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Neuroscience Research 40 (2001) 205–210

Neuroscience Research

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Update Article

Endogenous cannabinoid as a retrograde messenger from depolarized postsynaptic neurons to presynaptic terminals

Takashi Maejima, Takako Ohno-Shosaku, Masanobu Kano *

Department of Physiology, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa 920-8640, Japan

Received 19 March 2001; accepted 16 April 2001

Abstract

Cannabinoid receptors are the molecular targets for the active component Δ^9-tetrahydrocannabinol of marijuana and hashish, and constitute a major family of G protein-coupled seven-transmembrane-domain receptors. They consist of type 1 (CB1) and type 2 (CB2) receptors of which the CB1 is rich in various regions of the CNS. Accumulated evidence suggests that endogenous cannabinoids function as diffusible and short-lived intercellular messengers that modulate synaptic transmission. Recent studies have provided strong experimental evidence that endogenous cannabinoids mediate signals retrogradely from depolarized postsynaptic neurons to presynaptic terminals to suppress subsequent neurotransmitter release, driving the synapse into an altered state. In hippocampal neurons, depolarization of postsynaptic neurons and resultant elevation of $[Ca^{2+}]_i$ lead to transient suppression of inhibitory transmitter release (depolarization-induced suppression of inhibition, DSI). In cerebellar Purkinje cells, on the other hand, depolarization-induced elevation of $[Ca^{2+}]_i$ causes transient suppression of excitatory transmitter release (depolarization-induced suppression of excitation, DSE). DSI and DSE appear to share the same properties and may be a general and important mechanism by which the postsynaptic neuronal activity can influence the amount of transmitter release.

Keywords: Cannabinoid receptor; Endocannabinoid; Retrograde messenger; Ca^{2+}; Synaptic transmission; Synaptic modulation

1. Introduction

The synapse is a main target of various neuromodulators in the CNS. Several forms of activity-dependent synaptic modulation have been described and thought to play important roles in neural functions. Some are suggested to involve retrograde messengers that are released from postsynaptic neurons and mediate signals retrogradely to presynaptic neurons (Bliss and Collingridge, 1993; Alger and Pitler, 1995). Candidate retrograde messengers reported so far include amino acids (Glitsch et al., 1996; Zilberter et al., 1999), monoamines (Cheramy et al., 1981), peptides (Kombien et al., 1997), and neurotrophic factors (McAllister et al., 1999). Recent studies that have appeared in *Neuron* (Kreitzer and Regehr, 2001; Ohno-Shosaku et al., 2001) and in *Nature* (Wilson and Nicoll, 2001) have provided strong experimental evidence for endogenous cannabinoids (endocannabinoid) as a new class of candidate retrograde messenger. In this up date article, we briefly review these studies and propose a possible scheme for the mechanisms how depolarization of the postsynaptic neuron leads to inhibition of transmitter release from presynaptic terminals through the endocannabinoid system.

2. Cannabinoid receptors and endocannabinoids

Several lines of evidence support a possible role of endocannabinoids as a diffusible neuromodulator at synapses. First, cannabinoid receptors are widely distributed in the CNS (Herkenham et al., 1991; Matsuda et al., 1993; Tsou et al., 1998; Egertova and Elphick,

* Corresponding author. Tel.: +81-76-265-2170; fax: +81-76-234-4224.

E-mail address: mkano@med.kanazawa-u.ac.jp (M. Kano).

0168-0102/01/$ - see front matter
PII: S0168-0102(01)00241-3

2000). Cannabinoid receptors are the molecular targets of the active component (Δ^9-tetrahydrocannabinol) of marijuana and hashish. They have amino acids characteristic of G protein-coupled seven-transmembrane-domain receptors, and consist of type 1 (CB1) and type 2 (CB2) receptors with different distributions (Matsuda et al., 1990; Munro et al., 1993; Felder and Glass, 1998). While the CB2 receptor is expressed mainly in the immune system of the periphery (Klein et al., 1998), the CB1 receptor exhibits a widespread distribution in the brain. In situ hybridization, autoradiographic and immunohistochemical studies on brain tissue show that the distribution of CB1 receptor is heterogeneous, with high levels in some areas including the hippocampus, associational cortical regions, the cerebellum, and the basal ganglia (Herkenham et al., 1991; Matsuda et al., 1993; Tsou et al., 1998; Egertova and Elphick, 2000), that correlates with the known effects of cannabinoids on memory, perception, and the control of movement. The distribution is also heterogeneous among different populations of neurons in a certain brain region. In the hippocampus, e.g., very high levels of CB1 immunoreactivity and mRNA are associated with subpopulations of GABAergic neurons (Katona et al., 1999; Tsou et al., 1999).

Second, potential endocannabinoids such as anandamide and 2-arachidonoylglycerol (2-AG) and pathways for their biosynthesis have been identified (Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995, 1999). These molecules are widely distributed in the brain, with high levels in the hippocampus, striatum, cerebellum, and cortex showing a good correlation with the CB1 receptor distribution (Bisogno et al., 1999a). These are lipid in nature, are synthesized from membrane phospholipid in activity- and Ca^{2+}-dependent manners (Cadas et al., 1996; Stella et al., 1997; Di Marzo et al., 1998; Bisogno et al., 1999b; Piomelli et al., 2000), and can diffuse out across the cell membrane due to its hydrophobicity. The released endocannabinoids are removed from the extracellular space through a selective and saturable uptake system or enzymatic degradation. The degradating enzyme fatty acid amide hydrolase is strongly expressed in the CB1 receptor-rich regions (Cravatt et al., 1996; Thomas et al., 1997; Goparaju et al., 1998), and is located complementally to CB1 receptors (Egertova et al., 1998).

Third, the activation of cannabinoid receptors induces a variety of actions on neural functions (Di Marzo et al., 1998; Felder and Glass, 1998). Cannabinoid agonists inhibit adenylate cyclase (Howlett and Fleming, 1984) and N- and P/Q-type Ca^{2+} channels, and activate inwardly rectifying potassium channels (Mackie and Hille, 1992; Felder et al., 1995; Mackie et al., 1995; Twitchell et al., 1997). They also suppress the release of neurotransmitters, such as glutamate, GABA, acetylcholine, and noradrenaline, probably via inhibition of presynaptic Ca^{2+} channels (Gifford and Ashby, 1996; Ishac et al., 1996; Shen et al., 1996; Katona et al., 1999; Hoffman and Lupica, 2000).

All these findings suggest that endocannabinoids can work as a diffusible and short-lived mediator that is released from activated neurons, binds to its receptors on neighboring neurons and modulate their functions.

3. Depolarization-induced suppression of inhibition

In cerebellar Purkinje cells (Vincent et al., 1992) and hippocampal neurons (Pitler and Alger, 1992; Ohno-Shosaku et al., 1998), direct depolarization of a postsynaptic neuron induces a transient suppression of inhibitory synaptic inputs to the depolarized cell (Fig. 1). A train of action potentials can also induce a similar transient suppression in hippocampal neurons (Fig. 1), indicating that this form of synaptic modulation may play a role in controlling neural excitability in vivo. This phenomenon is termed depolarization-induced suppression of inhibition (DSI), and is thought to be a good example that requires the action of some retrograde messengers (Alger and Pitler, 1995). The postsynaptic depolarization triggers Ca^{2+} influx through voltage-gated Ca^{2+} channels (Lenz et al., 1998), and induces a transient elevation of intracellu-

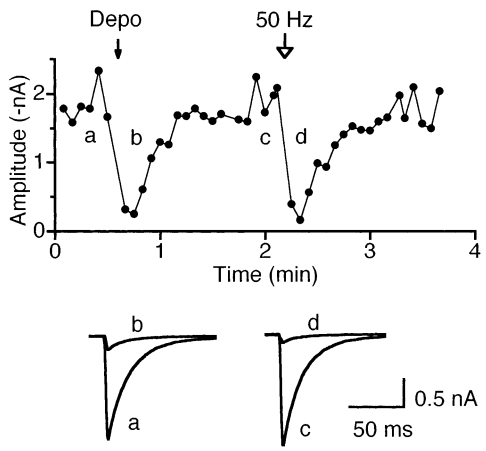

Fig. 1. An example of DSI observed with a pair of cultured neurons from the hippocampus of newborn rats. Inhibitory postsynaptic currents (IPSCs) were evoked by stimulating the presynaptic neuron at 0.2 Hz, and were measured from the postsynaptic neuron at −80 mV. DSI can be induced by either a continuous depolarization (0 mV, 5 s) or a train of action potentials (50 Hz, 5 s) in the postsynaptic neuron. The time course of the change in IPSC amplitudes (upper) and the IPSC traces (lower) acquired at the indicated time points are shown.

lar Ca^{2+} concentration ($[Ca^{2+}]_i$). When the Ca^{2+} influx is inhibited by perfusing the postsynaptic neuron with a Ca^{2+}-free solution during depolarization (Ohno-Shosaku et al., 1998), or when the fast Ca^{2+} buffer BAPTA is injected into the postsynaptic neuron (Pitler and Alger, 1992; Vincent and Marty, 1993; Ohno-Shosaku et al., 2001), the depolarization fails to induce DSI. Thus, it is evident that the postsynaptic Ca^{2+} elevation is required for the induction of DSI. While the site of induction for DSI is postsynaptic, the site of expression is apparently presynaptic. The postsynaptic response to the exogenously-applied GABA is not suppressed significantly after the postsynaptic depolarization (Pitler and Alger, 1992; Ohno-Shosaku et al., 2001). DSI accompanies a clear increase in the paired-pulse ratio (Ohno-Shosaku et al., 1998; Wilson and Nicoll, 2001), a widely used indicator for presynaptic modulation (Zucker, 1989). These data indicate that the depolarization-induced elevation of $[Ca^{2+}]_i$ transiently suppresses the release of the inhibitory transmitter GABA from presynaptic terminals. Thus, it follows that some retrograde messengers must mediate signals from the depolarized postsynaptic neuron to the inhibitory presynaptic terminals.

In slice preparations from the cerebellum (Llano et al., 1991) and the hippocampus (Pitler and Alger, 1992), DSI has been reported to be mediated by glutamate or a glutamate-like substance (Glitsch et al., 1996; Morishita et al., 1998). It is proposed that glutamate or a glutamate-like substance acts on metabotropic glutamate receptors (mGluRs) on the inhibitory presynaptic terminals to reduce GABA release (Glitsch et al., 1996; Morishita et al., 1998).

However, because the DSI in the cerebellum was little affected by a widely used mGluR antagonist, MCPG (Glitsch et al., 1996), and DSI in the hippocampus was blocked only partly by MCPG even with a high concentration (5 mM; Morishita et al., 1998), it is suggested that glutamate may not be the sole and major mediator of DSI in slice preparations.

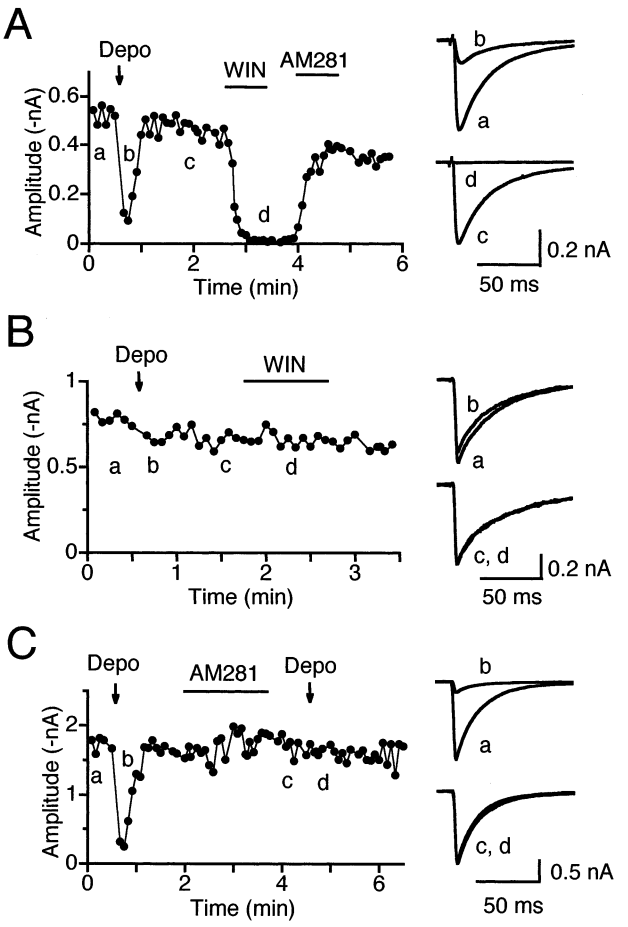

Fig. 2. Effects of an agonist (WIN55,212-2) and an antagonist (AM 281) for cannabinoid receptors on IPSCs and DSI in cultured hippocampal neurons. (A, B) In a neuron pair exhibiting DSI, but not a pair without DSI, IPSCs were always suppressed by WIN55,212-2 and recovered by AM 281. The bath was perfused with the solution containing 0.1 μM WIN55,212-2 or 0.3 μM AM 281. (C) DSI was completely blocked after application of AM 281.

4. Endocannabinoid as a retrograde messenger in DSI

Recently, we (Ohno-Shosaku et al., 2001) and Nicoll's group (Wilson and Nicoll, 2001) have reached independently the same conclusion, by using primary cultures and slices, respectively, that endocannabinoids mediate the retrograde signal of DSI in the hippocampus. In our culture preparation, this conclusion is supported by the following observations. First, the cannabinoid receptor agonist WIN55,212-2 mimics DSI at the synapses with the ability to express DSI (Fig. 2(A)). Second, the WIN55,212-2-insensitive synapses, probably lacking presynaptic cannabinoid receptors, invariably fail to express DSI (Fig. 2(B)). Third, the paired-pulse ratio increases similarly during DSI and the WIN55,212-2-induced suppression. Fourth, DSI is completely eliminated by cannabinoid receptor antagonists (Fig. 2(C)), AM 281 and SR141716A, but not by widely used mGluR antagonists or a selective and potent $GABA_B$ receptor antagonist, CGP55845A. These results suggest that neither glutamate nor GABA is a major retrograde messenger for DSI in the hippocampus. Wilson and Nicoll (2001) present essentially the same results in the hippocampal slice as those obtained in culture preparation. In addition, they show that DSI was not inhibited by postsynaptically-applied botulinum toxin, making vesicular glutamate release from the postsynaptic cell highly improbable. They also demonstrated that liberation of Ca^{2+} alone via flash photolysis of caged Ca^{2+} was sufficient to induce DSI. All these

data are consistent with the notion that endocannabinoids function as a retrograde messenger for DSI.

5. Depolarization-induced suppression of excitation

CB1 receptors are reported to be present at not only inhibitory but also excitatory presynaptic fibers (Egertova and Elphick, 2000). It is therefore, highly likely that endocannabinoids released from postsynaptic neurons can act on CB1 receptors on excitatory terminals and reduce excitatory transmitter release. A recent paper has demonstrated that brief depolarization of cerebellar Purkinje cells induces a transient suppression of excitatory synaptic transmission at both parallel fiber synapses and climbing fiber synapses (Kreitzer and Regehr, 2001). This depolarization-induced suppression of excitation (DSE) lasts for tens of seconds, is blocked by the postsynaptic injection of BAPTA, and is associated with a change in paired-pulse ratio (Kreitzer and Regehr, 2001). DSE is prevented by the cannabinoid receptor antagonist AM251, but not by mGluR antagonists, LY 341495, CPPG and MCPG (Kreitzer and Regehr, 2001). All these properties are quite similar to those of DSI, and suggest that depolarization-induced elevation of $[Ca^{2+}]_i$ in Purkinje cells induces the release of endocannabinoids, thereby suppressing the glutamate release from presynaptic terminals via the activation of presynaptic CB1 receptors. Because CB1 receptors are widespread in the CNS, these findings strongly suggest that retrograde inhibition by endogenous cannabinoids is an important and widespread mechanism in the CNS that control the amount of transmitter release at both excitatory and inhibitory synapses.

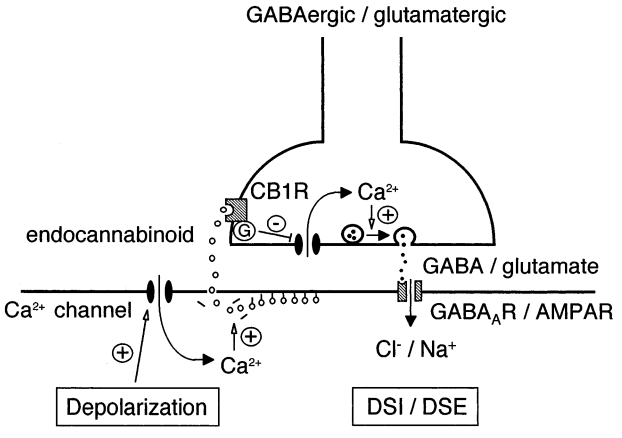

Fig. 3. A model for mechanisms of DSI/DSE. Postsynaptic depolarization causes an elevation of $[Ca^{2+}]_i$ via activation of Ca^{2+} channels, which in turn stimulates the generation and the release of endocannabinoids. The released endocannabinoids then activate presynaptic CB1 receptors and suppress the release of GABA or glutamate, probably by inhibiting presynaptic Ca^{2+} channels.

6. Possible mechanisms for DSI and DSE

Fig. 3 shows a current model for the mechanisms of DSI and DSE. Postsynaptic depolarization triggers Ca^{2+} influx by activating voltage-gated Ca^{2+} channels, and causes a transient elevation of $[Ca^{2+}]_i$. The elevated $[Ca^{2+}]_i$ stimulates the biosynthesis of endocannabinoids and induces their release from the depolarized postsynaptic neuron. The released endocannabinoids diffuse retrogradely and bind to CB1 receptors on the inhibitory or excitatory presynaptic terminals contacting onto the depolarized neuron. The binding of endocannabinoids to CB1 receptors activates Gi/o proteins in the presynaptic terminals and suppresses the release of GABA or glutamate, presumably by inhibiting voltage-gated Ca^{2+} channels (Hoffman and Lupica, 2000).

In this model, however, several important points remain to be elucidated. (1) What molecule(s), anandamide, 2-AG or some other substance, is released from depolarized neurons and mediate DSI/DSE? (2) What biochemical pathways in postsynaptic neurons are involved in the biosynthesis of retrograde messenger(s)? (3) Which enzyme(s) is Ca^{2+}-dependent and rate-limiting? (4) How is the retrograde messenger(s) inactivated?

7. Possible physiological significance of endocannabinoids

Endocannabinoid release is triggered by a transient elevation of $[Ca^{2+}]_i$ in postsynaptic neurons and may lead to DSI or DSE. A study on the cerebellar DSI shows that the extent of DSI is a function of the peak $[Ca^{2+}]_i$, and that the half-saturation point as measured in dendrites is near 200 nM (Glitsch et al., 2000). This effective level of $[Ca^{2+}]_i$ for DSI induction is comparable to that for LTD in the cerebellum (Konnerth et al., 1992) and the hippocampus (Cormier et al., 2001), and lower than that for LTP in the hippocampus (Cormier et al., 2001). It is therefore, likely that DSI/DSE may function in vivo to modulate the strength of synaptic transmission and thus control the neuronal excitability. It may also be possible that endocannabinoids are released from the activated neurons during the induction of LTD or LTP and might modulate its induction.

Most of the candidate retrograde messengers are thought to be stored in vesicles and released through exocytosis. In contrast, endocannabinoids are synthesized upon demand from their phospholipid precursors existing in cell membranes (Di Marzo et al., 1998; Felder and Glass, 1998; Piomelli et al., 2000). The release of endocannabinoids does not require any special apparatus, such as vesicles, besides biosynthetic enzymes, and can occur overall at the membrane sur-

face following an appropriate stimulation. These properties may be an advantage as a retrograde messenger.

The widespread distribution of CB1 receptors in the CNS indicates that endocannabinoids may be of general importance in neural functions. Moreover, an elevation of Ca^{2+} that causes the release of endocannabinoids can be induced following neural activities under various conditions. It is therefore, likely that a retrograde modulation mediated by endocannabinoids is a general and important mechanism by which the postsynaptic activity can influence the presynaptic function.

Acknowledgements

This work was partly supported by grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (to T.O.-S. and M.K.) by Human Frontier Science Program (to M.K.), and by Special Coordination Funds for Promoting Science and Technology from Science and Technology Agency of Japan (to M.K.).

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