NEUROSCIENCE

REVIEW

D. Yang et al. / Neuroscience 456 (2021) 114–130

Cholinergic and Adenosinergic Modulation of Synaptic Release

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Abstract—In this review we will discuss the effect of two neuromodulatory transmitters, acetylcholine (ACh) and adenosine, on the synaptic release probability and short-term synaptic plasticity. ACh and adenosine differ fundamentally in the way they are released into the extracellular space. ACh is released mostly from synaptic terminals and axonal bouton of cholinergic neurons in the basal forebrain (BF). Its mode of action on synaptic release probability is complex because it activate both ligand-gated ion channels, so-called nicotinic ACh receptors and G-protein coupled muscarinic ACh receptors. In contrast, adenosine is released from both neurons and glia via nucleoside transporters or diffusion over the cell membrane in a non-vesicular, non-synaptic fashion; its receptors are exclusively G-protein coupled receptors. We show that ACh and adenosine effects are highly specific for an identified synaptic connection and depend mostly on the presynaptic but also on the postsynaptic receptor type and discuss the functional implications of these differences.

This article is part of a Special Issue entitled: Metabotropic Regulation of Synaptic Plasticity.

Key words: Neuromodulation, Short-term synaptic plasticity, G-protein coupled receptors, acetylcholine, adenosine.

INTRODUCTION

The neurotransmitter release probability at different synapses in the brain differs widely and has been reported to be as low as 0.1 and as high as 0.9 (Branco and Staras, 2009). In addition, the release probability is developmentally regulated and appears to decrease with neuronal maturation as the increase in the paired-pulse ratio (PPR) observed for many synapses (for a review s. Feldmeyer and Radnikow, 2009).

Voltage-gated Ca^{2+} (Ca_v) channels fall into three different subfamilies, named Ca_v1 (L-type), Ca_v2 (N-, P/Q- and R-subtypes), and Ca_v3 channels (T-type). Each of those consists of a pore-forming α_1 subunit consisting of four pore-forming domains in the cell membrane that are interconnected via cytoplasmic loops. In addition, the Ca_v1 and Ca_v2 channels have several accessory subunits, the extracellular $\alpha_2\delta$-, intramembranous γ_1-, and the intracellular β-subunit. These subunits are involved in determining the time course of Ca^{2+} channel activation, deactivation and inactivation (Nanou and Catterall, 2018).

Of the four Ca_v1 channel subtypes only $Ca_v1.2$ and $Ca_v1.3$ are expressed in the central nervous system. Neuronal $Ca_v1.2$ channels which are located in the membrane of *postsynaptic* dendrites and dendritic spines of excitatory neurons are part of a signalling cascade involved in the induction of long-term synaptic potentiation. These channel subtypes are generally located postsynaptically in neuronal soma and dendrites. $Ca_v1.2$ channels play an important role in the establishment of long-term synaptic plasticity. In contrast $Ca_v1.3$ channels are involved in increased excitability of substantial nigra dopaminergic neurons and striatal medium spiny neurons. In addition, $Ca_v1.3$ is the primary Ca_v channel in the sound-transducing inner hair cells of the inner ear; here it initiates glutamate release from the specialised 'ribbon' synapse at the base of the hair cell (Calin-Jageman and Lee, 2008; Simms and Zamponi, 2014; Nanou and Catterall, 2018).

Most Ca^{2+} channels that mediate voltage-dependent neurotransmitter release and determine short-term synaptic plasticity belong to the Ca_v2 subfamily comprising the $Ca_v2.1$ (P/Q-type), $Ca_v2.2$ (N-type), and

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Abbreviations: ACh, acetylcholine; DAG, diacylglycerol; FS, fast-spiking; GPCR, G protein-coupled receptor; IP_3, inositol trisphosphate; LTD, long-term depression; LTP, long-term potentiation; mAChRs, muscarinic ACh receptors; nAChRs, nicotinic ACh receptors; PIP_2, phospholipid phosphatidyl-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; PPR, paired-pulse ratio; SNR, signal-to -noise ratio; TRP, transient receptor potential; VIP, vasoactive intestinal peptide.

https://doi.org/10.1016/j.neuroscience.2020.06.006

$Ca_v2.3$ (R-type) channels (Uchitel et al., 1992; Reid et al., 2003; Pietrobon, 2005; Nanou and Catterall, 2018; Mochida, 2019). Ca_v2 channels are located close to the docking sites of synaptic vesicle in the active zone of a presynaptic terminal. If an action potential invades the *presynaptic* terminal the resulting depolarisation leads to channel opening and rapid Ca^{2+} influx that will initiate the fusion of synaptic vesicles with the presynaptic membrane; the absolute amplitude and time course of the change in presynaptic Ca^{2+} determines also the short-term synaptic plasticity which is specific for different synapse types (Meinrenken et al., 2003; Südhof, 2012, 2014; Walter et al., 2018). For different presynaptic terminals, synaptic transmission may be mediated by only one of these channel types but synapses with the contribution of two or even three types have also been identified (e.g. Takahashi and Momiyama, 1993; Wu et al., 1998; Bischofberger et al., 2002; Miyazaki et al., 2005; Shin et al., 2018). In this context it is of note that at inhibitory synapses in insular cortex the depressive and facilitative short-term plasticity is mediated by presynaptic $Ca_v2.1$- and $Ca_v2.2$ channels, respectively (Yamamoto and Kobayashi, 2018).

Ca_v3 (T-type) channels are not directly involved in neurotransmitter release but have been found to drive low-frequency (1–4 Hz) rhythmic activity in thalamic neurons that contributes to the occurrence of delta waves in the EEG of humans and animals during non-rapid eye movement (NREM) sleep (Crunelli and Hughes, 2010; Deleuze et al., 2012; see also Zamponi et al., 2015). The rhythmic spiking activity is mediated through a dynamic interaction of Ca_v3 channels with hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels via a Ca^{2+}-mediated increase in adenylate cyclase activity and a concomitant rise in the intracellular cyclic adenosine monophosphate (cAMP) concentration (McCormick and Pape, 1990; Leresche et al., 1991; Soltesz et al., 1991; Steriade et al., 1993; Contreras and Steriade, 1995). In addition, Ca^{2+} influx through dendritic Ca_v3 channels activates among other ion channels Ca^{2+}-dependent, voltage-insensitive 'small conductance' (SK) K^+ channels which are essential for the generation of regular burst-like action potential firing (McCormick and Pape, 1990; Wei et al., 2005; Cueni et al., 2009; Berkefeld et al., 2010).

Ca_v channels are tightly regulated by different types of G protein-coupled receptors (GPCRs). GPCRs are a family of seven transmembrane receptors tightly coupled to G proteins with an extracellular binding site e.g. neurotransmitters, peptides, nucleotides etc. (Hilger et al., 2018). G proteins are a family of integral heterotrimeric membrane proteins consisting of an α, β and γ subunit of which the β and γ subunits form an obligate $\beta\gamma$ subunit complex. In the resting state the α and $\beta\gamma$ subunits of G proteins are associated but dissociate upon activation of the GPCR; following that they will initiate different intracellular signalling cascades. Based on their α subunit, G proteins are subdivided into four different types, the G_s, G_i, G_q, and G_{12} proteins (for reviews see Oldham and Hamm, 2008; Syrovatkina et al., 2016). Of those only the first three are involved in the regulation of ion channel activity including that of neuronal Ca_v channels (s. Fig. 1A–C).

Activation of G_s coupled receptors will result in a dissociation of the α_{Gs} and $\beta\gamma$ subunit complex. The $\beta\gamma$ subunit complex will rapidly activate both $Ca_v2.1$ and $Ca_v2.2$ (P/Q- and N-type) Ca^{2+} channels in a direct, membrane-delimited interaction; the α subunit will stimulate AC thereby increasing the concentration of cyclic adenosine monophosphate (cAMP), a positive modulators of Ca_v1 Ca^{2+} channels (Fig. 1A). In contrast, dissociation of the α and $\beta\gamma$ subunit complex of G_i proteins results in an inhibition of $Ca_v2.1$ and $Ca_v2.2$ channels via $G_{\beta\gamma}$ signalling; In addition, AC activity is inhibited by the α_{Gi} subunit so that the cAMP concentration decreases resulting in a reduced Ca_v1 channel activity.

The dissociation of the α_{Gq} and $\beta\gamma$ subunits of G_q proteins causes an α_{Gq}-mediated activation of phospholipase C (PLC). PLC hydrolyses the membrane phospholipid phosphatidyl-bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol trisphosphate (IP_3). IP_3 binds to its receptor in the endoplasmic reticulum to produce intracellular Ca^{2+} release that directly contributes in synaptic enhancement (Fernandez de Sevilla et al., 2008. DAG, on the other hand, enhances the activity of protein kinase C (PKC) and its downstream signalling pathways. In addition, DAG activates ion channels such as transient receptor potential (TRP) channels thereby inducing Ca^{2+} influx which is, however, not tightly coupled to synaptic transmission. Phospholipids such as PIP_2 increase the open probability of many ion channel types such as inward rectifier K^+ (K_{ir}) channels, Ca^{2+}-activated K^+ channels and $Ca_v2.2$ channels (for reviews see Delmas et al., 2005; Hille et al., 2015; Logothetis et al., 2015). Because the PIP_2 concentration is reduced following G_qPCR activation, Ca^{2+} influx through $Ca_v2.2$ channels (N-type Ca^{2+} channels) decreases and in turn the synaptic release probability is reduced.

In this review we will discuss mainly two neuromodulatory transmitters, namely acetylcholine (ACh) and adenosine, which differ in their metabotropic receptor type, G protein type, and mode of release. ACh binds to both ligand-gated ion channels (nicotinic ACh receptors, nAChRs) and to G-protein-coupled receptors (muscarinic ACh receptors, mAChRs). There are five subtypes of mAChRs, the M_1—M_5 receptors. Of those, the M_2 and M_4 are coupled to G_i proteins while the M_1, M_3, and M_5 receptors are coupled to G_q proteins (for reviews s. Thiele, 2013; Fernández de Sevilla et al., 2020). Adenosine receptors are exclusively G protein-coupled receptors; four different subtypes exist, the adenosine receptors A_1, A_{2A}, A_{2B}, and A_3; A_1 and A_{2A} receptors have a high adenosine affinity while A_{2B} and A_3 have a low affinity. A_1 receptors are coupled to G_i, A_{2A} to G_s, A_{2B} to G_s, and G_q and A_3 to G_i proteins (Dunwiddie and Masino, 2001; Chen et al., 2014).

Furthermore, ACh and adenosine differ fundamentally in the way they are released into the extracellular space. ACh is released mostly from axonal afferents of cholinergic neurons located in an extracortical brain region, the basal forebrain (BF) (see below). Its mode of

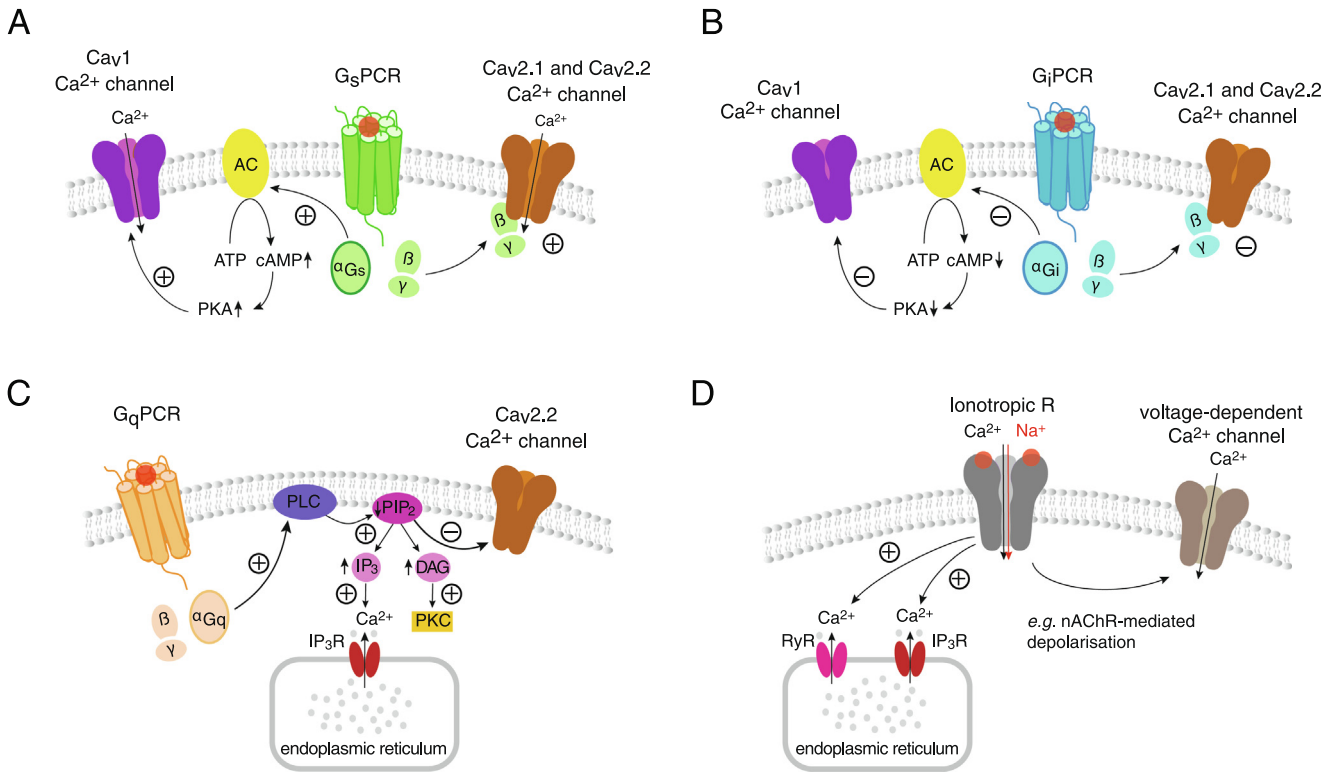

Fig. 1. G protein- and ionotropic receptor mediated regulation of Ca^{2+} channel activity. **(A)** G_s protein activation results in the dissociation of α_{Gs} and $\beta\gamma$ subunits. The α_{Gs} subunit activates adenylate cyclase (AC) resulting in an increase in cAMP levels which in turn activates Ca_v1 (L-type) Ca^{2+} channels. The $\beta\gamma$ complex binds directly to $Ca_v2.1$ and $Ca_v2.2$ channels (N- and P/Q-type Ca^{2+} channels) to enhance Ca^{2+} influx. **(B)** G_i protein activation results in the dissociation of α_{Gi} and $\beta\gamma$ subunits. Adenylate cyclase (AC) is inhibited by α_{Gi} and the cAMP level decreases, resulting in an inhibition of Ca_v1 channels. The $\beta\gamma$ complex binds directly to $Ca_v2.1$ and $Ca_v2.2$ channels channels to inhibit Ca^{2+} influx. **(C)** $G_{q/11}$ protein activation results in the dissociation of α_{Gq} and $\beta\gamma$ subunits. The α subunit of G_q proteins activates phospholipase C (PLC) which hydrolyses membrane-bound phosphatidyl-bisphosphate (PIP_2) to inositol trisphosphate (IP_3) and diacylglycerol (DAG). The resulting reduction in PIP_2 causes a reduction in the Ca^{2+} current through $Ca_v2.2$ channels. IP_3 binds to its receptor in the endoplasmic reticulum to produce intracellular Ca^{2+} release. DAG remains bound to the membrane and increases the activity of protein kinase C (PKC) which modulates several downstream signalling cascades including Ca^{2+} channels. **(D)** The activation of ionotropic receptors results in direct Ca^{2+} and Na^+ influx which will also produce a depolarisation (DP). In turn, this may activate voltage-dependent Ca^{2+} channels. For nicotinic AChRs it has been shown that this leads to the activation of ryanodine and/or IP_3 receptors and a subsequent Ca^{2+} release from the sarcoplasmic/endoplasmic reticulum.

action is complex because it binds to both ionotropic, so-called nicotinic ACh receptors and G protein-coupled, muscarinic ACh receptors. ACh is released from cholinergic axonal boutons binds to postsynaptic nAChRs and may also activate pre- and postsynaptic mAChRs; in addition, ACh may be released from free, i.e. non-synaptic axonal terminals/boutons into the extracellular space. In contrast, adenosine is released from both neurons and glia via nucleoside transporters or diffusion over the cell membrane in a non-vesicular, non-synaptic fashion; its receptors are exclusively GPCRs. Therefore, describing the action of these two transmitters types may highlight the many ways neuromodulation affects the neuronal excitability, synaptic transmission, and plasticity.

ACETYLCHOLINE

The neurotransmitter ACh plays an important role in many cognitive functions including sleep, wakefulness, attention, learning, memory and sensory processing (Jasper and Tessier, 1971; Donoghue, 1987; Voytko et al., 1994; Hasselmo, 2006; Kuo et al., 2009). Both subsets of acetylcholine receptors, the nAChRs and the mAChRs, are expressed in different cortical neurons. Nicotinic AChRs are ligand-gated cation channels (ionotropic receptors) that are permeable to Na^+, K^+ and Ca^{2+}; opening of these channels results invariably in a depolarisation of the neuronal membrane potential (Gotti et al., 2006). Muscarinic AChRs are metabotropic GPCRs. Different subtypes of mAChRs couple to either G_q or G_i proteins, which activate or inhibit intracellular signalling cascades, respectively (Kubo et al., 1986; Bonner et al., 1987; Caulfield and Birdsall, 1998; Thiele, 2013). Both mAChRs and nAChRs have been reported to modulate synaptic transmission (Vidal and Changeux, 1993; Amador and Dani, 1995; Bennett et al., 2012). In the central nervous system, mAChRs and nAChRs show a strong brain region- and neuronal cell type-dependent expression pattern, which contributes to the complexity and specificity of cholinergic modulation (Kunitake et al., 2004; Obermayer et al., 2017).

Cholinergic modulation of short-term plasticity at neocortical synapses

The main cholinergic pathway that innervates the neocortex originates from the nucleus basalis of

Meynert (NBM) in the BF; neurons from different parts of NBM project to distinct cortical areas. A small population of choline acetyltransferase (ChAT)-positive cells exist also in the neocortex, the majority of which are vasoactive intestinal peptide (VIP)-positive, GABAergic interneurons (Eckenstein and Thoenen, 1983; von Engelhardt et al., 2007; Obermayer et al., 2019). Stimulation of the BF leads to ACh release in the entire neocortex; cholinergic terminals are distributed throughout all cortical layers (Mesulam et al., 1992). Originally, ACh was considered to be released only from non-synaptic axonal boutons into the extracellular space where it reaches only low concentrations ($<10\ \mu M$; Zoli et al., 1999; Sarter et al., 2009; Badin et al., 2016). Recently, mounting evidence suggest that in the neocortex functional synaptic contacts are also stablished by cholinergic afferents, mediating fast ACh signalling (Turrini et al., 2001; Bennett et al., 2012; Hay et al., 2016; Obermayer et al., 2019). ACh is then released into the synaptic cleft, where it reaches very high concentrations (>1 mM). Given the morphology of individual synaptic contacts, i.e. whether there is little or no restriction to transmitter diffusion (e.g. by glial cells), it is conceivable that transmitter molecules escape from the synaptic cleft and subsequently activate perisynaptic mAChRs on both presynaptic boutons and the postsynaptic dendrites. The concentration of ACh in the perisynaptic space is also likely to be relatively low and may serve as feedback modulation of cholinergic synaptic transmission or direct modulation of adjacent glutamatergic or GABAergic synapses.

A classic view is that in the neocortex ACh acting on presynaptic nAChRs enhances the synaptic release probability of pyramidal cells (Dani and Bertrand, 2007) while it increases their excitability through activation of postsynaptic mAChRs (Woody and Gruen, 1987; Desai and Walcott, 2006). In fact, both nicotinic and muscarinic AChRs were found to be expressed in presynaptic axons and on the soma and dendrites of postsynaptic neurons. It should be noted however, that in the hippocampus and other brain regions cholinergic presynaptic inhibition of glutamatergic synaptic transmission has been described in a number of previous studies (Hounsgaard, 1978; Valentino and Dingledine, 1981; for reviews see Hasselmo, 2006; Dannenberg et al., 2017). The effects of ACh on the neocortical neuronal microcircuitry exhibit a striking complexity due to the layer- and cell type-dependent receptor distribution and density. ACh may act via mAChRs or nAChRs (or both) to modulate short-term synaptic plasticity by means of presynaptic regulation of transmitter release. The cholinergic modulation of intracortical synaptic transmission was found in different cortical layers, resulting in an increase of the 'signal-to-noise ratio (SNR)' in cortical networks thereby increasing the sensitivity of cortical neurons to external stimuli (Hsieh et al., 2000; Oldford and Castro-Alamancos, 2003).

Excitatory synapses

Both subtypes of G_i protein-coupled mAChRs, M_2 and M_4-type receptors, are expressed at presynaptic terminals of both rodent and human neocortical neurons (Levey et al., 1991; for reviews see Thiele, 2013; Obermayer et al., 2017). The activation of these receptors affects glutamate release by decreasing the open probability of $Ca_v2.1$ and $Ca_v2.2$ channels (P/Q and N-type Ca^{2+} channels, repsectively) at the axons of excitatory neurons (Muñoz and Rudy, 2014). In layer 2/3 of somatosensory cortex and olfactory cortex, cholinergic activation causes a suppression of neurotransmitter release probability at excitatory recurrent synaptic connections (Hasselmo and Bower, 1992; Gil et al., 1997). The increase in short-term facilitation was induced by muscarine but not nicotine indicating that this effect was mediated by presynaptic mAChRs (Fig. 2B; Gil et al., 1997). Notably, a recent study has shown that ACh enhances synaptic transmission between L2/3 pyramidal cells and somatostatin-positive interneurons via nicotinic receptors and presynaptic protein kinase A (PKA) signalling (Fig. 2B), but does not affect connections with postsynaptic pyramidal cells or parvalbumin-positive interneurons (Urban-Ciecko et al., 2018). This suggests that the mechanism underlying cholinergic modulation of excitatory synapses is highly complex and specific to the synaptic connection type.

Immunohistochemical studies indicate that M_2 AChRs are more abundant while M_4 receptors are less prevalent in neocortical layer 4 (Levey et al., 1991; Groleau et al., 2015). In marked contrast to this, electrophysiological studies on neocortical synaptic connections revealed that ACh acting via M_4 receptors reduces neuronal excitability and decreases the release probability and increases the PPR at intralaminar excitatory synaptic connections between L4 spiny stellate neurons (SSNs) in rat somatosensory barrel cortex, auditory cortex, and visual cortex (Fig. 2C). A similar effect was also observed for translaminar connections between presynaptic L4 SSN and L2/3 pyramidal cell (Fig. 2D; Eggermann and Feldmeyer, 2009); in both cases ACh is probably released from BF cholinergic afferents (Dasgupta et al., 2018). In mouse auditory cortex L4, muscarinic modulation can strongly suppress intracortical synaptic transmission while enhancing thalamocortical inputs (Hsieh et al., 2000). This indicates that mAChR modulation of synaptic plasticity is conserved across sensory cortices and dependents on the presynaptic input. A direct contribution of M_2 receptors, however, has so far not been found for identified synaptic connection.

As found in other layers, glutamatergic transmission between L5 pyramidal cells is inhibited by ACh (Tsodyks and Markram, 1997) and carbachol (a non-specific cholinergic agonist) (Fig. 2E; Levy et al., 2006). The changes in the PPR and the coefficient variation (CV) were blocked by atropine indicating that the effect was largely mediated by mAChRs. It should be noted that a nicotinic reduction of EPSP was also observed. This has been suggested to result from a postsynaptic depolarisation or nicotinic enhancement of GABA release from neighbouring inhibitory interneurons (Levy et al., 2006).

Layer 6 is the developmentally oldest and deepest neocortical layer, and displays a large neuronal diversity. The majority of L6 pyramidal cells falls into two subtypes, corticocortical (CC) and corticothalamic (CT)

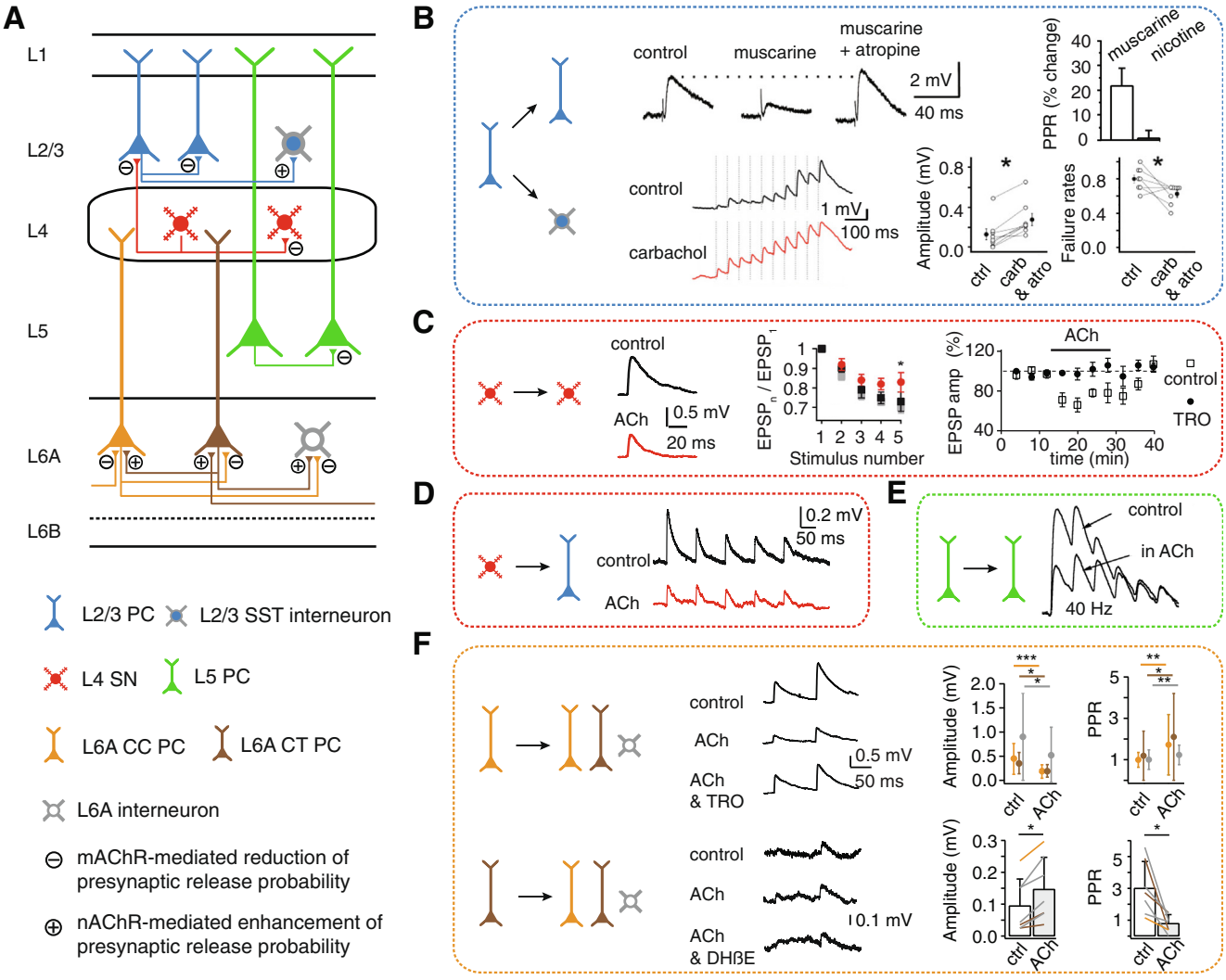

Fig. 2. Muscarinic and nicotinic AChR-mediated modulation of synaptic efficacy and short-term plasticity on excitatory synaptic connections in many neocortical layers. **(A)** Diagram of the cholinergic effects on excitatory synaptic connections via activating mAChRs/nAChRs in different neocortical layers. PC, pyramidal cell. L4 SSN, layer 4 spiny stellate neuron, SST, somatostatin-positive interneuron. **(B)** L3–L3 neocortical excitatory synaptic transmission was decreased by muscarine, an effect that could be reversed by atropine. The EPSPs were judged to be monosynaptic using criteria of short latency, monophasic time course, and minimal amplitude variance. An increase of the PPR was found following application of muscarine but not nicotine. Modified from Gil et al. (1997). However, ACh enhanced EPSP efficacy at L2/3 Pyr–SST Connections via nAChRs (Urban-Ciecko et al., 2018). **(C, D)** Monosynaptic connections between L4 SNs in rat barrel cortex were recorded in dual-whole cell mode. ACh decreased the EPSP amplitude and increased PPR via activating M_4Rs. A similar reduction of synaptic efficacy was also found in L4 SSN – L2/3 PC connections. Modified from Eggermann and Feldmeyer (2009). **(E)** ACh decreased EPSP amplitude with reducing the short-term depression on synaptic connections between neocortical L5 PCs. This effect could be reversed by applying atropine. Adapted from Tsodyks and Markram (1997). **(F)** ACh reduced the uEPSP amplitude and increased the PPR of L6A connections in rat barrel cortex established by a presynaptic CC PC. The effects were mediated by M4R activation and were found in different type of connections with a postsynaptic CC PC, CT PC or a interneuron. In contrast, an nAChR-mediated enhancement of synaptic efficacy was found at connections with a presynaptic CT PC. Modified from Yang et al. (2019).

pyramidal cells (Zhang and Deschênes, 1998; Egger et al., 2019). Unlike the homogeneous cholinergic response found in other layers, excitatory connections in layer 6A of rat barrel cortex are affected differentially by ACh. ACh inhibits the synaptic connections with a presynaptic CC pyramidal cell via M_4 mAChRs (Fig. 2F), but enhances the synaptic efficacy of the connections established by CT pyramidal cells via $\alpha_4\beta_2$ subunit-containing nAChRs. The concomitant change in the PPR was also found for both types of synapses suggesting the effect was mediated presynaptically. In addition, the cholinergic response is independent of the type of postsynaptic neuron (e.g. CC, CT pyramidal cell or interneuron; Yang et al., 2019). This is in marked contrast to a study of L2/3 pyramidal cell-interneuron connections suggesting that a nicotinic enhancement of excitatory synaptic transmission is selectively found in connections with a postsynaptic somatostatin-positive interneuron (Urban-Ciecko et al., 2018).

Hence, ACh modifies glutamatergic release via metabotropic M_2-type AChRs and/or nAChRs. Due to the cell-specific distribution of AChRs, the effect of ACh on the synaptic release probability is specific for connections with different pre- or postsynaptic neuron

types. The mAChR-mediated inhibitory response was found in all cortical layers while the facilitatory nicotinic response was observed only in layers 2/3 and 6. It should be noted that the L2/3 pyramidal cell-SST interneuron connections and connections established by L6 CT pyramidal cells are generally weak, facilitating connections with a low connectivity ratio (West et al., 2006; Yang et al., 2019). Thus, in the neocortex, many excitatory connections in virtually all layers may be inhibited by ACh via activation of presynaptic mAChRs.

Inhibitory synapses

Compared to excitatory synapses, cortical interneuron connections have not been investigated in detail because interneurons are highly diverse and their density is low (10-20% of all neocortical neurons) (Markram et al., 2004; Ascoli et al., 2008; Tremblay et al., 2016; Gouwens et al., 2019; Yuste et al., 2019). A classification of interneurons depends on the expression of chemical markers (e.g. somatostatin or parvalbumin), dendritic/axonal projection patterns (e.g. basket, chandelier, or Martinotti cell), and/or firing properties (fast spiking or non-fast spiking interneurons) (Feldmeyer et al., 2018). The short-term plasticity of inhibitory synapses changes during development (Frick et al., 2007; Takesian et al., 2010) and depends critically on the presynaptic interneuron subtype (e.g. Reyes et al., 1998; Ma et al., 2012). Therefore, the identification of pre- or even postsynaptic neuron subtype is important for adequately studying the dynamics of functional inhibitory circuits.

Using patch clamp recordings from monosynaptic connections in the rat visual cortex maintained in cell culture, Kimura and Baughman found that ACh significantly suppresses inhibitory synapses via M_4 mAChRs although excitatory synapses were found to be even more sensitive to suppression by ACh (Kimura and Baughman, 1997). A similar finding was reported for a fast-spiking (FS) L5 basket cell-L5 pyramidal cell connections in mouse somatosensory cortex (Kruglikov and Rudy, 2008). Here, muscarine application resulted in a decrease in the IPSP amplitude and an increase in short-term IPSP facilitation (Kruglikov and Rudy, 2008). This suggests that in all these cases the modulation of GABAergic release was induced by the activation of mAChRs located on presynaptic axonal boutons. A study on GABAergic interneuron connections in layer 5 of insular cortex showed a mAChR-mediated suppression of GABAergic synaptic transmission in both FS and nFS interneuron to pyramidal cell synapses but heterogeneous responses are induced in inhibitory-to-inhibitory connections (Yamamoto et al., 2010). A depression or facilitation of the postsynaptic response can be observed in connections between presynaptic FS-postsynaptic nFS and presynaptic non-FS-postsynaptic FS interneuron connections, respectively. This difference in the short-term synaptic plasticity may result from a differential expression of mAChR subtypes.

In addition, ACh also modulates inhibitory neurotransmission by affecting action potential firing of presynaptic interneurons. In neocortical layer 1, the activation of inhibitory microcircuits with either presynaptic neurogliaform cells (NGFCs) or interneurons classified as ‘classical accommodating (c-AC)’ cells is under tight cholinergic control (Brombas et al., 2014). In the resting state, the excitability of these two L1 interneuron types is enhanced via nAChRs. However, in an active, action potential firing mode, ACh increased the activity of c-AC L1 interneurons further. In contrast, NGFCs activity was inhibited via a mAChRs-mediated, IP_3 receptor-dependent increase of intracellular Ca^{2+} resulting in a recruitment of Ca^{2+}-activated K^+ channels. However, the mAChR subtype underlying this mechanism was not identified in this study. This activity-dependent modulation, in concert with the effect of ACh on presynaptic GABAergic release, regulates inhibitory signalling in the neocortical network in layer 1, in particular through a dynamic control of inhibitory input to distal portions of the apical dendrite of pyramidal cells.

Very recently, co-release of GABA and ACh has been described for BF cholinergic terminals in the hippocampus (Takács et al., 2018) and neocortical VIP-expressing neocortical interneurons (Obermayer et al., 2019). However, it is so far not known whether this GABA/ACh co-release is involved in the modulation of neurotransmitter release.

Cholinergic modulation of synaptic transmission in subcortical microcircuits

BF cholinergic neurons act through subcortical targets to promote arousal, motivation and other behavioural processes (Agostinelli et al., 2019). In BF, cholinergic neurons from medial septal nucleus and the vertical limb of the diagonal band project predominately to the hippocampus whereas neurons from the horizontal limb of the diagonal band project to the olfactory bulb. Apart from this, two other pathways arise from the pedunculopontine tegmental nucleus (PPT) and laterodosal tegmental nucleus (LDT) send brainstem cholinergic projection to thalamus and hypothalamus (Mesulam et al., 1983; Paul et al., 2015). Deficits of cholinergic projections in subcortical regions have been identified in Alzheimer’s and Parkinson’s disease (Lange et al., 1993; Kuhl et al., 1996). A co-modulation of synaptic transmission exists in different subcortical areas by both mAChRs and nAChRs. These will be discussed separately below.

Hippocampus

The hippocampus receives abundant cholinergic inputs that are considered to be critical for its central role in learning and memory (Hasselmo, 2006). In addition to inducing long-term potentiation (LTP) and long-term depression (LTD) (Watabe et al., 2000; Ge and Dani, 2005; Dennis et al., 2016), which may be the underlying mechanisms in memory formation and maintenance, ACh also modulates short-term plasticity of hippocampal synapses that are thought to play a role in learning and memory. For instance, it has been shown that contextual learning induces synaptic strengthening of CA1 pyramidal cells via the mediation of mAChRs (Mitsushima et al., 2013). In addition, co-activation of β-adrenergic and M_1

muscarinic receptor can boost short-term potentiation (STP) to LTP through an extracellular signal-regulated kinase-dependent mechanism (Connor et al., 2012).

In the hippocampus, ACh modulates short-term synaptic plasticity in a pathway-specific way by activating presynaptic AChRs. At the CA3-to-CA1 synapse (the Schaffer-collateral pathway) ACh suppresses glutamate release via M_4 AChRs (Hasselmo and Schnell, 1994; Dasari and Gulledge, 2011). In the Schaffer-collateral pathway it is of note that only functional synapses are inhibited by ACh; the silent synapses which lack functional expression of AMPA receptors show no mAChR-mediated inhibition (Fernandez de Sevilla et al., 2002). Another study showed that the activation of α_7 nAChRs enhances synaptic release at silent synapses and helps in converting them into conductive, mature synapses (Maggi et al., 2003). This indicates cholinergic modulation of synaptic plasticity in hippocampus plays an important role in synaptic maturation.

Similarly, cholinergic suppression of synaptic transmission has also been found at recurrent CA3 pyramidal cell connections and excitatory CA1-to-subiculum connections (Hasselmo et al., 1995; Kunitake et al., 2004). This M_4R-mediated suppression of presynaptic release combined with postsynaptic M_1R-induced depolarisation, may enhance the SNR in hippocampal pyramidal cells and sharpen place fields (Brazhnik et al., 2003). In contrast, nicotine application increases glutamate release in cultured hippocampal neurons, an effect that is mediated by α_7 subunit-containing nAChRs (Radcliffe et al., 1999).

ACh has been shown to act on $\alpha_4ß_2$ and α_7 nAChRs at inhibitory synapses in CA1 as well, which in order to enhance the amplitude and frequency of IPSCs but display no changes in paired-pulse behaviour(Alkondon and Albuquerque, 2001; Mitsushima et al., 2013). The effect could be attributed to a local depolarisation near the axon terminals via activating preterminal but not presynaptic nAChRs (Alkondon and Albuquerque, 2001). In addition, ACh has been shown to either induce postsynaptic LTP or a depolarization-induced suppression of inhibition (DSI) depending on the preceding postsynaptic activity (Dominguez et al., 2014). Nevertheless, untilk now there is no evidence that ACh can affect GABAergic release or short-term plasticity of inhibitory synapses in hippocampus.

Olfactory bulb

The cholinergic system is crucial to olfactory perception and is known to play an important role in odour discrimination and olfactory learning (Chaudhury et al., 2009; Hellier et al., 2012; Chan et al., 2017; Ross et al., 2019). Similar to neocortex, apart from the cholinergic inputs from the BF there are also ChAT-positive neurons distributed within olfactory bulb (Krosnowski et al., 2012). The main and accessory olfactory bulb both receive abundant cholinergic projections and are regulated differentially via mAChR activation. Excitatory mitral and tufted cells, as well as local inhibitory granule cells, are inhibited following M_2 AChR activation in the main olfactory bulb; however, in the accessory olfactory bulb these neurons are excited by M_1 AChR activation (Pressler et al., 2007; Smith et al., 2015). This implies that in olfactory bulb, mAChR activation affects the neuronal excitability of excitatory and inhibitory neurons in a region-specific way. Although binding of ACh to mAChRs suppresses the firing rate of granule cells in the main olfactory bulb, the presynaptic GABA release to postsynaptic mitral tufted cells is simultaneously increased (Castillo et al., 1999; Ghatpande et al., 2006). A more recent paper demonstrated that ACh enhances GABAergic transmission in olfactory bulb glomeruli by affecting presynaptic mAChRs in the presence of tetrodotoxin, suggesting that the effect is action potential-independent (Liu et al., 2015). Therefore, different types of mAChRs may be expressed on soma, dendrites and synaptic boutons in olfactory bulb, resulting in a complex change of neuronal excitability and short-term synaptic plasticity.

Thalamus

Cholinergic neurons in the brainstem densely innervate thalamic neurons. ACh released by these neurons may enhance glutamate release of thalamic afferents which in turn facilitate thalamocortical input via activating presynaptic $ß_2$ subunit- containing nAChRs (Parikh et al., 2010). This will leads to an increase of the magnitude of sensory-evoked cortical responses and facilitates the sensitivity to sensory stimuli (Masri et al., 2006). Activation of nAChRs containing α_4 and β_2 subunits also enhances excitatory synaptic efficacy at corticothalamic terminals (Sottile et al., 2017). ACh release from cholinergic terminals is considered to regulate excitability of thalamic neurons by slow and persistent volume transmission (McCormick and Prince, 1986; McCormick and Bal, 1997). However, fast cholinergic synaptic transmission in the thalamic reticular nucleus (TRN) can activate presynaptic M_2 mAChRs thereby suppressing glutamate release resulting in an increase in short-term facilitation (Sun et al., 2013). In contrast, ACh has been shown to have no effect on GABAergic transmission in the TRN (Sottile et al., 2017).

Hypothalamus

In the hypothalamus ACh plays a crucial role in the control of food intake by depolarising anorexigenic proopiomelanocortin (POMC) neurons and orexigenic neuropeptide Y neurons in the hypothalamic arcuate nucleus (Huang et al., 2011). This effect is mediated not by mAChRs but postsynaptic $\alpha_4ß_2$ and α_7 subunit-containing nAChRs. However, activation of presynaptic mAChRs and nAChRs competitively regulates appetite by affecting hypothalamic inhibitory synaptic transmission. It has been shown that in the dorsomedial hypothalamus, ACh enhances GABAergic transmission onto anorexigenic proopiomelanocortin neurons via mAChRs therefore promoting food intake (Jeong et al., 2017). In contrast to this, nicotine administration into the lateral hypothalamus significantly decreases food intake (Miyata et al., 2001). The α_7 nAChR-mediated enhancement of GABAergic inputs on melanin-concentrating hormone neurons in lateral hypothalamus contributes to this

cholinergic effect on appetite control (Jo et al., 2005). This suggests that also in the hypothalamus, cholinergic modulation of GABAergic release is subregion and cell type-specific.

ADENOSINE

Adenosine is a ubiquitous endogenous neuromodulator that plays important roles in sleep homoeostasis and energy metabolism (Strecker et al., 2000; Dunwiddie and Masino, 2001; Ribeiro et al., 2002; Basheer et al., 2004; Porkka-Heiskanen and Kalinchuk, 2011). Nucleotidase-mediated hydrolysis of intracellular adenine nucleotides such as ATP during high neuronal activity, leads to an accumulation of adenosine in the extracellular space via ATP-dependent ion transporters (such as the Na^+–K^+ and Ca^{2+} ATPases) that maintain the intracellular ionic homeostasis (Fredholm et al., 2005; Sebastiao and Ribeiro, 2009). Adenosine transporters (so-called equilibrative nucleoside transporters) are located in the membrane of all neuronal compartments, i.e. soma, dendrites and axon. High adenosine concentrations in the cytoplasm result in net outward flux through these transporters leading to an increased extracellular adenosine concentration. Through binding to adenosine receptors adenosine can then act as a feedback modulator of neurotransmitter release. During hypoxia, elevated metabolic demand, and prolonged wakefulness this type of neuromodulation is enhanced and leads mostly to an inhibition of neuronal activity (van Calker and Biber, 2005; Fredholm, 2007).

Adenosine receptors and their distribution in the brain

As mentioned above, there are four subtypes of adenosine receptors, the A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors (A_1AR, A_{2A}AR, A_{2B}AR, A_3AR) that display distinct tissue distribution, pharmacological characteristics and down-stream cellular signal transduction mechanisms (Dunwiddie and Masino, 2001; Jacobson and Gao, 2006; Dias et al., 2013; Chen et al., 2014). Among these four types of adenosine receptors, the A_1AR shows the highest adenosine affinity and is the most abundant receptor in the brain. It is densely expressed in the CNS including neocortex, hippocampus, cerebellum, and spinal cord (Dunwiddie and Masino, 2001; Bauer et al., 2003; Bauer et al., 2005; Meyer et al., 2006; Sachdeva and Gupta, 2013). A_1ARs couple to G_i proteins which inhibits adenylyl cyclase activity leading to a decrease in the intracellular cAMP concentration and increases activity of phospholipase C (Fig. 1B; Gerwins and Fredholm, 1992; Rogel et al., 2005; Tawfik et al., 2005). In contrast, stimulation of the A_{2A}AR results in an increase of AC activity through activation of the G_s protein and in turn leads to an elevation of the intracellular cAMP level (Jacobson and Gao, 2006; see also Fig. 1A). A_{2A}ARs are found only in a few brain regions at high expression levels including the striatum, the olfactory tubercle and the nucleus accumbens; it is expressed only at very low levels elsewhere in the CNS (Fredholm et al., 2003; Boison et al., 2012; Sachdeva and Gupta, 2013). A_{2B}AR and A_3ARs are widely expressed in the brain but have a low adenosine affinity and thus have not been investigated in detail in the field of neuronal connectivity (Dunwiddie et al., 1997; Feoktistov and Biaggioni, 1997; Macek et al., 1998). However, A_{2B}ARs are involved in the anti-inflammatory process and participated in the gap junction communication of folliculostellate cells in the anterior pituitary gland (Sun et al., 2006; Ham and Rees, 2008). A_3ARs have been suggested to modulate the activity of other adenosine receptors, e.g. under elevated endogenous adenosine condition, activation of A_3ARs would subsequently desensitize A_1ARs and block the A_1AR-mediated effect (Dunwiddie et al., 1997).

Adenosine modulation of synaptic transmission at neocortical synapses. Adenosine modulates excitatory glutamatergic neurotransmission and plays a role in the interaction between energy metabolism and neuronal excitability. The A_1AR-mediated activation of G_i proteins results in an increased open probability of $K_{ir}3$ channels leading to a hyperpolarisation of the resting membrane potential, a decreased input resistance and hence a decreased excitability of most excitatory neurons (Bannon et al., 2014; van Aerde et al., 2015). In glutamatergic neurons A_1ARs down-regulate Ca^{2+} channels of the $Ca_v2.2$ (N-type); other Ca_v channel types were found to be insensitive to adenosine (Ambrosio et al., 1996; Wang et al., 2002). However, for piriform cortex it has been reported that in addition to $Ca_v2.2$ channels $Ca_v2.1$ (P/Q-type) channels are also affected by A_1AR receptor activation (Yang et al., 2007).

Excitatory synapses

The activation of N-methyl-D-aspartate (NMDA) glutamate receptors by glutamate release can induce the release of adenosine, the concentration of which may be sufficiently high to indirectly counteract NMDA-mediated depolarisation by its effect on voltage-sensitive K^+ currents at postsynaptic sites as a feedback inhibition (de Mendonca and Ribeiro, 1993; Marro et al., 1999) and induce an inhibition of glutamate release at presynaptic axon terminals (Manzoni et al., 1994; Brambilla et al., 2005). This is in line with the finding that A_1ARs are richly expressed at presynaptic sites instead of dendrites and cell bodies (Rebola et al., 2003). Therefore, the effects of adenosine on presynaptic release probability are far more pronounced and occur at lower concentrations than those on neuronal excitability (Fontanez and Porter, 2006; Kerr et al., 2013; Bannon et al., 2014; van Aerde et al., 2015; Qi et al., 2017). Both presynaptic (e.g. PPR, CV and failure rate) and postsynaptic properties (EPSP decay time) determine the function of different synapse types in the neocortex, including their short-term plasticity (Feldmeyer et al., 1999; Feldmeyer et al., 2002; Silver et al., 2003; Branco and Staras, 2009; Qi and Feldmeyer, 2016). In a study in layer 2/3 of rat visual cortex synaptic responses were recorded extracellularly as local field potentials while stimulating neurons in layer 4. Responses recorded during application of adenosine were smaller due to the reduction of synaptic release, which altered short-term plasticity markedly by reducing

the degree of paired-pulse depression (Varela et al., 1997). Intracellular recordings from L2/3 pyramidal neurons in the same brain area using extracellular stimulation in layer 4 showed similar results. Application of adenosine induced an A_1AR-dependent reduction of miniature EPSC frequency and evoked EPSP amplitude, accompanied by an increase in their PPRs. K^+ channels and NMDA receptors were blocked in these experiments to exclude a possible contribution of postsynaptic adenosine effects, where the decrease in EPSP amplitude and the increase of the PPR were still observed, confirming that adenosine suppresses excitatory transmission via a presynaptic mechanism (Fig. 3A; Bannon et al., 2014).

L4 neurons of barrel cortex were recorded while stimulating the thalamus extracellularly to investigate how thalamocortical excitation is modulated by adenosine (Fontanez and Porter, 2006). Adenosine reduced the amplitude of the thalamocortical EPSCs with an increase of the PPR and CV, both of which are correlated with the probability of neurotransmitter release (e.g. Clements and Silver, 2000; Feldmeyer et al., 2002). Paired recording data on excitatory synaptic connections in this brain region showed that adenosine suppresses synaptic transmission between L4 excitatory neurons through both pre- and postsynaptic A_1ARs. This is reflected in an increase in the presynaptically determined synaptic properties PPR, CV and failure rate of the EPSPs and a decrease of decay time resulting from a decrease in the input resistance of the postsynaptic neuron (Fig. 3B; Qi et al., 2017). A purely presynaptic effect of

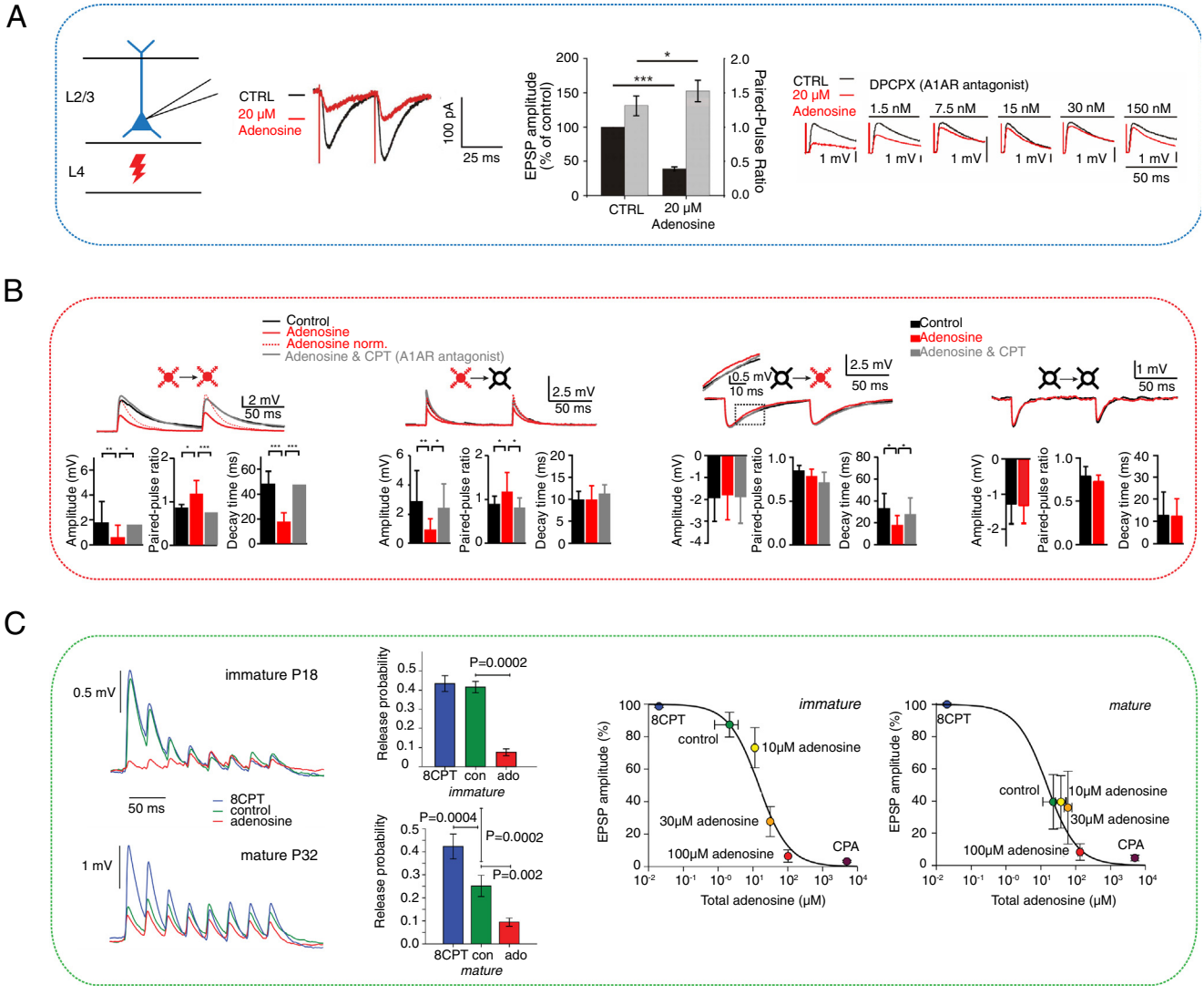

Fig. 3. Adenosine modulation of synaptic efficacy and short-term plasticity in different cortical areas and layers via A_1ARs. **(A)** Evoked EPSCs in L2/3 pyramidal neurons of rat visual cortex were recorded with Cs-based pipette solution and in the presence of the NMDA receptor blocker APV. Adenosine causes a concentration-dependent reduction of the EPSC amplitude and an increase of the PPR via presynaptic A_1ARs. Adapted from Bannon et al. (2014). **(B)** Monosynaptic connections between L4 excitatory neurons, excitatory and inhibitory neurons and between inhibitory neurons of rat somatosensory cortex were recorded in dual-whole cell mode. Adenosine caused a suppression of excitatory synaptic transmission via pre- and/or post-synaptic However, A_1ARs had a minor effect on inhibitory transmission. Modified from Qi et al. (2017). **(C)** Developmental change of the probability of neurotransmitter release on the L5 pyramidal cell synapses are mediated via an increased activation of presynaptic A_1ARs. The endogenous adenosine concentration was found to be increased more than tenfold during development. Modified from Kerr et al. (2013).

adenosine was observed for excitatory transmission between L4 excitatory and inhibitory neurons due to the fact that adenosine showed negligible effects on the membrane potential of inhibitory neurons (van Aerde et al., 2015; Qi et al., 2017). This suggests that adenosine suppresses synaptic transmission mainly by suppressing presynaptic neurotransmitter release via an A_1AR-mediated reduction of the open probability of presynaptic Ca^{2+} channels. It has been hypothesised that this will result in an overall shift to lower excitability in cortical microcircuits (Prince and Stevens, 1992; Scanziani et al., 1992; Wu and Saggau, 1994, 1997; Arrigoni et al., 2001; Qi et al., 2017; Radnikow and Feldmeyer, 2018).

Studies in neocortical L5 reveal a similar reduction of connection strength and increase of PPR (Murakoshi et al., 2001; Kerr et al., 2013). During development, cortical glutamatergic synapses switch from an immature state that exhibits a high probability of neurotransmitter release, large unitary amplitude and strong synaptic depression to a mature state with lower release probability, smaller unitary amplitude and to weak synaptic depression or even facilitation (Fig. 3C; Reyes and Sakmann, 1999; Gonzalez-Burgos et al., 2008; Feldmeyer and Radnikow, 2009; Etherington and Williams, 2011). This developmental change has been suggested to be mediated via an increased activation of presynaptic A_1ARs. This has been attributed to an increase in the extracellular adenosine concentration in the perisynaptic space during development (Kerr et al., 2013). Furthermore, tonic inhibition of synaptic transmission by endogenous adenosine via A1AR is well documented (Dunwiddie and Diao, 1994; Wu and Saggau, 1994; Manita et al., 2004; Kerr et al., 2013; Qi et al., 2017; see also Fig. 3C). The endogenous adenosine concentration was estimated to be 1–2 μM, suggesting that the tonic effect on neuronal excitability is negligible while that on the release probability is still present (Kerr et al., 2013; Qi et al., 2017). This shows that adenosine acts primarily to modulate synaptic transmission in a reciprocal way.

Inhibitory synapses

At a subset of inhibitory connections, adenosine also induces a minor suppression of the postsynaptic IPSP amplitude. It has been suggested, that at least for some GABAergic connections this adenosine-mediated inhibition is mediated by a 'shunting' effect, i.e. changes in postsynaptic membrane properties instead of a direct suppression of presynaptic GABA release (Takigawa and Alzheimer, 2002; Ilie et al., 2012; Qi et al., 2017). Inhibition of GABAergic synapses by adenosine was also found in immature rat hippocampus and visual cortex. Adenosine reversibly decreased the frequency of GABAergic mIPSC frequency with affecting the amplitude in immature neurons (Jeong et al., 2003). Blockade of presynaptically located A_1ARs in GABAergic boutons caused an increase in the amplitude of evoked IPSPs and a decrease in the PPR during development.

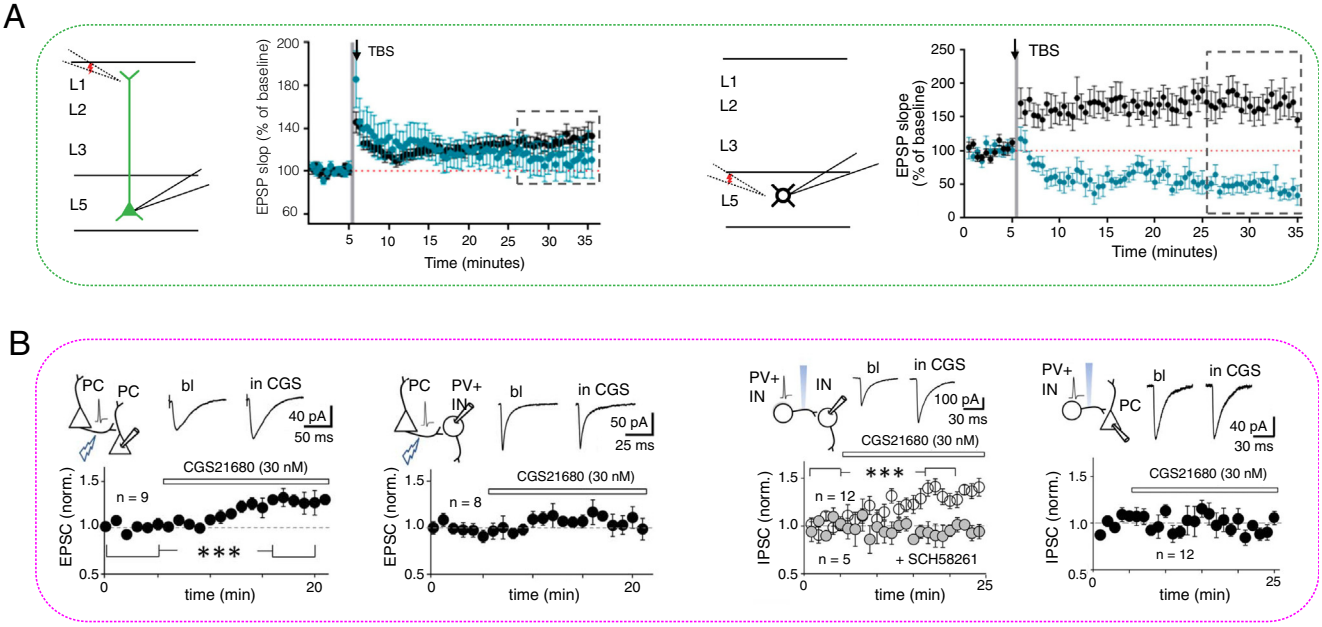

Fig. 4. Adenosine modulation of synaptic activity via A_{2A} adenosine receptors in different brain regions. **(A)** A_{2A}AR blockade does not affect glutamatergic synapses LTP in layer 5 pyramidal neurons, but shifts reverses LTP to LTD at excitatory synapses in layer 5 FS interneurons of prefrontal cortex. Control recordings are shown in black and recordings in the presence of SCH58261, an A_{2A}AR antagonist, are given by blue symbols in the time–course plot. TBS: theta burst stimulation. Adapted form (Kerkhofs et al., 2018) **(B)** Two leftmost panels: Schaffer collateral electrical stimulation was performed during intracellularly recording of postsynaptic CA1 pyramidal cells or interneurons. Activation of A_{2A}AR selectively facilitates glutamatergic synapses onto pyramidal cells but not onto PV + interneurons. Two rightmost panels: GABAergic synapses from PV + CA1 interneurons were activated optogenetically while intracellularly recording postsynaptic CA1 interneurons or pyramidal cells. A_{2A}ARs selectively enhance GABAergic inhibition at PV + interneuron-interneuron connections but not at PV + interneuron-pyramidal cell connectionss in the CA1 area of hippocampus. bl: Baseline; CGS21680: an A_{2A}AR agonist. Adapted from Rombo et al. (2015).

(Kirmse et al., 2008). Kruglikov and Rudy (Kruglikov and Rudy, 2008) found that in cortical L5 FS interneuron-pyramidal cell connections, adenosine caused a decrease in IPSP amplitude and an increase in the the PPR, suggesting a decrease in GABA release probability at this inhibitory connection; in this study, the adenosine receptor subtype was not identified (Fig. 4A).

A_{2A} adenosine receptors

A_{2A}ARs were found to be involved in the modulation of inhibitory network, however, by heterogenous mechanisms. Studies in the neostriatum showed a paradoxical effect of A_{2A}ARs with some finding a A_{2A}AR-mediated facilitation of GABAergic synaptic transmission (Shindou et al., 2003; Shindou et al., 2008), and others reporting an A_{2A}AR-mediated decrease of GABAergic transmission (Mori et al., 1996). It has been reported that A_{2A}ARs facilitate excitatory Schaffer collateral-CA1 pyramidal cell synapses, but not Schaffer collateral-interneuron synapses (Fig. 4B; Rombo et al., 2015). Moreover, A_{2A}ARs enhance GABAergic transmission between CA1 interneurons leading to a disinhibition of pyramidal cells. However, this effect of A_{2A}ARs is indirect, i.e. no A_{2A}AR-mediated effect on GABAergic synapses was found. It has been suggested that A_{2A}Rs change the excitatory–inhibitory balance resulting in an enhanced CA1 neuronal activity (Rombo et al., 2015). Dependence of the A_{2A}AR effects on the A_1AR availability suggests interaction between these receptors, whereby A_{2A}ARs exert their facilitatory effect on synaptic transmission by inhibiting the A_1AR-mediated suppression. Our results demonstrate functional pre and postsynaptic A_1ARs and presynaptic A_{2A}ARs in layer 2/3 of the visual cortex, and suggest interaction between presynaptic A_{2A}ARs and A1Rs.

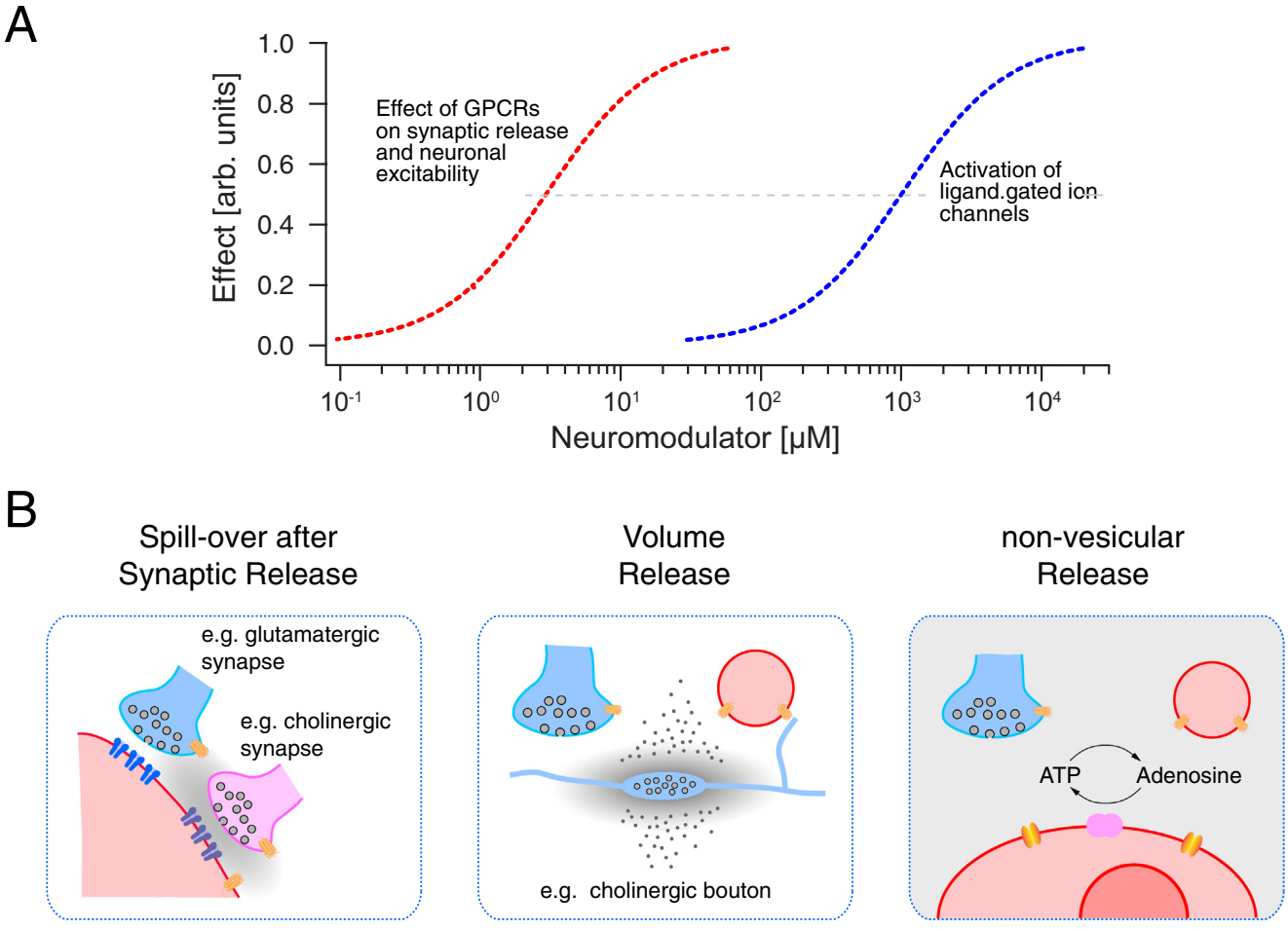

Fig 5. Modes of neuromodulator release. In general, neuromodulators activate GPCRs at significantly lower concentrations (in the low micromolar range) than ligand-gated ion channels **(A)** as can be seen from the dose–response curves (red) for GPCR effects on both neuronal excitability and synaptic release probability and the curve for the activation of postsynaptic ligand-gated ion channels (blue); the grey dashed line marks the EC_{50} for the curves. There are three mechanisms by which neuromodulators are released in the extrasynaptic space. **(B)** At synapses with a clear pre- and postsynaptic site, the transmitter (glutamate, GABA, ACh and serotonin) is released into the synaptic cleft at millimolar concentrations; the transmitter diffuses out of of the cleft to activate perisynaptic receptors on both bouton and dendrite (left). Neuromodulatory transmitters can also be released from free axonal boutons into the extracellular space to activate GPCRs at synaptic terminals, dendrites and soma of surrounding neurons (middle). The neuromodulator adenosine is either released by a transporter or produced by degradation of extracellular ATP via a membrane-bound ectonucleotidase. In both case, the release of adenosine is non-vesicular (right). See text for details.

In layer 2/3 of the visual cortex, activation of A_{2A}ARs was found to be associated with a facilitation of excitatory transmission. However, this facilitation was removed by blockade of A_1ARs, indicating that A_{2A}ARs enhance excitatory transmission via an A_1AR-dependent mechanism (Bannon et al., 2014).

Here, using two distinct groups of GPCR as examples, the mAChRs and adenosine receptors, we tried to illustrate how GPCRs may up- or downregulate neurotransmitter release synaptic plasticity. From this short overview two main principles emerge:

First, GPCR-mediated effects on synaptic transmission are generally mediated at low concentrations, i.e. in the range of 1.0–10 μM. Such concentrations are far lower than those necessary for the activation of ligand-gated ion channels which are in the range of ~1 mM (s. Fig. 5A) and have little overlap with those for GPCRs. Activation of GPCRs is less directional than synaptic transmission; there are several different mechanisms by which neuromodulatory transmitters are released into the perisynaptic or extracellular space activating both pre- and postsynaptic receptors.

Some neurotransmitters such as e.g. ACh, serotonin but also glutamate and GABA, the excitatory and inhibitory neurotransmitters in the neocortex, respectively, can be released at defined synaptic contacts into the synaptic cleft (termed 'wired' or directional release). They will activate mostly ionotropic receptors in the postsynaptic membrane. These neurotransmitter can escape from the synaptic cleft – a mechanism termed '*spill-over*' and may either activate GPCR autoreceptors in the presynaptic bouton of the same synapse or heteroreceptors in the presynaptic bouton of adjacent synapses (Fig. 5B, left; Kullmann and Asztely, 1998; Chen and Diamond, 2002; Bekkers, 2003). For example, ACh, GABA, and glutamate may bind to perisynaptic mAChRs, $GABA_B$ receptors or the metabotropic glutamate receptors (mGluRs), respectively, resulting in a feedback regulation of neurotransmitter release probability. Furthermore, these neurotransmitters may also activate GPCR heteroreceptors (i.e. those on adjacent presynaptic terminals) thereby fine-tuning local synaptic release.

Neuromodulatory transmitters may also be released from axonal boutons not in close contact with a postsynaptic site from which the diffuse to the soma, dendrites and axon terminals of surrounding neurons; here they activate GPCRs that changes the excitability and release probability in a spatially less restricted fashion. This mechanism is called '*volume transmission*' (Fig. 5B, middle; for reviews see Borroto-Escuela et al., 2015; Badin et al., 2016) and may occur an additional pathway for neuromodulator release (for s. For example, in the case of ACh, the length constant of volume transmission has been estimated to be in the range of ~9–15 μm (Jing et al., 2018). Volume transmission and synaptic transmission may occur in parallel for the same neurotransmitter type (for an overview for ACh see Disney and Higley, 2020).

In the special case of the neuromodulator adenosine – a metabolite of ATP – may be produced either extracellularly by ectonucleotidases or transported by a facilitative nucleoside transporter from the intracellular to the extracellular space (Fig. 5B, right; Fredholm et al., 2005; Dias et al., 2013). These processes take place in dendrites and axons of neurons as well as in glia cells.

Second, the GPCR-mediated neuromodulation of synaptic function and plasticity is highly specific for a defined neuronal connections and depends on both pre- and postsynaptic neuron type as we tried to show in this review. The mode and extent of neuromodulation depend to a large degree on the expression of the G-protein subtype mostly at pre- but also at postsynaptic sites. Therefore, it is of paramount importance to study neuromodulation of synaptic transmission in identified excitatory and inhibitory synaptic connections to elucidate its role in setting the excitatory–inhibitory balance of neuronal microcircuits.

ACKNOWLEDGEMENTS

We thank Werner Hucko for excellent technical assistance and Dr. Karlijn van Aerde for custom-written macros in Igor Pro software. This work was supported by the Helmholtz Society, the European Union's Horizon, 2020 Research, Innovation Programme under Grant Agreement No. 785907 (HBP SGA2; to DF) and the Chinese Scholarship Council (to D.Y. and C.D.).

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(Received 17 April 2020, Accepted 1 June 2020)
(Available online 13 June 2020)