Characterization Of BU09057, BU09058 And BU09059, Novel Ester Derivatives Of Trans-(3R,4R)-Dimethyl-4-(3-Hydroxyphenyl)Piperidine, At The Kappa Opioid Receptor

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Selective kappa opioid receptor (KOR) antagonists are being explored as potential treatments for a variety of disorders, including cocaine addiction and mood disorders. The standard KOR antagonists, norbinaltorphimine (norBNI) and (3R)-7-hydroxy-N-((1S)-1-[[3R,4R]-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]-methyl)-2-methylpropyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (JDTic), have a very slow onset and long duration of action (Carroll et al., 2004). The introduction of a potentially shorter acting KOR antagonist, is desirable. With this in mind, the novel compounds BU09057, BU09058 and BU09059 were synthesised, with ester linkers replacing the original amide containing chain in JDTic. The antagonist profiles of these novel ester derivatives were investigated in vitro and in vivo.

KOR antagonist activity was studied in ileum preparations isolated from adult male guinea pigs (300-350g) and maintained in Tyrode’s solution at 37°C (95%O₂/5%CO₂). Electrical field stimulation was applied and concentration response curves for the KOR agonist U50-488 (1nM-1µM) were constructed in the absence and presence of increasing concentrations of BU09057, BU09058 and BU09059 (20-200nM, n=3-4 tissues per compound). The selectivity of BU09059 for KOR was confirmed using the electrically stimulated isolated mouse vas deferens preparation. Concentration-response curves for the mu opioid receptor agonist DAMGO (1nM-1µM, n=4) or the delta opioid receptor agonist DPDPE (0.1nM-10nM, n=4) were constructed in the presence of increasing concentrations of BU09059 (up to 2µM). KOR antagonist activity was also investigated in vivo in adult male CD1 mice using the warm water (50°C) tail withdrawal assay. Animals were group housed and randomly assigned to drug-treated or control (0.9% saline w/v) groups (n=10 per group). Mice were injected (10mg/kg i.p.) with saline, norBNI, BU09057, BU09058 or BU09059 (3 mg/kg and 10 mg/kg). Antagonist activity was assessed at 1h, 2h, 3h, 24 h and 7, 14 and 21 days post-injection, against the KOR agonist U50,488 (10 mg/kg). The latency to a rapid tail-flick was the behavioural endpoint and the % maximum possible effect calculated (cut off latency was 15s). In vivo data were analysed using a repeated measures two-way ANOVA, with time (within subjects) and treatment (between subjects) as main factors, and Bonferroni post-hoc test.

The isolated guinea pig ileum studies revealed that increasing concentrations of BU09057, BU09058 and BU09059 produced parallel rightward shifts in the concentration-response curve for U50-488. Using Schild plot analysis, pA₂ values were determined as 6.8 for BU09057, 6.7 for BU09058 and 8.1 for BU09059 compared with 9.9 for norBNI. Furthermore, in the mouse vas deferens preparation, BU09059 showed no antagonist activity against DAMGO or DPDPE indicating that it is a selective KOR antagonist. In vivo, all three novel compounds blocked the antinociceptive effects of KOR agonists 1-24h post-injection but differed in their pharmacokinetic profiles. The standard KOR antagonist norBNI significantly blocked the effects of U50-488 at 7 and 14 days, but not 21 days, post-injection. Compared to equivalent doses of norBNI, at 7 days post-treatment, BU09059 3mg/kg and 10mg/kg showed significantly diminished ability to block the effects of U50-488 (P<0.05).

The rank order of KOR antagonist potency of these novel JDTic derivatives in vitro was norBNI>BU09059=BU09057=BU09058 while, in vivo, the three novel compounds showed similar potency to norBNI. However, BU09059 did have a shorter duration of action than norBNI. This data suggests that the approach of replacing the amide containing chain in JDTic with ester linkers does yield selective KOR antagonists with significantly shorter durations of action than norBNI.
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