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Commentary

The fascination of complex regional pain syndrome

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ABSTRACT

Complex regional pain syndrome (CRPS) is a pain disorder involving the somatosensory, the somatomotor and the sympathetic nervous systems. Based on experiments conducted by Bove (2009), it is suggested that changes in impulse activity in small-diameter afferents and postganglionic axons generated by neuritis can contribute to signs of early CRPS. The potential mechanisms involved are discussed. These mechanisms include the possibility that CRPS, a disorder of the central nervous system, may be caused by a nerve inflammation.

Experimental neuritis and impulse activity in afferent and efferent (sympathetic) fibers. In a recent issue of Experimental Neurology, Dr. Bove (Bove 2009) puts forward the interesting idea that focal nerve inflammation leads to changes in activity in small diameter afferent neurons (conduction velocity <4 m/s) and in postganglionic neurons and that these changes in neural activity are responsible for signs of early complex regional pain syndrome (CRPS). He applied complete Freund's adjuvant to the sciatic nerve in rats generating a perineuritis (see Bove et al., 2003). In anesthetized rats (3–4 days and 7–8 days following induction of neuritis) and in controls without neuritis, he recorded from bundles isolated from the sural nerve containing postganglionic axons and afferent axons. The axons were disconnected from their peripheral targets and centrally intact. Afferent fibers were identified by electrical stimulation of the dorsal roots L4–L6 (>80% of the afferent neurons projecting in the sural nerve have their cell bodies in dorsal root ganglion L5 [Baron et al., 1988; Sittiracha and McLachlan 1986]). Some 30% to 50% of the small diameter afferent fibers in the rats with sciatic nerve neuritis developed ongoing activity. Postganglionic axons showed ongoing activity that was inhibited during an epinephrine-induced blood pressure increase. These axons were mechanoinsensitive. The rate of ongoing activity in the postganglionic axons significantly decreased during sciatic nerve neuritis.

Some of the data are of concern to me in the light of previous studies:

(1) The proportion of small diameter afferent fibers that projected in the sural nerve (in which about 90% of the afferent fibers innervated skin [Gorodetskaya et al., 2009]) and developed ongoing activity is high. Whether the discharging axons were also activated by mechanical stimulation of the inflamed sciatic nerve is not reported in the paper. However, in a previous study, Bove et al. (2003) reported that mechanosensitivity and some ongoing activity appeared in small-diameter (C- and Aδ-) afferent fibers innervating skeletal muscle and possibly other deep somatic tissues after sciatic neuritis, but only 2 of 43 cutaneous afferent fibers conducting at <4 m/s exhibited ongoing activity in neuritis rats. Cutaneous afferent fibers did not respond to mechanical stimulation of the inflamed sciatic nerve section. So what is different in the experimental approach using focal nerve inflammation reported in the present paper and in the previous paper as far as the ongoing activity is concerned?

(2) The rate of ongoing activity in *single* postganglionic axons in the control rats (2.26 ± 0.21 imp/s)[1] is higher than that recorded in systematic investigations of the ongoing and reflex activity in postganglionic axons innervating hairy skin of the rat hindlimb. Under rigorously controlled experimental conditions and under various anesthetics (Häbler et al., 1994, 1999), the mean rate of ongoing activity in postganglionic neurons with reflex patterns typical of cutaneous vasoconstrictor neurons was 0.7 to 1.1 imp/s.

The idea. Notwithstanding my concerns about some of the data, the idea about the potential mechanisms underlying the generation of early CRPS is interesting. Dr. Bove argues that the neuritis-induced changes could explain some of the changes observed in patients with CRPS:

(1) Ongoing pain as a consequence of ongoing activity in small diameter afferents, projected particularly into the deep somatic

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[1] The original record in Fig. 2A in Dr. Bove's paper shows the activity in two postganglionic axons (if one ignores the small signals) and not in one postganglionic axon.

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tissues. This ongoing activity could also be responsible for maintaining the central sensitization of dorsal horn neurons and therefore the secondary deep somatic and superficial mechanical hyperalgesia/allodynia.

(2) Ectopically generated ongoing activity in afferent fibers conducted antidromically could generate neurogenic inflammation in the peripheral tissues consisting of arteriolar vasodilation by release of calcitonin-gene-related peptide (CGRP) and substance P, and to postcapillary (venular) plasma extravasation by release of substance P. This could be a mechanism contributing to the cutaneous hyperemia and particularly to edema in CRPS patients. In healthy humans, venular plasma extravasation does not exist in skin (Sauerstein et al., 2000) and arteriolar vasodilation is generated by activation of a subset of peptidergic afferents, the so-called mechanoinsensitive C-fibers (Schmelz et al., 2000). However, using microdialysis in CRPS patients, transcutaneous stimulation of afferent C-fibers elicited a weak increase of protein extravasation in skin compared to healthy controls (Weber et al., 2001). Peptidergic afferent fibers innervating deep somatic tissues could be more important by generating neurogenic inflammation and contributing to edema and trophic changes in these tissues in CRPS patients. Thus, ongoing activity generated ectopically in small-diameter afferents by neuritis could theoretically contribute to the changes in skin and elsewhere observed in CRPS patients.

(3) The decreased ongoing activity in cutaneous vasoconstrictor neurons could also be linked to the ectopic ongoing activity in nociceptive afferent nerve fibers via an inhibitory reflex. In anesthetized cats and rats, noxious stimulation of skin leads to inhibition of ongoing activity in most cutaneous vasoconstrictor neurons. This reflex is spinal (although under supraspinal control) and local, i.e. stimulation of nociceptors of the territory of skin innervated by the cutaneous vasoconstrictor neurons or adjacent to it elicits this reflex, with a weaker reflex from the contralateral limb (Horeyseck and Jänig 1974; Häbler et al., 1994; for discussion see Jänig 1985, 2006). Whether this reflex exists in humans is debated (Blumberg and Wallin 1987, see Jänig 2006). In chronic spinal cats, this reflex is very powerful and long-lasting (Jänig and Spilok 1978; Jänig and Kümmel 1981).[2] However, whether this spinal inhibitory reflex operates under chronic conditions has to be shown.

Can it be shown using the Evans Blue technique that extravasation in skin and/or subcutaneous tissues is increased 7–8 days after induction of sciatic neuritis in rats involving antidromically conducted impulses in peptidergic afferents? This is an important experiment to do. It is doubtful whether a significant increase in blood flow through (plantar) skin can be measured using laser-Doppler flowmetry, because of methodical difficulties (related to control of anesthesia, arterial blood pressure, body core temperature, ambient temperature) and because only superficial cutaneous blood flow is measured. However, it might be possible to measure temperature differences between the affected paw and the contralateral paw in unanesthetized rats since this reflects total blood flow (Häbler et al., 1998) provided one has absolute control of the core body temperature, the ambient temperature and the "emotional state" of the rats (in rats as in humans, any emotional/affective stimuli or situation are reflected in activation of cutaneous vasoconstrictor neurons). A further aspect that may be of interest in this context is that vasoconstriction elicited in skin by stimulation of cutaneous vasoconstrictor neurons at frequencies $\leq$3 Hz (the normal range of impulse activity in which these systems are working) is dominated by vasodilation generated by antidromically conducted impulses in peptidergic afferents at rather low frequencies (0.1–1 Hz) showing how powerful the effect of antidromic afferent impulses on the arterioles is (Häbler et al., 1997). Thus Dr. Bove's experiments are important and interesting since they show that nerve inflammation is followed by antidromically conducted impulses in small diameter afferents.

Implications for understanding the mechanisms underlying CRPS. We learn from the experiments of Dr. Bove and colleagues, and hopefully will continue to learn in the future (see above), that peripheral neuritis could be a mechanism to start and maintain the early signs of CRPS. Such a hypothetical mechanism is completely compatible with the idea that CRPS is a disorder of the central nervous system (Jänig and Baron 2002, 2003). Taking the caveats and concerns I have raised above into consideration, Dr. Bove's data could explain some clinical phenomena of CRPS (e.g., ongoing pain, secondary hyperalgesia, hyperemia and swelling). Neuritis could be an initiating event, but it should be kept in mind that the expression of the clinical signs and symptoms of CRPS is disproportionate to the traumatic events. These initiating events can be strong or weak and associated with the affected extremity or occur (more rarely) remotely. Thus, the interesting experimental approach of Dr. Bove gives us some information about potential peripheral mechanisms triggering (and maintaining?) CRPS.

From the studies of Dr. Bove we do not learn about mechanisms underlying the following diverse observations made on CRPS patients that involve sympathetic, somatomotor and somatosensory (including nociceptive) systems and in particular the brain:

(1) Distorted regulation of sympathetic systems (e.g., to skin; see Wasner et al., 1999, 2001).

(2) Changes in non-painful somatosensory perceptions that may spread over the whole extremity, a quadrant or even half of the body (Rommel et al., 1999, 2001) and that are paralleled by changes in various cortical areas, including the primary and secondary somatosensory, insular, frontal and parietal cortices (Juottonen et al., 2002, Maihöfner et al., 2004, 2007, McCabe and Blake 2008, Pleger et al., 2004).

(3) Somatomotor changes (Deuschl et al 1991, Schwartzman and Kerrigan 1990, van Hilten et al., 2005).

(4) Strong body perception disturbances of the affected extremity (Förderreuther et al., 2004, Lewis et al., 2007) combined with referral of sensations to areas of the body immediately adjacent to the stimulated body sites (McCabe et al., 2003a).

(5) Sympathetically maintained pain (SMP) in a subgroup of CRPS patients (Ali et al., 2000, Baron et al., 2002, Schattschneider et al., 2006, Torebjörk et al., 1995) and pain relief lasting days or longer following sympathetic blocks in CRPS patients with SMP (Price et al., 1998, Jänig 2008).

(6) Decreased swelling following sympathetic blockade or spinal cord anesthesia (Blumberg et al., 1994). Sympathetic block reduces activity in sympathetic neurons. Spinal anesthesia could (a) reduce antidromically conducted impulses in small-diameter afferents generated by primary afferent depolarization of their central terminals in the spinal dorsal horn via GABAergic interneurons (Willis 1999) or possibly by cytokine release from activated glia (Milligan and Watkins 2009) and (b) reduce activity in sympathetic neurons innervating the affected extremity.

(7) Graded motor imagery followed by mirror feedback from a moving unaffected limb can reduce pain and swelling in patients with chronic CRPS and re-establish the pain-free relationship between sensory feedback and motor execution, thus repairing a postulated mismatch between the cortical motor output and the sensory feedback from skeletal muscle and visual system (McCabe and Blake 2008, McCabe et al., 2003b, Moseley 2004, 2005, 2006).

[2] This reflex was originally described for the innervation of the skin of the hindlimb and ear in rabbits by Christian Lovén working Carl Ludwig's laboratory in Leipzig (Lovén 1866).