

Antidepressant-like effect induced by Cannabidiol is dependent on brain serotonin levels.

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Abstract

Cannabidiol (CBD) is a compound of *Cannabis sativa* with relevant therapeutic potential in several neuropsychiatric disorders including depression. CBD treatment has shown significant antidepressant-like effects in different rodent preclinical models. However, the mechanisms involved in CBD-induced antidepressant effects are still poorly understood. Therefore, this work aimed at investigating the participation of serotonin (5-HT) and/or noradrenaline (NA) in CBD-induced antidepressant-like effects in the forced swimming test (FST) by: 1) testing if CBD co-administration with serotonergic (fluoxetine, FLX) or noradrenergic (desipramine, DES) antidepressants would have synergistic effects; and 2) investigating if 5-HT or NA depletion would impair CBD-induced behavioral effects. Results showed that CBD (10 mg/kg), FLX (10 mg/kg) and DES (5 mg/kg) induced antidepressant-like effects in mice submitted to FST. Ineffective doses of CBD (7 mg/kg), when co-administered with ineffective doses of FLX (5 mg/kg) or DES (2.5 mg/kg) resulted in significant antidepressant-like effects, thus implicating synergistic and/or additive mechanisms. Pretreatment with PCPA (an inhibitor of serotonin synthesis: 150 mg/kg, i.p., once per day for 4 days), but not DSP-4 (a noradrenergic neurotoxin: 1 µg/µl, i.c.v., 24 h before the test), reduced monoamine levels in the brain. However, only PCPA treatment abolished CBD-induced behavioral effects in FST, indicating the participation of serotonergic mechanisms. None of the treatments induced locomotor effects. Our results suggest that the antidepressant-like effect induced by CBD in the FST is dependent on serotonin levels in the central nervous system (CNS).

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