Letters

RESEARCH LETTER

Psilocybin and Inflammatory and Mitochondrial Stress Markers in Parkinson Disease: A Nonrandomized Clinical Trial

Serotonergic psychedelics, including psilocybin, show early promise for treating diverse neuropsychiatric disorders, but their therapeutic mechanisms are unclear. In a nonrandomized, single-arm pilot trial[1] that enrolled people with Parkinson disease (PD) and mood dysfunction, psilocybin therapy was associated with improvements in depression as well as motor function. Elevated inflammation and mitochondrial stress are common in PD and may contribute to both mood and motor symptoms.[2] Preclinical studies[3,4] indicate that serotonergic psychedelics reduce inflammation and mitochondrial stress, suggesting potential mechanisms underlying clinical benefits. Prior studies[4] have examined immunomodulatory effects of psychedelics in humans with mixed results but, to our knowledge, none have included people with PD or any other neurodegenerative disease. Further, to our knowledge, no published psychedelic study has measured mitochondrial markers in humans. In this analysis, we examined whether psilocybin administration was associated with changes in systemic markers of (1) inflammation and (2) mitochondrial stress in a sample of people with PD and mood dysfunction.

Supplemental content

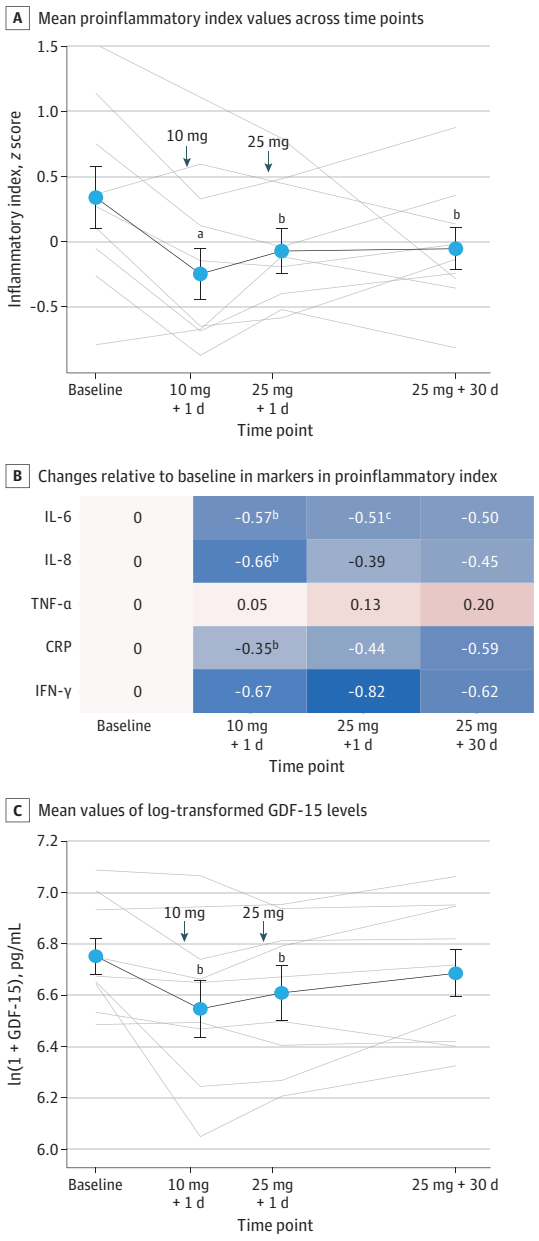
Methods | Twelve participants aged 40 to 75 years with mild- to moderate-stage PD (Hoehn and Yahr stages 1-3) and mood dysfunction completed the trial protocol (NCT04932434) as described previously.[1] The trial was approved by the University of California, San Francisco, institutional review board. All participants provided written informed consent. Key exclusion criteria were cognitive impairment, psychotic symptoms with loss of insight, significant cardiovascular issues, use of medications aside from levodopa for motor symptom management, or inability to maintain a stable outpatient treatment regimen throughout the trial. No participant had psychedelic exposure within the past year. The study intervention involved oral administration of 10-mg and 25-mg doses of synthetic psilocybin approximately 2 weeks apart. We collected plasma samples from 9 of these participants at 4 time points: baseline, 1 day after each psilocybin administration, and 30 days after the 25-mg administration. To assess systemic inflammation, our primary outcome was a proinflammatory index[5] computed as the mean *z* score of the log-transformed concentrations of interleukin (IL)-6, IL-8, tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), and high-sensitivity C-reactive protein (CRP), each measured using multiplex immunoassays (Meso Scale Discovery). Components of the proinflammatory index as well as 1 anti-inflammatory cytokine, IL-10, were secondary outcomes. To evaluate mitochondrial stress, we measured growth differentiation factor 15 (GDF-15) and fibroblast growth factor 21 (FGF-21) using validated enzyme-linked immunosorbent assays (ELISA R&D Systems). These 2 mitokines are circulating protein markers of systemic mitochondrial stress.[6] GDF-15 is elevated in PD,[7] recombinant FGF-21 improves parkinsonian pathology in animal models,[8] and both markers are altered with mood dysfunction.[9,10] For all outcomes, mixed-effects models were used to evaluate changes in log-transformed values from baseline to each follow-up time point, with participants as random intercepts. Both raw *P* values and *P* values adjusted via the false discovery rate (FDR) procedure are shown. See the eMethods in Supplement 1 for details. See the eTable in Supplement 1 for demographic and clinical characteristics of participants and the eFigure in Supplement 1 for a participant flow diagram.

Results | Relative to baseline, the inflammatory index was significantly lower at all follow-up time points: 1 day after 10 mg of psilocybin (standardized mean difference [SMD], −0.72; adjusted $P = .003$), 1 day after 25 mg (SMD, −0.60; adjusted $P = .02$), and 30 days after 25 mg (SMD, −0.62; adjusted $P = .047$) (**Figure**, A). Component markers of the index, including IL-6 (SMD, −0.50; adjusted $P = .01$), IL-8 (SMD, −0.51; adjusted $P = .01$), and CRP (SMD, −0.37; adjusted $P = .047$), were significantly lower 1 day after the 10-mg dose, but not at the other time points (Figure, B). IL-10 was significantly higher 1 day after the 10-mg dose (SMD, 0.25; adjusted $P = .03$), but not at other time points in FDR-adjusted models (**Table**). GDF-15 was significantly lower relative to baseline 1 day after each psilocybin administration (10 mg: SMD, −0.65; adjusted $P = .048$; 25 mg: SMD, −0.54; adjusted $P = .048$), but was not significantly different from baseline at 30 days after the 25-mg dose (Figure, C). FGF-21 was nonsignificantly higher 1 day after each psilocybin administration (10 mg: SMD, 0.41; 25 mg: SMD, 0.44) (Table).

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Figure. Levels of Inflammatory and Mitochondrial Stress Markers Before and After Psilocybin Administration



A, Mean values of the proinflammatory index (mean *z* score of log-transformed interleukin (IL)-6, IL-8, tumor necrosis factor α (TNF-α), C-reactive protein (CRP), and interferon γ (IFN-γ), across time points: baseline, 1 day after 10-mg psilocybin administration, 1 day after 25-mg psilocybin administration, and 30 days after 25-mg psilocybin administration. Lines show individual participant trajectories. Error bars represent standard errors of the mean. Footnotes indicate significance levels of standardized mean difference from baseline to each follow-up time point, adjusted for multiple comparisons using the false discovery rate procedure. B, Changes relative to baseline in the individual markers in the proinflammatory index at each time point, shown as *z* scores (standardized mean difference in log-transformed individual markers from baseline to each follow-up time point). C, Mean values of log-transformed growth differentiation factor 15 (GDF-15) levels across time points.

[a] $P < .01$.

[b] $P < .05$.

[c] $P > .10$.

Discussion | In this nonrandomized clinical trial, markers of systemic inflammation and mitochondrial stress were reduced in people with PD-associated mood dysfunction following psilocybin therapy. To our knowledge, this is the first report of changes in inflammatory or mitochondrial markers after psychedelic administration in humans with any neurodegenerative disease. Causal inference is limited by the open-label study design, lack of a control group, and small sample size. Despite correction for multiple comparisons, observed associations could reflect false positives. Placebo effects, regression to the mean, clinical heterogeneity, and physiological and behavioral factors, such as stress and sleep changes, may have influenced outcomes. Further, the mitokines GDF-15 and FGF-21 are sensitive but not specific indices of circulating mitochondrial stress. Future work should address these limitations and include repeated blood sampling, follow-up beyond 30 days, and more direct measures of immune and brain mitochondrial biology. Altogether, this study provides initial data to support further investigation of the role of psilocybin's immunomodulatory and mitochondrial effects in its therapeutic mechanisms of action.

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Table. Model-Generated Estimates for the Inflammatory Index and Each Marker Relative to Baseline

Measure	Time point	Estimate	SEM	95% CI	SMD	*P* value	Adjusted *P* value[a]
Inflammatory index	10 mg + 1 d	−0.464	0.143	0.184 to 0.744	−0.72	.001	.003
Inflammatory index	25 mg + 1 d	−0.408	0.165	0.084 to 0.732	−0.6	.01	.02
Inflammatory index	25 mg + 30 d	−0.392	0.197	0.005 to 0.779	−0.62	.047	.047
IL-6	10 mg + 1 d	−0.186	0.055	0.079 to 0.293	−0.5	.001	.01
IL-6	25 mg + 1 d	−0.159	0.069	0.024 to 0.294	−0.44	.02	.09
IL-6	25 mg + 30d	−0.159	0.077	0.008 to 0.31	−0.42	.04	.11
IL-8	10 mg + 1 d	−0.224	0.069	0.088 to 0.36	−0.51	.001	.01
IL-8	25 mg + 1 d	−0.133	0.098	−0.06 to 0.325	−0.35	.18	.23
IL-8	25 mg + 30 d	−0.155	0.083	−0.007 to 0.317	−0.38	.06	.12
TNF-α	10 mg + 1 d	0.004	0.02	−0.043 to 0.035	0.04	.83	.83
TNF-α	25 mg + 1 d	0.014	0.021	−0.056 to 0.028	0.12	.52	.57
TNF-α	25 mg + 30 d	0.024	0.015	−0.054 to 0.006	0.19	.11	.18
CRP	10 mg + 1 d	−0.101	0.039	0.025 to 0.117	−0.37	.009	.047
CRP	25 mg + 1 d	−0.116	0.076	−0.033 to 0.265	−0.35	.13	.19
CRP	25 mg + 30 d	−0.165	0.1	−0.031 to 0.361	−0.5	.10	.17
IFN-γ	10 mg + 1 d	−0.247	0.126	0.001 to 0.494	−0.6	.049	.11
IFN-γ	25 mg + 1 d	−0.29	0.135	0.024 to 0.555	−0.8	.03	.11
IFN-γ	25 mg + 30 d	−0.209	0.106	0 to 0.417	−0.65	.05	.11
IL-10	10 mg + 1 d	0.027	0.009	−0.045 to 0.009	0.25	.004	.03
IL-10	25 mg + 1 d	−0.018	0.018	−0.016 to 0.053	−0.2	.30	.37
IL-10	25 mg + 30 d	−0.009	0.024	−0.038 to 0.057	−0.08	.70	.73
GDF-15	10 mg + 1 d	−0.191	0.077	0.04 to 0.341	−0.65	.01	.048
GDF-15	25 mg + 1 d	−0.15	0.062	0.028 to 0.273	−0.54	.02	.048
GDF-15	25 mg + 30 d	−0.067	0.054	−0.04 to 0.173	−0.26	.22	.33
FGF-21	10 mg + 1 d	0.315	0.304	−0.91 to 0.281	0.41	.30	.36
FGF-21	25 mg + 1 d	0.431	0.243	−0.907 to 0.045	0.44	.08	.15
FGF-21	25 mg + 30 d	−0.025	0.337	−0.635 to 0.685	−0.03	.94	.94

Abbreviations: CRP, C-reactive protein; FGF-21, fibroblast growth factor 21; GDF-15, growth differentiation factor 15; IFN-γ, interferon γ; IL, interleukin; SEM, standard error of the mean; SMD, standardized mean difference; TNF-α, tumor necrosis factor α.

[a] Corrected via false discovery rate.

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Data Sharing Statement: See Supplement 2.

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