Role of Endocannabinoids in 5-HT2 Receptor-Mediated Effects

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Endocannabinoids are lipid retrograde messengers that can be released by postsynaptic depolarization and/or activation of certain metabotropic receptors. We review a recent report that activation of metabotropic 5-HT2 receptors by endogenous serotonin induces the release of endocannabinoids in the olivary nucleus and suppresses glutamatergic input through a presynaptic action. This serotonin–endocannabinoid interaction has implications in the pathophysiology of pain and mental illness and raises the possibility that drugs targeting the 5-HT2 receptor may act by modulating endocannabinoid release.

Receptor-driven endocannabinoid (eCB) release was first demonstrated in the cerebellum, where glutamate released from climbing fiber terminals acted on metabotropic glutamate subtype 1 receptors (mGluR1) expressed on Purkinje cells. The activation of mGluR1s subsequently caused the release of eCBs, thus depressing climbing fiber input. Later research showed receptor-driven eCB release is not confined to mGluRs. Orexin-B and muscarinic acetylcholine M1 and M3 receptors are all capable of inducing eCB release (reviewed by Hashimotodani et al. 2007). eCB release can also be triggered by the Ca transient evoked by strong postsynaptic depolarization.

Because eCBs are lipid molecules and are released as soon as they are synthesized, synthesis is a key event in initiating eCB signaling. The pathways of eCB synthesis are not fully characterized. However, there appear to be independent mechanisms involving phospholipase C (PLC) in some cases (receptor-driven eCB release) and increased intracellular Ca2+ in others (i.e., depolarization-induced eCB synthesis). These two pathways can interact synergistically so, when combined, they allow eCBs to be released by levels of depolarization and metabotropic receptor activation that would not produce eCB release on their own (reviewed by Chevaleyre et al. 2006).

eCBs can inhibit neurotransmitter release over both short- and long-term timescales. Short-term depression manifests via CB1R-mediated inhibition of presynaptic Ca2+ channels, enhanced presynaptic K+ conductance, and by affecting release machinery downstream of Ca2+ influx. Long-term depression is less well defined and is thought to involve coactivation of presynaptic N-methyl-D-aspartate receptors and CB1Rs. eCB-mediated synaptic plasticity has been implicated in learning and memory and the distribution of CB1Rs in the brain suggests specific roles in the control of pain, motivation, emotion, learning, and cognition (reviewed by Chevaleyre et al. 2006).

In recent work, Best and Regehr (2008) add serotonin (5-HT) to the list of neurotransmitter systems with receptors able to trigger eCB release. In this study, both 5-hydroxytryptamine 2 receptor (5-HT2R) and 5-hydroxytryptamine 1B receptor (5-HT1BR) activation decreased the probability of glutamate release in the inferior olive and the effect of 5-HT2Rs was prevented by a CB1R antagonist. The authors took advantage of a novel brain stem slice that preserves serotonergic neurons and their synapses onto the inferior olive. Because these serotonergic inputs are physically separated from glutamatergic input from mesodiencephalic regions, they were able to study the interactions of these two inputs on olivary neurons (Fig. 1A). Whole cell voltage clamp of neurons in the dorsal principal olive revealed that exogenous 5-HT (10 μM) depressed the amplitude of evoked excitatory postsynaptic currents (EPSCs) by >80%. This effect was mimicked by the high-affinity 5-HT2R agonist TCB-2, but was fully suppressed only by a combination of 5-HT2R and 5-HT1BR antagonists. This modulation was presynaptic because it increased the paired-pulse ratio of the evoked EPSCs and had no effect on the amplitude of currents evoked by exogenous glutamate application.

Given that other Gq-coupled receptors can evoke eCB release, Best and Regehr investigated whether the serotonergic suppression of evoked EPSC amplitude was cannabinoid dependent. CB1R agonists depressed the amplitude of evoked EPSCs to a similar extent as serotoninergic agonists and, importantly, the reduction of evoked EPSC amplitude produced by selective activation of 5-HT2R was blocked by selective CB1R antagonists.

Activating receptors with exogenous agonists does not replicate physiological recruitment. First, there is always the risk of nonselective effects caused by ligands straying onto other receptors. Second, 5-HT2A receptors undergo agonist-directed trafficking, meaning that different agonists can preferentially recruit different second-messenger cascades (Parrish and Nichols 2006). Finally, the temporospatial characteristics of agonist stimulation will vastly differ between bath application and neuronal release of a neurotransmitter.

To stimulate 5-HT2 receptors with greater physiological validity than afforded by exogenous agonists, the researchers electrically stimulated the slice dorsal to the inferior olive with a 1-s 50-Hz train. This initiated a slow 5-HT2R–mediated postsynaptic inward current (presumably by activating serotonergic fibers from the nucleus reticularis paragigantocellularis; Fig. 1B). A single train induced a serotonergic current that lasted for about 10 s but depressed evoked EPSCs for about 25 s in a manner that was sensitive to 5-HT2–5-HT1B antagonist coapplication. The inhibition of glutamate release induced by endogenous serotonin was mediated by eCB release because a CB1R antagonist blocked it. Thus one effect of serotonin in the inferior olive is 5-HT2R–mediated eCB release.
activated serotonergic fibers (Regehr 2008) with permission. The whole cell recording (bottom right electrode), and area where stimulation activated serotonergic fibers (top right electrode). Inset: plane and angle of the inferior olivary slice.

In their discussion, Best and Regehr suggest that many of the clinically significant effects of 5-HT2R may be mediated by eCBs. This is an intriguing idea. 5-HT2AR agonists, such as LSD, and high doses of CB1R agonists, such as Δ9-tetrahydrocannabinol, have similar hallucinogenic effects that may model some aspects of schizophrenia and recreational use of cannabinoids may increase susceptibility to schizophrenia/psychosis (reviewed in Roser et al. 2008). This raises the natural question of whether cannabinoid manipulations might have a role in treatment of psychosis. A 4-wk, controlled, double-blind clinical trial of cannabidiol, a weak partial CB1R antagonist, in 42 schizophrenic patients, showed that cannabidiol reduced acute psychotic signs and symptoms to a degree that did not differ from the antipsychotic D2/D3 receptor antagonist amisulpride. However, the selective CB1 antagonist rimonabant (SR141716) was no more effective than a placebo in a trial of 72 patients with schizophrenia or schizoaffective disorder (reviewed in Roser et al. 2008). Even if CB1R blockade does not prove useful on its own, it is possible that this approach may find use as an adjunct to dopamine D2 receptor antagonism, much in the same way as atypical antipsychotics derive additional efficacy from 5-HT2R antagonism.

FIG. 1. Schematic of the experimental protocol and the pathway by which endocannabinoid (eCB) release is caused by 5-hydroxytryptamine 2 receptors (5-HT2Rs). A: diagram showing the position of the stimulating electrode for recruiting glutamatergic input into the inferior olive (left electrode), location of the whole cell recording (bottom right electrode), and area where stimulation activated serotonergic fibers (top right electrode). Inset: plane and angle of the inferior olivary slice. B: by activating serotonergic fibers a 5-HT2–mediated current could be induced that produced a depression in glutamate release: 1 shows the slow serotonergic current and the fast glutamatergic currents before, during, and after the evoked serotonin release; 2 shows the sensitivity of the serotonergic current to a 5-HT2 antagonist, ritanserin; 3 shows the depression of excitatory postsynaptic current amplitude by the serotonergic current (time 0) and its sensitivity to the CB1 receptor antagonist AM251. C: 5-HT is released by serotonergic neurons and activates 5-HT2Rs that produce diacylglycerol (DAG), via the action of phospholipase C (PLC). DAG is metabolized by DAG lipase (DAGL) to eCBs, which in turn cause eCB release, acting in a retrograde fashion to depress glutamate release. Depolarization, presumably by activating voltage-sensitive Ca2+ channels and increasing intracellular Ca2+ concentration, can also generate eCBs. Pathways outlined in gray were not directly demonstrated by Best and Regehr (2008) but exist in other brain regions and potentially act here too. A and B were modified from Best and Regehr (2008) with permission.
The interaction between serotonin and eCB systems reported by Best and Regehr (2008) suggests that therapeutic drugs acting via 5-HT2Rs may produce their action, at least in part, by modulating eCB release. Because there are many (patho)physiological states that involve heightened serotonergic activity, it may prove fruitful to investigate the role of eCB release in these states. One may also ask how many more Gq-linked receptors may directly activate eCB synthesis. This study opens new vistas for understanding the serotonin system and reveals a potential rationale for therapeutic approaches to treating psychosis and neuropathic pain.

REFERENCES


