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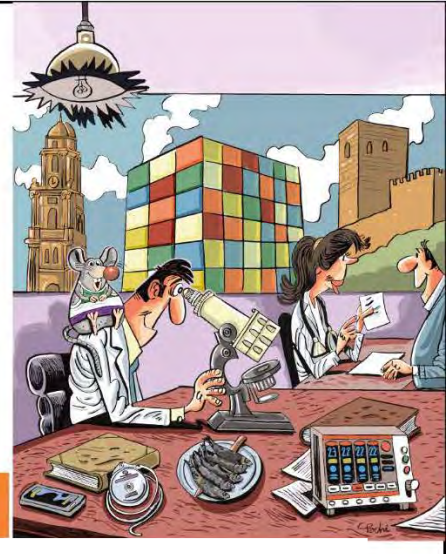

PGN34: A Novel Cannabinoid Agonist with Promising Effects on Inflammation and Pain in Animal Models

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INTRODUCTION

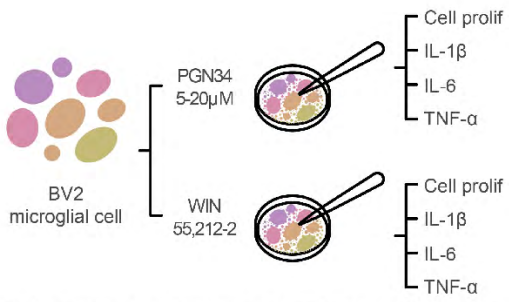
Cannabinoid receptors were identified as potential modulators of pain. In this context, and searching for new CBRs ligands, the new compound PGN34, derived from indazole, was developed (**Patent number 200930775**) whose preliminary evaluation demonstrated agonist activity, preferential CB2,and antioxidant capacity [1].

AIM

To characterize the anti-inflammatory and antinociceptive cannabinoid effects of PGN34.

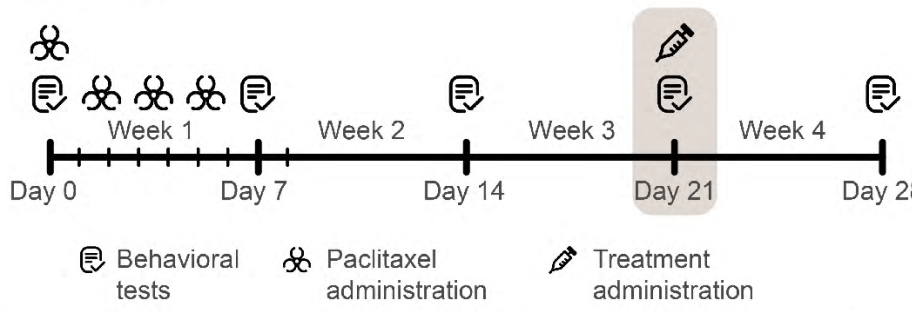
MATERIAL AND METHODS

In Vitro Assay

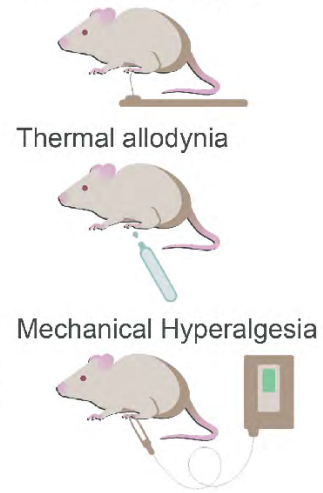


BV2 microglial cells were used to evaluate PGN34 (5-20 μM) effects on LPS-induced proliferation and pro-inflammatory mediator release (IL-1β, IL-6, TNF-α). WIN 55,212-2 (CB1R/CB2R agonist), AM630 (CB2R antagonist), and AM251 (CB1R antagonist) were used in reversal assays. Proliferation was assessed via colorimetric assay, and cytokine release via ELISA (450 nm absorbance).

In Vivo Tests

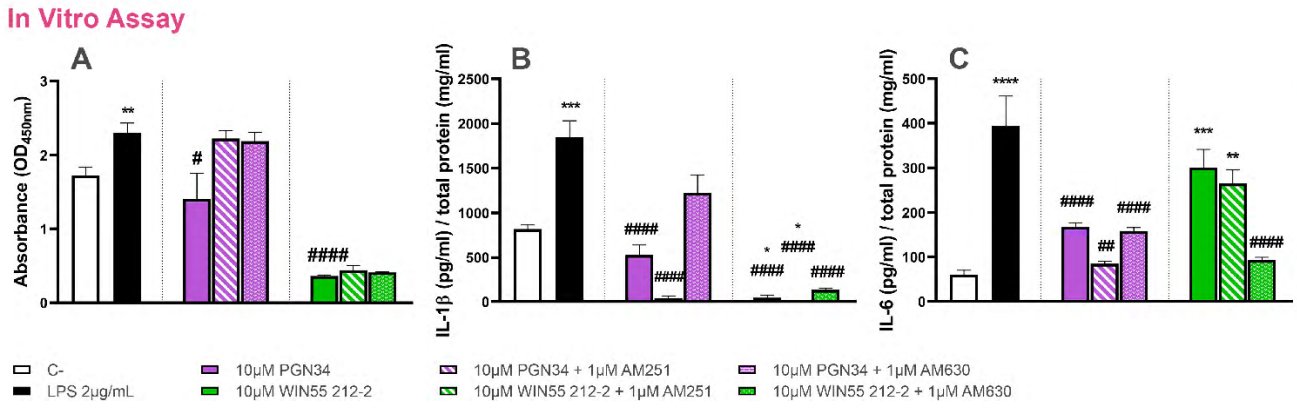


In vivo, **craniofacial muscle pain model** was induced by hypertonic serum injection (100μL) in the masseter muscle of male Wistar rats. The total number of shakes produced by the animal were considered a nociceptive response. **Neuropathic pain model** was induced by paclitaxel (2 mg/kg, i.p./day) in male and female Wistar rats, with mechanical and cold allodynia and hyperalgesia assessed via von Frey, acetone, and Rodent Pincher tests. PGN34 (3, 5 mg/kg, i.p.) effects were compared with WIN 55,212-2 and evaluated with AM630 or AM251.



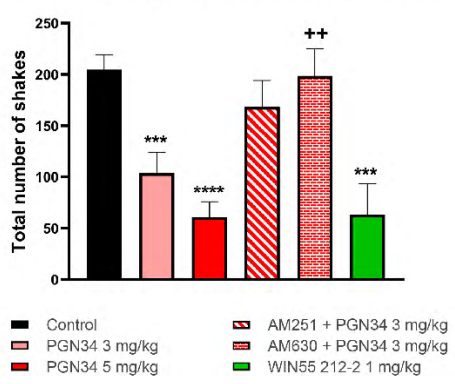
RESULTS

In Vitro Assay



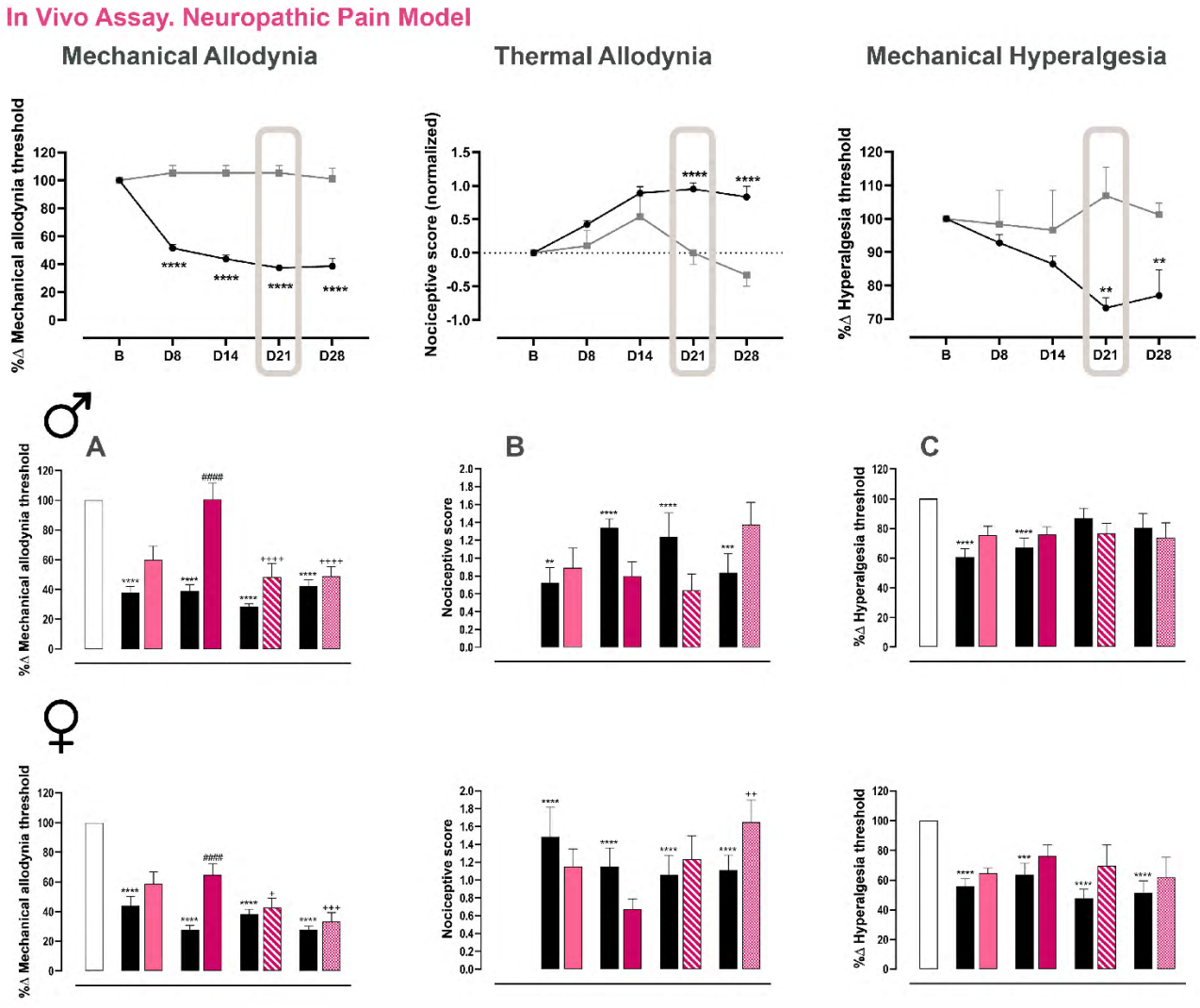
The graphs show the effects of PGN34 and WIN 55,212-2 at the concentration of 10μM and their reversion by the cannabinoid antagonists AM630 and AM251 (1μM). (A) Effect of compound PGN34 on cell proliferation. (B) Effect of compound PGN34 on IL-1β release from activated microglia. (C) Effect of compound PGN34 on IL-6 release from activated microglia. Results are expressed as mean ± S.E.M. *n* = 4-8. Statistical analysis: * *vs.* negative control group (C-); # *vs.* positive control group with LPS. Statistical test: one-way ANOVA followed by Dunnett's Multiple Comparisons test. ●*P*<0.05; ●●*P*<0.01; ●●●*P*<0.001; ●●●●*P*<0.0001.

In Vivo Assay. Muscular Pain Model



Effect of PGN34 in the craniofacial muscle pain model. Bars show the total nº. of shakes produced by i.m. administration of SH in rats treated with vehicle (control); compounds WIN 55, 212-2 and PGN34 at different doses and their reversal with antagonists AM630 or AM251 (0.5 mg/kg i.p.). Results are expressed as mean ± S.E.M. *n* = 7-12. Statistical analysis: * *vs.* control; + *vs.* PGN34 3 mg/kg. Statistical test: one-way ANOVA followed by Dunnett's Multiple Comparisons test. ●●*P*<0.01; ●●●*P*<0.001; ●●●●*P*<0.0001.

In Vivo Assay. Neuropathic Pain Model



Establishment of the paclitaxel neuropathic pain model.

The grey squares express the rats administered Vehicle-Paclitaxel and the black dots those administered the Paclitaxel 2 mg/kg. Results are expressed as mean ± S.E.M. of % change from baseline threshold for mechanical allodynia and hyperalgesia and normalized to 0 for thermal allodynia. *n* = 9-15. Statistical analysis: * *vs.* baseline. Statistical test: One-way ANOVA followed by Dunnett's Multiple Comparisons test. ●●P<0.01, ●●●*P*<0.001, ●●●●*P*<0.0001.

Vehicle-Paclitaxel Paclitaxel 2 mg/kg

Effect of PGN34 in the paclitaxel-induced neuropathic pain model.

(A) Mechanical allodynia and (C) mechanical hyperalgesia: The bars express the pressure threshold eliciting nociceptive behavior. (B) Thermal allodynia: The bars express the nociceptive score achieved by animals of the different experimental groups in the acetone test. Results are expressed as mean ± S.E.M. of % change from baseline threshold for mechanical allodynia and hyperalgesia and normalized to 0 for thermal allodynia. *n* = 9-15. Statistical analysis: * *vs.* baseline; # *vs.* D21 Paclitaxel 2 mg/kg; + *vs.* PGN34 5 mg/kg. Statistical test: one-way ANOVA followed by Dunnett's Multiple Comparisons test. ●*P*<0.05; ●●*P*<0.01; ●●●*P*<0.001; ●●●●*P*<0.0001.

CONCLUSION

PGN34 has demonstrated significant anti-inflammatory and antinociceptive effects, primarily through CB2 receptors. It is a promising candidate for further characterization, with potential applications in pharmacological research on pain treatment.

FUNDING RESOURCES

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[1] González-Naranjo et al. Eur J Med Chem. 2014 Feb 12;73:56-72. doi: 10.1016/j.ejmech.2013.11.026.