Putative Mechanisms for the Treatment of Depression with Psilocybin: A Systematic Review

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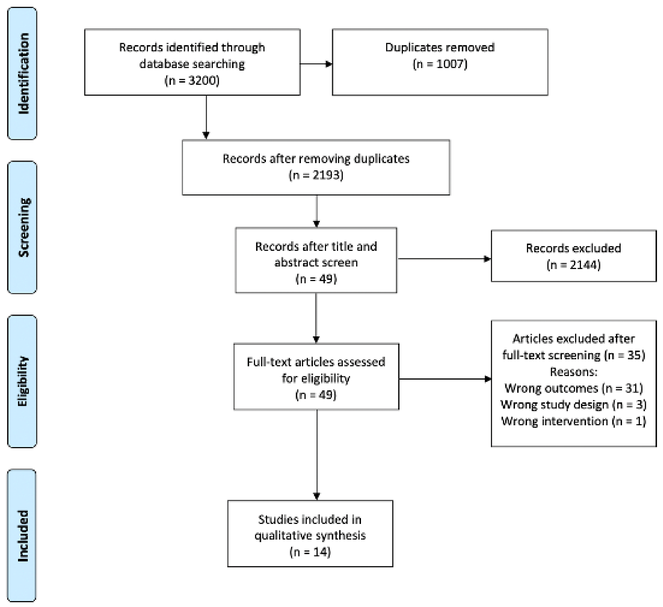
Introduction

Emerging evidence suggests that psilocybin has a therapeutic benefit for treating mood disorders such as depression[1,2,3,4,5]. However, there is little consensus over the exact mechanism by which psilocybin elicits these antidepressant effects. Considering the growing interest in psilocybin as a treatment for depression, this systematic review summarizes the existing evidence of the potential mechanism of action with which psilocybin may alleviate depressive symptoms.

Methods

The databases Ovid MEDLINE, EMBASE, psychINFO and Web of Science were searched using a combination of MeSH Terms and free text keywords in September 2021. The search included both human and animal studies, as long as testing of the mechanism of action of psilocybin was included. To isolate the mechanism of action to one clinical outcome, only antidepressant effects were considered. No other mood disorders or psychiatric diagnoses were included. Only original papers available in English were included. Two independent researchers screened at every stage of the review, and a third researcher resolved any conflicts. PROSPERO registration number: 282710

PRISMA Flow Diagram



Results

Table 1: Summary of the neurobiological changes and proposed mechanisms of action post-psilocybin administration for qualitative synthesis

Author last name, year of publication	Number of subjects (n), patient type, type of study	Method of imaging (if any)	Neurobiological changes and proposed mechanisms of action
Bernasconi et al., 2014	30, healthy humans, double-blind, placebo-controlled RCT	Continuous EEG	Increased top-down control of the PFC, resulting in reduced initial neural response to both negative and neutral faces
Carhart-Harris et al., 2012	15, healthy human controls, subject-controlled RCT	ASL (arterial spin labeling) and fMRI/BOLD	Decreased brain blood flow and venous oxygenation. Reduced CBF in ACC/mPFC; Decreased positive coupling between mpFC and PCC; Decreased mPFC activity via 5-HT2A receptor stimulation
Carhart-Harris et al., 2017	19, patients suffering from treatment-resistant depression, open-label clinical trial	ASL and BOLD RSFC (resting state functional connectivity) analysis	Decreased cerebral blood flow in whole brain; Increased default mode network integrity; Rreduced amygdala CBF and RSFC between bilateral parahippocampus and PFC
Dudysova et al., 2020	20, healthy human participants, double-blind placebo-controlled crossover design	Whole-night polysomnography (EEG spectral analysis)	Decreased absolute delta power during SWS in first sleep cycle (similar to other antidepressants)
Grandjean et al., 2021	50, mice, placebo-controlled trial	fMRI/BOLD – Resting state	Reduced FC within ventral striatum; The RSN predominantly affected by psilocybin was enriched in DA receptors
Hesselgrave et al., 2021	8, mice, exposed to a chronic multimodal stress paradigm		Strengthened excitatory synapses in the hippocampus and increased AMPA/NMDA ratios, unaffected by ketanserin (5-HT2A blocker)
Kometer et al., 2012	17, healthy human controls, double blinded RCT	EEG recordings, with additional electrodes attached near the eyes	Higher P300 amplitudes for positive and negative faces compared with neutral stimuli, unaffected by ketanserin (5-HT2A blocker)
Kraehenmann et al., 2015	25, healthy human controls, double-blinded, placebo-controlled RCT	fMRI/BOLD	Reduced amygdala activation to negative pictures; Decreased activation in visual cortex
Mahmoudi et al., 2018	8 groups (8 mice each), placebo-controlled behavioral trial		NMDA antagonist and psilocybin co-administration led to most significant antidepressant behavioral change
Mason, et al., 2003	60, healthy human controls, double blind RCT	fMRI/BOLD and structural MRI	Higher relative glutamate concentration levels in the mPFC, and lower relative glutamate concentration levels in the hippocampus
Mertens et al., 2020	20, humans with moderate to severe MDD, case series study	fMRI/BOLD - Anatomical scan	Increased FC between amygdala and visual areas; Increased FC between vmPFC and other regions
Raval et al., 2021	24, pigs, placebo-controlled trial	In vitro autoradiography	Transient decrease in 5-HT2AR density in hippocampus and PFC; Higher SV2A density in hippocampus
Roseman et al., 2018	20, humans with moderate to severe MDD, case series study	fMRI/BOLD – Anatomical scan	Increased BOLD signal in right amygdala (and visual areas)
Shao et al., 2021	12, mice, placebo-controlled trial	Two-photon microscopy	Increased neurotransmission and spine density in medial frontal cortex, unaffected by ketanserin (5-HT2A blocker)

Discussion

- Studies mostly noted increased amygdala activity and increased glutamate levels in the mPFC post-psilocybin administration
- Psilocybin appears to increase functional connectivity and neuroplasticity in the brain as a mechanism for treating depression
- Supportive animal models also noted increased PFC synaptic plasticity with psilocybin administration
- Most studies observed changes in the hippocampus consistent with greater synaptic plasticity and neurogenesis
- A subset of studies found increased AMPA/NMDA receptor ratios after psilocybin administration independent of the 5-HT2A pathway
- Patients showed clinical improvements to validated depression scales such as the QIDS-SR16, BDI and QIDS; scores were also increased in the 5D-ASC and EDI scale as well as correlated scores in 5D-ASC, PANAS and STAI scales

Limitations

Relatively small number of studies included after full-text review led to:

- Homogenous grouping of human with animal studies, as well as studies using either healthy or depressed patients
- Grouping of neuroimaging and other investigative modalities, with their integration requiring reference to other studies positing pathways yet to be established in the literature

References

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