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Are 10 kHz Stimulation and Burst Stimulation Fundamentally the Same?

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Background: Spinal cord stimulation (SCS) is routinely used for intractable pain syndromes. For SCS to be efficacious the painful area needs to be covered by SCS induced paresthesia symptoms. Recently, novel stimulation designs have been developed for spinal cord stimulation (SCS) that are superior to classical spinal cord stimulation and exert their effects without the mandatory paresthesia. Two such stimulation designs are burst stimulation and 10 kHz stimulation.

Objective: Whereas the mechanism of action of burst SCS has been partly elucidated, in that it modulates the medial pain pathway in contrast to tonic stimulation, the mechanism of action of 10 kHz SCS is still enigmatic. The goal of this paper is to provide a perspective or informed opinion on the differences and similarities between burst SCS and 10 kHz stimulation by using a literature search on the two stimulation designs.

Discussion/Conclusion: Human clinical data, simulation studies, quantitative sensory testing, cellular investigations, and comparative animal and human studies all point in the same direction, namely that 10 kHz and burst SCS might both modulate the medial pain pathway, and could be fundamentally similar neurostimulation designs.

Keywords: 10 HF, 10 kHz, Burst, medial pathway, pain, SCS, spinal cord, stimulation

Conflict of Interest: Dirk De Ridder has IP on burst stimulation but has no more financial interest in the context of this perspective article. Sven Vanneste and Sanjaya Perera have no conflicts of interest to disclose.

INTRODUCTION

Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (1). Global pain can thus be seen as a combination of a sensory component, namely painfulness and an emotional/motivational component, namely suffering. Whereas physiologic, nociceptive pain can be considered as a protective sense, chronic neuropathic pain has become independent of and dissociated from this protective sense (2). Chronic neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (3).

The suffering of the pain, expressed by unpleasantness, has a motivational capacity to do something about the pain, that is, to orient behavior to withdraw from the painful stimulus. Pain is processed by at least three pathways, two ascending pain generating pathways (4,5) and at least one descending pain inhibitory pathway (6). There are more pathways that relay nociceptive information to the brain, such as the spinoreticular and spinohypothalamic pathways, but these fall out of the scope of this perspective. The medial pain pathway encodes the motivational/affective component of pain (4,5), that is, the unpleasantness, (5,7) in sum, the suffering. The lateral pathway encodes the discriminatory/sensory (5) components of pain, such as intensity, type of pain (burning, aching, throbbing, etc.), the location and so forth, and the descending pain inhibitory pathway suppresses ongoing pain in a state dependent manner (6). The medial and lateral pain pathways are processed in parallel (8), and can be individually modified without affecting the other pathway (5), as is already known for a long time. Indeed cingulotomies can reduce pain suffering without reducing pain intensity (9). It is clear that the ascending pain evoking and descending pain inhibitory pathways need to interact is some way, and it has been suggested that these interactions are dynamically changing (10) depending on the context (11), and that it is ultimately the balance between pain input and pain suppression that results in whether someone feels pain or not, both in neuropathic (12), and fibromyalgia pain (13). The exact anatomical and functional connectomics in pain have yet to be unraveled, but both structural (i.e., anatomical) and functional (i.e., resting state) MRI studies in pain demonstrate complex interactions between somatosensory cortex, cingulate cortex, insula, amygdala, thalamus and frontal cortex (14,15).

Chronic, intractable neuropathic pain is routinely treated by electrical stimulation of the spinal cord (SCS) (16). Spinal cord stimulation (SCS) is based on the "gate–control" theory (17), which postulates that activity in large diameter cutaneous fibers (type Aß) inhibits the transmission of noxious information via small Aδ and unmyelinated C fibers to the brain. Electrical stimulation of these large afferents elicits a tingling sensation (paresthesia) (18,19) in the corresponding dermatomes. To obtain successful treatment of chronic, neuropathic pain by tonic SCS, the stimulation-induced paresthesia's have to cover the pain area as completely as possible

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(20,21). Recently, 2 SCS stimulation designs have been developed that can reduce pain without the mandatory paresthesia: Burst stimulation (22) and 10 kHz stimulation (23). Burst stimulation consists of intermittent packets of 5 high frequency stimuli delivered at 500 Hz (500 Hz spike mode) and this 40 times per second (40 Hz burst mode), with a long pulse width of 1000 μs and 1000 μs interspike interval delivered in constant current mode. The monophasic pulses are charge balanced at the end of the burst, differentiating it from clustered high frequency tonic stimulation. It was initially developed for auditory cortex stimulation as a treatment for noise-like tinnitus, which did not respond to classical tonic auditory cortex stimulation (24). The underlying philosophy was that noise-like tinnitus was generated by hyperactive burst firing in the nontonotopic (hence noise-like sound perception) extralemniscal auditory system and that suppressing hyperactive burst firing requires a more powerful stimulation than tonic stimulation (25). Considering the pathophysiologic and clinical analogies between pain and tinnitus (26), it was hypothesized that noise-like tinnitus could be the clinical analogon for paresthesias and pure tone tinnitus the analogon for pain (27). Thus burst stimulation was developed, by mimicking burst firing properties of the thalamus, involved both in pain and tinnitus generation (27). On the other hand, for 10 kHz SCS the reason for its inception is unclear. It is claimed that high-frequency stimulation of wide dynamic range (WDR) neurons, which are hyperactive in chronic pain conditions, results in decreased output of these cells (desensitization) and brings them closer to preinjury states (data on file at Nevro Corp.) (23). It is proposed that control of the "wind-up" phenomena in WDR neurons may be one of the ways this therapy provides pain relief. 10 kHz SCS is in principle a form of tonic stimulation, using 30 μsec pulse width and individually actively charge balanced pulses delivered at very high frequencies (23).

The mechanistic view of the pain gate mechanism has evolved from a local effect at the level of the spinal cord as initially postulated, to a combination of a local spinal as well as supraspinal mechanism (28,29). Using fMRI it has been shown that tonic stimulation modulates the lateral and descending pathways but not the medial pathway (30). Furthermore, animal studies have shown that tonic stimulation exerts its effect via modulation of the proprioceptive/touch pathways, as WDR and tactile C fibres in the nucleus gracilis are activated by tonic stimulation (31) and the effect could be blocked by a GABA antagonist, suggesting that tonic stimulation exerts its effect, at least partially by activating the inhibitory GABA neurotransmitter system. In addition, 10 kHz stimulation has been developed as a novel way of SCS also in a paresthesia-independent way (32). However, no mechanism of action has been proposed that can explain the clinical symptoms, which are very reminiscent of burst SCS. Based on a computational model it was proposed that 10 kHz stimulation may not function through direct activation or conduction block of dorsal column or dorsal root fibers (33), which has been the generally assumed mechanism of action (34). The authors of the computational study proposed that additional concepts and/or alternative hypotheses should be considered when examining the pain relief mechanisms of 10 kHz SCS (33).

The goal of this paper is to provide a perspective or opinion on the differences and similarities between burst SCS and 10 kHz stimulation by using a literature search on the two stimulation designs.

OPINION

Clinically both burst and 10 kHz stimulation seem to result in a better pain suppression than classical tonic stimulation, without the mandatory paresthesia, in about the same quantities. On average preoperative pain improves from 8/10 to 5/10 with classical tonic stimulation to 3/10 with burst and 10 kHz SCS (22,32,35,36). Furthermore, on average 10 kHz SCS and burst SCS reduce back pain better than tonic stimulation (32,37,38). This is confirmed in the only study that compared burst and 10 kHz SCS head to head (39). In this study 16 consecutive patients were randomized to either burst or 10 kHz ($N = 8$ burst vs 8 HF). There were two nonresponders to HF, but all patients responded to burst SCS. Burst induced significant pain suppression in the limbs whereas HF did not. But more interestingly, both burst and 10 kHz SCS resulted in similar pain suppression for back pain, a similar improvement in mood and sleep. This suggests that from a clinical point of view both burst and tonic stimulation modulated the medial pain pathway resulting in an improvement in mood and sleep. But if so, what would be the mechanism of action for 10 kHz stimulation to do so?

Simulation studies have shown that at clinical high frequency stimulation (HFS) frequencies and pulse widths, HFS preferentially blocks larger-diameter fibers and recruits medium and smaller fibers (40). Indeed, at amplitudes >3V and frequencies >6 to 7 kHz large diameter fibers are blocked, whereas C-fibers are not (40). This would suggest that the medial C-fiber mediated system is still modulated whereas the lateral system is suppressed. If this simulation study is correct than this should be reflected in clinical data. It has since long been known that large fibers mediate touch, proprioceptive and vibration sense, and that C-fibers transmit pain and temperature stimuli (41). In a clinical study using quantitative sensory testing, the effect of 10 kHz SCS on sensory processing was evaluated, and it was confirmed that 10 kHz stimulation alters processing in large fibers without modulating C-fibers (42). Indeed, 10 kHz stimulation resulted in a decreased vibratory sense and pinprick detection versus classical tonic stimulation (Aα and Aβ), but no effect on temperature thresholds (C-fibers) was noted for 10 kHz versus tonic SCS, confirming the simulation data clinically. The fact that in the simulation studies the blocking effect only was present at frequencies more than 6 to7 kHz could potentially explain why a placebo-controlled SCS study applying stimuli at 5000 Hz on the spinal cord didn't yield any better results than sham (43). Unfortunately, similar simulation studies have not been performed for burst stimulation.

At a systems level burst and tonic SCS commonly modulate the lateral (discriminatory) (5) and descending pain inhibitory (6,44) pathways (12,22). But burst stimulation in addition to modulating the descending and lateral pain pathway also modulates the medial pathway, which encodes the affective/motivational component of the pain, as demonstrated clinically by a dramatic change in pain vigilance awareness questionnaire (37) and the affective component of the McGill questionnaire (45,46) and the pain catastrophizing scale (47).

So, based on simulation and human clinical electrophysiologic studies it seems that both burst and 10 kHz modulate the C-fiber mediated medial system.

Further animal studies have shown that bursts at 500 Hz maximally inhibit post-synaptic potentials (48), more so than 500 Hz tonic stimuli. But that does not exclude that bursts at 1000 Hz would not be better, and 10 kHz even better than 1000 Hz. A clinical study comparing bursts at 500 Hz and bursts at 1000 Hz did not show any benefit for 1000 Hz spike mode more than 500 Hz spike mode, suggesting that frequencies beyond 500 Hz in burst mode might not exert an extra benefit (38). An animal study further showed that 500 Hz, 1000 Hz, and 10 kHz have similar effect in SCS (49), but 10,000 Hz differs from 50 Hz tonic mode. SCS at 50 Hz increases firing in the nucleus gracilis, but not so for 10 kHz (49), analogous to what has

been shown for burst mode (50). In other words, 10 kHz is fundamentally different from classical tonic stimulation in that it also does not modulate the proprioceptive dorsal column pathways, similar to what has been shown for burst stimulation (31).

In summary, human clinical data, simulation studies, quantitative sensory testing, cellular investigations, and comparative animal and human studies all point in the same direction, namely that 10 kHz and burst SCS might both modulate the medial pain pathway, and could be fundamentally similar neurostimulation designs.

An electrophysiologic (EEG, QST) or other functional imaging study comparing 10 kHz SCS and burst SCS could prove or disprove whether this perspective on 10 kHz and burst SCS is correct or not. Indeed, a conjunction analysis could determine what 10 kHz and burst SCS have in common and a subtraction analysis what is different between the two stimulation designs. This comparative neurophysiologic study could shed scientific light on the elusive mechanism of action of the enigmatic 10 kHz stimulation. Furthermore, it is of scientific interest that two opposite philosophic approaches to SCS could lead to a similar effect. Whereas burst SCS is fundamentally based on mimicking nature (27) and attempting to be as physiologic as possible, 10 kHz SCS seems to arrive at similar effects based on a very nonphysiologic mechanism, as no cells, nor axons can follow frequencies up to 10 kHz.

A simple neuroimaging study could confirm or disprove the conceptual analogy between burst stimulation and 10 kHz HF stimulation. By performing EEGs or PET or fMRI studies a conjunction analysis can demonstrate whether both stimulation designs modulate the dACC, that is, the medial pain pathway, and a subtraction analysis can demonstrate where they differ, analogous to what has been done for burst versus classical tonic stimulation (12,22).

Authorship Statement

Dirk De Ridder, Sanjaya Perera, and Sven Vanneste wrote and revised the manuscript.

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