Neuroscience 456 (2021): 1-3

**DOI:** https://doi.org/10.1016/j.neuroscience.2020.10.006

HHS Public Access
Author manuscript
*Neuroscience*. Author manuscript; available in PMC 2023 June 06.

Published in final edited form as:
*Neuroscience*. 2021 February 21; 456: 1–3. doi:10.1016/j.neuroscience.2020.10.006.

# Metabotropic Regulation of Synaptic Plasticity

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Synaptic plasticity, defined as the activity-dependent changes in synaptic efficacy, is one of the most fascinating properties of the Central Nervous System (CNS) that provides mechanisms to modify, through experience, the operation and development of neuronal circuits. Synaptic plasticity is thought to be the cellular basis of learning and memory in the CNS (Bliss and Lomo, 1973) that can lead to processing and storing information through increases or depressions in synaptic strength which can endure from milliseconds to days or longer (Citri and Malenka, 2008).

The SNC fundamentally functions by receiving sensory information and generating the required output response, an operation that involves rapid and efficient synaptic transmission of information between neurons. Rapid transmission is mediated by the presynaptic release of neurotransmitters that trigger the quick opening of postsynaptic ion channels leading to fast membrane potential changes. Importantly, a "slow neurotransmission", lasting hundreds of milliseconds to seconds, also occurs as a mechanism of communication between neurons in the brain. It is typically mediated by metabotropic receptors that, upon activation by neurotransmitters, initiate intracellular second messenger pathways in the pre- or postsynaptic neuronal compartments.

Both fast ionotropic (ion channel coupled) and slow metabotropic (second messenger coupled) receptors contribute to signal processing and to short- and long-term activity-dependent forms of plasticity. Metabotropic transmission supports several key functions because due to: (1) its activation, involving intracellular second messenger cascades, it can regulate different downstream process; (2) the existence of different metabotropic receptors in diverse CNS regions makes possible to act in a cellular- and/or synaptic-specific manner; (3) its long time-course facilitates the temporal summation of synaptic inputs favoring the induction of plasticity; (4) its protracted effects makes it an ideal candidate to contribute in plasticity leading to cognitive processes including, learning, memory, attention and arousal.

This Special Issue focuses on the key role of metabotropic receptors in the induction and regulation of plasticity and circuit operation in the CNS and its impact on signal processing and behavior. The Issue contains two sets of reviews: the first includes articles covering aspects of metabotropic receptors in the regulation of ionic conductances and in short- and long term synaptic plasticity at molecular and cellular levels; the second set is mainly focused on the regulation of neuronal circuits and on the contribution of metabotropic receptors to behavior and human diseases of the CNS.

In this Special Issue, Fernández-Fernández and Lamas examine the role of metabotropic receptors in translating the activation of different neurotransmitters into their final effect in the regulation of several potassium channel types. They evaluate the outcome of this regulation in the induction and maintenance of different forms of synaptic plasticity (Fernández-Fernández and Lamas, 2021). The three following reviews examine the role of metabotropic receptors in synaptic plasticity mediated by glutamatergic receptors. Valbuena and Lerma summarize experimental evidence of the involvement of kainate receptor signalling in the regulation of short- and long-term synaptic plasticity. They focus on the key role of the metabotropic effects of kainate receptors and emphasize the interesting novel role of kainate receptors as homeostatic modulators of neurotransmitter release (Valbuena and Lerma, 2021). Lutzu and Castillo summarize current knowledge on the molecular and cellular mechanisms underlying NMDAR modulation by second messenger coupled receptors. They discuss the implications of this modulation spanning from synaptic transmission and plasticity to circuit function and brain disease (Lutzu and Castillo, 2021). Dore and Malinow provide information on long-term depression (LTD) mediated by unconventional NMDA receptors where ligand-induced conformational changes in the intracellular domain of the NMDA receptor can lead to LTD in the absence of ion-flux. A novel angle from this study is that both ion flux-dependent and -independent mechanisms coexist, and their relative prevalence may depend on the interaction between NMDA receptors and scaffolding molecules, such as PSD95. This attractive idea points to NMDARs operating both through ionotropic and metabotropic actions (Dore and Malinow, 2021). The following three articles review the regulation of synaptic plasticity by metabotropic receptors in the cortex and hippocampus. Griego and Galvan review data concerning the effects of metabotropic glutamate receptors with particular emphasis on hippocampal CA3 area. They examine changes in the expression and function of mGluRs during the aging process and present original data showing modifications in synaptic transmission and intrinsic excitability of aged CA3 pyramidal cells in response to the pharmacological manipulation of different metabotropic glutamate receptors (Griego and Galván, 2021). Fuenzalida and Chavez review the role of dopaminergic, serotoninergic and cholinergic metabotropic receptors in activity-dependent synaptic plasticity in the prefrontal cortex and hippocampus and discuss endocannabinoid-mediated forms of plasticity in other brain regions (Fuenzalida et al., 2021). Fernández de Sevilla, Nuñez and Buño review the current literature on the role of metabotropic cholinergic receptors in the regulation of both excitatory and inhibitory synaptic plasticity, circuit activity and the excitatory/inhibitory balance in the hippocampal and cortical circuits. They also address functional processes where acetylcholine has been shown to play a key role in regulating brain rhythms, information processing, behaviour and cognition (Fernández de Sevilla et al., 2021). Kofuji and Araque review the functional relevance of the expression of metabotropic receptors by astrocytes. While electrically non-excitable, astrocytes display a form of excitability based on intracellular $Ca^{2+}$ variations that are triggered by neurotransmitter-mediated activation of second messenger coupled receptors. Through metabotropic receptor activation astrocytes can sense synaptic activity and the astrocyte $Ca^{2+}$ signal triggers the release of gliotransmitters that can control neuronal excitability, synaptic transmission and plasticity (Kofuji and Araque, 2021). Cachope and Pereda provide a detailed review of the regulatory effects of metabotropic glutamate receptors in the synaptic communication mediated through neuronal gap junctions (i.e. electrical synapses). This regulation is of critical relevance during brain development and contributes to the pathological mechanisms that follow brain injury (Cachope and Pereda, 2021). Four articles review the role of metabotropic receptors in the operation of synapses and circuits and its impact on behaviour and human diseases of the CNS. Harms, Parras, Michie and Malmierca analyse the importance in sensory processing of Mismatch Negativity, a measure of memory-based changes in detection that occurs in response to unexpected stimuli. They discuss findings that suggest that NMDARs are involved in the generation of Mismatch Negativity and point to metabotropic receptors as key players in the generation of auditory prediction errors (Harms et al., 2021). Yang, Ding, Qi and Feldmeyer focus on the regulation of the synaptic release probability and short-term synaptic plasticity induced by acetylcholine and adenosine in different CNS structures. They discuss the contribution of cholinergic and adenosine receptors in the modulation of neuronal networks (Yang et al., 2021). Sanchez-Vives, Barbero-Castillo, Perez-Zabalza and Reig summarize results showing that metabotropic $GABA_B$Rs affects information flow between brain areas by controlling rhythmicity as well as synaptic plasticity. They discuss the relevant participation of $GABA_B$Rs in the generation of rhythmic activity in the cortico-thalamic network (Sanchez-Vives et al., 2021). Hasselmo, Alexander, Hoyland, Robinson, Bezaire, Chapman, Saudargiene, Carstensen and Dannenberg review network of metabotropic action in the CNS and propose network models that include the metabotropic modulation of synaptic plasticity in the hippocampus. They highlight the importance of metabotropic receptors in regulating both neuronal and network dynamics and suggest that neuroscience research would greatly benefit by building models that include both cell and network dynamics, aspects that have been under-explored (Hasselmo et al., 2021).

In summary, this Special Issue offers a broad and up to date view of the effects of metabotropic receptors in the regulation of synaptic plasticity. However, important questions remain open in the field, not only related to the mechanisms of the regulation of synaptic plasticity but also to broader aspects of metabotropic actions and dysfunction in the operation of the circuits of the CNS. Novel molecular, pharmacological and optical tools targeting G-Protein Coupled Receptors will help to achieve precise spatiotemporal control of synaptic plasticity and will promote new exciting experiments that will provide crucial data on this topic in the following years.

## REFERENCES

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356. [PubMed: 4727084]

Cachope R, Pereda AE (2021) Regulatory roles of metabotropic glutamate receptors on synaptic communication mediated by gap junctions. Neuroscience 456:85–94. [PubMed: 32619474]

Citri A, Malenka RC (2008) Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology 33:18–41. [PubMed: 17728696]

Dore K, Malinow R (2021) Elevated PSD-95 blocks ion-flux independent LTD: a potential new role for PSD-95 in synaptic plasticity. Neuroscience 456:43–49. [PubMed: 32114099]

Fernaández-Fernández D, Lamas JA (2021) Metabotropic modulation of potassium channels during synaptic plasticity. Neuroscience 456:4–16. [PubMed: 32114098]

Fernández de Sevilla D, Núñez A, Bunño W (2021) Muscarinic receptors, from synaptic plasticity to its role in network activity. Neuroscience 456:60–70. [PubMed: 32278062]

Fuenzalida M, Chiu CQ, Chávez AE (2021) Muscarinic regulation of spike timing dependent synaptic plasticity in the hippocampus. Neuroscience 456:50–59. [PubMed: 32828940]

Griego E, Galván EJ (2021) Metabotropic glutamate receptors at the aged mossy fiber – CA3 synapse of the hippocampus. Neuroscience 456:95–105. [PubMed: 31917351]

Harms L, Parras GG, Michie PT, Malmierca MS (2021) The Role of glutamate neurotransmission in mismatch negativity (MMN), a measure of auditory synaptic plasticity and change-detection. Neuroscience 456:106–113. [PubMed: 32045628]

Hasselmo ME, Alexander AS, Hoyland A, Robinson JC, Bezaire MJ, Chapman GW, Saudargiene A, Carstensen LC, et al. (2021) The unexplored territory of neural models: potential guides for exploring the function of metabotropic neuromodulation. Neuroscience 456:143–158. [PubMed: 32278058]

Kofuji P, Araque A (2021) G-protein-coupled receptors in astrocyte-neuron communication. Neuroscience 456:71–84. [PubMed: 32224231]

Lutzu S, Castillo PE (2021) Modulation of NMDA receptors by G-protein-coupled receptors: role in synaptic transmission, plasticity and beyond. Neuroscience 456:27–42. [PubMed: 32105741]

Sanchez-Vives MV, Barbero-Castillo A, Perez-Zabalza M, Reig R (2021) GABAB receptor-modulation of thalamocortical dynamics and synaptic plasticity. Neuroscience 456:131–142. [PubMed: 32194227]

Valbuena S, Lerma J (2019) Kainate receptors, homeostatic gatekeepers of synaptic plasticity. Neuroscience. 456:17–26. [PubMed: 31866560]

Yang D, Ding C, Qi G, Feldmeyer D (2021) Cholinergic and adenosinergic modulation of synaptic release. Neuroscience 456:114–130. [PubMed: 32540364]