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Review

Glutamatergic synaptic transmission in neuroendocrine cells: Basic principles and mechanisms of plasticity

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ABSTRACT

Glutamate synapses drive the output of neuroendocrine cells in the hypothalamus, but until recently, relatively little was known about the fundamental properties of transmission at these synapses. Here we review recent advances in the understanding of glutamate signals in magnocellular neurosecretory cells (MNCs) in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus that serve as the last step in synaptic integration before neurohormone release. While these synapses exhibit many similarities with other glutamate synapses described throughout the brain, they also exhibit a number of unique properties that are particularly well suited to the physiology of this system and will be discussed here. In addition, a number of recent studies begin to provide insights into new forms of synaptic plasticity that may be common in other brain regions, but in these cells, may serve important adaptive roles.
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1. Introduction

Neurons are highly specialized to integrate and relay information; they rely on specific morphological, electrophysiological and molecular characteristics to generate precise patterns of electrical activity. How patterns of synaptic activity are interpreted and integrated by neurons is a central problem in the field of neuroscience. Understanding both basal synaptic parameters and activity-dependent synaptic plasticity is fundamental to understanding how the interactions between pre- and postsynaptic neurons determine the output of the system. However, the output of many neuronal networks can be difficult to ascertain. Achieving a more complete understanding of synaptic transmission requires a system where the output of the neurons is readily measurable. Here we will focus on one such system, the magnocellular neurosecretory cells (MNCs) of the paraventricular (PVN) and supraoptic (SON) nucleus of the hypothalamus. MNCs integrate incoming signals to generate a distinct output: the secretion of the hormones oxytocin (OT) or vasopressin (VP) from their nerve terminals in the posterior pituitary. Therefore factors that change their excitability will produce predictable changes in hormone output, with well-defined physiological consequences.

While the cell bodies of OT and VP cells are intermingled in both the SON and PVN, the physiological roles of these two cell types are quite different. Likewise, the patterns of action potential firing in response to physiological stimulation and hence the profiles of hormone secretion into the blood are also markedly different.

VP released from nerve terminals in the posterior pituitary serves to control blood volume and osmolarity by regulating vasoconstriction of the vasculature and fluid reabsorption from the kidney. In response to dehydration or hemorrhage, VP cells show an increase in firing and may even switch into a phasic bursting pattern of firing [147]. This increase in VP release acts to restore blood volume/osmolarity levels back towards homeostatic set points. Because the firing rate of VP neurons is roughly proportional to the amount of secreted hormone, regulation of VP cell excitability is extremely important. VP cells can display several different firing patterns *in vivo* ranging from phasic bursting to continuously firing to silent [10,109]. Phasic bursting appears to be the most efficient firing pattern in VP cells for producing maximal hormone secretion. Phasic bursts consist of long duration episodes (20–60 s) of spiking at 5–15 Hz interspersed with periods of quiescence of similar duration. The bursts are not synchronized across VP neurons and thus VP secretion from the posterior pituitary is continuous rather than pulsatile [75]. Both excitatory synaptic inputs and depolarizing postsynaptic conductances are important for

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generating these long phasic discharges. Specifically, a depolarizing afterpotential (DAP) generated after a short burst of spikes can result in the emergence of a plateau potential [1,39] that when summed with synaptic activity can generate prolonged spiking [12,60].

The role of OT secretion is very different to that of VP and appears to be more significant in the female. OT secretion from the posterior pituitary is essential for the milk let down reflex during lactation and important for parturition [75,94]. While action potential firing in OT cells is irregular in unstimulated conditions, during parturition and lactation, these cells fire in short, high-frequency (20–50 Hz) bursts at ~5–10 min intervals. These bursts are synchronized (approximately within 400 ms of each other) across all OT cells both in the SON and PVN [4,5,146]. These bursts produce near maximal activation of peripheral OT receptors whereas continuous low levels of OT produce very little receptor activation due to strong receptor desensitization [7]. The mechanisms of burst generation in OT cells are complex and will not be reviewed in detail here and the reader is directed to several other excellent reviews on this topic [75,115,118]. Instead, we will focus on the properties and plasticity of synapses that enable these unique activity patterns in MNCs.

2. Glutamate input and MNC activity

MNCs receive afferent inputs from a number of forebrain structures including, the median preoptic nucleus (MnPo), the subfornical organ (SFO) and the organum vaculosum of the lamina terminalis (OVLT) as well as brainstem nuclei [132] and other intrahypothalamic nuclei [19,20]. These fibers contain biogenic amines [133], neuropeptides [77], γ-aminobutyric acid (GABA) [25] and glutamate [143], among others.

While GABA mediates the majority of fast inhibitory transmission onto MNCs [113,112,142] glutamate is responsible for the majority of fast excitatory neurotransmission onto MNCs in the PVN and SON [143,30,44]. Stimulation of nuclei that project to MNCs produces both short and long latency increases in spike activity [34]. While the long latency responses are due to the release of peptide transmitters [76], the short latency responses are likely the result of glutamate actions on MNCs. Consisetent with this idea are observations that stimulation of afferent nuclei, with either a local osmotic stimulus [114] or electrical activation increases glutamatergic drive to MNCs [138].

3. Glutamate synapses

3.1. Basic features

Glutamate filled vesicles can be released either stochastically or in response to the invasion of an action potential into the nerve terminal. Both modes of release have been described in MNCs and their properties and regulation will be discussed here. Various receptors for glutamate have been localized to either pre- or postsynaptic elements of MNCs including the ionotropic α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and N-methyl-D-aspartic acid (NMDA) receptors that are primarily located at the postsynaptic density. Metabotropic glutamate receptors (mGluRs) that mediate slower neuromodulation are located in the peri-synaptic region. Anatomical evidence indicates that group I mGluRs are localized postsynaptically [141,144] and signal through $G_{q/11}$ pathways. Activation of these receptors in MNCs increases intracellular Ca^{2+} [49]. Group II/III mGluRs are $G_{i/o}$ G-protein coupled receptors (GPCRs) that are located presynaptically and mediate feedback inhibition [123,101,40].

3.2. Synaptic activity regulates burst firing in MNCs

The unique firing patterns of MNCs both *in vitro* and *in vivo* are highly dependent on excitatory glutamatergic afferents. Application of NMDA can induce repetitive burst like discharges in MNCs that resemble phasic bursting [56,3]. More importantly, spontaneously occurring burst discharges in OT or VP cells observed both *in vivo* and *in vitro* are silenced by infusions of AMPA or NMDA receptor antagonists [10,60,95,61] indicating that this bursting activity is not intrinsically regenerative but rather requires ongoing glutamatergic activity. Moreover, both VP spike activity in response to intravenous infusion of hypertonic NaCl and suckling induced bursts in OT neurons (and OT release) are eliminated when AMPA/NMDA receptors are blocked [10,104]. Finally, phasic action potential bursts in VP cells *in vivo* can be induced by electrical stimulation of excitatory afferents [119]. Intriguingly, afferent activity appears to have state-dependent effects on burst firing in VP neurons. If afferent stimulation is delivered tens of seconds after the end of a burst, it evokes a subsequent phasic burst. If, however, afferent inputs are activated during a phasic burst, they have the opposite effect – resulting in premature burst termination [119]. A potential cellular mechanism for this state-dependent effect of synaptic activity will be discussed later in this review.

Collectively, these studies illustrate the importance of fast synaptic signaling in controlling the excitability of MNCs *in vivo* and provide the foundation for more recent work investigating the intricacies of this signaling. This work, in turn has led to the emergence of new ideas on how synaptic transmission and plasticity can 'fine-tune' excitability and hence hormone output from neuroendocrine cells.

3.3. Stochastic release

Miniature excitatory postsynaptic currents (mEPSCs) result from the release of single quanta (vesicles) of glutamate, which in turn, activate postsynaptic AMPA receptors. mEPSCs do not require presynaptic action potentials. Rather, they result when vesicles filled with neurotransmitter stochastically fuse with the presynaptic plasma membrane. Their seemingly random nature and their lack of reliance on action potentials has led many to dismiss them as 'synaptic noise'. There is, however, growing evidence from different brain regions, that they have several important functions including regulating the basal level of excitability in neurons [16] and maintaining the integrity of dendritic spines [87,131].

While there do not appear to be marked differences between quantal glutamate transmission between OT and VP expressing MNCs, Stern et al. have previously shown that OT expressing cells exhibit larger amplitude and faster decaying mEPSCs compared to VP cells, likely due to different complements of AMPAR subunits [129]. These differences, which do not extend to the quantal NMDA currents could be important in dictating the different firing patterns in these cells. Although individual mEPSCs do not rely on action potentials, both the frequency and amplitude of these events is highly regulated in MNCs by prior synaptic activity and by neuromodulators.

3.4. Evoked release – contributions of voltage-gated calcium channels (VGCCs)

The influx of calcium through voltage-gated calcium channels (VGCCs) links presynaptic depolarization to vesicle release. Calcium channels are classified as high voltage-activated (HVA) channels, namely N-, P-, Q-, L-, R-type or low voltage-activated (LVA) channels, T-type based on their kinetics and voltage-dependence. While MNCs themselves likely express a variety of VGCCs [35,120], the VGCCs lo-

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