Endothelin ETA Receptor Antagonist Reverses Naloxone-Precipitated Opioid Withdrawal in Mice
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Purpose
The long term use of opioid analgesics for the treatment of pain results in the rapid development of tolerance and dependence leading to severe withdrawal symptoms. Several neurotransmitter mechanisms have been proposed to play a role in the actions of opioid analgesia and withdrawal. We have previously demonstrated that endothelin-A (ET\textsubscript{A}) receptor antagonists potentiate morphine and oxycodone analgesia in rodents. We also demonstrated that ET\textsubscript{A} receptor antagonists eliminated tolerance by restoring the antinociceptive responses to both morphine and oxycodone in opioid tolerant animals. The present study was designed to investigate the involvement of central endothelin mechanisms in opioid withdrawal. The effect of intracerebroventricular administration of ET\textsubscript{A} receptor antagonist, BQ123, on morphine and oxycodone withdrawal was determined in male Swiss Webster mice.

Methods
Opioid tolerance was induced by twice-daily injections of morphine for three days, and once-daily injections of oxycodone for five days. Withdrawal was precipitated by opioid receptor antagonist, naloxone, on day 4 for morphine studies and day 6 for oxycodone studies. Expression of ET\textsubscript{A} receptors, ET\textsubscript{B} receptors, VEGF and NGF was determined using Western Blotting technique.

Results
Pretreatment with BQ123 reversed the hypothermia and loss of body weight in mice undergoing morphine and oxycodone withdrawal. BQ123 also significantly reduced the number of wet shakes, rearing and jumping behavior during withdrawal. Western blotting studies indicated no changes in the expression of VEGF, ET\textsubscript{A} receptors, and ET\textsubscript{B} receptors following administration of vehicle or BQ123 in the brain. Although statistically insignificant, we observed a slight tendency toward decrease in ET\textsubscript{A} receptor expression in BQ123-treated animals in control and withdrawal groups. NGF expression was not affected in morphine withdrawal but significantly decreased in the brain during oxycodone withdrawal. Expression of NGF was not altered by BQ123 pretreatment.

Conclusion
These studies are the first to demonstrate that ET\textsubscript{A} receptor antagonists not only eliminate antinociceptive tolerance but also reverse withdrawal symptoms of morphine and oxycodone. These findings support the hypothesis that ET\textsubscript{A} receptor antagonists in combination with opioid analgesics provide adequate analgesic response without the addiction potential and withdrawal symptoms of opioids.