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G-PROTEIN-COUPLED RECEPTORS IN ASTROCYTE-NEURON COMMUNICATION

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Abstract

Astrocytes, a major type of glial cell, are known to play key supportive roles in brain function, contributing to ion and neurotransmitter homeostasis, maintaining the blood-brain barrier and providing trophic and metabolic support for neurons. Besides these support functions, astrocytes are emerging as important elements in brain physiology through signaling exchange with neurons at tripartite synapses. Astrocytes express a wide variety of neurotransmitter transporters and receptors that allow them to sense and respond to synaptic activity. Principal among them are the G-protein-coupled receptors (GPCRs) in astrocytes because their activation by synaptically released neurotransmitters leads to mobilization of intracellular calcium. In turn, activated astrocytes release neuroactive substances called gliotransmitters, such as glutamate, GABA, and ATP/adenosine that lead to synaptic regulation through activation of neuronal GPCRs. In this review we will present and discuss recent evidence demonstrating the critical roles played by GPCRs in the bidirectional astrocyte-neuron signaling, and their crucial involvement in the astrocyte-mediated regulation of synaptic transmission and plasticity.

Introduction

Presynaptic action potentials trigger the release of chemical substances (neurotransmitters) into the synaptic cleft to elicit a multitude of postsynaptic responses that ultimately affect the excitability of the postsynaptic cell. This intercellular signaling that occurs at synapses, originally thought to encompass only presynaptic and postsynaptic neurons, forms the basis of all complex brain functions. However this view upheld until the 1980s was perhaps too simplistic. Now it is clear that glial cells, known as astrocytes, are also active players in synaptic transmission. Astrocytes are as numerous as neurons and have important house-keeping functions such as buffering of excess potassium and neurotransmitters in the extracellular space, providing essential nutrients to neurons and providing structural support around synapses (Sidoryk-Wegrzynowicz et al., 2011; Sofroniew and Vinters, 2010; Vasile et al., 2017). However astrocytes also contain the molecular machinery to respond to neurotransmitters released by neurons and more importantly, to release neuroactive substances termed as gliotransmitters to influence nearby neurons (Araque et al., 2014;

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Halassa et al., 2007; Perea and Araque, 2010; Perea et al., 2009; Santello et al., 2012; Savtchouk and Volterra, 2018). Such bidirectional communication between astrocytes and neurons was epitomized in the concept of a tripartite synapse in which presynaptic, postsynaptic elements, and intervening astrocyte processes interact and signal to each other (Araque et al., 1999; Halassa et al., 2007; Perea et al., 2009). The tripartite synapse has now been demonstrated in diverse brain regions and in multiple organisms including humans (Allen, 2014, 2019; Guerra-Gomes et al., 2017; Martin-Fernandez et al., 2017; Navarrete et al., 2013; Santello et al., 2019). Central to this view of astrocytes as active contributors in brain information processing are the astrocytic receptors that bind and respond to neurotransmitters and the neuronal receptors that are activated or inhibited by gliotransmitters. These receptors are mainly of the G-protein coupled receptor (GPCR) class which are seven helix transmembrane proteins that initiate intracellular signaling via coupling to G-proteins (Ross, 1989; Vassilatis et al., 2003). In this review we discuss the main types of GPCRs found in astrocytes and neurons that partake in this bidirectional glia-neuronal communication. Our emphasis are on the studies using either *in situ* or *in vivo* preparations. Other excellent reviews related to this topic can be found elsewhere (Araque et al., 2014; Papouin et al., 2017; Santello et al., 2012; Savtchouk and Volterra, 2018; Zorec et al., 2012).

1. Neuron to astrocyte communication via GPCRs: general principles

1.1 GPCRs in astrocytes transduce neuronal signals into Ca^{2+} responses—

It has become clear that although astrocytes are electrically unexcitable cells, they are highly responsive to neurotransmitters secreted by neurons. Such responses in astrocytes are manifested by intracellular Ca^{2+} fluctuations in their processes and soma. Generally, GPCR activation in astrocytes promotes increases of astrocytic Ca^{2+} levels (Guerra-Gomes et al., 2017; Khakh and McCarthy, 2015; Shigetomi et al., 2016; Zorec et al., 2012) although in some instances Ca^{2+} decreases have been reported (Jennings et al., 2017; Xin et al., 2019). These astrocytic responses were reported in a wide variety of brain regions both *in vitro* and *in vivo* preparations as discussed below. Fluorescent Ca^{2+} indicators such as fluo-3 or fura-2 were first deployed to monitor astrocytic Ca^{2+} fluctuations at rest conditions and following GPCR activation (Bernstein et al., 1998; Perea and Araque, 2005; Yagodin et al., 1995). Robust Ca^{2+} signals evoked by GPCR activation were spatially associated with the astrocytic cell body and sometimes to the thick branches as well. Astrocytic Ca^{2+} responses is linked to the activation of the phospholipase C (PLC)/inositol 1,4,5-trisphosphate (IP3) pathway as follows: upon GPCR activation, PLC hydrolyzes the membrane lipid phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol (DAG) and IP3, leading to IP3 receptor (IP3R) activation and Ca^{2+} release from the endoplasmic reticulum (ER) (Agulhon et al., 2008)(Figure 1). Accordingly, the genetic knockout of the primary IP3R in astrocytes, the IP3R2 (Holtzclaw et al., 2002; Petravicz et al., 2008; Sharp et al., 1999), largely ablates Ca^{2+} responses in astrocytes. However, *in situ* astrocytes have a highly complex morphology with numerous fine processes which were not technically accessible for Ca^{2+} imaging in these early studies. In the past few years, remarkable advances in multiphoton microscopy and development of novel genetically encoded Ca^{2+} indicators (GECI) have finally allowed the crossing of several technical thresholds and begun to generate high-resolution, quantitative and comprehensive data sets Ca^{2+} signals

in astrocytes (Poskanzer and Yuste, 2016; Shigetomi et al., 2013; Stobart et al., 2018; Ye et al., 2017). Indeed, evidence from these studies showed a high level of Ca^{2+} activity in astrocytic processes. Ca^{2+} signals in astrocytes in discrete regions of their processes, termed microdomains, are often uncorrelated with events in the soma (Bindocci et al., 2017; Otsu et al., 2015). These results suggest that astrocyte Ca^{2+} dynamics are highly heterogeneous and more complex than previously assumed and that activity in microdomains may be subject to local independent modulation (Volterra et al., 2014). Moreover, these microdomains spontaneous signals may originated form Ca^{2+} sources other than by release from IP3R2 as they remain largely unaffected in the IP3R2 knockout mouse (Stobart et al., 2018). Thus, Ca^{2}+ sources in astrocytes may involve other pathways such as mitochondrial release (Agarwal et al., 2017) or opening of TRPC1 channels (Malarkey et al., 2008). Nevertheless, there is broad agreement that GPCR activation leads to an enhanced probability of Ca^{2+} signals in astrocytes in their microdomains and later, at higher levels of activation, these Ca^{2+} transients are propagated to the soma (Araque et al., 2014; Volterra et al., 2014).

1.2 GPCRs are efficient signal transducers in astrocytes even at low levels of expression—We can conjecture that GPCRs in astrocytes are particularly well suited for translating neurotransmitter signals to Ca^{2+} responses for various reasons (Araque et al., 2014). First, the multi-step amplifying signaling cascade afforded by the G-protein signaling (Ross, 1989) allows the detection of neurotransmitter by astrocytes even at very low levels of expression. Hence it is not surprising that expression of various GPCRs in astrocytes is relatively low in comparison to their neuronal counterparts and escaped detection using common immunocytochemical or *in situ* hybridization techniques. The endocannabinoid receptor CB1R, for instance, are abundantly expressed in neurons while in astrocytes they seem to be expressed in such low levels that its functional significance remained in doubt until recently (Busquets-Garcia et al., 2018; Navarrete and Araque, 2008; Navarrete et al., 2014) Second, in comparison to ionotropic receptors, GPCRs have a much higher affinity for their ligand, favoring astrocytic responses at tripartite synapses. While ionotropic receptors are usually activated in micromolar range, many GPRCs are activated at nanomolar concentrations. The purinergic signaling in astrocytes illustrates this point. Astrocytes in many brain regions are thought to express both ionotropic P2X receptors and metabotropic P2Y receptors (Abbracchio and Ceruti, 2006). However, P2Y receptors are activated at much lower concentrations then P2X receptors (Del Puerto et al., 2013). Therefore, Ca^{2+} increases in astrocytes elicited by synaptically released ATP is mostly associated with P2Y receptors (Shigetomi et al., 2018). Third, GPCRs in astrocytes may respond to neurotransmitters with extended time course due to their relatively slow desensitization properties. Temporal integration of GPCR responses afforded by slow desensitization again allows receptor signaling even at low levels of expression. This may be the case of mGluR5 in astrocytes to which glutamate signal to intracellular effectors showed little decreased responses even after 15 min agonist exposure (Balazs et al., 1997). Fourth, GPCRs are not focally expressed in astrocytic membranes rather they are expressed broadly, allowing the detection and integration of neurotransmitter signals of multiple synaptic contacts in a single astrocyte. For instance, for $GABA_B$ receptors in hippocampal astrocytes, immunoreactivity is found in glial cell bodies and in astrocyte processes surrounding and adjacent to the synapses (Charles et al., 2003). This broad membrane expression of GPCRs in astrocytes allows

the efficient temporal integration of GPCR-mediated signals even if these receptors are expressed at relatively low levels (Araque et al., 2014).

1.3 GPCR expression in astrocytes: regional and local heterogeneity—

Describing cell types on the basis of their morphology has been a common practice in neurobiology. Astrocytes residing in the gray matter or in the white matter have long been morphologically distinguished as protoplasmic and fibrous astrocytes, respectively (Peters et al., 1976). In addition, some heterogeneity in regard to expression of Glial Acidic Fibrillary Protein (GFAP) or ion channels in astrocytes were noted (Miller, 2018). More recently, with the advent of genetically labeling techniques of astrocytes and molecular profiling, an unexpected level of heterogeneity among astrocytes has been revealed (Chai et al., 2017). RNA-sequencing and proteomics in distinct brain regions portrays a complex picture of local and age-dependent heterogeneity among astrocytes (Chai et al., 2017; Cuevas-Diaz Duran et al., 2019; John Lin et al., 2017; Morel et al., 2017). The implication of such molecular diversity among astrocytes is that astrocyte responses to GPCR activation may differ among brain regions (inter-regional) or even within a brain region (intraregional). This is notably apparent in the dorsal striatum, in which two distinct subpopulations of astrocytes intermingle, each communicating selectively with a distinct subpopulation of medium spinal neurons (D1 or D2 type) (Martin et al., 2015).

1.4 Both inhibitory and excitatory neurotransmitters increase astrocyte Ca^{2+} activity—

Specificity of neurotransmitter actions via GPCRs in neurons relies on activation of unambiguous G-protein pathways (Weis and Kobilka, 2018). G-proteins are heterotrimers (encompassing a&Y subunits) generally classified into four families, G_s, $G_{i/o}$, G_q, and $G_{12/13}$ based on the functional similarity of the Ga subunit (Cabrera-Vera et al., 2003; Ross, 1989; Weis and Kobilka, 2018). In neurons, Ga subunits of G_s and G_q classes in general, have an excitatory action in Ca^{2+} and electrical activity through activation of adenylyl cyclase and the phospholipase C pathway (Dunlap et al., 1987; Hille, 1992; Huang and Thathiah, 2015). On the other hand, $G_{i/o}$ pathways in neurons are known to decrease Ca^{2+} signaling and electrical excitability (Hille, 1992; Huang and Thathiah, 2015). This is exemplified by the multitude of recent studies using DREADDs (designer receptors exclusively activated by designer drugs) in neurons (Roth, 2016). To date, the reported actions on many neuronal types are by either silencing (e.g., Gi-based DREADDs) or activation (e.g., G_q -based DREADDs) of neuronal electrical and Ca^{2+} activity. However, the opposing actions of G_q and $G_{i/o}$ pathways and their cognate GPCRs in cellular excitability are less clear in astrocytes. Both G_q and $G_{i/o}$ coupled receptors when activated by endogenous neurotransmitters seem to evoke increases in Ca^{2+} activity in astrocytes (Covelo and Araque, 2018; D'Ascenzo et al., 2007; Durkee et al., 2019; Navarrete and Araque, 2008). Moreover both G_q and $G_{i/o}$ protein-coupled DREADDs promote Ca^{2+} increases in astrocytes (Durkee et al., 2019). In summary, the dominant effect of GPCR activation via multiple G-protein signaling pathways in astrocytes is elevation of Ca^{2+} levels.

2. GPCRs in astrocytes activated by neurotransmitters

2.1 Neurotransmitter Adenosine triphosphate (ATP)—

Purinergic neurotransmission involving ATP as the signaling molecule is found in many synapses in the

central and peripheral nervous systems (Abbracchio et al., 2009). Purinergic signaling are mediated by two families of GPCRs: P1 receptors that bind to adenosine and P2 receptors that are sensitive to ATP and adenosine diphosphate (ADP)(Abbracchio et al., 2009). ATP released as neurotransmitter or neuromodulator by neurons can act directly in astrocytic purinergic receptors as ATP or as a breakdown down product as ADP, AMP, and adenosine (Del Puerto et al., 2013; Fields and Burnstock, 2006). Breakdown of ATP occurs via extracellular ectonucleotidases. A plethora of different subtypes of P1 receptors have been described in astrocytes although A1R an A2ARs have received the most attention (Boison et al., 2010). In regard to P2 receptors in astrocytes, there are reports for both ionotropic P2X and the metabotropic P2Y receptors (Abbracchio and Ceruti, 2006). The presence of multiple purinergic receptors at the same astrocyte may lead to an abundance of effects, the common denominator being an increase in intracellular Ca^{2+}. P2Y receptors which are coupled to Gq proteins, the activation of which stimulates phospholipase C and subsequent release of Ca^{2+} from intracellular stores and activation of protein kinase C in response to inositol 1,4,5-trisphosphate and diacylglycerol production, respectively (Erb et al., 2006; Erb and Weisman, 2012; Weisman et al., 2012). In the acutely isolated optic nerve, P2X and P2Y agonists raised intracellular astrocyte Ca^{2+}. However, P2Y receptors were activated at nanomolar concentrations, whereas P2X purinoreceptors were only activated above 10 μM (James and Butt, 2001). In hippocampal slices, exogenous application of ATP or electrical stimulation of neuronal afferents lead to intracellular Ca^{2+} increases of astrocytes mediated by P2Y1 receptors (Bowser and Khakh, 2004; Di Castro et al., 2011; Shigetomi et al., 2008). Astrocytes in the hippocampus via P2Y1 receptors show localized Ca^{2+} events that are sensitive to spontaneous synaptic events (Di Castro et al., 2011). In the olfactory bulb, purinergic signaling via A2A and P2Y1 receptors in astrocytes evoke Ca^{2+} responses in astrocytes (Doengi et al., 2008). In the nucleus accumbens, P2Y1 receptor-mediated Ca^{2+} transients are also present (Molnar et al., 2011). In contrast to the well documented actions of purinergic receptor activation on Ca^{2+} signaling in astrocytes, the physiological consequences of this signaling remain less clear. The intercellular glia-to-glia signaling over long distances via ATP release to evoke intercellular calcium waves has been observed in retinal explants (Newman, 2001) but it is unclear whether such intercellular Ca^{2+} waves occur *in vivo.* Activation of P2Y1 receptors in astrocytes has been linked to actions in either the postsynaptic or presynaptic neuron in the tripartite synapse. For example, P2Y1 receptor activation of astrocytes in the spinal promotes the release of glutamate from astrocytes and subsequent activation of postsynaptic extrasynaptic NMDARs to generate the so called slow inward currents or SICs (Table 1)(Bardoni et al., 2010). SICs, which have been detected in several brain areas, increase neuronal excitability. P2Y1 receptor induced release of glutamate from astrocytes in the hippocampus also have been linked to activation of presynaptic NMDARs to cause an increase if excitatory receptor activity (Santello et al., 2011). Other actions of P2Y1 receptor activation in astrocytes has been the activation of neuronal mGluRs or P2X receptoes to promote increases of neuronal excitability or modulation of synaptic activity (Table 1).

2.2 Neurotransmitter GABA—GABA is the main inhibitory neurotransmitter in the central nervous system and act on ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. There has description of expression of both types of GABA receptors in astrocytes

(Charles et al., 2003; Fraser et al., 1994). In the ventral tegmental area (VTA) and the ventrobasal (VB) thalamic nucleus, the $GABA_B$ selective agonist baclofen elicited intracellular Ca^{2+} increases in astrocytes (Gould et al., 2014). In hippocampal slices, $GABA_B$ receptor-mediated calcium signals in astrocytes were also noted (Andersson et al., 2007; Meier et al., 2008). The mechanism of $GABA_B$-mediated Ca^{2+} events was shown to involve G-proteins and Ca^{2+} release from internal stores (Meier et al., 2008). It is unclear, however, which G-protein is responsible for the Ca^{2+} response, because GABAB receptors are known to be coupled to Gi/o proteins, at least in neurons, while Ca^{2+} release from internal stores usually requires Gq protein activation (however see above). In hippocampal slices, activation of gabaergic interneurons evoke astrocytic calcium signals which were blocked by the $GABA_B$ receptor antagonist CGP55845A (Kang et al., 1998; Perea et al., 2016)(Table 1). Direct stimulation of astrocytes potentiated miniature inhibitory postsynaptic currents (mIPSCs) in pyramidal neurons through activation of kainate receptors in inhibitory terminals (Kang et al., 1998). Interestingly, activation of interneurons and $GABA_B$ receptor signaling in astrocytes also can potentiate glutamatergic transmission of pyramidal neurons (Perea et al., 2016). Thus, an inhibitory GABA signal has the potential to become an excitatory signal through astrocyte activation. Other aspects of astrocytic mediated synaptic modulation has also been linked to $GABA_B$ receptors in astrocytes. For example, heterosynaptic depression in CA1 hippocampus also may depend on $GABA_B$ receptor signaling in astrocytes (Andersson et al., 2007). In the striatum, GABAergic medium spiny neurons trigger astrocytic calcium elevations via $GABA_B$ receptors. Chemogenetic of the Gi pathway of striatal astrocytes resulted in acute behavioral hyperactivity and disrupted attention (Nagai et al., 2019). Results in vivo also support the role of $GABA_B$ receptors in astrocytes in brain function. Conditional knockout of GABAB receptors in astrocytes induced alterations in hippocampal oscillatory activity in vivo suggesting the direct participation of $GABA_B$ receptor signaling of astrocytes in neuronal information processing (Perea et al., 2016).

2.3 Neurotransmitter Endocannabinoids—Endocannabinoids (ECBs) are released from neurons upon depolarization induced Ca^{2+} influx and serves as a retrograde acting neurotransmitter (Castillo et al., 2012; Kano, 2014; Kano et al., 2009; Ohno-Shosaku et al., 2012). The first conclusive evidence supporting retrograde ECB signaling came from the observation of depolarization-induced suppression of inhibition (DSI)/excitation (DSE) (Castillo et al., 2012; Kano, 2014; Kano et al., 2009; Ohno-Shosaku et al., 2012). Later, it was discovered that the ECB system is involved not only in short-term depression, but also in long-term depression (LTD) at both excitatory and inhibitory synapses (Castillo et al., 2012; Kano, 2014; Kano et al., 2009; Ohno-Shosaku et al., 2012). Since then, the ECB system has become the most-studied retrograde signaling system in the brain. In most cases, ECB-mediated retrograde signaling starts with the production of 2-AG, in response to increased intracellular Ca^{2+} concentration and/or activated Gq/11-coupled receptors (Kano, 2014; Kano et al., 2009; Ohno-Shosaku et al., 2012). 2-AG is then released into and traverses the extracellular space and arrives at the presynaptic terminal where it binds to the CB1R. Activated CB1R suppresses the release of neurotransmitter in two ways: first, by inhibiting voltage-gated Ca^{2+} channels, which reduce presynaptic Ca^{2+} influx; second, by inhibiting adenylyl cyclase (AC) and the subsequent cAMP/PKA pathway, which is

involved in LTD (Castillo et al., 2012; Kano et al., 2009). Albeit expressed in low levels in comparison to their neuronal counterparts, the CB1Rs in astrocytes are responsive to ECB signaling (Navarrete and Araque, 2008, 2010; Navarrete et al., 2014). ECBs released from neurons trigger the mobilization of Ca^{2+} from internal stores in astrocytes. Interestingly, ECB-induced astrocyte Ca^{2+} elevations are mediated by CB1Rs coupled to Gq/11 proteins that activate phospholipase C and produce inositol triphosphate (Busquets-Garcia et al., 2018). Several forms of synaptic plasticity have been linked with CB1R signaling in astrocytes (Table 1). In the somatosensory cortex, astrocyte CB1 receptors mediates spike-timing-dependent depression in the L4 to L2/3 synapses (Min and Nevian, 2012). In the hippocampus, astrocyte CB1 receptors are necessary for heterosynaptic short-term facilitation of synaptic transmission (Navarrete and Araque, 2010). Longer lasting forms of synaptic plasticity in some conditions can be modulated by astrocyte CB1 receptors (Robin et al., 2018). ECBs in the striatum can induce lateral heterosynaptic Potentiation in a CB1R astrocyte dependent manner (Martin et al., 2015).

2.4 Neurotransmitter Glutamate—Glutamate is the main excitatory neurotransmitter in the CNS and not surprisingly acts on astrocytes in many brain regions. Although few reports have suggested the existence of ionotropic glutamate receptors in astrocytes, it is generally accepted that glutamatergic signaling in these glial cells proceeds mainly via metabotropic glutamate receptors (mGluR). mGluRs are subclassified into three groups based on sequence homology, G-protein coupling, and ligand selectivity. Group I includes mGluRs 1 and 5, Group II includes mGluRs 2 and 3, and Group III includes mGluRs, 4, 6, 7, and 8. mGlul, mGlu3, and mGlu5 receptors are found in astrocytes in different levels depending on the developmental stage and brain region. There is ample evidence supporting the notion that mGluR5 is the most relevant glutamate receptor expressed in astrocytes *in culture* and *in situ.* Stimulation of glutamatergic neuronal afferents in hippocampal slices triggers Ca^{2+} waves in astrocytes inhibited by mGluR5 antagonists. In other brain regions such as the nucleus accumbens and the thalamus, mGluR5s are also critically involved in astrocytic responses to glutamatergic neurotransmission. Moreover, *in vivo* sensory stimulation also evoke astrocyte Ca^{2+} responses that are sensitive to mGluR5 antagonists. The expression of mGlu5 in astrocytes is high prenatally and decreases during development (Cai et al., 2000; Sun et al., 2013), when mGluR3 are upregulated, which has suggested that mGluR5 might play a minor role in adult stages (Sun et al.,2013). However, although the relative mGluR5/mGluR3 expression is reduced, mGluR5 receptors still play prominent functional role in astrocytes in adults, as demonstrated of mGluR5-dependent responses in a number of studies in *ex vivo* and *in vivo* preparations (Table 1). Moreover, it is clear that many receptors are expressed in astrocytes at low abundance and yet have a prominent role. For example, CBIRs in astrocytes are expressed in seemingly low levels in astrocytes in situ, but they can be detected by electron microscopy (Han et al., 2012) and they can respond to neuronal released ECBs (see above).

2.5 Neurotransmitter Norepinephrine—The neurotransmitter norepinephrine is mainly released from the locus cerueleus (LC) and has broad influence in multiple brain areas. Norepinephrine as other catecholamines are released from neurons from axonal varicosities and therefore act via “volume transmission”. Astrocytes express a_1, a_2 and

β_1 adrenergic receptors (Cahoy et al., 2008; Hertz et al., 2010) and are able to respond to norepinephrine released from neurons (Bekar et al., 2008; Ding et al., 2013). *In vivo,* stimulation of LC neurons trigger transient increases in cortical astrocytic Ca^{2+}, which can be blocked with the non-specific a-adrenergic receptor blocker, phentolamine (Bekar et al., 2008). Moreover, locomotion triggers activation of astrocyte networks in multiple brain regions and this activation is blocked by a -adrenoceptor antagonists (Paukert et al., 2014).

2.6 Neurotransmitter Dopamine—While dopamine action in cultured astrocytes has been largely documented, the functional presence of dopamine receptors *in situ* has been elusive until recent studies that have shown astrocyte responses to dopamine in several brain areas. dopamine D2R activation of astrocytes has been shown to suppress ap-crystallin mediated neuroinflammation *in vivo* (Shao et al., 2013) and to decrease intracellular Ca^{2+} levels in hippocampal (Jennings et al., 2017) and ventral midbrain astrocytes (Xin et al., 2019), whereas D1R activation by exogenous dopamine elevates intracellular Ca^{2+} in hippocampal astrocytes (Jennings et al., 2017). Moreover, we have recently shown by electron microscopy the presence of D1Rs in astrocytes of the nucleus accumbens, and that their activation *in vivo* and *in situ by* synaptically-released dopamine triggers their intracellular Ca^{2+} elevations through GPCR signaling cascade involving IP3R2 and intracellular Ca^{2+} mobilization (Corkrum et al., 2020).

2.7 Neurotransmitter Acetylcholine—Acetylcholine (ACh) was the first neurotransmitter identified by Loewi by its actions on the heart (Brown, 2006). Since then, the multiple roles of ACh in synaptic communication have been identified (Picciotto et al., 2012). Cholinergic circuits have been implicated in normal and abnormal cognitive functions and disruption of cholinergic circuitry is likely to be at least partly responsible for the cognitive impairments seen in neurodegenerative disorders (Ballinger et al., 2016; Hampel et al., 2018). While the mechanism by which cholinergic signaling influences cognitive processes has been assumed to be direct cholinergic stimulation of pre- and postsynaptic neuronal receptors, a neglected area of investigation is the role of ACh in astrocytes. Muscarinic and nicotinic receptors have been identified in astrocytes (Guizzetti et al., 2008; Hernandez et al., 2014; Murphy et al., 1986; Van Der Zee et al., 1993). Cholinergic agonists or synaptically released ACh evoke $Ca2^{+}$ elevations of astrocytes in hippocampal slices (Araque et al., 2002; Perea and Araque, 2005). Pharmacological approaches have revealed that muscarinic receptors mediate such effects (Araque et al., 2002; Perea and Araque, 2005). In vivo cholinergic activity evoked by sensory stimulation or electrical stimulation of the septal nucleus increases Ca^{2+} in hippocampal astrocytes and induces LTP of CA3-CA1 synapses (Navarrete et al., 2012). Moreover, this cholinergic-induced LTP requires activation of muscarinic receptors in astrocytes, $Ca2^{+}$ elevations in astrocytes and astrocytic glutamate release (Navarrete et al., 2012). Thus in this form of synaptic plasticity in the hippocampus, astrocytes integrate afferent cholinergic activity via muscarinic receptor activation which then triggers the release of glutamate in the CA3-CA1 synapse to induce LTP (Navarrete et al., 2012). Likewise, in the mouse barrel cortex the plasticity induced by sensory stimulation concomitant with activation of cholinergic afferents from nucleus basalis of Meynert (NBM) is dependent upon muscarinic activation of astrocytes and astrocytic $Ca2^{+}$ elevations (Takata et al., 2011). Moreover, pairing electrical stimulation of the NBM and visual stimulation

potentiated visual responses in excitatory neurons of the primary visual cortex through activation of muscarinic AChRs in cortical astrocytes (Chen et al., 2012). Interestingly, although not the topic of this review, nicotinic receptors expressed in hippocampal astrocytes have been linked to another form of synaptic plasticity also in the hippocampus (Pabst et al., 2016). ACh released by septal projection neurons can activate astrocytes in the hilus not via muscarinic receptors but via $Ca2^{+}$ -permeable nicotinic receptors. Such astrocytic activation is then followed by excitatory input to GABAergic hilar interneurons, resulting in inhibition of dentate gyrus granule cells (Pabst et al., 2016).

3. GPCRs in neurons activated by gliotransmitters

As described above, a major consequence of the GPCR activation in astrocytes by synaptically- released neurotransmitters is mobilization of the Ca^{2+} from internal stores. The elevated intracellular Ca^{2+} is known to stimulate the release of gliotransmitters, such as glutamate, D- serine, ATP, adenosine and GABA (Figure 2). Indeed, while several molecular mechanisms, probably not mutually exclusive, has been proposed to mediate gliotransmitter release (Guerra- Gomes et al., 2017; Hamilton and Attwell, 2010; Rusakov et al., 2014; Shigetomi et al., 2016; Volterra et al., 2014), a considerable amount of evidence indicates that the calcium- and SNARE protein-dependent process is a prominent mechanism underlying gliotransmitter release from astrocytes (Araque et al., 2000; Bezzi et al., 2004; Bohmbach et al., 2018; Perea and Araque, 2005; Schwarz et al., 2017); for a recent review, see (Savtchouk and Volterra, 2018).

Astrocytes can release a plethora of neuroactive substances that can control different aspects of neuronal development and function, such as prostaglandins (Clasadonte et al., 2011), thrombospondin (Christopherson et al., 2005; Eroglu et al., 2009), or TNFa (Beattie et al., 2002; Stellwagen and Malenka, 2006). In the following paragraphs, we will focus on the regulatory effects on synaptic transmission and plasticity of gliotransmitters that are known to act through activation of GPCRs in neurons. Hence, we will not discuss other important gliotransmitters, like D-serine, which is known to be co-agonist of NMDA receptors, that have relevant effects on synaptic transmission and plasticity (Araque et al., 2014; Oliet and Mothet, 2009).

3.1 Gliotransmitter Glutamate—

Glutamate was the first gliotransmitter identified as mediator of astrocyte-neuron signaling. It was originally reported to evoke neuronal calcium increases and slow inward currents (SICs) by activation of neuronal NMDA receptors (Angulo et al., 2004; Araque et al., 1998a; Fellin and Carmignoto, 2004; Parpura et al., 2004; Perea and Araque, 2005). The astrocytic glutamate was also soon reported to regulate synaptic efficacy through activation of neuronal metabotropic glutamate receptors mGluRs (Araque et al., 1998a; Araque et al., 1998b). Later studies in brain slices demonstrated that mGluR-dependent synaptic regulation by astrocytes occurs in different brain areas.

In the hippocampus, activation of type 1 mGluRs present at presynaptic terminals of the Schaffer collaterals by astrocytic glutamate induces a transient short-term enhancement of synaptic efficacy (Covelo and Araque, 2018; Gomez-Gonzalo et al., 2017; Navarrete and Araque, 2010; Perea and Araque, 2007; Perea et al., 2016). In contrast, a heterosynaptic

depression in these synapses has been found to be mediated by type 2/3 mGluRs activated by astrocytic glutamate (Andersson et al., 2007). Furthermore, glutamatergic signaling from astrocytes has also been reported to be able to trigger the long-term potentiation or depression of hippocampal synaptic transmission (Adamsky et al., 2018; Gomez-Gonzalo et al., 2017; Han et al., 2012; Min and Nevian, 2012; Navarrete et al., 2012; Perea and Araque, 2007).

Similar mGluR1-dependent transient potentiation of synaptic transmission has been reported in the striatum (Martin et al., 2015). Notably, the astrocyte-induced synaptic regulation in this brain area was found to be synapse-specific, i.e., subpopulations of astrocytes that selectively respond to the activity of medium spiny neurons of the two main corticostriatal circuits —the direct and indirect pathways— specifically regulate corticostriatal synapses belonging to either pathways (Martin et al., 2015). These findings indicate that the gliotransmitter glutamate may trigger a variety of synaptic effects, depending on the specific neuronal GPCRs activated at the Tripartite Synapse.

3.2 Gliotransmitter ATP/adenosine—Purinergic signaling mediated by activation of neuronal GPCRs can also lead to synaptic regulation through several mechanisms and in different brain areas. ATP released from astrocytes is known to be metabolized by extracellular ATPases to produce adenosine, which acting on metabotropic A1 and A2A receptors regulate synaptic transmission. In addition, the direct astrocytic release of adenosine has been found to occur in experimental models of hypoxia to depress synaptic transmission in Schaffer collateral- CA1 hippocampal synapses (Martin et al., 2007). Astrocyte derived adenosine have been shown to activate neuronal presynaptic A1 or A2A receptors to distinctly regulate synaptic transmission, enhancing or depressing synaptic transmitter release, respectively. For example, activation of A1 receptors by astrocytic ATP/adenosine has been shown to depress synaptic transmission in the hippocampus (Chen et al., 2012; Covelo and Araque, 2018; Pascual et al., 2005; Perez- Rodriguez et al., 2018; Serrano et al., 2006; Zhang et al., 2003), cortex (Halassa et al., 2009), cerebellum (Brockhaus and Deitmer, 2002), retina (Newman, 2003), amygdala (Martin- Fernandez et al., 2017), and nucleus accumbens (Corkrum et al., 2019). In contrast, A2A receptor activation has been reported to enhance neurotransmission in the hippocampus (Panatier et al., 2011) and hypothalamus (Gordon et al., 2005; Gordon et al., 2009).

Remarkably, the release of ATP/adenosine from the same astrocyte can differentially affect specific neuronal circuits depending on the presynaptic receptors expressed. Indeed, we have recently shown in the centromedial nucleus of the amygdala that astrocytic ATP/adenosine depresses excitatory neurotransmission in synaptic inputs from the basolateral amygdala through activation of presynaptic A1 receptors, whereas it enhances synaptic transmission of inhibitory inputs from the central lateral amygdala through activation of presynaptic A2A receptors (Martin-Fernandez et al., 2017).

3.3 Gliotransmitter GABA—The activity of GABA transporters in astrocytes controls the extracellular levels of GABA, contributing to the magnitude of GABA tonic currents that may have several physio-pathological consequences (Cope et al., 2009; Shigetomi et al., 2011; Yu et al., 2018). In addition, astrocytes are able to release GABA (Gaidin et al., 2019;

Kozlov et al., 2006; Le Meur et al., 2012; Lee et al., 2010), which acting on GPCR $GABA_B$ receptors may influence synaptic transmission. The work of Justin Lee's group has shown novel mechanisms of GABA production and release from astrocytes (Oh and Lee, 2017; Yoon and Lee, 2014), and has reported GABA-mediated synaptic regulation in different brain areas. In the hippocampus, activation of $GABA_B$ receptors in GABAergic interneurons by astrocytic GABA leads to the disinhibition of hippocampal excitatory synapses from the perforant pathway into dentate granule neurons (Yarishkin et al., 2015), which has been suggested to have relevant implications in Alzheimer's disease (Jo et al., 2014). In the cerebellum, astrocytic GABA regulation of parallel fiber-Purkinje cell synapses contributes to motor coordination (Woo et al., 2018).

4. Concluding remarks

In summary, the GPCR-mediated bidirectional communication between astrocytes and neurons presents a high degree of diversity (Durkee and Araque, 2019). Indeed, astrocytes respond with Ca^{2+} elevations to multiple neurotransmitters (e.g., glutamate, GABA, ACh, norepinephrine, etc.) that activate astrocytic GPCRs, which, in turn, stimulate the release of diverse gliotransmitters (e.g., glutamate, GABA, ATP/adenosine or D-serine). Such a high diversity of signaling grants a plethora of potential effects that may have important functional consequences. However, several questions can be formulated regarding this issue. For example, do different neurotransmitters acting on different GPCRs lead to the release of different gliotransmitters? This is interesting question remains to be investigated. On the other hand, can a single neurotransmitter acting on a specific GPCR stimulate the release of different gliotransmitters? We have recently addressed this question showing that a single hippocampal astrocyte is capable of releasing two gliotransmitters, i.e., glutamate and ATP/adenosine, in response to the stimulation of a single interneuron that signal to astrocytes through activation of astrocytic $GABA_B$ receptors (Covelo and Araque, 2018). Furthermore, we have found that the astrocytic glutamate- ad ATP/adenosine-mediated effects on synaptic transmission depended on the duration and frequency of the interneuron stimulation, indicating that astrocytes can decode neuronal inputs and integrate this information into specific gliotransmitter release (Covelo and Araque, 2018). Since the research on the bidirectional communication between astrocytes and neurons is still in its infancy it is likely that future research will provide novel and exciting new findings on the role of GPCR-mediated astrocyte neuron signaling in brain physiology and pathology.

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Highlights

- Astrocytes sense synaptic activity through G protein-coupled receptor activation
- GPCR activation in astrocytes increases their intracellular calcium
- GPCR activation stimulates gliotransmitter release from astrocytes
- Gliotransmitters regulate synaptic function by activation of neuronal GPCRs
- GPCR-mediated bidirectional communication astrocyte-neuron regulates behavior

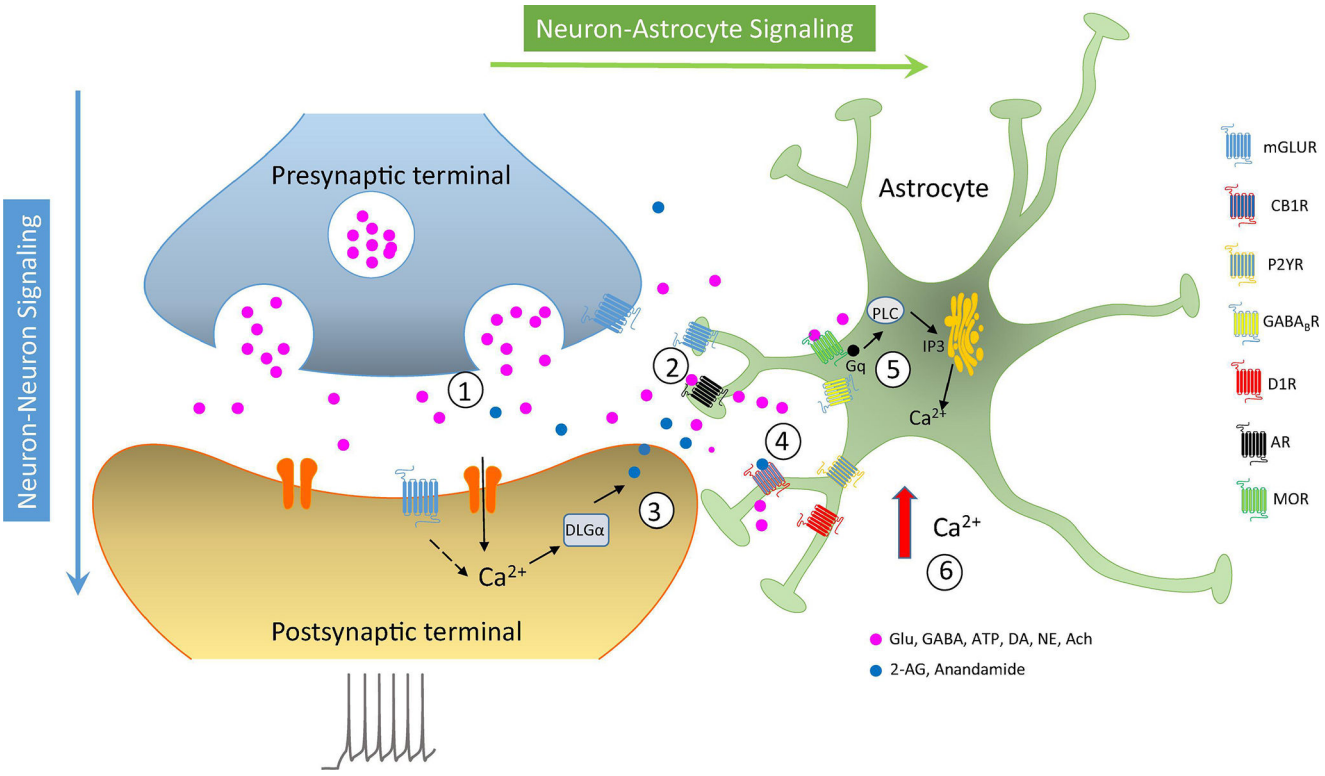

FIGURE 1: Neuron-Astrocyte Signaling at the Tripartite Synapse.

Presynaptic neurons release neurotransmitters (1) that bind to GPCR in postsynaptic cells and astrocytes (2). Activation of GPCRs in astrocytes elicits the activation of PLC cascade (5) resulting in elevation of intracellular Ca^{2+} (6). Increases in postsynaptic Ca^{2+} also leads to release of ECBs (3) that activate CBIRs (4). mGluR, metabotropic glutamate receptor; CB1R, cannabinoid receptor type 1; P2YR, purinergic receptor type 2; $GABA_BR$, GABA receptor type B; D1R; dopamine receptor type 1; AR, adenosine receptor; MOR, p-type opioid receptor; DLGa, diacylglycerol lipase type a; PLC, phospholipase C.

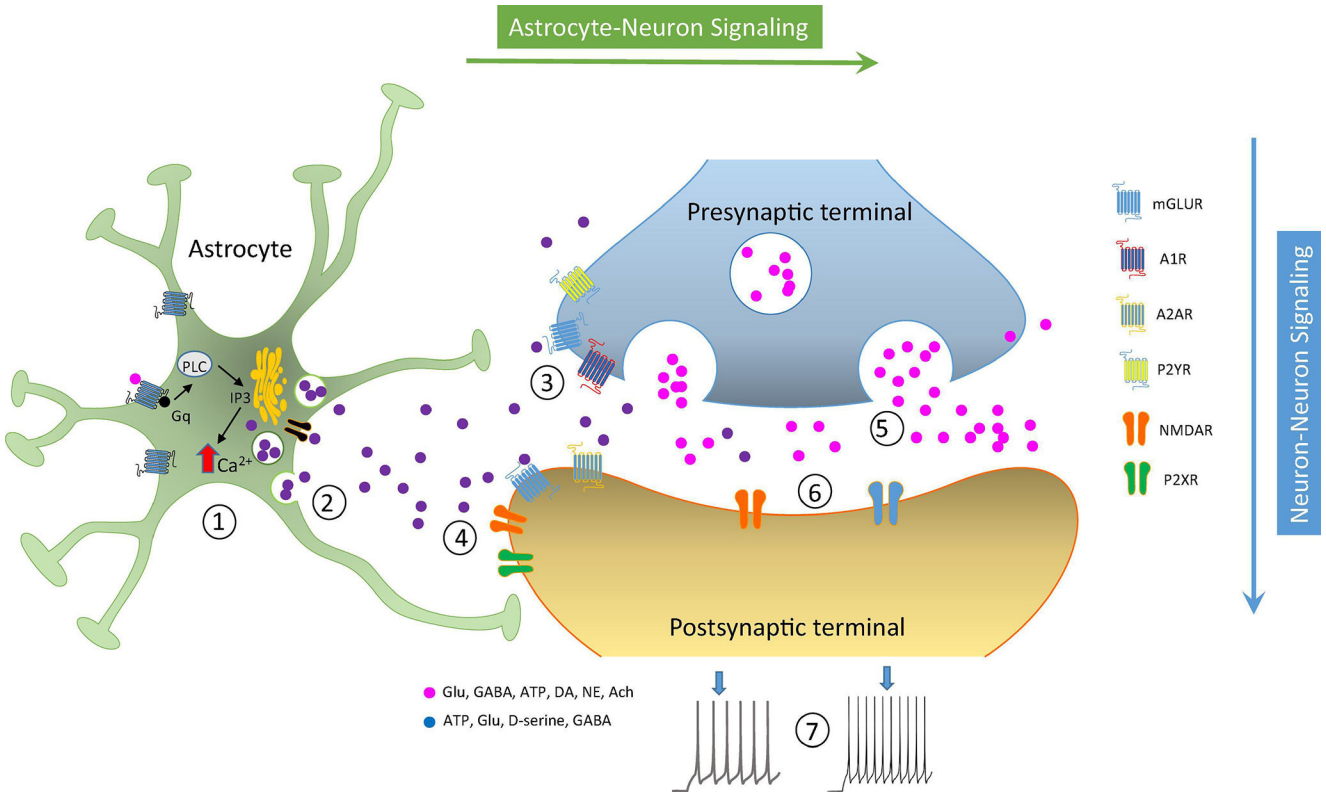

FIGURE 2: Astrocyte-Neuron Signaling at the Tripartite Synapse.

Activation of PLC cascade and resulting intracellular Ca^{2+} increases (1) promotes release of gliotransmitters (2) that act upon presynaptic (3) or postsynaptic (4) GPCRs or channels. Presynaptic release (5) or postsynaptic excitability are therefore regulated by astrocytic released gliotransmitters. mGluR, metabotropic glutamate receptor; P2YR, purinergic receptor type 2; A1R, adenosine receptor type 1; A2AR, adenosine receptor type 2A; NMDAR, N-methyl-D-aspartate receptor; P2XR, purinergic receptor type P2X; PLC, phospholipase C.

TABLE 1:

GPCR astrocyte to neuronal signaling in diverse brain areas and actions in neurons.

GPCR in astrocytes	Brain Region	Gliotransmitter	Receptor in the Neuron	Action in the Neuron	Reference
Alpha-1 Adrenergic	Hypothalamic paraventricular nucleus	ATP	AMPA	Increase of EPSC amplitude	(Gordon, Baimoukhametova et al. 2005)
Alpha-1 Adrenergic	Cortex	ATP	ATP	LTP modulation	(Pankratov and Lalo 2015)
CB1	Cortex	ATP and D-serine	P2X	LTP modulation	(Rasooli-Nejad, Palygin et al. 2014)
CB1	Hippocampus	Glutamate	mGlu	Heterosynaptic potentiation	(Navarrete and Araque 2010)
CB1	Hippocampus	Glutamate	NMDA	LTD	(Han, Kesner et al. 2012)
CB1	Cortex	Glutamate	NMDA	LTD	(Min and Nevian 2012)
CB1	Hippocampus	Glutamate	mGluR	Synaptic Potentiation	(Covelo and Araque 2018)
CB1	Striatum	Glutamate	mGLuR1/5	Heterosynaptic potentiaon	(Martin, Bajo-Graneras et al. 2015)
CB1	Hippocampus	D-serine	NMDA	LTP modulation	(Robin, Oliveira da Cruz et al. 2018)
CB1	Amygdala	ATP	A1	Synaptic Inhibition	(Martin-Fernandez, Jamison et al. 2017)
CB1	Neocortex	ATP	P2X	LTP modulation	(Rasooli-Nejad, Palygin et al. 2014)
D1	Nucleus Accumbens	Dopamine	ATP/ adenosine	EPSC amplitude depression	(Corkrum et al., 2020)
$GABA_B$	Hippocampus	Glutamate	AMPA/ NMDA	Frequency increase of miniature IPSCs	(Kang, Jiang et al. 1998)
$GABA_B$	Hippocampus	Glutamate	mGlu	Transient Heterosynaptic Depression	(Andersson, Blomstrand et al. 2007)
$GABA_B$	Medial nucleus of the trapezoid body	D-serine	NMDA	Slow Inward Currents	(Reyes-Haro, Muller et al. 2010)
$GABA_B$	Hippocampus	ATP	A1	Heterosynaptic depression of EPSCs	(Serrano, Haddjeri et al. 2006)
$GABA_B$	Striatum	thrombospondin-1		Enhance synaptic transmission and excitability	(Nagai, Rajbhandari et al. 2019)
$GABA_B$	Hippocampus	ATP	A1	Enhancement of synaptic inhibition	(Matos, Bosson et al. 2018)
$GABA_B$	Hippocampus	ATP	A1	Synaptic Depression	(Covelo and Araque 2018)
$GABA_B$	Hippocampus	Glutamate	mGlu	Synaptic Potentiation	(Perea, Gomez et al. 2016)
$GABA_B$	Hippocampus	Glutamate	mGlu	Synaptic Potentiation	(Covelo and Araque 2018)
mACh	Hippocampus	Glutamate	NMDA	Slow Inward Currents	(Perea and Araque 2005)
mACh	Hippocampus	Glutamate	mGlu	LTP	(Navarrete, Perea et al. 2012)
mACh	Cortex	Glutamate	NMDA	Slow Inward Currents	(Chen, Sugihara et al. 2012)
mACh	Cortex	D-serine	NMDA	Modulation of LTP	(Takata, Mishima et al. 2011)
Group I mGlu	Hippocampus	Glutamate	NMDA	Slow Inward Currents	(Fellin, Pascual et al. 2004)

GPCR in astrocytes	Brain Region	Gliotransmitter	Receptor in the Neuron	Action in the Neuron	Reference
mGlu	Hippocampus	Glutamate	NMDA	Slow Inward Currents	(Sasaki, Kuga et al. 2011)
mGlu	Ventro basal thalamus	Glutamate	NMDA	Slow Inward Currents	(Pirttimaki, Hall et al. 2011)
mGlu	Hypothalamic paraventricular nucleus	ATP	P2X	Increase of EPSC amplitude	(Gordon, Iremonger et al. 2009)
mGlu	Hippocampus and Cortex	Glutamate	NMDA	Slow Inward Currents	(Gomez-Gonzalo, Martin-Fernandez et al. 2017)
mGluR2	Thalamus	Glutamate	mGlu	Synaptic inhibition	(Copeland, Wall et al. 2017)
mGluR3	Hippocampus	eCB	CB1	Transient Heterosynaptic Depression	(Smith, Bekar et al. 2019)
mGluR5	Cortex	Glutamate	NMDA	Slow Inward Currents	(Ding, Fellin et al. 2007)
mGluR5	Hippocampus	ATP	A2A	Increase basal synaptic transmission	(Panatier, Vallee et al. 2011)
mGluR5	Nucleus Accumbens	Glutamate	NMDA	Slow Inward Currents	(D'Ascenzo, Fellin et al. 2007)
mGluR5 and CCK2	Dorsomedial Hypothalamus	ATP	P2X	LTP modulation of GABA synapses	(Crosby, Murphy-Royal et al. 2018)
Mu-opioid	Nucleus Accumbens	Glutamate	NMDA	Slow Inward Currents	(Corkrum, Rothwell et al. 2019)
P2Y1	Cerebellum	Glutamate	NMDA	Activation of inhibitory interneurons	(Rudolph, Jahn et al. 2016)
P2Y1	Hippocampus	Glutamate	NMDA	Frequency increase of miniature PSCs	(Santello, Bezzi et al. 2011)
P2Y1	Hippocampus	Glutamate	NMDA	Frequency increase of spontaneous EPSCs	(Jourdain, Bergersen et al. 2007)
P2Y1	Hippocampus	Glutamate	mGlu	Increase neuronal excitability	(Alvarez-Ferradas, Morales et al. 2015)
P2Y1	Cortex	ATP	P2X	Synaptic modulation	(Lalo, Bogdanov et al. 2019)
P2Y	Spinal cord	Glutamate	NMDA	Slow Inward Currents	(Bardoni, Ghirri et al. 2010)
PAR1	Hippocampus	Glutamate	NMDA	Slow Inward Currents	(Shigetomi, Bowser et al. 2008)