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REVIEW

In search of lost presynaptic inhibition

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Abstract This chapter presents an historical review on the development of some of the main findings on presynaptic inhibition. Particular attention is given to recent studies pertaining the differential GABAa control of the synaptic effectiveness of muscle, cutaneous and articular afferents, to some of the problems arising with the identification of the interneurons mediating the GABAergic depolarization of primary afferents (PAD) of muscle afferents, on the influence of the spontaneous activity of discrete sets of dorsal horn neurons on the pathways mediating PAD of muscle and cutaneous afferents, and to the unmasking of the cutaneous-evoked responses in the lumbosacral spinal cord and associated changes in tonic PAD that follow acute and chronic section of cutaneous nerves. The concluding remarks are addressed to several issues that need to be considered to have a better understanding of the functional role of presynaptic inhibition and PAD on motor performance and sensory processing and on their possible contribution to the shaping of a higher coherence between the cortically programmed and the executed movements.

The synaptic effectiveness of afferent fibers can be modulated by central mechanisms

Hagbarth and Kerr (1954) reported that synaptic afferent transmission in the cat spinal cord could be influenced by tonic descending pathways from the bulbar and midbrain reticular formation and the cerebral cortex at the level of the first synapse in the spinal cord (see also Hernández-Peón and Hagbarth 1955). Almost at the same time, Howland et al. (1955) indicated that electrical interactions between afferents could produce conduction block, and suggested that some types of inhibition could block afferent nerve impulses before they have reached the region of the cells. Shortly after, Frank and Fourtes (1957) showed that the Ia EPSPs recorded in motoneurons could be depressed by conditioning volleys to muscle nerves without significant changes in motoneuron properties, and ascribed this depression to presynaptic inhibition.

Although later on Frank (1959) proposed remote dendritic inhibition as an alternative mechanism to presynaptic inhibition, the possible existence of extrinsic mechanisms affecting transmitter release of sensory fibers (i.e. of presynaptic inhibition) was a conceptual breakthrough, but it was not until Dudel and Kuffler (1961) when a direct demonstration of presynaptic inhibitory mechanisms possibly operating via a chemical synapse became available. In that same year, Eccles and collaborators presented their studies on presynaptic inhibition in the cat spinal cord (Eccles 1961). They proposed that the Ia EPSP depression assumed to be due to presynaptic inhibition, resulted from the *depolarization* of the Ia afferent fibers that decreased "*the size and number of Ia afferent impulses*" (see also Eccles et al. 1961). Later on, they suggested that this presynaptic depolarization (primary afferent depolarization or PAD) was due to the activation of GABAergic interneurons making axo-axonic synapses with the intraspinal terminals of the sensory fibers (Eccles et al. 1963a).

It took a while for investigators to accept the existence of presynaptic inhibition. Most arguments against were based on the possibility that there was always some concurrent "remote" postsynaptic inhibition that could not be

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detected by intracellular recordings from the motoneuron cell body because it was mostly dendritic (Granit et al. 1964; for more references see Rudomin and Schmidt 1999). Subsequent electrophysiological studies ended with this controversy by showing that pre- and postsynaptic inhibition could coexist (Solodkin et al. 1984; Rudomin et al. 1987). Morphological studies have further supported this view by showing that the same last order GABAergic interneurons can make synapses with the afferent fibers and the postsynaptic target neurons (for review see Rudomin and Schmidt 1999). However, it is still unclear if all synaptic boutons of the GABAergic interneurons that make axo-axonic synapses with the terminals of the afferent fiber also contact the postsynaptic neuron. Yet, at present time, a reasonable assumption would be that the pre- and postsynaptic inhibition exerted by the same GABAergic interneuron may complement each other by preventing interfering sensory activation whenever these neurons are commanded by descending inputs (see below and Seki et al. 2003).

It is now well established that the terminal arborizations of muscle and cutaneous afferents in mammals have GABAa as well as GABAb receptors. Activation of the GABAa receptors via GABAergic interneurons increases the permeability to chloride ions, which move according their electrochemical gradient and produce PAD. Presynaptic inhibition of transmitter release occurs either because of PAD, or because the associated shunt that may prevent conduction of action potentials. Activation of GABAb receptors instead reduces the calcium currents associated with the action potential and transmitter release (for review see Rudomin and Schmidt 1999). Activation of GABAa receptors appears to be geared for short term, short lasting presynaptic inhibition such as that required during performance of specific motor tasks (Seki et al. 2003), while activation of GABAb receptors would appear to be involved in long term presynaptic modulations (Soto et al. 2006; Castro et al. 2006), among them, those occurring during peripheral inflammation or peripheral nerve damage (Castro et al. 2006).

At present is not clear whether the GABAa and GABAb receptors have the same or separate spatial distribution within the intraspinal arborizations of the sensory fibers (however, see Sugita et al. 1992; Quevedo et al. 1997). An overlapping distribution could imply coactivation of both receptors by the same last-order interneurons, while a non-overlapping distribution would allow a differential activation of the GABAa and GABAb receptors.

Local character and selective modulation of PAD

For almost four decades, it was assumed that, because of the cable properties of the afferent fibers, PAD would spread passively through most of the intraspinal arborizations of individual afferents (Eccles et al. 1961). However, the finding that direct activation of the last-order GABAergic interneurons could produce PAD in some but not in other, nearby, intraspinal collaterals of the same Ia afferent (Quevedo et al. 1997), together with the finding that pairs of collaterals of individual afferents could display different PAD patterns (Rudomin et al. 2004a, b), provided strong evidence in favor of the local character of PAD.

It thus became clear that the intraspinal arborizations of the afferent fibers are not fixed routes for information transmission, as it was believed for long time, but rather dynamic substrates in which information arising from the periphery can be addressed to specific neuronal targets by central mechanisms (Rudomin et al. 2004a, b). This seems to be the case for the differential adjustment of the synaptic effectiveness of muscle spindle afferents during voluntary movements in humans (Hultborn et al. 1987; Iles 1996) and for cutaneous afferents during active movements in monkeys (Seki et al. 2003).

Demonstration of a differential PAD in different collaterals of the same afferent does not necessarily imply that this will lead to a differential activation of the postsynaptic targets, because of additional effects exerted by other segmental or descending pathways. Yet, Gosgnach et al. (2000) found during fictive locomotion a differential tonic modulation of the synaptic effectiveness of muscle spindle afferents ending in the motor pool. More recently, Menard et al. (2002) recorded intra-axonally in group I afferents during fictive locomotion. Their results indicate that cutaneous interneurons may act, in part, by modulating the transmission in PAD pathways activated by group I muscle afferents (see also Manjarrez et al. 2000). Cutaneous inputs, especially from the skin area on the dorsum of the paw, appeared to subtract presynaptic inhibition in some group I afferents during perturbations of stepping (e.g., hitting an obstacle) and could thus adjust the influence of proprioceptive feedback onto motoneuronal excitability. In addition, Menard et al. (2003) showed that muscle afferents can induce an important phase-dependent presynaptic inhibition of monosynaptic transmission and that concomitant activation of cutaneous afferents can alter this inhibition, but only for a restricted part of the step cycle. Yet, despite these findings, there is still limited information on how the differential modulation works during the performance of specific motor tasks in addition to that provided time ago by Hultborn et al. (1987) for muscle spindle afferents synapsing with motoneurons in humans.

The monosynaptic actions of group II and of cutaneous afferents can be also differentially modulated during fictive locomotion. In the case of the group II fields there is good evidence for a more powerful reduction in transmission to interneurons located in intermediate than to those in dorsal

laminae. The extent to which this preferential depression contributes to selection of reflex actions during locomotion must await further study and it is not unlikely that this is due, at least in part, to a differential presynaptic inhibition (Perreault et al. 1999).

Experiments on "reflex" control of muscle activity during various forms of movements have revealed that the actions from specific sensory inputs are not only gated, but actually "re-routed" and mediated via different neuronal networks. Although much work remains before it is understood how the brain uses the spinal networks during actual voluntary movement, it is not unlikely that changes in tonic presynaptic inhibition are also involved in the "state" dependency of spinal reflexes and modulation of sensory feedback (see below and Hultborn 2001).

Patterns of PAD

Group I muscle afferents

It was believed for several years that all muscle spindle afferents were depolarized by group I muscle afferents (mostly from flexors), but not by stimulation of cutaneous nerves, nor by stimulation of the motor cortex, red nucleus, bulbar reticular formation and raphe nuclei, which instead inhibited the PAD generated by stimulation of muscle afferents (type A PAD pattern). In contrast, all tendon organ afferents were assumed to be depolarized by stimulation of muscle and cutaneous afferents and by supraspinal structures [type B PAD pattern; see (Rudomin et al. 1983; Harrison and Jankowska, 1989)]. A more detailed analysis of PAD in functionally identified group I muscle afferents (Jiménez et al. 1988; Enríquez et al. 1996a) revealed, however, a third (type C) PAD pattern. Namely, stimulation of supraspinal structures and of muscle nerves produced PAD, in contrast with stimulation of cutaneous nerves that inhibited the PAD. These studies indicated in addition that individual muscle spindle and tendon organ afferents could display either a type A, B or C PAD pattern. Yet, most muscle spindle afferents had a type A PAD pattern and most fibers from tendon organs had a type C PAD pattern. The relative distribution of the three PAD patterns within the population of muscle spindle and tendon organ afferents was not fixed but could be modified after a chronic peripheral nerve crush (see below and Enríquez et al. 1996b).

Group II afferents

Studies on PAD of group II muscle afferents showed that these fibers are strongly depolarized by stimulation of other group II afferent fibers, very little by group I fibers, by cutaneous afferents, by stimulation of the locus coeruleus and midline raphe nuclei and to a lesser extent by stimulation of the red nucleus (Harrison and Jankowska 1989). In addition to the modulation of the synaptic effectiveness of the group II afferents by GABAa mechanisms producing PAD (Riddell et al. 1993), monoamines have a differential action on the collaterals of these fibers ending in the dorsal horn versus those ending within the intermediate nucleus. Bras et al. (1989, 1990) found that iontophoretic application of noradrenalin and serotonin agonists depressed the monosynaptic components of the extracellular field potentials produced by stimulation of group II afferents. However, these agonists differed in the potency with which they depressed transmission from group II afferents to different functional types of neuron. This depression may involve different membrane receptors at different locations, primarily alpha2 adrenoceptors in the intermediate zone/ventral horn and 5-HT1A serotonin receptors in the dorsal horn. The depression of the group II monosynaptic field potentials has been taken as an indication of presynaptic actions (Jankowska et al. 2000, 2002). However, it is still unclear if these differential actions are exerted presynaptically on different collaterals of the same fiber or on different fibers.

Articular afferents

Studies on PAD of joint afferents have indicated that low and intermediate threshold myelinated fibers of the posterior articular nerve (PAN) are strongly depolarized by stimulation of cutaneous nerves, as well as by stimulation of the bulbar reticular formation and by the midline raphe nuclei. Stimulation of gr. II muscle afferents also produces PAD, which is larger in the L3 than in the L6 segments. As with group I muscle afferents, the PAD elicited in PAN afferents by stimulation of muscle nerves can be inhibited by conditioning stimulation of cutaneous afferents (Jankowska et al. 1993; Rudomin and Lomelí 2007).

In contrast with Ib afferents (Zytnicki and Jami 1998), the PAN afferents show a rather small autogenetic PAD, particularly when the PAD is compared with the effects of heterogenetic stimulation (Jankowska et al. 1993; Rudomin and Lomelí 2007). Therefore, the depression of the PAN intraspinal fields produced by autogenetic stimulation described by Rudomin et al. (2007) may be due to other mechanisms besides GABAa presynaptic actions. The feeble autogenetic PAD displayed by the joint afferents could prevent presynaptic filtering of their synaptic actions and thus preserve the original information generated in the periphery, which may be important for proper adjustment of limb position during the execution of voluntary movements. The reasons for a low autogenetic PAD of joint afferents are not clear. It is possible that the required spinal pathways are tonically inhibited either by descending or by segmental influences, but this requires further investigation.

Cutaneous afferents

Under normal conditions cutaneous fibers are depolarized by stimulation of other cutaneous afferents (Eccles et al. 1963b). This effect is modality specific (Jänig et al. 1967; Schmidt et al. 1967; Schmidt 1971) and plays a relevant role in the spatial focusing of sensory discrimination in the cutaneous domain. The low threshold cutaneous afferents are also depolarized by stimulation of groups Ib, II and III muscle fibers and by supraspinal stimulation (for review see Rudomin and Schmidt 1999). In contrast with group I muscle and articular afferents whose PAD can be inhibited by stimulation of cutaneous nerves or supraspinal structures (Jankowska et al. 1993), there seem to be no reports of inhibitory actions exerted by nerve or supraspinal stimulation on the interneurons mediating PAD of cutaneous afferents. However, inhibition of PAD seems to occur during fictive locomotion (Dueñas and Rudomin 1988) or during scratching, as shown by Cote and Gossard (2003), who compared the level of presynaptic inhibition during locomotion and scratch in decerebrate cats and found that in both conditions there were cyclic oscillations in the dorsal root potentials (DRPs) and antidromic discharges of single afferents (most likely cutaneous). Yet, although the amplitude of these oscillations were smaller during locomotion that during scratch, PAD was significantly more reduced during scratch leading to a task-dependent decrease in transmission.

Although it has been established that PAD produced in large cutaneous fibers by stimulation of cutaneous nerves or supraspinal structures is not due to extracellular accumulation of potassium ions, but rather to more specific GABAergic mechanisms (Jiménez et al. 1984, 1987), the situation is not so clear with finely myelinated and unmyelinated fibers, particularly because these afferents appear not to be the targets of synapses made by GABAergic interneurons. This is an important issue because during inflammation there is a clear increase of the antidromic discharges of delta and C cutaneous afferents due to the augmented PAD (Willis, 1999; Lin et al. 2000), that contributes to further inflammation. It is possible that these antidromic discharges are generated by extrasynaptic GABAergic mechanisms (Kullmann et al. 2005; Takahashi et al. 2006).

Identification of PAD mediating interneurons

There have been in the past several attempts to identify the interneurons mediating PAD of muscle and cutaneous afferents using electrophysiological techniques. They relied on the response patterns of the presumed PAD-mediating neurons to electrical stimulation of peripheral nerves (Eccles et al. 1962; Lucas and Willis 1974). This led to the suggestion that the same set of interneurons mediated the PAD of muscle and cutaneous afferents (Eccles et al. 1962). However, by examining the spinal sites where microstimulation produced PAD with monosynaptic latencies, Jankowska et al. (1981) showed that the pathways mediating the segmental PAD of cutaneous and muscle afferents had at least two interposed interneurons and that the last-order interneurons mediating the PAD of cutaneous afferents were located within the dorsal horn, while the interneurons mediating the PAD of muscle afferents were located within the intermediate zone.

To identify the interneurons mediating PAD of muscle afferents Rudomin et al. (1987) recorded the spontaneous activity of single neurons in the intermediate zone of the lumbosacral region, together with cord dorsum (CDP), dorsal root (DRP) and ventral root (VRP) potentials. Averaging of the cord potentials triggered by the neuronal activity disclosed two different classes of neurons. Class I neurons showed time locked ventral root inhibitory potentials (iVRPs) with a monosynaptic latency occurring without any concurrent DRPs. These neurons were shown to mediate the Ib non reciprocal (glycinergic) inhibition of motoneurons. Class II neurons showed instead time locked "monosynaptic" DRPs as well as iVRPs and it was assumed they mediated the GABAergic PAD of muscle afferents (Rudomin et al. 1990).

One of the problems with the interpretation of these findings was that the spontaneous interneuronal activity of the interneurons assumed to mediate PAD of muscle afferents appeared in synchrony with a negative CDP which started 25–50 ms before the interneuronal activity used to trigger the DRP and VRP recordings (Rudomin et al. 1987). These CDPs were assumed to be generated by a population of dorsal horn neurons with excitatory actions on the pathways mediating PAD.

Subsequent studies indicated that the spinal neurons activated in synchrony with the spontaneous negative CDPs were located in the dorsal horn and that many of them responded with monosynaptic latencies to stimulation of low threshold cutaneous afferents (Manjarrez et al. 2000, 2003). The spontaneous negative CDPs appeared synchronously in the L3–S1 segments, both ipsi- and contralaterally. When generated, there was a concurrent modulation of impulse transmission along many reflex pathways, including those mediating presynaptic inhibition. The acute section of both the intact sural and the superficial peroneal nerves, or a low thoracic spinalization increased the variability of the spontaneous CDPs without affecting their segmental distribution. However, the coupling between potentials recorded in the left side of segments L5 and L6 was partly reduced following an interposed lesion of the ipsilateral dorsolateral spinal quadrant and completely abolished after an equivalent contralateral lesion (García et al. 2004a).

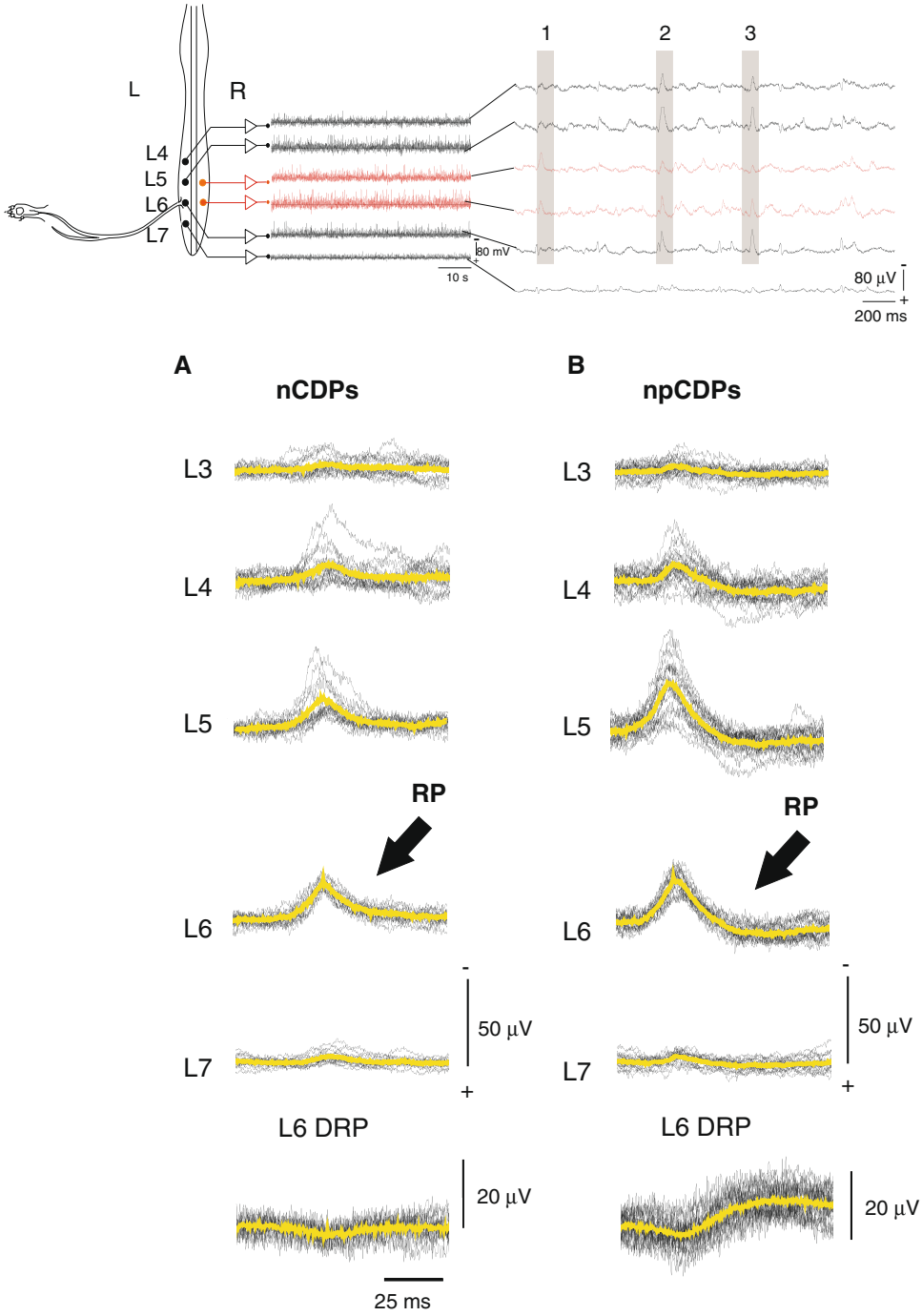

Fig. 1 Spontaneous DRPs appear in association with negative-positive but not with purely negative CDPs. Diagram shows sites of cord dorsum recordings. *Black traces* CDPs recorded from the left (*L*) side. *Red traces* CDPs recorded from the right side (*R*). In the expanded traces, *gray bar* numbered *1* comprises spontaneous negative wavelets that were larger in the right than in the *left side*, and *bars 2* and *3* potentials that were larger in the left than in the *right side*. **a**, **b** Superposed traces of spontaneous CDPs recorded from different spinal segments, as indicated, and of L6 DRPs appearing in synchrony with L6 spontaneous negative (*nCDPs*) or negative positive potentials (*npCDPs*) selected by means of predetermined templates (labeled RP; see *arrows*). The *yellow traces* show the averages. Note that spontaneous DRPs appear only in association with the spontaneous npCDPs. Note also that the nCDPs and npCDPs recorded from the *L5* and *L4* segments had a higher variability than the *L6* reference potentials. In all CDP and DRP recordings negativity is upward

García et al. (2003, 2004b) characterized the spinal networks generating different types of spontaneous potentials and their possible actions on the pathways mediating PAD. Using pre-determinated templates they selected purely negative or negative positive spontaneous CDPs (nCDPs and npCDPs, respectively). These potentials appeared synchronously in spinal segments L7–L4. Yet, although both types of CDPs were generated by neurons that receive mono and/or oligosynaptic excitation from low-threshold cutaneous afferents, spontaneous DRPs appeared synchronized only with the spontaneous npCDPs (Fig. 1). This suggested that different sets of spinal neurons are involved in the generation of the npCDPs and nCDPs. At present it is not clear if the involved interneurons are local or if they have ascending axons that send information to supraspinal structures.

The functional role of the correlated activity of the neuronal aggregates generating the spontaneous npCDPs is still unclear. It may contribute to the generation of tonic PAD in cutaneous (probably together with neurons in Laminae I and II; see Lidierth and Wall 1998) as well as in Ib afferents

(Manjarrez et al. 2000) and modulate, in a synchronous manner, the PAD and the synaptic effectiveness of many afferent fibers, thus leading to a correlated activation of a substantial fraction of their target neurons (Rudomin et al. 1975). Studies on the PAD patterns of pairs of collaterals of single muscle afferents now indicate that this correlating system can affect discrete sets of PAD-mediating interneurons with spatially restricted and selective actions on the intraspinal collaterals of the afferent fibers compatible with a modular organization (Rudomin et al. 2004a, b).

The concept of a modular organization of dorsal horn neurons was proposed time ago by Szentagothai (1983). Supportive physiological evidence has been provided by Schouenborg and Kalliomaki (1990) and by Schouenborg et al. (1992) on the withdrawal reflex system and by Lu and Perl (2005) on Lamina I and II neurons. More recently, Saltiel et al. (1998), Tresch and Bizzi (1999) and Lemay and Grill (2004) examined the motor responses produced in the frog, rat and cat by intraspinal microstimulation or by NMDA microinjections and proposed that some spinal neural circuits are organized into a number of distinct functional modules, mostly located within the dorsal horn and intermediate nucleus. Their activation would lead to a patterned activation of motoneurons. However, the findings of Gaunt et al. (2006) and of Barthelemy et al. (2006) do not appear to support this proposal, because intraspinal electrical or chemical stimulation as well as mechanical stimulation of the skin may also introduce a synchronous activation of neurons and/or afferent fibers.

Studies on the correlation of the spontaneous activity of dorsal horn neurons have provided limited information on their possible modular or distributed organization (Sandkuhler and Eblen-Zajjur 1994; Sandkuhler et al. 1995; Biella et al. 1997; Eichler et al. 2003; Galhardo et al. 2002). By using thin flexible flat arrays of 8 × 4, 30 micron electrodes, each of them separated 1 mm from the other placed over the cord dorsum in segments L5–L6, Yang et al. (2007) found that the CDPs produced by stimulation of the low-threshold SU afferents are distributed more or less evenly throughout the surface covered by the flat array, while the spontaneous CDPs have segmented spatio-temporal patterns, probably due to activation of discrete neuronal aggregates, as suggested previously (Manjarrez et al. 2003; García et al. 2004a). At present it is difficult to decide if these segmented spatio-temporal patterns are equivalent to the modules proposed by Bizzi and collaborators or if they just represent the activation of a distributed neuronal system in which the spatial distribution of the responding neurons depends on the instantaneous balance between the excitatory and inhibitory influences of segmental and supraspinal origin received by the network. Since this system of dorsal horn neurons is also active in non-anesthetized unrestrained preparations (Kasprzak and Gasteiger 1970), an attractive possibility would be that the presumed modular organization of the dorsal horn and intermediate nucleus neurons leads to a modular and selective control of the synaptic effectiveness of the afferent fibers, that may contribute to the development of a higher coherence between the programmed and the executed voluntary movements.

Plasticity of PAD

One important feature of the modulation of the information conveyed to the spinal cord by the sensory receptors is the plasticity of the spinal cord pathways that includes the learning capabilities of the involved neuronal circuitry (Wolpaw 2007), as well as the central sensitization induced by inflammation and by peripheral nerve damage (see Willis 1999, 2002).

The unmasking phenomenon

The long range caudal projections of cutaneous afferents in the rat spinal cord appear not to normally conduct action potentials because of tonic GABAergic influences. Removal of the GABAa actions resumes conduction in these collaterals (Wall 1994; Wall and Bennett 1994; Wall and McMahon 1994). In anesthetized rats, the acute section or anesthesia of the sciatic nerve also "unmasks" the actions of saphenous afferents in the regions of sciatic nerve projections. This effect has been attributed, at least in part, to reduction of tonic presynaptic inhibition exerted on the intraspinal terminals by the signals conveyed by intact afferents (Biella and Sotgiu 1995).

More recently, García et al. (2005) examined the effects of the acute nerve section on the spontaneous and evoked CDPs and DRPs. They found that the acute section of the main sural nerve (mSU) and of the superficial peroneal (SP) nerves increased the CDPs and L6 dorsal root potentials (DRPs) produced by stimulation of the Saph nerve (Fig. 2a, b), but had no effect on the averaged spontaneous DRPs associated to the spontaneous L6 or L4 npCDPs (Fig. 2c–f). This suggested that the unmasking of the cutaneous-nerve evoked CDPs and DRPs was due to a presynaptic mechanism, as proposed by Biella and Sotgiu (1995).

To examine this possibility more directly, García et al. (2006, 2007) measured the effects of the acute section of the Saph and/or the SP nerves on the tonic PAD of the mSU terminals. In five experiments sectioning the Saph nerve was found to increase the L7 CDPs produced by stimulation of the mSU nerve as well as the intraspinal field potentials (IFPs) recorded in the same segment (Fig. 3a, b). This facilitation was considered equivalent to the unmasking of the Saph actions produced by sectioning or anesthetizing

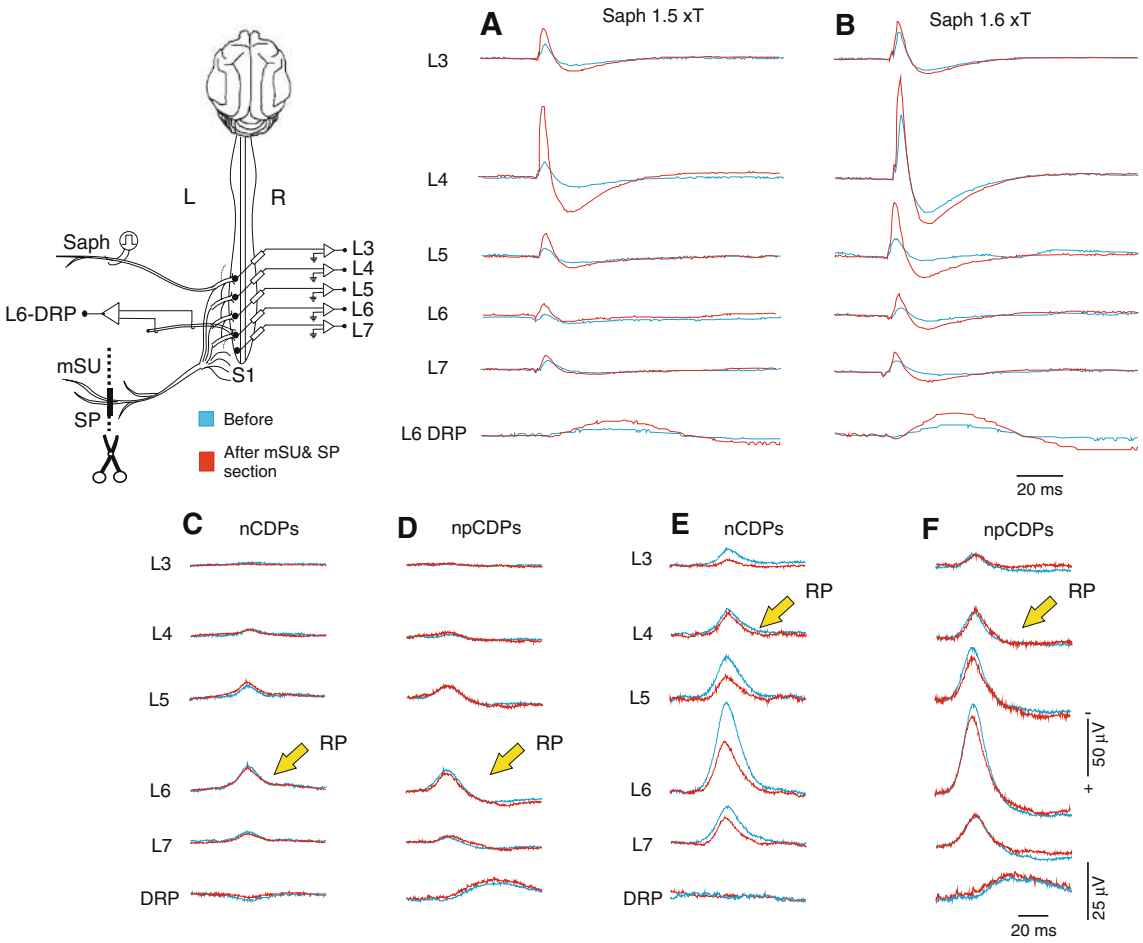

Fig. 2 The acute section of the mSU and SP nerves facilitates the Saph-evoked CDPs and DRPs without increasing the spontaneous CDPs and DRPs. Diagram shows location of cord dorsum and DRP recordings. **a**, **b** Superposed averages of the *L3–L7* CDPs and of the L6 DRPs evoked by Saph nerve stimulation (single pulses 1.5 and 1.6 × *T*). *Blue traces* before, *red traces* after sectioning the main sural (mSU) and superficial peroneal (*SP*) nerves. Note that mSU and SP nerve section facilitates the L3–L7 Saph-evoked CDPs and L6 DRPs. **c–f** Averages of spontaneous nCDPs, npCDPs and L6 DRPs occurring in association with reference nCDPs and npCDPs recorded either from the L6 or L4 segments (*RP* and *arrows*). All traces are averages of 32 potentials. **c**, **d** Sectioning the SP and mSU nerves had virtually no effect on the spontaneous CDPs and DRPs associated to either the L6 reference nCDPs or npCDPs. **e**, **f** Although the spontaneous CDPs associated with the L4 nCDPs and npCDPs were reduced after sectioning the mSU and SP nerves, the spontaneous L6 DRPs were unaffected. In all traces negativity is upward

the sciatic nerve in the rat (Biella and Sotgiu 1995). In these experiments sectioning the Saph nerve *reduced* the mSU antidromic responses produced by intraspinal microstimulation elicited with strengths varying from 1.1 to 2.0 × *T* (Fig. 3c, d). The PAD produced in the mSU terminals by conditioning stimulation of the SP nerve was also reduced following the Saph nerve section (Fig. 3e, f). It thus seems that sectioning the Saph nerve reduced the tonic PAD of the mSU terminals which now became more effective and generated larger nerve-evoked responses, as proposed by Biella and Sotgiu (1995). In other 3 experiments, sectioning the SP nerve also increased the mSU-IFPs (Fig. 4a, b). However, and quite unexpectedly, the mSU antidromic responses produced by intraspinal microstimulation were found to be larger, suggesting increased tonic PAD (Fig. 4d, e). It then follows that the unmasking of the mSU evoked responses induced by the SP nerve section cannot be solely attributed to changes in the tonic presynaptic inhibition of the mSU intraspinal terminals.

The above experiments suggested that the acute section of a cutaneous nerve induced a state of central sensitization during which the responses produced by stimulation of another, intact, cutaneous nerve were enhanced. This led to the question on the extent to which this change in state would affect the effects on the tonic PAD produced by a second nerve section. García et al. (2007) found in 3 experiments that sectioning the Saph nerve, about one hour after the SP nerve was cut, further increased the amplitude of the evoked mSU CDPs and mSU IFPs (Fig. 4c), but now increased the antidromic mSU responses produced by intraspinal stimulation (Fig. 4f). This reversal of the changes in the tonic PAD of the mSU terminals was seen in

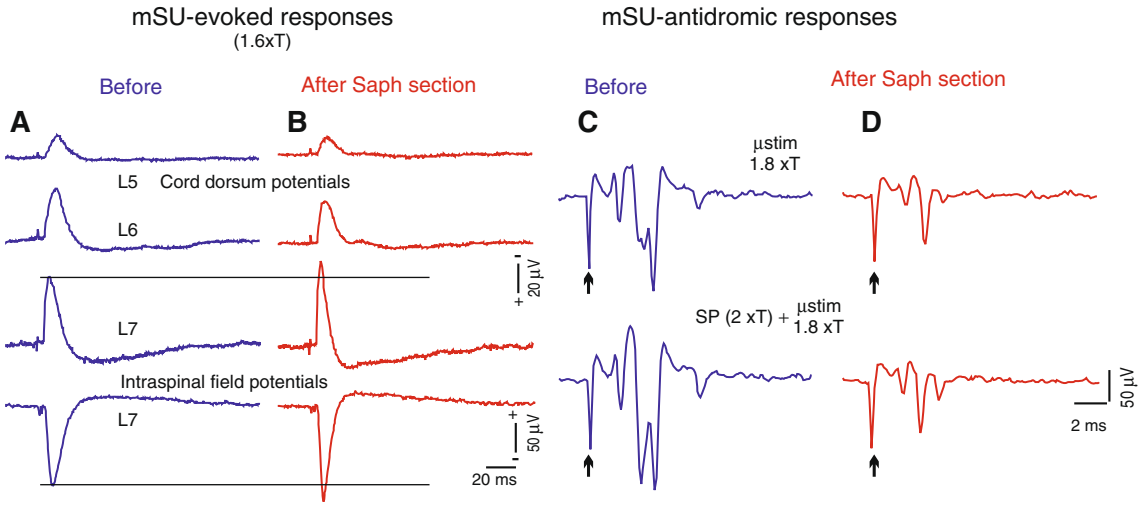

Fig. 3 The acute section of the Saphenous nerve unmasks the mSU evoked responses and reduces the tonic PAD of mSU terminals. **a**, **b** Averaged *L5–L7* CDPs and L7 intraspinal field potentials (*IFPs*) produced by stimulation of the mSU nerve with single pulses 1.6 × *T* before (*blue traces*) and after (*red traces*) the acute section of the Saph nerve. Note facilitation of the L7 CDPs and IFPs. **c** *Upper traces* averaged antidromic responses recorded from the intact mSU nerve following intraspinal microstimulation with single pulses 1.8 times the threshold of the most excitable fibers. *Lower traces* effects of SP conditioning stimulation on the mSU antidromic responses. The SP nerve was stimulated with single pulses 2 × *T* applied 35 ms before the intraspinal test stimulus. **d** Same as **c** but 30 min after the acute section of the Saph nerve. Note reduction of the test and conditioned antidromic responses. Negativity upward for CDP and downward for IFP recordings. *Arrows* in **c**, **d** indicate stimulus artifact

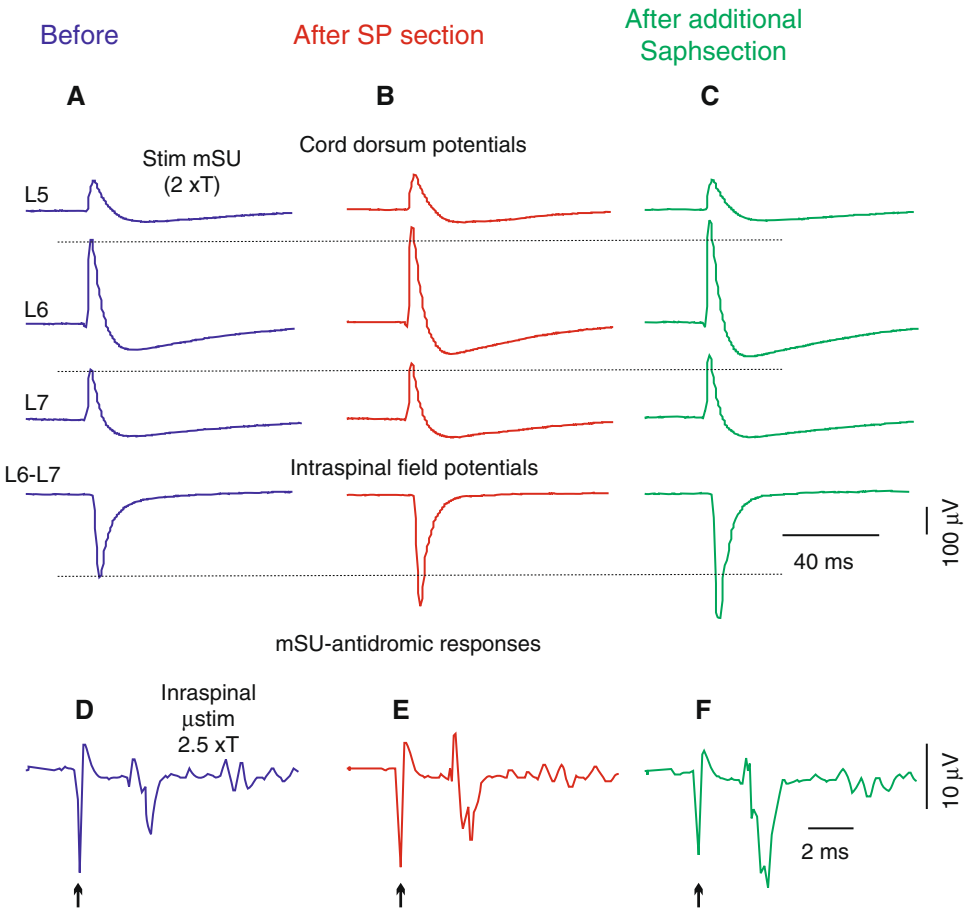

Fig. 4 A previous section of the SP nerve reverses the effects produced by sectioning the Saph nerve on the tonic PAD of the mSU terminals. **a** Control averaged *L5–L7* CDPs and *L6–L7* IFPs produced by stimulation of the mSU nerve with single pulses 2 × *T* (*blue traces*). **b** The same but 30 min after the acute section of the SP nerve (*red traces*). **c** Effects produced 30 min after the additional section of the Saph nerve (*green traces*). **d–f** Changes of the antidromic mSU nerve responses produced by intraspinal microstimulation before (**d**), after sectioning the SP nerve (**e**) and after the additional section of the Saph nerve (**f**). Strength of the intraspinal stimulus was the same in **d–f** (2.5 × *T*). Note that the acute section of the SP as well as the section of the Saph nerve increased the mSU-evoked and the mSU antidromic responses. Negativity upward for CDP and downward for IFP recordings. *Arrows* in D-F indicate stimulus artifact

2/3 experiments. Likewise, in two experiments, sectioning the SP nerve after cutting the Saph nerve also increased the mSU evoked CDPs and IFPs but reduced the mSU antidromic responses.

At present it is not clear if the changes in the tonic PAD produced by the acute section of cutaneous nerves were due to the suppression of the information conveyed from the periphery (Biella and Sotgiu 1995), or if they were due to the lesion-induced discharges of unmyelinated afferents (Cervero and Laird 1996; Willis 1999; see also Vanegas and Schaible 2004). Since the injury discharges produced by sectioning the cutaneous nerves promote a local increase in the extracellular concentration of potassium ions (Heinemann et al. 1990), sectioning the Saph nerve would be expected to increase the extracellular potassium mainly in the L3 and L4 segments and very little in the more caudal L6 and L7 segments, where mSU afferents project. Sectioning the SP nerve would on the other hand increase the potassium concentration mostly in the L6 and L7 segments and probably depolarize nearby mSU afferents and their target neurons. However, this may not explain the reversal of the effects on the tonic PAD produced by a preceding nerve section, nor the long lasting increase of the mSU antidromic responses, because the lesion-induced increase of extracellular accumulation of potassium fades away within seconds (Heinemann et al. 1990). It is of course possible that the increased extracellular potassium promoted the release of peptides and neurotransmitters from nearby neurons and glia which in turn contributed to the central sensitization (Cervero et al. 2003; Keller et al. 2007), but this requires further investigation.

Even though these are relatively few observations, the effects produced by a first nerve section on the tonic PAD produced by a second nerve section remind the learned long term alterations in spinal reflex excitability produced by altered or sustained sensory inputs (for references see Sandkuhler 2000), which may be related to the state-dependent reversal of spinal reflexes where the same stimulus may activate either excitatory or inhibitory pathways, depending on the excitability of the particular interneurons or the strength of excitation from other sources (Jankowska 2001). These state dependent changes in the pathways mediating the tonic PAD could be involved in setting of presynaptic inhibition following nociceptive stimulation, a feature that may be of relevance for the presynaptic interactions between low threshold mechanoreceptors and nociceptors (see Cervero et al. 2003).

The state dependency of the tonic PAD may also explain the old controversy pertaining the changes in PAD of low-threshold cutaneous mechanoreceptors during nociceptive stimulation (Mendell and Wall 1964; Burke et al. 1971; Janig and Zimmermann 1971), which could well be due to differences in the preparations used for these studies (i.e., nerves intact or sectioned, spinal, anesthetized or decerebrate cats).

Effects of chronic nerve lesions on PAD

Another expression of plasticity of the pathways mediating PAD of muscle and cutaneous afferents are the changes produced by chronic crush or section of peripheral nerves. Two to 12 weeks after crushing the medial gastrocnemius nerve, stimulation of the bulbar reticular formation produced PAD in most fibers reconnected with muscle spindles while stimulation of cutaneous afferents produced PAD in all fibers reconnected with tendon organs (Enríquez et al. 1996b). The increased number of muscle spindle afferents in which reticulo-spinal stimulation produced PAD could allow a more effective central control of the information provided by damaged afferents, while the increased number of tendon organ afferents that are depolarized by cutaneous afferents could be relevant during stepping (see Iles 1996). At present it is not clear if the changes in the PAD patterns of the muscle afferents were due to the development of new connections or to compensatory changes in synaptic efficacy of already existing pathways.

In contrast with what has been observed in muscle afferents, the PAD elicited in cutaneous fibers by stimulation of other cutaneous nerves has been reported to be strongly depressed when examined 1 month after crushing their peripheral axons (Horch and Lisney 1981; Wall and Devor 1984). Recovery was slow and the depression of the PAD persisted for up to 9 months. The temporal loss of PAD of segmental origin in cutaneous afferents observed after crushing their peripheral axons was attributed by Horch and Lisney (1981) to atrophy or shrinkage of the intraspinal arborizations of the damaged afferents that became separated from the last-order GABAergic interneurons. This proposal was based on the morphological and histochemical observations of Knyihar and Csillik (1976). Since PAD was not depressed when impulse conduction in cutaneous nerves was blocked by chronic application of tetrodotoxin (Devor 1983), it was further suggested that the generation and conduction of action potentials in damaged cutaneous afferents played a rather minor role in the depression of PAD, which could be due to loss of trophic factors. In fact, the depression of PAD produced by sectioning the cutaneous nerves was prevented by continuous application of NGF to the central end of the sectioned nerve (Fitzgerald et al. 1985). More recent observations in the rat indicate that sectioning cutaneous nerves promotes the selective loss of GABAergic inhibition in dorsal horn neurons without affecting the fast excitatory actions (Moore et al. 2002). However, this reduction in the GABAergic actions seems not to be associated with a decreased number of GABAergic dorsal horn neurons (Polgar et al. 2003).

García et al. (2008) examined the extent to which the unmasking and the changes in tonic and phasic PAD of mSU terminals produced by the acute section of the SP nerve are modified after a chronic mSU nerve crush (CSNC). In contrast to what was reported by Horch and Lisney (1981) they found in 3 cats that 2 weeks after CSNC, SP conditioning pulses (1.5–2 × T) produced strong phasic PAD of the mSU intraspinal terminals and inhibited the L6–L7 IFPs generated within the dorsal horn (1.4–1.6 mm depth) by stimulation of the previously crushed mSU nerve with single pulses 1.2–2 × T. Under these conditions, the acute section of the intact SP nerve failed to unmask the otherwise "normal" responses of dorsal horn neurons to stimulation of low threshold mSU afferents, but still increased the mSU antidromic responses produced by intraspinal microstimulation to about the same extent as in the non-chronic preparations, suggesting increased tonic PAD. By 3 weeks after crushing the mSU, the acute SP nerve section ($n = 2$) was found to reduce the mSU IFPs as well as the mSU antidromic responses (suggesting decreased tonic PAD), even though conditioning stimuli still produced a strong phasic PAD and inhibited the mSU IFPs. These observations further support a state dependency of the tonic PAD and suggest that the underlying mechanisms and/or pathways are different from those involved in the generation of the phasic PAD and in the unmasking of the mSU responses.

Concluding remarks

After 50 years of continuous research it is fairly well established that the synaptic effectiveness of muscle, articular and cutaneous afferents can be modulated by a variety of peripheral and central mechanisms. Some of them involve the action of neurotransmitter substances released by neurons making axo-axonic synapses with the intraspinal terminals of the afferent fibers, as it is the case of the GABA-ergic or the serotonergic and adrenergic modulations, while others involve paracrine or extra synaptic actions as in the case of histamine and other peptides. With the exception of the GABAergic and the monoaminergic systems, there is still limited information on the functional organization of the pathways involved in these modulatory actions, and even less information on their role in the control of sensory information in behaving organisms.

Pertaining the GABAa modulation, which is the main subject of this chapter, we know, mostly from anesthetized preparations, that this modulation can be rather local and that it may affect in a differential manner the synaptic effectiveness of different collaterals of the same afferent fiber. This allows the intraspinal arborizations of the sensory fibers to function as dynamic substrates in which information flow can be directed to specific targets, depending, at least in principle, on the task to be performed. Work performed in humans during the execution of voluntary movements has provided convincing evidence on such a differential control, in this case of the synaptic effectiveness of muscle spindle afferents, but very little is known on the differential modulation of the synaptic effectiveness of Ib, group II, articular and cutaneous afferents in humans. Research in monkeys has indicated that the synaptic effectiveness of the cutaneous afferents is reduced during the active contraction of the arm muscles and that this inhibition is associated with increased PAD, but no information is available on a possible differential control of the information transmitted under these conditions. Information on the involvement of GABAb receptors in motor performance or in sensory discrimination is also scarce.

Seen in perspective, there are important issues on the role of the GABAergic presynaptic modulation of the synaptic effectiveness of sensory fibers, both during the execution of movements and during sensory discrimination that still need to be clarified. For example, it has been established that many second order neurons receive converging information from both muscle spindle and tendon organs. For some time it was believed that separate sets of last order interneurons mediated the PAD of Ia and Ib afferents, thus allowing an independent control of the information on muscle length and muscle tension provided by these receptors, a situation of possible relevance during the performance of specific motor tasks (Rudomin et al. 1983). However, it is now clear that muscle spindles as well as tendon organs have similar PAD patterns, but it is still unknown if these patterns result from activation of common or from separate sets of last order GABAergic interneurons, and how these sets are activated during voluntary isometric or isotonic contractions.

A related issue is whether the sets of dorsal horn neurons affecting transmission along the PAD pathways are organized in a modular or in a distributed fashion and the extent to which this organization is reflected in the control of the synaptic effectiveness of the afferent fibers and in the activation of their target neurons, including motoneurons. The development of computational models considering these two possibilities could perhaps throw some light on their implications on the central control of the information generated by the peripheral receptors under normal and pathological conditions.

Last but not least, it must be emphasized that presynaptic inhibition is not only engaged with the control of sensory information from muscle, skin and articular receptors during the planning and execution of voluntary movements. It has also a relevant role in the spatial and temporal focusing of tactile information at spinal levels, as initially proposed by Schmidt and colleagues, but also with the shaping of the sensory information conveyed to the cerebral cortex and

other rostral structures. In this regard, it is tempting to consider that the GABAa interneurons synapsing with the intraspinal terminations of the sensory fibers have other functional roles besides reducing the synaptic efficacy of the afferent fibers. For example, one could speculate that they function as a mechanism that introduces correlated noise to specific sets of intraspinal collaterals of afferent fibers and changes, in a rather selective manner, the information transmitted along these channels (Rudomin and Madrid 1972). Yet, further studies are required to disclose the implications of these correlated influences on motor performance and sensory processing and their role in shaping of a higher coherence between the cortically programmed and the executed movements.

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