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Peripheral nervous system origin of phantom limb pain

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ABSTRACT

Nearly all amputees continue to feel their missing limb as if it still existed, and many experience chronic phantom limb pain (PLP). What is the origin of these sensations? There is currently a broad consensus among investigators that PLP is a top-down phenomenon, triggered by loss of sensory input and caused by maladaptive cortical plasticity. We tested the alternative hypothesis that PLP is primarily a bottom-up process, due not to the loss of input but rather to exaggerated input, generated ectopically in axotomized primary afferent neurons in the dorsal root ganglia (DRGs) that used to innervate the limb. In 31 amputees, the local anesthetic lidocaine was applied intrathecally and/or to the DRG surface (intraforaminal epidural block). This rapidly and reversibly extinguished PLP and also nonpainful phantom limb sensation (npPLS). Control injections were ineffective. For intraforaminal block, the effect was topographically appropriate. The suppression of PLP and npPLS could also be demonstrated using dilute lidocaine concentrations that are sufficient to suppress DRG ectopia but not to block the propagation of impulses generated further distally in the nerve. PLP is driven primarily by activity generated within the DRG. We recommend the DRG as a target for treatment of PLP and perhaps also other types of regional neuropathic pain.

1. Introduction

The origin of phantom limb pain (PLP) remains uncertain. Religious and psychiatric interpretations once predominated [54,58], but these have since been supplanted by neurobiological and cognitive theories. The fact that pressure on amputation stump neuromas provokes PLP (Tinel sign), and the discovery that neuromas generate ectopic impulse discharge (ectopia), favored the stump as the pain generator [5,14,29,49,50,55,56,63]. However, PLP frequently persists despite neuroma infiltration and nerve/plexus block [4,27,46]. For this reason most investigators have abandoned peripheral nervous system (PNS) explanations in favor of the hypothesis that PLP is a consequence of maladaptive cortical plasticity induced by loss of input from the limb [1,23,28,39,46,48].

The cortical origin of PLP has considerable empirical support. For example, limb amputation or corresponding nerve injury leads to conspicuous neuroplastic remapping of somatotopic representations in the primary somatosensory cortex (S1) [16,21,24,25,31,32,53,66], with the extent of remapping proportional to the intensity of the pain [22]. Likewise, distortions in body schema perception occur when conflict is induced experimentally between the appearance of an individual's limb and proprioceptive feedback. In the rubber hand illusion, for example, the perceptual integration of the rubber hand is so striking that threatening it with injury evokes anxiety and pain affect–related cortical activations [18]. Some subjects report unpleasant sensations, perhaps even pain, due to such sensory–sensory mismatch [28]. Resolving this mismatch, as implemented in mirror box therapy, can relieve PLP, at least temporarily [48,53].

However, a second PNS source, outside of the stump, has never been adequately considered. For decades there has been direct electrophysiological evidence that afferent somata in the dorsal root ganglia (DRGs) also generate ectopia [33,37,52,62]. Indeed, in head-to-head comparisons, the DRG has proved to be a more robust source of spontaneous firing than neuromas [2,42]. Evidence, if indirect, is even available in humans [38,40,49,50]. For example, Nystrom and Hagbarth [50] showed that blocking

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stump neuromas eliminated the percussion-evoked Tinel sign and associated spike activity, but not the ongoing discharge recorded in the nerve. This likely originated in the DRG. DRG electrogenesis could account for the therapeutic failure of neuroma, nerve, and plexus infiltration because these distal blocks do not affect the DRG.

Because DRGs share the same cerebrospinal fluid compartment as the spinal cord, spinal blocks and intraforaminal blocks both have the potential to arrest all PNS ectopia: stump and DRG. We are unaware of any systematic reports on effects of either type of block on PLP. However, spinal block is frequently used in stump revision surgery, and practitioners we have consulted attest that this indeed transiently stops PLP (R. Boas and A. Stav, personal communications). Paradoxically, case studies have reported transient rekindling of quiescent PLP after spinal block, but this is rare [60]. A likely explanation is that the injectate used transiently excited DRG neurons, or the spinal neurons they drive, by a mechanical, thermal, or chemical mechanism (rapid injection of large volumes in a restricted space, cold solution, inaccurate pH/osmolarity, or preservatives). Here we used diagnostic spinal and intraforaminal blocks in human amputees to determine whether preventing central nervous system (CNS) access of ectopic signals generated in the DRG might affect PLP and/or nonpainful phantom limb sensations (npPLS).

2. Methods

2.1. Subjects, experimental design, and rationale

We report results of 4 related procedures intended to block the access of nerve impulse discharge originating in the PNS from reaching the brain. These are represented in 4 experimental groups. In group 1, our primary focus, we tested effects of blocking abnormal afferent input by epidural intraforaminal injection. In group 2, for comparison, we also examined spinal (intrathecal) block. In a few cases (group 3), local infiltration of stump neuromas or peripheral nerve block was performed. Procedures were carried out in 2 centers located in regions that have known recent military conflict and that serve relevant patient populations; staff at such facilities are acutely aware of the limits of current treatment and encouraged the introduction of better therapeutic options. At the Trauma University Hospital and the associated Galenus Clinic (Tirana, Albania), we treated 16 lower limb amputees with ongoing PLP (11 men, 5 women). These participated in experimental groups 1 to 3, where some of the amputees participated, on separate occasions, in 2 or 3 of the groups. Each of the 16 individuals is identified by a unique number to facilitate tracking who underwent which procedure. Finally, group 4 comprised an additional 15 amputees (14 men and 1 woman) who were treated with a modified protocol of intraforaminal injection at the Pain Rehabilitation Unit, Chaim Sheba Medical Center (Tel Hashomer [Tel Aviv], Israel).

Inclusion criteria were age >18 years, good general health, ability to communicate and understand instructions, and presence of significant PLP with a frequency and intensity that interfered with daily life. Subjects were excluded if they had significant sensory deficits, major pain complaints other than PLP (including severe stump pain, which might have distracted from their ability to report on their PLP), major CNS or PNS neurological disorders other than diabetic polyneuropathy and trauma associated with the cause of amputation, major cognitive or psychiatric disorders, or contraindication to the injection of lidocaine, corticosteroids, or contrast agents.

Subject background and demographic information is provided in Tables 1 and 2. Experimental protocols were approved by authorities on human experimentation (Helsinki committees) at both institutions.

Most subjects had experienced traumatic amputation; in Tirana, it was frequently from stepping on a land mine. Some amputations, however, were due to vascular insufficiency or other causes. PLP tends to be similar regardless of the precipitating pathology [7]. The objectives and risks of the blocks were explained to the subjects in their language, including the fact that treatment results may have no effect on PLP, may produce partial and reversible analgesia, or may yield more prolonged pain relief. Informed consent was obtained. We then initiated a protocol that was standardized but subject to minor variations depending on the individual patient. First, a history was taken, and the present quality and location of PLP and npPLS was documented by text, photos, body charts, and sketches. Information on the circumstances of amputation, frequency and duration of PLP, changes over time, and exacerbating and relieving factors was also noted. Special care was taken to ensure that subjects fully understood the difference between sensations experienced in the phantom limb (PLP and npPLS) and those experienced in the stump.

The amputation stump was then systematically examined, and tender points and points at which a Tinel sign could be evoked by palpation or percussion were marked on the skin. Finally, subjects were prepared for injections. No sedation was used so that subjects

Table 1
Subject demographics, baseline pain, and results of spinal (intrathecal) block.

Patient no.	Sex/ age, y	Amputation, cause, interval since amputation	Baseline phantom, effect of percussion over stump neuromas (Tinel →), (notes)	Level	Effect of spinal block on phantom and Tinel
1	M/61	R AKA, diabetes, 30 y	PLP lateral foot (severe), npPLS leg below knee, Tinel → PLP	L3–4	PLP, npPLS and Tinel lost, recovery after >3 h
2	F/40	AKA bilateral, trauma, 11 mo	bilateral PLP, bilateral npPLS (numbness, sensation of movement), Tinel → stump pain (“electric”)	L3–4	PLP lost, npPLS and Tinel persists, all bilaterally
3	F/65	BKA, scleroderma, 7 days	PLP, npPLS, Tinel → stump pain	L3–4	PLP, npPLS and Tinel lost
4	M/52	L AKA, trauma, 3 y, R AKA, vascular, 1 y	L PLP (modest “shooting”), R PLP (severe, “pulsing”), npPLS bilaterally, Tinel → stump pain	L3–4	PLP, npPLS and Tinel lost bilaterally
5	F/24	R hip disarticulation, trauma, 2 y	PLP (severe), npPLS (knee to foot), Tinel → PLP	L3–4	PLP, npPLS and Tinel lost
6	M/61	R AKA, vascular, 5 d	PLP (“electric”), npPLS, Tinel → PLP	L2–3	PLP, npPLS and Tinel lost
7	M/48	R AKA, trauma, 10 y	PLP, npPLS, stump (itch + burning), Tinel → PLP (lateral toes)	L4–5	PLP, npPLS and Tinel lost. Stump pain lost
8	M/22	R lateral foot (toes 2–5), trauma, 9 y	PLP (toe 5), npPLS, Tinel → stump pain, scar “cold”	L4–5	PLP, npPLS and Tinel lost
9	M/24	R BKA, trauma, 10 y	PLP (toes 4, 5), npPLS, Tinel → PLP, ongoing stump pain	L4–5	PLP↓, npPLP and Tinel lost
10	M/39	R BKA, trauma, 10 y	PLP, Tinel → PLP + stump pain, ongoing stump pain (cold)	L4–5	PLP, Tinel and stump pain lost
11	M/51	L foot, trauma, 10 y	PLP (sole), npPLS (foot) Tinel → stump pain	L4–5	PLP, npPLS and Tinel lost

R, right; AKA, above knee amputation; PLP, phantom limb pain; npPLS, nonpainful phantom limb sensation; Tinel, evoked Tinel sign; BKA, below knee amputation; L, left.

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