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Neuronal pericellular baskets: neurotransmitter convergence and regulation of network excitability

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Abstract

A pericellular basket is a presynaptic configuration of numerous axonal boutons outlining a target neuron soma and its proximal dendrites. Recent studies show neurochemical diversity of pericellular baskets and suggest that neurotransmitter usage together with the dense, soma-proximal boutons may permit strong input effects on different time scales. Here we review the development, distribution, neurochemical phenotypes, and possible functions of pericellular baskets. As an example, we highlight pericellular baskets formed by projections of certain *Pet1/Fev* neurons of the serotonergic raphe nuclei. We propose that pericellular baskets represent convergence sites of competition or facilitation between neurotransmitter systems on downstream circuitry, especially in limbic brain regions, where pericellular baskets are widespread. Study of these baskets may enhance our understanding of monoamine regulation of memory, social behavior, and brain oscillations.

Keywords

Serotonin; *Pet1/Fev*; co-transmission; VGLUT3; pericellular basket; memory

Presynaptic pericellular baskets – what and where are they?

The strength and temporal dynamics of neuronal input are modulated by multiple factors. Among them is the spatial arrangement of presynaptic axonal boutons on the postsynaptic cell, i.e., the boutons' locations and densities. One particularly striking bouton arrangement comprises what is called a pericellular basket, a presynaptic organization of boutons from one or multiple axons that surround the postsynaptic cell body and proximal dendrites. This innervation is typically dense, such that the shape of the postsynaptic soma can be discerned from the basket itself, like climbing vines around the trunk and limbs of a tree [1,2]. Historically, this configuration has also been referred to as a pericellular nest or

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Declaration of Interests

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pericellular array [3–5]. Pericellular baskets are thought to confer privileged control over the targeted cell via the high number of boutons and their location proximal to the soma and axon hillock, potentially overriding effects of more distal inputs [6].

Pericellular baskets in the cerebellum, hippocampus, and cortex were originally described by Ramon y Cajal, and later determined to be GABAergic [7]. Since this foundational work, diverse neuron types have been reported to configure pericellular baskets at their axon termini. These include certain monoaminergic neuron subtypes [2,8], some neuropeptide-releasing neurons [4,9], some glutamatergic projection neurons [10], and cells themselves called basket cells found in the cerebellum [11], cerebral cortex, and hippocampus [12,13]. These basket-extending neurons have cell soma residing in regions such as the median raphe (MR) nucleus [1,8,10,14], cerebral cortex [15], hypothalamus [16], hippocampus [13], and cerebellum [11]. While basket cell interneurons project locally to excitatory principal cells [15], other basket-extending monoaminergic neurons send long-range projections to target primarily GABAergic cells [10,14,17]. The presence of pericellular baskets is phylogenetically widespread, being found in reptiles, songbirds, rodents, non-human primates, and humans [2,3,18–21]. Even with their prevalence across organisms and brain regions and their likely gate-keeper role in controlling target neuron activity, little is known about the development, electrophysiology, and specific functions of pericellular baskets.

In this article, we review pericellular baskets, focusing on those formed by projection neurons of the serotonergic brainstem raphe nuclei. We discuss pericellular baskets as sites of convergence of neurotransmitter systems, suggesting that their privileged control over postsynaptic neuron excitability is complex and may span different time scales if the different neurotransmitters signal ionotropically (e.g., “fast” glutamatergic signaling) versus metabotropically (e.g., “slow” serotonergic signaling). We consider functional roles for pericellular baskets, for example, in the regulation of target neuron activity in the hippocampus and septum, possibly shaping brain theta rhythm and memory formation. We close with a set of questions, intending to stimulate future advances in this exciting area.

Neurochemical and structural diversity of pericellular baskets

A diverse set of neurotransmitters have been detected singly or co-expressed in boutons comprising pericellular baskets. These include serotonin (5-hydroxytryptamine, 5-HT), dopamine, noradrenaline, acetylcholine, glutamate, gamma-amino-butyric acid (GABA), enkephalin (Met- and Leu-), substance P, somatostatin, neuropeptide Y (NPY), and cocaine- and amphetamine-regulated transcript (CART) peptide [2,4,14,22–25]. Precedent for co-transmission deploying glutamate has been reported in monoaminergic, cholinergic, and GABAergic neurons [26], perhaps applying to pericellular basket terminals as well.

Architectural features of pericellular baskets

Pericellular baskets, even of different neurotransmitter phenotypes, share certain cytoarchitectural features. Boutons are characteristically large, and typically 20–30 of them decorate the target soma [12,14]. The contained synapses are typically symmetric, as revealed in electron micrographs of septal and hippocampal pericellular baskets [27–30]. In these cases, the immunodetected neurotransmitters have included GABA, 5-HT, and/or

Met-Enkephalin. Collectively, these features predict inhibitory postsynaptic effects, albeit still to be discerned electrophysiologically in most cases. Smaller boutons in baskets have been found to deploy CART peptide and to harbor asymmetric synapses [22], suggesting postsynaptic excitation. Excitatory control also seems possible by some pericellular baskets using glutamate and/or 5-HT. These neurotransmitters may trigger excitatory postsynaptic receptors such as ionotropic and metabotropic glutamate receptors [26,31] or the excitatory ionotropic 5-HT receptor 3A (5-HT3aR) [32] and the metabotropic 5-HT receptors 2A [33,34] and 2C [35], as examples. Additionally, cultured 5-HT neurons have been found to release glutamate at asymmetric synapses [36], suggesting asymmetric synapses may be more common in cases of co-transmission of glutamate and serotonin.

Pericellular baskets as sites of neurotransmitter convergence

The degree to which neurochemically distinct pericellular baskets target the same soma is largely unknown. In the septum, different neurotransmitter systems form pericellular baskets in broadly similar distributions [1,2,4], raising the possibility that different basket systems interact by projecting to the same downstream target neurons or by axo-axonic synapses onto other baskets. A convergence-organization model suggests that different neurotransmitter systems may compete with each other or facilitate modulation of the targeted cell, either by affecting postsynaptic cellular processes or by inhibiting or exciting other basket terminals. Indeed, multiple neurochemically distinct fibers (serotonergic vs. non-serotonergic) have been observed as making baskets on the same septal cells [8,14], supporting the idea of basket convergence (Figure 1). An alternative possibility is that separate basket systems “tile” innervated regions, targeting largely distinct postsynaptic cells. A distributed, non-overlapping pattern of basket systems would suggest high target specificity for postsynaptic cell types, and possibly even repulsive or non-permissive environments underlying the development of basket stratification. In the septum, glutamatergic pericellular baskets (expressing vesicular glutamate transporter 3 [VGLUT3]) rarely overlap topographically with baskets immunopositive for parvalbumin (PV), tryptophan hydroxylase 2 (TPH2, the rate-limiting enzyme for 5-HT synthesis), calretinin, or choline acetyltransferase [2]. However, they do occasionally target the same somata as do separate, tyrosine hydroxylase^{+} (presumably dopaminergic) baskets [2] (Figure 1A). The extent of pericellular basket convergence may vary between different basket systems or as a function of region.

Pet1 neuronal subsystems form serotonergic and glutamatergic baskets

Brainstem raphe neurons defined molecularly by expression of *Pet1* (aka *Fev*) are referred to as *Pet1* neurons [37–40] and include a neuron subset that collectively forms pericellular baskets in the septum, hippocampus, and cerebral cortex [14]. *Pet1* encodes for a transcription factor master regulator of differentiation of the serotonergic fate [41–43]. Recent findings, however, show that a substantial subset of basket-forming *Pet1* neurons express low or undetectable levels of serotonergic pathway genes such as *Tph2* and *Slc6a4,* the latter encoding the serotonin re-uptake transporter. Rather, these *Pet1* neurons express high levels of VGLUT3, enabling glutamate packaging into synaptic vesicles [26,44]. This pattern contrasts some other *Pet1* neurons, which co-express serotonergic and glutamatergic

identity genes, permitting glutamate and serotonin co-transmission [38]. These *Pet1*-neuron soma that are high in *Vglut3* but low in *Tph2* transcripts reside in the MR and comprise part of the *Pet1* neuronal population that derives developmentally from the hindbrain compartment referred to as rhombomere 2 (r2) [14,37,38]. *Pet1* neurons arising from r2 are referred to as 'r2-*Pet1*' neurons [37] and can be accessed genetically by exploiting the overlap (intersection) of expression of two driver transgenics – the r2-specific *r2Hoxa2-cre* [45] and the *Pet1*-specific *Pet1-Flpe* [37]. Pericellular baskets are characteristic of a subgroup within the r2-*Pet1* neuron population – the VGLUT3-positive, TPH2-low-or-negative subset of r2-*Pet1* neurons referred to as r2-*Pet1*$^{Vglut3\text{-high}}$ [14]. The more classical, serotonergic subgroup of r2-*Pet1* neurons, referred to as r2-*Pet1*$^{Tph2\text{-high}}$, expresses high levels of TPH2, 5-HT, and SLC6A4 and are low-or-negative for VGLUT3. This group does not form pericellular baskets, and projects to brain regions different from the basket-forming r2-*Pet1*$^{Vglut3\text{-high}}$ cells [14].

The majority of baskets from r2-*Pet1*$^{Vglut3\text{-high}}$ cells are immunoreactive for VGLUT3 but not 5-HT, perhaps unsurprisingly given their soma transcriptome just mentioned [14,38]. Interestingly, some of the r2-*Pet1*$^{Vglut3\text{-high}}$-targeted postsynaptic cells are ensheathed by additional baskets that are serotonergic and derive from non-r2 *Pet1* neurons (Figure 1B). These baskets are likely formed by other MR serotonergic neuron subgroups referred to as *r1En1-Pet1* or *r3Egr2-Pet1* neurons [37,46]. Thus, in some cases, axons from developmentally distinct subsets of *Pet1* neurons (derived from different hindbrain rhombomeres) converge and ensheath the same target cell with one deploying glutamate and the other 5-HT. Such 'composite' pericellular baskets are prevalent in the septum [14; Figure 1C] and likely explain at least a portion of the baskets formed by serotonergic and non-serotonergic fibers reported decades ago [8].

Proposed models of action of composite baskets

We propose various models for composite baskets based on existing data on serotonin and glutamate postsynaptic effects. A cooperative model describes fast glutamatergic input as prepotentiating the target cell, setting up enhanced responsiveness to subsequent excitatory serotonergic receptor signaling [47]. Also possible is that neuromodulatory input from 5-HT^{+} pericellular basket terminals may prime synapses to be more or less inducible to plasticity, as has been reported with cholinergic, dopaminergic, and adrenergic fibers [48,49]. An alternative oppositional model involves postsynaptic inhibitory 5-HT receptors, such that serotonergic signaling would oppose that of excitatory glutamate [50]. Relevant to both cooperative and oppositional models, serotonergic and glutamatergic signaling typically operate at different timescales. Glutamate typically elicits fast synaptic responses through ionotropic receptors while serotonin typically operates with slower dynamics usually through metabotropic receptors [47,51]. Resolving the functional impact of these basket complexities is an exciting next step.

Some individual *r2-Pet1* neuron baskets co-localize VGLUT3 and 5-HT to the same boutons, raising the possibility for co-transmission [26,44,52,53]. This is especially prevalent for r2-*Pet1* basket boutons in the septum, as compared to non-basket *Pet1* boutons [14]. Thus, septal pericellular baskets from *Pet1* neurons may be centers for co-transmission

that offer concurrent yet kinetically different control of the postsynaptic neuron and its embedded network via glutamate versus 5-HT signaling. It is possible that glutamate versus 5-HT may require different thresholds of excitation for release. Indeed, certain serotonergic fibers in the amygdala, though not comprising baskets, showed differential neurotransmitter release depending on stimulation frequency: low frequency stimulation was sufficient to evoke glutamate release, higher frequencies were needed to elicit 5-HT release [54]. This suggests that 5-HT deployment is reserved for specific environmental or physiological circumstances. It also suggests that 5-HT and glutamate are packaged into separate synaptic vesicles. Pericellular baskets have yet to be probed for such graded transmission. An alternative possibility worth exploring is co-release of 5-HT and glutamate from the same synaptic vesicle. Both options suggest the possibility for sophisticated and complex modes of target cell modulation and septal network control by r2-*Pet1* neuron baskets.

Developmental elaboration of basket structure parallels target neuron maturation

In rodents, septal pericellular baskets typically form in the early postnatal period. For example, it is during the first postnatal week of life that dopaminergic (TH^+) baskets and met-enkephalin$^+$ baskets are first detectable developmentally, increasing in abundance and complexity by week two [55]. In addition to this temporal axis of septal basket development, there is also a significant spatial axis, with baskets elaborating first in the medial septum, and later in the lateral septum. Notably, this pattern matches that of septal neuron maturation including dendritic arborization [56]. Similar temporal dynamics describe the formation of pericellular baskets in other brain regions, such as the cerebellum [57], cortex and hippocampus [58–60]. It may be a common feature for pericellular baskets to form as the cytoarchitectonics of a region and its resident cells mature. The development of *Pet1* neuron pericellular baskets remains to be mapped, though in rat, $5\text{-}HT^+$ fibers form baskets in the septum starting after postnatal day (P) 7 [28]. These baskets increase in number and complexity throughout the early postnatal period. Serotonin axon arborization and morphology reach an adult-like pattern shortly after weaning, ~P28 [61,62]. Also unknown is whether early life experiences, such as stress or sensory experiences, affect the formation of pericellular baskets. Indeed, a different pericellular structure comprised of secreted glycoproteins, called the perineuronal net (described in Box 1), is affected in its development by postnatal stressors [63].

The elaboration of septal pericellular baskets during the early postnatal period parallels the development of certain septum-dependent social behaviors. One example is kinship recognition. At about two weeks postnatally, rat pups switch preference from siblings to non-siblings, which is blocked by lesioning the lateral septum [64]. Moreover, lateral septal neurons responsive to sibling versus non-sibling cues differentially localize across the intermediate lateral septum, a subregion rich in pericellular baskets, including *Pet1* neuron baskets [2,8,14]. These baskets elaborate and mature along a similar time course to behavioral preference switching, suggesting they may mediate or reflect this behavioral shift. Consistent with this notion, albeit in the adult rodent, optogenetic stimulation of the MR reduced aggression to a novel (non-sibling) intruder mouse [65].

Pet1 axon-derived pericellular baskets in the septohippocampal circuit may modulate memory

Based on functional anatomy, *Pet1*-derived pericellular baskets seem to be well positioned to influence memory and reinforcement of learned behaviors through modulating theta rhythm generation in the septohippocampal circuit. Theta rhythm describes sinusoidal (4–12 Hz) electroencephalographic oscillations related to activity in the hippocampus, neocortex, and amygdala during attentive wake and REM sleep [72,73]. Hippocampal theta oscillations are important in memory encoding [72–75] and abnormalities in theta rhythm are associated with attention and cognitive disorders such as schizophrenia [76] and attention deficit/hyperactivity disorder [77]. Hippocampal theta rhythms are generated within a broader limbic septohippocampal system in which projections from the medial septum drive theta in the hippocampus. The hippocampus in turn sends reciprocal regulatory connections back to the septum including both medial and lateral subdivisions [78]. This circuit is modulated by the MR, generally in a desynchronizing fashion [79–81] driven by serotonergic (*Pet1*) neurons residing therein [82,83]. Serotonergic neurons show diversity in their activity during theta [84], suggesting some subpopulations are better positioned to interact with theta-generating circuits. Subsets of *Pet1* neurons form pericellular baskets in the hippocampus, medial septum, and lateral septum [14], positioning them to modulate hippocampal theta and memory at several key nodes.

Perhaps the most direct route whereby *Pet1* neuron pericellular baskets may modulate theta rhythms is via hippocampal GABAergic neurons, which they preferentially innervate relative to excitatory principal cells [17]. Theta oscillations can be generated by interactions between pyramidal neurons and specific classes of interneurons, including those referred to as basket cells. Basket cells send highly collateralized axons to form pericellular baskets on many pyramidal neurons, coordinating their activity [15,85]. Basket cell interneurons are divided into two classes: the fast-spiking parvalbumin-expressing (PV) basket cells [86,87] and the regular-spiking cholecystokinin-expressing (CCK) basket cells [29]. The latter express 5-HT3aR and are heavily innervated by 5-HT^+ and $VGLUT3^+$ MR fiber pericellular baskets, suggesting excitatory, fast responsiveness to 5-HT and glutamate [14,15,29,88,89]. 5-HT3aR antagonists promote theta [90], suggesting 5-HT signaling to CCK basket cells may desynchronize theta. It is possible that glutamate vs. 5-HT release from *Pet1* neuron pericellular baskets has differential effects on CCK basket cell firing and thus theta synchrony. Glutamate acting on CCK basket cells may promote inhibitory tone, theta, and thus memory formation [72,75]. Conversely, 5-HT inputs may desynchronize CCK basket cells, suppress theta [83], and promote extinction of memories through 5-HT3 receptors [91]. CCK basket cells have a slow membrane time constant and high input resistance [85,92]. Thus, it is possible they are especially desynchronized by coincident glutamatergic and serotonergic basket input, which may force adaptation (see Box 2).

There are additional pathways through which *Pet1* pericellular baskets may modulate theta and memory. r2-*Pet1* pericellular baskets also target hippocampal neurons expressing calbindin [14], a population that sends inhibitory projections to the medial septum [93], a major generator of theta [94]. *Pet1* neuron pericellular baskets are also prevalent

within the medial and lateral septum, where they innervate GABAergic neurons (possibly interneurons), some of which express the excitatory 5-HT2C receptor [8,14]. If *Pet1* pericellular basket input (glutamate, serotonin, or both) excites these cell types as predicted by the cognate receptor function, their subsequent release of GABA would increase inhibitory tone in the septum. We predict this suppression of activity would reduce theta [95] and disrupt memory formation [96].

Based on the predicted effects of basket neurotransmission and identity of cellular targets, we propose *Pet1* neuron basket activation generally reduces memory durability and increases circuit plasticity. Consistent with this idea, chemogenetic inhibition of r2-*Pet1* neurons during the encoding of a cocaine conditioned place preference increased resistance to extinction of that behavioral preference in the cocaine-free state [97]. This suggests that diminished r2-*Pet1* neuron activity strengthens the durability of cocaine memory. Conversely, this predicts that r2-*Pet1* neuron activity normally functions to limit this durability, allowing for plasticity or flexibility in learning and memory [97]. 5-HT3aRs, expressed by hippocampal neurons targeted by r2-*Pet1* pericellular baskets, seem particularly important in erasing stored memories. 5-HT3aR knockout mice are less able to extinguish fear memories [98] and express high levels of anxiety-related behaviors [99]. In line with these findings, systemic administration of 5-HT3aR antagonists improved baseline memory in rodents and primates and counteracted memory deficits induced by scopolamine [100] and pentylenetetrazole-kindling in a rodent model of epilepsy [101]. Exciting next steps will involve 5HT3aR manipulations specific to septohippocampal circuitry.

Approaches to manipulate memory durability may have translational implications. Malleable memories are essential to behavioral flexibility. A foraging animal, for example, must update its internal map to reflect when a food source is depleted, or it risks returning again and again to diminishing returns and enhanced predation risk. In some circumstances, unfruitful perseveration of memories can be highly detrimental and even life threatening. This is the case for instance in certain neuropsychiatric conditions, including post-traumatic stress disorder (PTSD) where prolonged and intrusive stressful memories are highly debilitating. Serotonin system abnormalities are thought to elevate risk for PTSD, and can be treated with serotonin-modulating drugs [102,103]. One may speculate that studies of *Pet1* pericellular baskets could offer previously underappreciated circuit nodes and molecular pathways for conceptualizing new therapeutic strategies for PTSD and other psychiatric disorders.

Concluding Remarks

Pericellular baskets are complex structures formed by one or several axons densely innervating the soma and proximal dendrites of a downstream target cell. This spatial organization of boutons may enable strong and even multi-modal control over target cell activity. Formed by many neuron types in different brain regions, the functions and physiology of pericellular baskets remain under-described. In this article, we argue that pericellular baskets may represent a neurochemically and functionally complex interaction point between different neuronal and neurotransmitter systems with potential functional roles regulating emotion processing, brain oscillations, and memory. Understanding the extent of convergence of pericellular baskets across different neurotransmitter systems, as

well as addressing central questions about their development and neurotransmission (see Outstanding Questions) would be essential to understanding their circuit function and impact on broader brain function and behavior.

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Box 1.

Pericellular baskets and perineuronal nets: the first, a presynaptic elaboration; the second, an extracellular matrix network; both regulate target cell function.

Pericellular baskets and perineuronal nets (PNNs) are sometimes mistaken for each other conceptually, and while they do share features related to ensheathing neuron soma, they are quite different structures. Pericellular baskets are a presynaptic neuronal specialization comprised of axonal boutons decorating the soma and proximal dendrites of the postsynaptic target cell. They are formed by multiple neuron types, including basket cell interneurons and monoaminergic neurons, among others [4,15]. By contrast, PNNS are extracellular structures composed of secreted chondroitin sulfate proteoglycans that ensheath neuronal soma [63]. The extracellular matrix components that form PNNs are expressed by both neurons and glia [63]. Pericellular baskets have been observed targeting excitatory and inhibitory neurons [8,14,15,17,21]. Similarly, PNNs most commonly target GABAergic interneurons, typically fast-spiking parvalbumin neurons, but have also been observed to surround excitatory neurons [66,67]. In mice, pericellular baskets and PNNs form during the early postnatal period when neurons in many brain regions are maturing and establishing synaptic connectivity, suggesting roles in circuit maturation. PNN formation is dependent on experience and sensory input during critical periods, as PNNs fail to form in visual cortex without exposure to light [68]. Whether early life experience shapes the formation of pericellular baskets remains an open question. Also unclear is whether or how often pericellular baskets and perineuronal nets overlap in cellular target. The gaps in perineuronal ‘netting’ are typically occupied by synaptic boutons [63], suggesting the PNN acts as a scaffold for highly specific synapse formation that also limits further plasticity [66]. A study in mice found that loss of PNNs around parvalbumin interneurons reduced the perisomatic innervation targeting them, suggesting the PNN scaffolding may be necessary to stabilize perisomatic innervation [69]. The same study proposed that a threshold of perisomatic innervation may be necessary for PNNs to form and stabilize this connectivity. These results suggest a potential interplay between pericellular baskets and PNNs, though there are relatively few reports examining whether PNNs and pericellular baskets target the same neurons. In the lateral septum for example, PNNs and glutamatergic ($VGLUT3^{+}$) pericellular baskets are reported to rarely overlap [2]. These observations offer perhaps a limited view, though, as only one type of PNN has been well characterized – that which binds the lectin *Wisteria floribunda* agglutinin (WFA) – whereas other PNNs exist as well, for instance those labeled by antibodies to aggrecan [63,70]. Additionally, a subset of serotonergic neurons forms pericellular baskets around parvalbumin interneurons [8], which as a population are common targets of PNNs [63]. As another line of evidence suggesting potential interactions between the serotonergic system and PNNs, selective serotonin reuptake inhibitors (SSRIs) administered during the early postnatal period affect PNN formation, reducing their number in the hippocampus [71]. Determining whether different pericellular basket systems target the same somata as PNNs, and

whether the formation of each structure affects the other are compelling direction for future research.

Box 2:

Pet1 neuronal pericellular baskets are poised to modulate memory

Hippocampal CCK basket cells deliver strong perisomatic inhibition to pyramidal cells. This inhibition is thought to gate circuit transmission such that only the strongest signals persist, creating sparse, precise encoding of memories with minimal overlap in circuit representation [12,87,104]. The most highly recruited pyramidal cells are able to thwart CCK basket cell inhibition by depolarization-induced suppression of inhibition (DSI). DSI can involve, for instance, activity-dependent retrograde release of cannabinoids, which activate presynaptic CB1 receptors on the CCK basket cell terminals, thereby preventing additional release of GABA [85]. r2-*Pet1* pericellular baskets might act to excite these CCK basket cells via glutamate release, and thereby promote a sparser neural code. When the pericellular basket is active presynaptically, the postsynaptic CCK basket cell is also likely excited. Subsequent stronger downstream inhibition of pyramidal cells would raise the threshold of circuit recruitment for a pyramidal cell to remain active. Alternatively, coincident glutamate and 5-HT release may greatly depolarize the CCK basket cell, causing adaptation that reduces CCK basket cell firing and acts to ‘reset’ this gain control and increase circuit plasticity.

Outstanding Questions

How frequently do different pericellular baskets target the same neuron, forming a ‘composite basket’? Does the prevalence of composite baskets vary with target region?

Do individual monoamine neurons, which often have highly collateralized axons, make baskets in multiple regions? For neurons forming multiple pericellular baskets, are the baskets of identical or heterogeneous neurochemical phenotypes?

For monoamine neurons, which commonly co-transmit multiple neurotransmitters, are baskets sites of co-transmission and if so, is co-transmission fixed or variable as a function of presynaptic excitation?

For composite baskets, how does the activation of one basket affect the target cell response to subsequent input from the other basket(s)? Do baskets formed by different neurons ever signal to each other via axo-axonic appositions?

How does modulating neurotransmitter release from *Pet1* pericellular baskets in target regions such as the septum and hippocampus affect memory formation? Given their often-different neurochemical profiles, do different developmental lineages of basket-forming *Pet1* neurons have differential effects on memory durability?

How do pericellular baskets form around targeted cells? Are cell-cell adhesion proteins involved in guiding axons to specific downstream targets?

Pet1 neuron pericellular baskets are formed in the early postnatal period and are commonplace in brain regions that exhibit neuroplasticity in response to early life stress, such as the hippocampus and septum. Is the formation of pericellular baskets also plastic in response to early life stress, and does this plasticity have functional consequences on later expression of stress coping behavior or memory?

Does disrupting postsynaptic cell maturation also disrupt basket formation? Conversely, does disrupting basket formation disrupt neuronal maturation?

Highlights

A pericellular basket is a presynaptic array of boutons from single or multiple axons that encase the target, postsynaptic cell body and proximal dendrites.

Pericellular baskets ensheathing cerebellar and cortical neurons were described by Ramón y Cajal in the late 1800s and early 1900s.

Pericellular baskets typically form postnatally after initial innervation of a brain region, suggesting possible induction by maturing target neurons.

Pericellular baskets often deploy multiple neurotransmitters either co-expressed in individual axons or separately deployed by different axons, suggesting complex target cell regulation.

The proximity to the postsynaptic soma of boutons configuring a basket suggests temporally precise inhibition or excitation of the encased cell.

Pet1 neurons of the raphe nuclei offer an example of pericellular basket projections. *Pet1* neuron pericellular baskets frequently target distant inhibitory GABAergic interneurons, and thus may exert privileged influence on target region networks and their excitability.

Cell types targeted by *Pet1* neuronal pericellular baskets suggest possible roles in regulating memory durability.

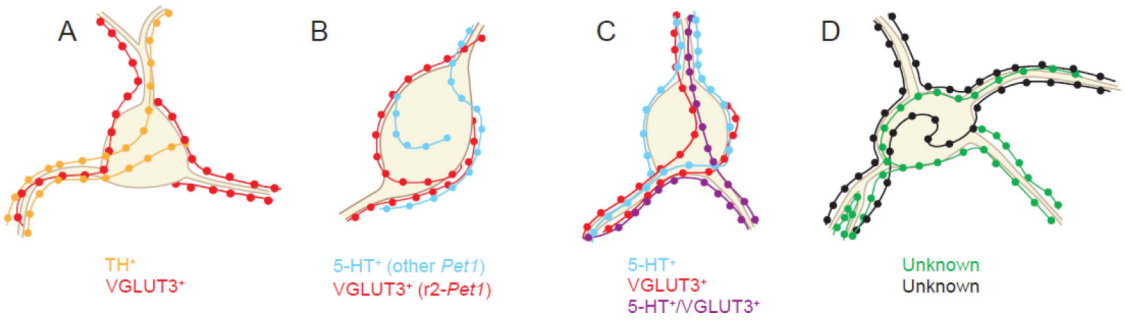

Figure 1. Combinations of neurochemically distinct pericellular baskets can target a shared cell soma.

(A) Convergence of TH^+ and $VGLUT3^+$ pericellular baskets has been reported in the lateral septum [2]. (B) $5\text{-}HT^+$ and $VGLUT3^+$ baskets from separate *Pet1* neuron lineages converge on the same targets in the cortex, hippocampus, and septum [14]. (C) Baskets comprised of $5\text{-}HT^+$, $VGLUT3^+$, and $VGLUT3^+/5\text{-}HT^+$ fibers are common in the septum [14]. (D) It remains to be tested whether other combinations of axons known to form pericellular baskets converge on their target neurons.