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Title:

Short-term plasticity in the spinal nociceptive system

Running title:

Short-term plasticity in the dorsal horn

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Abstract

Somatosensory information is delivered to neuronal networks of dorsal horn (DH) of the spinal cord by the axons of primary afferent neurons that encode the intensity of peripheral sensory stimuli under the form of a code based on the frequency of action potential firing. The efficient processing of these messages within the DH involves synapses that are frequency-tuned, a phenomenon linked to their ability to display activity-dependent forms of short-term plasticity (STP). By affecting differently excitatory and inhibitory synaptic transmissions, these STP properties allow a powerful gain control in DH neuronal networks that may be critical for the integration of nociceptive messages before they are forwarded to the brain where they may be ultimately interpreted as pain. Moreover, these STPs can be finely modulated by endogenous signaling molecules such as neurosteroids, adenosine or GABA. The STP properties of DH inhibitory synapses might also, at least in part, participate in the pain-relieving effect on non-pharmacological analgesic procedures such as Transcutaneous Electrical Nerve Stimulation (TENS), electroacupuncture or Spinal Cord Stimulation (SCS). The properties of target-specific STP at inhibitory DH synapses, and their possible contribution to electrical stimulation-induced reduction of hyperalgesic and/or allodynic states in chronic pain will be reviewed and discussed.

Keywords

Short-term plasticity, pain, nociception, spinal cord, information processing

Introduction

In sensory neurons, the average number of spikes per unit of time encodes the intensity of adequate stimuli [1; 2; 22; 146], and temporal summation in response to electrical, thermal or mechanical stimulation, is frequency-dependent [4; 97; 147]. As a consequence, the subjective magnitude of pain perceived by humans during intraneural stimulations of sensory fibers increases monotonously with the frequency of electrical impulses [97]. Among sensory neurons, C and A δ primary afferents conveying nociceptive information project to networks within the DH (DH) of the spinal cord, and mainly to superficial-most layers (layers I-III) [27]. The impact of C and A δ primary afferent recruitment by a natural stimulation at a given intensity is therefore expected to strongly depend on the frequency-response properties of synapses among neurons within these DH networks.

Indeed, in other structures of the nervous system, frequency-selective synapses have been involved in the processing of frequency-coded information. These synapses display short-term plasticity processes changing dynamically their efficacy over time as a function of the time interval between presynaptic action potentials [21; 106]. Short-term plasticity can either correspond to a short-term potentiation or a short-term depression during repetitive activity. This kind of plasticity can therefore be expressed even in the case of a single pair of synaptic events: the first event impacting the efficacy of the second. In addition to changes occurring during repetitive activity, short-lasting changes following repeated activity are also recognized as a situation of short-term plasticity [159]. Activity-dependent short-term plasticity has been observed in numerous structures [55; 83; 86], including in the spinal nociceptive system. Here we review recent insights into the short-term plasticities expressed at synapses within DH networks as well as the involvement of endogenous modulators in these processes. The possible impact of these plasticities on the processing of nociceptive information within the DH as well as their possible contribution to the analgesic effects of non-pharmacological neuromodulatory spinal cord stimulation approaches will be discussed.

Methods

We searched electronic databases (PubMed, Sciencedirect, Web of science) using the terms: dorsal horn AND plasticity, or spinal cord AND plasticity, or spinal nociceptive system AND plasticity, or primary afferent fibers AND plasticity. All the articles were examined to define whether the plasticity processes they describe corresponded to short-term plasticity and whether they provided data relevant for the processing of nociceptive information. Since articles examining modulations of synaptic transmissions often use paired-pulse stimulation protocols we also searched for information on short-term plasticity in the spinal nociceptive system in articles describing modulations on dorsal-horn networks.

The electronic searches were supplemented by an extensive eclectic search using the references cited by the articles resulting from the electronic search, as well as the articles citing these articles.

Results

1. Nociceptive information and spinal nociceptive networks

1.1. Frequency coding of stimulation intensity by primary afferent fibers

In basal physiological conditions, nociceptors are not spontaneously active [4], but these can discharge action potentials despite the absence of nociceptive behavioral responses [51; 146]. For example, activity ≤ 2 Hz occurs in vivo in rat C-fibers during non-noxious stimulations [51], indicating that downstream networks filter these low frequency inputs which are not relevant for nociception in control conditions. Upon stimulation with adequate stimuli, nociceptors discharge action potentials at frequencies correlated with stimulus intensities [1; 2; 22; 62; 146]. At stimulation onset, primary afferents display a dynamic response adapting more or less rapidly with time, depending on the type of primary afferent fiber. During the first hundreds of milliseconds, the instantaneous frequency of action potential discharges can reach several tens of Hz in C- fibers [40; 62; 118; 146] (see Table 1). Since C-fibers adapt rapidly, the frequency calculated over the first second drops to ca. 10 Hz or below [4; 22] (Table 1). The discharge frequency of C fibers reach a plateau of only a few Hertz when longer and/or later time windows are considered [2; 4; 22; 62]. However the lower frequencies observed during the plateau phase of C-fiber discharges are still correlated with the intensity of the applied stimulus [4; 62].

In A δ fibers, the instantaneous frequency at the stimulation onset exceeds 50 Hz [4; 62; 118]. Some A δ fibers adapt rapidly whereas other adapt much more slowly and the average frequencies measured over the first second of stimulation are comprised between 5 and 50 Hz [4]. Interestingly, regardless of the stimulation intensity, the final firing rate of A δ fibers approaches a common value of 5 Hz [62]. Therefore, in contrast with the initial dynamic phase of A δ fiber activity, the late plateau firing frequency of these fibers does not encode stimulus intensity.

Importantly, the frequency of inputs onto DH neurons might not be strictly correlated with the frequency of primary afferent discharge initially induced in the fiber at the peripheral nerve terminal following sensory transduction. Indeed, in 70% of C fibers and in 10 % of A δ fibers recorded in vitro, there was at least one failure to trigger antidromic action potentials with 20 extracellular stimulations at 10 Hz [108], suggesting that failures of action potential propagation might occur, particularly in a large proportion of C fibers. The rate of failure in action potential propagation may even be larger when propagation from the periphery to the central ending of the primary afferent is considered. Indeed, the T-junction of sensory neurons connecting to their cell body acts as a low pass filter, particularly in C fibers [59].

In addition to propagation failures, repetitive stimulation of C-fibers results in a gradual decrease in action potential velocity termed activity-dependent slowing. This slowing can reach one third of the initial velocity after 20 s of activity at 20 Hz or 180 s at 2 Hz. This results in an increased response latency in both rodents and humans [58; 132; 143]. In inflammatory and neuropathic conditions, changes in the excitability of primary afferent fibers have been extensively described (reviewed in [3; 57; 63; 119; 150]) as well as changes in activity-dependent slowing [42]. These modifications occurring under inflammatory or neuropathic conditions can result in alterations of frequency coding.

The above presented experimental evidence suggests that (1) nociceptive stimulus intensity is encoded by an action-potential frequency code for both C and A δ fibers, with a possible exception for the late phase of A δ fibers activity and that (2) most neurons in DH networks might receive synaptic inputs at frequencies that can reach at least several tens of Hz during the initial phase of the nociceptive message.

1.2. Convergence of sensory afferents onto DH neurons

Most neurons in DH lamina II receive mono or polysynaptic inputs from C-primary afferents, with about three quarter receiving monosynaptic C-fibers inputs [61; 93]. Among these neurons, 30-80 % are directly contacted by TRPV1-expressing nociceptors [109; 112], and over 20% of GABAergic neurons in lamina II are contacted by A δ fibers [93].

Moreover, primary afferent fibers converge onto DH neurons, including fibers having distinct conduction velocities and stimulation thresholds [61]. This convergence is particularly large for C-fibers contacting islet cells in lamina II [61].

The discharge frequency of primary afferents together with their convergence onto DH neurons, particularly in lamina II, indicate that these neurons can be activated at up to several tens of Hertz at the onset of nociceptive stimulations.

Neurons within these networks can discharge action potentials in response to the stimulation of these primary afferent inputs [93; 96]. Moreover, lamina II neurons can reliably discharge action potentials following the stimulation of excitatory inputs, at least up to frequencies of 50 Hz [24].

2. The wind-up phenomenon

The wind-up phenomenon was first characterized by Mendell and Wall who observed that repeated low-frequency stimulation of the sural nerve induced progressively longer bursts of action potentials in neurons projecting in the dorso-lateral column of the spinal cord [103]. More generally, the wind-up phenomenon corresponds to a progressive increase in action potential frequency response in spinal cord neurons during repetitive stimulation of primary afferent fibers at constant frequency [102; 103]. The stimulation used to induce wind-up is usually electrical, but this phenomenon can also be induced using repetition of more physiologically-relevant mechanical or thermal stimuli [30; 60; 64]. Such short-lasting changes induced in response to a repeated activity is considered as a type of homosynaptic activity-dependent short-term plasticity [159]. Wind-up is therefore among the first short-term plasticities described in the in the spinal cord. The wind-up phenomenon is evoked by C-fiber stimulation and usually not by the stimulation of other types of primary afferents, although wind-up evoked by stimulation of A δ fibers has occasionally been reported [30; 77; 102; 103; 116]. The repetition rate at which primary afferent stimulation elicits wind up is relatively low, ranging from 0.33 Hz to - to 5 Hz [30; 116]. Since the early observation by Mendell and Wall, wind-up was reported from neurons localized in various areas of the dorsal and ventral spinal-cord, including in motoneurons (reviewed in [7; 34; 48; 65; 136]).

In the DH, wind-up has been recorded in neurons localized in deep laminae (laminae V-VI) where this phenomenon was comprehensively examined. Some studies suggested that neurons localized in superficial laminae (laminae I-II) displayed little or no wind-up [39; 94; 156], whereas a few others observed it in these laminae [30; 73; 129; 134]. Hence, the DH neurons that are most likely to display a wind-up receive non-nociceptive and nociceptive inputs and are localized in the deep DH [129].

In all DH laminae, wind-up results from the summation of slow synaptic potentials evoked at low frequency of primary afferent stimulation. The mechanisms allowing such a summation have been characterized in neurons localized in laminae V-VI and in the ventral horn. Very early, the importance of NMDA receptors in the wind-up phenomenon has been highlighted [36; 38; 39]. In these neurons, summated excitatory postsynaptic potentials result in a cumulative depolarization leading to the removal of the voltage-dependent Mg²⁺ ions block of N-methyl-D-aspartate (NMDA) receptors. The progressive recruitment of NMDA receptors in excitatory postsynaptic potentials gradually increases the action potential response evoked by each stimulus in a train of stimulations [39; 144]. Interestingly, NMDA receptors localized

in superficial laminae of the dorsal horn inhibit wind-up in neurons located in deeper laminae, highlighting the complex role of these receptors in controlling the gain of wind-up [151]. In neurons localized in DH laminae, summated excitatory postsynaptic potentials can recruit L-type Ca^{2+} channels in concert with activation of NMDA receptors. The plateau potentials resulting from activation of L-type Ca^{2+} channels contribute the sustained and progressive development of the slow membrane depolarization observed during the course of a train of stimuli [105; 111; 122]. The joined contribution of L-type Ca^{2+} channels and NMDA receptors is critical for the wind-up phenomenon [52].

The summation of excitatory synaptic potentials leading to wind-up involve also the prolonged slow depolarization induced by the activation of G-protein coupled receptors such as substance P and calcitonin-gene-related peptide (CGRP) receptors [19; 28; 76; 141; 154]. These peptides are localized in dense-core vesicles of a subset of C-fibers [14]. These vesicles are expected to be released upon sustained electrical activity [18; 107].

Interestingly, when observed, the wind-up expressed in lamina I differs from that in deeper laminae of the DH. In lamina I, wind-up involving NMDA receptors is almost absent [131]. Moreover, there is a difference in the magnitude of wind-up observed in deep versus superficial DH laminae. Indeed, whereas in deep laminae of the DH wind-up correspond to a 10-20 fold increase in the frequency of action potential discharge, there is only a 2-3 fold increase in lamina I. Wind-up in this lamina is therefore often referred to as “reduced wind up” [140]. In addition, in lamina I, omission of one or more stimulations allows a fast recovery from wind-up termed referred as “wind-up reset” under basal physiological conditions [147]. This suggests that lamina I wind-up involves other mechanisms and/or that it is subjected to a control by another type of short-term plasticity [30].

The wind-up phenomenon can be recorded in spinalized animals as well as in acute spinal cord slices, and is therefore mostly a spinal mechanism [64; 65]. Nevertheless, this phenomenon is modulated by descending controls recruited by NK1-expressing neurons localized in the superficial DH horn. These controls facilitate wind-up by activating spinal 5-HT₃ receptors [142]. Other receptors can facilitate the wind-up phenomenon, such as sigma 1 receptors [101; 117; 120].

Protocols on human subjects consisting in repeated stimulation at constant intensity have been proposed to provide a behavioral correlate of wind-up. In these protocols, the declared

pain increases as the stimulation is repeated. This increase in perceived pain has been reported for electrical, [6; 97], mechanical [81; 137] and thermal stimuli [115; 147].

Importantly these temporal summations may engage different types of short-term plasticities within networks of the central nervous system such as those described at synapses connecting DH neurons [24; 26; 50; 66; 68; 84; 158].

Although the exact relevance of wind-up is not straightforward [65], there are clear links between wind-up and nociceptive information processing. Together with other phenomena such as activity-dependent slowing in action potential propagation velocity [42; 133], windup represents an important phenomenon controlling dynamically action potential frequency-coding in the spinal nociceptive system. Wind-up is therefore often interpreted as an information processing operation allowing to amplify nociceptive inputs. This is consistent with data indicating an alteration of this process and its control during chronic pain states. For example, wind-up is enhanced in models of neuropathy or inflammatory pain [46; 78]. Moreover, dysfunction of the “wind-up reset” described in lamina I has been proposed to underlie the declared pain wind-up occurring in patients with chronic pain [30]. All these data indicate that although wind-up differs from central sensitization [152], it shares mechanisms with this long-term plasticity, and is considered as one among other initiators allowing this sensitization to take place [48; 110].

3. Short-term plasticity at primary afferent synapses

The short-term plasticity expressed by primary afferent connections onto DH neurons has been little examined (Table 2). In newborn rats, synapses from muscle and cutaneous primary afferents onto spino-parabrachial projection neurons of lamina I display a strong paired-pulse ratio (PPR) depression for stimulation intervals ranging between 75 and 500 ms. This depression of PPR is significantly larger at short stimulation intervals for connection from afferents innervating muscles indicating a larger probability of release at these synapses. Connections from both muscle and cutaneous territories displayed a similar and strong depression when stimulated at frequencies between 1 Hz a 10 Hz [89]. In lamina II and laminae III-IV of 2.5-3 weeks old rats, short-term depression is dominant at A δ connections for stimulation frequencies between 0.5 and 20 Hz. The magnitude of depression increases with frequency of stimulation owing to a presynaptic mechanism [148; 149]. In the same model, A β connections with neurons localized in laminae III-IV also exhibit an activity-

dependent depression that is particularly pronounced for the second excitatory synaptic current evoked during a train of four afferent stimulations at 10 Hz (Fig. 1A). This strong depression of the second synaptic current is due to the activation of presynaptic GABA_A receptors activated by the GABA released from inhibitory interneurons recruited upon primary afferent stimulation [16].

Schouenborg recorded the field potentials evoked by stimulation of cutaneous C and A δ fibers in the dorsal horn of adult rats anesthetized with halothane [128]. In lamina II but not lamina V, the amplitude of the C-fiber-evoked field potentials increased with repeated stimulations at frequencies between 0.2-10 Hz, with a maximal increase at 1-2 Hz [128]. This increase in field potential amplitude may result from the wind-up phenomenon since it is induced by similar stimulation parameters. Therefore, although depression dominates at A δ primary afferent connections in the DH, evidence indicates that field potential responses to C-fibers stimulation at low frequency can be potentiated in lamina II.

Electrical stimulation of C-fibers at low frequency (1 Hz) evokes calcium responses in both excitatory and inhibitory neurons localized in the superficial DH. When this stimulation is preceded by electrical stimulation of A β -fibers from adjacent segments at 50 Hz during 10 minutes, responses recorded in excitatory neurons are potentiated whereas those recorded in inhibitory neurons are depressed [49]. This differential modulation may at least in part involve short-term plasticities at primary afferent synapses, and results in a frequency-dependent and target-specific interaction between information conveyed by A β and C-fibers.

4. Short-term plasticity of excitatory synaptic transmission in the DH.

Paired-pulse ratio

The paired-pulse ratio (PPR) at excitatory synapses from local interneurons has been examined in lamina II of 2-6 weeks old rats [125] and in lamina II-V of 1-2.5 weeks old Syrian hamsters [158]. In both studies, excitatory synapses displayed paired-pulse depression (i.e. PPR < 1) at least for some inter-stimulus intervals (see below). However, the intervals at which paired-pulse depression occurred were very different in the two studies. In Santos et al (2009), PPR was significantly different from 1 for intervals of 320 ms and 640 ms, but not for shorter intervals. In Zhang & Schneider (2011), excitatory synapses displayed a strong paired-

pulse depression at a short stimulation interval of 25 ms, and a reduced depression at longer intervals. Indeed although reduced in magnitude, the depression remained significant at intervals of 500 ms. It is important to emphasize that these two studies not only used different the animal species (rat vs hamster), but also differed with respect to the age, the recording mode (current clamp vs. voltage clamp) and the frequency of paired-pulse stimulation (every 5 s versus every 10 s). Unfortunately, in both cases, the neurochemical identity of the postsynaptic neuron was not determined.

Trains of action potentials

The short-term synaptic plasticity expressed in the DH by excitatory connections from DH interneurons during trains of stimulation has been little examined. STP evoked during 10 Hz stimulation of presynaptic glutamatergic synapses is illustrated in Zhang & Schneider (2011), however without detailed analysis. It appears that at least some excitatory synaptic connections display short-term depression, reaching a maximal amplitude of depression after the 3rd stimulation. It must be emphasized, that given the high repetition rate of the stimulation trains (every 10 seconds) tonic modulations might be engaged. These studies nevertheless concur in showing that excitatory connections within the DH displayed mainly short-term depression during paired-pulse or stimulation trains experiments.

Although data on trains of action potentials are scarce, data on paired-pulse ratio suggest that a fraction of excitatory connections of superficial DH laminae depress only at low frequency of activity. Such short-term plasticity would allow controlling the gain of sensory information by filtering stimulations at low intensity.

5. Short-term plasticity of inhibitory synaptic transmission in the DH

Paired-pulse ratio

The paired-pulse ratio of inhibitory synapses between DH neurons has been examined only in a small number of studies [24; 25; 66; 68; 79; 158]. In spinal acute slices of adult rats, minimal electrical stimulation within lamina I evoked glycinergic inhibitory postsynaptic currents (eIPSCs) in lamina I neurons. When paired stimulations were applied, the second glycinergic eIPSC was smaller in amplitude with a maximal depression of about 50% for inter-

stimulus intervals of 150-200 ms [25] (Fig. 1B). Should this short-term plasticity apply to trains of activity, it would allow reducing the inhibition in lamina I at frequencies of activity corresponding to low intensities of sensory stimulations. In GAD65-expressing neurons of lamina II, glycinergic eIPSCs showed a paired-pulse facilitation (PPR of 1.2) for inter-stimulus intervals of 50 ms [79]. In laminae II-V of 1-2.5 weeks old Syrian hamsters [158], evoked inhibitory postsynaptic potentials displayed preferentially paired-pulse facilitation but paired-pulse depression was sometimes observed [158]. At facilitating synapses, facilitation was significant for 50-100 ms intervals but not for longer intervals; at depressing synapses, depression was significant at 50 ms intervals but not for longer intervals [158]. In primary cultures of superficial DH neurons from postnatal rats, paired-pulse depression of GABAergic eIPSCs was preferentially observed (84 %), but paired-pulse facilitation was also occasionally present (16 %) [66].

In all these studies, the repetition rate of paired-pulse stimulation might speculatively engage tonic modulations, particularly for repetitions at short intervals (3.3 s in Chery and De Koninck [25], 5 s in Zhang and Schneider [158]).

Paired-pulse ratios of GABAergic connections recorded in non-identified neurons of laminae I-II of P3-P21 neonatal rats were similar at all ages, displaying a moderate facilitation at 100 ms of inter-stimulation interval (ISI) [68]. Paired-pulse ratio of GABAergic connections onto inhibitory or excitatory neurons was assessed in lamina II neurons from acute slices prepared from adult GAD65-eGFP mice [24]. Inhibitory connections onto excitatory or inhibitory neurons displayed either paired-pulse facilitation or paired-pulse depression, but the proportion of connections showing facilitation or depression depended on the ISI and on the excitatory or inhibitory nature of the postsynaptic neuron. Most GABAergic connections onto excitatory neurons displayed a paired-pulse facilitation, particularly at short ISIs (25-50 ms). No preferential plasticity was displayed by GABAergic connections onto inhibitory neurons for ISIs up to 100 ms, but depression was dominant for longer ISIs (200-300 ms) [24]. These results indicate that in some instances the short-term plasticity engaged during paired stimulations might be target specific.

Trains of action potentials

The short-term plasticity of inhibitory synaptic transmission in the DH evoked during trains of activity has been assessed in few works, using frequencies of stimulation ranging from 2.5 Hz to 50 Hz [24; 26; 50; 66; 68; 84; 158] (Table 3).

In laminae I-II of P3-P21 neonatal rats, GABAergic connections depressed in a frequency-dependent manner during trains at 1-20 Hz [68]. Similarly, in primary cultures of superficial DH neurons from postnatal rats, amplitudes of GABAergic eIPSCs depressed during trains at 2.5 Hz [66].

The impact of trains at 5 Hz has been assessed on GABAergic transmission between DH excitatory or inhibitory neurons. GABAergic neurons of lamina II simultaneously contacted excitatory and inhibitory neurons, but these connections displayed very different frequency-dependent short-term plasticities. Connection onto excitatory interneurons displayed no plasticity during 5 Hz trains, whereas connections onto inhibitory ones displayed a strong depression (Fig. 1C) [24].

Zhang and Schneider (2011), have stimulated inhibitory synapses in laminae II-V of Syrian hamsters with trains at 10 Hz and noticed that eIPSPs either potentiated or depressed. However, it cannot be excluded that these data were impacted by intra-train shifts in intracellular concentrations of Cl⁻, as shown by Cordero-Erausquin et al. (2005), since animals used in that work were quite young.

In lamina II of adult mice, Labrakakis et al. (2009) examined the plasticity expressed during trains at 20 Hz delivered to a presynaptic inhibitory neuron synapsing onto a postsynaptic inhibitory neuron [84]. The amplitude of the 1st eIPSC of the 1st train was significantly smaller than that of the 1st eIPSC in subsequent trains, indicating the engagement of a train-to-train plasticity. However, the authors did not distinguish between glycinergic or GABAergic components or nature of eIPSCs. Therefore, the facilitation in the first train might speculatively involve glycinergic component which has been shown to display strong paired-pulse facilitation [79]. Within individual trains, short-term plasticity followed opposite trends, depending whether the 1st eIPSC of the train was potentiated or not (larger or not than that from isolated eIPSCs): potentiated 1st eIPSCs were followed by a depression during the train whereas non-potentiated 1st eIPSCs were followed by a facilitation during the train. Therefore, first trains usually had a non-potentiated 1st eIPSC followed by potentiated eIPSCs whereas subsequent trains had potentiated 1st eIPSCs followed by a short-term depression of subsequent trains.

During trains at 50 Hz, GABAergic connections onto excitatory neurons in lamina II displayed no plasticity, allowing a time-dependent summation, whereas connections onto GABAergic neurons displayed strong depression and a moderate time dependent summation (Fig. 1C) [24].

These results indicated that inhibitory connections onto lamina II neurons displayed different forms of activity-dependent plasticities. These plasticities appeared to differ as a function of the neurotransmitter involved: glycinergic connections onto inhibitory neurons displayed a strong paired-pulse potentiation at short ISIs whereas GABAergic connections onto inhibitory neurons displayed little or no potentiation at these intervals. This suggests an increased disinhibition in lamina II involving glycinergic transmission at high intensities of sensory stimulations.

These plasticities also depended on the postsynaptic target: GABAergic connections onto excitatory neurons showed potentiation at short ISIs and during trains of stimulation, whereas GABAergic connections onto inhibitory neurons displayed little paired-pulse plasticity and depressed during trains of stimulation.

In addition, train repetition had an impact on the plasticity expressed during the trains. Such combinations of plasticities at different repetition frequencies, and time scales has been observed in other CNS structures such as hippocampal networks, and may represent a relatively common phenomenon [5].

Short-term plasticities and Cl⁻-extrusion capability.

Rapid changes in the equilibrium potential of Cl⁻ ions can be involved in STP at GABAergic synapses. In lamina I neurons recorded in acute slices from immature rats (before 3 weeks), Cordero-Erausquin et al (2005) examined the eIPSCs evoked by trains of 20 local stimulations applied at various frequencies (20, 40 and 100 Hz). In a proportion of neurons responding to single stimulations by outward eIPSCs, the direction of eIPSCs changed from outward to inward during the train. The proportion of neurons displaying such a shift in eIPSCs direction during the train increased with the frequency of stimulation. This shift in eIPSCs direction during sustained activity is due to reduced Cl⁻-extrusion capability by immature DH neurons [26]. Recent work by the same team indicated that, in lamina I, repeated activity of inhibitory synapses was sufficient to induce a significant shift in Cl⁻ equilibrium potential, even in adult

mice [50]. Such a shift accounted for one quarter of the eIPSC amplitude decrease observed at the end of 25 stimulations at 20 Hz, and was only observed in lamina I and not lamina II neurons [50]. These data indicate that even in adult animals, the Cl⁻-extrusion capability can be challenged at physiologically relevant frequencies in lamina I. Importantly, reduced Cl⁻-extrusion capability is also observed in neuropathic conditions [29]. Experimental and modeling studies suggest that gradients of intracellular concentrations of Cl⁻ can exist between the cell bodies and the dendrites of the same neurons [44; 135]. These results support the idea that different short-term plasticities occur at somatic and dendritic inhibitory synapses due to differences in local changes of intracellular Cl⁻-concentrations in these distinct compartments. Importantly, inhibition mediated by GABA_A and glycine receptors involve an hyperpolarizing shift of membrane potential with respect to action potential threshold and an electrical shunting of membrane resistance that reduces the impact of incoming excitatory postsynaptic potentials. Interestingly, these mechanisms operate at distinct spatial and temporal scales [72]. Therefore, the outcome of depolarizing IPSCs results from the complex interplay between parameters including shunting (inhibitory) and depolarizing (excitatory) effects of Cl⁻-conductance and driving-force, as well as the frequency of activity [17]. Consequently, depolarizing IPSPs occurring at low frequency produce an excitatory effect by dragging the membrane potential to the threshold for spikes, whereas high frequencies of depolarizing IPSPs result in an inhibitory effect owing to the temporal summation of shunting conductances [17].

Discussion

6. Target-specific short-term plasticities and their possible impacts

The characteristics of short-term plasticities has been shown to depend on the nature of either pre- and/or postsynaptic neurons [11; 15; 100] with some exceptions [43]. GABAergic interneurons from lamina II simultaneously contact excitatory and inhibitory interneurons from the same lamina, and these connections display very distinct short-term plasticities ([24], Fig. 1C, see above). These connections may correspond to synapses from islet cells onto excitatory and inhibitory central cells which are the most likely inhibitory connections recorded under our experimental conditions [96]. Importantly, such a differential target-specific short-term plasticity involving synapses contacting excitatory and inhibitory neurons directly impacts the dynamic properties of networks and their excitation/inhibition balance

[13; 20; 80; 95; 104; 114; 121]. We have shown that in lamina II of the adult mouse spinal cord, stimulation of GABAergic presynaptic neurons at frequencies comparable to those of primary nociceptor discharges triggered by low intensity sensory stimulation will induce short-term depression at synapses with postsynaptic inhibitory (GABAergic) neurons whereas the inhibitory control onto excitatory neurons will not display short-term plasticity. However, at frequencies corresponding to sensory fiber activity at high intensity of sensory stimulation, the inhibitory control onto excitatory neurons will be increased owing to time-dependent summation whereas it will remain unaffected at inhibitory synapses onto inhibitory neurons. Interestingly, *vivo* imaging experiments in mice indicate that inhibitory neurons in lamina I-IIo display a linear increase in intracellular calcium as a function of mechanical stimulation intensity whereas increase in intracellular calcium in excitatory neurons reach an asymptote for mechanical stimulations above 8 psi [139]. This difference may involve the stronger inhibitory control targeted on excitatory neurons involved in the processing of mechanical information. This work also indicates that increase in intracellular calcium following thermal stimuli are larger in excitatory than in inhibitory laminae I-IIo neurons [139].

Inhibitory neurons display a tonic action-potential firing profile upon membrane depolarization [96]. It follows that these inhibitory neurons can probably follow excitatory synaptic inputs at relatively high frequencies. Therefore, in order to secure an efficient control of synaptic excitation in these neurons there must be a reliable and stable inhibitory control of these neurons in GABAergic inputs. It is therefore important that the GABAergic inputs to these inhibitory neurons displays no (or very limited) frequency depression.

To summarize, under basal physiological conditions, both target-specific STP characteristics and the firing properties of excitatory vs inhibitory postsynaptic neurons will concur to favor an inhibitory control of nociceptive messages in Lamina II of the DH, in particular at high intensity of sensory stimulation [24]. Hence, by affecting differently excitatory and inhibitory neurons, these STP properties allow a powerful gain control in lamina II that may be critical for the integration of nociceptive messages.

7. Modulation of short-term plasticities

Short-term plasticities are subjected to modulations and controls by both presynaptic and postsynaptic mechanisms. Some of these modulations and controls, such as descending

controls, may be altered in ex-vivo preparations. These modulations of short-term plasticities may be engaged during physiological or pathological pain, but also during electrical stimulation procedures for alleviating pain.

Frequency dependent short-term plasticities and deactivation kinetics of postsynaptic currents

Temporal summation of postsynaptic currents, and of the corresponding changes in membrane potential can lead to short-term plasticity. This short-term plasticity depends on the degree of saturation of postsynaptic receptors by the synaptically released neurotransmitter [153]. A summation of synaptic currents can occur during trains of activity when the current has not fully returned to baseline at the onset of the following stimulation. The required conditions for a summation to occur will depend on both the frequency of stimulation and the deactivation kinetics of the synaptic currents.

Interestingly, GABAergic eIPSCs recorded in lamina II inhibitory neurons have been shown to display slower decay kinetics than those recorded in excitatory neurons [85]. Such slower kinetics should allow a better temporal summation of eIPSCs during trains of activity. Nevertheless, at high frequency, summated eIPSCs recorded in excitatory neurons reached larger amplitudes than summated eIPSCs in inhibitory neurons, indicating that differences in decay kinetics can be compensated/counterbalanced by other target-specific properties of GABAergic synapses [24], and might possibly involve distinct degrees of postsynaptic receptors saturation.

Importantly, since summation resulted from an interplay between the frequency and synaptic currents deactivation kinetics, modulators inducing changes in these kinetics may impact the frequency-dependence of this type of short-term plasticity. This may be particularly relevant for GABAergic eIPSCs in lamina II neurons, the decay kinetics of which are prolonged by locally synthesized 3α -reduced neurosteroids during early postnatal developmental stages as well as following peripheral inflammation, this phenomenon having an antihyperalgesic effect [69; 75; 113; 127].

Activity-dependent activation of GABA_B receptors

Several studies have indicated that synaptically released GABA can modulate synaptic transmission by activating GABA_B receptors. In lamina I of the DH, minimal electrical stimulation-evoked synaptic GABA release can preferentially activate presynaptic GABA_B

autoreceptors leading to a paired-pulse depression of glycinergic IPSCs that can amount 50 % of reduction in IPSC amplitude at ISIs of 150-200 ms. This depression involved presynaptic GABA_B autoreceptors activated by the GABA coreleased with glycine, but that was not codetected by the postsynaptic neuron [25] (Fig. 1B).

In cultured DH neurons, presynaptic GABA_B autoreceptors control a subset of GABAergic synapses in an activity-dependent manner [66]. At synapses displaying a GABA/ATP cotransmission, the four last eCPSIs of the train (8 stimulations with an ISI of 400 ms (2.5 Hz)) were under phasic inhibitory control by GABA_B and A1 receptors. By contrast, GABAergic-only synapses were under tonic inhibition involving GABA_B receptors only. Both effects involved at least presynaptic GABA_B and A1 autoreceptors [66], but recording conditions may have precluded the observation of postsynaptic effects.

Our recent results also indicate that in lamina II of control adult mice, GABA_B receptors are also involved in a phasic modulation of GABAergic connections between lamina II neurons. This involvement of GABA_B receptors is target- and frequency-specific: it only occurs at synapses between two inhibitory neurons and at low stimulation frequency [24].

In addition to these phasic actions of endogenously released GABA on GABA_B receptors, a tonic activation GABA_B receptors by ambient extracellular GABA has been reported. Importantly, affinity of GABA_B receptors for GABA is higher than that of GABA_A receptors. Therefore GABA_B receptors might be the main target at low ambient GABA concentrations [70; 155].

Activation of spinal muscarinic receptors evokes the release of GABA [8], which can activate GABA_B receptors localized on presynaptic terminals of glutamatergic neurons and inhibit the release of glutamate [88]. Inhibition of GAT-3 transporters in the DH induces antinociception in control rats by a mechanism involving at least in part the activation GABA_B receptors [74]. It has also been shown that antagonists of GABA_B receptors increase the frequency of glutamatergic EPSCs recorded *in vivo* in rats [56] and that glutamate release from A β fibers in deep laminae of rat DH is placed under a tonic inhibition by presynaptic GABA_B receptors [124].

Interestingly, injection of GABA_B antagonists in the DH is pronociceptive in rats *in vivo* [98]. Moreover, in monkey spinothalamic neurons, GABA_B receptor antagonists increase spontaneous action potential discharge activity as well as action potential firing following cutaneous stimulation [90].

These results indicate that GABA_B receptors can be tonically activated in the DH under basal physiological conditions, as suggested by the fact that mice lacking the obligatory GABA_{B1} subunit of GABA_B receptors are hyperalgesic [130].

Tonic activation of GABA_B receptors by endogenous GABA can be increased by positive allosteric modulators of these receptors such as 5,7-ditert-butyl-3-hydroxy-3-(trifluoromethyl)-1-benzofuran-2-one (rac-BHFF) which has analgesic effects on control but not on neuropathic mice [157]. This is in line with previous work suggesting that the GABA tone in the DH may be reduced in neuropathic conditions [87], whereas it is increased in inflammatory conditions [23]. This situation could in part explain why GABA_B agonists are apparently ineffective to alleviate nociception in inflammatory pain models whereas these are analgesic in most neuropathic pain models.

Activity dependent activation of adenosine receptors

Endogenous levels of adenosine can phasically or tonically modulate synaptic transmission. Under basal physiological conditions, the estimated extracellular concentration of adenosine in the striatum of awake rats ranges from 40 to 460 nM [10]. At such concentrations, adenosine can significantly activate A1 and A2A receptors, and this could account for the inhibitory effect of adenosine, and the excitatory effect of A1 and A2A antagonists, which have been reported in various models [47]. Adenosine may speculatively be linked to circadian changes in pain sensitivity observed in humans and various animal models (see for example [123]). Indeed, regulation of ATP release from astrocytes is regulated by glucocorticoids and this release impacts pain sensitivity [82].

In lamina II of the DH, glutamatergic transmission is under an inhibitory tone of endogenous adenosine [145]. Interestingly, the data presented in this work do not fully support a modulation of mEPSCs by adenosine tone, and may suggest that spontaneous activity is required to reveal this tone.

In cultured DH neurons, presynaptic A1 autoreceptors control a subset of GABAergic synapses in an activity dependent manner [66]. These synapses are also under the inhibitory control of GABA_B autoreceptors; both signaling pathways engaged by A1 and GABA_B receptors being convergent [66]. Interestingly, the synapses modulated by A1 receptors coreleased GABA and ATP.

Recent results indicate that in lamina II of control adult GAD65-eGFP mice, A1 receptors tonically inhibit GABAergic connections onto excitatory neurons by 50% when trains at 5 Hz and 50 Hz are applied. This tonic control was only engaged when trains were repeated every 20 s and not every 60 s, indicating that the tone of adenosine controlling GABAergic connections onto excitatory neurons was linked to the level of activity of the modulated synapse. Adenosine also tonically controlled GABAergic connections onto inhibitory neurons, but this effect was still present when trains were repeated every 60 s. These results indicated that A1 receptors could tonically inhibit GABAergic connections in lamina II. This tonic inhibition was stronger on connections onto excitatory neurons and only experimentally detected when trains were repeated at short intervals [24].

Electrical stimulation procedures for alleviating pain: possible contribution of activity-dependent tones of adenosine and GABA controlling short-term plasticities

By applying repeated stimulations to the spinal nociceptive system, non-pharmacological procedures used to alleviate pain such as Transcutaneous Electrical Nerve Stimulation (TENS), electroacupuncture or Spinal Cord Stimulation (SCS) engage activity dependent processes, which could in part correspond to the short-term plasticities presented above.

The analgesia induced by TENS is blocked by caffeine at concentrations that may be reached by dietary sources [99]. The primary targets of caffeine are A1 and A2A receptors; other effects of caffeine such as inhibition of phosphodiesterases, release of Ca^{2+} from internal stores, etc. occur at higher concentrations [54]. This suggests that stimulations at standard TENS frequencies induce the activation of adenosine receptors with antinociceptive properties. This is in line with data from *in vivo* recordings in the cat showing that vibrations in the periphery induce adenosine-mediated inhibitory potentials in the DH [37]. Dietary caffeine consumption may therefore interfere with this mechanism, but this has not been confirmed by preliminary clinical investigations [41]. Interestingly, TENS frequencies are in the same range as those inducing an adenosine-dependent inhibition of GABAergic transmission on neurons of lamina II [24]. As indicated in the previous paragraph, this inhibition and the conditions of its engagement depend on the excitatory or inhibitory nature of the postsynaptic neuron [24]. More generally, endogenous adenosine has been involved in the modulation and/or the effect of various pharmacological antinociceptive agents (this

point has been extensively reviewed in [126]). Spinal adenosine is also involved in the analgesic effects of electroacupuncture in a rodent model of neuropathic pain [35].

Since endogenous adenosine acting on A1 receptors seems to be a major player in endogenous antinociceptive mechanisms, the use of A1 receptors positive allosteric modulators appear as a promising antinociceptive strategy [53]. Nevertheless, the development of such clinically-relevant A1 modulators proved to be challenging, although recent advances are promising [12; 45; 67; 71].

Interestingly, the analgesic effect of spinal cord stimulation is potentiated by intrathecal injection of GABA_B and A1 agonists whereas it is inhibited by antagonists of these receptors [31; 91; 92]. Thus one could speculate that activation of these receptors by GABA and adenosine released in an activity-dependent manner might play a key role in the analgesia mediated by spinal cord stimulation. This is in agreement with experimental evidence showing that spinal cord stimulation increased the release of GABA in the spinal cord of responding animals [9; 31-33; 138].

The combination of non-pharmacological neuromodulation approaches together with pharmacological modulations targeting GABA_B and A1 receptors may therefore represent a promising strategy for pain alleviation.

8. A possible role for certain short-term plasticities

A precise role has been proposed for some of the short-term plasticities described in the spinal nociceptive system. For example, the wind-up phenomenon is usually considered as involved in the increase of declared pain during repeated nociceptive stimulations [6; 81; 97; 115; 137; 147], and the wind-up “reset” phenomenon as a mechanism allowing to discriminate changes in this repetition [30]. The short-term synaptic depression at primary afferent synapses with deep DH neurons has been suggested to enhance the sensitivity of postsynaptic neurons to changes in the frequency of primary afferent discharge. This would allow the postsynaptic neuron to reliably detect a subsequent sensory stimulus [149]. Within lamina I, the short-term plasticity of glycinergic transmission may allow reducing inhibition at frequencies of activity corresponding to low intensities of sensory stimulations [25] and would therefore represent a gain control mechanism. Within lamina II, short-term plasticities affecting differently excitatory and inhibitory synaptic transmissions has been proposed to represent a gain control affecting the inhibitory/disinhibitory balance in DH neuronal

networks [24]. This short-term plasticity would allow controlling the gain of sensory information by filtering stimulations at low intensity.

More generally, short-term plasticity is the major type of operation involved in the processing frequency coded information [21; 106]. Overall, this type of plasticity is therefore not restricted to a peculiar function in the processing of sensory information, and is expected to be engaged in the processing of any afferent sensory information to the spinal nociceptive system. Understanding and modeling the overall processing of nociceptive inputs will require to take this type of plasticity into account.

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Table 1. Frequency of action-potentials induced by nociceptive stimulations of C and A δ fibers.

These data correspond to single-unit recordings. Since responses are dynamic, the time window used to measure and calculate the frequency has a strong impact on the values. Therefore, this window is given in the column entitled *Phase of response for frequency measurement*. This window of frequency measurement does not necessarily encompasses the whole primary afferent response.

Table 2. Short-term plasticity of primary afferent connections on DH interneurons during trains of stimulation

Table 3. Short-term plasticity of inhibitory connections during trains of stimulation

Figure 1. Examples of short-term plasticities in the DH of the spinal cord.

A. Example of short-term plasticity at primary afferent synapses. When stimulated 4 times at 10 Hz, connections of A β primary afferents on laminae III-IV neurons exhibit an activity-

dependent depression that is particularly pronounced for the second excitatory synaptic current. This depression results most likely from the recruitment of GABAergic interneurons by A β fibers. The GABA released activates presynaptic GABA_A receptors inhibiting the release of glutamate by the phenomenon of primary afferent depolarization. Modified after [16].

B. Example of short-term plasticity at glycinergic connections in lamina I. When paired stimulations were applied at these connections, the second glycinergic eIPSC was depressed with a maximal depression of about 50% for inter-stimulus intervals of 150-200 ms [25]. This depression involve a presynaptic inhibition by GABA_B receptors most likely activated by GABA released by the same synapse. Modified after [25].

C. Example of short-term plasticities at GABAergic connections in lamina II. In lamina II, GABAergic interneurons simultaneously contact excitatory and inhibitory interneurons. These connections display a target-specific short-term plasticity. Connections on excitatory interneurons display no plasticity at 5 Hz, and a strong summation at 50 Hz (top right trace) whereas connections onto inhibitory interneurons depress at 5 Hz (top left trace) and weakly potentiate at 50 Hz. After [24].

Type of fibers	Model	Stimulation	Action-Potential frequency	Phase of response for measurement	Reference
C	Human	pinpricks or heat (burning match)	50-60 Hz	Initial (First hundreds of ms)	[146]
C	Rat	acute subcutaneous injection of formalin in hind paw	82.3 Hz	Initial (mean peak firing in the first 10 min, 100 ms time windows)	[118]
C	Rat	calibrated noxious mechanical simulation of tail	ca. 20 Hz (4 N) > 50 Hz (6 N) > 100 Hz (8 N)	Initial (Peak of Instantaneous frequency at stimulation onset)	[62]
C	Cat	Thermic stimulations at 50°C	ca. 100 Hz	Initial (Maximum discharge rate)	[40]
C	Cat	Mechanical stimulation	15 Hz (50 g) 57 Hz (100 g) 140 Hz (250 g) 170 Hz (500 g)	Initial (Peak at stimulus onset)	[2]
C	Rat	noxious mechanical simulation of paw	> 5 Hz (25 g) > 10 Hz (50-100 g)	First second	[4]
C	Human	Mechanical	11 Hz	First second	[22]
C	Human	Heat (50°C)	8 Hz	First second	[22]
C	Human	Cold (0°C)	4 Hz	First second	[22]
C	Rat	noxious mechanical simulation of paw	≥ 1 Hz	Late (25 s after stimulation onset)	[4]
C	Rat	acute subcutaneous injection of formalin in hind paw	3 Hz	Late (Average from first 150 s)	[118]
C	Human	Mechanical	ca. 0 Hz	Late (at 5 s)	[22]
C	Human	Heat (50°C)	2 Hz	Late (at 5 s)	[22]
C	Human	Cold (0°C)	< 0.5 Hz	Late (at 30 s)	[22]
C	Rat	calibrated noxious mechanical simulation of tail	0.6 Hz (4 N) 0.9 Hz (6 N) 1.2 Hz (8 N)	Late (after 120 s)	[62]
Aδ	Rat	acute subcutaneous injection of formalin in hind paw	115 Hz (60 Hz glabrous skin fibers, 143 Hz Hairy skin fibers)	Initial (mean peak firing in the first 10 min, 100 ms time windows)	[118]
Aδ	Rat	calibrated noxious mechanical simulation of tail	ca. 20 Hz (4 N) > 50 Hz (6 N) > 100 Hz (8 N)	Initial (Peak of Instantaneous frequency at stimulation onset)	[62]
Aδ	Rat	noxious mechanical simulation of paw	ca. 5 Hz (25 g) ca. 15 Hz (50-100 g)	First second	[4]
Aδ	Rat	acute subcutaneous injection of formalin in hind paw	ca. 2.5 Hz (glabrous skin) ca. 6 Hz (hairy skin)	Late (Average from first 150 s)	[118]
Aδ	Rat	noxious mechanical simulation of paw	≥ 5 Hz (slowly adapting Aδ fibers) < 1 Hz (rapidly adapting fibers)	Late (25 s after stimulation onset)	[4]
Aδ	Rat	calibrated noxious mechanical simulation of tail	ca. 5 Hz (at 4, 6, 8 N)	Late (After 120 s)	[62]

Table 1. Frequency of action-potentials induced by nociceptive stimulations of C and Aδ fibers.

Model	Lamina	Post-synaptic neuron	Type of primary afferent fiber	Stimulation	Effect and mechanism	Reference
Ex-vivo spinal cord (postnatal rat)	I	Spino-parabrachial projection neuron	Muscle afferent (gastrocnemius nerve, sural nerve)	Electrical, 40 stimulations @ 1 Hz to 10 Hz	Measured on the 5 last synaptic-currents Depression of ca. 45% (1 Hz) 50% (2 Hz) 70% (5 Hz) 80% (10 Hz) Presynaptic mechanism	[89]
3 weeks old rats	II	"central cells" (by opposition with "limiting" cells)	A δ -fibers	Electrical, 10 stimulations @ 0.5 Hz to 20 Hz	Measured in the 3 last synaptic-currents Depression ranging from ca. 20% (@0.5Hz) to 90 % (@20 Hz) Presynaptic mechanism not involving NMDA receptors	[148]
3 weeks old rats	III-V	Unknown	A δ -fibers	Electrical, 10 stimulations @ 0.5 Hz to 20 Hz	Measured in the 3 last synaptic-currents Depression ranging from ca. 15% (@0.5Hz) to 75 % (@20 Hz) Presynaptic mechanism not involving GABA $_A$ nor NMDA receptors.	[149]
3 weeks old rats	III-V	Unknown	mainly A β and possibly some A δ fibers	Electrical, 4 stimulations @ 10 Hz	Depression of the 2 nd -4 th synaptic currents. Depression of the 2 nd synaptic current involved presynaptic inhibition by GABA $_A$ receptors.	[16]
Adult rats	II	Unknown (field potential)	C-fibers	Electrical, 20-160 stimulations @ 0.1-20 Hz	Potentiation of field potential response for stimulations between 0.2-10 Hz (maximum of 200% at 1-2 Hz)	[128]
Adult rats	V	Unknown (field potential)	C-fibers	Electrical, 20-160 stimulations @ 0.1 and 1 Hz	No plasticity of field potential response	[128]
Adult rats	III-IV	Unknown (field potential)	A δ fibers	Electrical, 20-160 stimulations @ 0.1 and 1 Hz	No plasticity of field potential response	[128]

Table 2. Short-term plasticity of primary afferent connections on DH interneurons during trains of stimulation

Model	Lamina	Post-synaptic neuron	Type of transmission	Neurons and stimulation protocol	Effect and mechanism	Reference
Primary culture (postnatal rat)	I-III	Unknown	GABAergic	Electrical stimulation of laminae I-III GABAergic interneurons 8 stimulations @ 2.5 Hz repeated every 20 s	Depression during the trains involving GABA _B and A1 receptors	[66]
Adult GAD65-eGFP mice	II	Excitatory (eGFP-) Possibly transient central	GABAergic	Electrical stimulation of lamina II GABAergic interneurons, possibly islet cells 11 stimulations @ 5 Hz repeated every 20 s	No change in eIPSCs amplitude	[24]
Adult GAD65-eGFP mice	II	Inhibitory (eGFP+) Possibly tonic central	GABAergic	Electrical stimulation of lamina II GABAergic interneurons, possibly islet cells 11 stimulations @ 5 Hz repeated every 20 s	Depression during the train, involving in part GABA _B receptors	[24]
1-2.5 week old Syrian hamsters	II-V	Unknown	GABAergic and/or glycinergic	Electrical stimulation of local inhibitory interneurons 10 stimulations @ 10 Hz	Potentiation or depression during the train	[158]
P3-P10-P21 rats	I-II	Unknown	GABAergic	Electrical stimulation of local GABAergic interneurons 40 stimulations @ 1 Hz, 5 Hz, 10 Hz, 20 Hz	Depression during the train	[68]
Adult GAD65-eGFP mice	II	Inhibitory (eGFP+)	GABAergic and/or glycinergic	Electrical stimulation of local inhibitory interneurons 12 stimulations at 20 Hz repeated every 20 s	train-to-train plasticity (the first train different from the next ones) depression or potentiation during the train	[84]
Adult GAD65-eGFP mice	II	Excitatory (eGFP-) Possibly transient central	GABAergic	Electrical stimulation of lamina II GABAergic interneurons, possibly islet cells 11 stimulations @ 50 Hz repeated every 20 s or 60 s	No change in eIPSCs amplitude, but large temporal summation. Involve strong activity dependent	[24]

Adult GAD65-eGFP mice	II	Inhibitory (eGFP+) Possibly tonic central	GABAergic	Electrical stimulation of lamina II GABAergic interneurons, possibly islet cells 11 stimulations @ 50 Hz repeated every 20 s or 60 s	inhibition by A1 receptors Depression during the train. Involve weak inhibition by A1 receptors	[24]
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Table 3. Short-term plasticity of inhibitory connections during trains of stimulation