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Review

Cutaneous silent periods – Part 1: Update on physiological mechanisms

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HIGHLIGHTS

- Review of stimulation and recording techniques for cutaneous silent period (CSP).
- Review of functional anatomy, neurophysiology, and neuropharmacology of CSPs.
- Understanding principles of CSP testing is fundamental for its clinical application.

ABSTRACT

Testing of exteroceptive electromyographic modulation of ongoing voluntary muscle activity is of interest in normal human physiology and in diagnostic clinical neurophysiology in normal and pathological conditions. The cutaneous silent period (CSP) is a robust and reproducible nociceptive EMG suppression, mediated at the spinal level by small-diameter A-delta afferents. This critical review surveys the literature on applied stimulation and recording techniques, physiological principles, involved fiber types, spinal circuitry, supraspinal modulation, neurotransmitters and pharmacology of CSPs. Understanding the principles of CSP testing is fundamental for a valid and thoughtful clinical application of CSPs (reviewed in part 2) (Kofler et al., 2019).

Contents

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1. Introduction

1.1. Definitions

Stimuli delivered at distal sites of upper or lower limbs influence the EMG activity related to voluntary contraction in muscles of the same or other extremities after sensorimotor integration at various levels of the central nervous system. Such influence is evident in relatively complex responses, which have received various names, depending on the stimulus modality and response characteristics. Transient inhibition caused by peripheral nerve stimulation is termed exteroceptive electromyographic (EMG) suppression. Such a reduction in EMG activity – either complete or incomplete – is common to a variety of external stimuli, e.g. mechanical, via stretching the muscle tendon, or electrical, via stimulation of cutaneous or mixed nerves located in the same or a neighboring dermatome (Shahani and Young, 1973). The first description of exteroceptive suppression originates from Hoffmann (1922) who studied the effect of an electrically induced muscle twitch during volitional EMG activity. Later, Caccia et al. (1973), McLellan (1973), and Kranz et al. (1973) contributed substantially to the understanding of its physiological mechanisms. The amount of EMG modulation depends mainly on stimulus intensity, site of stimulation, and muscle recorded from.

Electrical stimulation to a peripheral nerve may induce short- and long-latency (or long-loop) reflexes (SLRs, LLRs), of which those induced by cutaneous nerve stimulation are usually called cutaneomuscular reflexes (CMRs). These CMRs consist of both excitatory and inhibitory reflex components. A particularly strong inhibition of EMG activity is caused by electrical stimuli of relatively high intensity to cutaneous fibers at the fingers, which has been termed cutaneous silent period (CSP) (Shahani and Young, 1973). Thus, a CSP is identified by a relative or absolute transient decrease in the voluntary EMG activity following noxious stimulation of a nearby cutaneous nerve. This inhibitory reflex is considered to be mediated at the spinal level, with an afferent arch supplied by A-delta fibers and an efferent arch supplied by alpha-motoneurons (Uncini et al., 1991; Leis et al., 1992; Shefner and Logigian, 1993). An example is shown in Fig. 1A.

Since the early descriptions of CSPs (Shahani and Young, 1973; Caccia et al., 1973; Kranz et al., 1973) much knowledge has accumulated on functional anatomy and physiology of this neurophysiological phenomenon, as it has been thoroughly studied in health (37 original publications) and disease (66 original publications). Therefore, it seems timely to review and summarize what is known to date, and to speculate on what is still missing in the field of CSPs. The publications included in this review were consecutively collected over the past 25 years by one of the authors (MK), with the addition of those found after database search (Medline, Web of Science) and screening abstract books on the topic, published after conferences and meetings. Publications were included if the authors used the CSP in human studies. Experimental studies in animals were only included if they were judged relevant for understanding findings in humans.

1.2. Stimulation and recording techniques

1.2.1. Electrical stimulation of cutaneous nerves

In order to record upper limb CSPs, cutaneous nerves of one finger are typically stimulated electrically using ring electrodes, with the anode applied to the distal phalanx and the cathode to the middle phalanx, in order to stimulate the most distal aspect of the digit. Adhesive tape may be helpful to secure the electrodes and to prevent them from slipping, when applied as distally as possible.

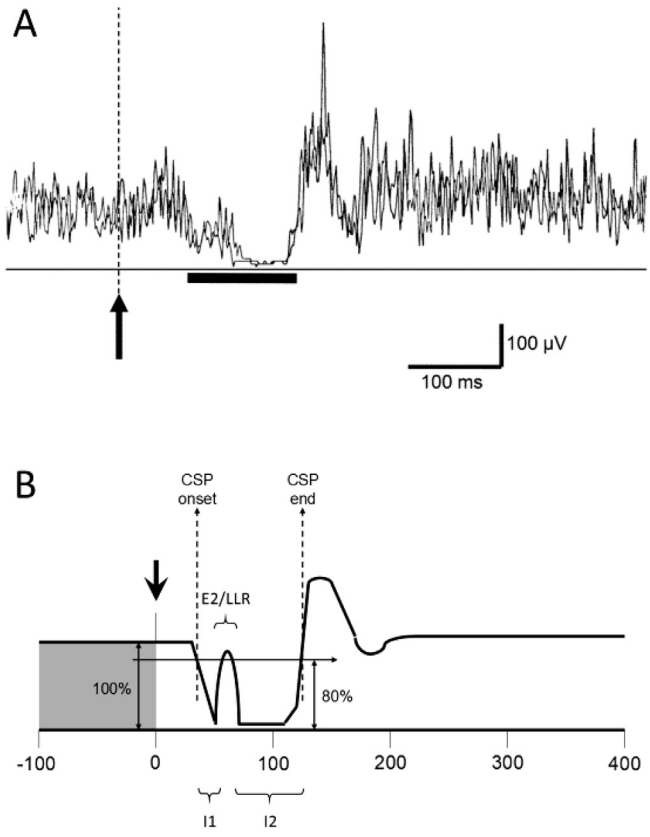

Fig. 1. Representative example of a normal cutaneous silent period (CSP), recorded from abductor pollicis brevis muscle following noxious index finger stimulation at 20x sensory threshold intensity; the arrow indicates stimulus onset; the bar below the baseline depicts the CSP (A). The lower panel (B) shows how CSPs may be defined by 80% of average baseline activity: E2/LLR is the excitatory component interrupting the CSP in certain finger-muscle combinations; I1 and I2 are the inhibitory periods before and after the LLR (if present).

1.2.1.1. Physical and physiological aspects of stimuli. ***Stimulation site.*** In 91 original publications about upper limb CSPs providing information on stimulation site, the index finger (D2) was used in 68, followed by the little finger (D5) in 29 papers. D3, D1, and D4, superficial radial nerve, hand dorsum and palm (C8 dermatome), lateral aspect of upper arm (C5 dermatome), musculocutaneous nerve, and contralateral D2 and D5 were studied in 8 or fewer publications each (for exact number and percentage of publications and respective references see Supplementary Table 1A). Occasionally, in order to achieve spatial summation, more than one finger was stimulated simultaneously. However, as stimulation at different locations may elicit slightly different CSPs (Kofler, 2003), this technique cannot be routinely recommended, except in cases of severe small-fiber neuropathies requiring spatial summation in order to elicit any measurable CSP at all (Corsi et al., 2002).

CSP have been less frequently studied in the lower limbs (24 publications), most often following stimulation of the sural nerve, and occasionally of the superficial peroneal nerve, big toe, or lateral femoral cutaneous nerve (Supplementary Table 1B).

Stimulus intensity is positively related to the presence of CSPs (Kofler, 2003; Kofler et al., 2004) and to the duration (Uncini et al., 1991; Shefner and Logigian, 1993; Inghilleri et al., 1997; Leis et al., 2000; Serrao et al., 2001; Kofler, 2003; Svilpauskaite et al., 2006b; Kim et al., 2009; Rodi and Springer, 2011) and depth of EMG suppression (Leis et al., 2000; Kofler, 2003; Kofler et al., 2004; Rodi and Springer, 2011). With increasing stimulation intensities, CSP onset latency shortens (Shefner and Logigian, 1993; Serrao et al., 2001; Kofler, 2003; Svilpauskaite et al., 2006b; Rodi and Springer, 2011) and CSP end latency lengthens (Kofler, 2003; Rodi and Springer, 2011) in hand muscles. Therefore, it is important to standardize stimulus intensity for adequate comparison of recordings among patients and centers. One way is to define stimulus intensity with respect to sensory threshold (ST). ST is defined as the lowest stimulus intensity that the subject can perceive, usually in 50% of stimulations (i.e. 3 out of 6, or 4 out of 8, or 5 out of 10 stimulations). When testing ST, care should be taken to avoid temporal summation by applying more than four repetitive stimuli of any given intensity at any single site (Kofler, 2003; Yoon et al., 2011). In situations when ST cannot be established, an alternative could be application of an intensity that would be clearly supramaximal for a sensory nerve action potential (Shefner and Logigian, 1993; Inghilleri et al., 1997). Subjective discomfort associated with high-intensity stimulation can be reduced by applying weak prepulse stimuli, which induce prepulse inhibition without affecting CSP parameters (Blumenthal et al., 2001; Kumru et al., 2009).

In the available literature, stimulus intensities were provided in 98 original publications, of which 60 reported the use of multiples of ST. Twenty-four papers used fixed intensities, given in mA or V for electrical stimuli, or W for laser stimuli. Eight studies listed stimulus intensities relative to pain threshold, three used multiples of SNAP threshold, and four applied intensities "raised until consistent/clear CSPs" or "maximum CSPs" were generated (for references see Supplementary Table 2). Stimulus intensity should be large enough to depolarize high-threshold, small-diameter A-delta fibers, usually exceeding 8–12 × ST (Shefner and Logigian, 1993), i.e. supramaximal for the respective sensory nerve action potential evoked from large-diameter fibers. Kim et al. (2009) suggested using stimuli of at least 40 mA and at least 0.2 ms duration, while others reported stable CSPs in healthy subjects with intensities of 20 × ST (Pullman et al., 1996; Kofler, 2003) and 0.5 ms constant current square wave pulses. Intensities of 10 × ST or below would be too low for persistently eliciting stable CSPs (Kofler et al., 2007; Rodi and Springer, 2011). Eight publications (8.2%) reported stimulus intensities below 40 mA, and 19 studies (19.4%) below 15 × ST. Thus, in some studies, the authors might not have employed sufficient intensity to ensure stable and reproducible CSPs (Kofler, 2003; Kofler et al., 2007; Kim et al., 2009; Rodi and Springer, 2011).

Stimulus duration of electrical square waves was reported in 87 original publications on CSPs. Most studies employed stimuli of 0.5 ms or 0.2 ms duration. Fewer studies reported 0.05 ms, 0.1 ms, 0.3 ms, 1 ms, and 5 ms (for references see Supplementary Table 2). Shorter stimulus durations require higher stimulus intensities in order to achieve maximum CSP duration (Serrao et al., 2001; Kim et al., 2009). Sensory afferents respond better to long-duration stimuli than motor axons, which have a lower threshold to short duration stimuli (Panizza et al., 1992; Mogyoros et al., 1996). However, increasing stimulus duration from 0.5 to 1.0 ms did not add further to CSP duration (Kim et al., 2009). Thus, it seems unnecessary to increase stimulus duration beyond 0.5 ms.

Number of delivered stimuli ranges from 1 (Corsi et al., 2002) to 400 stimuli (Rogasch et al., 2012), but in two thirds of 94 studies authors used between 3 and 12 stimuli. The remaining studies reported between 15 and 100 stimuli, and in case of single motor unit recordings up to 400 stimuli (for exact number and percentage of publications and respective references see Supplementary Table 3). The minimum number of stimuli to be delivered in order to yield a valid result has been studied by Stokić et al. (2010), who found that less than 60 and as few as 5 rectified and averaged responses may serve to adequately describe the relationship between stimulus intensity and CSP duration. Hence 20 averages seem to be a good compromise between number of unpleasant stimuli and response variability. A smaller number may suffice in case of very clear and profound inhibition, rendering reliable identification of the period of EMG suppression amid ongoing volitional EMG activity. In case of very short and incomplete CSPs, this clear distinction may not be easily discernible hence a larger number of repetitions may be advisable.

Stimulation rates reported in 78 publications range from single stimuli at random intervals between 5 s and 2 min (67.9%) to stimuli delivered at fixed rates from 0.3 to 1 Hz (30.8%) (for exact number and percentage of publications and respective references see Supplementary Table 3). Recurrent stimulation at 3 Hz (Serrao et al., 2001) and 0.5–5 Hz (Uncini et al., 1991) exerted no influence on CSP parameters. In a paired pulse paradigm, interstimulus intervals ranging from 60 to 100 ms caused a delayed onset and a shorter duration of the second CSP relative to single pulse stimulation (Yoon et al., 2011), while interstimulus intervals from 100 to 500 ms (Uncini et al., 1991; Inghilleri et al., 1997; Serrao et al., 2001; Floeter, 2003; Yoon et al., 2011) had no influence on CSP parameters.

Notably, with recurrent stimulation, frequency should be sufficiently low in order to avoid superposition of inhibitory and excitatory events derived from subsequent stimuli depicted within the same sweep, as the whole sequence of responses may take up to 300 ms (Kofler, 2003; Kumru et al., 2009). Kofler (2003) used sweeps of 500 ms including a prestimulus delay of 100 ms, and a stimulation rate of 0.7 Hz. Occasionally, particularly in case of tremor which may be aggravated by recurrent stimulation, reducing stimulation rate, e.g. to 0.5 or 0.3 Hz (Kofler et al., 2014), or irregular stimulation (Rossi et al., 2000; Rodi and Springer, 2011; Eckert et al., 2016) may be advisable.

1.2.1.2. Physical and physiological aspects of CSP recording. A CSP is identified by a relative or absolute transient decrease in the voluntary EMG activity. A minimum duration of EMG suppression of at least 10 ms to qualify for a CSP was arbitrarily decided in several studies (Leis et al., 2000; Serrao et al., 2001, 2002; Kofler, 2003; Rossi et al., 2003; Kofler et al., 2004; Yoon et al., 2011); one study excluded inhibitory periods of less than 20 ms (Don et al., 2008), another one less than 5 ms (Eckert et al., 2016). In our opinion,

CSPs shorter than 10 ms cannot be reliably discerned and should therefore be classified as absent.

Presentation of CSPs recordings may be as single trace, array of traces, superimposed waveforms, or as a rectified averaged waveform. In 40 studies of healthy volunteers, single sweeps were recorded in 10 reports (25.0%), and rectified averaged waveforms in 29 papers (72.5%). One study (2.5%) reported single trace recording with post-hoc averaging. In contrast, in 59 patient studies, single sweeps were recorded and displayed in 39 reports (66.1%), but rectified averaged waveforms in only 16 papers (27.1%). Four studies (6.8%) reported single trace recording with post-hoc averaging (for respective references see Supplementary Table 4).

Single sweeps, either superimposed or displayed as an array, were more likely to be associated with fewer than 10 stimuli, often delivered at random, in clinical studies of patients. In contrast, rectified and on-line averaged traces were more often associated with more than 20 stimuli, delivered in fixed repetition rates, in research studies of healthy subjects.

Muscle force may have an influence on the CSP, with CSP end latencies and CSP duration becoming shorter with increasing force levels (Uncini et al., 1991; Shefner and Logigian, 1996; Pullman et al., 1996; Don et al., 2008). Serrao et al. (2001) reported an influence of muscle force on the exteroceptive EMG suppression induced by low-threshold afferents (=CMR). Other studies, however, could demonstrate that muscle activation in the range of 10–60% of maximum voluntary contraction (MVC) did not influence any of the CSP parameters (Kofler et al., 2007; Rodi and Springer, 2011). Even on the small amount of tonic muscle activity that can still be observed at attempted rest (less than 5% MVC), noxious stimuli still gave rise to CSPs of similar latency and duration as compared to those induced in the same muscles when intentionally activated around 25% MVC (Kofler and Poustka, 2005). Only at strong contraction levels (80–100% MVC) the CSP of the first dorsal interosseous became shorter and/or incomplete (Uncini et al., 1991; Serrao et al., 2001; Don et al., 2008).

A force transducer may be helpful to monitor muscle contraction (Manconi et al., 1998; Syed et al., 2000; Leis et al., 2000; Serrao et al., 2002; Kofler et al., 2004, 2007; Osio et al., 2004; Lo et al., 2007a, 2007b; Kumru et al., 2009; Kim et al., 2009; Isak et al., 2011; Rodi and Springer, 2011; Yoon et al., 2011), but concomitant monitoring of the EMG signal – both visually and auditory – is still mandatory to ensure constant and stable muscle activation of the target muscle, in order to exclude that the requested task is actually delivered by remote muscles, e.g. thumb abduction might be supported by elbow flexion or even retraction of the shoulder, which may go undetected by mere force transducer monitoring. One should also bear in mind that prolonged voluntary muscle activation at high force levels may be influenced by muscle fatigue.

Only some 50% of 94 original publications reported force levels in the recommended range of 10–60% MVC (Kofler et al., 2007; Rodi and Springer, 2011), while one third of the studies reported 80–100% MVC, which may have underestimated exteroceptive EMG suppression (for exact number and percentage of publications and respective references see Supplementary Table 5).

Kahya et al. (2010, 2016) used minimum muscle force below 5% MVC in order to "activate 1 or 2 single motor units" for recording peristimulus time histograms and peristimulus frequencygrams. However, although CSP parameters during slight muscle activation were similar to those obtained during moderate activation (Kofler and Poustka, 2005), there may still be significant differences when only 1 or 2 motor units are activated, which may lead to biased conclusions.

Recording muscle can be any one in which surface electrodes are mounted in standard belly-tendon fashion. Most recordings in upper limbs were obtained from ipsilateral thenar muscles, followed by first dorsal interosseous and abductor digiti minimi. Tibialis anterior was the most frequently used muscle in the lower limbs (for exact number and percentage of publications and respective references see Supplementary Tables 6A and 6B).

Filters settings adhere to general recommendations for EMG recordings. Most of the 82 publications providing information about filter settings used a low-pass filter of 30 Hz, as increasing the high-pass filter may help to render a more stable baseline.

1.2.1.3. Response analysis. For clinical purposes, visual inspection of individual traces is usually sufficient to determine whether a CSP is present or not, provided that EMG suppression exceeds 10 ms duration. In our opinion, CSPs shorter than 10 ms cannot be reliably discerned and should therefore be classified as absent.

Latencies and duration may vary from trace to trace, depending on when during its excitation cycle a given motoneuron would be inhibited (Kranz et al., 1973; Uncini et al., 1991). The end of the CSP is typically more consistent across individual traces (Floeter, 2003). Interindividual variability, too, is smallest for CSP end latency (Kofler et al., 2007, 2014; Rodi and Springer, 2011). Hence, some authors elected to use the interval from stimulus artifact to CSP end-point, which they termed "CSP duration", in order to overcome the problem of variable onset latencies (Pullman et al., 1996; Serrao et al., 2002). This may have led to some confusion, as the values obtained this way would have been termed "CSP end latency" by others. Some variability in latency measurements may also be imposed by using different display sensitivities in individual traces. Superposition of CSP traces allows for easier detection of certain characteristics of the CSP waveform, e.g. the presence of excitatory LLRs within the CSP. However, exact quantification of latencies, duration, and amount of suppression relative to background EMG activity can only be achieved after rectification and averaging of a sufficient number of stimuli (Hallett et al., 1994; Floeter, 2003; Kofler, 2003; Stokić et al., 2010). Rectification and averaging further reduces trial-to-trial timing differences (Uncini et al., 1991). In the rectified trace, the beginning and end of the CSP can be defined by quantitative criteria, such as a drop of the EMG trace below 50–100% of the baseline preceding the stimulus, usually 100 ms (Fig. 1 B) (for exact number and percentage of publications and respective references see Supplementary Table 4).

Magnitude of EMG suppression can be expressed as the index of suppression, i.e. the ratio of average EMG amplitude during the CSP divided by the average EMG amplitude during a baseline period (Kofler, 2003, 2004; Kofler et al., 2004, 2007, 2014; Kumru et al., 2009; Rodi and Springer, 2011). Others reported the reciprocal value of the index of suppression (Nakashima and Takahashi, 1992). EMG suppression can also be quantified by estimating the area by which the ongoing EMG is reduced (Leis et al., 2000; Floeter, 2003; Osio et al., 2004) by calculating the formula "CSP area divided by prestimulus area times 100", or "100 minus index of suppression times CSP duration" (Kofler and Poustka, 2004). Area measurements can also be used to quantify the post-inhibitory EMG rebound following the CSP (Uncini et al., 1991; Floeter, 2003; Kumru et al., 2009).

The degree of reproducibility of CSP recordings was remarkably high in repeat studies, either performed serially three times every 15 minutes (Kofler, 2004), or some 1–2 years apart (Pullman et al., 1996; Kofler, 2003).

1.2.1.4. Single motor unit recordings. Important information on the physiological basis of exteroceptive motoneuron inhibition can be derived from single motor unit recordings. Kranz et al. (1973) observed that the time to onset of inhibition is variable for any given motoneuron and depends on (1) the conduction velocity of the efferent alpha-motoneuron, (2) on the timing when the afferent inhibitory impulse arrives in relation to the discharge of the

motoneuron, as the afferent input produces more inhibition when it hits the motoneuron later in its excitation cycle, and (3) on the discharge rate of a given motoneuron, as shorter inhibition is induced on motoneurons which fire faster. Thus, successive identical stimuli may exert different effects even on the same motoneuron (Kranz et al., 1973).

Kahya et al. (2010, 2016) presented *peristimulus time histograms* and *peristimulus frequencygrams* to visualize motoneuron discharges with wire electrodes in the first dorsal interosseous muscle following noxious stimulation to the hand dorsum with either electrical (Kahya et al., 2010) or laser stimuli (Kahya et al., 2016). They concluded that probability-based analysis methods (surface EMG and peristimulus time histograms) best reflect the onset of the CSP, while frequency-based analysis methods (peristimulus frequencygrams) better indicate the end of the CSP. While this may well be the case, the combination of two different methods for the assessment of CSP duration may lead to confusing results, as the physiology underlying each method is different. In fact, frequency determination requires at least two events and, therefore, the instantaneous frequency will be available only when the second event has been produced. On the contrary, rectified and averaged EMG activity (and peristimulus time histograms) reveal the instantaneous motoneuron firing. As a consequence, both declines and increases in discharge rate, will become apparent later in frequency-based than in probability-based analysis methods.

Also, in the lower extremities, peristimulus-time histograms and peristimulus-frequencygrams were applied for exteroceptive EMG suppression in gastrocnemius muscle following electrical stimulation over the Achilles tendon and over the sural nerve (Rogasch et al., 2011, 2012).

1.2.2. Other types of stimulation

1.2.2.1. Stimulation of mixed nerves. When stimulating a ***mixed nerve*** during sustained voluntary contraction of the muscle supplied by that nerve, EMG activity undergoes several phases of transient suppression (Merton, 1951). This so-called mixed nerve silent period (MNSP) is comprised of at least 3 periods of EMG suppression (Leis et al., 1991; Leis and Kofler, 2014; Leis, 1994). The first one results from collision of electrically evoked antidromic with volitionally induced orthodromic motor impulses (Merton, 1951; Shahani and Young, 1973), and ends with the appearance of F-wave or H-reflex (Leis et al., 1991; Leis, 1994). The second portion of the MNSP corresponds to the segment from the end of the F-wave or H-reflex to the beginning of what has been designated the 'long-loop reflex' (LLR). This segment of the MNSP has been attributed to Renshaw cell inhibition. It has been found reduced in patients with amyotrophic lateral sclerosis, which the authors attributed to abnormalities of Renshaw cell function (Shefner and Logigian, 1998). However, a precise physiological description of the role of Renshaw cells in CSP generation remains to be elucidated, and researchers must take into account that motoneurons innervating certain distal muscles (in the cat) may lack Renshaw cell inhibition (Illert and Wietelmann, 1989; Hörner et al., 1991). The excitatory EMG component between the second and third period of inhibition of the MNSP may be of various origins. The nomenclature may vary according to the method of stimulation and other features: V2 (Upton et al., 1971; Stanley, 1978; Leis, 1994); V response (McLellan, 1973); E1 (Caccia et al., 1973; Eckert et al., 2016); C-reflex (Sutton and Mayer, 1974); cortical response (Shibasaki and Kuroiwa, 1975); C response (Conrad and Aschoff, 1977); E2 (Jenner and Stephens, 1982; Chen and Ashby, 1993); R2 (Eisen et al., 1984); long-loop or long-latency reflex (Deuschl et al., 1985; Deuschl and Eisen, 1999); M2 response (Claus et al., 1986; Rothwell, 1998). Most authors attributed this EMG activity to an excitatory transcortical LLR, which requires intact afferent and efferent conduction along large myelinated fibers. However, the presence of clearly defined LLR activity in two patients with severe sensory neuropathy, who lacked sensory nerve action potentials and somatosensory evoked potentials (SEPs), suggests that this activity may reflect the return of voluntary potentials conducted through normal motor fibers rather than reflex activity that is dependent on preserved afferent conduction. Indeed, the duration of the LLR appears to be related to the timing of the third portion of the mixed nerve SP. Conditions that delay the onset of the third portion, as in patients with some forms of pure sensory neuronopathy, may prolong the LLR by delaying its endpoint. The greater the delay in the third inhibitory period, the later the end point of the LLR (Leis, 1994). The third segment of the MNSP is mediated by afferent impulses carried in higher threshold slower conducting A-delta fibers within the mixed nerve. This concept is supported by shorter latencies of EMG suppression with more proximal stimulation (Leis et al., 1991), and by persistence of silent periods in studies devoid of motor axon activation either due to stimulus intensities below motor threshold (Leis et al., 1991), or after employing selective nerve blocks (Leis et al., 1991), or following stimulation to a non-homonymous nerve, e.g. ulnar nerve while recording from abductor pollicis brevis (Leis et al., 1991). Notably, this part of the MNSP was absent following stimulation distal to a lidocaine block despite inducing a muscle twitch (Leis et al., 1991). Furthermore, there is evidence that conduction abnormalities that selectively delay or abolish the third portion of the MNSP also delay or abolish the CSP (Leis, 1994; Inghilleri et al., 1995; Štětkářová et al., 2001; Štětkářová and Chrobok, 2002). The main difference between the CSP and the third part of the MNSP is the contribution of muscle afferents to the MNSP, which may not only play a role in the reflexive generation of exteroceptive EMG suppression but could also induce presynaptic modulation of afferent inputs from smaller fibers. The fact that nerve fibers innervating the skin of the fingertips, which are known to produce the CSP, are also activated during more proximal stimulation of the homonymous mixed nerve, is a strong argument to support the idea that the third portion of the MNSP corresponds to the CSP (Leis et al., 1991; Leis, 1994; Štětkářová et al., 2001). This concept has recently been questioned by Cogez et al. (2016), who were unable to demonstrate consistent overlap of CSP and MNSP in two patients with symptomatic paroxysmal kinesigenic dyskinesia. Certainly, these findings warrant further documentation.

1.2.2.2. Other stimulus modalities and special cases. Silent periods can be induced by a variety of stimuli. In most instances, though, the following stimulation modalities have been used only in the context of physiological studies, with only limited clinical applicability at present.

Mechanical taps induce silent periods when applied to tendons (Hoffmann, 1922), fingertips (Caccia et al., 1973; Garnett and Stephens, 1980; Gutierrez et al., 2014), and muscle belly (Garnett and Stephens, 1980).

Electrical stimulation of tendons induced transient suppression of voluntary EMG activity in forearm extensor muscles, which was previously attributed to activation of a polysynaptic inhibitory pathway mediated by Ib afferents originating from Golgi organs (Burne and Lippold, 1996). Similar stimulation nearby, but not directly overlying the tendon, failed to elicit an EMG suppression, whereas stimulation following ischemia-induced nerve-block to large-diameter fibers, as well as double pulse stimulation, produced unaltered EMG suppression, concurring with activation of slow-conducting tendon afferents, possibly group III fibers, connected through an oligo- or disynaptic inhibitory spinal circuit (Priori et al., 1998). Also, in the lower limbs, electrical stimulation over the Achilles tendon produced exteroceptive EMG suppression in medial and lateral gastrocnemius, however, at different latencies

as compared to EMG suppression following noxious sural nerve stimulation (Khan and Burne, 2009, 2010). This was later confirmed in single fiber recordings by peristimulus time histograms and peristimulus frequencygrams (Rogasch et al., 2011, 2012).

Laser stimuli activate myelinated type I and type II A-delta mechano-heat nociceptors (AMH I, AMH II) and unmyelinated C mechano-heat nociceptors without skin contact. The latter conduct too slowly to contribute to the CSP in the time window of electrically evoked nociceptive EMG suppression (Romaniello et al., 2004). AMH I units require long-lasting heat stimuli, hence their heat-related response has a delay in the order of seconds (Treede et al., 1998). Yet they have lower mechanical thresholds and higher conduction velocities than AMH II units. On the other hand, AMH II units respond to short-lasting heat stimuli with short latencies (Treede et al., 1998). Thus, due to their respective receptor characteristics, AMH I units respond first to mechanically-induced pain, whereas AMH II units respond first to heat-induced pain (Treede et al., 1995). Laser-induced heat alone is considered insufficient to evoke AMH I responses, but rapid heat-induced evaporation of water from the outer layers of skin may serve as a mechanical stimulus to activate AMH I units (Romaniello et al., 2004). Thus, both AMH I and AMH II units may contribute to CSP generation via different mechanisms, but exact onset times of their respective actions following a laser pulse are difficult to ascertain. Laser stimuli delivered to the palm of the hand elicited silent periods in first dorsal interosseous (Romaniello et al., 2004; Kahya et al., 2016), whereas stimulation to the hand dorsum and foot dorsum failed to do so (Rossi et al., 2000; Romaniello et al., 2004). Also, in our own experience, both laser and contact heat stimuli on the dorsal aspect of hand and forearm failed to induce reproducible and consistent silent periods in hand muscles (personal observation by Valls-Solé and Kofler). Unlike electrical square wave stimuli, which generate a very synchronized afferent volley, heat stimuli are long-lasting and, thus, may not be able to create a sufficiently synchronized afferent volley for generating a silent period (see for discussion on short- versus long-lasting stimuli also Castellote et al. (2017)).

Cranial nerve mediated silent periods need to be addressed separately from those of limb muscles. Trigeminal nerve stimulation produces periods of exteroceptive EMG suppression in a variety of cranial muscles, e.g. masseter and temporalis, which, however, differ considerably from CSPs in limb muscles. In contrast to CSPs in limb muscles, which are typically unilaterally wired (Kofler and Poustka, 2005), a unilateral stimulus to either mental or infraorbital nerve induces two bilateral periods of exteroceptive inhibition, termed I1 and I2, or ES1 and ES2. While the pathways for I1 overlap considerably with those for the R1 component of the blink reflex, the I2 circuit corresponds anatomically in part to the R2 circuits (Cruccu et al., 2005). Both periods of inhibition are induced by A-beta fiber activation (Cruccu and Ongerboer de Visser, 1999), yet are mediated by two different neural circuits (Cruccu et al., 1984). Whether the exteroceptive silent period in thenar muscles following supraorbital nerve stimulation (Uncini et al., 1991) follows the rules of bilateral brainstem reflexes or rather those of unilateral spinal reflexes (CSP) remains to be elaborated.

2. Physiology of cutaneous silent periods

2.1. Physiological principle of CSP: protective reflex

The CSP represents a spinal inhibitory reflex mediated primarily by small-diameter, slow-conducting A-delta fibers (Uncini et al., 1991; Leis et al., 1992; Shefner and Logigian, 1993; Leis, 1994; Inghilleri et al., 1997; Kofler et al., 2001a; Kofler, 2003; Romaniello et al., 2004). Upper limb CSPs constitute the inhibitory part of a complex pre-attentional protective reflex mechanism (Inghilleri et al., 1997; Leis et al., 2000; Kofler, 2003; Kofler et al., 2004), which operates in a timely manner with excitatory cutaneous withdrawal reflexes that serve to retract the hand away from a noxious stimulus (Floeter et al., 1998; Rossi et al., 2003). Both inhibitory and excitatory reflex components seem to share common spinal neural circuitry which is activated by high-threshold, small-diameter fibers (Kofler et al., 1998; Rossi et al., 2003). The basic physiological background of CSPs seems to be the simplification of complex motor behavior by simply 'turning off' muscle synergies (Leis et al., 2000).

Several features of CSPs corroborate their potential role in protective reflex physiology. The topographic distribution of CSPs in the human upper limb fits well with a protective purpose, as CSPs show distinct timing and magnitude in different hand muscles: noxious fingertip stimulation preferentially inhibits contraction of synergistic muscles involved in prehensile pinch and grasp, while concomitant activation of low-threshold afferents produce excitation presumably via a transcortical route which may allow for adjusting grip force and performance of explorative movements (Kofler, 2003). CSPs are more pronounced in hand, forearm, and arm muscles involved in reaching, grasping, and pinching objects (e.g. thenar, first dorsal interosseous, flexor digitorum superficialis, triceps brachii) than in muscles involved in withdrawal (e.g. extensor digitorum communis, biceps brachii, brachioradialis, and deltoid) (for references see Supplementary Table 6A). In fact, biceps brachii and brachioradialis hardly ever show any EMG suppression (Inghilleri et al., 1997; Leis et al., 2000; Kofler et al., 2001a; Serrao et al., 2001; Don et al., 2008; Eckert et al., 2016). Hence there is no simple distal to proximal gradient of EMG attenuation (Leis et al., 2000). CSPs can be produced by laser stimulation of the palm, but not the hand dorsum, compatible with reflexively releasing a potentially noxious source (Romaniello et al., 2004). CSPs can be easily elicited following noxious stimulation to any ipsilateral fingertip, yet with subtle differences among different fingers, as e.g. CSP duration in abductor pollicis brevis was longer following D2 than D5 stimulation (Svilpauskaite et al., 2006b; Kofler et al., 2007), while in abductor digiti minimi it was longer following D5 than D2 stimulation (Svilpauskaite et al., 2006b). CSPs cannot readily be evoked following stimulation to the proximal arm (Inghilleri et al., 1997; Leis et al., 2000), chest wall (Leis et al., 2000), or a contralateral fingertip (Leis et al., 2000; Kofler and Poustka, 2005; Svilpauskaite et al., 2006b). While fingertip stimulation induced a CSP in masseter (Uncini et al., 1991), it failed to produce CSPs in orbicularis oculi (Uncini et al., 1991; Inghilleri et al., 1997), a muscle in which protective reflexes are associated with eye closure. CSP onset latencies and magnitude of EMG suppression differ slightly among various hand muscles supplied by the same myotome, indicating a functional organization of the underlying spinal circuitry that is not based on a mere anatomical metameric order of activation but rather on the functional relevance of the respective 'input-output units', which consist of corresponding digit and hand muscle (Kofler, 2003; Kofler et al., 2008). The latter is supported by a different time course of nociceptive MEP modulation at rest in abductor pollicis brevis versus abductor digiti minimi following either D2 or D5 stimulation (Kofler et al., 2001a; Urban et al., 2004). CSP latencies in different upper limb muscles also concur with a protective reflex, with earlier inhibition in distal hand muscles involved in grasping as compared to later facilitation in proximal flexor muscles, e.g. biceps brachii, which is involved in retraction of the hand from the noxious stimulus (Kofler et al., 2001a; Kofler, 2003; Urban et al., 2004). CSP onset occurs earlier than volitional activation of antagonist muscles (Uncini et al., 1991), or voluntary muscle relaxation in the target muscle in

reaction time paradigms (Caccia et al., 1973; Uncini et al., 1991; Leis et al., 2000). Furthermore, CSPs do not habituate (Uncini et al., 1991; Inghilleri et al., 1997; Serrao et al., 2001; Floeter, 2003; Yoon et al., 2011), which is an important feature when it comes to protect the hand from repeated noxious stimuli.

2.2. Evidence for A-delta fiber involvement in CSP generation

Stimulus intensities required to induce a clear CSP need to be at least unpleasant or painful, compatible with the activation of A-delta fibers (Uncini et al., 1991; Shefner and Logigian, 1993; Inghilleri et al., 1997; Kofler et al., 2001a; Kofler, 2003). The same intensities were needed to induce corresponding nociceptive modulation of MEPs at rest (Uncini et al., 1991; Inghilleri et al., 1995; Kofler et al., 2001a, 2008). When eliciting CSPs at different locations along a nerve, e.g. wrist versus elbow versus upper arm, calculated *conduction velocities* were on average 12 m/s (range 9–18 m/s) (Inghilleri et al., 1997) and 12.5 ± 2.1 m/s (Lopergolo et al., 2015) based on CSP onset latencies, and 10 to 15 m/s based on CSP end latencies (Leis et al., 1991), i.e. in the range of A-delta fibers. These values concur well with the appearance of slowly conducting late components following the "standard" sensory nerve action potential in near-nerve needle recordings in sural nerve, revealing conduction velocities around 15–20 m/s, that were not observed with stimulus intensities below 10 × ST (Shefner and Logigian, 1993). Comparison of afferent conduction times (i.e., CSP latency minus efferent conduction time, based on F wave latency) in upper and lower limbs, and respective distances of stimulation sites from the spine, also yielded conduction velocities of 13 m/s (Uncini et al., 1991). When electrical motor-root stimulation was applied to obtain efferent conduction times, estimated afferent conduction velocity amounted to 13.6 m/s (Lopergolo et al., 2015).

Ischemia-induced nerve block of large-diameter fibers did not eliminate the CSP (Serrao et al., 2001). Further evidence for the role of A-delta fibers in CSP generation derives from studies demonstrating the influence of *limb temperature* on CSP latencies (Kofler et al., 2014) and the influence of *local anesthesia* on CSP (Leis et al., 1991; Mota et al., 2015), both showing differential effects on large- and small-diameter fibers. *Laser stimuli*, which selectively activate A-delta fibers, were able to elicit CSPs in few studies (Romaniello et al., 2004; Kahya et al., 2016). Finally, CSPs may be normally preserved in patients with severe neuropathy of large-diameter fibers (Uncini et al., 1991; Leis et al., 1992; Leis, 1994), while being abnormal in patients with isolated small fiber neuropathy (Syed et al., 2000).

All these features point to a major role in CSP generation of slower-conducting, smaller-diameter A-delta fibers, as classified by Erlanger and Gasser (1937), which range in diameter from 1 to 6 μm, conduct impulses at approximately 10–20 m/s, and correspond to group III afferents in Lloyd's Roman numeral classification (Lloyd, 1943).

2.3. Evidence for contribution of other fiber types to CSP generation

The excitability of a nerve fiber is directly related to its diameter. Axons within a nerve differ markedly in their diameter, and thus in their thresholds for activation and their conduction velocity. A low-intensity electrical stimulus to a cutaneous nerve will generate reflex responses mediated primarily by low-threshold, large-diameter fibers, whereas a high-intensity electrical stimulus to the same nerve will additionally produce responses that are mediated by high-threshold, small-diameter fibers, resulting in a complex superimposed waveform derived from both large-diameter and small-diameter fibers (Inghilleri et al., 1997; Serrao et al., 2001; Floeter, 2003; Mota et al., 2015).

There is indeed evidence suggesting a contribution of large-diameter thick-myelinated afferents to CSP generation. Several studies have reported that low stimulus intensities, around 2 × ST, may produce some inhibition of EMG activity in hand muscles (Uncini et al., 1991; Shefner and Logigian, 1993; Inghilleri et al., 1997; Serrao et al., 2001; Kofler, 2003). The respective onset latency of such "low-threshold" exteroceptive EMG suppression was some 10 ms longer than that of the corresponding CSP, exhibited rapid habituation, and could be blocked by ischemia (Serrao et al., 2001). Heterotopic painful stimulation inducing diffuse noxious inhibitory controls had no influence on this "low-threshold" inhibition, while significantly shortening the CSP to high-intensity stimulation (Rossi et al., 2003). The preservation of a short (and late) period of EMG suppression following local anesthesia when subjects no longer perceived pain, suggesting that most fibers conveying pain were actually blocked, also concurs with some contribution of large-diameter fibers to exteroceptive EMG suppression (Mota et al., 2015).

The above data indicate that both low- and high-threshold cutaneous afferents contribute to EMG inhibition with a similar timing, but mediated by distinct neural circuitry (Floeter, 2003; Kofler, 2004; Mota et al., 2015). Alternatively, high- and low-threshold afferents could converge on a common pathway that is only weakly activated by low-threshold afferents (Floeter, 2003).

These findings also concur with generation of some form of MNSPs following low-intensity stimulation to the median nerve sufficient to elicit an H-reflex, but below the threshold for elicitation of a direct muscle response (Leis et al., 1991).

Notably, studies of conditioned MEPs at rest revealed that such a contribution of large-diameter fibers to exteroceptive inhibition was particularly evident following D2 stimulation in thenar muscles, but not in abductor digiti minimi, biceps and triceps brachii muscles, while MEP latency facilitation was seen in all four muscles at ISI 60 ms, but not at longer ISI, compatible with a transcortical excitatory effect mediated by large-diameter fibers (Kofler et al., 2001a).

Interestingly, cortical silent periods may be readily evoked in patients with complete absence of CSP and MNSP due to syringomyelia (Štětkářová et al., 2001), implying that there may be another separate spinal inhibitory network for the purported spinal part of the cortical silent period (Fuhr et al., 1991; Ziemann et al., 1993) that is disparate from the spinal inhibitory network for both CSP and MNSP.

2.4. Excitatory components within and following the CSP

In the human upper limb, a high-intensity electrical stimulus applied at the fingertip elicits a CSP, attributed to activation of A-delta fibers, and a CMR, attributed to low-threshold cutaneous afferents. Low-intensity electrical stimuli also produce alternating periods of excitation and inhibition (Fuhr and Friedli, 1987; Deuschl and Eisen, 1999). A first inhibitory phase, often termed I1, is usually differentiated from a second phase I2 (Caccia et al., 1973), separated by an excitatory period (Fig. 1A, B). This excitatory period, occurring at a latency of some 60 to 70 ms in hand muscles (Kofler, 2003), corresponds to the LLR (for alternative nomenclature see chapter 1.2.2 on MNSP). This burst is reduced or even abolished by increasing stimulus intensities in distal and proximal muscles (Kofler, 2003; Kofler et al., 2004), and facilitated by increasing voluntary muscle contraction (Nakajima et al., 2006; Kofler et al., 2007). The influence of stimulus intensity, however, suggests that there is in fact only one inhibitory phase which may be interrupted by an LLR as long as the transcortical control over a given muscle is not yet fully overruled by spinally mediated inhibition. When the LLR is finally suppressed by the noxious stimulus, both early and late parts of the same inhibitory phase merge.

This assumption correlates to a long-lasting suppression of MEPs at rest observed in abductor pollicis brevis and abductor digiti minimi in the time range of LLRs following conditioning noxious cutaneous nerve stimulation (Kofler et al., 2001a, 2008).

Notably, this EMG burst remained relatively stable even in the presence of local anesthesia, when small-diameter fibers were already blocked, but large-diameter fibers remained (at least partially) intact (Mota et al., 2015). In contrast, the LLR amplitude decreased following 15 and 30 minutes of high-frequency, low-intensity transcutaneous electrical nerve stimulation (Kofler, 2004).

Occasionally, an LLR remains superimposed upon the initial CSP segment, thereby interfering with CSP onset measurements and resulting in a seemingly delayed CSP onset and shorter CSP duration. Thus, Kofler (2003) suggested classifying CSPs in "early-onset" and "delayed-onset", in order to quantify meaningful group data. The concept of "delayed-onset" CSPs is further supported by profound nociceptive MEP suppression at rest during the time window of the LLR, irrespective of whether the LLR was separating an I1 from an I2 phase ("early onset" CSP), or whether it was superimposed upon the initial CSP segment ("delayed-onset" CSP) (Kofler et al., 2008). Respective cut-off values to differentiate early- from delayed-onset CSPs were published for various muscle-finger combinations (Kofler, 2003). Probability and magnitude of the LLR also vary with stimulus location and recorded muscle. Large LLRs which divided the CSP or delayed its onset were most frequently observed in first dorsal interosseous following D2 stimulation, and abductor digiti minimi following D5 stimulation, while neither were present in abductor pollicis brevis following D5 stimulation, nor in abductor pollicis brevis and abductor digiti minimi with high-intensity D2 stimulation (Kofler, 2003), indicating a functional organization not only of the CSP, but also of the concomitant transcortical LLR.

Post-inhibition facilitation of EMG activity following the CSP occurs regularly at latencies exceeding those of transcortical LLRs (Deuschl and Eisen, 1999). This EMG rebound was somewhat equivocally termed E2 (Caccia et al., 1973; Eckert et al., 2016) and E3 by others (Türker and Powers, 2005). It has been mainly attributed to resynchronization of motoneuronal firing (Kranz et al., 1973), but in the lower limbs has also been suggested to represent a spino-bulbo-spinal reflex mediated by group III afferents (Gassel and Ott, 1970). Kofler and Poustka (2005) postulated occasional startle reflex activity coinciding in time with the EMG rebound, which was later confirmed by prepulse inhibition of the superimposed startle component (Kumru et al., 2009). The EMG rebound was diminished in two patients with Friedreich's ataxia and one patient with chronic idiopathic ataxic neuropathy, possibly due to large-diameter fiber deafferentation and hence lack of muscle afferent input (Uncini et al., 1991).

2.5. Spinal circuitry

Fibers mediating the CSP presumably take a route passing close to the central canal of the spinal cord (Fig. 2). In fact, collaterals and terminal branches of thinly myelinated A-delta fibers end in the dorsal horn in laminae I and V of Rexed. They give rise to propriospinal projections that ascend or descend in the spinothalamic pathways to suppress activity in spinal motor nuclei. Patients with circumscribed spinal lesions involving the spinothalamic tract present with abnormal CSPs (Kaneko et al., 1997; Štětkářová et al., 2001; Štětkářová and Chrobok, 2002; Kofler et al., 2003b). In fact, small centromedullary lesions may even abolish CSPs and MNSPs without affecting somatosensory and motor evoked potentials. Notably, the postsynaptic cervical potential N13 following median nerve stimulation, with its presumed intramedullary generator lateral to the central canal, may remain intact despite complete lack of the CSP (Kofler et al., 2003b).

The CSP may be a consequence of: (1) postsynaptic inhibition of spinal motoneurons; (2) pre- or postsynaptic inhibition of spinal interneurons that relay corticospinal impulses to the spinal motoneurons; (3) presynaptic inhibition of the corticospinal tract; or (4) a combination of these mechanisms. At any rate, propriospinal interneurons play a prominent role in the generation of the CSP. Both presynaptic and postsynaptic inhibitory mechanisms have been proposed to explain EMG suppression by A-delta afferents at the spinal level (Grana, 1994; Leis et al., 1995; Inghilleri et al., 1997; Manconi et al., 1998; Kofler et al., 2008; Khan and Burne, 2010). H reflexes were suppressed during the CSP in both upper (Leis et al., 1995) and lower extremities (Logigian et al., 1999). In contrast, median nerve F waves remained unaltered in the volitionally contracted abductor pollicis brevis muscle during the CSP induced by D5 stimulation in healthy subjects (Leis et al., 1995), concurring with spinal motoneurons remaining excitable to an antidromic volley in motor axons when a conditioning stimulus to a digital nerve profoundly inhibits voluntary EMG activity mediated by the same neurons. Such a finding favors exteroceptive suppression of voluntary EMG activity either by presynaptic inhibition of the corticospinal tract or by inhibition of spinal interneurons that relay the corticospinal signal to spinal motoneurons, whereas postsynaptic inhibition of spinal motoneurons seems less likely (Leis et al., 1995, 1996). Interestingly, conditioning nociceptive fingertip stimulation failed to completely suppress MEPs during the time window of a CSP, both at rest (Inghilleri et al., 1995, 2002; Kofler et al., 2008) and during volitional activity (Uncini et al., 1991), even when the same stimulus was capable of inducing complete silence in the tonically activated muscle. All this suggests that exteroceptive EMG suppression may be directed at an interneuronal (oligosynaptic) rather than at the monosynaptic cortico-motoneuronal connection. The diagrams of Fig. 3 show three possible models for the effects of A-delta afferent inputs to account for suppression of EMG activity while there may be disparate reduction in the size of H reflex and MEP during the CSP.

In contrast, F waves elicited in first dorsal interosseous muscle at rest were suppressed when conditioned by a noxious stimulus to D4 + D5 timed to occur during the time window of the CSP, suggesting a postsynaptic action (Inghilleri et al., 1997). Based on similar suppression of H reflexes and size-matched MEPs following transcranial magnetic stimulation, Manconi et al. (1998) also suggested postsynaptic inhibition of the motoneurons as the predominant underlying mechanism. This notion was challenged, however, by Leis (1998) who provided arguments for why the behavior of the H-reflex, which is known to be subject to exquisite presynaptic control, would not be expected to parallel that of a synchronized MEP. Indeed, Priori et al. (1998) also assessed MEPs and H-reflexes during the CSP and provided experimental evidence of dissimilar behavior of H reflexes and MEPs. They concluded that there was no evidence of postsynaptic inhibition (Priori et al., 1998). Khan and Burne (2010) reported partial inhibition by noxious sural nerve stimulation of both Achilles tendon reflexes and MEPs in medial and lateral gastrocnemii, with a time course resembling exteroceptive inhibition seen in voluntary EMG. These authors attributed the observed suppression to postsynaptic inhibition of motoneurons by cutaneous afferents.

Confounding issues related to H- and F-waves during the CSP are that the F wave occurs at a latency at which the cutaneous part of the MNSP has not yet commenced, and the application of a second stimulus to a mixed nerve to examine the F wave during the CSP may transiently overcome any ongoing postsynaptic inhibition in some motoneurons or may activate non-inhibited motoneurons. Presynaptic inhibition is a well-known feature of large diameter Ia afferents, but so far this has neither been unequivocally demonstrated for descending corticospinal neurons, nor for small-

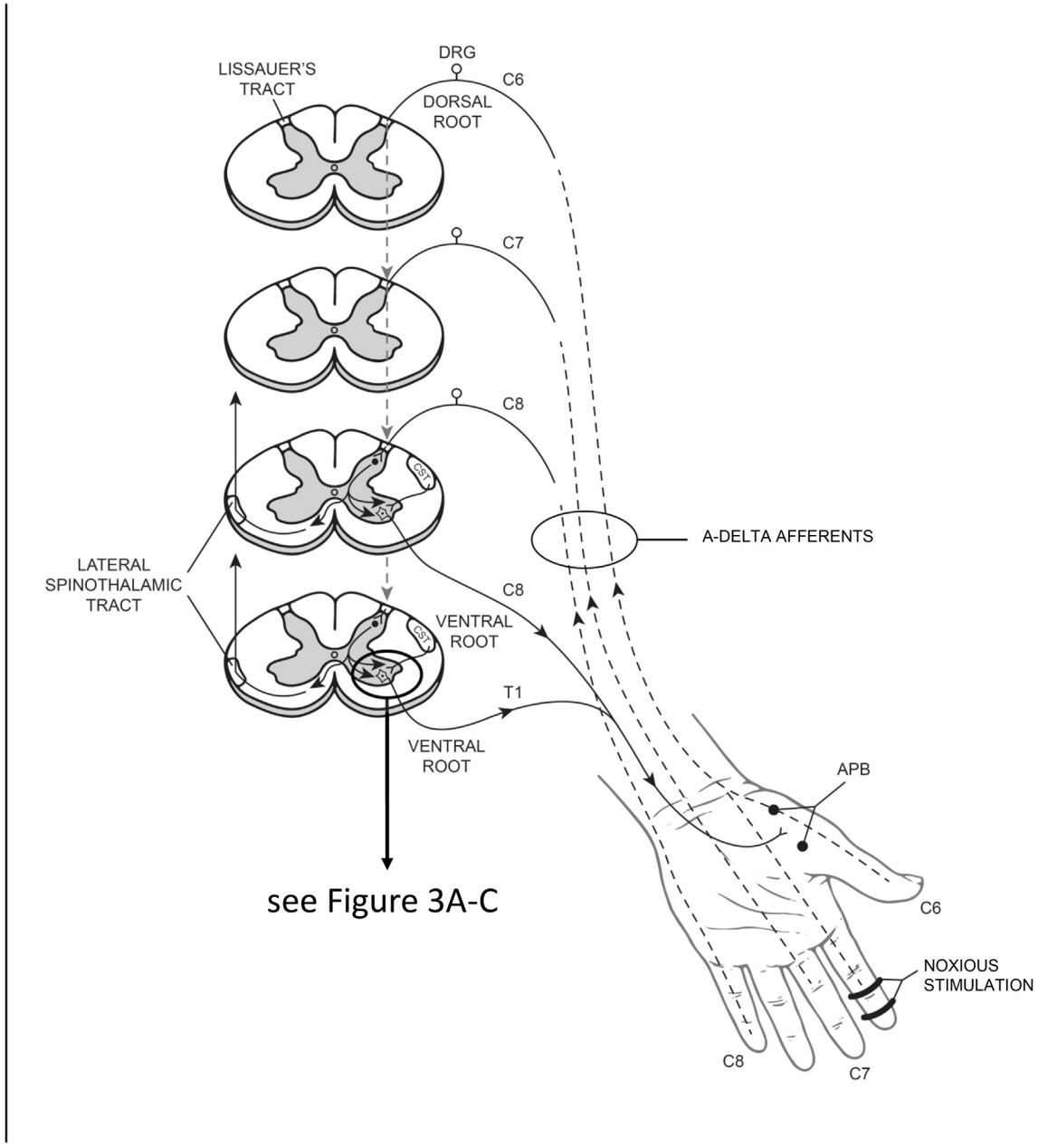

Fig. 2. Diagram of the proposed pathways mediating the cutaneous silent period following noxious digital nerve stimulation. Afferent impulses in thinly myelinated A-delta fibers enter the spinal cord via the lateral portion of the dorsal root, where they descend several segments in Lissauer's tract. Collaterals and terminal branches synapse on dorsal horn cells in laminae I and V of Rexed, where they give rise to propriospinal projections that suppress activity in alpha-motoneurons of limb muscles. APB = abductor pollicis brevis muscle (as one exemplary muscle); DRG = dorsal root ganglion.

diameter A-delta afferents. While presynaptic inhibition by A-alpha afferents upon Ia afferent excitatory input to the motoneuron may indeed diminish some EMG activity, the role of segmental excitatory inputs to maintain contraction are not fully elucidated. It remains unclear whether a similar mechanism is exerted by small-diameter A-delta afferents and, if this is the case, whether it would suffice to explain long-lasting profound inhibition of alpha-motoneurons. There seems to be little role for Renshaw cell inhibition in the context of cutaneous afferents.

Other investigators provided evidence that A-delta afferents in turn may be subjected to presynaptic inhibition by large-diameter afferent fibers. Demonstration comes from the observation that 30 minutes of high-frequency, low-intensity transcutaneous electrical nerve stimulation shortened CSP duration (Kofler, 2004). This was also the case with forearm vibration on CSPs of the abductor pollicis brevis to D2 stimulation (Aydin et al., 2015).

At any rate, the verdict is not yet final on whether the mechanisms leading to EMG suppression during the CSP are presynaptic, postsynaptic, or both. Even if the precise physiologic mechanisms of the CSP remain to be fully elucidated, several tests have been carried out to characterize the reflex circuit. It seems clear nowadays that the circuit is not polysynaptic, as previously suggested (Caccia et al., 1973; Syed et al., 2000). Only one or a few synapses should be involved, since double pulse stimulation with interstimulus intervals ranging from 100 to 500 ms (Uncini et al., 1991; Inghilleri et al., 1997; Yoon et al., 2011), as well as repetitive stimulation of 3 Hz (Serrao et al., 2001) and 5 Hz (Uncini et al., 1991), did not induce any habituation, which would be expected with polysynaptic impulse transmission (Desmedt and Godaux, 1976).

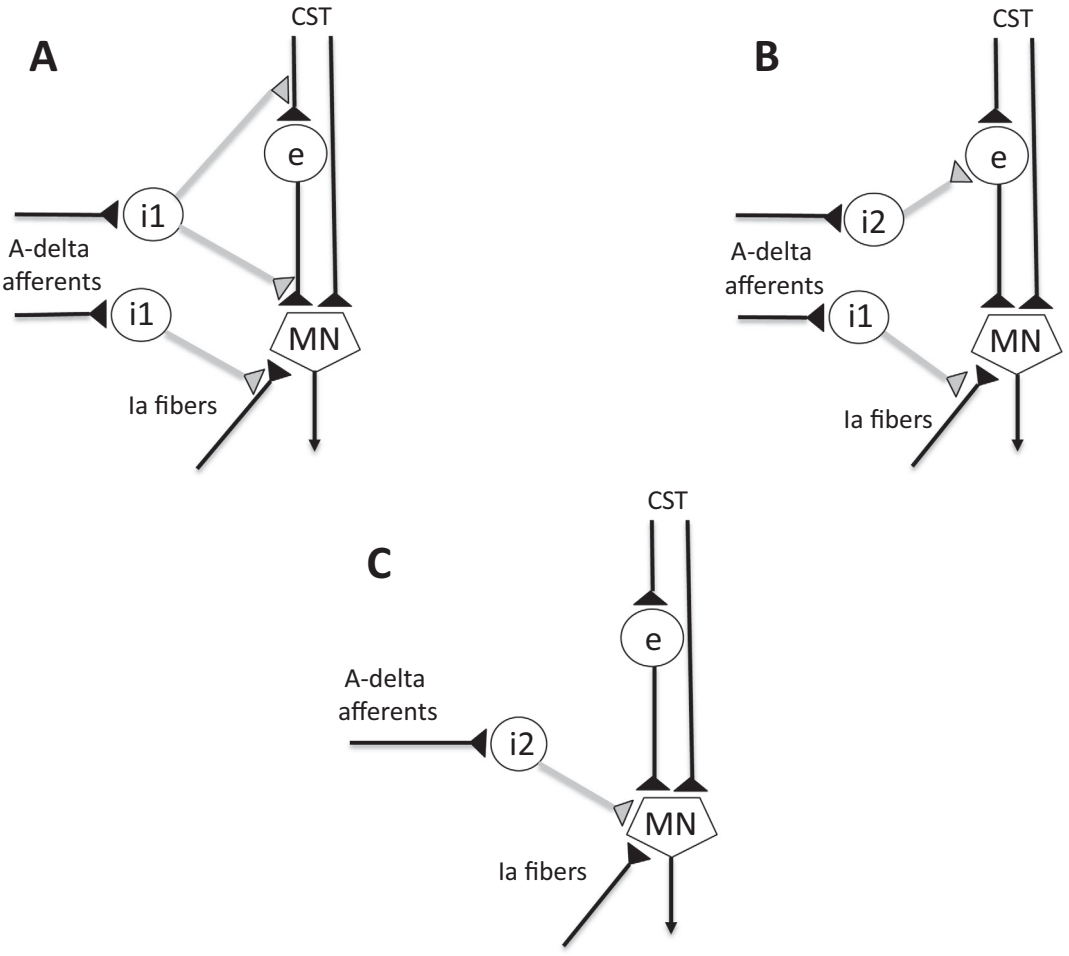

Fig. 3. Three possible models for the effects of A-delta afferent input to account for exteroceptive EMG suppression. A. **Classic presynaptic inhibition**: in this model, cutaneous A-delta afferent impulses from digital nerve stimulation activate interneurons (i1) that presynaptically control the synaptic effectiveness of the corticospinal tract (CST), of excitatory premotor interneurons (e), and of Ia afferent connections (Ia fiber) to the alpha-motoneuron (MN). B. **Inputs to specific interneurons with different roles**: In this model, cutaneous A-delta afferent impulses from digital nerve stimulation activate an inhibitory interneuron (i2), which exerts postsynaptic inhibition onto the excitatory premotor interneuron (e), thereby reducing descending corticospinal drive to the alpha-motoneuron (MN), while Ia-afferent input (Ia fiber, similarly depicted as in A) to the same alpha-motoneuron is presynaptically inhibited by a different inhibitory interneuron (i1). C. **Classic postsynaptic inhibition**: In this model, cutaneous A-delta afferent impulses from digital nerve stimulation activate an inhibitory interneuron (i2), that directly inhibits the alpha-motoneuron (MN) postsynaptically. In all three models, a small proportion of CST neurons, which connect directly with alpha-motoneurons remain uninhibited, explaining that residual motor evoked potentials can be detected even during maximum exteroceptive EMG suppression during the cutaneous silent period. In models A and B only, however, a different proportion of inhibition of Ia fiber input versus CST input would also explain disparate suppression of H-reflexes versus motor evoked potentials during the cutaneous silent period. Connections depicted in grey indicate inhibitory interneurons, exerting either presynaptic (i1) or postsynaptic (i2) inhibition.

Furthermore, there was no evidence of habituation in both surface and needle recordings even up to 140 stimuli delivered at 0.5 Hz (Kranz et al., 1973). Following repetitive delivery of 50 stimuli, there was no habituation from the first to the last average response obtained in 10 subjects for abductor pollicis brevis, abductor digiti minimi, extensor and flexor carpi radialis, and triceps brachii, while habituation was found for the few responses recorded from anterior and posterior deltoid and biceps brachii (Eckert et al., 2016). Notably, the excitatory response seen in biceps brachii following noxious fingertip stimulation was strongly susceptible to habituation (Inghilleri et al., 1997), a prominent feature of cutaneous withdrawal reflexes (Floeter et al., 1998).

The dominant physiologic effect following a single painful stimulus to the fingertips is inhibition of distinct muscle sets. This strategy simplifies motor control by deactivating the same basic elements that are activated to produce movement (Leis et al., 2000). Yet despite being presumably simple, CSPs seem to be organized in a clever functional way: different muscles supplied by the same myotome show different CSP characteristics (probability, onset and end latency, duration, magnitude of suppression), even when the same fingertip is stimulated, and conversely, the same target muscle expresses distinct CSPs when different fingers are stimulated (Shahani and Young, 1973; Kofler, 2003; Svilpauskaite et al., 2006b).

CSPs are embedded within ongoing motor activity in the human being as a whole. CSPs in triceps brachii are modulated depending on the amount of elbow flexion or extension (Kofler et al., 2004). They are progressively shortened and less profound with increasing instability of the body in sitting versus standing on a firm surface versus standing on a wobble board (Eckert et al., 2016). There is also evidence of task-related modulation of CSPs in upper limb muscles during reaching and grasping, with a pattern of modulation that differs from that reported for the excitatory component of the withdrawal reflex (Don et al., 2008).

The relationship between CSPs and cutaneous withdrawal reflexes is complex (Floeter et al., 1998; Rossi et al., 2003; Svilpauskaite et al., 2006b). Both share A-delta afferents, both are suppressed by heterotopic painful stimulation, both have a functional rather than purely anatomical-metameric organization, yet their spinal circuitry differs. Rossi et al. (2003) suggested wide

dynamic range neurons within the spinal cord to be the main convergence site mediating both CSPs and cutaneous withdrawal reflexes. These wide dynamic range neurons connect with excitatory interneurons, predominantly subserving proximal upper limb motoneurons involved in withdrawal movements, and with inhibitory interneurons for predominantly distal motoneurons involved in reaching and grasping, respectively (Rossi et al., 2003). Notably, however, cutaneous withdrawal reflexes are polysynaptic, as they habituate rapidly (Floeter et al., 1998). Bladder filling was shown to suppress cutaneous withdrawal reflexes (Serrao et al., 2014; Fragiotta et al., 2015), but did not affect CSP duration in both upper and lower limbs of healthy subjects (Fragiotta et al., 2015).

CSPs are confined to the limb receiving the stimulus, with no significant interside differences in any CSP parameter (Kofler and Poustka, 2004; Svilpauskaite et al., 2006b; Isoardo et al., 2012). Normative values for maximum interside differences were reported for thenar muscles following D2 stimulation (Kofler and Poustka, 2004) and for vastus medialis muscle following lateral femoral cutaneous nerve stimulation (Tataroglu et al., 2005). No EMG suppression could be elicited in leg muscles when stimuli were applied on the arm and vice versa (Svilpauskaite et al., 2006b). Spinal CSP circuitry also seems to be strictly unilateral, as bilateral recordings following unilateral stimulation did neither induce any exteroceptive EMG suppression on the contralateral side (Kofler and Poustka, 2005; Svilpauskaite et al., 2006b), nor was exteroceptive EMG suppression influenced by contralateral noxious fingertip stimulation (Kofler and Poustka, 2005). Only few exceptions of occasionally appearing small CSPs in thenar muscles following contralateral D2 stimulation have been reported in the literature (Uncini et al., 1991; Leis et al., 2000; Kofler and Poustka, 2005). It cannot entirely be ruled out, however, that these inhibitory responses are due to low-threshold CMRs.

2.6. Suprasegmental influence on the CSP

There is modulatory influence on circuits mediating the CSP imposed by higher-order motor control centers along the neuroaxis, with documented influence from spinal cord, brainstem, basal ganglia, and cerebral cortex.

Logigian et al. (1999) reported H reflex suppression by conditioning noxious sural nerve stimulation in the time course corresponding to the CSP, which was reduced in patients with complete spinal cord injury in comparison to healthy subjects. The authors attributed the reduced suppression to the lack of suprasegmental influence on spinal inhibitory circuitry (Logigian et al., 1999).

Influence from the brainstem is suggested by a startle reflex component during the post-inhibitory EMG rebound (Kumru et al., 2009), and by progressively shortened CSPs in triceps brachii with increasing instability of the body in sitting versus standing on a firm surface versus standing on a wobble board (Eckert et al., 2016), considering that postural control is substantially regulated by the brainstem. A spino-bulbo-spinal reflex mediated by group III afferents has once been suggested in the lower limbs (Gassel and Ott, 1970).

Influence from the basal ganglia is suggested by studies in patients with idiopathic Parkinson's disease (Nakashima and Takahashi, 1992; Pullman et al., 1996; Serrao et al., 2002), atypical parkinsonism (Serrao et al., 2002; Štětkářová et al., 2015), dystonia (Pullman et al., 1996; Espay et al., 2006), Huntington's disease (Sandyk, 1982; Sandyk et al., 1988; Eisen et al., 1989), restless legs syndrome (Han et al., 2007; Isak et al., 2011; Öz et al., 2012), and essential tremor (Akgün et al., 2014; Ipekdal and Karadas, 2014; Sonkaya et al., 2015). Delayed CSP end latencies (reported as prolonged CSPs) in Parkinson's disease and dystonia once prompted the idea that the latter half of the CSP might be mediated by supraspinal mechanisms (Pullman et al., 1996).

In patients with upper motoneuron lesions, supraspinal influence has been suggested by delayed CSPs in patients with stroke (Gilio et al., 2008) and amyotrophic lateral sclerosis (Gilio et al., 2008; Kim and Kwak, 2010). These findings concur with a facilitating effect of corticospinal motoneurons on spinal circuitry that serves to suppress corticospinal activity by imposing more profound and accelerated inhibition.

In healthy subjects, performing higher cortical functioning tasks, such as reading, listening to music, watching cues on a video screen, writing, playing on a musical keyboard, and performing targeted movements, led to longer CSP onset latencies, shorter CSP end latencies, and shorter CSP durations in opponens pollicis (Su et al., 1998).

2.7. Other physiological factors influencing the CSP

Body height has an obvious effect on CSP onset latencies, which increase with height (Floeter, 2003; Kofler and Poustka, 2004; Svilpauskaite et al., 2006b; Koo et al., 2010) although others found no such correlation (Han et al., 2007; Baek et al., 2016) In order to overcome the limitation of an association of CSP onset latencies with body-height, some authors suggested to use the latency difference between upper and lower limb CSPs (Onal et al., 2010; Yücel et al., 2015). Also, CSP duration was once reported to correlate with height (Koo et al., 2010).

Age was reported to either have no influence on CSPs (Serrao et al., 2002; Han et al., 2007; Yaman et al., 2007a; Isoardo et al., 2012; Tekatas et al., 2014; Baek et al., 2016), or to be associated with increasing onset latencies in upper limbs (Leis et al., 1992; Leis, 1994; Koo et al., 2010), particularly in male subjects (de Leonni Stanonik et al., 2010), as well as with increasing onset latencies in lower limbs (Mota et al., 2015). Three studies reported longer CSP duration with increasing age (Leis et al., 1992; Leis, 1994; Koo et al., 2010), which was attributed to dopaminergic deficit with age in one study (Koo et al., 2010) and discussed as possibly being due to decreased synaptic power that occurs with age (Mota et al., 2015). One study found shorter CSP durations with increasing age (Tirić-Čampara et al., 2014).

Gender was reported to have either no influence on CSP parameters (after correcting for body height) (Svilpauskaite et al., 2006b; Isoardo et al., 2012; Tekatas et al., 2014; Tirić-Čampara et al., 2014; Fragiotta et al., 2015), or to have a mild effect with females presenting slightly more nociceptive EMG suppression in their upper limbs than males (Kofler and Poustka, 2004; Yaman et al., 2007a; de Leonni Stanonik et al., 2010). More pronounced protective reflexes in females than males concur with previous reports on respective gender differences in cutaneous withdrawal reflex thresholds (France and Suchowiecki, 1999; Sandrini et al., 2005; Mylius et al., 2005), auditory startle responses (Kofler et al., 2001b), and prepulse inhibition of the blink reflex (Kofler et al., 2013). Notably, one study reported gender differences in response to propranolol, which shortened the duration of prolonged CSPs in female but not in male patients with essential tremor (Sonkaya et al., 2015).

Limb temperature exerts a significant influence on conduction properties of small-diameter nerve fibers, causing a delay in CSP onset by 12 ms when cooling the forearm from some 34 to 25 °C (Kofler et al., 2014).

Hand dominance had no significant influence on CSP parameters (Kofler and Poustka, 2004; Yaman et al., 2007a), although left-handers tended to develop less profound nociceptive EMG suppression on their non-dominant side (Kofler and Poustka, 2004).

The influence of *muscle fatigue* has not been specifically addressed in any of the published CSP studies to date.

3. Neurotransmitters and pharmacology of cutaneous silent periods

Little is known about neurotransmitters involved in CSP generation. In fact, most is known about neurotransmitters which are not involved. Gamma-amino butyric acid (*GABA*) is a widely distributed and potent inhibitor in the central nervous system, however, intrathecal *baclofen*, a $GABA_B$ agonist, failed to influence CSPs in patients with spinal cord injury, while at the same time caused prolongation of cortical silent periods induced by transcranial magnetic stimulation (Štětkářová and Kofler, 2013). This finding concurs with previously observed lack of influence of intravenous baclofen on MNSPs in healthy subjects (Inghilleri et al., 1996). Notably, however, absence or abnormal shortening of the CSP have been reported in single patients with either stiff-limb (Thaler et al., 1998) or stiff-person (Boček et al., 2016a) syndromes, which are known to be mediated by GABA-ergic deficit.

Inghilleri et al. (2002) demonstrated lack of effect of intramuscular *fentanyl* in healthy subjects on CSP onset latency and duration. This was not the case with concomitantly studied lower limb cutaneous withdrawal reflexes, which were significantly attenuated.

Antihistaminic medication has been examined in a systematic study of CSP onset and end latencies, duration, and index of suppression. Subjects underwent serial CSP testing after ingestion of cetirizine, with no significant change over a period of 6 hours (Kofler et al., 2009).

Other incidental observations on pharmacology include *botulinum toxin*, which did not influence altered CSPs in focal dystonia (Pullman et al., 1996; Floeter, 2003); and *(-)-trans-Δ9-tetrahydro cannabinol (THC)*, a partial agonist on cannabinoid receptors, in particular CB1, which did not influence CSPs in abductor digiti minimi of 13 healthy volunteers (Fionda et al., 2016).

Three months of treatment with *alpha-lipoic acid* improved delayed CSP onset latencies without significant influence on CSP duration in upper and lower extremities of 17 patients with diabetic small-fiber polyneuropathy (Yücel et al., 2015). The authors did not elaborate on potential mechanisms leading to shortened CSP latencies, which was presumably unrelated to synaptic function, but rather due to improved conduction function in affected nerve fibers (Yücel et al., 2015).

In contrast, distinct influences on CSPs were observed for various *monoaminergic* substances. Abnormally delayed CSP end latencies (corresponding to prolonged CSP durations, as CSP onset latencies were normal) were partially normalized by *levodopa* in idiopathic Parkinson's disease, but not in patients with atypical parkinsonism who did not respond clinically to levodopa (Serrao et al., 2002). Prolonged CSPs were also noted in extensor digitorum brevis of patients with restless legs syndrome, which were normalized by *dopamine agonist* treatment (Han et al., 2007). Notably, in another study *pramipexole* served to increase abnormally shortened CSPs in tibialis anterior in restless legs syndrome (Öz et al., 2012). Conversely, the abnormally reduced I1 phase of the CMR in patients with idiopathic Parkinson's disease was normalized by levodopa (Fuhr et al., 1992), and cutaneomuscular inhibition was substantially enhanced by subcutaneous *apomorphine* (Clouston et al., 1996). These seemingly contradictory findings of an increase in EMG inhibition following low-intensity afferent stimulation and reduced inhibition following high-intensity stimulation are consistent with distinct spinal circuitry mediated by low- and high-threshold afferents (Serrao et al., 2001; Kofler et al., 2001a; Floeter, 2003; Kofler, 2003). These findings, however, do not allow certainty as to whether dopamine alters CSPs or whether it only influences that "portion" of the CSP that is due to concomitant activation of low-threshold afferents, which inevitably occurs when applying electrical stimuli to peripheral nerves.

Tramadol, which has low affinity for opioid receptors but inhibits serotonin and noradrenaline reuptake, increased the duration of CSPs elicited in first dorsal interosseous muscle in parallel with reduction of subjective pain perception (Pujia et al., 2012). *Escitalopram*, a selective serotonin reuptake inhibitor, prolonged CSPs in first dorsal interosseous in a similar manner, but to a lesser degree (Pujia et al., 2014). The authors suggested an increase in tonic activity of descending modulatory pathways leading to post-synaptic reinforcement of the serotonergic descending control via reticulospinal and/or tectospinal tracts on the spinal inhibitory interneurons mediating the CSP, or alternatively drug-mediated inhibition of the descending corticospinal volley on the excitatory inputs to motoneurons that sustain voluntary contraction (Pujia et al., 2014). These findings concur with an opposite effect of neurochemical modulation between pyramidal and extrapyramidal systems on the CSP. Predominant impairment of extrapyramidal pathways leads to prolonged CSP duration, whereas predominant impairment of the corticospinal pathway causes increased CSP onset latency and/or a decreased CSP duration.

The CSP is considered a protective reflex, and other protective reflexes, such as the auditory startle response, involve *glycine* as an inhibitory neurotransmitter (Bakker et al., 2006), rendering glycine another potential candidate in CSP generation, which has not been studied so far. Glycine receptors are abundantly present on alpha-motoneuron synapses and are closely involved in motor control (Rekling et al., 2000).

4. Concluding remarks and outlook

Clinical interest in CSPs derives from its potential usefulness for evaluating segments and components of sensory nerves that are not well assessed by standard electrodiagnostic methods. Clinical applications are reviewed in part 2 (Kofler et al. 2019). Yet there are still many open questions to be addressed in future research.

An important issue relates to delineating the exact CSP circuitry at the spinal segmental level, including pre- versus post-synaptic inhibition of alpha-motoneurons, interneurons, or corticospinal neurons.

Involved neurotransmitters have not yet been identified. It seems likely that more than one neurotransmitter might be involved, because of the importance of a protective reflex, and hence the necessity to have some kind of redundancy in case one system fails. On the other hand, only very few synapses seem to be involved, hence the possible number of neurotransmitters seems limited.

For accurate clinical utility, it seems important to define a better "separation" of the reflex into afferent, central, and efferent segments. The efferent segment may be estimated by F-wave or root stimulation, however, both are suboptimal. The central segment is difficult to estimate, as the exact number of synapses is not known, as well as the time needed for impulse transmission per synapse. Up to 15 ms have been proposed for the central processing time (Shefner and Logigian, 1993).

Another problem in clinical routine is the fact that stimulus intensity is routinely given in multiples of ST, which is a function of large-diameter fibers. But thresholds for detecting electrical impulses may not be relevant for, and not comparable to, thresholds of pain perception, which is a small-diameter fiber function. On the other hand, pain threshold is difficult to establish, and difficult to compare across subjects. A particular problem arises in patients with polyneuropathy and subsequent alteration in perception threshold for large-diameter fiber qualities, but not necessarily for small-diameter fiber qualities. In their case "overstimulation" may be an issue to consider.

Small-diameter fibers outnumber large-diameter fibers in any given nerve. It seems that the former convey many different sensory qualities, e.g. sharp pain perception, cold sensation, cold pain, itch, and possibly many more. It seems interesting to elaborate which of the qualities correlate to CSPs, and which clinical functions are lost in case a CSP is reduced or absent. Notably, neuropathic pain intensity did not correlate with CSP duration (Truini et al., 2009b).

CSPs in lower limbs have been suggested to be similarly organized as CSPs in the upper limbs. However, no study so far has addressed the specificity of CSPs in the lower limbs, yet their role in a protective reflex reaction in analogy to the upper limbs was suggested based on a similar configuration of both inhibitory and excitatory components, as well as on their response to local anesthesia (Mota et al., 2015). We cannot, however, be sure that they are really identically organized in the upper and lower extremities in biped humans.

Finally, effort should be undertaken to come up with a common standard for routine CSP testing, in order to be able to easier compare results across different studies, as some of the contradictory findings in the literature may be due to inconsistent examination techniques, in particular pertaining to recording single traces versus rectification and online averaging. Other discrepancies may be due to different methods of measuring latencies: some authors measure CSP onset before the LLR, some prefer to measure after the LLR, thus actually measuring only the I2 phase of the CSP.

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Conflict of interest

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Appendix A. Supplementary material

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