. They have been described as a subgroup of the third largest population of 5-hydroxytryptamine 3a (5HT3a) receptor-expressing interneurons, non-overlapping with interneuron populations expressing parvalbumin (PV) or somatostatin (SST). However, it was recently shown that only half of VIP interneurons display a 5HT3a receptor response and a subset of VIP interneurons in visual cortex co-express SST. Over the last several years, due to new technical advancements, many facts have emerged relating to VIP interneuron phylogenetic origin, operational mechanisms within local circuits and functional significance. Some of these discoveries have dramatically shifted the perception of VIP interneurons. This review focuses on the function of the VIP interneurons residing in layer 2/3 of the mouse neocortex.

Key words: VIP-expressing interneurons, vasoactive intestinal peptide, VIP, GABAergic interneurons, inhibition, disinhibition, cortex, bipolar neurons

## INTRODUCTION

Vasoactive intestinal peptide (VIP)-expressing interneurons exhibit a combination of features that rather clearly distinguish them from other interneuron populations. Primarily, VIP interneurons exhibit a different distribution than parvalbumin-expressing (PV+) or somatostatin-expressing (SST+) cells, which are most abundant in layer 4 or in deep layers, respectively (Tremblay et al., 2016; Yavorska and Wehr, 2016). In contrast, VIP interneurons mainly occupy layer 2/3. In layer 1 they comprise only 10 % of neurons and below layer 2/3 their number progressively diminishes with depth (Prönneke et al., 2015; He et al., 2016). Regarding neuronal morphology, all large populations of interneurons (PV+ and SST+ groups) include cells of multipolar, transcolumnar and translaminar extent (Xu and Callaway, 2009; Lee et al., 2010; Prönneke et al., 2015; 2019; He et al., 2016; Tremblay et al., 2016; Zeng and Sanes, 2017; Feldmeyer et al., 2018). This is also the case for VIP interneurons; however, the great majority are bipolar or tripolar cells. VIP bi- or tripolar cells represent a variant of translaminar neuron and many exhibit the unique feature of an axonal arbor specifically spanning layer 2/3 and layer 5 (Prönneke et al., 2015; He et al., 2016; Feldmeyer et al., 2018; Prönneke et al., 2019). Additional unique features of VIP interneurons are described in detail in the subsequent sections.

## VASOACTIVE INTESTINAL PEPTIDE (VIP)

In the brain, VIP interneurons comprise greatly heterogeneous group in terms of electrophysiological activity and morphology, with their primary unifying



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feature being the expression and release of VIP. VIP was first isolated from the porcine duodenum (Said and Mutt, 1970; 1972). VIP neurons exist not only in the submucous plexus throughout the digestive tract but in many other organs, such as heart, lung, kidney and exocrine glands and within the urogenital tract and immune system, supporting many vegetative functions. VIP stimulates the process of vasodilation (Lundberg et al., 1980; Wilkins et al., 2004) and glycogenolysis and gluconeogenesis (Matsumura et al., 1977; Magistretti, 1990). Originally, it appeared that neurons were the sole source of VIP, but immune and endocrine cells were later reported to also express and secrete VIP (reviewed in: Delgado et al., 2004).

In the neuron, VIP is synthesized in the soma, exported to the axons and dendrites (Iversen et al., 2012) and synaptically released in a K+-sensitive, Ca2+-dependent mechanism (Giachetti et al., 1977; Emson et al., 1978). VIP belongs to a family of structurally related neuropeptides and hormones that includes secretin, glucagon, growth hormone releasing factor, glucagon-like peptide-1 and -2, helodermin, gastric inhibitory peptide and pituitary adenylate cyclase-activating polypeptide (PACAP) (Delgado and Ganea, 2013). Among these members, VIP shows particularly high homology to PACAP. Both peptides are ligands of the VIP/ PACAP membrane receptors VPAC1, VPAC2 and PAC1, which belong to the class II B G protein-coupled receptor family (Taylor and Pert, 1979; Martin et al., 1992; Harmar et al., 1998; Shen et al., 2013). Binding of VIP to the receptors initiates the adenylyl cyclase-dependent signaling pathway, resulting in an increase in cyclic adenosine monophosphate (cAMP) concentration and cAMP-dependent activation of transcription factors and/or ion transporters.

VIP and PACAP have retained high phylogenic sequence conservation from their obscure origin embedded in the rise of vertebrates or even slightly (on the scale of evolution) earlier – with the emergence of cephalochordates (Cardoso et al., 2010; Ng et al., 2012; Jékely, 2013). Interestingly, VIP's pleiotropic effects do not seem to have a simultaneous evolutionary origin. Phylogenetic analysis indicates that VIP and PACAP's signaling originated in the brain and during subsequent evolution spread alongside the central nervous system and to the periphery (Ng et al., 2012). It is worth noting that the early VPAC receptors present in agnathans acted through calcium signaling pathway, resembling a putative protostome G protein-coupled receptor associated with calcium homeostasis and stress response (Ng et al., 2012).

In the brain, VIP plays an important role in CNS development (Hill et al., 1994; Batista-Brito et al., 2017), exhibits neuroprotective and neurotrophic properties (Brenneman et al., 1998; 1999; Moody et al., 2003), contributes to communication between neurons, glia and blood vessels (Paspalas and Papadopoulos, 1998) and participates in circadian rhythm regulation in the suprachiasmatic nuclei (Hughes et al., 2011; Kudo et al., 2013; Blasiak et al., 2017; Liu et al., 2018). VIP stimulates carbohydrate metabolism that satisfies the rapid energy demands during neuronal activation in the brain (Magistretti et al., 1981; Sorg and Magistretti, 1992). Targeting the membranes of astrocytes, VIP stimulates glycogenolysis and gluconeogenesis (Sorg and Magistretti, 1992) along other neuromodulators from subcortical nuclei (Subbarao and Hertz, 1991; Chen et al., 1995). Some of the VIP interneurons produce perivascular neuronal endings (Martin et al., 1992; Chédotal et al., 1994). The most recent *in vivo* finding, however, indicates that different gamma aminobutyric acid (GABA)-ergic interneurons can contribute to neurovascular coupling in the cerebral cortex (Krawchuk et al., 2019). The power supply-function of VIP neurons is controlled with great spatial resolution by the restricted horizontal spread of their dendritic and axonal arbor (Magistretti, 1986; Karnani et al., 2016; Prönneke et al., 2015, 2019). All of the actions of VIP are exerted via subtypes of VIP receptors that are differentially distributed across astrocytes, microvessels and neuronal membranes (Martin et al., 1992; Joo et al., 2004).

The influence of VIP on the electrical activity of neurons in the cortex or hippocampus has been primarily investigated in rat (*in vivo* by extracellular single-unit recordings in the cortex – Phillis et al., 1978; Lamour et al., 1983; Ferron et al., 1985; Sessler et al. 1991; *in vitro* by extracellular or intracellular recordings in the hippocampus – Haas and Gähwiler, 1992; Cunha-Reis et al., 2004). *In vivo* iontophoretical or *in vitro* bath application of VIP was shown to produce non-uniform effects across targeted cortical neurons belonging to the same pyramidal cell class. These effects were excitatory, inhibitory, biphasic or none, depending on the particular neuron (Phillis et al., 1978; Lamour et al., 1983; Ferron et al., 1985). In the hippocampus, VIP action on pyramidal cells is also diverse (Haas and Gähwiler, 1992; Cunha-Reis et al., 2004). VIP signaling was shown to potentially influence the operation of local circuits in the hippocampus, mainly by supporting release of inhibition, exerted by other interneurons, on the pyramidal cells (Cunha-Reis et al., 2004). At least two subtypes of VIP cells selectively innervate other inhibitory interneurons in the hippocampus (Cunha-Reis et al., 2004). VIP enhances inhibition imposed on GABA-ergic interneurons by utilizing pre- and postsynaptic receptors (Cunha-Reis et al., 2004). Interestingly, a similar mechanism of pyramidal neuron disinhibition by VIP interneurons was described in cortical neuronal networks

and considered to be the primary mechanism of VIP interneuron action in cortical circuits (Fu et al., 2014; Lee et al., 2013; Pi et al., 2013). However, in these studies the action of VIP alone on postsynaptic neurons was not investigated. Though, enhancement of GABA-induced inhibition by VIP was described in the cortex (Sessler et al., 1991). It is worth noting that, in the majority of the target cortical neurons, VIP enhanced responses to GABA while having little effect on spontaneous firing activity (Sessler et al., 1991).

The effect of VIP on target neurons can differ when occurring simultaneously with the release of other neurotransmitters (Lamour et al., 1983; Ferron et al., 1985; Magistretti, 1986; Sessler et al., 1991). Inhibition produced by VIP was enhanced by norepinephrine (NE), even if NE was applied at doses that alone produced little or no change in spontaneous firing rate (Ferron et al., 1985; Magistretti, 1986). Interestingly, in neurons, in which VIP alone produced depolarization, NE reversed the VIP-excitatory effect, and the combination of VIP and NE resulted in inhibition even when NE was applied at a subthreshold dose (Ferron et al., 1985; Sessler et al., 1991). VIP mainly facilitates discharges of cortical neurons evoked by acetylcholine (ACh); however, it can also act antagonistically (Lamour et al., 1983; Sessler et al., 1991). VIP and NE interaction produces a particularly interesting effect on GABA- or ACh-induced responses in the target cortical neuron. VIP together with NE facilitates GABAergic inhibition, while the modulatory effects of VIP on ACh-induced excitation can be reversed or enhanced by NE, independent of the direction of the effect of VIP alone on the target neuron (Sessler et al., 1991). It is challenging to explain the complex effects produced by VIP and NE, though the underlying mechanism is likely related to the machinery of cAMP-pathways activated by the receptors for VIP and NE.

## HETEROGENEITY OF VIP INTERNEURONS

Studies attempting to define diverse interneuron populations in terms of their morphological and electrophysiological characteristic have provided evidence of significant VIP interneuron heterogeneity (Xu and Callaway, 2009; Miyoshi et al., 2010; Lee et al., 2010; Rudy et al., 2011; Prönneke et al., 2015; He et al., 2016; Tremblay et al., 2016; Prönneke et al., 2019) (Fig. 1, Table I). In these studies, differing methods were used for neuronal identification. VIP interneurons were studied in several transgenic mouse lines in which different selected subsets of neurons was visualized with genetically encoded fluorescent proteins (Xu and Callaway, 2009; Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015; 2019; He et al., 2016). The morphologies of VIP interneurons were reconstructed by staining biocytin-filled neurons (Xu and Callaway, 2009; Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015; 2019; He et al., 2016). The co-expression of other interneuron markers by VIP interneurons was assessed with immunochemistry (Chédotal et al., 1994; Gonchar et al., 2008; Xu and Callaway, 2009; Miyoshi et al., 2010; Xu et al., 2010) or genetic modification in VIP-Flp;CR-Cre and VIP-Flp;CCK-Cre;Ai65 mutants (He et al., 2016).

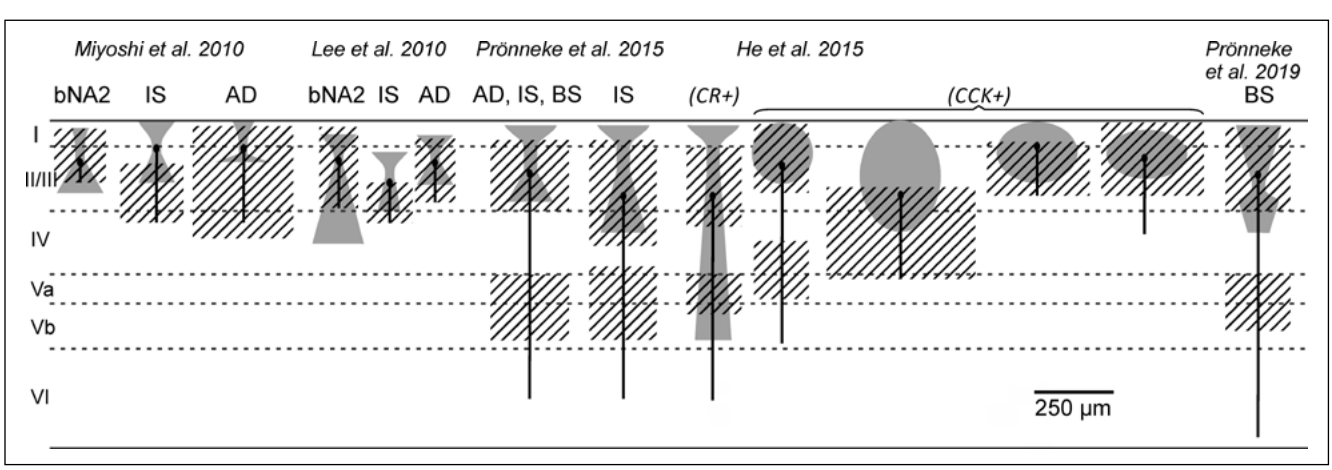


Fig. 1. A schematic drawing of the range of dendritic and axonal arbors in examples of individual VIP-expressing interneurons based on their reconstructions as presented in different studies (Prönneke et al. (2019) showed a superimposition of 12 vertically aligned somato-dendritic and axonal reconstructions). Gray areas of hyperbolic or oval shape represent bi-/tripolar or multipolar dendrite morphology, respectively. Hatched areas represent the highest axonal density and a black vertical line represents the deepest extent of the single axonal branch. The small black ovals represent the position of the neurons' somas. In many of the studies the type of firing activity of the morphologically identified neurons has been described: IS – irregular spiking, AD – adapting, BS – burst spiking, bNA2 – burst non-adapting type 2, while He et al. (2016) showed morphology reconstructions of VIP interneurons classified according to expression of calretinin (CR+ expressing) or cholecystokinin (CCK+ expressing).

Table I. Types of VIP-expressing (VIP+) interneurons distinguished on the basis of morphology and firing pattern. CR+, calretinin-expressing; CCK+, cholecystokinin-expressing; CGE, caudal ganglionic eminence.

| VIP INTERNEURON SUBTYPES | | MORPHOLOGY | |
|---|---|---|---|
| | | dendrite morphology:<br>bipolar/tripolar or modified bipolar, often tufted<br>Most commonly axonal density peaked in layer 2/3 or in layers 2/3 and 5a (but see Fig.1) | multipolar dendrite morphology |
| FIRING PATTERN | irregular-spiking (IS) | CR+<br>(CCK+ subpopulation found by He et al., 2016)<br><br>(22% of CGE-derived interneurons – Lee et al. 2010,<br>10% of CGE-derived interneurons – Miyoshi et al. 2010,<br>15% of VIP interneurons in layer 2/3 – Prönneke et al., 2015) | CCK+ or CR+<br>Localized mainly in the upper part of layer 2/3 but also in deep layers, presumably small basket cells<br>(Xu and Callaway, 2009; He et al., 2016) |
| | adapting (AD) | mainly CR-<br>(CR+ subpopulation found by He et al., 2016;<br>CCK+ subpopulation found by He et al., 2016)<br><br>(12% of CGE-derived interneurons – Lee et al., 2010,<br>25% of CGE-derived interneurons – Miyoshi et al., 2010,<br>68% of VIP interneurons in layer 2/3 – Prönneke et al., 2015) | |
| | burst spiking (BS) | Expression of interneuron markers other than VIP was not investigated.<br>Localized mainly in the upper part of layer 2/3. Found only in layer 2/3.<br><br>(12-20% of VIP interneurons in layer 2/3 – Prönneke et al., 2015; 2019) | |
| | burst non-adapting type 2 (bNA2)<br>(or high threshold bursting non-adapting by Prönneke et al., 2015) | CR+<br>(CCK+ subpopulation found by He et al., 2016)<br>Found only in layer 2/3.<br><br>(4% of CGE-derived interneurons – Lee et al., 2010; Miyoshi et al., 2010,<br>6% of VIP interneurons in layer 2/3 – Prönneke et al., 2015) | |

It appears that not all VIP neurons could be detected with each method, as diverse subpopulations emerged across different studies.

Using the fate mapping method, Miyoshi et al. (2010) and Lee et al. (2010) characterized neurons that originated from the caudal ganglionic eminence (CGE). This group of neurons comprises all interneurons other than PV and SST cells (which in turn have their origin in the medial ganglionic eminence). VIP interneurons account for nearly 35% of all CGE-derived interneurons (Miyoshi et al., 2010). Among them, the most numerous subtypes present in layer 2/3 are cells with bipolar/tripolar dendrite morphology, which display irregular-spiking (IS) or adapting (AD) electrophysiological responses (Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015). The percentage attributed to these two neuronal subtypes varies greatly among studies (Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015). It appears that AD bipolar/tripolar neurons are more numerous than IS neurons in cortical layer 2/3 (Miyoshi et al., 2010; Prönneke et al., 2015). The AD cells, exhibiting a mostly VIP+/calretinin negative (CR-) phenotype, cease firing before the end of a 500 ms current injection (Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015). The IS bipolar/tripolar neurons, which have been classified as VIP+/CR+, exhibit considerable interspike interval variability in response to moderate stimulation and pronounced spike height adaptation throughout suprathreshold current injection (Miyoshi et al., 2010; Lee et al., 2010; He et al., 2016). These neurons exhibit the closest resemblance to VIP interneurons, innervating other interneurons and minimally innervating pyramidal cells, described by Caputi et al. (2009).

It was estimated that approximately 20% of VIP interneurons in layer 2/3 exhibit burst spiking (BS) activity and bipolar morphology (Prönneke et al., 2019). Their localization is restricted to layer 2/3 with preference to the upper part of the layer. These neurons show an interesting firing pattern. They respond with burst at minimal to moderate current stimulation, but when depolarized to more than -50 mV, they switch to tonic activity (Prönneke et al., 2019). There is a lack of information on the interneuron markers, other than VIP, that BS neurons could express (Prönneke et al., 2019).

BS, IS or AD responses were also exhibited by VIP interneurons belonging to an interesting group with the distinctive feature of multipolar morphology and characteristic local axon branching around somata of excitatory neurons. These are small basket cells existing mainly in upper layer 2/3 but also in deep layers (Xu and Callaway, 2009; He et al., 2016). Some were classified as VIP+/CR+ and others as VIP+/cholecystokinin (CCK+) (Xu and Callaway, 2009; He et al., 2016).

A small subgroup of layer 2/3 VIP interneurons was found by fate mapping of CGE-derived neurons. The subgroup includes burst non-adapting type 2 (bNA2) interneurons generating at above, but not at, threshold bursts of two or three spikes followed, after a delay, by regular spiking. They have bipolar morphology and show VIP+/CR+ immunoreactivity (Lee et al., 2010; Miyoshi et al., 2010; He et al., 2016).

In the above-mentioned mouse studies (Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015) immunolabeling for choline acetyltransferase (ChAT) was not performed and only He et al. (2016) detected CCK; therefore, it is unclear whether some of the described subpopulations of VIP interneurons, especially those not expressing CR, also synthesize ACh or CCK. The existence of a subgroup of VIP+/ChAT+ interneurons has been confirmed (Chédotal et al., 1994; Xu et al., 2010).

Data is lacking on the electrophysiological characteristics of a significant group of VIP+/SST+ interneurons found in the visual cortex (Gonchar et al., 2008). This group has not been detected in another study investigating interneuron molecular markers in the visual cortex and other cortices (Xu et al., 2010). Therefore, some observed differences or, alternatively, a lack of differences among cortical areas could result from varied methodology. To what extent the composition of VIP interneuron subtypes varies between cortical areas remains to be fully elucidated.

## LONG-RANGE INPUTS TO VIP INTERNEURONS

In comparison to PV or SST interneuron populations, VIP cells are major recipients of long-range transmission as individual VIP neurons receive the largest number of inputs from thalamus and distal cortical areas (Lee et al., 2013; Wall et al., 2016). It appears that the quantity of long-range inputs is the most significant discriminatory factor between VIP interneurons and interneurons of other groups as each interneuron class received factory a similar proportion of thalamic *vs.* distal cortical inputs, about 40-50% *vs.* 40-50% of inputs per neuron, respectively (Wall et al., 2016). Direct neuromodulatory cholinergic synaptic transmission from the basal nucleus of Meynert is provided to each interneuron population at a similar low level within the overall input proportion per group (Fanselow et al., 2008; Alitto and Dan, 2012; Wall et al., 2016; Askew et al., 2019; Prönneke et al., 2019). Interneurons of PV+, SST+ and VIP+ populations receive NE inputs, while the effect of NE on target neurons is complicated and highly modulated (Polack et al., 2013; Aston-Jones and Waterhouse, 2016). VIP interneurons have been classified to as a subgroup of the third largest, after SST+ and PV+ populations, group of interneurons expressing 5HT3a receptors (Lee et al., 2010). Interestingly, it was found that only half of all layer 2/3 VIP neurons display 5HT3a receptor-mediated responses, but they are all activated via metabotropic 5HT2 receptors (Prönneke et al., 2019).

## LOCAL CONNECTIONS OF LAYER 2/3 VIP INTERNEURONS

Within the local circuit of layer 2/3, VIP interneurons are reciprocally connected with pyramidal cells, SST interneurons and PV interneurons (Caputi et al., 2009; Pi et al., 2013) (Fig. 2). Focusing on layer 2/3 VIP interneuron interactions with pyramidal cells, there is need to consider translaminar connections as they are excited by inputs from layer 2/3 pyramidal cells to a lesser degree than other local interneurons (Lee et al., 2013) (Fig. 2). Layer 2/3 VIP interneurons, at least these belonging to the subgroups of AD bi/tripolar cells or IS multipolar cells, receive considerable excitatory input from layer 4 and layer 5 (Xu and Callaway, 2009). Excitatory transmission from layer 5 is provided in a higher proportion to layer 2/3 VIP cells than to the SST neurons (Xu and Callaway, 2009). Recent findings have shown that pyramidal cells, and not inhibitory interneurons as was previously thought, comprise the most prominent targets for layer 2/3 VIP neurons (Wall et al., 2016; Zhou et al., 2017). Presumably, a considerable amount of VIP interneuron to pyramidal cell transmission targets layer 5 pyramidal cell apical dendrites that extend to superficial layers (Jiang et al., 2013; Zhou et al., 2017). This could explain the low connection ratio between VIP interneurons and local layer 2/3 pyramidal cells detected by paired recordings (Lee et al., 2013; Pi et al., 2013). Layer 2/3 VIP interneurons, together with VIP neurons residing within layer 1 and 4, strongly innervate also non-GABAergic cells in these layers (Zhou et al., 2017). In the layer 5, in contrast, axons of VIP interneurons target mainly dendrites of GABAergic neurons (GABAergic neurons in layer 5 receive also many perisomatic axonal endings form layer 5 VIP interneurons, Zhou et al., 2017) (Fig. 2).

Considering GABAergic translaminar inputs to layer 2/3 VIP interneurons, they mainly mirror translaminar inputs from excitatory cells. Therefore, layer 2/3 VIP interneurons, at least these belonging to the subgroups of AD bi/tripolar cells or IS multipolar cells, receive GABAergic transmission from layer

4 and 5 (Zhou et al., 2017). Additionally, IS multipolar cells are inhibited also by interneurons from layer 1 (Fig. 2).

There is considerable evidence that VIP interneurons within the local circuit of layer 2/3 provide strong inhibitory inputs to SST neurons (in the primary visual cortex – Pfeffer et al., 2013; Karnani et al., 2016; in the primary auditory cortex – Pi et al., 2013; and in the primary somatosensory cortex – Lee et al., 2013; Walker et al., 2016) acting through synapses that exhibit frequency-dependent facilitation (Walker et al., 2016). It has been proposed that this VIP to SST interneuron inhibition could be functionally engaged for information processing during active behavioral states (Lee et al., 2013; Pi et al., 2013; Fu et al., 2014). Putative circuit operation includes arousal-mediating neuromodulatory inputs from bottom-up projections to induce the VIP interneuron activation, which in turn, by way of SST interneuron inhibition, leads to the eventual release of pyramidal neurons from SST interneuron inhibitory influence. However, other studies that used a similar experimental paradigm with additional sensory (visual) conditions put forward another mechanism of pyramidal cell disinhibition – that SST interneurons remain active during VIP interneuron activation (Polack et al., 2013; Pakan et al., 2016; Dipoppa et al., 2018). These studies showed that neural circuit operation depended on the context and increase in pyramidal neu-

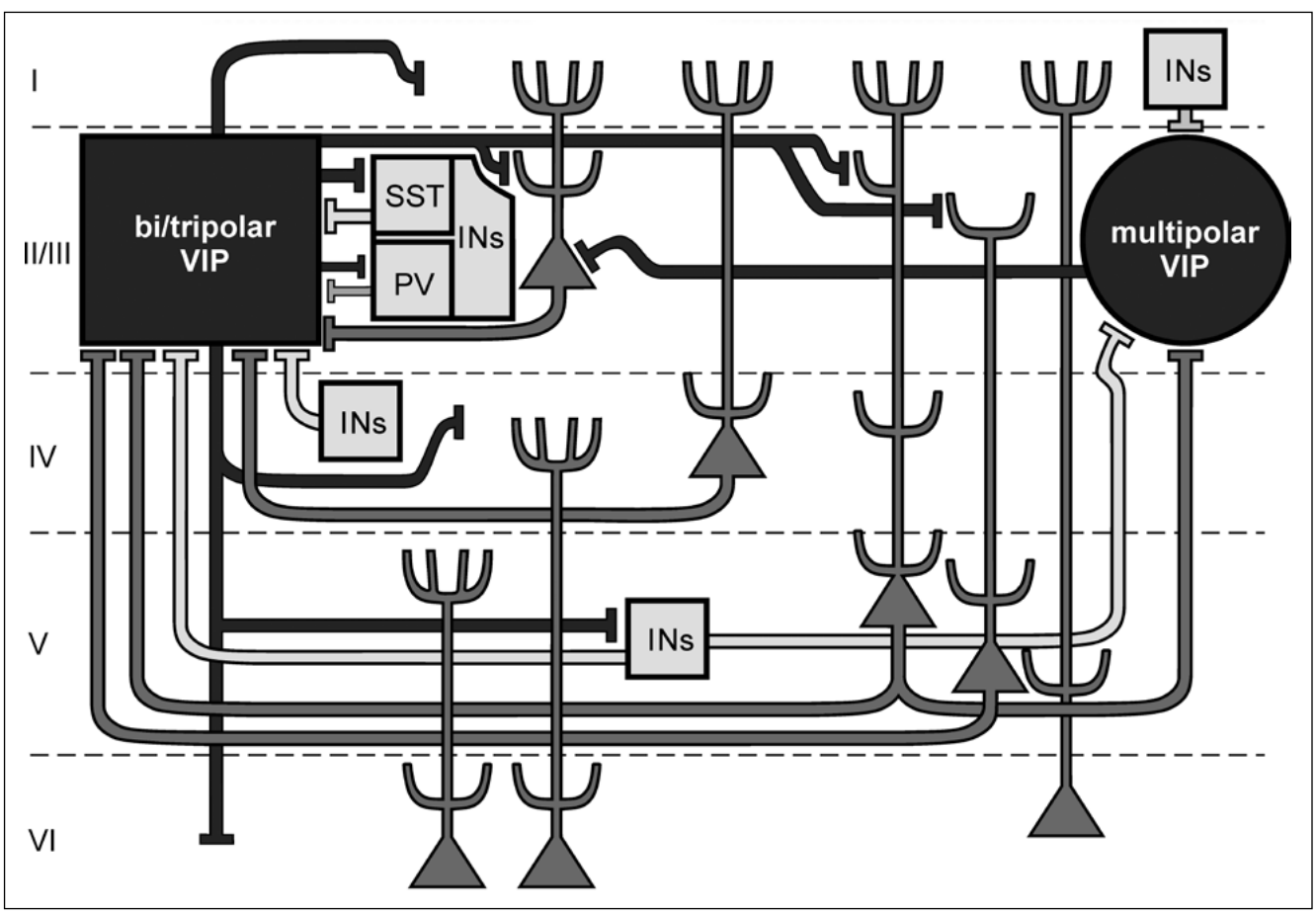


Fig. 2. Scheme of the primary cortical layer 2/3 VIP-expressing interneuron (VIP INs) connections, generally differentiable as two morphologically distinct groups: bipolar/tripolar type – innervating dendrites, or multipolar type – innervating perisomatic regions. Both groups include diverse types of neurons, varying in terms of electrophysiological properties, as well as the extents of their dendritic and axonal arbors (see Fig. 1). Therefore, not every input or output occurs for each neuron within the group. In the figure, the axonal endings of VIP INs extending to layer 1 and layer 4 are not assigned to a particular type of neuron but in these layers they primarily target dendrites of non-GABAergic cells (Zhou et al., 2017). The scheme of local inputs to layer 2/3 VIP INs is based on work by Xu and Callaway (2009). The illustrated inputs to bipolar/tripolar VIP INs of layer 2/3 are accurate for the fraction of cells displaying accommodating (adapting) spiking patterns of activity. The illustrated inputs to layer 2/3 multipolar VIP INs are accurate for the fraction of cells displaying irregular-spiking or burst-spiking patterns of activity (Xu and Callaway, 2009). Irregular-spiking VIP INs receive strong excitatory inputs from layers 2/3 and layer 5a and inhibitory inputs from layers 1, 2/3 and 5a, b (Xu and Callaway 2009). Excitatory and inhibitory inputs for burst-spiking VIP INs originate in layer 2/3 (Xu and Callaway, 2009). VIP – vasoactive intestinal peptide-expressing interneurons of bipolar, tripolar or multipolar dendritic arbors, SST – somatostatin-expressing interneurons, PV – parvalbumin-expressing interneurons, INs – interneurons.

ron activity during arousal was mediated by VIP interneurons only in some selected conditions. It seems plausible that, while important in some behavioral situations, VIP interneuron operation based on SST cell inhibition is not the major mechanism of their action within the local circuit. Another question concerns the types of VIP interneurons that inhibit SST cells. These are represented, at least in part, by a subtype of bipolar VIP+/CR+ neurons displaying IS activity (Caputi et al., 2009). However, this group does not appear to be the most numerous among VIP interneurons (Miyoshi et al., 2010; Lee et al., 2010; Prönneke et al., 2015). Other layer 2/3 VIP interneuron subtypes could also innervate SST interneurons, but that has not yet been established. Due to technical obstacles in isolating individual VIP interneuron subgroups, it is difficult to fully elucidate their connections and functional significance. Furthermore, within PV+ and SST+ interneuron cortical populations diverse subtypes of neurons have already been identified (Liguz-Lecznar et al., 2016; Urban-Ciecko and Barth, 2016; Yavorska and Wehr, 2016; Garcia-Junco-Clemente et al., 2019; Knoblich et al., 2019). They exhibit distinct functional relevance and, in many cases, an opposite pattern of activity during different behaviors (Garcia-Junco-Clemente et al., 2017; 2019; Knoblich et al., 2019). Many studies have reported heterogeneity in responses within interneuron populations, which could reflect the existence of different subtypes within them (Lee et al., 2013; Fu et al., 2014; Pakan et al., 2016; Khan et al., 2018; Yu et al., 2019). The connectivity between newly identified neuronal subtypes and the behavioral significance of their operation remains to be described.

PV interneurons, as compared to SST interneurons and pyramidal neurons, appear to be inhibited to a lesser degree by VIP interneurons (Lee et al., 2013; Pi et al., 2013). Therefore, considering the proposed disinhibitory mechanism initiated by VIP interneurons acting during periods of arousal, it should be noted that inhibition of SST interneurons by VIP neurons could in turn potentiate inhibition of pyramidal cells imposed by PV cells (Pfeffer et al., 2013; Yu et al., 2019). It is also worth noting that VIP neurons display a spontaneous spike rate comparable to that of PV cells, at least in the primary visual cortex (V1) and primary somatosensory cortex (S1) (Mesik et al., 2015; Yu et al., 2019). Although the majority of VIP neurons have spike shapes narrower than but resembling those of putative pyramidal cells, some VIP interneuron groups were also found that generated narrow spikes similar to PV cells (Mesik et al., 2015). It appears that under some conditions, VIP and PV interneurons could co-operate (Knoblich et al., 2019; Williams and Holtmaat, 2019; Yu et al., 2019).

## ROLE OF VIP INTERNEURONS IN INFORMATION PROCESSING WITHIN CORTICAL CIRCUITS

Based on the available data, a rather complicated picture emerges of VIP interneuron contribution to sensory information processing. The sensitivity of VIP interneurons for sensory inputs differs dramatically among cortices of diverse modalities. In V1, it was shown that the spontaneous spike rate of VIP interneurons was comparable to that of PV cells, while it was decreased in response to visual stimuli (Mesik et al., 2015). The feature selectivity of VIP interneurons in V1 was most comparable to that of broadly tuned PV interneurons (Kerlin et al., 2010; Mesik et al., 2015). In S1, similarly as in V1, VIP interneurons fired at a high spike rate spontaneously, but in response to specific stimulus (touch) they fired fewer action potentials or were suppressed (Yu et al., 2019). In contrast, the spontaneous spike rate of VIP interneurons in primary auditory cortex (A1) was significantly lower than that of PV cells, but they exhibited responses to sound that resembled the selectivity of narrowly tuned pyramidal cells, and they were even better tuned than pyramidal neurons for low sounds (Mesik et al., 2015).

On the other hand, VIP interneurons in S1 are strongly activated by projections from primary motor cortex during whisking (Gentet et al., 2012; Lee et al., 2013; Yu et al., 2019). The stimulating effect of motor inputs on VIP interneurons is well established also in V1 (Polack et al., 2013; Fu et al., 2014; Jackson et al., 2016; Pakan et al., 2016; Dipoppa et al., 2018). In contrast, activation of VIP interneurons in A1 during locomotion disrupts their sophisticated contribution to stimuli processing (Bigelow et al., 2019).

The image which emerge from data indicates that VIP interneurons are minimally engaged in the processing of the stimulus specific to visual and somatosensory cortex, and they are actually more excited during spontaneous activity than in response to stimuli (Mesik et al., 2015; Yu et al., 2019). Contrastingly, they strongly contribute to the selectivity of stimulus feature in the auditory cortex, as they are well-tuned for the sound of diverse frequencies and intensities (Bigelow et al., 2019). They display an opposite effect when activated by motion-mediating inputs. Then, they increase responses to visual and tactile stimuli and cease to improve auditory stimuli processing (Bigelow et al., 2019). This pattern of VIP interneuron involvement in stimuli processing suits their plausible functional priority, which is providing alertness in the awake animal. During stationary behavior, when the head can be lowered and eyes can be closed, auditory processing is

more effective at detecting signals of danger from the environment. In contrast, during movement, especially during flight response, information processing needs to shift its focus toward processing stimuli important for navigation.

It was found that VIP interneurons contribute to high cortical activation induced not only by locomotion but also to activation occurring during other behavioral states, including quiet immobility or anesthesia (Jackson et al., 2016). It is likely that the circuit effects of VIP interneurons require modulation of the other cortical units' activity by long-range inputs (Neske and Connors, 2016), but the issue requires further clarification.

A role for VIP neurons in learning has been implicated specifically in mediating bottom-up information relating to reinforcement, while punishment evoked stronger VIP neuron responses than reward (Pi et al., 2013). On the contrary, VIP interneurons in visual cortex did not appear to be directly involved in the learning of a visual discrimination task (Khan et al., 2018). The result, however, might reflect poor VIP interneuron selectivity *per se*, which appeared to be unaffected by learning (Khan et al., 2018). Moreover, it is also possible that learning-induced sharpening of feature selectivity could require suppression of VIP interneuron (Ibrahim et al., 2016). Regardless of the learning protocol, at some stage of the learning process, suppression of VIP interneurons could be crucial for acquisition of learning-dependent information (Mardinly et al., 2016).

## CONCLUSIONS

VIP interneurons, with their phylogenetic origin embedded in the brain, perform a set of functions related to neuronal activation in the neocortex that ranges from supplying neurons with energy to modulation of information processing during states of high cortical activity. In performing their specific roles in the cortical circuits, VIP interneurons primarily utilize a translaminar neuronal morphology that uniquely spans layers 2/3 and 5, which is responsible for the integration of top-down and bottom-up information. In the neocortex, they appear to be the "best-informed" neurons, relating to the global brain state as they receive and process, at a level incomparable to other neurons, numerous inputs from the other cortical areas and subcortical structures. The pattern of VIP interneuron involvement in stimuli processing indicates their plausible functional priority, which is providing alertness. VIP interneurons, a very heterogeneous group, remain broadly unexplored. The connections of particular VIP interneuron subtypes with other neuronal populations and their functional significance require further investigations.

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