Evidence for the involvement of the opioid system in the antidepressant-like effect of folic acid in the mouse forced swimming test.

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OBJECTIVE: The opioid system has been implicated in major depression and in the mechanism of action of antidepressants. This study investigated the involvement of the opioid system in the antidepressant-like effect of the water-soluble B-vitamin folic acid in the forced swimming test (FST).

METHODS AND RESULTS: The effect of folic acid (10 nmol/site, i.c.v.) was prevented by the pretreatment of mice with naloxone (1 mg/kg, i.p., a nonselective opioid receptor antagonist), naltrindole (3 mg/kg, i.p., a selective delta-opioid receptor antagonist), naloxonazine (10 mg/kg, i.p., a selective mu(1)-opioid receptor antagonist, 24 h before), but not with naloxone methiodide (1 mg/kg, s.c., a peripherally acting opioid receptor antagonist). In addition, a sub-effective dose of folic acid (1 nmol/site, i.c.v.) produced a synergistic antidepressant-like effect in the FST with a sub-effective dose of morphine (1 mg/kg, s.c.). A further approach was designed to investigate the possible relationship between the opioid system and NMDA receptors in the mechanism of action of folic acid in the FST. Pretreatment of the animals with naloxone (1 mg/kg, i.p.) prevented the synergistic antidepressant-like effect of folic acid (1 nmol/site, i.c.v.) and MK-801 (0.001 mg/kg, i.p., a non-competitive NMDA receptor antagonist).

CONCLUSION: Together the results firstly indicate that the anti-immobility effect of folic acid in the FST is mediated by an interaction with the opioid system (mu(1) and delta), likely dependent on the inhibition of NMDA receptors elicited by folic acid.

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