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# Lack of mechanical and thermal allodynia, and thermal hyperalgesia induced by peripheral neuropathic pain in NOS2 knockout mice

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## Background

Neuropathic pain is a clinical manifestation characterized by the presence of spontaneous pain, hyperalgesia and allodynia. Several works have demonstrated that selective NOS2 inhibitors might reverse the hypersensitivity to pain induced by neuropathy [1,2]. Although these studies suggest a potential role of NOS2 in the modulation of neuropathic pain, the exact involvement of NOS2 in the development of peripheral neuropathic pain remains unclear. The aim of this study is to investigate the involvement of nitric oxide synthesized by NOS2 in the development and expression of neuropathic pain after total sciatic nerve injury.

## Materials and methods

Neuropathic pain induced by the chronic constriction of the sciatic nerve (CCI) was performed in NOS2 knockout (NOS2-KO) mice and their wild type (WT) littermates. The development of mechanical and thermal allodynia, and thermal hyperalgesia was evaluated by using the von Frey filaments, cold plate and plantar tests, respectively. Both, NOS2-KO and WT mice were tested in each paradigm on days 1, 4, 7, 10, 14 and 21 after CCI induction. We used sham-operated NOS2-KO and WT mice as controls.

## Results

Pre-surgical tactile and thermal withdrawal thresholds were similar in both genotypes. In WT mice, the chronic constriction of the sciatic nerve led to a neuropathic pain syndrome characterized by a marked and long lasting reduction of the paw withdrawal thresholds to mechanical and thermal stimuli. In contrast, NOS2-KO mice failed to display peripheral nerve injury-induced mechanical and thermal allodynia as well as thermal hyperalgesia. Indeed, significant differences were observed when compared the paw withdrawal thresholds to mechanical and thermal stimuli between the ipsilateral paws of both genotypes ($P < 0.001$; Student's t-test). As expected, no significant changes in withdrawal thresholds to mechanical and thermal stimuli were seen on the contralateral paw in either WT or NOS2-KO operated mice, as well as on the contralateral and ipsilateral paws of both WT and NOS2-KO sham-operated mice. Although a significant decrease of the thermal withdrawal latencies was observed in NOS2-KO mice when compared the ipsilateral vs. contralateral paw, from day 7 to 21 after CCI ($P < 0.05$; Student's t-test).

## Conclusion

These results indicate that nitric oxide synthesized by NOS2 plays a critical role in the development and expression of peripheral neuropathic pain in mice.

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