Cannabis and Health

Module 13: Inflammation and the Microbiome

Lecture 4: Cannabis and Inflammatory Disease States

Cannabinoids may alleviate symptoms in many inflammatory diseases

- Autoimmune
- Chronic inflammatory pain
- Inflammatory bowel disease
- Psychiatric & mood disorders (e.g., anxiety, schizophrenia)
- Neurodegenerative diseases (e.g., Alzheimer's, Multiple sclerosis)

Autoimmune disease

- A disorder where your immune system attacks and damages its own tissues

- ECS is upregulated
  - CB1 upregulated on T cells
  - Enhancing anandamide → reduces disease severity
  - CB1 activation → reduced symptomology

Sativex treatment reduced pain symptoms in RA patients

TABLE 2. Efficacy endpoints: difference between change from baseline between CBM and placebo after 5 weeks of treatment

	Baseline (mean/median)[a]		Endpoint (mean/median)[a]				
Efficacy endpoint	CBM	Placebo	CBM	Placebo	Difference (mean/median[a])	95% confidence interval	*P*
Morning pain on movement[a]	7.0	6.7	4.8	5.3	−0.95	−1.83, −0.02	0.044
Morning pain at rest[a]	5.3	5.3	3.1	4.1	−1.04	−1.90, −0.18	0.018
Morning stiffness[a]	3.5	3.8	3.0	3.2	−0.09	−0.58, 0.23	0.454
Quality of sleep	5.7	5.8	3.4	4.6	−1.17	−2.20, −0.14	0.027
DAS 28	5.9	6.0	5.0	5.9	−0.76	−1.23, −0.28	0.002
SF-MPQ, total intensity of pain[a] (a)	15.0	20.0	10.5	13.0	3.00	−3.00, 9.00	0.302
SF-MPQ, intensity of pain at present[a] (b)	48.0	50.0	33.0	50.0	−3.00	−18.0, 9.00	0.574
SF-MPQ, pain at present (c)	3.2	3.2	2.6	3.3	−0.72	−1.30, −0.14	0.016

MPQ = McGill pain questionnaire

DAS28 = joint disease activity (e.g., swelling, tenderness)

Sativex (n=31)

Placebo (n=27)

5-week trial

Blake et al, 2006, *Rheumatology*

Inflammatory Bowel Disease (IBD)

- A disorder that involve chronic inflammation of the digestive tract
- ECS is altered in IBD patients

Disease		Diverticulitis	Celiac disease		IBS		IBD			CRC	
		Human	Human	Animal	Human		Human		Animal	Human	Animal
					IBS-D	IBS-C	CD	UC			
Ligands	AEA	Increased	Increased	Increased	No change	No change	Decreased	Increased or Decreased	Increased	Increased	No change
	2-AG	Decreased		Increased	Increased	No change	No change	No change	No change	Increased	Increased
Receptors	CB_1	No change (R,P)	Increased (R,P)		Genetic polymorphism	Genetic polymorphism	Increased (R,P) Genetic polymorphism	No change (R,P) or Increased (P) Genetic polymorphism	Increased (P)	Decreased (R,P)	No change (R)
	CB_2		Increased (R,P) Genetic polymorphism				Increased (P) or No change (R,P)	Increased (P) or No change (R,P)	Increased (R)	Increased (P) or No change (R)	No change (R)
	TRPV1				Increased (P)	Increased (P)					Decreased (R)

Lee et al., 2016, *AM J Physiol Gastrointest Liver Physiol*

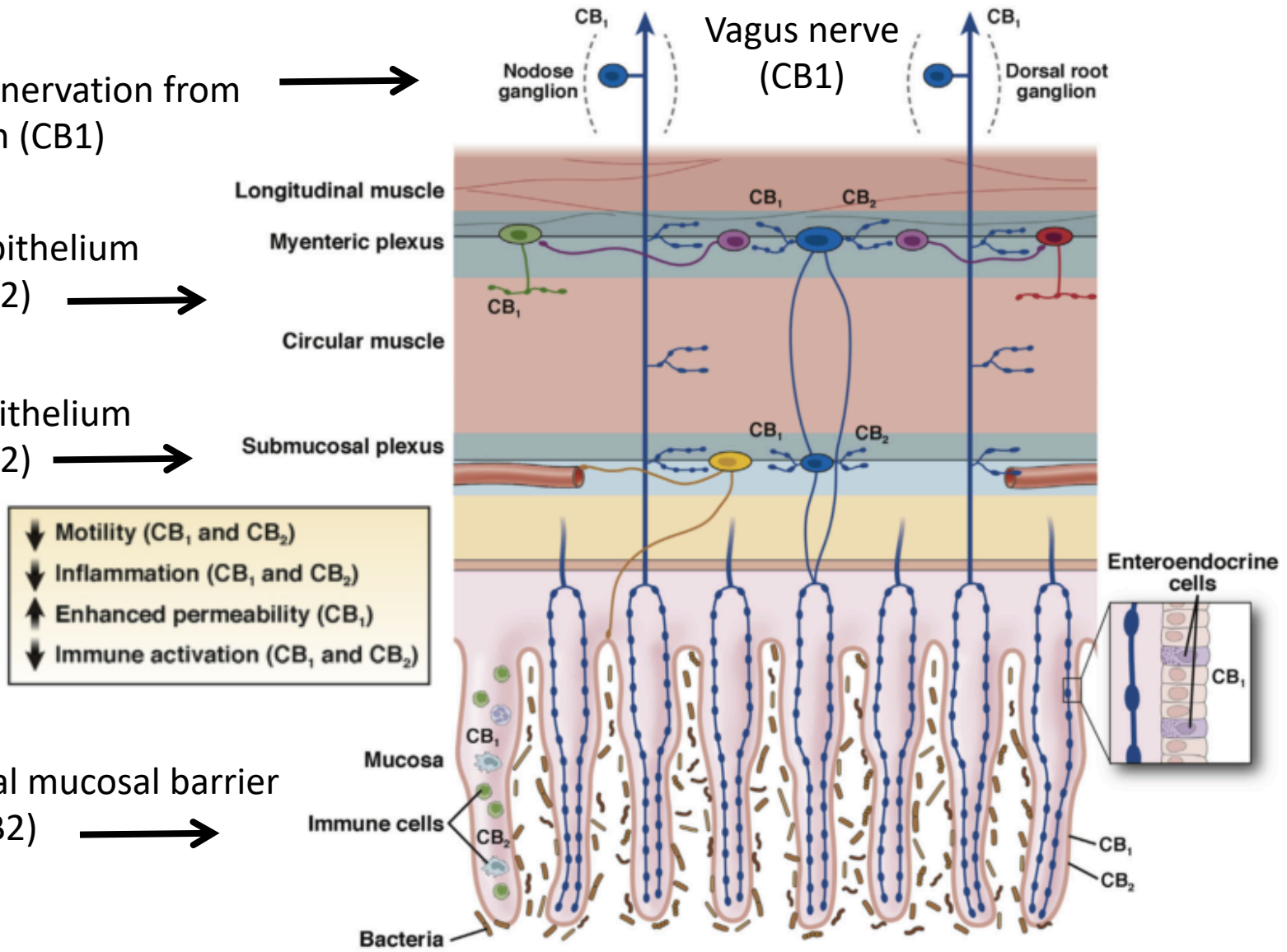
Endocannabinoid regulation of the GI

Nerve innervation from the brain (CB1)

Outer epithelium (CB1, CB2)

Inner epithelium (CB1, CB2)

Intestinal mucosal barrier (CB1, CB2)



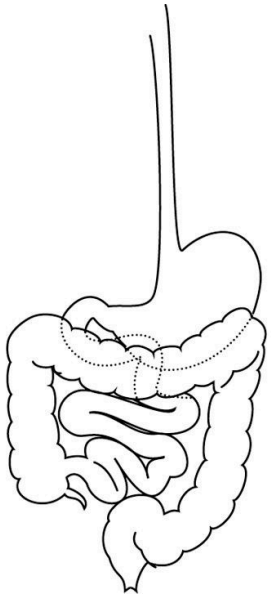
Inner intestinal tract (CB1, CB2)

Sharkey et al., 2016, *Gastroenterology*

Endocannabinoid regulation of the GI

↓ CANNABINOID TONE

Vomiting
↓ Gastroparesis
↑ Motility
Diarrhea
↓ Constipation, ileus



↑ CANNABINOID TONE

↓ Gastroesophageal reflux
↓ Vomiting
↓ Acid secretion, gastric emptying
↓ Motility, inflammation, diarrhea
↓ Visceral pain
Cell homeostasis

Uranga et al., 2018, *Biochemical Pharmacology*

Cannabinoids and neurological and psychiatric conditions

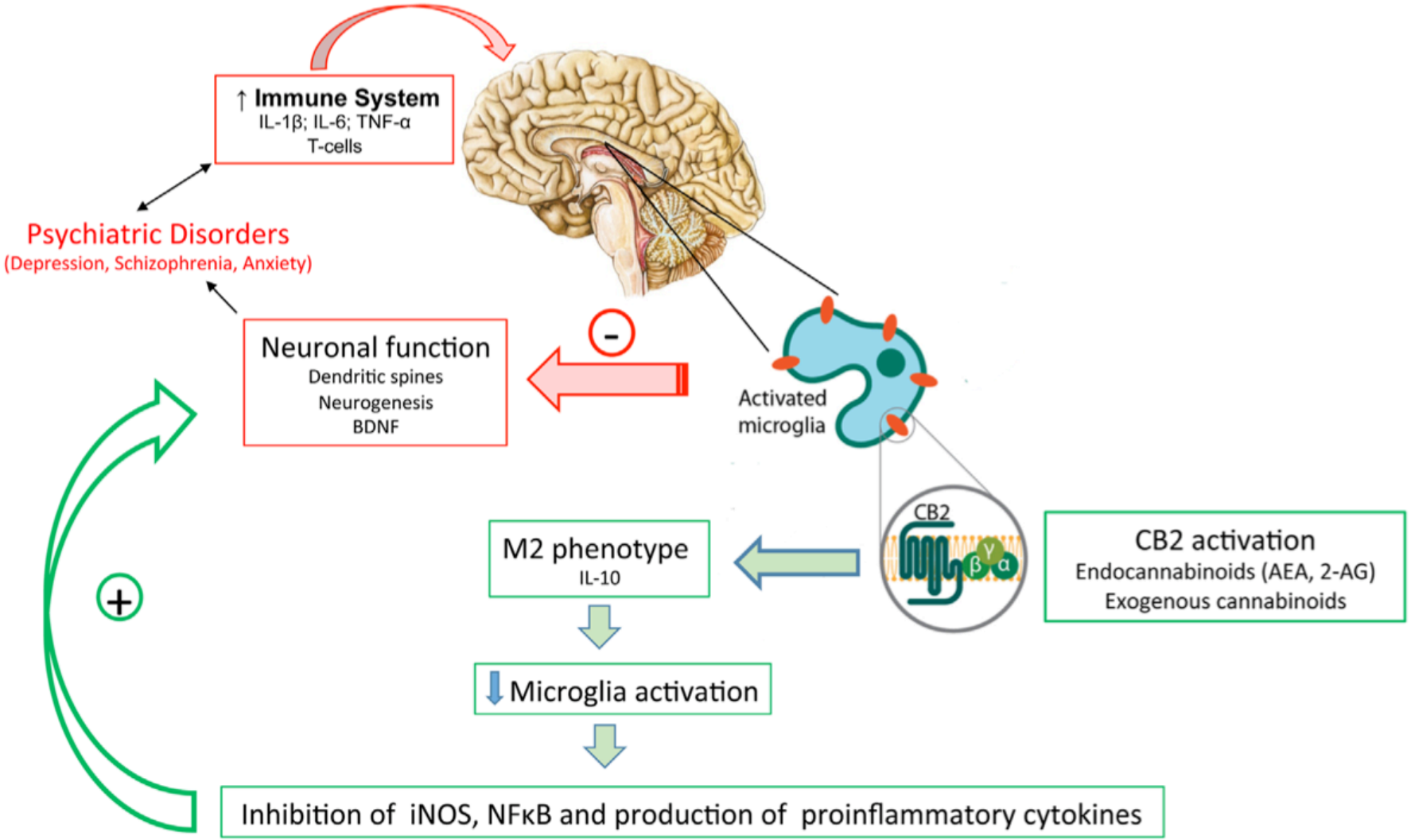
- Cannabinoids may be useful in alleviating symptoms in several inflammatory-mediated neurological conditions

TABLE 1 | Neurological conditions for which cannabis-based treatments have been employed (revised, reformatted and supplemented from MacCallum and Russo, 2018).

Condition	Preparation	Level of evidence	Type of evidence
Multiple sclerosis (MS) spasticity	Nabiximols	Conclusive	Phase III RCTs, Regulatory approval
Epilepsy (Dravet and Lennox-Gastaut syndromes)	Cannabidiol (Epidiolex®)	Conclusive	Phase III RCTs, Regulatory approval
Chronic pain	THC, nabiximols	Substantial	Phase II RCTs
Schizophrenia, positive and negative symptoms	CBD	Substantial	Phase II RCTs
Sleep disturbance secondary to neurological symptoms	THC, nabilone, nabiximols	Moderate	Phase II–III RCTs
Glaucoma	THC, cannabis	Moderate	Phase II RCTs
Lower urinary tract symptoms (LUTS) in MS	Nabiximols	Moderate	Phase II RCTs
Tourette syndrome	THC, cannabis	Moderate	Phase II RCTs, observational studies
Dementia with agitation	THC, cannabis	Limited	Observational studies
Parkinson disease symptoms	THC, CBD, cannabis	Limited	Observational studies
Post-traumatic stress disorder	Cannabis	Limited	Observational studies
Social anxiety	CBD	Limited	Phase II RCT, observational studies

Russo, 2018, *Frontiers in Integrative Neuroscience*

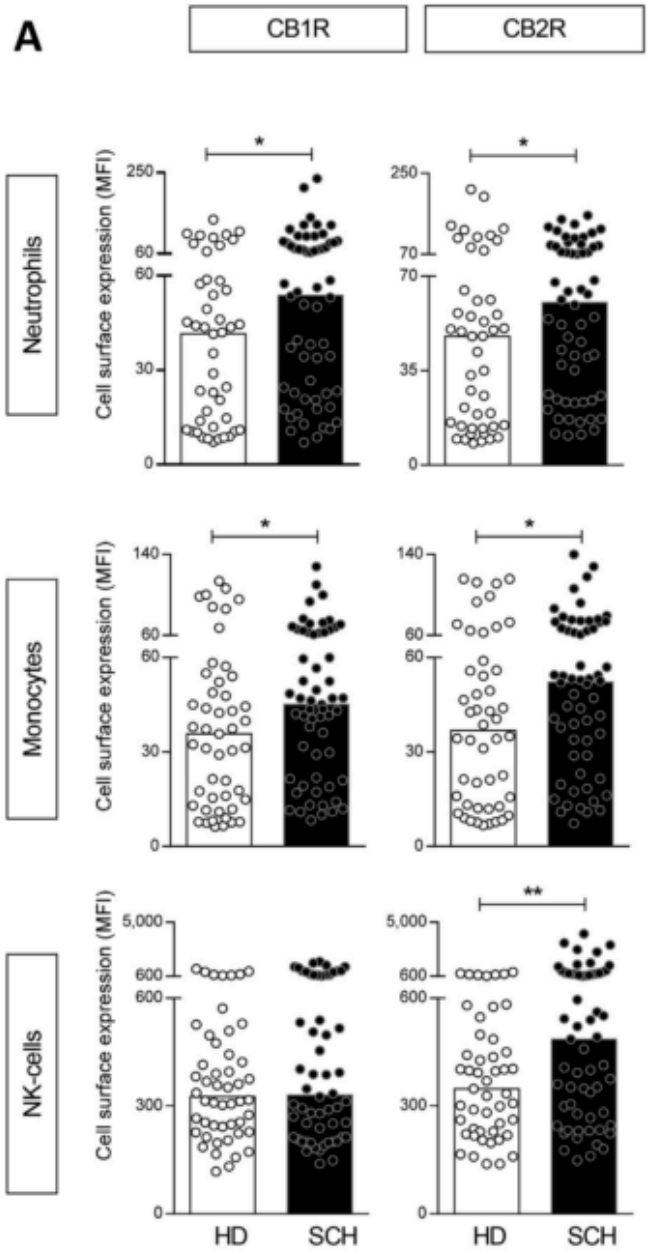
Cannabinoids and psychiatric disorders



Lisboa et al., 2016, *Frontiers in Neurology*

Schizophrenia

- Higher CBR expression of immune cells in schizophrenia patients compared to controls
- Defective ECS-mediated immunomodulation



De Campos-Carli et al., 2017, *Journal of Psychiatric Research*

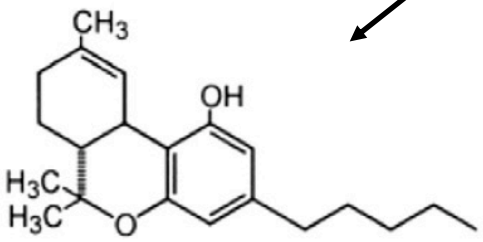
Neurodegenerative diseases

- Associated with over active microglia, inflammation and oxidative stress, leading to the degeneration of neurons
- CBRs are overexpressed in post-mortem human brains of patients with these diseases

Disease	Causes	Symptoms/Affects
Alzheimer disease (AD)	Beta-amyloid plaques	Dementia
Parkinson disease (PD)	Loss of basal ganglia nuclei	Abnormal regulation of movement
Amyotrophic lateral sclerosis (ALS)	Selective loss of motor neurons in cortex, brainstem, spinal cord	Loss of voluntary muscle control
Multiple sclerosis (MS)	Autoimmune, demyelination of axons	Nerve loss, spasticity, pain

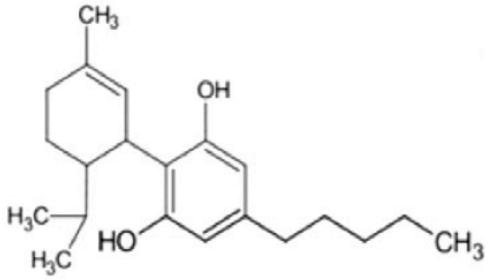
Cannabis flower

THC



- Neuroprotective
- Anticonvulsant
- Muscle relaxant
- Pro-microbiome
- Anti-TNFa
- Anti-emetic

CBD



- Neuroprotective
- Antioxidant
- Antineoplastic
- Anti-anxiety
- Anti-psychotic
- Antibiotic
- 5HT1a agonist
- Anticonvulsant

Russo, 2018, *Frontiers in Integrative Neuroscience*

Conclusions

- It has become increasingly clear that the immune system and gut microbiome play important roles in a number disorders
- Studies in preclinical models suggest diseases with underlying inflammatory mechanisms may be helped with cannabinoids
- Clinical studies that test cannabinoids like THC and CBD have yet to be one (but should be!)