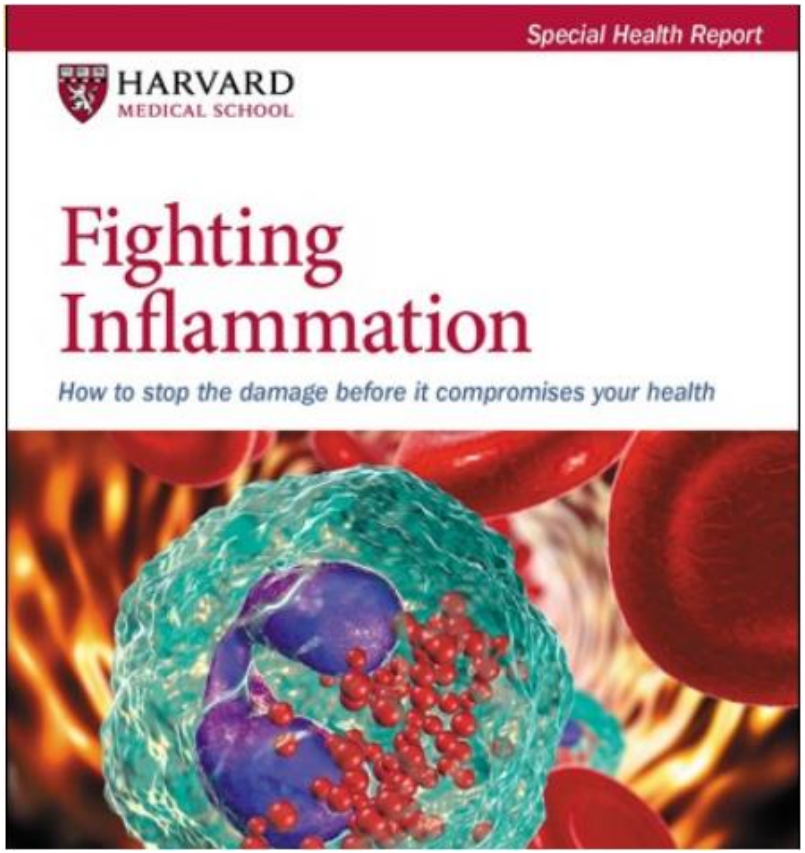
MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Potential Medical Applications of Psychedelics:
Psychedelics and Inflammation

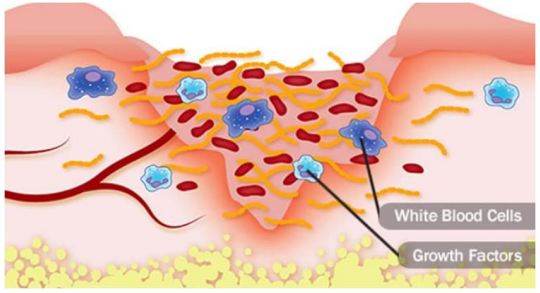
Jeremy Ruskin, MD
November 5, 2022

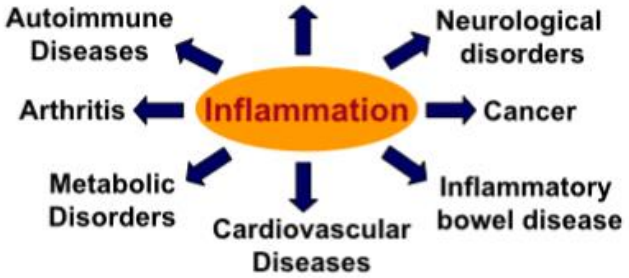


Three out of 5 people worldwide die from diseases that have been linked to chronic inflammation including cardiovascular disease, stroke, cancer, chronic respiratory diseases, obesity, and diabetes.

Acute vs Chronic Inflammation

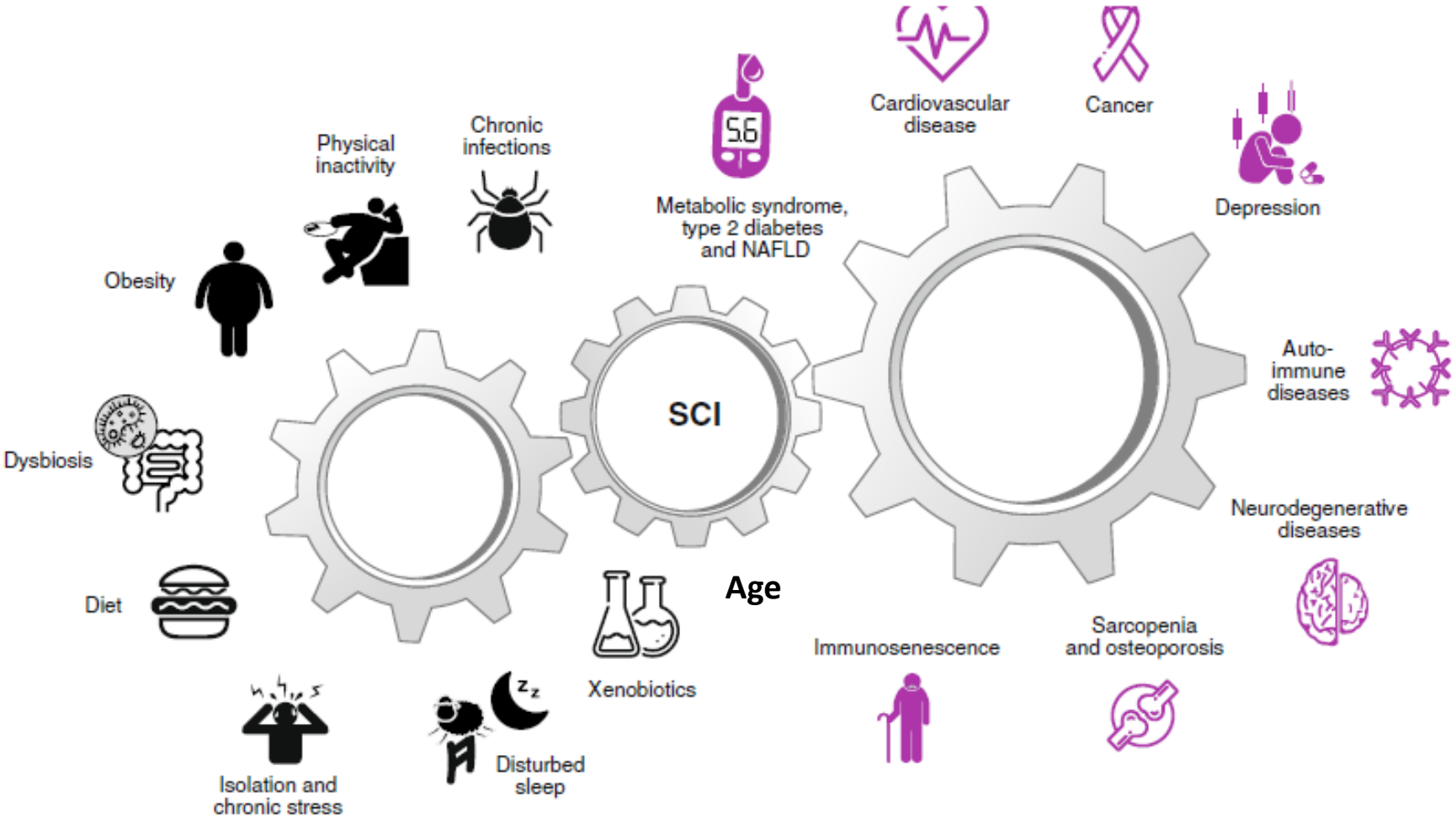
Inflammation	Acute	Chronic
Triggers	Pathogens, injury, toxins	Varied
Age-related	No	Yes
Magnitude	High grade	Low-grade
Duration	Transient/Self-limiting	Prolonged (months-years)
Type of response	Adaptive	Maladaptive
Outcomes	Healing/Repair/Trigger clearance	Tissue Damage/Chronic disease
Biomarkers	IL-6; TNF-a; IL-1b; CRP	Varied/No canonical standard





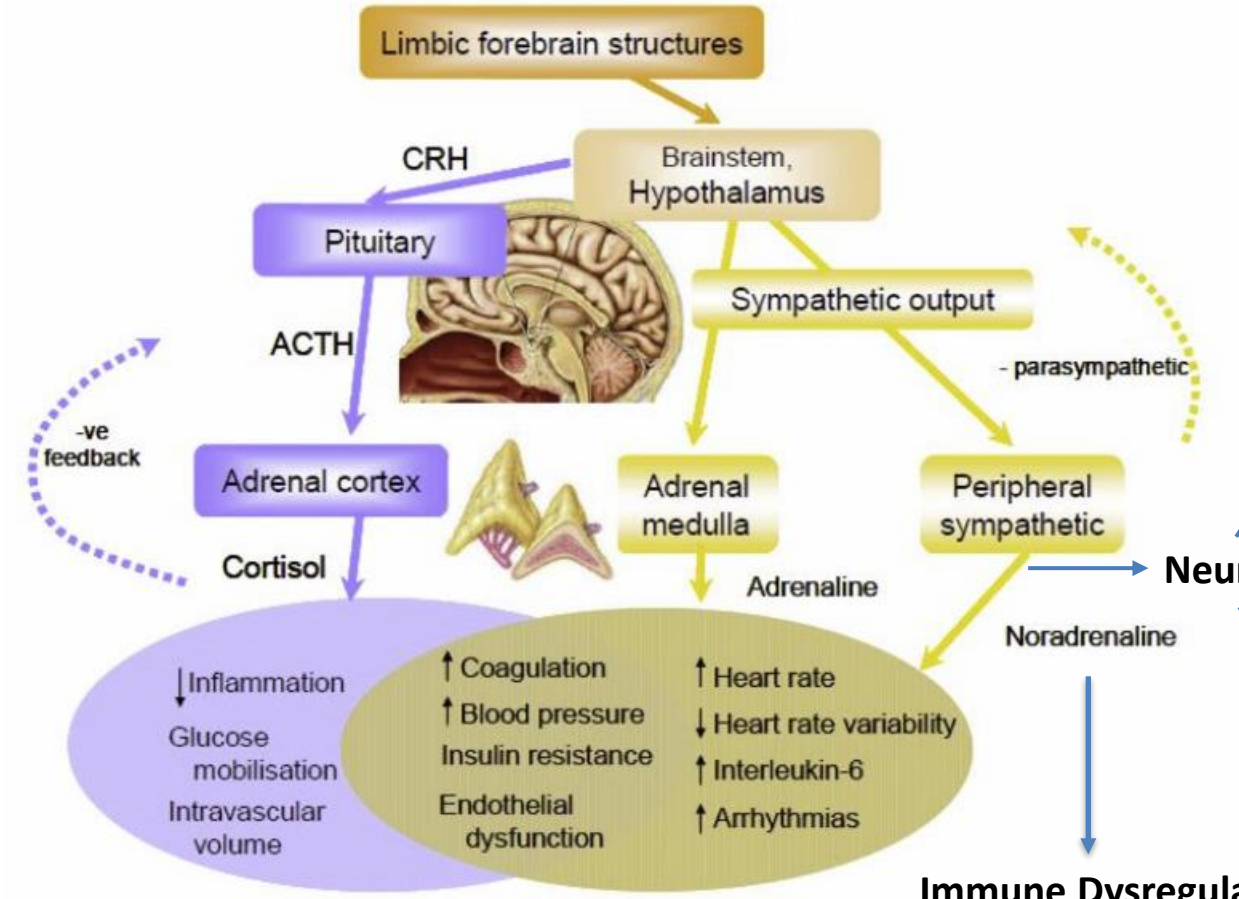
Modified from Furman et al. Nature Medicine 2019; 25:1822–1832.

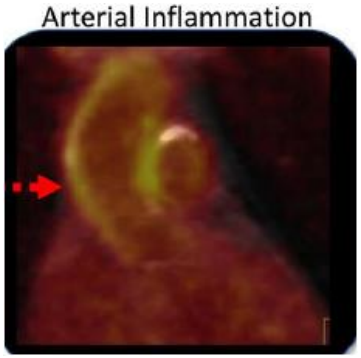
Inflammation and Chronic Disease



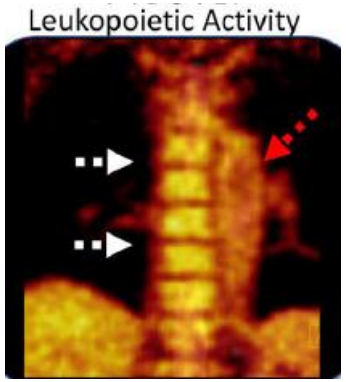
Furman et al. Nature Medicine 2019; 25:1822–1832.

Chronic Stress - Systemic Sequelae





Neural-Inflammatory-Arterial Axis

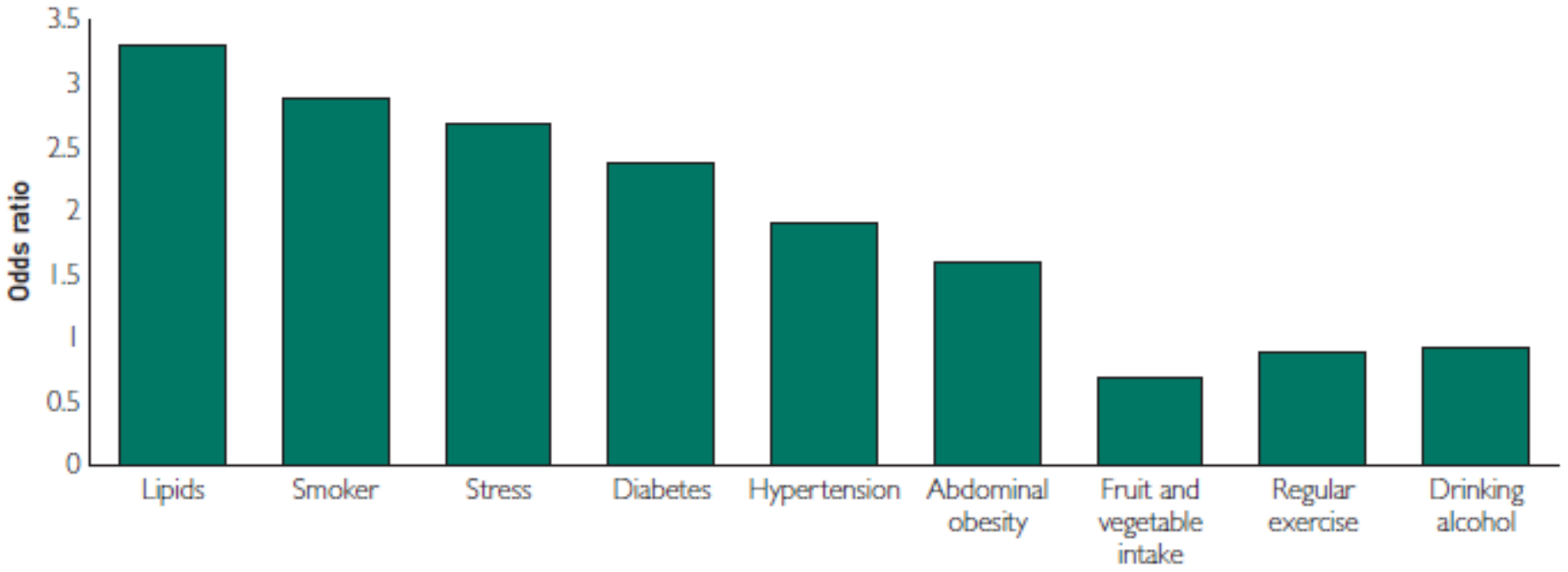


Immune Dysregulation
Inflammatory cells
Cytokine release

Modified from Osborne Circ Cardiovasc Imaging. 2020;13:e010931

Psychosocial Stress and Myocardial Infarction

(INTERHEART study)



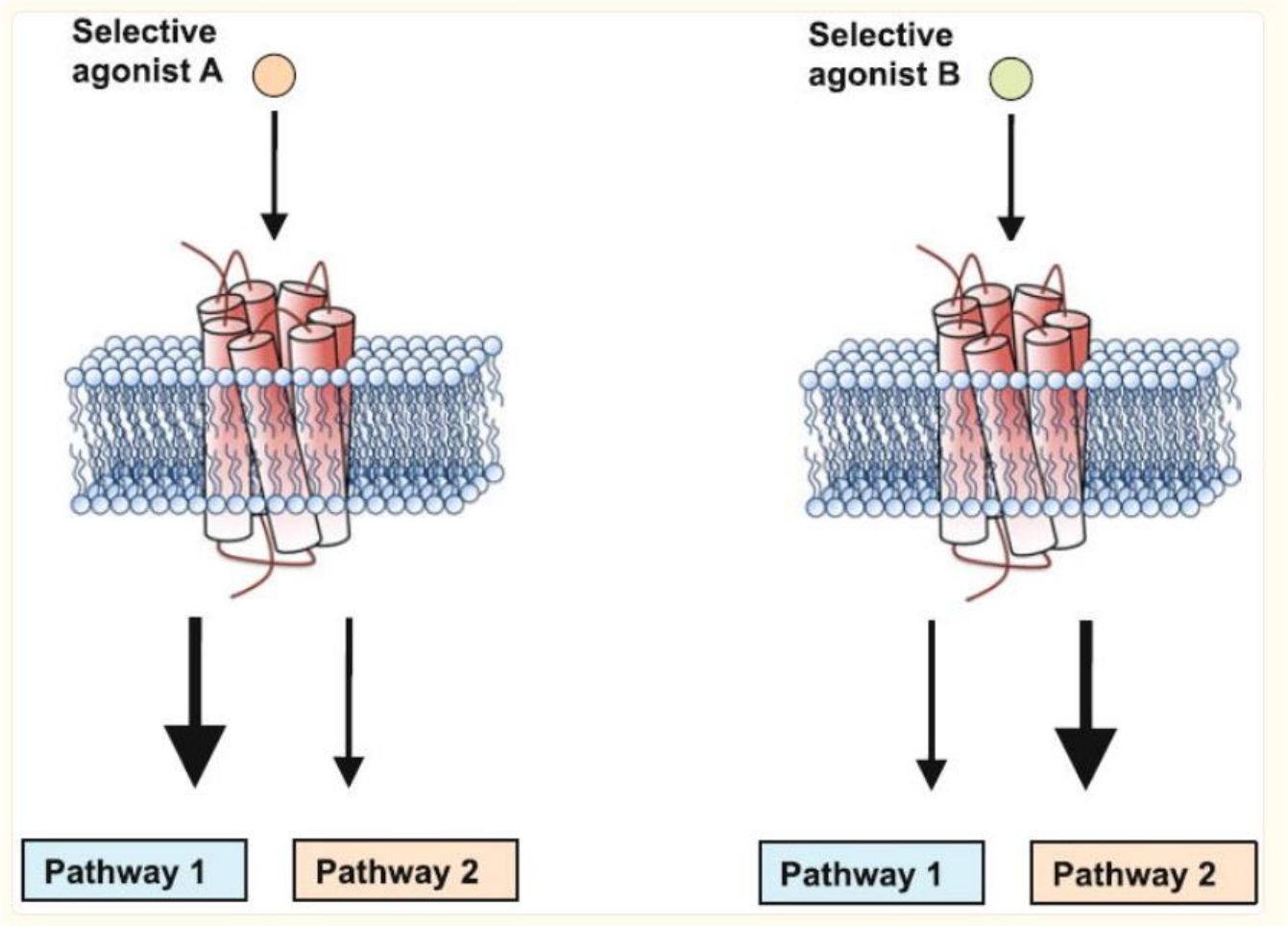
Lancet 2004 Sep 11-17;364(9438):953-62

Psychedelics and Inflammation

- 5-HT2A is the most widely expressed serotonin receptor:
  Lung, Heart, GIT, Immune System, Bone, Muscle, Skin, Eye
- Serotonin is primarily pro-inflammatory
- Psychedelics are anti-inflammatory
- Psychedelics recruit different pathways than serotonin at the 5-HT2A receptor
- Functional selectivity/Biased agonism - property of G-protein-coupled receptors: structurally different agonists may have different effects at the same receptor.
- 5-HT receptors interact with many G-proteins and thereby regulate multiple signal transduction pathways. This diversity creates opportunities for future therapeutics (functionally selective ligands).

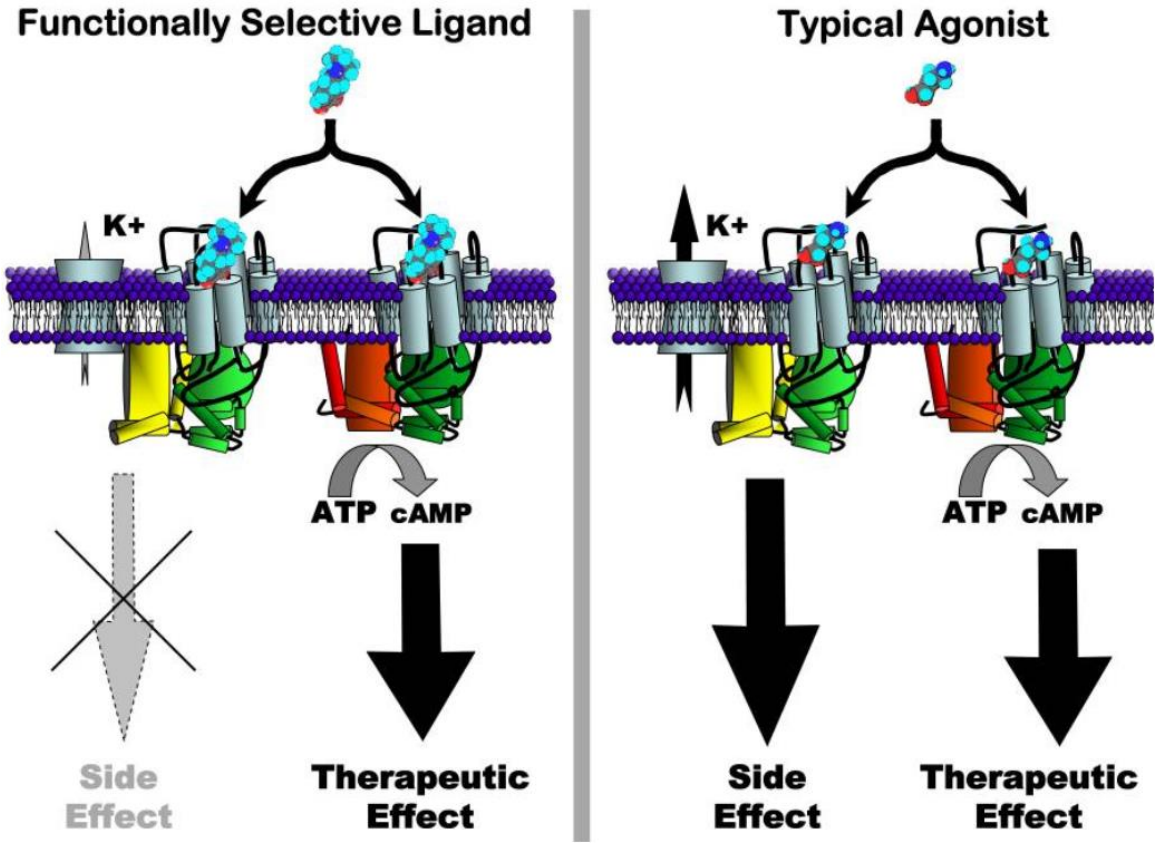
Flanagan & Nichols: Nature Scientific Reports (2019) 9: 13444

Functional Selectivity



Curr Top Behav Neurosci. 2018; 36: 45–73.

Functional Selectivity and GPCR-Related Signaling

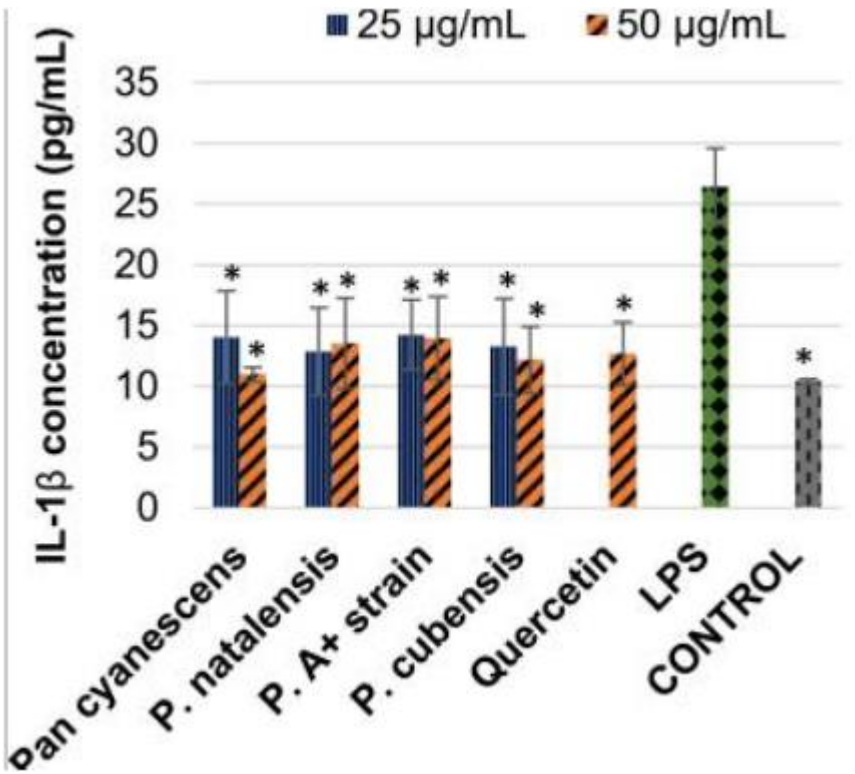


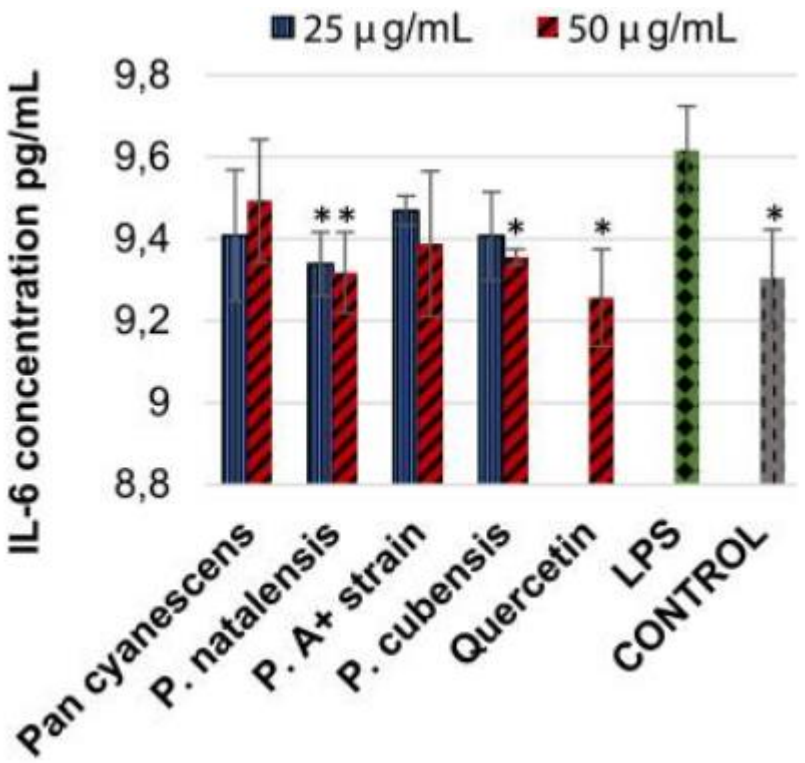
Trends Pharmacol Sci. 2007 Aug; 28(8): 390–396.

Psychedelics and Inflammation

- Psychedelics are anti-inflammatory
- Preclinical data in animal models establish proof of principle
  - Vascular inflammation (atherosclerosis)
  - Glucose intolerance/insulin resistance/lipids
  - Inflammatory bowel disease
  - Asthma
  - Ocular inflammation
- Psychedelics are efficacious at sub-behavioral levels
- Steroid sparing mechanism (no systemic immunosuppression)
- Possibly fewer AEs than traditional anti-inflammatories (?)

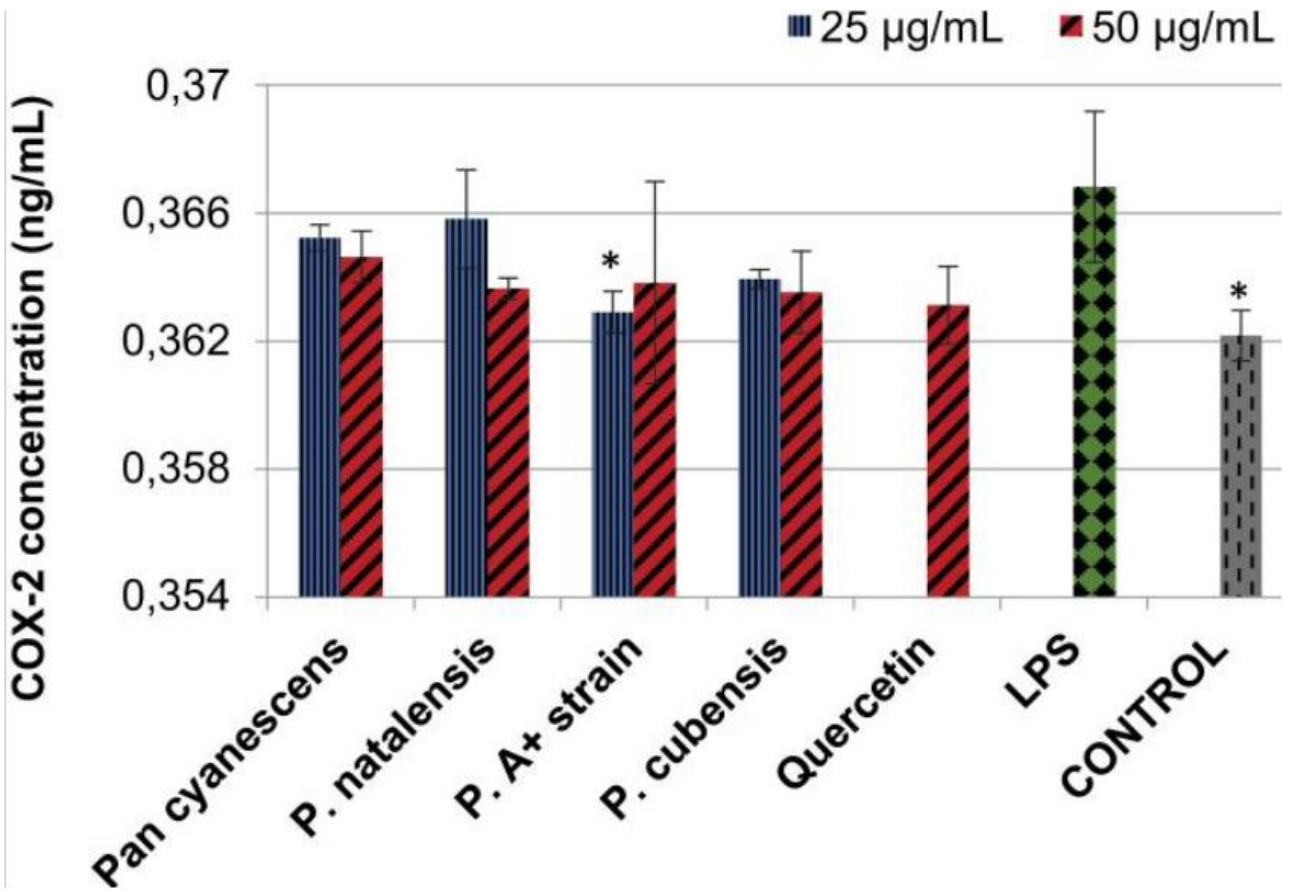
Anti-Inflammatory Effects of Four Psilocybin-Containing Mushroom Extracts on LPS-Induced Inflammatory Cytokines in Cultured Human Macrophages





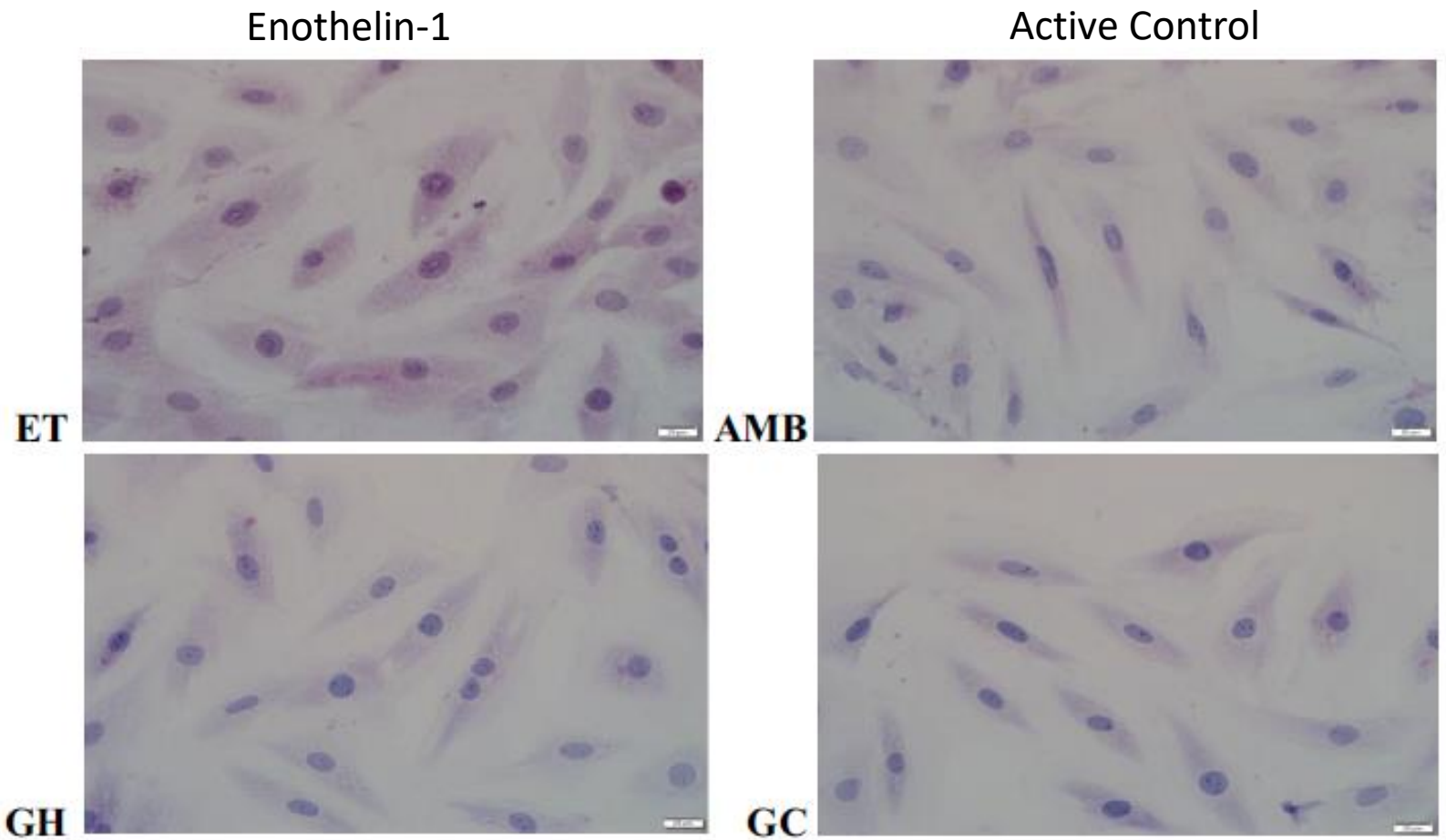
J Inflamm Res. 2021; 14: 3729–3738

Anti-Inflammatory Effects of Four Psilocybin-Containing Mushroom Extracts on LPS-Induced COX-2 in Cultured Human Macrophages



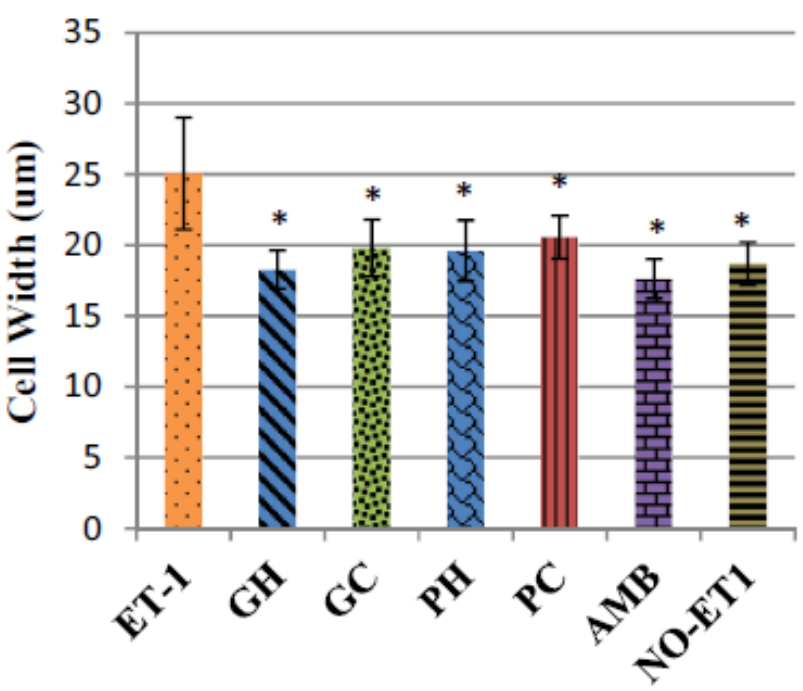
J Inflamm Res. 2021; 14: 3729–3738

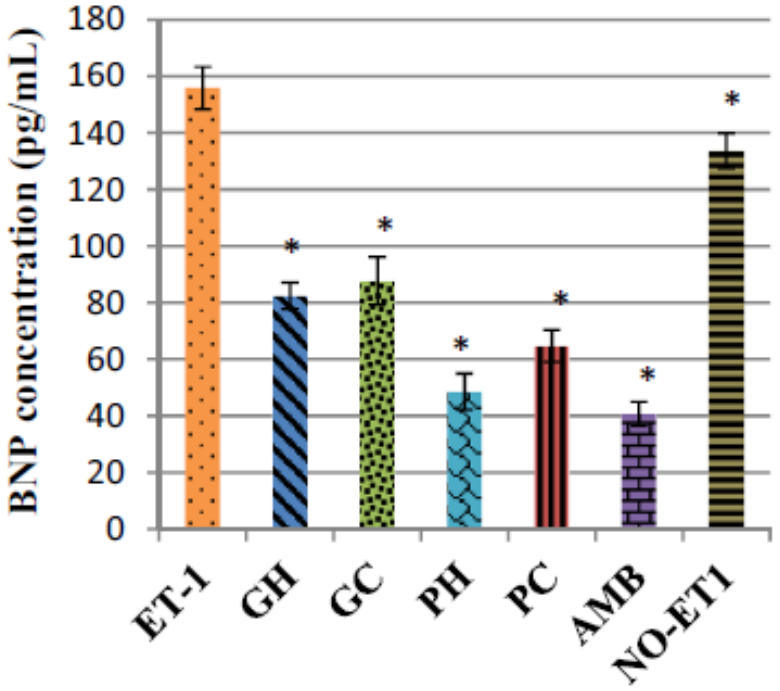
Effects of Psilocybin Mushroom Extracts on Endothelin-1-Induced Hypertrophy and Cell Injury in Rat Cardiomyocytes



Nkadimeng & Eloff Nature Sci Rep. 2020; 10: 22314.

Effects of Psilocybin Containing Mushroom Extracts on Endothelin-1-Induced Hypertrophy in Rat Cardiomyocytes: Cell Width and BNP Levels





ET-1: Endothelin-1
GH, GC, PH, PC: Mushroom extracts
AMB: Ambrisentan (active control)
NO-ET1: Untreated control

Nkadimeng & Eloff Nature Sci Rep. 2020; 10: 22314.

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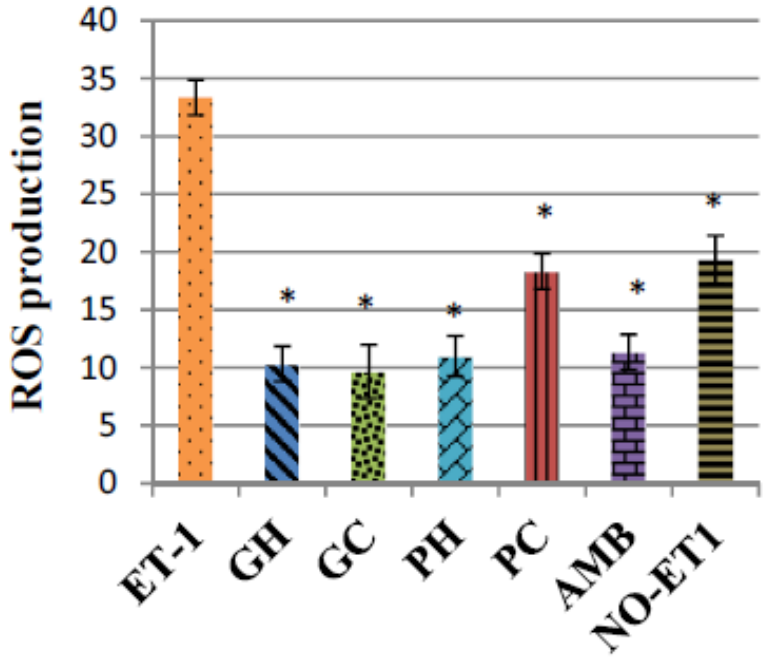

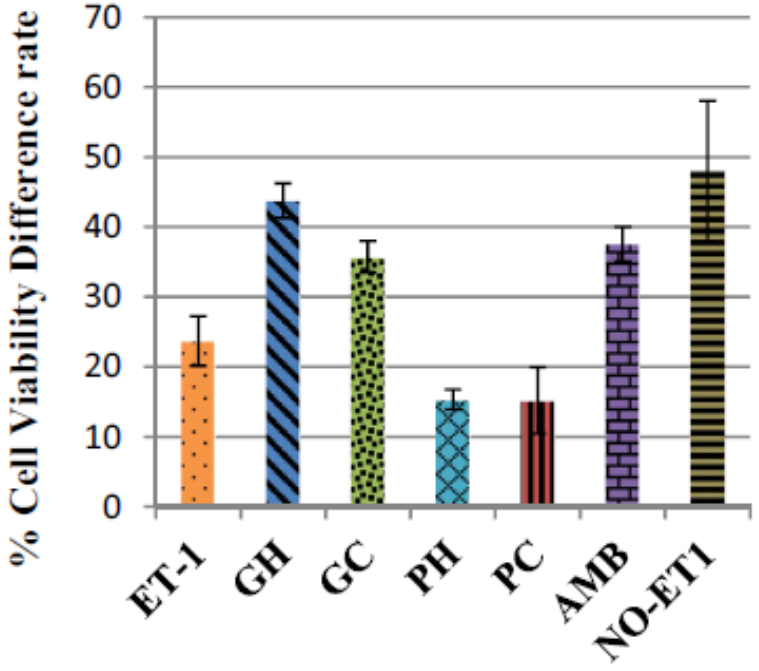

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AMB: Ambrisentan (active control)
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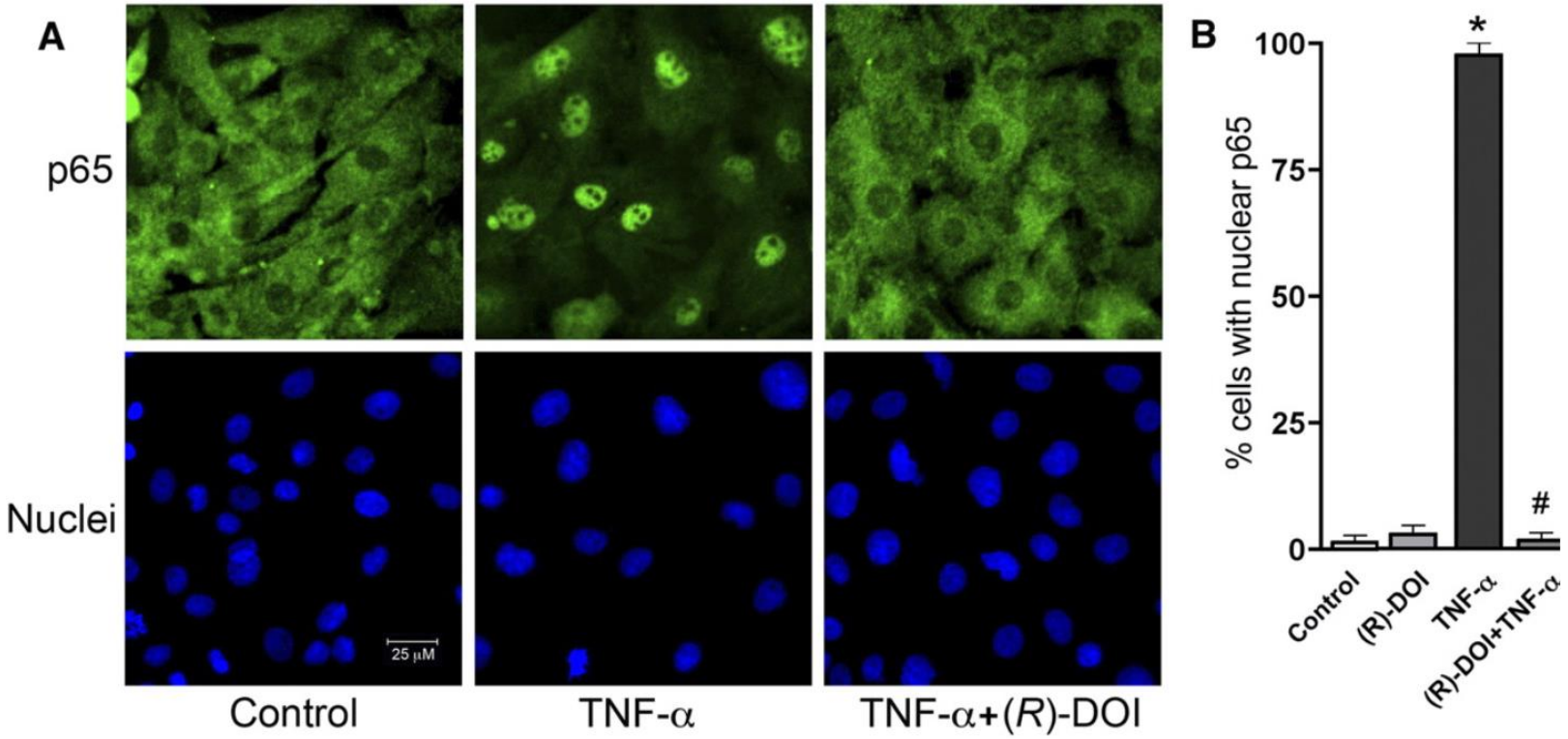
Nkadimeng & Eloff Nature Sci Rep. 2020; 10: 22314.

(R)-DOI: 2,5-dimethoxy-4-iodoamphetamine

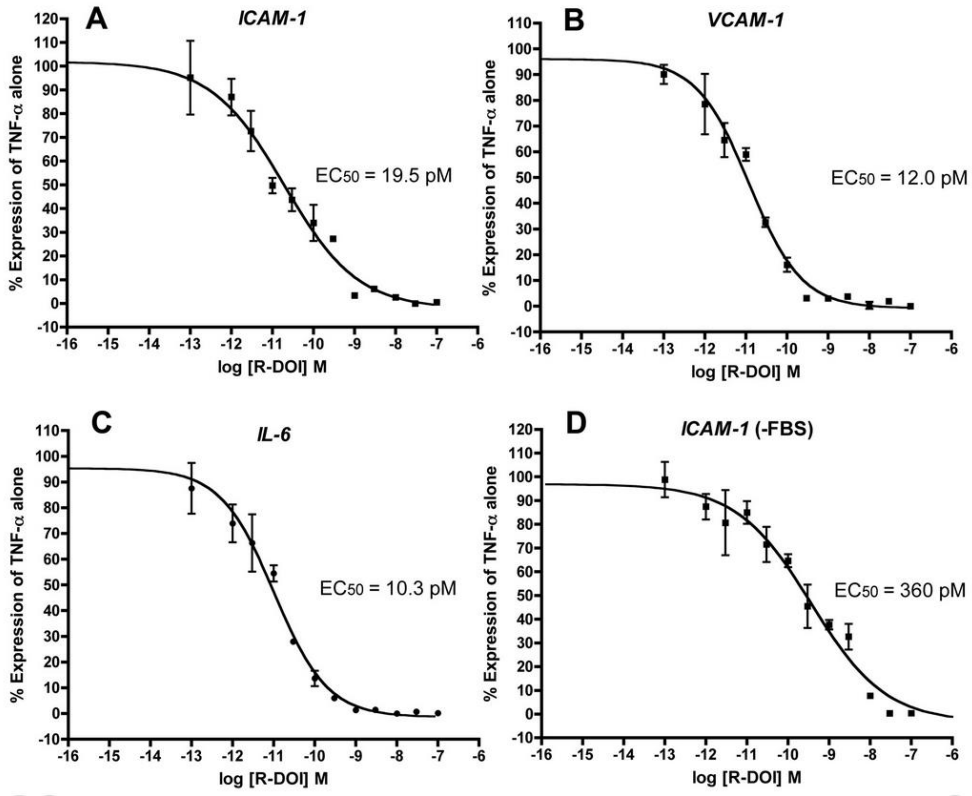
- DOI: 2,5-dimethoxy-4-iodoamphetamine
- Synthetic psychedelic
- Substituted amphetamine (phenethylamine family)
- Not a stimulant
- High affinity agonist for 5-HT2A receptors
- Originally used as a radioligand to study 5-HT2A receptors
- Behavioral effects: 1.5-3 mg PO (16-30 hours)
- Sold as substitute for LSD
- Significant anti-inflammatory effects (at sub-behavioral doses)

(*R*)-DOI Potently Inhibits TNF-α-Induced Activation and Translocation of NF-κB p65 in Rat Aortic Smooth Muscle Cells

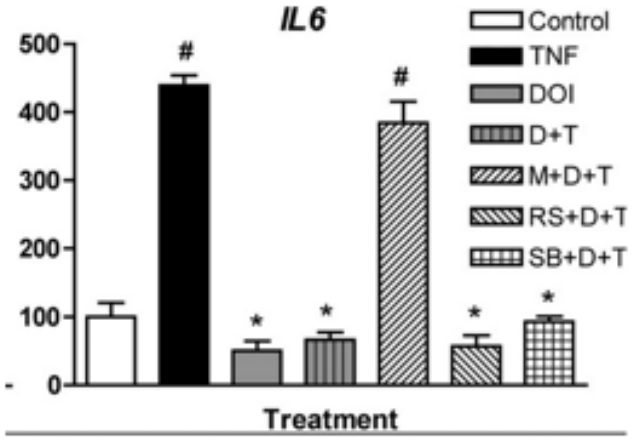


Yu J. Pharm & Exp Therapeutics Nov 2008, 327 (2) 316-323

(*R*)-DOI Potently Inhibits TNF-α-Induced Expression of Proinflammatory Genes in Rat Aortic Smooth Muscle Cells

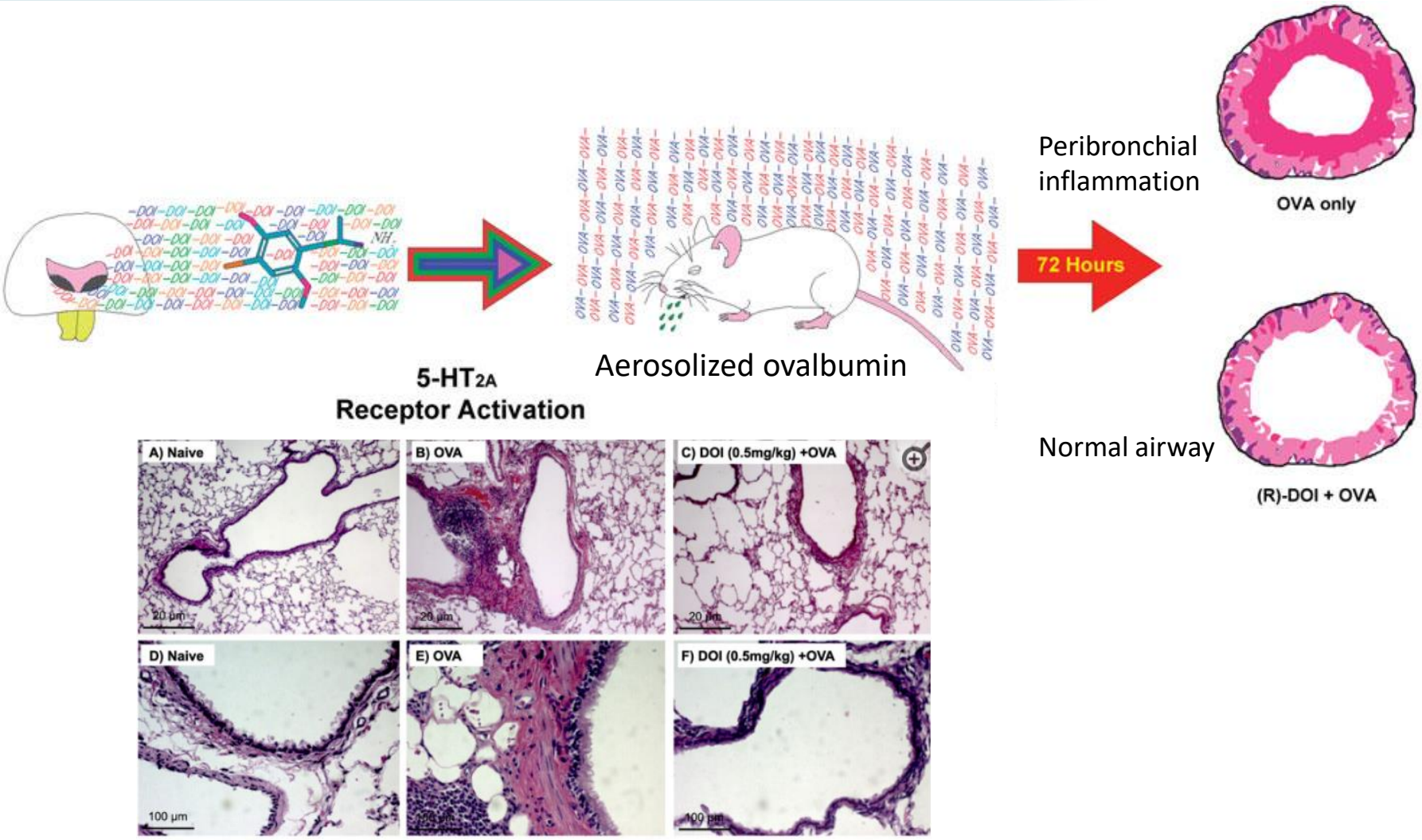


- Effects are mediated through 5-HT2A
- Blocked by selective 5-HT_{2A}antagonism
- Pretreatment with 5-HT_{2B} and 5-HT_{2C} antagonists have no effect on results



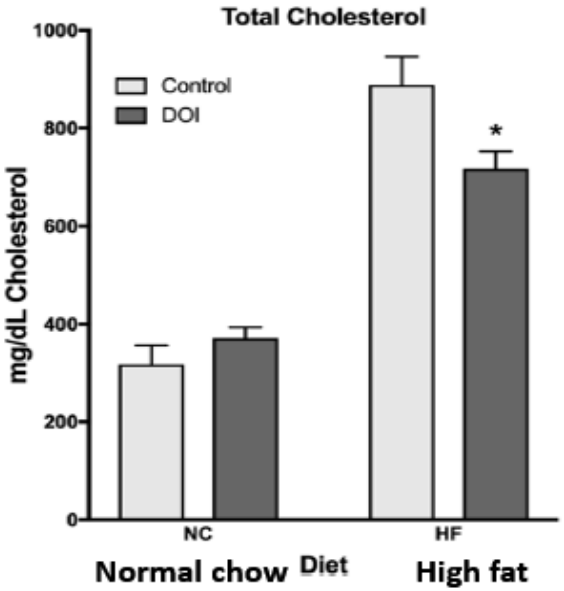
Yu J. Pharm & Exp Therapeutics Nov 2008, 327 (2) 316-323

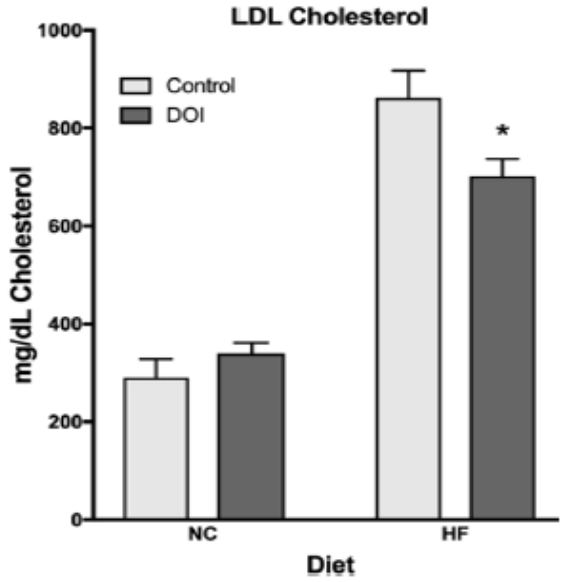
Anti-Inflammatory Effects of Psychedelics (R)-DOI in Murine Asthma Model

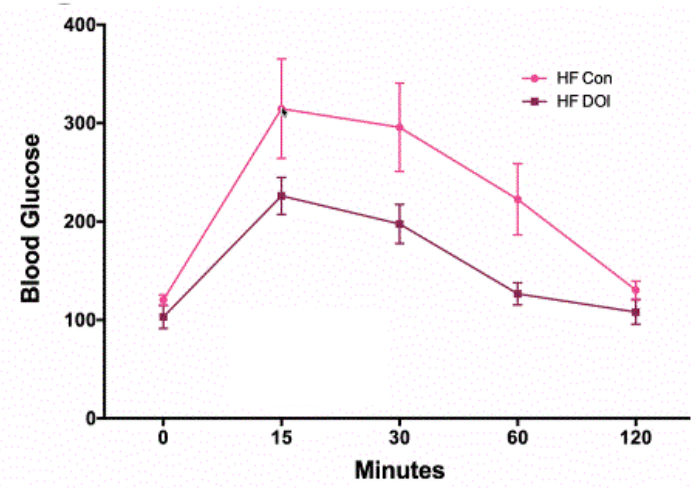


Flanagan & Nichols. Int Rev Psychiatry 2018, 30(4):363-375.

(R)-DOI: Cholesterol and Glucose in ApoE−/− Mice on High Fat Diet

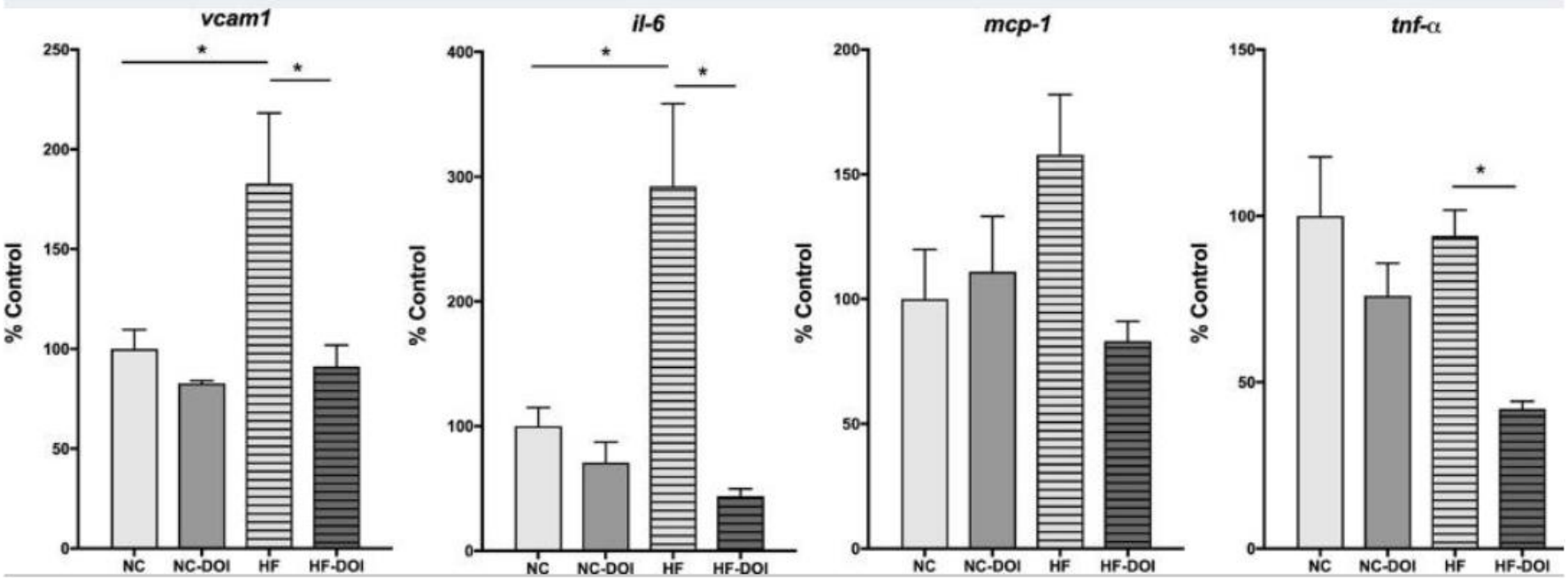






Flanagan. Scientific Reports-Nature 2019; 9:13444

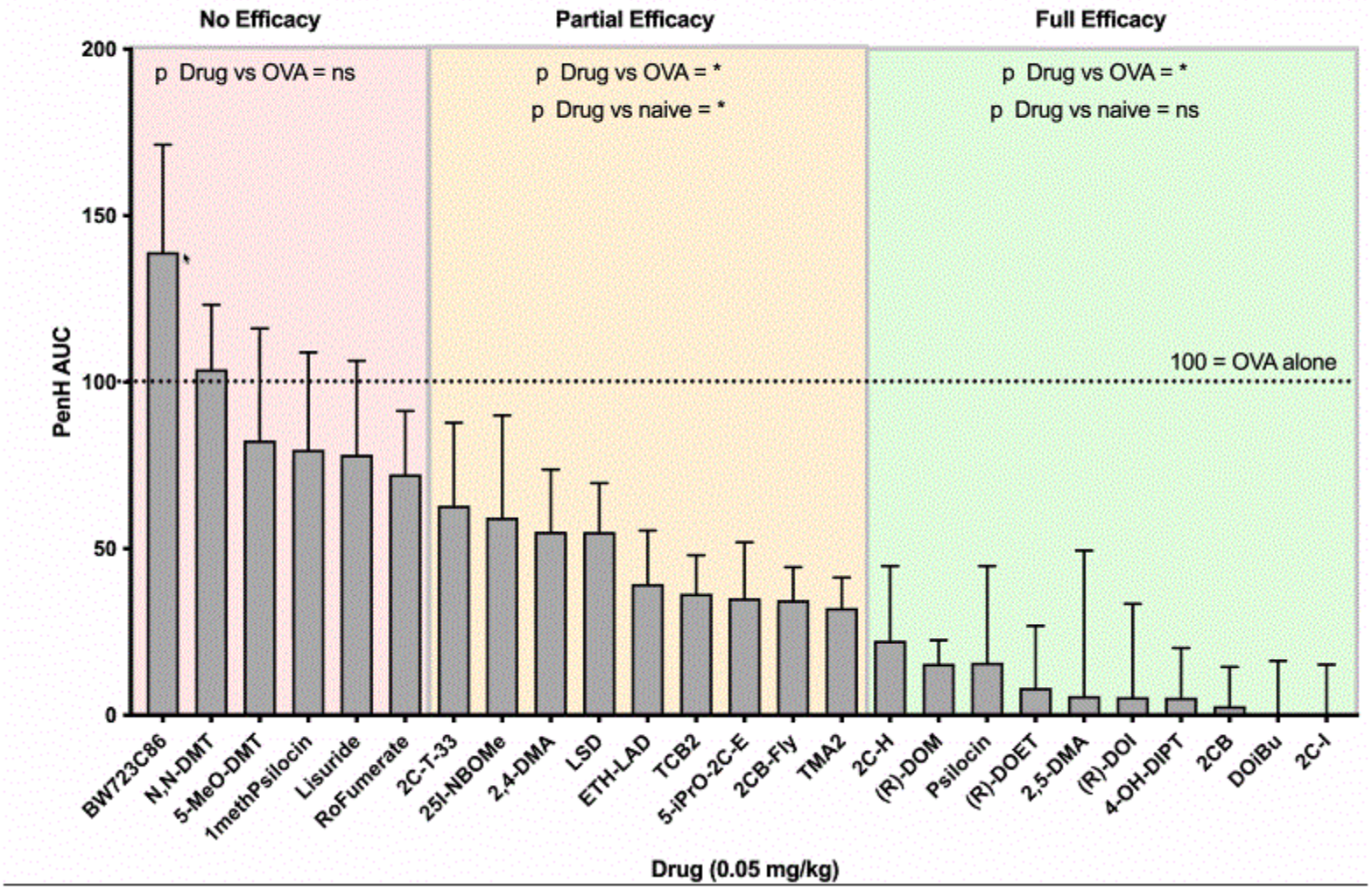
(R)-DOI and Pro-Inflammatory Gene Expression in Aortic Tissue in ApoE−/− Mice



NC-normal chow
HF-high fat diet

Flanagan. Scientific Reports-Nature 2019; 9:13444

Anti-inflammatory Activity Does Not Correlate With Behavioral Activity



Flanagan ACS Pharmacol. Transl. Sci. 2021, 4, 488−502

Association Between Lifetime Classic Psychedelic Use and Hypertension in the Past Year (NSDUH)

Variable	aOR (95% CI)	*P* value
Hypertension in the past year		
Model 1		
Lifetime classic psychedelic use	0.86 (0.81–0.91)	<0.0001
Model 2		
Lifetime tryptamine use	0.80 (0.73–0.89)	0.0001
Lifetime LSD use	0.96 (0.87–1.05)	0.3361
Lifetime phenethylamine use	0.97 (0.87–1.08)	0.5595

Hypertension. 2021;77:1510–1516.

Associations between Lifetime Classic Psychedelic Use and Cardiometabolic Disease (NSDUH)

Variable	aOR (95% CI)	*p* value
Heart disease in the past year		
Model 1		
Lifetime classic psychedelic use	0.77 (0.65–0.92)	.006
Model 2		
Lifetime tryptamine use	0.85 (0.69–1.06)	.152
Lifetime LSD use	0.88 (0.73–1.07)	.199
Lifetime phenethylamine use	0.92 (0.75–1.13)	.402
Diabetes in the past year		
Model 1		
Lifetime classic psychedelic use	0.88 (0.78–0.99)	.036
Model 2		
Lifetime tryptamine use	0.86 (0.74–1.00)	.055
Lifetime LSD use	0.92 (0.80–1.06)	.236
Lifetime phenethylamine use	1.01 (0.86–1.19)	.891

Associations between Lifetime Classic Psychedelic Use and Cardiometabolic Disease (NSDUH)

Variable	aOR (95% CI)	*p* value
Heart disease in the past year		
Model 1		
Lifetime classic psychedelic use	0.77 (0.65–0.92)	.006
Model 2		
Lifetime tryptamine use	0.85 (0.69–1.06)	.152
Lifetime LSD use	0.88 (0.73–1.07)	.199
Lifetime phenethylamine use	0.92 (0.75–1.13)	.402
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Lifetime phenethylamine use	1.01 (0.86–1.19)	.891

Associations between Lifetime Classic Psychedelic Use and Markers of Physical Health (NSDUH)

	aOR (95% CI)	*p* value	*N*
Self-reported overall health	1.08 (1.02–1.14)	.0048	168,123

	aOR (95% CI)	*p* value	*N*
Heart condition and/or cancer in the past year	0.89 (0.77–1.02)	.0917	168,147

	aRRR (95% CI)	*p* value	*N*
Normal weight (Reference)			56,955
Underweight	0.93 (0.72–1.20)	. 5753	3940
Overweight	0.86 (0.80–0.93)	.0002	51,212
Obesity – Class 1	0.80 (0.74–0.87)	<.0001	28,913
Obesity – Class 2	0.76 (0.69–0.83)	<.0001	13,831
Extreme obesity – Class 3	0.78 (0.68–0.88)	.0002	8926

J Psychopharmacology 2021, 35(4): 447–452

Psychedelics and Inflammation
Summary

- Psychedelics are anti-inflammatory (some at sub-behavioral levels)
- Psychedelics and serotonin recruit different signaling pathways at the 5-HT2A receptor (functional selectivity)
- Pathways responsible for behavioral vs anti-inflammatory effects of psychedelics are different
- Structural differences between ligands appear to result in different anti-inflammatory potencies and efficacy among psychedelics
- These anti-inflammatory properties may constitute a novel steroid-sparing, non-immunosuppressant therapeutic approach to diseases linked to chronic inflammation
- Understanding interactions between ligands at the 5-HT_{2A} receptor is crucial for the development of new 5-HT_{2A} receptor agonists with reduced behavioral effects but with retained potent anti-inflammatory activity.
- Whether some classic psychedelics may have long term effects on physical health is an intriguing question that merits further exploration.

Flanagan Nature Scientific Rep (2019) 9: 13444
Flanagan ACS Pharmacol. Transl. Sci. 2021, 4, 2, 488–502