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The use of spinal wide dynamic range neuron recording in the mouse as a routine screen for candidate analgesic drugs

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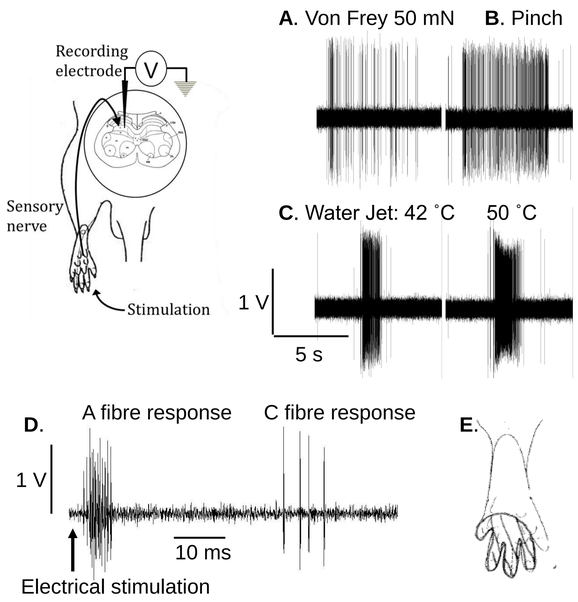
Objectives

Prediction of the clinical efficacy of analgesic drug candidates using only behavioural tests is difficult. Recording of spinal Wide Dynamic Range (WDR) neurons, the "pain transmission cells" of the gate control theory[1,2] provides essential complementary data to behavioural tests. Indeed, recording from spinal WDR neuron, the preclinical equivalent of a tolerance test, allows:

- Measure of a pain endpoint in response to stimuli identical to the ones used in clinical test as well as to highly noxious stimuli.
- Differentiation of A from C fibre mediated activity.

However, recording of spinal WDR neurons is challenging. Our objective was to assess the use of WDR recording in the mouse as a routine drug screening model for analgesic efficacy.

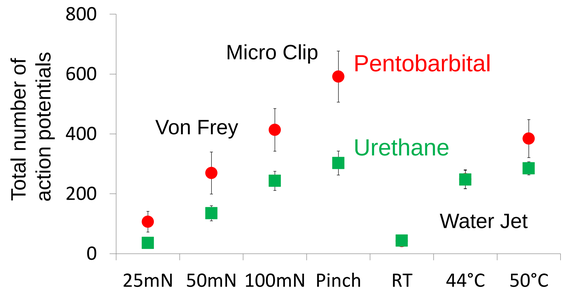
Illustrations



- Response of a spinal WDR neuron to mechanical and thermal stimuli (A-C), and to a single electrical stimulation (D) of the receptive field (E).

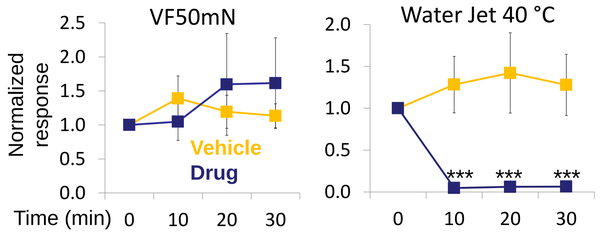
Results

1. Pentobarbital facilitates responses compared with urethane



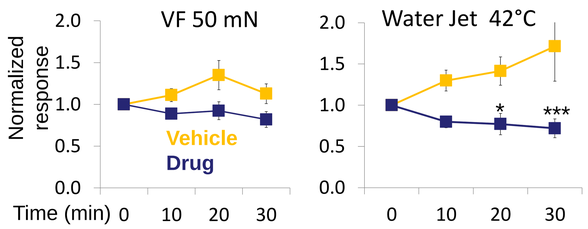
- CFA pretreated mice; n=13 per group.

2. A TRPV1 antagonist abolishes responses to specific stimuli



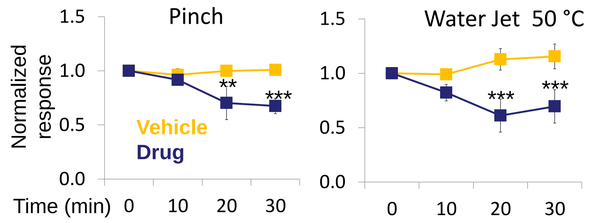
- BCTC[3] : 6 mg/kg/h.
- Naïve mice; n=7-8 per group.

3. Naproxen reduces responses to "weakly" noxious stimuli



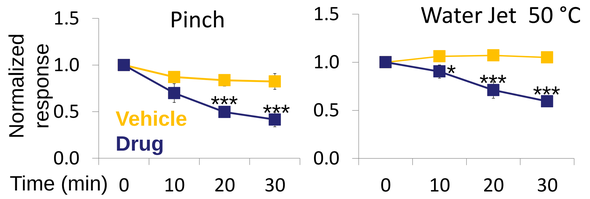
- Naproxen: 120 mg/kg/h.
- CFA pretreated mice; n=6-7 per group.

4. Oxycodone reduces responses to highly noxious thermal and mechanical stimuli



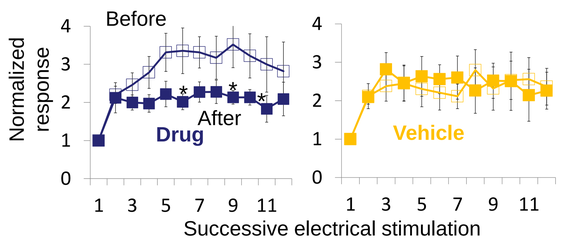
- Oxycodone : 6 mg/kg/h.
- CFA pretreated mice; n=6-7 per group.

5. A Nav1.7 blocker reduces responses to highly noxious thermal and mechanical stimuli



- Nav1.7 blocker[4]: 40 mg/kg/h.
- CFA pretreated mice; n=6-7 per group.

6. A Nav1.7 blocker tends to decrease (C fibre mediated) wind up responses



- C fibre mediated response at time 0 and 30 min.
- Nav1.7 blocker[4]: 40 mg/kg/h.
- CFA pretreated mice; n=6-7 per group.

Methods

- Male mice were anesthetised with urethane or pentobarbital.
- Inflammation : sc injection with Complete Freund Adjuvant 24-30 h prior to the experiment.
- Electrical activity measured with a 2 MΩ tungsten electrode.
- Mechanical stimuli: Von Frey generating a force of 25, 50 or 100 mN and pinching with micro clip (force approximately 600 mN) for 5 s.
- Thermal stimuli: 10 ml water delivered by gravity from a pipette.
- Electrical stimuli: 12 square wave pulses of 2 ms duration, 5 mA delivered at 1 Hz.
- Responses were measured before (Time 0) and 10, 20 and 30 min after the onset the iv infusion of the drug to be tested. Responses were normalized as ratio at Time X/Time 0.
- Statistical analysis: 2 way ANOVA with repeated measures; *, p<0.05; **, p<0.01; ***, p<0.001.

Conclusions

- With an experienced operator, 2 recordings could be generated each day (90% success rate).
- WDR recording demonstrated pharmacological activity of a TRPV1 antagonist in naïve mice (behaviour requires an inflammatory state[3]).
- WDR recording demonstrated the analgesic activity of oxycodone in response to highly noxious stimuli (eg pinch). This would have been impossible to use in behavioural experiments.
- WDR responses to naproxen and oxycodone correlate well with the clinical efficacy of these drugs.
- WDR recording could be useful to assess the potency of analgesic drug candidate such as Nav1.7 blocker.

- WDR recording is essential as a routine screen for candidate analgesic drug assessment.

References

1 Price et al, Pain, 2003, 106: 215-219.
2 Craig, Ann. Rev. Neurosci., 26: 1-30.
3 Pomonis et al, JPET, 2003, 306:387-393.
4 Bregman et al, J. Med. Chem., 2011, 54:4427-4445.