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Safe opioid analgesics targeting nociceptin receptor in primates

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Although mu opioid peptide (MOP) receptor agonists are widely used as standard analgesics, the abuse potential and some adverse effects have contributed to escalating medical and economic burdens in the global community. Given that the nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptor agonists exert antinociception without producing nonpreferable effects at analgesic doses in nonhuman primates, we hypothesized that bifunctional NOP/MOP agonists may be a viable approach to generate safer opioid analgesics.

Newly developed bifunctional NOP/MOP receptor agonists, which shows partial agonist activity for both NOP and MOP receptors, exerted morphine-comparable antinociception without causing itch sensation following systemic or intrathecal administration in rhesus monkeys. Unlike other MOP receptor agonists, bifunctional NOP/MOP receptor agonists did not show adverse effects commonly associated with MOP receptor agonists (i.e., respiratory depression, abuse potential, opioid-induced hyperalgesia, and physical dependence).

Our findings in nonhuman primates suggest that bifunctional NOP/MOP agonists with the appropriate balance of NOP and MOP agonist activity, may provide innovative safer opioid analgesics that beget ideal pain control.