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Role of Cannabinoid System in the Enhanced Antinociceptive Effects of the Combination of Indomethacin with Minocycline Against Paclitaxel-induced Neuropathic Pain

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Introduction: This study was conducted to investigate whether the combination of minocycline and indomethacin have enhanced antinociceptive effects in mice with paclitaxel-induced neuropathic pain and the role of the cannabinoid (CB) system in this enhanced antinociceptive effects. In previous studies, we observed that coadministration of these two drugs potentiates their effects and results in antinociception against inflammatory pain at doses where either drug alone had no significant activity (Abu-Ghefreh & Masocha, 2009). Both drugs can independently alter the endocannabinoid system, which might contribute to their antinociceptive activity (Guasti et al, 2009; Guhring et al, 2002).

Methods: The reaction latency to thermal stimuli (hot plate test) of female BALB/c mice (8 to 12 weeks old, n = 88) was recorded before and at day 7 after treatment with paclitaxel (2 mg/kg, i.p.), or its vehicle for 5 consecutive days, as described previously (Parvathy & Masocha, 2013), and at various time points after treatment with minocycline (50 mg/kg), indomethacin (1 or 10 mg/kg) and/or a CB1 antagonist AM 251 (N-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide; 3 mg/kg) alone or in combination (n= 8 per treatment group). All procedures were approved by the Ethical Committee for the use of Laboratory Animals in Teaching and in Research Health Sciences Centre, Kuwait University. Statistical analyses were performed using the unpaired t test, one-way ANOVA followed by Newman-Keuls multiple comparison test or two-way repeated measures ANOVA followed by Bonferroni posttests. The differences were considered significant at $p < 0.05$. The results in the text are expressed as the means ± SEM.

Results: Administration of paclitaxel reduced reaction latency time to thermal stimuli (thermal hyperalgesia) from 9.4 to 5.3 s ($p < 0.01$) at day 7 after treatment with paclitaxel, similar to our previous studies (Parvathy & Masocha, 2013). Coadministration of minocycline with indomethacin produced enhanced antinociception (more than either drug alone i.e. vehicle produced 21.7 ± 9.9% increase in reaction latency at 2h post treatment, minocycline 50 mg/kg 45.1 ± 14.4%, indomethacin 1 mg/kg 48.7 ± 9.4% and minocycline 50 mg/kg plus indomethacin 1 mg/kg 84.3 ± 9.3% ; $p < 0.05$) in mice with paclitaxel-induced hyperalgesia. This enhanced activity was blocked by the administration of AM251 (i.e. vehicle produced 18.2 ± 6.3% increase in reaction latency at 2h post treatment, minocycline 50 mg/kg plus indomethacin 10 mg/kg 71.0 ± 7.7% and minocycline 50 mg/kg plus indomethacin plus AM251 1 mg/kg 9.2 ± 4.5%; $p < 0.05$)

Conclusion: In conclusion the present findings show that the combination of minocycline and indomethacin has enhanced antinociceptive activity against paclitaxel-induced neuropathic pain compared to either drug alone and the potentiation of the antinociceptive effects of this drug is possibly through modulation of the cannabinoid system.

References

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