Which Neuronal Elements are Activated Directly by Spinal Cord Stimulation

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■ **ABSTRACT**

The purpose of this paper is to discuss which nerve fibers in the various quadrants of the spinal cord are immediately activated under normal conditions of spinal cord stimulation, ie, at voltages within the therapeutic range. The conclusions are based on both empirical and computer modeling data. The recruitment of dorsal column (DC) fibers is most likely restricted to Aβ fibers with a diameter $\geq$ 10.7 μm in a 0.20–0.25 mm layer under the pia mater and fibers of 9.4–10.7 μm in an even smaller outer layer when a conventional SCS lead is used. In a 0.25-mm outer layer of the T11 segment the number of Aβ fibers $\geq$ 10.7 μm, as estimated in a recent morphometric study, is about 56 in each DC. Because a DC at T11 innervates 12 dermatomes, a maximum of 4–5 fibers ($\geq$ 10.7 μm) may be recruited in each dermatome near the discomfort threshold. The dermatome activated just below the discomfort threshold is likely to be stimulated by just a single fiber, suggesting that paresthesia and pain relief may be effected in a dermatome by the stimulation of a single large Aβ fiber. The depth of stimulation in the DCs, and thereby the number of recruited Aβ fibers, may be increased 2–3 fold when stimulation is applied by an optimized electrode configuration (a narrow bi/tripole or a transverse tripole). Assuming that the largest Aβ fibers in a dorsal root have a diameter of 15 μm, the smallest ones recruited at discomfort threshold would be 12 μm. The latter are presumably of proprioceptive origin and responsible for segmental reflexes and uncomfortable sensations. Furthermore, it is shown to be unlikely that, apart from dorsal roots and a thin outer layer of the DCs, any other spinal structures are recruited when stimulation is applied in the dorsal epidural space. Finally, anodal excitation and anodal propagation block are unlikely to occur with SCS. ■

KEY WORDS: anodal block, anodal excitation, dorsal column stimulation, dorsal root stimulation, spinal cord stimulation.

INTRODUCTION

For the investigation of the effects of spinal cord stimulation (SCS) on the neurophysiologic and neuropharmacologic mechanisms of pain it is relevant to know which pathways should be considered as potential inputs of these mechanisms. Basically, any neuronal element in or near the spinal cord can be directly activated by SCS if the stimulus amplitude is sufficiently high. Apart from the dorsal columns (DCs) and dorsal roots (DRs), it has been suggested that the pyramidal tract, reticulospinal tracts, ventral roots, motoneurons, the dorsal horn, and sympathetic tracts can be affected by SCS as well (1,2). However, the

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small therapeutic range (TR) of stimulation amplitudes has to be taken into account. This range between the perception threshold of paresthesia (PT) and the discomfort threshold (DT) has a mean value of about 40% of PT when conventional leads with 9–10 mm electrode separation (center-to-center) are used (3,4). Therefore, the voltage ratio of DT and PT is obviously more relevant than their difference. According to Law (5) TR is defined as a ratio

$$TR = (DT - PT)/PT = DT/PT - 1 \qquad (1)$$

Furthermore, it has to be considered where the current in the anatomic structures between cathode(s) and anode(s) will flow during a stimulation pulse. This is primarily determined by the electrical resistivity of the various structures, because current will take the path having the lowest resistance. In Table 1, the approximate resistivities of the spinal cord gray and white matter, the cerebrospinal fluid (CSF) in the dural sac and the epidural fat and vertebral bone surrounding the dural sac are presented (6). Table 1 indicates that spinal white matter (and a nerve fiber bundle in general) is anisotropic, which means that its resistivity is different in different directions, being lowest in the axial direction of the fibers. It is also shown in Table 1 that CSF has the lowest resistivity, followed by the spinal white and gray matter, whereas the tissues surrounding the CSF have by far the highest resistivities. Therefore, a large proportion of the current flowing between two (or more) electrodes situated in the epidural space leaves this space in the immediate neighborhood of the anode(s) via the thin dura mater, flows via the CSF towards the cathode(s) and enters the epidural fat in the immediate neighborhood of the cathode(s). We calculated that about 90% of the injected current flows via the CSF and that less than 10% enters the spinal cord at the side near the electrodes. The high transverse resistivity of the white matter restricts current flow into the spinal cord. The simplest representation of the anatomic and electric properties of the spinal cord and surrounding structures is a model consisting of three concentric cylindrical compartments, as shown in Fig. 1. The outer compartment is an insulator, the middle one (CSF) is well conducting and the central one (spinal cord) is poorly conducting the stimulation current. The current density distribution as calculated with the more realistic University of Twente SCS computer model (6–8) is shown in Fig. 2. The current density distribution is indicated by iso-current density lines in the transverse plane of the cathode, which borders the dura mater medially in the dorsal epidural space. The current density is highest in the CSF next to the electrode and is reduced with increasing distance from the electrode. Although the main direction of the current is longitudinally towards the anode, it spreads also laterally in the CSF, as shown in Fig. 2. In a ventral direction the current density is reduced markedly when entering the spinal cord. As a consequence, the amplitude of a stimulus pulse necessary to excite a spinal nerve fiber rises steeply with increasing depth inside the spinal cord, whereas it rises only slightly from medial to lateral. We calculated an increase in threshold of about 20% and 500% when a longitudinal nerve fiber was displaced 1.6 mm from the dorsomedial border of the spinal cord in a lateral and a ventral direction, respectively (9). It is thus the CSF that allows stimulation of nerve fibers in a large part of the mediolateral extent of the DCs.

Table 1. Approximate Tissue Resistivities (R) and Normalized Values (R_{norm})

Structure		R(Ω.cm)	R_{norm}
Spinal gray matter		435	7.4
Spinal white matter	Transverse	1205	20.4
	Longitudinal	167	2.8
Cerebro-spinal fluid		59	1.0
Epidural fat		2500	42.4
Vertebral bone		2500	42.4

DORSAL COLUMNS

With the UT-SCS computer model (6–8) the threshold voltage of a nerve fiber as a function of its depth below the pia mater in the DCs was calculated for two models with a thickness of the dorsal CSF layer of 1.0 mm and 3.5 mm, respectively. The anode and cathode were 9 mm

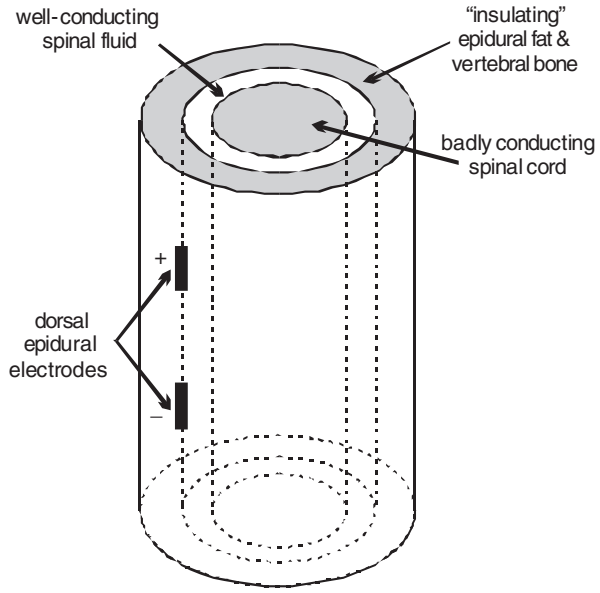

Figure 1. Simple cylindrical conductor model representing the spinal cord surrounded by the well conducting CSF and the almost insulating epidural space, vertebral bone, and ligaments.

apart (center-to-center). In Fig. 3 the threshold stimulus of a 12-μm fiber is shown as a function of the ventral distance from the dorsomedial DC border. The thresholds are normalized to a value of 1.0 at this border.

Assuming that PT corresponds with the excitation of the largest Aβ fiber(s) at the dorsal DC border (having the lowest threshold) and that DT is about 1.4 PT (3,4), Twelve-μm DC fibers will only be recruited in a 0.20–0.25 mm layer below the pia mater, as shown in Fig. 3. Even if DT is as high as 1.7 PT (North et al. ''Spinal cord electrode design: a prospective, randomized, controlled trial comparing percutaneous and laminectomy electrodes, Part I. Technical outcomes'', submitted), this layer would still be as small as 0.30–0.40 mm. When a longitudinal bipole with a smaller electrode separation than 9 mm, or a transverse tripole is used, DT/PT is generally higher. Law (10) reported a mean value of 1.6 (n = 46), whereas we measured a mean value of 2.5 (n = 7) in bipolar stimulation with a 5.0-mm electrode separation (center-to-center) and, with the same lead, a mean DT/PT of 2.2 with the transverse tripole (11). According to Fig. 3, a DT of 2.2–2.5 PT will, depending on the thickness of the dorsal CSF, still result in the recruitment of 12 μm DC fibers in a superficial layer of only 0.46–0.69 mm under the pia mater.

Starting at PT, the largest Aβ fibers are activated sequentially in different mediolateral sections of the DCs (corresponding to different dermatomes) until DT is reached. Only in the initially activated DC section will these fibers be recruited up to the maximum depth of 2–2.5 mm, whereas in the section activated just below DT fewer fibers will be recruited. Assuming that paresthesia and pain relief are induced in four dermatomes and that the corresponding thresholds PT_1, PT_2, PT_3 and PT_4 are at 1.0, 1.1, 1.2, and 1.3 PT, respectively, and DT = 1.4 PT_1, DT/PT_4 is only about 1.1. Since smaller Aβ fibers are activated as well when the stimulus is increased, it was calculated with the UT-SCS model how the threshold to activate a nerve fiber varies with its diameter. As shown in Fig. 4, this threshold rises with decreasing fiber diameter. Assuming that the largest DC fibers have a diameter of 12 μm (threshold = 1.7 V in Fig. 4), the smallest fibers in the DC section recruited first will have a diameter of ~9.4 μm (at 1.4 PT, see Fig. 4), whereas in the section recruited last (at

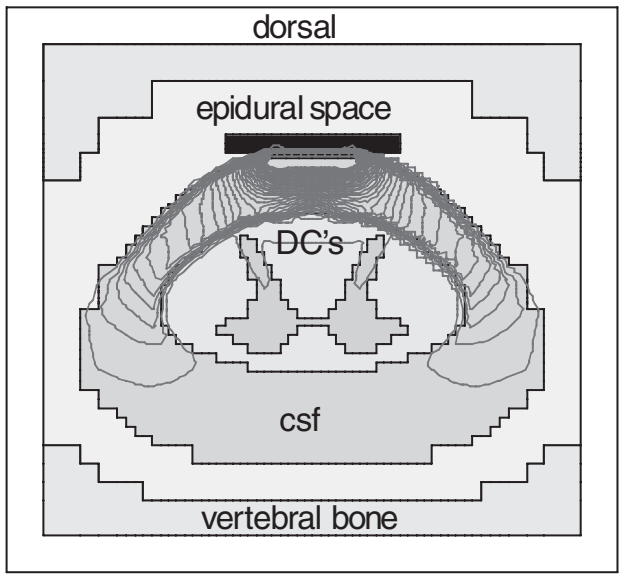

Figure 2. Current density distribution in the transverse plane of the cathode of an SCS computer model, indicated by iso-current density lines; highest current density in the csf near the electrode; bipolar dorsomedial stimulation with 9-mm electrode distance (center-to-center).

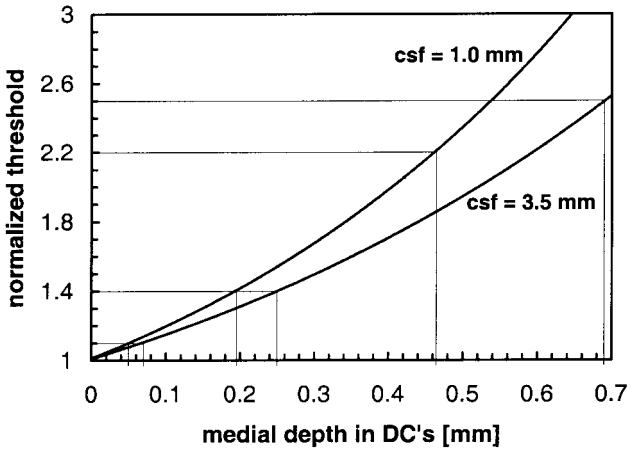

Figure 3. Normalized threshold stimulus of a 12-μm nerve fiber as a function of the medial depth in the DC's, calculated with UT-SCS models having an electrode-to-spinal cord distance (dorsal CSF thickness) of 1.0 and 3.5 mm, respectively; bipolar dorsomedial stimulation with 0.21-ms pulses and 9-mm electrode distance (center-to-center); best fit of data points by 2nd order exponential functions (correlation with data points: $R^2 = 0.998$).

1.1 PT) only fibers $\geq$ 11.2 μm at a maximum depth of ~0.06 mm (Fig. 3) would be recruited.

Using the calculated depth of the recruited area in the various sections of the DCs and the diameter range of nerve fibers that can be activated, the number of recruited DC fibers can be estimated when the fiber size distribution in the corresponding layer of the DC is known. In a recent morphometric study the size distribution of the DC fibers in the superficial 0.3 mm layer of the T10–11 spinal segments of two human subjects was analyzed (Feirabend et al. "Morphometry of human superficial dorsal and dorsolateral column fibers: significance to spinal cord stimulation", submitted). From these data it was determined that only ~0.5% of the fiber population in the outer 0.25-mm layer of the DC has a diameter $\geq$ 10.7 μm, which corresponds to a mean of about 56 fibers on either side of the midline. In the outer 0.06-mm layer (see above) only 13–14 fibers $\geq$ 10.7 μm are present on either side. Since these 13–14 recruitable fibers in the T10–11 segment innervate 12–13 dermatomes, the dermatome recruited last would be stimulated by just a single large Aβ fiber. In contrast, the DC section recruited first (at PT) would be stimulated to a depth of about 0.25 mm (see above), which corresponds to about 5 fibers $\geq$ 10.7 μm and, in addition, a similar number of recruitable Aβ fibers of ~9.4–10.7 μm in diameter. These calculations suggest that paresthesia and pain relief can be effectuated in a dermatome by the stimulation of just a single large Aβ fiber. By analogy with the neuromuscular system, in which the largest motor units are innervated by the largest motor axons ("size principle") (12), the largest Aβ fibers would innervate the largest cutaneous receptive fields, each covering a substantial part of a dermatome. It is also likely that pain relief can be improved when DT/PT is increased, because more fibers will be recruited in each DC section.

DORSAL ROOTS

Although DRs are generally further away from the SCS electrodes than DCs, the Aβ fibers in a DR may have a lower threshold for their excitation than Aβ fibers in a DC, particularly when the distance between the (midline) electrodes and the spinal cord is large (7,13,14). Computer modeling predicts that the relatively low DR fiber threshold is primarily due to the substantial increase in electrical resistivity of the medium surrounding the dorsal rootlets at their

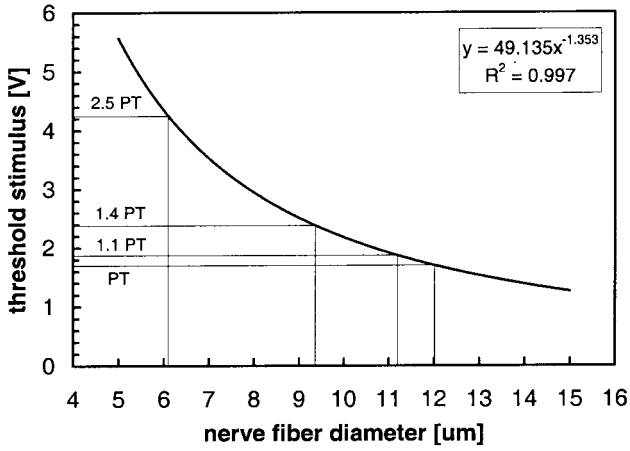

Figure 4. Threshold stimulus as a function of the diameter of a myelinated nerve fiber at the dorsomedial border of the DCs calculated with an UT-SCS model having a 1.0-mm electrode-to-spinal cord distance; bipolar dorsomedial stimulation with 9 mm electrode distance (center-to-center) and 0.21-ms pulses; best fit of data points by power function; inset: equation and squared correlation with data points.

entrance into the spinal cord (from CSF to spinal white matter, see Table 1). Accordingly, the excitation of DR fibers occurs most probably in the dorsal root entry zone (DREZ). The curved shape and the diameter of DR fibers, being larger than the corresponding DC fibers, add to their lower excitation threshold (7,8,13). Assuming that the largest DR fibers have a diameter of 15 μm, the smallest ones being recruited at DT (= 1.4 PT) will have a diameter of ~12 μm. These fibers are presumably of proprioceptive origin and are responsible for segmental motor reflexes and uncomfortable sensations (14–17).

OTHER SPINAL TRACTS

Ventral Roots

Empirical studies have shown that it is very unlikely that ventral root fibers can be directly activated by SCS (15). The current-density distribution in the spinal cord model (Fig. 2) shows that this density is very low on the ventral side when stimulation is applied dorsomedially. It was calculated with the UT-SCS model that the stimulus amplitude to excite a 15-μm α-motor fiber exceeds the value to stimulate a 15-μm Aß-fiber in the DR by a factor 14 (W.A. Wesselink, J. Holsheimer, unpublished results).

Dorsolateral Columns

The dorsolateral column (DLC) comprises substantially more large fibers than the DC. The proportion of the fiber population in a 0.3-mm deep superficial layer of the human DLC (segments T10–11) with a diameter $\geq$ 10.7 μm is ~2% in the DLC and only ~0.5% in the DC, whereas the mean diameters of these fiber populations ($\geq$ 10.7 μm) are identical (12.0 μm), as well as their maximum size (16.0 μm) (Feirabend et al. Morphometry of human superficial dorsal and dorsolateral column fibers: significance to spinal cord stimulation. submitted). Taking into account the lower thresholds of both lateral DC fibers [particularly due to the presence of collaterals (6)] and DR fibers in the same size range, it is unlikely that large DLC fibers will be recruited in SCS at amplitudes below DT.

Lateral Corticospinal Tract

As shown in Fig. 2 the current density in the spinal cord, except for a small superficial layer in the DCs, is too low to allow the immediate activation of any nerve fibers (apart from DC and DR fibers) when SCS is applied dorsally in the epidural space. It is therefore most unlikely that for example fibers of the lateral corticospinal tract are activated by SCS. Coburn (13) calculated that the threshold stimulus of a 5-μm pyramidal tract fiber is 4.1-fold the value of a 2.5-μm DR fiber. From the equation in Fig. 4 it follows that this ratio is even 6.9 for an (unrealistically large) 20-μm pyramidal tract fiber as compared to a (realistic) 15-μm DR fiber.

Ventral Spinothalamic Tract

Similar to the ventral roots, it is very unlikely that the ventral spinothalamic tract can be stimulated with a dorsally placed SCS lead. Stimulation of this tract at the ventral border of the spinal cord is only possible when at least the cathode is placed on the ventral side, as has been shown empirically by Larson et al. (18) and Hoppenstein (19). They stimulated on the ventral and dorsal side with subdural and subarachnoidal electrodes and observed pain relief in both dorsal and ventral SCS, the latter without any tingling, buzzing or vibrating sensations (paresthesias).

MISCELLANEOUS

Dorsal Horn

Little is known about the direct effect of SCS on neurons in the dorsal horn. Several stimulation studies on spinal and cerebral gray matter have shown that the immediate targets are axons, primarily afferents, and not somadendritic structures (20–23). Similar to nerve fibers in the DC, only large axons in the outermost part of lamina 1 of the dorsal horn may be stimulated by SCS. Because large afferents entering the dorsal horn are most likely activated in the DREZ (see section on Dorsal Roots), direct activation of dorsal horn axons will be a minor effect in SCS. Secondary,

synaptically mediated effects of Aß fiber stimulation on dorsal horn cells, effectuating a.o. pain perception and peripheral blood flow, are beyond the scope of this paper.

Ligamentum Flavum Nerve Fibers

North et al. (24) have proposed that sensory nerve fibers in the ligamentum flavum may contribute to nonradiating discomfort sensations when percutaneous SCS leads are used. Contrary to plate electrodes, these electrodes allow some current flow in the dorsal epidural space and ligamentum flavum, which presumably results in the activation of local nerve fibers. However, no data on the diameter and position of these fibers are available. It is be expected that the probability of this side effect of SCS increases when PT gets higher.

ANODAL EXCITATION AND BLOCKING

It has been suggested repeatedly in the literature that anodal excitation and anodal propagation block of DC (and DR) fibers might occur in SCS. However, Bement and Ranck reported that the anodal excitation threshold of central myelinated axons is, depending on the stimulation conditions, 3–7 fold their cathodal excitation threshold (PT) (25). Coburn (13) and Struijk et al. (7) calculated that the threshold to excite a DR fiber near an anode is almost 3-fold the threshold near a cathode. Rijkhoff et al. (26) have shown empirically that the anodal block threshold is 5–8 fold the cathodal excitation threshold. High thresholds for both anodal excitation and anodal block have recently been reported from studies on human peripheral nerve as well (27,28). These values largely exceed DT, which is generally only 40–70% larger than PT. Even with a narrow bipole or a transverse tripole giving a mean ratio DT/PT of 2.2–2.5 (11), anodal excitation and blocking are very unlikely.

In SCS these phenomena might occur only under one of the following conditions: when the anode is much closer to the spinal cord than the cathode(eg, when the anode is at a midcervical level and the cathode at a lower thoracic level), or when a single anode is used in combination with several cathodes. These improbable conditions would result in a current density in the DCs and the DRs near the anode which is substantially larger than near the cathode(s). An additional condition to be fulfilled for anodal block is that the pulse width is at least equal to the propagation delay between cathode and anode plus the duration of the action potential (~0.3 ms). Therefore, it is very unlikely that anodal excitation and anodal block may occur in SCS.

CONCLUSIONS

In SCS applied with electrodes in the dorsal epidural space only large, myelinated nerve fibers in the DCs and DRs are most likely targeted directly by the stimulus pulses. In the DCs the recruited area is likely to be restricted to a 0.20–0.25-mm deep dorsal layer in which only fibers $\geq$ 9.4 μm are activated. It is also likely that activation of just a single Aβ fiber ($\geq$ 10.7 μm) is sufficient to induce paresthesia in a dermatome, as would occur for a dermatome activated just below DT. At this stimulus level those dermatomes recruited first (near PT) may be activated by up to 5 Aβ fibers ($\geq$ 10.7 μm) and a similar number of smaller Aβ fibers ($\geq$ 9.4 μm). When the therapeutic range is larger, which can be obtained by using a narrow bi/tripolar or transverse tripolar electrode configuration, these numbers of fibers can be increased 2–3 fold, and may result in an improved relief of pain sensations. Finally, it is very unlikely that anodal excitation and anodal propagation block occur in SCS.

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