Investigation of the plasma cytokine/chemokine profile of the chronic constriction injury rat model of neuropathic pain: relevance to pharmacological reversal of allodynia.

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Introduction

Neuropathic pain (NeuP) describes heterogeneous group of chronic pain disorders arising from lesion or disease of the somatosensory system.

Two anticonvulsants: gabapentin (GBP) and pregabalin (PGB) are recommended as a first line of treatment in NeuP. Unfortunately, both are associated with poor efficacy and undesirable side-effects.

Chronic constriction injury (CCI) is one of the most widely used models

Identifying a plasma biomarker to track disease progression or predict pharmacological efficacy will facilitate drug discovery in NeuP.

The aim of this study was to investigate plasma cytokine/chemokine profile in the CCI model after NeuP induction followed by GBP and PGB treatment. .

Methods

The CCI model was induced in male Sprague-Dawley rats (n=16)
by unilateral ligation of the sciatic nerve.

Paw withdrawal threshold (PWT; mechanical allodynia) was assessed using von-Frey hairs.

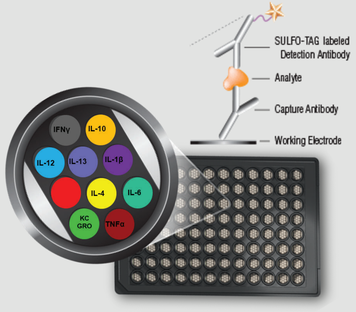
PWT was measured at:
baseline (BL; day 0),
day 20 following nerve ligation,
2hr and 24hr (day 27) post-GBP (100mg/kg, p.o.)
2hr and 24 hrs. (day 42/43) post-PGB (30mg/kg, p.o.).

Meso Scale Discovery (MSD) V-Plex mice Proinflammatory assay
Plasma samples from CCI rats were analysed using MSD platform:

- IL-1β
- IL-6
- TNF-α
- IFN-γ
- IL-10
- IL-5
- IL-13
- KC-GRO
- IL-4

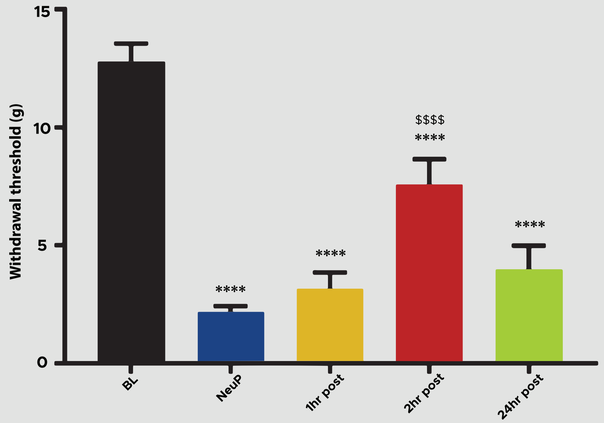
V-PLEX®

MSD® Meso Scale Discovery



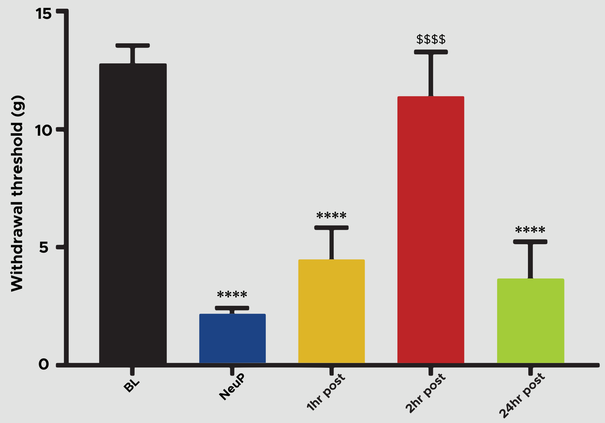
Results

Effect of Gabapentin on paw withdrawal threshold.



****p<0.0001 vs. Pre-surgery baseline (BL), $$$$p<0.0001 vs. NeuP,

Effect of Pregabalin on paw withdrawal threshold.

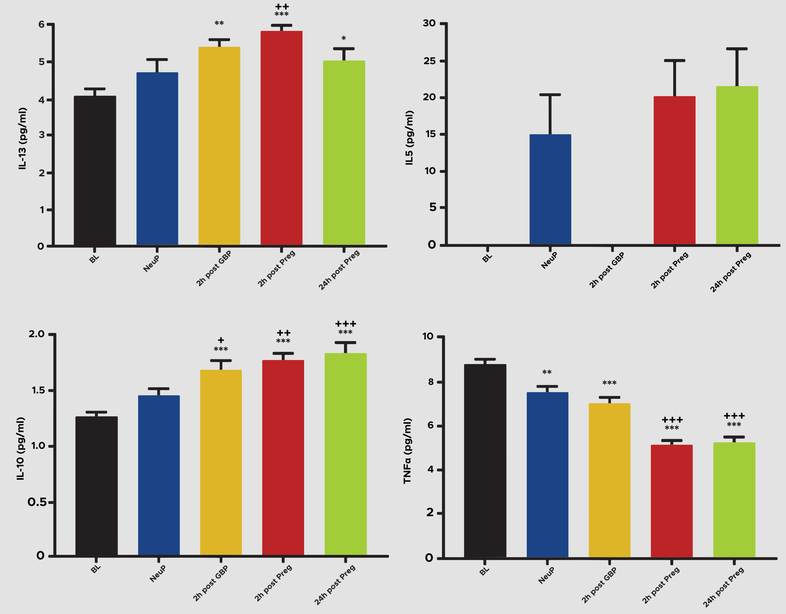


****p<0.0001 vs. Pre-surgery baseline (BL), $$$$p<0.0001 vs. NeuP,

Results

Plasma: Cytokine/Chemokine expression

pg/ml	BL	NeuP	2hr post GBP	2hr post PGB	24hr post PGB
IFNγ	5.98±0.34	7.54±0.51	7.7±0.54	8.97±0.32	8.18±0.51
IL-1β	**ND**	**ND**	**ND**	5.5±1.37	5.97±1.02
IL-4	1.86±0.11	2.25±0.14	2.41±0.14	2.59±0.13	2.64±0.18
IL-6	18.44±3.05	42.67±6.62	86.15±11.13	80.92±11.79	96.89±13.28
KC/GRO	173.3±8.76	170.8±9.94	124.7±10.88	123.9±7.34	125.3±8.83



*p<0.05, **p<0.01, ***p<0.0001 vs. BL
+p<0.05, ++p<0.01, +++p<0.0001 vs. NeuP
Values are Mean ± SEM

Conclusions

- Reversal of increased plasma IL-5 following CCI induction was specific to GBP treatment only.
- IL-13 a cytokine associated with suppression of NeuP, was actually increased by PGB consistent with its efficacy.
- The plasma cytokine/chemokine profile here suggests a complex interaction between NeuP disease progression, pharmacological intervention and inflammatory signaling.
- This study has identify potential plasma markers of NeuP progression and treatment efficacy.

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