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ANXIOLYTIC- AND PROCOGNITIVE-LIKE EFFECTS OF A 30-DAY CHRONIC TREATMENT WITH A LOW NON-PSYCHEDELIC DOSE OF PSILOCYBIN IN C57BL/6J MICE

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Background: For centuries, American indigenous populations have utilized psilocybin-containing mushrooms for both traditional medical and religious purposes, often in the context of psychedelic experiences. More recently, there has been a notable increase in the

interest for and in the practice of psilocybin 'microdosing': regular intake of psilocybin-containing mushrooms in amounts that induce minimal to no apparent acute effects, but with the anticipation of various overall health benefits. However, there is a lack of preclinical and clinical studies having thoroughly assessed the potential pharmacological effects of psilocybin microdosing.

Aims & Objectives: To investigate whether chronic treatment with a non-psychedelic dose of psilocybin (0.05 mg/Kg) in mice is well-tolerated and whether it induces changes in anxiety- and depression-like behaviors, or changes in social behavior and in memory performance, and to discuss the findings.

Method: Adult male (2 months old) C57BL/6J mice were treated for 30 days with an intraperitoneal injection of vehicle or 0.05 mg/Kg psilocybin. We monitored the weight of the mice every 3 days, and after the 30- day treatment, mice were tested in the Open Field (OFT), Light/dark box Test (LDBT), Forced Swim test (FST), T-Maze and Elevated Plus Maze (EPMT) tests, Three Chamber Sociability test, and Cued Morris Water Maze test.

Results: We did not observe any effect of psilocybin on the weight of the mice over the 30 days of treatment. We found an anxiolytic-like effect of psilocybin measured as increased time spent in the light part of the LDBT, a lower latency to choose the first arm in the T-Maze test, and a reduced timing of grooming in the OFT. No effects of treatment were seen in the EPMT, forced swim test and three chamber sociability test. Finally, in the Cued Water Morris Test, a test we performed to study spatial memory and learning, the animals treated with psilocybin showed a shortening of the time taken to reach the submerged platform with a flag emerging from the water level during all the three days of the experiment, compared to the animals treated with vehicle. Moreover, the number of trials per day in which the animals reached the platform was higher in mice treated with psilocybin than with saline solution (controls) on day 1 and 2 of the experiment.

Discussion & Conclusion: This is the first study in rodents reporting the behavioral effects of repeated treatment with a low non- psychedelic dose of psilocybin for 30 days. The treatment was safe and well tolerated. Interestingly, we found significant anxiolytic-like effects in some of the behavioral paradigms of anxiety, consistent with the effects observed in trials of psychedelic doses in humans and reported by subjects practicing psilocybin microdosing in the form of mushrooms. The other interesting finding, needing confirmation in future studies, is the possible enhancement of spatial memory and learning observed in mice treated with psilocybin.

Keywords: psilocybin, microdosing, anxiety, cognition, animal models