AN *IN VIVO* STUDY OF THE SITE OF ACTION OF SD118/SNL043 IN CCI RATS.

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BACKGROUND: SD118/SNL043 is a novel chemical entity in clinical development for the treatment of pain. Initial behavioural studies revealed that this compound is effective in reversing mechanical allodynia in the rat chronic constriction injury (CCI) and STZ-induced diabetic neuropathy models of neuropathic pain. Electrophysiological experiments also suggested that this compound inhibits ectopic discharge of peripheral nerve fibres in CCI rats (Zhao *et al*., 2008). In the current study we investigated the site(s) of action of SD-118/DRP-43 using *in vivo* electrophysiological recording techniques.

METHODS: Electrophysiological studies were undertaken in rat chronic constriction injury (CCI) models of neuropathic hypersensitivity, validated with von Frey hairs. The protocols to record dorsal root ganglion (DRG) generated and neuroma-generated ectopic discharge in CCI rats are shown in Figures 1 and 2.

The spontaneous activity of dorsal horn WDR neurons in CCI rats was made after a laminectomy to expose the spinal cord segments L4-L6, with and without section of the ipsilateral drosal roots. SD118 was administered intravenously.

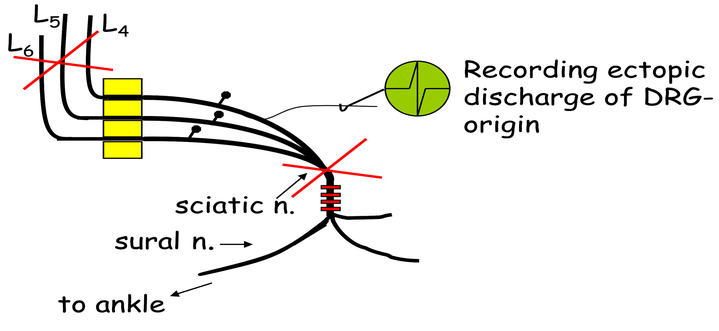


Figure 1. A schematic diagram showing the protocol used to record DRG-generated ectopic discharge

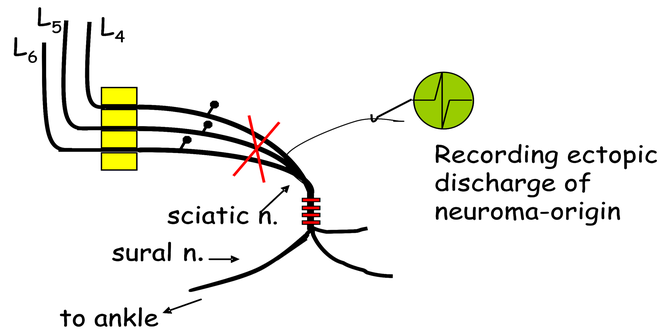


Figure 2. A schematic diagram showing the protocol to record neuroma-generated ectopic discharge

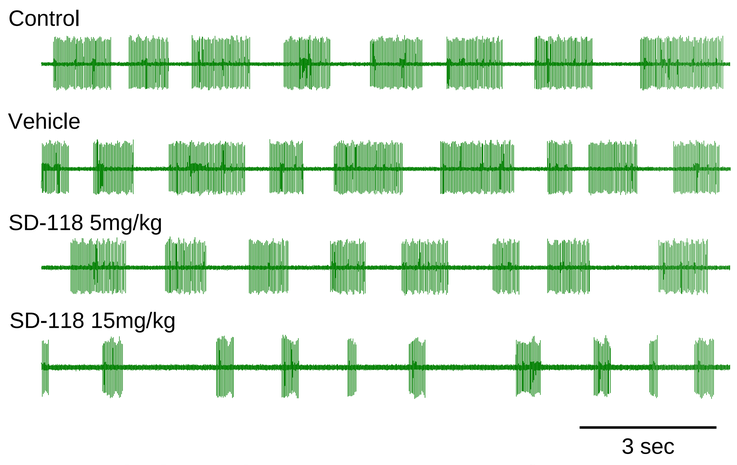


Figure 3. SD-118 induced inhibition of neuroma-generated ectopic discharge.

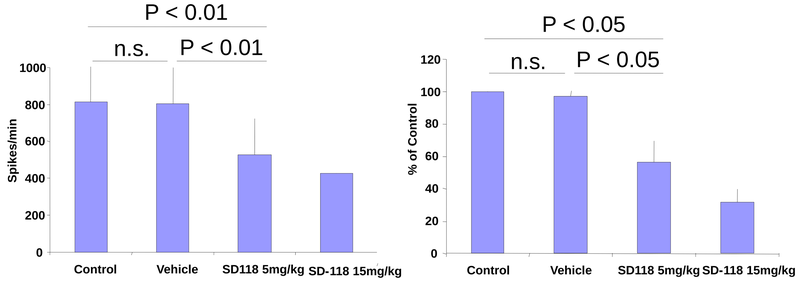


Figure 4. The effects of SD-118 on ectopic discharge generated in DRG and neuroma are not significantly different.

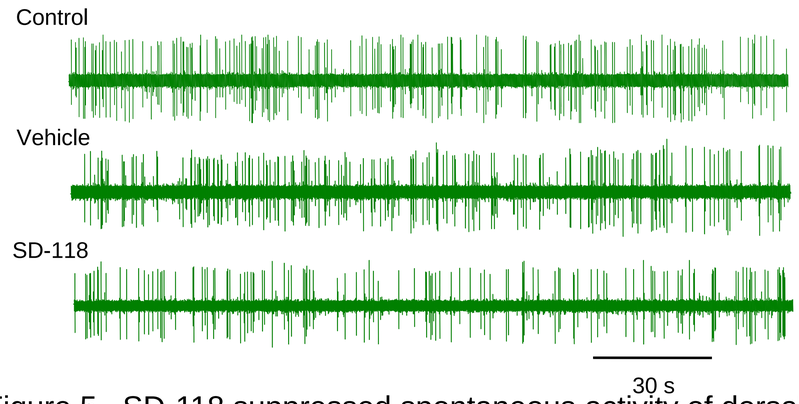


Figure 5. SD-118 suppressed spontaneous activity of dorsal horn neurones in CCI rats with dorsal roots intact.

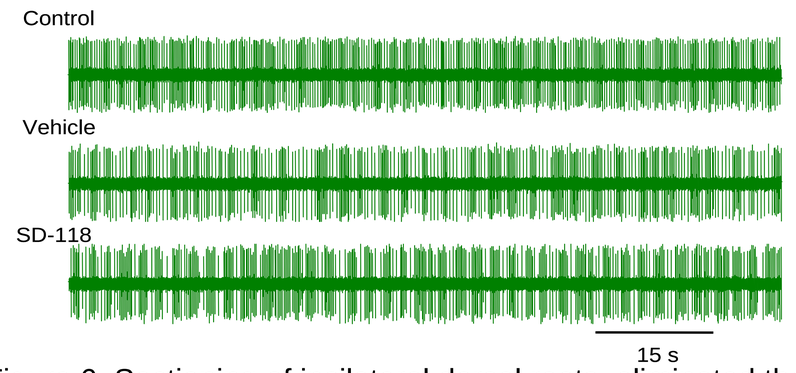


Figure 6. Sectioning of ipsilateral dorsal roots, eliminated the effects of SD-118 on spontaneous activity of dorsal horn neurones.

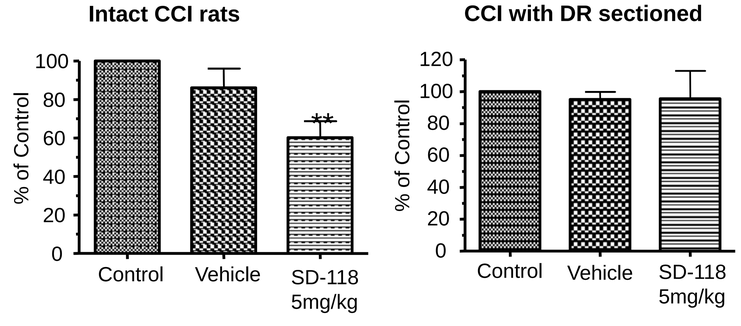


Figure 7. Effect of SD-118 on spontaneous activity was eliminated after section of ipsilateral dorsal roots in CCI rats.

CONCLUSIONS: Taken together, these data suggest the primary site of action of SD -118/SNL043 resides at the level of the peripheral nerve.

Acknowledgement: This research is a collaborative, joint project between Sosei and NeuroSolutions Ltd.