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

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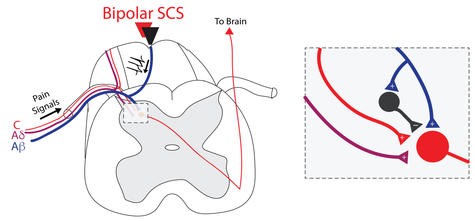
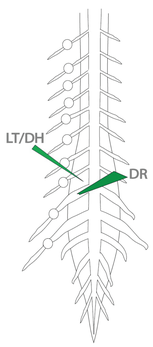
Background

Spinal cord stimulation (SCS) is a clinical therapy for intractable neuropathic pain in the lower limbs and low back. Its mechanism of action remains unclear despite its clinical use for over 50 years. The gate control theory is a theoretical framework by which electrical stimulation of the dorsal column can block transmission of peripheral pain signals from being perceived in the brain, but this theory has not been able to explain why SCS seems to preferentially block chronic neuropathic and not nociceptive pain. Few studies have explored how recruitment of Aβ afferents can inhibit transmission of ***spontaneous nociceptive activity.*** Here, I use 4-aminopyridine to pharmacologically induce spontaneous activity and to investigate if recruitment Aβ afferents from the segment of interest is required for modulation of spontaneous nociceptive activity in the dorsal spinal cord.



Methods

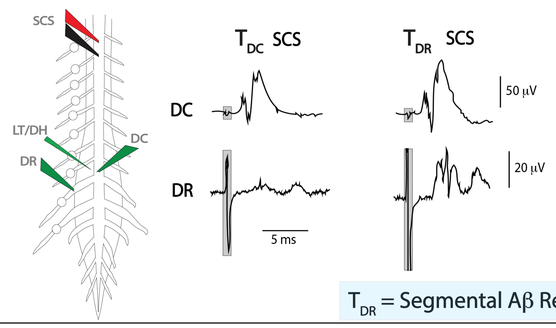
Adult mouse spinal cord- dorsal root ganglia preparation



Step 1:
Characterize spontaneous nociceptive and non-nociceptive activity generated with 4-aminopyridine (10-20 mM)

4-aminopyridine (4-AP): K+ channel blocker

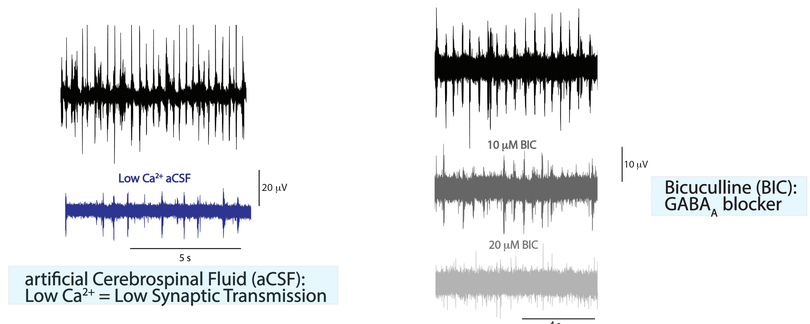
Step 2:
Investigate SCS modulation of spontaneous nociceptive activity at subthreshold and threshold amplitudes for dorsal root Aβ recruitment



T_{DR} = Segmental Aβ Recruitment

4-AP generates spontaneous dorsal root bursts that are mediated by oscillations in dorsal horn circuits

Spontaneous bursting in lumbar dorsal root with bath applied 4-AP



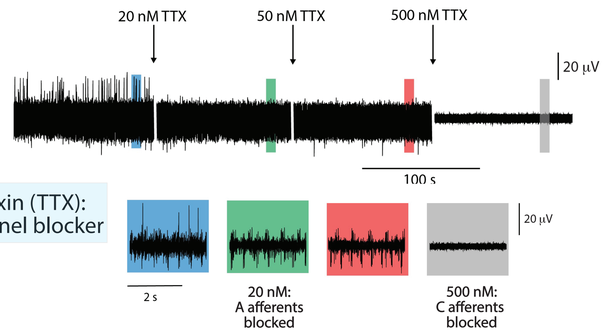
artificial Cerebrospinal Fluid (aCSF): Low Ca^{2+} = Low Synaptic Transmission

Bicuculline (BIC): $GABA_A$ blocker

Dorsal root bursting is reduced following depression of synaptic transmission and block of $GABA_A$ receptors

Peripheral actions of 4-AP produces spontaneous firing in A and C primary afferents

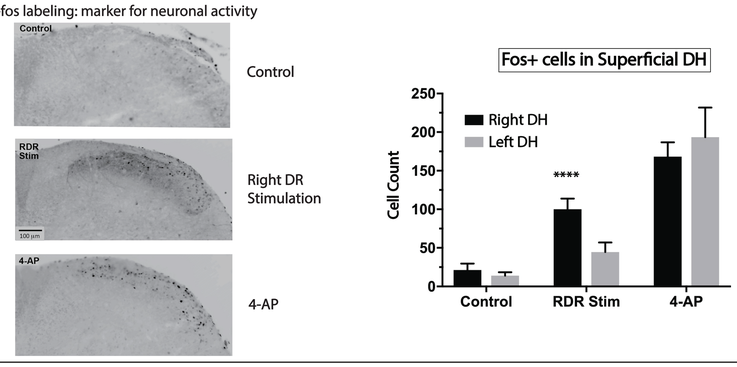
Spontaneous firing in lumbar dorsal root with bath applied 4-AP + blocked synaptic transmission



Tetrodotoxin (TTX): Na + channel blocker

Histological evidence of superificial dorsal horn activation in 4-AP spontaneous hyperexcitability model

c-fos labeling: marker for neuronal activity

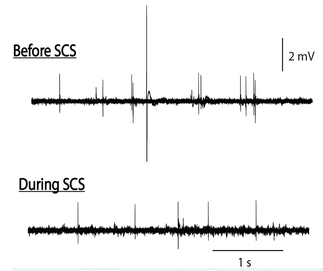


n = 2

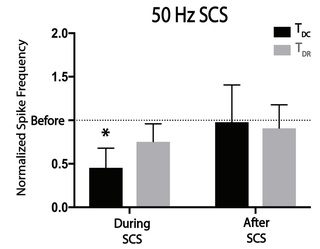
50Hz spinal cord stimulation (SCS) at dorsal column threshold (TDC) modulates spiking in pain encoding circuits.

Spontaneous activity in LT/DH

n = 4



SCS Parameters Studied:
10, 50, 100 Hz | TDR or TDC amplitude



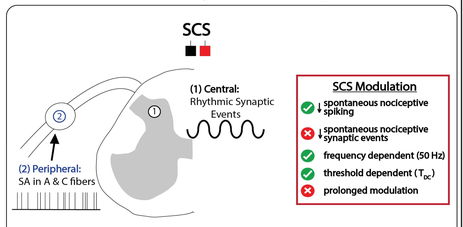
Only 50 Hz stimulation at TDC reduced spontaneous spiking
No parameters modulated synaptic events or produced modulation after SCS was turned off.

Conclusions

Segmental Aβ recruitment does not enhance SCS modulation of spontaneous pain-like activity

Prolonged modulation may require longer periods of stimulation or descending 5-HT or NE signaling

Summary of Findings:



Model of Sensory Hyperexcitability

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