Involvement of endocannabinoid mechanisms in the antinociceptive effect of N₂O in mice

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Introduction

- Nitrous oxide (N₂O) and cannabinoid (CB) drugs both modulate pain and anxiety by interacting with multiple different systems, including the endogenous opioids, GABA and glutamatergic synaptic activity, nitric oxide (NO) and K⁺ "leak" channels.
- N₂O-induced antinociception is only partly antagonized by opioid receptor blockers.
- The aim of the work is to determine whether N₂O might owe part of its antinociceptive effect to endocannabinoid mechanisms, which are also known to be involved in antinociception.

Methods

- Animal model of acute pain
  - Abdominal constrictrions were induced by i.p. injection of a 1% acetic acid solution.
- Drugs
  - AM 251 – CB₁ antagonist
  - AM630 – CB₂ antagonist
  - AM404 – anandamide transport inhibitor
  - URB597 – FAAH inhibitor
  - URB602 – MAGL inhibitor
- Experiment design

Results

- Statistical analysis of data
  - Dose–response curves were constructed for N₂O-induced antinociception for each treatment group. Antinociceptive dose, 50% (AD₅₀) values and 95% confidence intervals were determined by the method of Litchfield and Wilcoxon.

Results

- Blocking CB₁ receptors by AM251 caused a dose-related increase in the AD₅₀ value for the antinociceptive effect of N₂O. The increase was statistically significant only at the 3.0 mg/kg dose.
- The CB₂ receptor antagonist AM630 did not have any effect on the N₂O-induced antinociceptive effect.
- At the doses tested, the FAAH-inhibitor, MAGL-inhibitor and endocannabinoid re-uptake–inhibitor failed to significantly alter the AD₅₀ value for N₂O-induced antinociception.

Discussion

- These results suggest that N₂O-induced antinociception may be partly mediated via the endocannabinoid system (ECS).
- Blockade of the CB₁ but not CB₂ receptor reduced N₂O-induced antinociception.
- At doses used in this study, inhibition of endocannabinoid-degrading enzymes or re-uptake did not consistently enhance N₂O-induced antinociception nor did they reduce the AD₅₀ value.
- A broader range of doses of cannabinoid pretreatment drugs needs to be run to understand the mechanism by which the ECS modulates N₂O-induced antinociception.

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