UMM UNIVERSITÄTSMEDIZIN MANNHEIM

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Fractalkine-induced hyperexcitability of spinal dorsal horn neurons in an animal model of non-specific low back pain

K. Sessler, V. Blechschmidt, U. Hoheisel, S. Mense, R.-D. Treede

Department of Neurophysiology, Medical Faculty Mannheim, University of Heidelberg

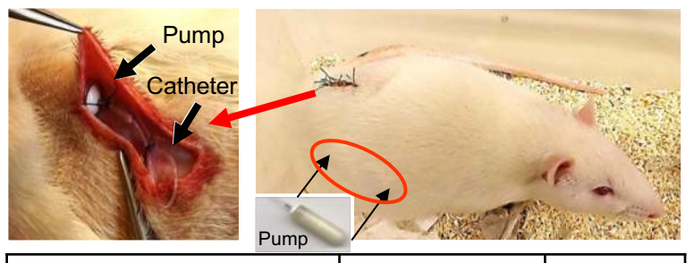
Background

Activated microglia plays a crucial role in spinal neuronal sensitization. Fractalkine (FKN) is an important modulator of spinal signaling cascades that specifically activates microglia.

In an animal model of non-specific low back pain (2 injections of nerve growth factor (NGF) into a low back muscle within 5 days) the sensitising effect of FKN on dorsal horn neurons was investigated.

Methods

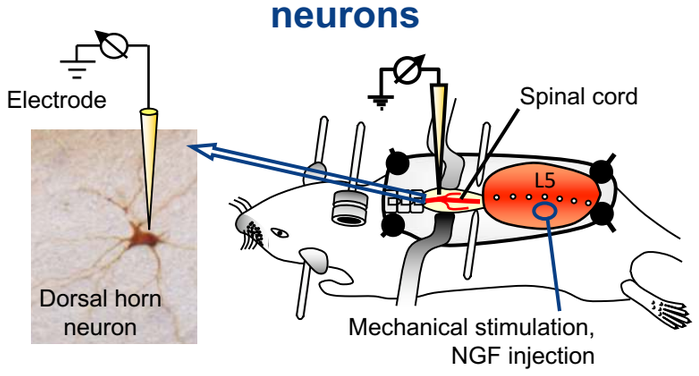
Continuous intrathecal administration



Test substance	Concentration	Duration
Neutralizing antibodies		6 days
Fractalkine	200 ng/ml	5 days
Fractalkine	20 ng/ml	5 days

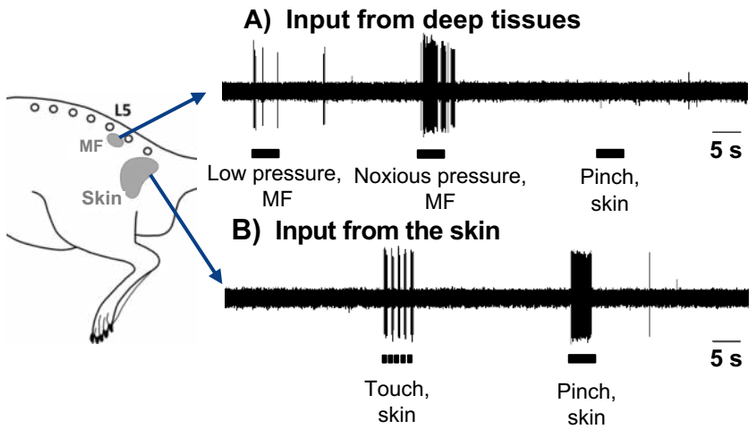
Test substances were applied intrathecally using a **subcutaneously implanted osmotic pump** (ALZET).

In vivo recordings of spinal dorsal horn neurons



In anesthetized rats the impulse activity of single dorsal horn neurons with **input from deep tissues of the low back** were recorded.

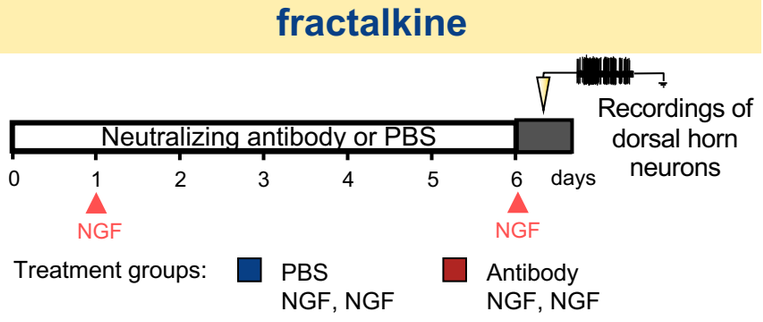
Impulse activity of a single dorsal horn neuron after mechanical stimulation



Impulse activity of a neuron activated by noxious pressure applied to the multifidus muscle (MF), but not by pinching the overlying thoracolumbar fascia **(A)**.
This neuron also responded to touching and pinching the hip skin **(B)**.

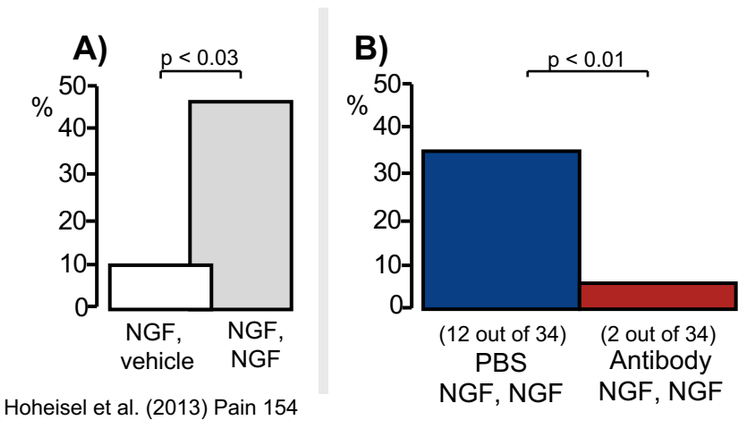
Results

Series 1: Neutralizing antibodies against fractalkine



To prevent neuronal hyperexcitability – induced by two NGF injections (red arrows) -, the FKN signaling pathway was blocked by neutralizing antibodies.

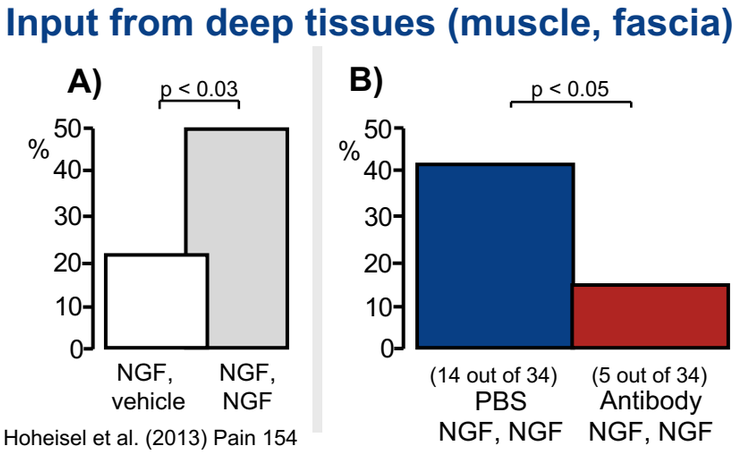
Convergent input from different types of tissues (muscle, fascia, skin)



Hoheisel et al. (2013) Pain 154

A) Neuronal hyperexcitability induced by 2 NGF injections indicated by an increased number of convergent neurons (Data from Hoheisel et al. (2013) Pain 154).
B) Intrathecally applied antibodies against FKN prevented the NGF induced increase in number of convergent neurons.

Input from deep tissues (muscle, fascia)

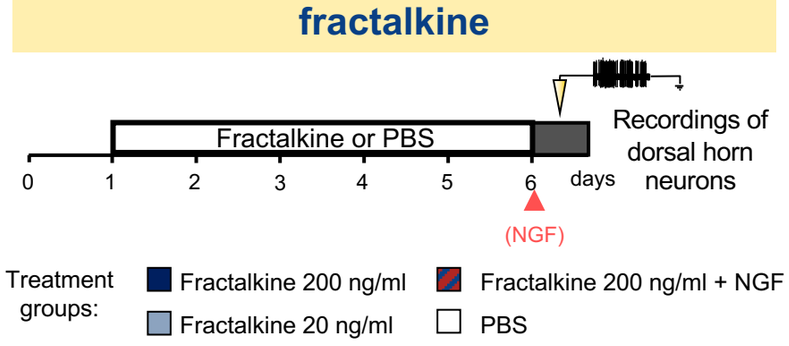


Hoheisel et al. (2013) Pain 154

A) NGF induced increase in the proportion of neurons with input from deep tissues (Data from Hoheisel et al. (2013) Pain 154).
B) Neutralizing antibodies also prevented this increase.

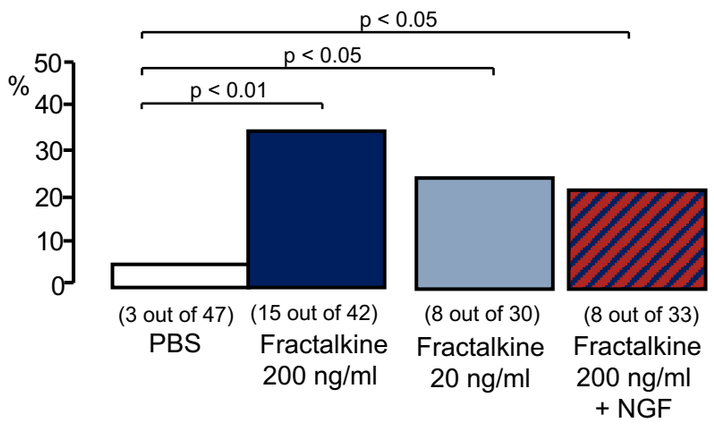
Neutralizing antibodies against fractalkine had the same effect as complete microglia inhibition by minocycline (Zhang et al. (2017) J Neurophysiol 118): both prevented NGF induced neuronal hyperexcitability.

Series 2: Direct administration of fractalkine



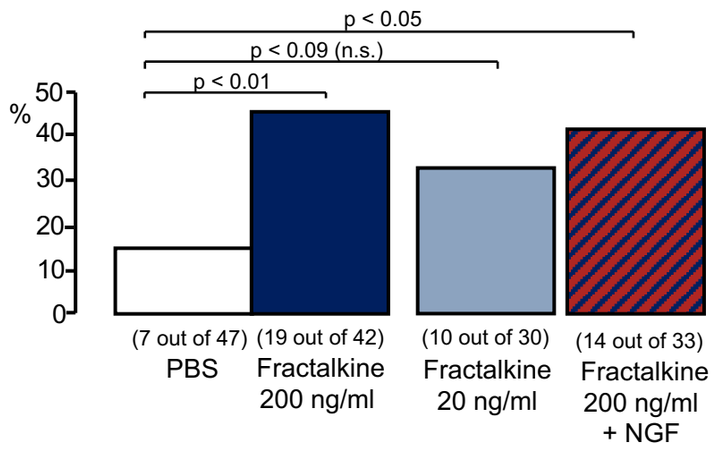
To further investigate the effect of FKN on neuronal sensitivity, FKN itself was applied intrathecally (concentration: 200 or 20 ng/ml for 5 days).

Convergent input from different types of tissues (muscle, fascia, skin)



200 ng/ml FKN significantly increased the proportion of convergent neurons; 20 ng/ml FKN had a similar effect. An additional NGF injection did not boost the FKN effect.

Input from deep tissues (muscle, fascia)



200 ng/ml FKN significantly increased the proportion of neurons with input from deep tissues; 20 ng/ml had a similar effect. An additional NGF injection did not boost the FKN effect.

Both tested fractalkine concentrations (200 and 20 ng/ml) showed similar sensitizing effects. An additional NGF injection into the lumbar muscles prior to the recordings did not add to neuronal hyperexcitability.

Conclusion

These data show that the spinal release of fractalkine plays a crucial role in neuronal sensitization as a precursor to chronic non-specific low back pain.

Acknowledgement:
We thank U. Hortscht and E. Maier for their excellent work in this project. This work was supported by the Deutschen Forschungs-gemeinschaft (DFG) (TR 236/24-1, ME 492/16-1).