

Mechanisms of Long-Term Plasticity of Hippocampal GABAergic Synapses

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Abstract—Long-term potentiation and depression of synaptic transmission have been considered as cellular mechanisms of memory in studies conducted in recent decades. These studies were predominantly focused on mechanisms underlying plasticity at excitatory synapses. Nevertheless, normal central nervous system functioning requires maintenance of a balance between inhibition and excitation, suggesting existence of similar modulation of glutamatergic and GABAergic synapses. Here we review the involvement of G-protein-coupled receptors in the generation of long-term changes in synaptic transmission of inhibitory synapses. We considered the role of endocannabinoid and glutamate systems, GABA_B and opioid receptors in the induction of long-term potentiation and long-term depression in inhibitory synapses. The pre- and postsynaptic effects of activation of these receptors are also discussed.

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The ability of synapses to change the efficiency of synaptic transmission in response to either frequency stimulation or under the action of metabolically active agents is recognized as synaptic plasticity. The first experimental indications for the possibility of changing the efficiency of synaptic transmission were demonstrated in the rabbit hippocampus, where high-frequency activation of excitatory synapses resulted in an increase in postsynaptic responses that could last for several hours or even

days [1, 2]. This phenomenon was termed long-term potentiation (LTP). For half a century, LTP and its opposing process, long-term depression (LTD), has attracted the attention of numerous scientific groups, because both these phenomena could represent cellular mechanisms of memory. It has been suggested that LTD plays the central role in memory consolidation – the ability of the brain to convert a short-term memory into a long-term memory [3, 4].

At the present time, LTP and LTD are intensely studied at hippocampal excitatory synapses. At the synapses formed by Schaffer collaterals on the spines of pyramidal neurons in the CA1 area of the hippocampus, both processes involve synaptic glutamate N-methyl-D-aspartate (NMDA) receptors [5].

It has been firmly established that the induction of LTP in the CA1 area of the hippocampus requires not only activation of NMDA receptors, but also significant depolarization of postsynaptic cells, which results in a decrease in voltage-dependent magnesium block of these channels and, respectively, an increase in the Ca²⁺

Abbreviations: AMPA receptors/channels, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-sensitive glutamate receptors/channels; CaMKII, calmodulin-dependent protein kinase II; CB1 and CB2, cannabinoid receptors of types 1 and 2, respectively; CNS, central nervous system; DSI, depolarization-induced suppression of inhibition; GABA, gamma-aminobutyric acid; LTD, long-term depression; LTP, long-term potentiation; NMDA receptors/channels, glutamate N-methyl-D-aspartate receptors/channels; PKA, cAMP-dependent protein kinase A.

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influx through NMDA channels. The significant NMDA receptor-mediated increase in calcium concentration in dendritic spines results, in turn, in activation of an intracellular signaling cascade that includes: (i) binding of free Ca^{2+} with calmodulin; (ii) binding of Ca^{2+} -calmodulin complex to calmodulin-dependent protein kinase II (CaMKII); (iii) autophosphorylation of CaMKII causing a multifold increase of its kinase activity; (iv) phosphorylation of a subtype of glutamate receptors (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-sensitive); (v) increase in the number of AMPA channels in postsynaptic density due to mobilization of phosphorylated AMPA receptors, which, in turn, increases amplitude of the postsynaptic response. LTD emerges in response to low-frequency stimulation, which causes significantly lower depolarization of postsynaptic spines and, respectively, results in lesser weakening of the magnesium block of NMDA channels. Hence, the Ca^{2+} influx through NMDA channels in this case is significantly lower than during high-frequency stimulation and is likely insufficient for CaMKII activation. Nevertheless, it is recognized that Ca^{2+} binds to calcineurin and activates Ca^{2+} -sensitive phosphatase I. Activation of the phosphatase causes dephosphorylation of the synaptic AMPA receptors and decrease in their density on the postsynaptic membrane [5].

Even though the clear majority of studies on long-term plasticity in recent decades were devoted to the excitatory synapses, an important role is played by similar changes in the efficiency of transmission in GABAergic inhibitory synapses, since a fine balance between excitation and inhibition is required for normal brain functioning. However, unlike the excitatory synapses formed by Schaffer collaterals on the pyramidal cells in the CA1 area of the hippocampus, the GABAergic synapses exhibit a wide diversity determined by the type of presynaptic GABAergic interneurons. For example, three types of excitatory cells have been identified in the hippocampus (granule cells of fascia dentata, pyramidal neurons of the CA3-CA4 area, and pyramidal neurons of the CA1-CA2 area), while there are more than 20 types of GABAergic interneurons [6]. Moreover, all these interneurons differ from each other not only by morphological features, but also by the type of inhibition (dendritic, perisomatic, etc.), expression of specific peptide or protein markers (such as Ca^{2+} -binding proteins) and metabotropic receptors capable of initiation of various intercellular cascades. It is most likely that the polymorphism of interneurons defines impressive variability of mechanisms underlying synaptic plasticity of GABAergic synapses [7-11]. Here, we review the participation and role of G-protein-coupled receptors in the emergence of long-term changes in the efficiency of synaptic transmission at GABAergic synapses formed by different types of hippocampal interneurons.

MECHANISMS OF LONG-TERM SYNAPTIC PLASTICITY AT GABAergic SYNAPSES IN THE HIPPOCAMPUS

Unlike excitatory synapses, long-term changes in synaptic transmission in GABAergic synapses involve G-protein-coupled signaling systems; moreover, participation of these systems is essential for the development of LTP and LTD. Nevertheless, the mechanism underlying long-term synaptic changes in various inhibitory synapses is similar to the one described for the excitatory connections. For example, high-frequency stimulation caused the NMDA-dependent activation of the calcineurin phosphatase in the synapses formed by interneurons localized in stratum radiatum onto the CA1 pyramidal neurons. Activation of this cascade resulted in long-term depression of postsynaptic inhibitory responses at these synapses [11]; furthermore, it was shown later that the LTD emerged not due to change in the protein phosphorylation, but rather due to the direct interaction of calcineurin with the $\gamma 2$ -subunit of the GABA_A channel [12]. It is likely that the release of glutamate required for activation of NMDA channels occurred from the neighboring excitatory synapses similarly to a process described in [13], but the experimental protocol did not allow either rejection or confirmation of this hypothesis. Meanwhile, the mechanisms of long-term synaptic changes induction in most GABAergic synapses involve intracellular cascades different from the ones participating in excitatory synapses.

In this review, we will discuss the involvement of the following G-protein-coupled cascades in the generation of long-term plasticity of GABAergic transmission: (i) endocannabinoid; (ii) glutamate; (iii) GABA_B ; and (iv) opioid. In many cases, the synergetic interaction of these systems is required for the induction of long-term synaptic changes; moreover, this interaction occurs not only inside one cell, but also involves spatially segregated signaling systems in pre- and postsynaptic neurons.

ENDOCANNABINOID AND GLUTAMATE SIGNALING SYSTEMS

The endocannabinoid system plays an important role in the central nervous system (CNS) functioning. Several endocannabinoids were identified and the effects of anandamide and 2-arachidonoylglycerol have been well studied. All known endocannabinoids are synthesized from cell lipids. The anandamide and 2-arachidonoylglycerol are synthesized via several cascades that often are functioning simultaneously in the cell and activated in neurons by an increase in intracellular Ca^{2+} level. It was shown that cannabinoids activate cannabinoid receptors of types 1 and 2 (CB1 and CB2).

The effects of endocannabinoids (2-arachidonoylglycerol, anandamide, N-arachidonoyl dopamine) in the CNS

are generally mediated by the type 1 cannabinoid receptors (CB1). These receptors are expressed mainly in interneurons [14], and moreover, 95% of hippocampal interneurons expressing CB1 receptors also synthesize cholecystokinin. These receptors are coupled with G_i proteins, whose activation inhibits adenylate cyclase activity and decreases the cyclic adenosine monophosphate (cAMP) concentration. In addition, activation of CB1 receptors results in dissociation of the $G\beta\gamma$ -subunit of the receptor, which can block voltage-gated Ca^{2+} channels via direct interaction [15]. Unlike many other receptors, these metabotropic receptors are located exclusively on presynaptic neurons [16].

Endocannabinoids significantly modulate the release of mediator from perisomatic synapses formed by CB1-expressing interneurons in all areas of the hippocampus. One form of the endocannabinoid-dependent short-term plasticity is depolarization-induced suppression of inhibition (DSI). DSI was first demonstrated in pyramidal neurons of the CA1 area of the hippocampus [17, 18]. However, the endocannabinoid system participates not only in short-term plasticity, but it is also involved in the formation of various forms of long-term synaptic changes at inhibitory synapses in many regions of the CNS [19-22]. Unlike neuromediators, which are released from presynaptic terminals, endocannabinoids are synthesized in postsynaptic neurons in response to an increase in intracellular Ca^{2+} concentration and play a role of retrograde messenger activating presynaptic CB1 receptors, which results in the suppression of transmitter release [23]. The endocannabinoid-mediated LTD in many brain areas also requires an increase in intracellular Ca^{2+} concentration and in addition to that activation of the postsynaptic metabotropic glutamate receptors (Fig. 1). Chevaleyre and Castillo demonstrated that high-frequency stimulation in the *stratum radiatum* in CA1 region activated postsynaptic metabotropic type 1 glutamate receptors and Ca^{2+} -dependent synthesis and release of endocannabinoids from postsynaptic neurons, which, in turn, caused long-term reduction of the GABA release via activation of presynaptic CB1 receptors [24]. Activation of CB1 receptors in this case is required for induction, but not for maintenance of LTD, which indicates involvement of CB1-mediated inhibition of adenylate cyclase activity in the presynaptic neuron. The authors made this conclusion because the blockade of CB1 receptors prior to the high-frequency stimulation blocked generation of LTD, while application of the CB1 receptor antagonist 20 min after the onset of LTD did not affect the response amplitude. It must be noted that these experiments were conducted using extracellular stimulation, which resulted in activation of both inhibitory and excitatory synapses. Activation of the latter ensured background level of glutamate needed for activation of metabotropic receptors; hence, in this case LTD induction was heterosynaptic.

The CB1 receptors are expressed at the presynaptic terminals of two subgroups of GABAergic interneurons in

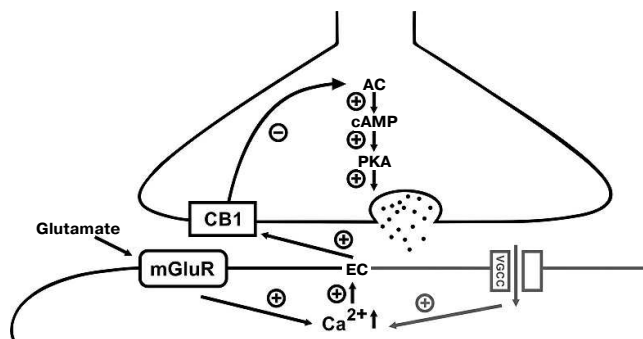


Fig. 1. Endocannabinoid-dependent mechanisms of LTD induction at GABAergic synapses. The postsynaptic cascade (indicated with gray color) is activated during depolarization of the postsynaptic neuron and activation of voltage-gated Ca^{2+} channels (VGCC), which triggers synthesis of endocannabinoids (ECs). ECs diffuse through the synaptic cleft and activate presynaptic CB1 receptors on the terminals of the GABAergic interneuron. This sequentially inhibits adenylate cyclase (AC) activity and decreases the level of cAMP leading to suppression of protein kinase A (PKA) activity. A similar reaction cascade is induced during activation of type I metabotropic glutamate receptors (mGluR) in the postsynaptic neuron (shown on the left). “+”, activating effect; “-”, inhibiting effect.

hippocampus: 1) cells innervating apical dendrites of pyramidal cells; 2) interneurons providing perisomatic inhibition of hippocampal excitatory neurons.

The phenomenon described above involved interneurons contacting dendrites of excitatory neurons, which was confirmed by the low basal level of DSI at CB1-positive synapses demonstrating endocannabinoid-dependent LTD [25, 26]. The mechanism of endocannabinoid-dependent LTD was further investigated in a study of Heifets and coauthors, where it was shown that the endocannabinoid-dependent inhibition of adenylate cyclase also resulted in the suppression of the function of PKA shifting the balance between phosphorylation and dephosphorylation towards dephosphorylation of PKA presynaptic targets. The latter notion was corroborated by experiments showing that blockade of the calcineurin phosphatase activity abolished the LTD induction [27]. The endocannabinoid-dependent LTD at the striatal GABAergic synapses does not require activation of metabotropic glutamate receptors, and the Ca^{2+} influx is provided via postsynaptic voltage-dependent L-type channels [28]. It is worth mentioning that the involvement of the endocannabinoid system in the induction of LTP at GABAergic synapses has not yet been demonstrated.

ROLE OF GABA_B RECEPTORS IN LONG-TERM PLASTICITY AT GABAergic SYNAPSES

The release of GABA at CNS synapses activates not only ionotropic GABA_A receptors, but also metabotropic

GABA_B receptors. The GABA_B receptor is a heterodimer consisting of GABA_{B1}- and GABA_{B2}-subunits and is coupled with G_{i/o}-proteins, whose activation decreases adenylate cyclase activity. Like the activation of CB1 receptors, activation of GABA_B receptors might result in the blocking of presynaptic voltage-gated Ca²⁺ channels and opening of the postsynaptic K⁺ channels due to the direct interaction of the Gβγ-subunit with these channels, which dissociates upon receptor activation. However, in contrast to endocannabinoid receptors, GABA_B receptors can be expressed both pre- and/or postsynaptically [29].

High-frequency (100 Hz) extracellular stimulation in *stratum radiatum* induces only short-term depression of GABA_A- and GABA_B-receptor-mediated responses recorded from the CA1 pyramidal neurons. However, theta frequency stimulation induces selective long-term potentiation of the GABA_A-mediated responses in monosynaptic connections between interneurons located in the *lacunosum-moleculare* layer and in pyramidal neurons in the CA1 area [30]. Combined activation of postsynaptic GABA_B and glutamate type I/II metabotropic receptors is required for generation of LTP. It is likely that the activation of glutamate metabotropic receptors results in an increase in intracellular Ca²⁺ level, which has been shown to be essential for LTP. The role of GABA_B receptors in this case remains unclear. Similar data were obtained for the inhibitory synapses in the hip-

poampus formed on GABAergic interneurons located in the *stratum radiatum* [31]. The presynaptic GABA_B receptors can also be involved in the induction of LTP in response to high-frequency stimulation (100 Hz, 2 s) [32]. Surprisingly, the necessity of activation of the cAMP-dependent protein kinase A is postulated by the authors of this study, which contradicts the GABA_B-dependent decrease in the cAMP level and indicates the possible participation of additional cascades in the LTP induction at these synapses.

Unlike the endocannabinoid system, GABA_B receptors can be involved in both LTP and LTD generation, depending on the type of inhibitory synapse. For instance, combined stimulation at theta-gamma frequencies of the perisomatic synapses formed by cholecystokinin-positive basket cells onto the CA1 pyramidal cells results in a long-term decrease in the amplitude of postsynaptic responses [33]. LTD at these synapses has postsynaptic nature, and activation of GABA_B receptors is required exclusively in the stage of induction of synaptic changes (Fig. 2). Even though these synapses are characterized by high expression of CB1 receptors, involvement of the endocannabinoid signaling system is not required for LTD induction, in contrast to CB1-positive interneurons innervating dendrites. Interestingly, combined theta-gamma stimulation causes LTP at the CB1-negative GABAergic synapses [33]. The two types of perisomatic synapses differ in the subunit composition of GABA_A receptors, which might be a basis for the different response to the same stimulation protocol. The synaptic transmission at synapses formed by CB1-positive interneurons is mediated by channels containing α2- and β3-subunits, while the currents in the CB1-negative contacts are conducted via channels containing α1- and β2(1)-subunits [34]. As discussed above, activation of metabotropic G_i-coupled receptors decreased the adenylate cyclase activity and, consequently, suppressed the function of PKA. The latter shifts the balance of phosphorylation and dephosphorylation of intercellular protein targets towards the dephosphorylated state. This may explain the differential effect of activation of GABA_B receptors at two different types of synapses. Dephosphorylation of the β1-containing receptors results in a significant increase in single channel conductance and, respectively, to the enhancement of the postsynaptic responses amplitudes. On the contrary, the β3-containing channels have higher conductance in the phosphorylated state [35, 36]. Hence, the type of plasticity at GABAergic synapses is determined not only by the involved signaling cascades, but also by the subunit composition of GABA_A receptors mediating the synaptic transmission. In particular, some data indicate that the LTP caused by high-frequency stimulation of GABAergic synapses in *stratum radiatum* results in structural modulation of postsynaptic receptors [37].

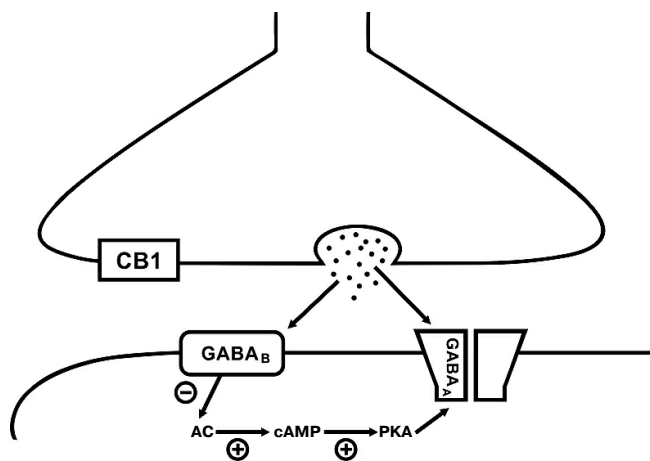


Fig. 2. Postsynaptic GABA_B-dependent mechanism of LTD induction at GABAergic synapses in the CA1 area of hippocampus. Release of GABA from presynaptic terminal activates GABA_A and GABA_B receptors. Activation of GABA_B receptors suppresses adenylate cyclase (AC) activity and, as a result, decreases cAMP level and PKA activity controlling the level of phosphorylation of GABA_A channels. The consequences of the PKA activity decrease depend on the subunit composition of GABA_A channels (see text). At synapses formed by CB1-expressing interneurons, the decrease in phosphorylation of GABA_A channels leads to reduction of the single channel conductance. “+”, activating effect; “-”, inhibiting effect.

ROLE OF OPIOID RECEPTORS IN LONG-TERM PLASTICITY AT GABAergic SYNAPSES

The opioid signaling system involves a set of opioid peptides and different types of their receptors. Three genes are known that encode precursors of opioid peptides: preproopiomelanocortin, preproenkephalin, and preprodynorphin. The peptides encoded by these genes are subjected to complex posttranslational modifications that result in formation of various active peptides. These compounds share the same sequence Tyr-Gly-Gly-Phe-(Met or Leu) termed the "opioid motif". The main opioid peptide encoded by the pre-proopiomelanocortin gene is β -endorphin. The preproenkephalin gene encodes met-enkephalin and leu-enkephalin. The preprodynorphin gene encodes three opioid peptides of different lengths: dynorphin A, dynorphin B, and neoendorphin, and all of those include the leu-enkephalin sequence [38]. All the above-mentioned peptides can activate all types of opioid receptors; however, their affinity varies significantly depending on the receptor type [38].

Three major types of opioid receptors are known: μ -opioid, δ -opioid, and κ -opioid. All these receptors can be localized either pre- or postsynaptically and are coupled with $G_{i/o}$ -protein. Binding of agonists to these receptors suppresses adenylate cyclase activity and decreases cAMP concentration [38, 39]. It was shown that the opioid signaling system participates in plasticity processes in CNS and can modulate either excitatory or inhibitory neurotransmission [40].

Even though activation of CB1, GABA_B, and opioid receptors induces similar intracellular signaling cascades such as inhibition of presynaptic voltage-gated calcium channels, activation of postsynaptic potassium transport, and suppression of adenylate cyclase activity both in pre- and postsynaptic cells, activation of these metabotropic receptors have multidirectional impact on induction of long-term synaptic changes. As established above, activation of presynaptic GABA_B receptors causes LTP, while involvement of the presynaptic endocannabinoid cascade is required for induction of LTD. The available data indicate that the blocking of δ -opioid receptors facilitates induction of LTP in response to high-frequency stimulation of GABAergic inputs to granular cells in dentate gyrus that are localized in the outer molecular layer [41]. It was found that the induction of LTP in this case was most likely heterosynaptic; hence, it requires the increase in intracellular Ca^{2+} via activation of glutamate NMDA channels. The authors did not clarify the source of glutamate, but it was reasonable to suggest that it was released during simultaneous stimulation of glutamatergic fibers located in the outer molecular layer of the dentate gyrus. It must be noted that the described work was devoted not to the process of activation of opioid receptors leading to the development of long-term changes in the inhibitory synaptic transmission, but rather to the fact that the opioid system con-

trolled the probability of development of such changes. Direct observation of opioid-dependent long-term depression was described for the CA2 area of the hippocampus [42]. The authors showed that high-frequency stimulation at GABAergic synapses formed by parvalbumin-expressing interneurons resulted in the development of LTD. It was found that the LTD at these synapses developed as a result of activation of δ -, but not μ -receptors at presynaptic terminals. Activation of the δ -receptors was required only in the stage of LTD induction because their blocking 10 min after the induction of plastic changes did not affect the amplitude of inhibitory responses. It is important to note that this type of synaptic plasticity was specific to GABAergic synapses formed by parvalbumin-positive interneurons in the CA2 area. High-frequency stimulation of synapses formed by interneurons of the same type in the CA1 area or application of δ -receptor agonists did not result in the development of long-term synaptic changes. It is not clear what the differences between the synapses formed by interneurons of this type are. It is also not known what intracellular mechanisms are activated during high-frequency stimulation that lead to development of δ -receptors-dependent LTD in the CA2 area.

The main difference in the induction mechanisms of LTP and LTD at GABAergic synapses from excitatory synapses is the differential involvement of multiple G-protein-coupled signaling systems. Furthermore, while at most excitatory synapses the LTP and LTD have a postsynaptic nature, and metabotropic receptors exert only modulating action, at GABAergic synapses the initiation locus for the long-term changes can be either pre- or postsynaptic, the direction of changes depends on the involvement of the particular signaling system, and, in a number of cases, on the subunit composition of GABA_A channels. It must be noted that despite the obvious importance of modulation of the inhibitory transmission for normal network functioning, the mechanisms of LTP and LTD at GABAergic synapses remain poorly understood, which most likely is due to the uniqueness of each type of synapses determined primarily by the nature of the presynaptic neuron.

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