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Blocking $Na_v1.7$ Reduces Spinal pERK1/2 Expression Evoked by Severe Burn Injury

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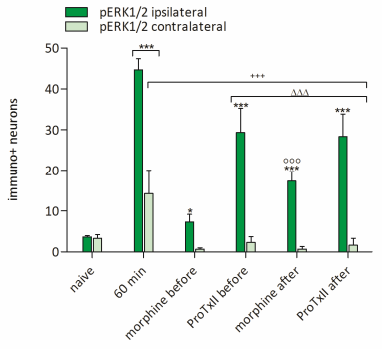
Introduction: controlling pain in burn injury patients, which is one of the most excruciating pain sensations that can be experienced, is still a major clinical challenge and an unmet medical need (1). There is evidence that the sodium channel expressing the α subunit $Na_v1.7$ ($Na_v1.7$) has an important role in nociceptive processing. $Na_v1.7$ has recently been implicated in the development of burn-induced hypersensitivity. Thus, $Na_v1.7$ is a potential therapeutic target for controlling pain after burn injury**.** Our aim was to find out whether blocking $Na_v1.7$ channels (2) is able to reduce nociceptive processing in the spinal cord.

Methods: experiments were performed in accordance with the requirements of the Animals (Scientific Procedures) Act 1986 (UK) Amendment Regulations 2012 (SI 2012/3039) and adhered to the guidelines of the Committee for Research and Ethical Issues of IASP published in Pain, 16 (1983) 109- 110. One of the hind paws of urethane-anaesthetised Sprague-Dawley adult male rats was immersed into 60^{o}C water for 2 minutes to induce a partial thickness second degree scalding type burn injury (3). The $Na_v1.7$ blocker, ProTx-II, was injected (0.1 mg/Kg; i.p.) 15 minutes before or after the burn injury. Morphine (3 mg/Kg; i.p.) was use as positive control. Following various survival times up to 3 hours, rats were perfused with 4% paraformaldehyde and the L4-5 spinal cord and DRG were collected and processed for immunostaining using an anti-pERK1/2 (phosphorylated extracellular-signal-regulated kinases 1 and 2) antibody, a recognised marker for spinal nociceptive processing.

Results: the skin in the injured hind paw showed similar pathological signs as described before in mice (1). The number of pERK1/2 positive neurons peaked at 5 minutes post-injury (90.75±28.2 immunopositive cells, $p < 0.001$), stabilised at a reduced level at later time points, and returned to control levels at 3 hours post-injury in lamina I and II_{outer} of the spinal cord. ProTX-II reduced the number of p-ERK1/2 immunopositive cells from 44.67±5.3 to 29.33±8.3 (n=3; $p < 0.001$) and to 28.33±8.09 (n=3; $p < 0.001$), when it was applied before and after the burn injury, respectively. Morphine reduced the number of p-ERK1/2 immunopositive cells from 44.67±5.3 (n=3) to 7.33±1.8 (n=3; $p < 0.001$) and to 17.33±2.09 (n=3; $p < 0.001$) when it was injected before and after the burn injury, respectively.



Immunollabeled pERK1/2 neurons in the DHSC of the burn-injury model after the different treatments

Conclusion: blocking $Na_v1.7$ could be a new means to reduce pain in burn injured patients.

(1) Laycock H et al. (2013). Eur J Pain 716: 169-178.

(2) Schmalhofer WA et al. (2008). Mol Pharmacol 74: 1476-1484.

(3) White JP et al. (2011). Eur J Pain 15: 683-690White JP et al. (2011). *European Journal of Pharmacology* **15:** 683-690