Analgesic and Side Effect Profiles of Novel Alpha-2 Adrenergic Receptor Agonists

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Alpha 2 adrenergic receptor (α₂-AR) agonists are effective analgesics while avoiding concerns surrounding opioid analgesia including misuse, diversion, and overdose. Clonidine, the best characterized α₂-AR agonist, is limited in widespread use for analgesia by side effects including hypotension and sedation. We therefore developed a series of novel, non-opioid α₂-AR agonists and assessed their kinetics, analgesic efficacy, α₂-AR subtype affinity, and side effects.

Methods: We designed and synthesized novel α₂-AR agonists, then determined dose ranges in female and male ICR mice (21–30 g) by intrathecally injecting the agonists with substance P to induce quantifiable transient nociceptive behaviors. Mice were pretreated with either an in-class control or the newly developed α₂-AR agonists as single agents or in combinations and the maximum percent effect (%MPE) in reduction of the Substance P (SP)-induced nociception was calculated as compared to saline control. Following MPE calculation, motor impairment was assessed by administration of high effective doses in the open field and rotarod assays. In parallel, the novel agonists were administered in spared nerve injury (model of neuropathic pain), and in SPARC-null transgenic mice (model of low back pain).

Results: The novel α₂-AR agonists, delivered either singly or in combination, were effective in reducing nociceptive behaviors in the SP assay. The efficacy of the novel compounds was inhibited by idazoxan or efaroxan, but not naloxone, supporting action at α₂-AR and not opioid receptors. Additionally, the novel α₂-AR agonists were also effective at reducing expression of pain behavior in chronic rodent models of neuropathic and low back pain. Additionally, the compounds showed attenuated sedation as compared to in-class controls. The pursuit of α₂-AR agonists may represent an improved non-opioid analgesic strategy.

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