Review

Changing the tune: plasticity and adaptation of retrograde signals

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Retrograde signaling is a fundamental means by which neurons communicate. The acceptance of this statement has required a revision of how we view transmission and storage of information at the synapse. Although there is a substantial body of literature on the diverse molecules that serve as retrograde signals, less is known about how retrograde signal capacity can be modified. Is retrograde signaling plastic? How does this plasticity manifest? Are there behavioral correlates that may bias a neuron towards 'changing its tune', retrogradely speaking, of course? Here, we review recent findings that retrograde signaling is a highly labile process that adds additional layers of complexity that must be untangled to understand information processing in the nervous system.

Introduction

That a postsynaptic neuron alters the release of neurotransmitter from its presynaptic partner represents a paradigm shift in our comprehension of how signals in the nervous system are transmitted. Retrograde transmitters can inform the presynaptic terminal about the level of postsynaptic activity. This can cause potent and long-lasting changes in presynaptic transmitter release. There are now many demonstrations that multiple levels of control impact the retrograde signals themselves. Here, we describe some of the key mechanisms that influence retrograde signals and then provide a broader context for how these changes may be initiated during different behavioral and pathological states.

A variety of different molecules function as retrograde transmitters; this includes the lipid-derived endocannabinoids (eCB) and endovanilloids, neuropeptides including opioids, catecholamines, amino acids, and gases. Although many of these retrograde signals are restricted to specific cell types, most central neurons produce eCBs. Consequently, much of our knowledge regarding retrograde signaling has come from the study of the eCB system. In this review, we focus predominantly, but not exclusively, on this system. For details of the other molecules that may act as retrograde transmitters as well the intricacies of eCB signaling, the reader is directed to several other excellent reviews [1–9].

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Mechanisms regulating retrograde plasticity

There is a diverse and rapidly expanding list of mechanisms that can modulate the expression and magnitude of retrograde signals and thus contribute to plasticity of retrograde signaling. Here, we broadly group them into three categories: (i) regulation by neuromodulators; (ii) regulation by neural activity; and (iii) regulation by co-released dendritic signals.

Regulation by neuromodulators

Release of retrograde transmitters is often driven by postsynaptic depolarizations, which ostensibly mimic the change in membrane potential in response to a burst of action potentials. These depolarizations open somatodendritic Ca^{2+} channels, elevate dendritic Ca^{2+}, and liberate retrograde molecules from the postsynaptic neuron.

eCBs, the most ubiquitous retrograde transmitters in the nervous system, are synthesized upon demand from lipid precursors in the postsynaptic neuron and act on presynaptic cannabinoid (CB) 1 receptors to inhibit neurotransmitter release. Large, rapid postsynaptic depolarizations sufficient to increase postsynaptic Ca^{2+} result in rapid eCB synthesis and release [10–12]. The resulting presynaptic inhibition is termed 'depolarization-induced suppression of inhibition' (DSI) or 'excitation' (DSE) when it occurs at GABA or glutamate synapses, respectively. The two most common eCBs are 2-arachidonoyl-glycerol (2-AG) and anandamide (AEA); however, recent evidence suggests that this fast, Ca^{2+}-dependent eCB inhibition is predominantly mediated by 2-AG [13,14]. The synthesis of 2-AG requires production of diacylglycerol (DAG) via the activation of phospholipase C (PLC). DAG is then converted to 2-AG by DAG lipase α. Thus, depolarization-induced 2-AG release is thought to be driven by Ca^{2+}-stimulated DAG synthesis and conversion to 2-AG.

G_q-linked G protein-coupled receptors (GPCRs) signal directly through PLC and are also efficient drivers of eCB release [15–23]. This pathway for eCB production can be enhanced if G_q-linked GPCR stimulation is paired with low levels of postsynaptic Ca^{2+} influx [16,24]. This phenomenon, termed 'Ca^{2+}-assisted receptor-driven eCB release' [25], occurs because of enhanced PLC activity (specifically PLCβ) in the presence of Ca^{2+} [7,26] (Figure 1). Consequently, it has been proposed that PLCβ functions as a coincidence detector to enable enhanced eCB release when G_q receptor activation is paired with increases in Ca^{2+} [26]. In support of this concept, both the magnitude of PLC

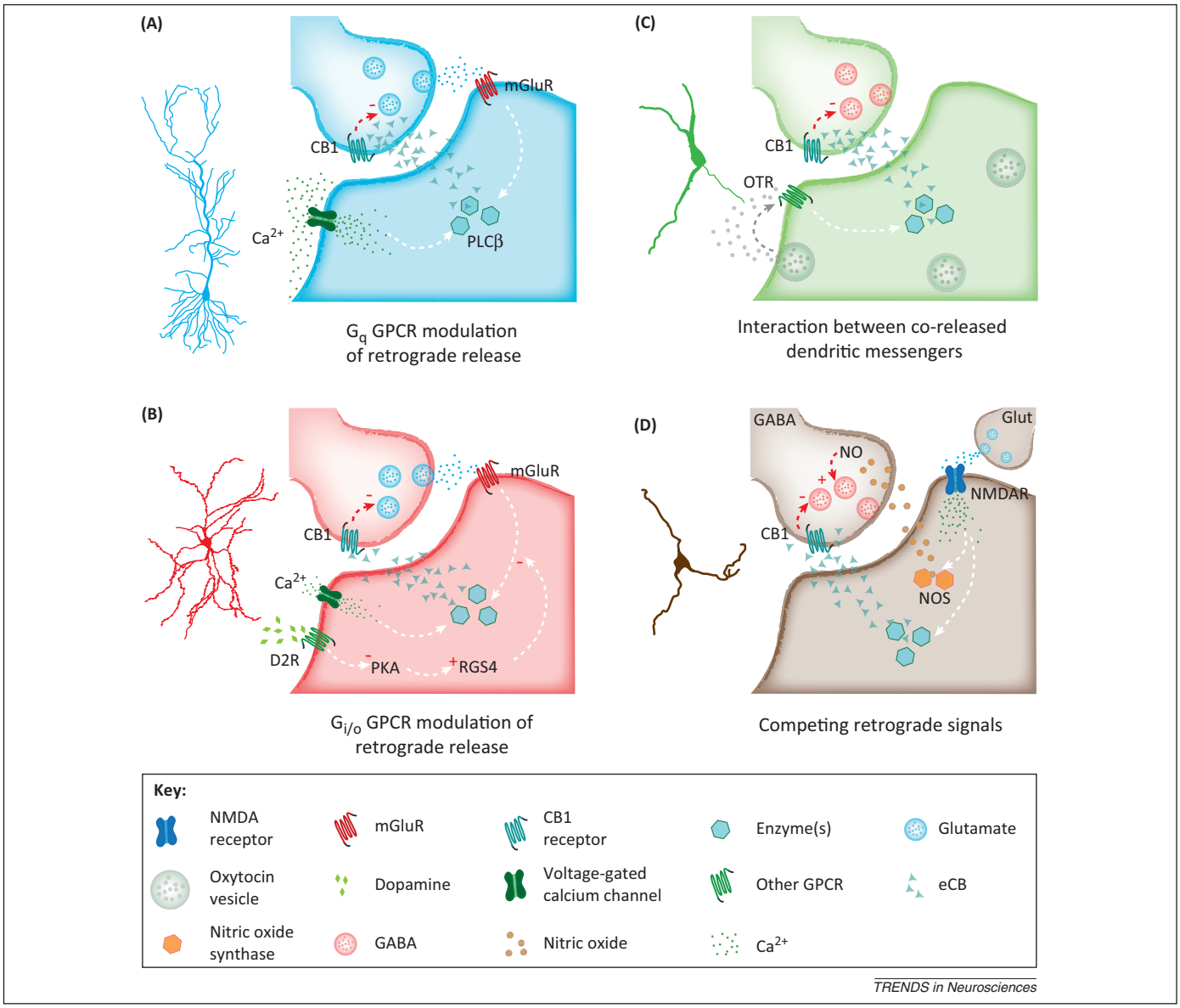

Figure 1. Cartoon illustrating four examples of modulation of retrograde plasticity and the underlying signaling cascades. Although initially characterized in the cell types shown, these retrograde pathways may be present in diverse neuronal populations throughout the central nervous system. **(A)** The ability of G_q-linked G protein-coupled receptors (GPCRs) to drive endocannabinoid (eCB) release is enhanced when combined with postsynaptic calcium increases. In hippocampal pyramidal neurons, this plasticity can be explained by the fact that there is enhanced activation of phospholipase C beta (PLCβ) and downstream eCB synthesis when these two stimuli occur together [26]. **(B)** Activation of dopamine D2 receptors (D2R) gates eCB long-term depression (LTD) in striatal medium spiny neurons. Activation of D2 receptors inhibits protein kinase A (PKA) and reduces the activation of regulator of G protein-signaling 4 (RGS4). This allows for greater activation of G_q GCPR pathways driving eCB synthesis [35]. Alternative signaling pathways have also been suggested [40]. **(C)** Many neurons are capable of releasing more than one transmitter from their dendrites. Oxytocin magnocellular neurons constitutively release oxytocin. This oxytocin acts in an autocrine and/or paracrine manner to drive the release of eCBs [22], which act to keep probability of GABA release low [62]. **(D)** In the dorsal medial hypothalamus (DMH), high-frequency stimulation of afferent axons induces glutamate release and the activation of NMDA receptors. The resulting calcium influx drives the release of both eCB and nitric oxide (NO). Importantly, whereas eCBs act to produce a LTD of GABA transmission, NO acts in the opposite manner to enhance GABA release. When CB1 receptors are blocked, GABA long-term potentiation (LTP) mediated by NO is unmasked. Interestingly, blocking nitric oxide synthase (NOS) also inhibits signaling via CB1 receptors through an unknown mechanism [70]. Abbreviations: mGluR, metabotropic glutamate receptors; Oxytocin receptor (OTR).

activation and eCB release induced by either group 1 metabotropic glutamate receptors (mGluR) or M1/M4 muscarinic receptor agonists is enhanced by elevating postsynaptic Ca^{2+}, but is absent in pyramidal neurons in which PLCβ is genetically eliminated [26]. PLCβ or other PLC isoforms may function as coincidence detectors for other neuromodulators that regulate eCB release through G_q receptors.

Unlike the G_q-receptor modulation of eCB release, the ability of $G_{i/o}$- and G_s-linked GPCRs to modulate eCB release has been more difficult to explain. Observations in several brain regions indicate that activation of $G_{i/o}$ coupled receptors, specifically dopamine (D) 2 [27–29] and noradrenaline α2 receptors [30], gate the induction of eCB-dependent synaptic depression. The mechanisms responsible for this modulation are complex and appear to vary depending on the neuronal cell type studied. In the striatum, coincident activation of D2 receptors, group 1 mGluRs and postsynaptic Ca^{2+} elevations leads to a presynaptic long-term depression (LTD) that requires postsynaptic eCB release [27,31–34]. The activation of postsynaptic $G_{i/o}$-coupled D2 receptors in medium spiny