Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Endocannabinoid-mediated retrograde modulation of synaptic transmission

Takako Ohno-Shosaku[1] and Masanobu Kano[2]

One of the two major endocannabinoids, 2-arachidonoylglycerol (2-AG), serves as a retrograde messenger at various types of synapses throughout the brain. Upon postsynaptic activation, 2-AG is released immediately after de novo synthesis, activates presynaptic CB_1 cannabinoid receptors, and transiently suppresses neurotransmitter release. When CB_1 receptor activation is combined with some other factors such as presynaptic activity, the suppression is converted to a long-lasting form. Whereas 2-AG primarily transmits a rapid, transient, point-to-point retrograde signal, the other major endocannabinoid, anandamide, may function as a relatively slow retrograde or non-retrograde signal or as an agonist of the vanilloid receptor. The endocannabinoid system can be up- or down-regulated by a variety of physiological and environmental factors including stress, which might be clinically important.

Addresses
[1] Department of Impairment Study, Graduate School of Medical Science, Kanazawa University, Kanazawa 920-0942, Japan
[2] Department of Neurophysiology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Corresponding author: Kano, Masanobu (mkano-tky@m.u-tokyo.ac.jp)

Current Opinion in Neurobiology 2014, **29**:1–8

This review comes from a themed issue on **Neuromodulation**

Edited by **David McCormick** and **Michael P Nusbaum**

For a complete overview see the Issue and the Editorial

Available online 18th April 2014

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2014.03.017

Introduction

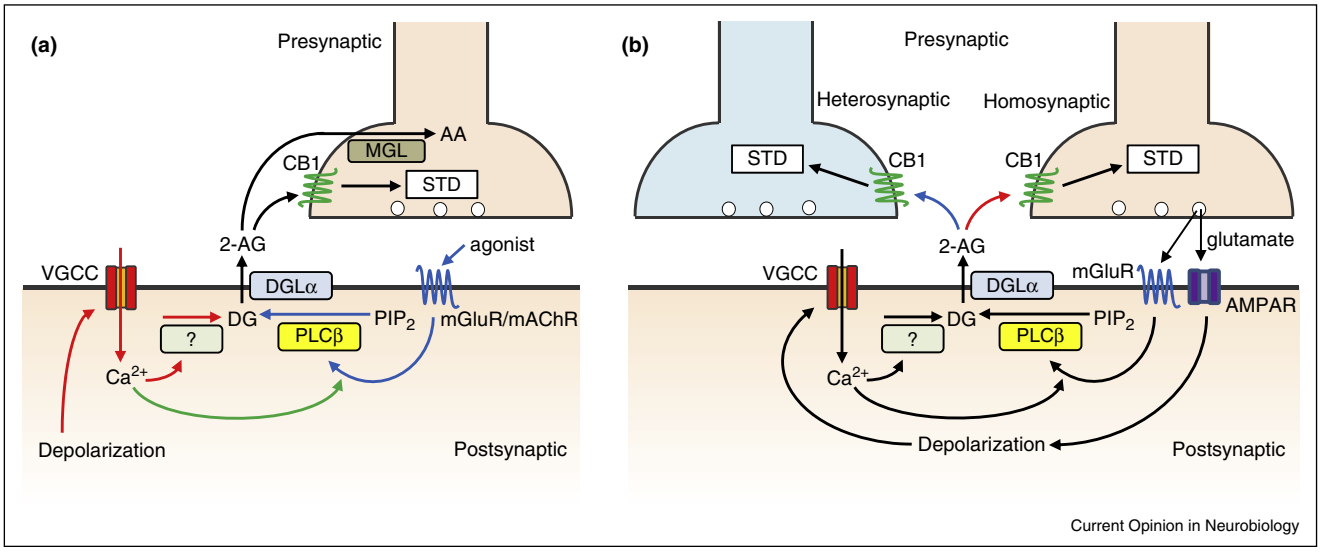
Endocannabinoids retrogradely modulate synaptic transmission widely throughout the central nervous system [1–5]. They are released from postsynaptic neurons, activate presynaptic CB_1 cannabinoid receptors, and suppress transmitter release either transiently (endocannabinoid-mediated short-term depression; eCB-STD) or persistently (endocannabinoid-mediated long-term depression; eCB-LTD). The eCB-STD and eCB-LTD are induced at various types of GABAergic and glutamatergic synapses throughout the brain. The ability of each synapse to express eCB-STD/LTD depends primarily on whether the presynaptic terminal expresses CB_1 receptors. In addition to their well-established functions as retrograde messengers, endocannabinoids might also function in non-retrograde manners [4]. In the last few years evidence has also accumulated to suggest that the endocannabinoid signaling system itself is regulated by various factors [6•]. In this article, we review recent advances in the molecular mechanisms of endocannabinoid signaling and its plastic changes induced by neuromodulators and environmental factors.

Standard 2-AG model of eCB-STD

The molecular mechanisms of endocannabinoid release involved in eCB-STD have been studied in a variety of preparations. Here we show the standard 2-AG model (Fig. 1), which can explain most, if not all, results of electrophysiological studies [1–5]. The conditions that induce the production and release of 2-AG are mechanistically classified into three types; increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) (Ca^{2+}-driven endocannabinoid release, CaER), activation of $G_{q/11}$-coupled receptors (basal receptor-driven endocannabinoid release, basal RER), and the combination of these two (Ca^{2+}-assisted RER) [1,2,6•]. After released from postsynaptic neurons, 2-AG activates presynaptic CB_1 receptors and suppresses transmitter release. Termination of the retrograde signal depends on degradation of 2-AG by monoacylglycerol lipase (MGL). Although the expression of MGL is highly heterogeneous [7,8••], 2-AG is degraded in a synapse non-specific manner by MGL concentrated in particular cell types [8••].

The CaER is responsible for the eCB-STD induced by depolarizing a postsynaptic neuron, which is termed DSI (depolarization-induced suppression of inhibition) or DSE (depolarization-induced suppression of excitation) for inhibitory or excitatory synapses, respectively. When depolarization causes a large, transient increase in $[Ca^{2+}]_i$ to micromolar levels through activation of voltage-gated Ca^{2+} channels, diacylglycerol (DG) is produced through some as yet unidentified mechanism (Fig. 1**(a)**, red arrows). DG is then converted to 2-AG by diacylglycerol lipase α (DGLα). The basal RER is responsible for the eCB-STD induced by activation of $G_{q/11}$-coupled receptors, such as group I metabotropic glutamate receptors (mGluRs) or M_1/M_3 muscarinic acetylcholine receptors (mAChRs), without need of postsynaptic Ca^{2+} elevation. Many other receptors have also been reported to induce RER, which include 5-HT_2-type serotonin receptors, protease-activated receptor 1 (PAR1), and the receptors for orexin, oxytocin and CCK [3]. When $G_{q/11}$-coupled receptors are activated, DG is produced by PLCβ, the subtype of which depends on brain areas (Fig. 1 **(a)**, blue arrows). DG

Fig. 1



Molecular mechanisms of endocannabinoid-mediated short-term depression (eCB-STD). **(a)** The production of diacylglycerol (DG) is induced by either a large Ca^{2+} elevation, which is caused by depolarization-induced activation of voltage-gated Ca^{2+} channels (VGCC), through unidentified mechanisms (red arrows), or strong activation of $G_{q/11}$-coupled receptors such as mGluRs and mAChRs through PLCβ (blue arrows). If weak activation of $G_{q/11}$-coupled receptors is combined with a small Ca^{2+} elevation, both of which are subthreshold for DG production when given alone, receptor-driven PLCβ stimulation is enhanced by Ca^{2+} to produce DG (green arrow). DG is then converted to 2-AG by diacylglycerol lipase α (DGLα). 2-AG is released from the postsynaptic neuron, and activates presynaptic CB_1 receptors to suppress transmitter release (STD). 2-AG is hydrolysed mostly by presynaptic monoacylglycerol lipase (MGL) and arachidonic acid (AA) is produced. **(b)** Excitatory synaptic activity releases glutamate, which activates postsynaptic AMPA-type glutamate receptors (AMPARs) and mGluRs. Activation of AMPARs causes Ca^{2+} elevation through activating VGCCs. The resulting postsynaptic Ca^{2+} elevation and/or mGluR activation causes the release of 2-AG through the mechanisms illustrated in a. 2-AG activates CB_1 receptors on the same presynaptic terminals releasing glutamate (red arrow, homosynaptic) or neighboring terminals (blue arrow, heterosynaptic), and suppresses transmitter release (STD).

is then converted to 2-AG by DGLα. The Ca^{2+}-assisted RER accounts for the eCB-STD induced by the combination of a small increase in $[Ca^{2+}]_i$ and weak receptor activation, both of which can be subthreshold for triggering endocannabinoid release. This synergistic effect can be explained by the Ca^{2+} dependency of receptor-driven PLCβ stimulation [9–11] (Fig. 1**(a)**, green arrow).

More physiological ways of inducing eCB-STD are via synaptic activity (synaptically driven eCB-STD) [1] (Fig. 1**(b)**). If glutamate is released from excitatory presynaptic terminals in a sufficient amount to induce postsynaptic Ca^{2+} elevation and/or mGluR activation, 2-AG is released through the mechanism for CaER, basal RER or Ca^{2+}-assisted RER. Excitatory synaptic activity is therefore potentially effective in inducing 2-AG release. Synaptically driven eCB-STD can be either homosynaptic (Fig. 1**(b)**, red arrow) or heterosynaptic [1] (Fig. 1**(b)**, blue arrow).

The standard 2-AG model described above is supported by a considerable number of studies. DSI, DSE, receptor-driven eCB-STD and synaptically driven eCB-STD are all inhibited by pharmacological blockade of DGL [12••] and genetic deletion of DGLα [13–15]. The mGluR- or mAChR-driven eCB-STD is blocked by genetic deletion of PLCβ1 for hippocampal neurons [9] or PLCβ4 for cerebellar Purkinje cells [10]. The termination of DSI/DSE is prolonged by genetic deletion [8••,16] and pharmacological blockade of 2-AG hydrolyzing enzyme (MGL), but not anandamide (another major endocannabinoid) hydrolyzing enzyme (fatty acid amide hydrolase, FAAH) [17].

On-demand vs. pre-formed

It is generally thought that 2-AG is not stored in neurons, but synthesized on demand upon stimulation. However, this 'on-demand synthesis model' was challenged by an alternative model that 2-AG is pre-formed by DGLα, pooled within cells, and mobilized from this hypothetical pre-formed 2-AG pools upon stimulation without the contribution of DGLα [18,19]. This model was developed to reconcile the apparent discrepancy in the experimental results between genetic and pharmacological blockade of DGL. DGLα knockout mice were generated independently by three groups, and they all exhibit complete loss of eCB-STD [13–15]. In contrast, the reported effects of acute pharmacological blockade of DGL were highly controversial [19]. A classical DGL inhibitor, tetrahydrolipstatin (THL), inhibited eCB-STD in some studies, but not in others. Inconsistent results were also observed with a novel potent DGL inhibitor, OMDM-188. OMDM-188 failed to inhibit DSI in one study [20], whereas it inhibited DSI but not mGluR-driven STD in another study [21].