Introduction: Ultra-low doses of non-selective alpha-2 adrenergic receptor antagonists such as atipamezole augment morphine antinociception and inhibit tolerance. However, when given alone such doses only result in a delayed weak antinociceptive response. The objective of this study was to investigate whether ultra-low or high doses of the alpha-2A antagonist, BRL 44408 (1), produced antinociception in a rat model of analgesia, and if its actions involved interaction with opioid or alpha-2 receptors. Also, we investigated whether repeated analgesia testing in this paradigm contributes to the delayed antinociceptive effect.

Methods: Following Animal Care Committee approval, male Sprague Dawley rats were implanted with PE10 intrathecal catheters under halothane anesthesia. Analgesia testing was subsequently performed using the tailflick and paw pressure tests over 240 min (n= 4-6/group). Significance of treatments was assessed using analysis of variance followed by Newman-Keuls post hoc test (p<0.05).

Results: In the tailflick test, intrathecal BRL 44408, administered at a dose known to antagonize the alpha-2 receptor (16.5ug) produced a significant, rapid and sustained analgesic response approximating a 90% MPE (maximum possible effect) value peaking at 30-60 min. Lower doses (1.65ug and 0.165ng) produced a significant but more delayed antinociceptive response that peaked after 120 min. Restricting the frequency of analgesia testing to two test periods (30 and180 min post drug injection) had no effect on the magnitude of the BRL 44408-induced antinociception. Antinociception by BRL 44408 (16.5 ug) was only partially but significantly reduced (from 90 to 40% MPE at peak analgesia) by naltrexone or atipamezole doses that produced receptor blockade.

Discussion: The potent and selective alpha-2A adrenergic receptor antagonist BRL 44408 produces significant thermal antinociception. This action is not related to frequency of analgesia testing and is only partially dependent on interaction with opioid or alpha-2 receptors. This class of agents may potentially be useful in the treatment of pain.