The selective κ-opioid receptor partial agonist HS666 produces antinociceptive, antiseizure and anticonvulsant effects without causing sedation or motor dysfunction after systemic administration in mice
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Background: Differential modulation of the κ-opioid (KOP) receptor is nowadays regarded as a promising strategy for developing pharmacotherapies for human disorders including pain, drug addiction, mood disorders (e.g. depression and anxiety), neurological conditions (e.g. epilepsy), and itching skin and inflammatory diseases. Accumulating evidence indicates that KOP receptor-mediated beneficial effects (antinociception, anticonvulsive, antipruritus) result from G protein-mediated signaling events, while alternative signaling pathways (i.e. β-arrestin-2) may promote adverse effects (dysphoria, sedation, motor dysfunction). The concept of biased agonism at the KOP receptor has gained significance to drug discovery, with G protein-biased KOP agonists emerging as prospective drugs with an improved benefit/risk profile. Encouraged by the recent in vivo findings on a new ligand from the class of diphenethylamines, HS666, a selective KOP partial agonist, with reduced liability for sedative/motor impairment and aversive effects after central (intracerebroventricular) administration to mice, correlating to its low efficacy in the β-arrestin-2 signalling pathway in vitro, we further investigated the pharmacology of HS666 after systemic administration in mice.

Methods: Antinociceptive activity was assessed in the mouse acetic acid-induced writhing test. Pentylentetrazole (PTZ)-induced acute seizures were induced in pDyn-knockout mice, and the kainic acid-induced model of temporal lobe epilepsy was performed in wild-type mice. The rotarod test was used for assessing sedation and the potential loss of coordinated locomotion.

Results: Dose-dependent inhibition of the writhing response was produced by HS666 after subcutaneous administration with an antinociceptive potency (ED50 = 3.23 mg/kg) comparable to the standard KOP agonist U50,488. Intraperitoneal administration of HS666 increased the threshold for PTZ-induced seizures and reduced paroxysmal activity in the mouse model of intra-hippocampal injection of kainic acid in a dose-dependent manner. The antinociceptive and antiseizure/anticonvulsant effects of HS666 after systemic administration were completely blocked by pretreatment with the selective KOP antagonist nor-binaltorphimine, demonstrating a KOP receptor-mediated mechanism of action. HS666 did not impact motor performance of mice at therapeutic doses.

Discussion: The current results establish the specific KOP receptor-mediated beneficial effects (antinociceptive and antiseizure/anticonvulsant) of HS666 following systemic administration in mice and its reduced liability for adverse effects. In summary, these findings offer valuable insights into the discovery of drugs targeting the KOP receptor with improved pharmacological profiles and enhanced therapeutic efficacies for the treatment of human disorders.

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