Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue3abst098P.pdf

Establishing the combination of buprenorphine and naltrexone as a functional kappa opioid receptor antagonist in mice.

AM Almatroudi, SM Husbands, CP Bailey, SJ Bailey. University of Bath, Claverton Down Bath, UK

Kappa (κ) opioid receptors are implicated in a number of psychiatric conditions including mood disorders and substance misuse. κ agonists induce dysphoric responses in humans, whereas κ antagonists have been proposed as potential antidepressants and anxiolytics. Existing high affinity, selective κ antagonists have a long duration of action (Carroll et al., 2004). Buprenorphine, a partial mu-opioid receptor agonist and κ antagonist, administered in combination with the opioid antagonist naltrexone, has been shown to produce a functional κ antagonism with potential for treating drug abuse (Cordery et al. 2013). As a prerequisite to testing antidepressant or anxiolytic potential, here, we have established the appropriate dose combination of buprenorphine/naltrexone to produce a short-acting functional kappa antagonist in mice.

Adult male CD-1 mice (8-10 weeks) were used throughout. Injections were administered ip in 0.9% (w/v) saline to a volume of 10ml/kg. The warm water (52°C) tail withdrawal assay was used to establish blockade of buprenorphine (1mg/kg) or U50, 488 (10mg/kg) - induced antinociception by naltrexone (0.3-3 mg/kg) and the combination of buprenorphine/naltrexone. Antinociception was calculated as percentage maximum possible effect (%MPE)=(test latency–control latency)/(15 s–control latency) ×100. Responses were measured at intervals to assess the duration of antagonist activity. The locomotor effects of buprenorphine and naltrexone, alone and in combination, were assessed in a 10 min open field (OF) test Conditioned place preference was assessed after 6 daily 30-minute training sessions alternating between drug (buprenorphine alone or buprenorphine + naltrexone combination) and saline. Time spent in drug-paired side during 15-minute pre-conditioning and post-conditioning sessions was measured. Values reported are mean +/- sem and statistical analysis (one-way ANOVA or mixed model repeated-measures ANOVA with least significant difference (LSD)) was performed using Invivostat software.

Buprenorphine (1mg/kg) alone or in combination with naltrexone (0.3 to 3 mg/kg) had no significant effects on total locomotion in the open field, compared to saline controls ($F=0.62$, $p= 0.657$, $n=5$). Naltrexone blocked the antinociceptive effects of buprenorphine (1mg/kg) (treatment*time $F(24,120) =2.46$, $p< 0.001$) and U50, 488 (treatment*time $F(24,114)=2.12$, $p< 0.004$). 1mg/kg and 3 mg/kg naltrexone significantly reduced tail withdrawal latency compared to buprenorphine alone at 30 (LSD $p< 0.009$,$p< 0.003$) or u50 alone at 30 (LSD $p< 0.001$, $p< 0.001$) .

In the conditioned place preference assay, buprenorphine (1mg/kg) alone showed a significant increase in the time spent in the drug-paired side (pre-conditioning: 451.5± 25.2 s, post-conditioning: 587.1±73 s; n=8, p=0.05) an effect that was blocked by naltrexone at both 1 mg/kg (pre-conditioning: 430.4 ± 28.4 s, post-conditioning: 395.7±57.4 s; n=8, p=0.609) and 3 mg/kg (pre-conditioning: 441.9 ± 24.9 s, post-

conditioning: 349.3±53.1 s; n=8, p=0.175).

These results show that the combination of buprenorphine (1mg/kg) with naltrexone (1mg/kg) is a functional short acting κ -receptor antagonist that is non-sedating and neither rewarding nor aversive.

Carroll, F.I. et al. (2004). Eur. J. Pharmacol.501, 111–119

Cordery SF . (2012). Addict Biol. doi: 10.1111/adb.12020