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

Amanda J. Sales ^a, Carlos C. Crestani ^b, Francisco S. Guimarães ^{a, c}, Sâmia R.L. Joca ^{c, d, e}  

^a Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil

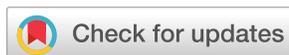
^b Laboratory of Pharmacology, School of Pharmaceutical Sciences of Araraquara, São Paulo State University (UNESP), Araraquara, SP, Brazil

^c Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of São Paulo, Brazil

^d Department of Physics and Chemistry, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil

^e Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Denmark

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Highlights

- CBD induces antidepressant-like effects in FST.
- Subeffective doses of CBD with FLX, but not DES, reduce the immobility time in the FST.
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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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Keywords

Cannabidiol; Antidepressant; Fluoxetine; Desipramine; Serotonin; Noradrenaline

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