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Characterisation of a novel delta opioid receptor (DOPr) ligand with improved therapeutic profile

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Introduction: Current options for the treatment of chronic pain are limited. However, activation of the delta opioid receptor (DOPr) is potentially effective in chronic pain states and emotional disorders. DOPr agonists have low abuse liability although some agonists have pro-convulsant properties and tolerance to the therapeutic effects can develop. PharmNovo AB have developed a series of selective, small molecule DOPr agonists and we have characterised the signalling, trafficking and anti-nociceptive activity of one of these, PN6047.

Methods: G protein signalling and arrestin recruitment to the DOPr was assessed using BRET technology in HEK-293 cells. Internalization of the DOPr was quantified using the DiscoveRx PathHunter® assay. Antihyperalgesia was assessed using the monoiodoacetate (MIA) osteoarthritis pain model and tolerance to anti-nociception measured using a sciatic nerve-ligation (SNL) model of neuropathic pain. Mechanonociceptive thresholds were measured with dynamic plantar aesthesiometry in C57Bl6 mice. Mice were injected with MIA (25 $mg.ml^{-1}$; 20 µl) or saline (20 µl) 7 days prior to experimentation. Mice were treated with PN6047 (10 $mg.kg.^{-1}$; p.o.;n=6) or vehicle (HPMC; n=7) for 60 min. For the SNL model, traumatic mononeuropathy was induced by tight ligation of 1/3 of the sciatic nerve. PN6047 (3 $mg.kg.^{-1}$; p.o.; n=8) or vehicle were administered every day from days 5 to 21 post-surgery. Mechanonociceptive measurements were taken on days 7,9,12,14,16,19 and 21. Seizure liability of PN6047 (20 $mg.kg^{-1}$;p.o.; n=11) was assessed using the pentylenetetrazole (PTZ) test in CD1 mice. Data are expressed as mean ± SEM.

Results: PN6047 fully engages G protein signalling but is a partial agonist in both the arrestin recruitment and internalisation assays. Acute treatment with PN6047 significantly reversed the MIA-induced hyperalgesia (23.4±7.6%), in comparison to vehicle (51.9±1.2%). In the SNL model, five days after the nerve ligation mechanical hyperalgesia had developed, treatment with PN6047 resulted in a significant inhibition of the mechanical hyperalgesia (from 44.8±3.0% to 22.7±2.5%). The antihyperalgesic effect was maintained during the 21-day experimental period. PN6047 did not lower seizure threshold in the PTZ test (90.9±8.0 v 101.2±5.7 $mg.kg.^{-1}$ dose of PTZ required to induce hindlimb tonic seizures in vehicle- and PN6047-treated animals, respectively).

Conclusion: PN6047 is effective in rodent models of chronic pain, shows no analgesic tolerance after prolonged treatment and had no effect on chemically induced seizures. Thus, DOPr ligands with limited arrestin signalling may be therapeutically beneficial in the treatment of chronic pain states.