The Role of Endocannabinoid Signaling in Motor Control

Cannabinoid receptors and endocannabinoid signaling are distributed throughout the rostrocaudal neuraxis. Retrograde signaling via endocannabinoid mediates synaptic plasticity in many regions in the central nervous system. Here, we review the role of endocannabinoid signaling in different parts of the vertebrate motor system from networks responsible for the execution of movement to planning centers in the basal ganglia and cortex. The ubiquity of endocannabinoid-mediated plasticity suggests that it plays an important role in producing motion from defined circuitries and also for reconfiguring networks to learn new motor skills. The long-term plasticity induced by endocannabinoids may provide a long-term buffer that stabilizes the organization of motor circuits and their activity.

Motor behavior represents the overt expression of integrated central nervous system (CNS) processing. The CNS comprises a number of networks, each controlling a defined motor function. The final motor output is the result of a sophisticated integration of their activity. These networks display a continuous plasticity to allow their activity to adapt to changes in the internal and external environments (7). These mechanisms allow animals to acquire new motor skills and to reorganize the remaining circuitry to recover function after injury or illness. One major substrate of the plasticity of neural circuits is the synaptic communication between the constituent neurons that can be changed by modulatory systems.

Neuromodulation of synaptic connections has been classically considered to depend on release of modulatory transmitters from presynaptic terminals that can act postsynaptically on axon terminals or dendrites to change synaptic strength (10, 11, 22, 35, 53, 71). This view has been revised following the discovery of endocannabinoid and nitric oxide signaling. Endocannabinoids are lipid molecules that can be released in a nonsynaptic fashion from postsynaptic neurons to travel back onto presynaptic terminals and act as retrograde messengers (27, 55, 69). They represent a prominent example of retrograde signaling in synaptic plasticity in many regions of the CNS. Most studies of endocannabinoid-mediated plasticity in the brain have concentrated on mechanisms related to memory and learning (2, 3, 13, 17, 20, 42). These studies have, however, been confronted with the difficulty of being able to quantify cognitive changes to link synaptic plasticity to behavior.

A major advantage of motor circuits is that their outputs can be readily measured and correlated to the motor behavior. This places them in a position to link the synaptic plasticity mediated by endocannabinoids to changes that occur in the operation of the network as a whole. An example is the spinal network that generates the basic locomotor pattern and also acts as a processing interface to adjust its output in response to influences from the brain and sensory afferents (15, 16, 26). Because endocannabinoids can in principle be released from all neurons in the spinal locomotor networks, they provide an important modulatory mechanism that is not only involved in fine-tuning of the ongoing activity but that also may be necessary for the generation of the locomotor activity.

In this review, we will first provide background on endocannabinoid signaling system by describing their synthesis and degradation, and the receptor types they activate. We will then give an account of the role of endocannabinoid-mediated synaptic plasticity in vertebrate motor systems proceeding from the spinal cord, where the final processing and execution of movement takes place, to the planning centers in the basal ganglia and cortex.

Endocannabinoids

Endocannabinoids are lipid molecules principally derived from membrane phospholipids. Unlike classical neurotransmitters and neuropeptides, endocannabinoids are not stored in vesicles in axon terminals, but rather they are synthesized on demand in somata and dendrites. They are subsequently released from cells and then exert an
immediate action as signaling molecules (8, 56). Two major endocannabinoids have been identified in the CNS: arachidonoyylethanolamide (AEA), commonly known as anandamide, and 2-arachidonoylglycerol (2-AG) that are synthesized and degraded by separate pathways (FIGURE 1).

The major route for the biosynthesis of anandamide is via the precursor N-arachidonoyl phosphatidylethanolamine (NAPE), which is generated by the enzyme N-acyltransferase in a calcium-dependent manner. Anandamide is then generated by hydrolysis of NAPE by a phospholipase D (NAPE-PLD) (8, 56, 63, 68). Thus the endocannabinoid anandamide seems to be produced “on demand” and released in an activity-dependent manner by enzymatic cleavage of lipid precursors. The biological inactivation of anandamide is mainly through hydrolyzation mediated by fatty acid amide hydrolase (FAAH) (47). The major pathway for the biosynthesis of 2-AG comprises sequential hydrolysis of arachidonic acid-containing inositol phospholipids by phospholipase C (PLC) and diacylglycerol lipase (8, 56, 63). In response to many extracellular signals such as neurotransmitters, PLC catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2), thereby generating two well-established second messengers, inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). DAG lipase (DAGL) is an enzyme hydrolyzing DAG to yield 2-AG. 2-AG is transported into neurons—the transporter is still unknown—and subsequently inactivated by the enzyme monoacylglycerol (MGL) (8, 56, 63). 2-AG synthesis and release can also be driven by activation by Gq-coupled receptors, such as group I mGluRs and muscarinic receptors, because the signaling pathway they activate leads to accumulation of the 2-AG precursor DAG (2, 11, 20, 25).

In summary, the synthesis and release of these two endogenous cannabinoids occurs on demand in an activity-dependent manner either in terms of firing of neurons or activation of Gq-coupled receptors, or a combination of the two. The separate synthesis and degradation pathways of anandamide and 2-AG offer an initial possibility of determining their distribution and defining their roles in controlling CNS function.

**Endocannabinoids as a New Player in Synaptic Plasticity**

Activity-dependent changes in synaptic efficacy play a critical role in shaping the functional architecture of neural circuits and determining their operational range. In this regard, endocannabinoids have attracted much attention in recent years because of their unconventional way of regulating synaptic transmission. There were initially

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**Cannabinoid Receptors: A Couple or More**

So far, two cannabinoid receptors (CB1 and CB2) have been characterized pharmacologically, anatomically, and by molecular cloning, but other cannabinoid receptors may exist (43). CB1 receptors are expressed virtually throughout the CNS from cortical to spinal cord regions (21). They are predominantly localized on presynaptic terminals, but there are reports of a postsynaptic localization on dendrites and somata of neurons (46). These receptors were initially thought to be coupled preferentially to a Gi/o G protein, but recent data show that they can also couple to Gq G-protein to induce release of Ca²⁺ from intracellular stores. The existence of CB2 receptors has been reported in some specific regions such as the brain stem (67), but their expression level is much lower than that of CB1. They are also primarily coupled to Gi/o G-protein, but their function in the CNS is not well defined (43). Recent data suggest that additional cannabinoid receptors may be present in the CNS based on a pharmacological characterization. Finally, the GPR55 receptor, first identified as an orphan receptor, has also been suggested to act as a cannabinoid receptor with a signaling profile distinct from CB1 and CB2 receptors (43).

Thus cannabinoid signaling in the brain is thought to be mediated primarily by CB1 receptors, but additional receptors may also be present. In addition, the anatomical localization of the receptors in relation to the site of synthesis and release of endocannabinoids will determine the direction of their signaling.

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**FIGURE 1. Main pathways of synthesis and degradation**

Main pathways of synthesis and degradation of the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG).
several reports showing that activation of CB1 receptors by agonists modulates synaptic transmission via presynaptic mechanisms (38). A turning point in endocannabinoid research was the demonstration that they act as retrograde messengers to mediate a previously unexplained form of short-term plasticity reported in cerebellum and hippocampus. A brief depolarization of principal neurons (Purkinje cells or pyramidal cells) suppresses GABAergic synaptic inputs over a few seconds (41, 57). This phenomenon was termed depolarization-induced suppression of inhibition (DSI). In addition, endocannabinoid retrograde signaling was simultaneously reported to mediate a similar suppression of excitation (DSE). The depolarization induces an increase in the intracellular Ca\(^{2+}\) levels in the postsynaptic neurons that mediates synthesis and release of endocannabinoids that act on CB1 receptors on presynaptic axons and inhibit synaptic release (27, 55, 69). Subsequently, endocannabinoids have also been shown to mediate long-term plasticity of both excitatory and inhibitory synaptic transmission in many regions of the CNS (2, 3, 13, 17, 20, 42).

The importance of endocannabinoids for short- and long-term synaptic plasticity and the underlying mechanisms have been thoroughly reviewed in recent years. In this review, we will instead focus on the role of endocannabinoid-mediated synaptic plasticity in motor systems using examples from CNS regions involved in motor behavior.

**Endocannabinoids Within the Spinal Locomotor Circuitry**

One region of the CNS where the link between endocannabinoid-mediated synaptic plasticity can be directly related to circuit function and motor behavior is the spinal cord. Locomotor movements are generated by spinal networks comprised primarily of interconnected populations of excitatory glutamatergic and inhibitory glycinergic interneurons. The motor output is generated by bursts of motoneuron firing that leads to the temporally sequenced muscle contractions underlying locomotion. This rhythmic locomotor pattern can be produced by the isolated spinal cord, while synaptic transmission from excitatory and inhibitory interneurons can be assessed (FIGURE 2). Using the lamprey spinal cord preparation in vitro, we have been able to link the effects of endocannabinoid-mediated plasticity on synaptic transmission to the modulation of the locomotor circuit operation.

Spinal neurons contain the necessary machinery for endocannabinoid signaling. For example, neurons in the dorsal horn express DAG lipase that is the synthesis enzyme for the endocannabinoid 2-AG. This enzyme colocalizes with group I mGlurRs (mGlur5) postsynaptically, whereas CB1 receptors are found presynaptically on axon terminals (54). It was first shown in the cat spinal cord that Δ\(^9\)tetrahydrocannabinol (THC; the active component of cannabis) changes synaptic transmission onto motoneurons (66). These data indicate that cannabinoid receptors exist in the spinal cord and raise questions regarding the origin of the endocannabinoid activating them and how it affects the locomotor output. In recent years, the role of endocannabinoids within the spinal locomotor circuitry has begun to be clarified (11, 25, 33).

Endocannabinoids play an important role in setting the baseline locomotor frequency in the isolated spinal cord in vitro (25, 33). This was demonstrated by first inducing the locomotor rhythm with bath application of NMDA while recording the motor pattern in opposing ventral roots of one segment. Blockade of CB1 receptors using a specific antagonist reduced the baseline frequency of the locomotor rhythm by >50%, showing that endocannabinoids are released within the locomotor circuitry and that they contribute to the expression of the motor pattern. Release of endocannabinoids in the lamprey spinal cord can be induced on activation of mGlur1 or tachykinin receptors by substance P (25, 33, 65).

What mechanisms do endocannabinoids use to influence the locomotor frequency? To address this question, we have examined the effect of blocking CB1 receptors on inhibitory and excitatory synaptic transmission during locomotion. Commisural interneurons mediate the reciprocal midcycle inhibition that ensures the left-right alternation of activity during locomotion, whereas the excitatory interneurons produce the on-cycle depolarization that drives motor activity. Blockade of CB1 receptors increased the amplitude of the midcycle inhibition, whereas it decreased that of on-cycle excitation. This indicates that activation of CB1 receptors by endocannabinoids released during locomotion regulates inhibitory and excitatory synaptic transmission differently, in such a manner as to increase the excitability in the spinal circuitry and thus accelerate the locomotor behavior (11, 24, 33).

**On Demand Release of Endocannabinoids and Plasticity in the Spinal Cord**

In the lamprey spinal cord, activation of mGlur1 occurs during fictive locomotion. It induces short- and long-term potentiation of the locomotor frequency (10, 31–33, 51). The long-term potentiation requires activation of CB1 receptors by endocannabinoids release on activation of mGlur1, and blockade of CB1 receptors completely suppresses
the long-term potentiation of the locomotor frequency (FIGURE 3). This long-term plasticity is mediated by a network of modulatory signaling involving mGluR1 and the release of endocannabinoids (33). The signaling pathways activated by mGluR1 lead to formation of DAG, which is a necessary precursor for the endocannabinoid 2-AG (23, 24, 33, 50, 51). Endocannabinoids are released from motoneurons and network interneurons “on demand” during locomotor network operation by activation of mGluR1 by glutamate released from excitatory CPG interneurons. The endocannabinoids then act as retrograde messengers to induce long-term depression of midcycle inhibition and long-term potentiation of on-cycle excitation. The endocannabinoid-mediated long-term plasticity of synaptic transmission and network activity also involves release of NO (FIGURE 3). Indeed, previous studies in the Xenopus tadpole spinal locomotor network have shown that NO plays a critical role in modulating the locomotor activity and midcycle inhibition (48, 49, 60). We have recently shown that NO is released endogenously in the lamprey spinal cord and also contributes to setting the frequency of the locomotor rhythm (34). Similar to the effects of CB1 receptors, NO increases the locomotor frequency by changing the balance between excitatory and inhibitory synaptic transmission from network interneurons (34). In the spinal circuitry, endocannabinoids and NO use similar synaptic mechanisms to regulate the locomotor activity. In addition, they are recruited by activation of mGluR1 to regulate the activity of the locomotor network. It thus appears that endocannabinoids and NO signaling act synergistically to mediate long-term plasticity in the spinal circuitry; the precise mechanisms of this interaction have not yet been clarified.

Endocannabinoids Maintain the Balance of the Basal Ganglia Output and Motor Function

The basal ganglia are thought to be responsible for the selection of appropriate motor behavior. They consist of a set of interconnected nuclei with the striatum as the primary input nucleus receiving excitatory inputs from cortex and thalamus and a dense dopaminergic innervation from midbrain nuclei. The vast majority of neurons in the striatum are GABAergic medium spiny neurons (MSNs), with a few cholinergic and other GABAergic interneurons (30, 64). The basal ganglia consist of two pathways involving two distinct populations of MSNs. Striatonigral MSNs expressing D1 receptors project directly to the output nuclei (the internal globus pallidus and substantia nigra reticulata), whereas striatopallidal MSNs express D2 receptors

**FIGURE 2. Levels of analysis of neural circuits controlling motor behavior**
A defined motor behavior is generated by networks of excitatory and inhibitory neurons. The activity of the constituent neurons and their synaptic interactions is continuously modulated by G-protein-coupled receptors such as those activated by endocannabinoids.
and project to output nuclei indirectly via the external globus pallidus and the subthalamic nucleus. These two pathways act in opposing way to control movement, with the direct one responsible for initiation of motor programs and the indirect one inhibiting them. Inputs to MSNs undergo synaptic plasticity that is thought to play a major role in shaping the striatal output and hence initiation and termination of motor activities.

The excitatory input to MSNs displays a strong activity-dependent plasticity in the form of long-term depression (LTD) and potentiation (LTP). The striatal LTD requires the elevation of Ca²⁺ levels in postsynaptic neurons and a convergence of modulatory inputs activating group I mGluRs and D2 receptors (30, 64). This combination of several signals leads to release of endocannabinoids from MSNs that act retrogradely to depress synaptic transmission from excitatory terminals. Evidence suggests that endocannabinoids released from MSNs is anandamide because blockade of its transporter facilitated striatal LTD (1, 14). Finally, the LTD was blocked by D2 receptor antagonists and enhanced by D2 agonists (30, 64). The apparent regulation of this endocannabinoid-mediated LTD by D2 receptors suggests that it is selectively restricted to excitatory inputs on MSNs of the indirect pathway. By comparing LTD in MSNs from the direct and indirect pathways, it was shown that only those of the indirect pathways express LTD mediated by endocannabinoids. D2 receptor activation enhances this LTD by potentiating endocannabinoid signaling (29, 30). However, endocannabinoids have been reported to mediate a form of LTD in MSNs of the direct pathway that does not depend on D2 receptor activation (59, 64). The expression of LTD in MSNs of the direct pathway is inhibited by D1 receptor activation, which instead induces LTP of FIGURE 3. 

Endocannabinoid-mediated long-term plasticity of the spinal locomotor network

Endocannabinoids are released in the spinal cord and set the baseline locomotor burst frequency. Their release is also triggered by activation of metabotropic glutamate receptor 1 (mGluR1). This receptor type activates Gq proteins and phospholipase C (PLC) that hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3). DAG is, in turn, hydrolyzed by DAG lipase to the endocannabinoid 2-AG. 2-AG acts as a retrograde messenger-induced long-term depression of inhibition and long-term potentiation of excitation. Nitric oxide (NO) is also released in the spinal cord and modulates inhibition and excitation. Endocannabinoids and NO seem to act synergistically to mediate the synaptic and network plasticity in the spinal cord.
excitatory synaptic transmission onto MSNs of this pathway (58). It thus appears that dopamine shifts the excitability balance between the direct and indirect pathway in favor of an increased activity of MSNs in the direct pathway, which promotes motor activity. In this scheme, the loss of dopamine innervation, as in the case of Parkinson’s disease, can disrupt this balance, leading to increased excitability of MSNs of the indirect pathway that inhibit movement. To test whether the D2-dependent, endocannabinoid-induced LTD in striatum can restore motor activity in the absence of dopamine innervation, co-administration of endocannabinoid degradation inhibitors and D2 agonists was performed (29, 30). As predicted, this combined treatment in animals with depleted dopaminergic innervation significantly enhanced locomotor activity in animals with depleted dopaminergic innervation (29, 30). As predicted, this combined treatment in animals with depleted dopaminergic innervation significantly enhanced locomotor activity in animals with depleted dopaminergic innervation (29, 30).

This synaptic suppression of excitation is blocked by CB1 receptor antagonists and is absent in CB1 receptor knockout mice, confirming a role of endocannabinoids in synaptic plasticity (3, 20).

As in basal ganglia, LTD is also a prominent form of plasticity in the cerebellum (6, 19, 37). Coincident activation of parallel and climbing fibers over time leads to weakening of parallel fiber synapses onto Purkinje cells. This LTD has been proposed to mediate motor learning in the vestibulo-ocular reflex pathway (18), whereby climbing fibers signal motor error and weaken simultaneously active parallel fiber synapses. This results in inhibition of the incorrect movement and an improvement of motor performance. There is a consensus that LTD is mediated postsynaptically, although the underlying mechanisms and its significance for motor performance has long been debated over several years (19). A recent contribution to this debate has been provided by evidence that LTD depends on the release of endocannabinoids from Purkinje cells (58). The question that arises is how can retrograde signaling by endocannabinoids mediate LTD that is expressed postsynaptically? One possible answer involves nitric oxide (NO), which has been suggested to be released from presynaptic terminals on activation of CB1 receptors and to act as an anterograde messenger (58). Further studies, however, are needed to determine precisely how an interaction between NO and endocannabinoid systems mediated LTD in the cerebellum.

The cerebellum contributes to the precision and smooth execution of motor tasks. Although endocannabinoid-mediated plasticity has been studied extensively in the cerebellum, very little is known about its significance for cerebellar function and motor behavior. Mice lacking CB1 receptors are not ataxic and do not display aberrant motor control (36, 72). To understand the function of endocannabinoid-mediated plasticity in terms of motor function, the analysis needs to be broadened from single synapses to circuit operation and ultimately to behaviorally relevant tasks.

Cerebellar Function: A Role for Endocannabinoids in Motor Learning

The cerebellum plays an important role in fine-tuning of motor behavior and in learning of new motor tasks. Purkinje cells are the only output from the cerebellar cortex and project to the deep cerebellar nuclei. Each Purkinje cell receives excitatory inputs from many parallel fibers arising from granule cells and from a single climbing fiber originating in the inferior olive. Excitatory synaptic transmission to Purkinje cells displays both short- and long-term changes that depend on release of endocannabinoids and activation of CB1 receptors. Endocannabinoids have been shown to mediate depolarization-mediated suppression of both inhibitory and excitatory synaptic transmission to Purkinje cells (9, 27, 28, 70). The suppression of excitatory transmission can also be induced by synaptic activation. It was shown that high-frequency stimulation of parallel fibers can lead to activation of mGluR1, resulting in endocannabinoid synthesis via the PLC-DAG pathway (44, 45). This synaptic suppression of excitation is blocked by CB1 receptor antagonists and is absent in CB1 receptor knockout mice, confirming a role of endocannabinoid release in this form of synaptic plasticity (3, 20).

Role of Endocannabinoids in Stabilizing Motor Map Formation and Maintenance

Specific regions of the neocortex, particularly the supplementary motor area, are important for planning of movement and execution of fine motor tasks. There is a continuous interaction between sensory and motor areas to integrate incoming sensory inputs and transform them into appropriate motor behavior. The organization of sensory maps not only defines representation of specific body regions in the cortex but may also be critical for the organization of the cortical motor circuits. We will now briefly review the role of endocannabinoids in synaptic plasticity in the neocortex and their significance in circuit plasticity.
Endocannabinoids have been shown to play a critical role in long-term depression (LTD) in the neocortex (61). Pairing of presynaptic and postsynaptic activity can trigger long-term potentiation (LTP) or depression depending on their relative timing. LTD occurs at many neocortical synapses and is elicited when postsynaptic firing precedes presynaptic firing (5). Postsynaptic calcium elevation and activation of group 1 mGluRs drive postsynaptic endocannabinoid synthesis and release, which signals retrogradely to presynaptic CB1 receptors, driving a long-lasting decrease in release probability (12, 17, 52, 61). This LTD also requires activation of presynaptic NMDA receptors. In this scheme, presynaptic CB1 receptors detect postsynaptic activity as a consequence of release of endocannabinoids, whereas presynaptic NMDA receptors are a sensor of presynaptic firing since they act as autoreceptors. Because endocannabinoids can diffuse to other synapses, the coincidence of activation of presynaptic CB1 and NMDA receptors could increase the specificity of this diffusible retrograde signal to restrict the plasticity to the active synapses.

Does endocannabinoid-mediated LTD occur in vivo, and what role does it play in motor control? In recent years, endocannabinoid-induced LTD has been suggested to contribute to depression of excitatory synaptic transmission in barrel (S1) and visual (V1) cortex. Whisker deprivation results in LTD of excitatory synaptic transmission in deprived columns in the barrel cortex that resembles endocannabinoid-induced LTD in vitro (12). The sensory deprivation may result in weakening of deprived whisker representation as a result of LTD of synaptic interactions by endocannabinoids. In a recent study, Li and colleagues (39) showed that signaling via CB1 receptors is required for whisker map development. These authors argue that endocannabinoid-mediated LTD may act to weaken inappropriate synapses and contribute to activity-dependent organization of sharp whisker borders (maps). Similarly, monocular deprivation depresses visually evoked responses, an effect also thought to be mediated by CB1 receptors (4). A systemic pharmacological blockade of CB1 receptors in vivo prevents depression of closed-eye responses, suggesting that CB1-LTD is a critical mechanism for response depression (40). Although endocannabinoid-mediated LTD has been shown to be involved in the organization of sensory maps, it is not the only mechanism involved, and other mechanisms also play a role (12, 62).

These two examples show that endocannabinoid retrograde signaling can shape map representation in the neocortex. Sensory signal processing in different cortical areas needs ultimately to be transformed into motor action, for example during visuo-motor coordination or exploratory movements. The endocannabinoid-mediated synaptic plasticity may thus play a role in refining sensory-motor circuit organization and adapting their range of operation during motor performance and during learning of new motor tasks.

**Balancing Motor Functions by Endocannabinoids**

From the example discussed above, it is clear that endocannabinoids play an important role in balancing the excitability of circuits controlling motor behavior. The long-term plasticity induced by endocannabinoids may provide a long-term buffer that stabilizes the organization of motor circuits and their activity. In the spinal cord, the shift in the excitability balance induced by endocannabinoids does not only lead to an increase in the locomotor frequency, but it also primes the circuitry to faster onset of locomotion with a lesser excitatory drive from descending command centers. The endocannabinoid-dependent plasticity in critical motor areas in the brain plays a role in refining and consolidating sensory-motor maps during learning of new motor task. In addition, by tuning synaptic transmission, this novel signaling mechanisms can provide a long-term buffer that stabilizes the decision-making process, initiation, and the control of precision of movement, thus permitting the motor programs to be effortlessly and unconsciously executed.

**Perspectives**

Like the motor systems they modulate, CB receptors and endocannabinoid signaling are distributed throughout the rostrocaudal neuraxis. This raises the possibility that 1) there are features that are common to the different systems in terms of endocannabinoid signaling, and 2) the spinal cord role could, for phylogenetic and developmental reasons, represent the primordial/ancient condition.

The possibility of on demand release of endocannabinoids from network neurons that are active during locomotion alters our understanding of modulatory systems. Initially, modulation was thought to arise from sets of dedicated neurons, with the modulatory transmitter being released from axon terminals. The ability of network neurons to release endocannabinoids from their dendrites and soma shows that every neuron, including motoneurons, can be transformed into a modulatory neuron in an activity-dependent manner and thereby set the strength of the excitatory and inhibitory synaptic transmission it receives. This adds to the dynamic processing taking place within the spinal circuitry to generate and regulate...
the locomotor pattern. Retrograde signaling by endocannabinoids can be considered an integral part of the locomotor pattern generation. Enhancing this signaling may help to promote recovery of function after spinal cord injury.

Motor behavior is orchestrated by interactions between many transmitters and modulatory systems. The final action of endocannabinoids does not always solely involve activation of CB receptors, but they can also interact with other signaling systems. In the cerebellum and in the spinal locomotor network, endocannabinoids interact in a synergistic manner with NO signaling to mediate synaptic and network plasticity. The interplay between these two unconventional signaling molecules suggests that the activity of a given network underlying motor behavior is not only dependent on synaptic connectivity but is also continuously regulated by a network of modulatory systems. Thus an understanding of how the CNS generates motor behavior will require defining the connectivity of both the neural circuit and the biochemical modulatory networks.

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