# Assessment of spinal cord stimulation-based modulation in the spontaneous hyperexcitability model of neuropathic pain

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Spinal cord stimulation (SCS) is used clinically for relief of chronic neuropathic pain. The gate control theory presents a theoretical framework of the therapy's mechanism of action associated with Aβ sensory afferent recruitment, but the true mechanisms remain unclear. Preclinical studies frequently investigate mechanisms leading to modulation of stimulus-evoked pain, despite the primary function of therapeutic SCS being modulation of chronic, stimulus-independent pain. Here, we utilized an *ex vivo* spinal cord-dorsal root ganglia preparation to generate a model of spontaneous hyperexcitability in sensory nociceptive circuits using 4-aminopyridine (4-AP). Applied 4-AP selectively increased Fos immunolabeling in superficial dorsal horn neurons - consistent with selective recruitment of pain circuitry (n=2). We characterized spontaneous activity by recording from sensory afferents in lumbar dorsal roots (DR), Lissauer's tract (LT), and neurons in the superficial dorsal horn (DH). 4-AP led to the emergence of spontaneous activity manifesting as rhythmic dorsal root potentials with superimposed burst firing, and coincident rhythmic field potentials with superimposed spikes in LT and the subjacent DH (n=4). To investigate modulation of spontaneous nociceptive activity by gate control theory mechanisms we assessed the effects of clinically-analogous SCS at dorsal column (DC) and dorsal root (DR) recruitment threshold intensities. We observed that 50 Hz SCS at DC threshold intensity depressed spiking activity in LT/DH during SCS, but it could not modulate field potentials or produce prolonged modulation following cessation of stimulation (n=4). These results demonstrate the utility of a 4-AP model of spontaneous hyperexcitability and the limitations of presumed selective Aβ recruitment as underlying SCS modulation of spontaneous nociceptive activity.