

Activity-dependent synaptic dynamics in motor circuits of the spinal cord

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In this article, we describe the most relevant recent research studies on the capability of spinal motor synapses to potentiate or depress their connectivity strength depending on their previous activity, termed activity-dependent synaptic plasticity (ADSP). Currently, ADSP in motor spinal circuits is mainly studied *in vivo*, with a significant body of work conducted in humans. Here, we review recent data obtained on the modulation of the post-activation depression of the electrically induced stretch reflex (H-reflex), and describe the use of spike-timing dependent plasticity (STDP)-like stimulation protocols to improve motor function after spinal cord insults. Altogether these recent findings point to the salient role played by ADSP in motor functional recovery. However, thus far there are few available data concerning the cellular basis of the synaptic dynamics of motor spinal networks. We, therefore, believe that we need to bridge this gap to accurately establish stimulation paradigms that restore spinal synaptic dynamics and enable the improvement of motor recovery after injury.

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A major feature of the central nervous system (CNS) is its ability to be reshaped throughout life. This CNS adaptability, or plasticity, is the basis of processes such as learning and memory, adaptation to morphological changes during development or ageing as well as functional recovery after injury. The word ‘plasticity’ is a catch-all term covering all the variety of mechanisms endowing the CNS with adaptive properties ranging from the macroscopic level such as the remodeling of cortical maps [1] to subcellular aspects such as synaptic receptor

trafficking [2]. Among this wide range of processes, a large body of research has focused on the capability of chemical synapses to amplify (potentiation) or decrease (depression) their connectivity strength for short or long periods of time depending on their previous activity: the so-called activity-dependent synaptic plasticity (ADSP).

Activity versus activity: a matter of definition

When considering ADSP in the ventral spinal cord networks that generate locomotor and postural commands, the term ‘activity’ may lead to some confusion as it could refer to ‘movement’ or ‘training’ instead of the ‘rate of action potential firing’ in presynaptic neurons. Several recent reviews have reported the numerous plastic changes (morphological changes, axonal sprouting, . . . etc.) induced by motor activities as well as by motor task learning in the spinal motor networks under both physiological and pathophysiological conditions (see for examples Refs. [3–5]). However, although interacting functionally through overlapping elements, a distinction should be made between the overall impact of the neuronal activity generated during training or learning and the continuous and dynamic integration of firing rate that occurs in synaptic connections. For example, a synapse that expresses long-term depression (LTD) following a 1 Hz presynaptic spike train, will express more, less or the same degree of depression or another form of ADSP in response to the same train after motor skill learning or training depending on how the network to which the synapse belongs has been reconfigured. This second order of plasticity, the plasticity of plasticity is termed metaplasticity [6] and reflects the functional adaptation of the synaptic dynamics to the global network changes. In this review, we will present recent data on ADSP in the context of its first definition whereby the term ‘activity’ refers to the action potential firing frequency of presynaptic neurons that in turn conditions the expression of long or short term depression (LTD, STD) or potentiation (LTP, STP) in synaptic terminals in spinal motor networks (see also Ref. [7]).

Surprisingly, while ADSP has been and is still mainly investigated using *in vitro* preparations in supraspinal areas, the vast majority of recent data collected on ADSP in spinal motor circuits has been obtained *in vivo*, with substantial amount of work performed in humans. As we will see below, this is mainly due to the fact that ADSP in the spinal cord is not studied *per se* but is used as a means to probe spinal network excitability and to promote functional recovery after injury.

Metaplasticity of the H-reflex post-activation depression

The H-reflex, the analogue of the mechanically induced stretch reflex, corresponds to the reflex muscle contraction observed after the electrical stimulation of the corresponding sensory nerve (Figure 1a). In contrast to the stretch reflex, the H reflex bypasses muscle spindle activation and, therefore, enables direct examination of the monosynaptic transmission between I_A afferents and motoneurons (MN). H-reflex responses exhibit post-activation depression (PAD) when trains or paired-pulse stimulations of sensory afferents are applied at stimulation rates ranging from 0.1 to 10 Hz [[14[•]],9] (Figure 1a). The H-reflex PAD is similar to the homosynaptic depression described in supraspinal structures and is characterized by a decreased probability of glutamatergic release in I_A afferent synaptic terminals following their repetitive activation [10]. Over the last decade, numerous investigations performed primarily in humans, have used the H-reflex PAD as a tool to evaluate spinal cord functions in both physiological and pathophysiological conditions [11]. In healthy subjects, PAD varies according to the activity of the sensory system, with an increase in depression occurring after motor training [12], but a PAD decreased after immobilization [13], upslope walking [14[•]] or during ageing [15 but see Ref. 16]. Interestingly, H-reflex PAD vanishes following the disuse of the monosynaptic loop after spinal cord injury (SCI) as patients progress from the acute to the chronic state [17,18] and is also strongly reduced in patients or in animal models after stroke [19,20]. These alterations in the I_A -MN synaptic depression with a resultant increase in stretch reflex amplitude are now well acknowledged to contribute to the development of the spasticity expressed in patients after stroke or SCI. Indeed, a direct link has been established between the degree of spasticity and the alterations in H-reflex PAD expression [21,22]. In healthy subjects, compressive loading of the hind limb decreases PAD of the soleus H-reflex [23,24]. In contrast, compressive loading of limb segments fails to modulate PAD in SCI patients, revealing a decreased capability of spinal segment below the lesion to respond to short episodes of sensory stimulation [25]. However, an ever-growing body of evidence suggests that the reactivation of sensorimotor pathways, for example, by passive cycling movements, treadmill training, physical therapy or robotic-assisted gait training improve functional motor recovery and restore PAD expression in both humans and animals after SCI or stroke [20,26–28]. The changes in PAD rate observed after motor mobilization requires the integrity of the sensory afferent pathways [29] and are accompanied by improvement in balance control [20]. Pharmacological compounds such as the GABA_B receptor agonist, baclofen or the neurotoxic protein, botulinum toxin, two standard treatments for spasticity have also been shown to modify the amplitude of the H-reflex PAD after stroke [19,30]. In the same way, pharmacological or functional

genetic manipulations of the potassium chloride cotransporter KCC2, whose downregulation parallels the development of spasticity after SCI, have been found to alter the amount of depression expressed by the H-reflex [31].

Altogether, these data show that the solicitation of I_A -MN synapses in normal and pathophysiological conditions changes the strength of the connection and restores part of the physiological dynamics of the reflex loop.

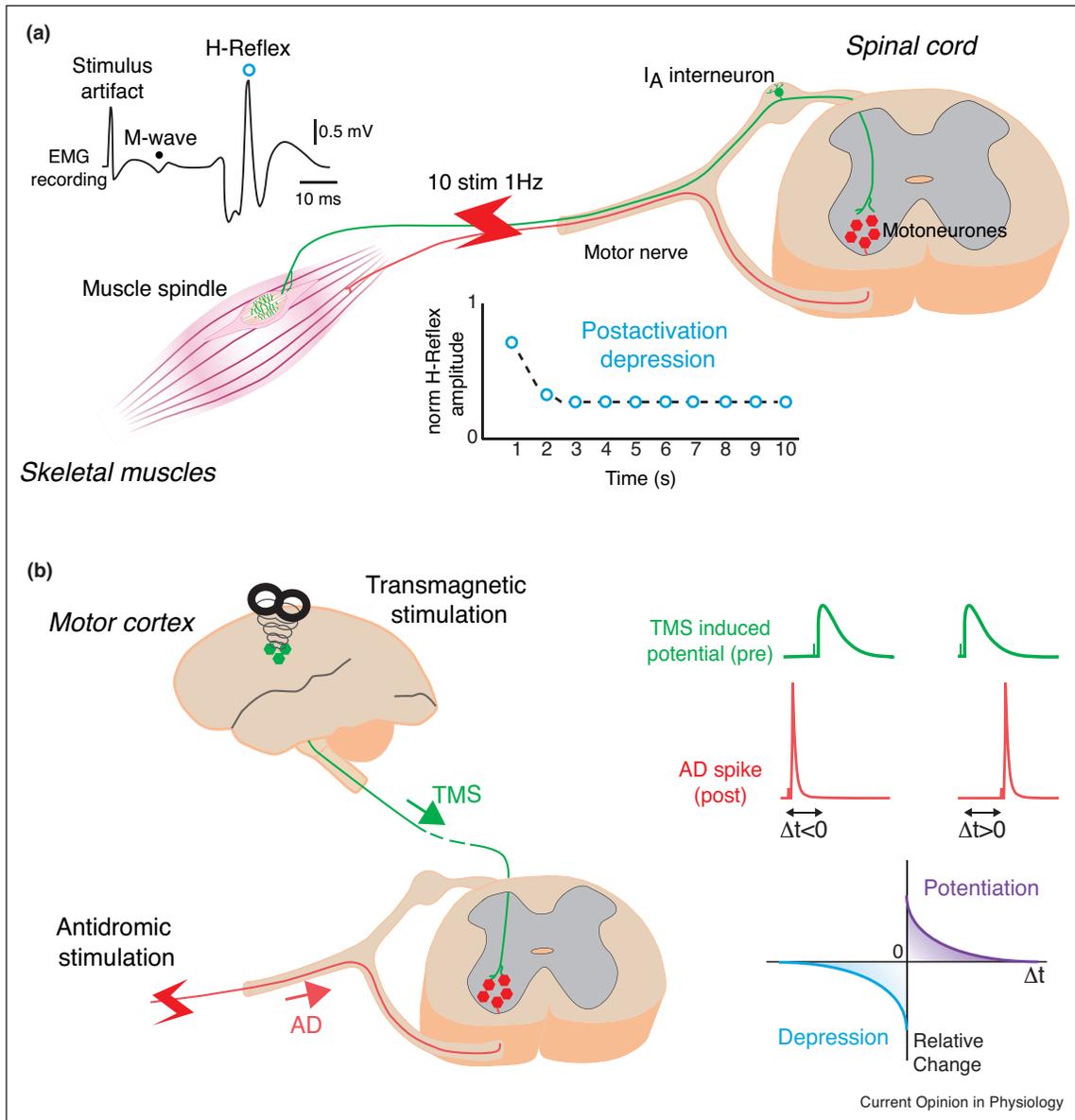
TBS and STDP-inspired-protocols

ADSP was for a long time studied using paired pulse stimulations and high or low frequency stimulus trains. In both animal models and humans, more physiological stimulations, the theta burst stimulations (TBS, 4–7 Hz) based on the theta burst rhythm recorded during exploratory behaviors in rodents are now frequently used to induce ADSP in different brain areas [see for examples: 32,33]. In the spinal cord, TBS stimulations (classically consisting of high frequency bursts of 3 or 4 stimuli delivered at 200–300 ms intervals) induce dynamics changes in H-reflex responses and motor evoked potentials [34–36] and reduce spasticity in humans [37].

Another type of electrical stimulation paradigm is now commonly used to enhance plasticity in motor spinal systems: spike-timing dependent plasticity (STDP) protocols. In supraspinal structures, the expression of STDP has been shown to rely on the precise temporal interval between presynaptic and postsynaptic neuronal activities (for reviews and details on STDP protocols see Refs. [38–41]). Indeed, when the presynaptic neuron is repetitively activated (by hundreds of stimulations) before its postsynaptic partner, an LTP is evoked while LTD is expressed when the postsynaptic neuron is repetitively activated before its presynaptic partner (Figure 1b). We have so far no evidence for STDP expression occurring in *in vitro* spinal motor circuits. However, several recent studies have emphasized the fact that STDP-like protocols succeeded in changing synaptic efficacy in spinal motor networks *in vivo*. Paired associative stimulations consisting of repeated pairs of single electrical stimulation of peripheral nerve followed by a transcranial magnetic stimulation (TMS) pulse delivered to the motor cortex (Figure 1b) have been shown to increase motor evoked potentials in the human spinal cord depending on the delay between the two paired stimuli [42,43,44^{••},45^{••},46–48]. Nishimura *et al.*, for example, tested the synaptic efficacy of corticomotoneuronal (CM) connections after pairing CM cell spiking activity to intraspinal stimulation (ISS) in behaving monkeys [49]. They reported increases in EMG activity amplitude when the ISS was applied 12–25 ms after the CM cell action potential.

Moreover, STDP-inspired protocols have been shown to improve motor recovery after SCI or stroke in rats [50^{••}] and humans [43,44^{••},51,52]. In their study, McPherson

Figure 1



Post-activation of the H-reflex and STDP-like protocols.

(a) Schematic representation of the H-reflex induction and post-activation depression. The electrical stimulation of a motor nerve triggers a direct activation of motoneuron axons that produces the first response observed in the electromyogram (EMG) known as the muscle response (the M-wave). In a second time, the synaptic activation of motoneurons by the sensory afferents causes the second potential of the EMG recording, the H-reflex. When a train of 10 stimulations (for example) are applied at 1 Hz on the motor nerve, the normalized amplitude of the H-reflex (norm H-reflex amplitude) exhibits a progressive decrease: a post-activation depression (blue trace and dots). Figure adapted from Refs. [3] and [8]. **(b)** Example of spike timing dependent plasticity (STDP)-like protocols used to induce synaptic plasticity in the spinal cord. The antidromic activation (AD) of motoneurons (postsynaptic partners, red traces) is paired with transmagnetic stimulations (TMS) of corticospinal motor neurons (presynaptic partners, green traces). This pairing is repeated several hundred times (usually 200–300 times). If we hypothesize that the STDP rules are similar in supraspinal neurons and in the spinal cord, the STDP expressed in motoneurons should be a function of the time difference ($\Delta t = t_{\text{post}} - t_{\text{pre}}$) between the presynaptic and postsynaptic activation: if the excitatory presynaptic potential precedes the postsynaptic spike, the synapse is potentiated (purple curve); on the contrary, if the presynaptic potential follows the postsynaptic spike, the synapse is depressed (blue curve). Relative changes: relative changes in the amplitude of postsynaptic potentials recorded after plasticity induction. Figure adapted from Refs. [39] and [43].

et al. attempted to strengthen synaptic transmission in spared motor circuits by associating an intraspinal microstimulation applied below the lesion site around 10 ms after the detection of an increased in forelimb EMG activity.

Animals submitted to this activity-dependent spinal stimulation (TADSS) paradigm exhibited an enhanced functional recovery of a reaching task compared to rats submitted to open-loop intraspinal microstimulation (stimulation

unassociated with EMG activity). This functional recovery was maintained over 3 weeks after the cessation of the stimulation, indicating long lasting-induced changes by the TADSS protocol in motor spinal circuits [50**]. These different studies reveal that the rules of temporal relationship between presynaptic and postsynaptic neuron activities described in various brain structures to induce STDP seem valid and applicable to the motor spinal cord circuits.

Cellular basis of spinal motor ADSP

In a previous review, we discussed the important role that ADSP should play in normal information processing in spinal motor circuits as well as in pathophysiological conditions [7]. The aforementioned recent advances in the field further underline the salient role of ADSP in motor functional recovery. Paradoxically, little effort has been made in exploring the cellular basis of ADSP in spinal motor networks. As previously mentioned, to the best of our knowledge, we still lack cellular evidence for STDP expression in the motor spinal cord. Similarly, we have no idea of the impact at the synaptic level of a TBS stimulation applied in spinal motor networks. It could be argued that both TBS and STDP protocols established on the basis of studies performed on the hippocampus or cortex seems to work perfectly well in the spinal cord *in vivo* and contribute to alleviate motor deficits after injury. However, the uniqueness of spinal neuronal circuits should be taken into account. For example, spinal MNs do not constitute a homogenous population, and we have previously shown that the same tetanic stimulation induces different types of ADSP depending on the flexor or extensor phenotype of the MNs [53*]. The function and neurotransmitter release properties of MN presynaptic partners together with the associated network excitability have been shown to determine the ADSP expressed in spinal motor synapses [54–56]. The various neuromodulatory inputs that shape the spinally generated locomotor command could also dramatically condition the expression of synaptic plasticity in spinal circuits [55]. Finally, it seems highly likely that after impairments of descending pathways and the massive remodeling of sublesion networks following stroke or SCI, the plastic capabilities of spinal synapses differ completely from those observed in pre-traumatic conditions. We currently have no data on this latter point.

Conclusions

This review highlights the interest of the field of spinal disorders in stimulation protocols that induce ADSP in order to enhance spinal plasticity as well as behavioral recovery after trauma. In this sense, TBS and STDP-like protocols appear to be highly valuable tools towards obtaining therapeutic benefits. In this context, it is noteworthy that the data gathered on the PAD of H-reflex show that functional motor recovery is always associated with the restoration of a capability for synaptic plasticity (or *vice versa*) [20,26–28]. Such findings lead to the

chicken and egg dilemma. Is a functional recovery due to the restoration of synaptic dynamics in spinal circuits or is it the contrary? In any case, the recuperation and/or re-emergence of synaptic dynamics (the same or those adapted to the new functioning of the network after insults) seems to be mandatory for reaching a certain degree of functional motor recovery.

It is now well accepted that combinatorial therapeutic approaches with synergistic effects are required to improve functional motor restoration (see for examples: [57]). To accurately induce synaptic plasticity in motor circuits of the spinal cord, a precise knowledge of the cellular aspects of ADSP is now required, in order (1) to refine the stimulation protocols or motor training strategies used to promote synaptic dynamics in spinal motor circuits, and (2) to identify appropriated pharmacological agents that will cooperatively favor the expression of adapted activity-dependent synaptic dynamics in spinal motor networks after insults or diseases. We, therefore, believe that establishing the most appropriate protocols to induce/restore the synaptic dynamics is a major goal towards improving motor recovery after injury. After the pioneering studies performed on ADSP in the spinal motor cord back in the early nineties (for review see Ref. [7]), data obtained recently should rekindle our interest in the cellular basis of synaptic dynamics in motor systems. It is time to re-open the game and to push forward the cellular studies of ADSP in motor circuits of the spinal cord: let's kick the ball off the 35-yard line!

Conflict of interest statement

Nothing declared.

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