

Cannabis and Health

Module 13: Inflammation and the Microbiome

Lecture 3: Cannabinoids and Inflammation

Endocannabinoid & immune system overview

- The endocannabinoid system (ECS) is expressed in many organs, tissues, and cells of the immune system
- **CB1** receptors are predominately expressed on T cells (adaptive - attack specific invading cells or virus), and **CB2** on macrophages (innate - attack any invading cell or virus)
- ECS enacts homeostatic control over immune reactions
- Immune cells express greater CB2 to CB1
 - Dependent on cell activation state
- Under inflammatory states:
 - Immune cells release endocannabinoids (AEA, 2-AG)
 - Macrophages upregulate CB2
 - T cells upregulate CB1

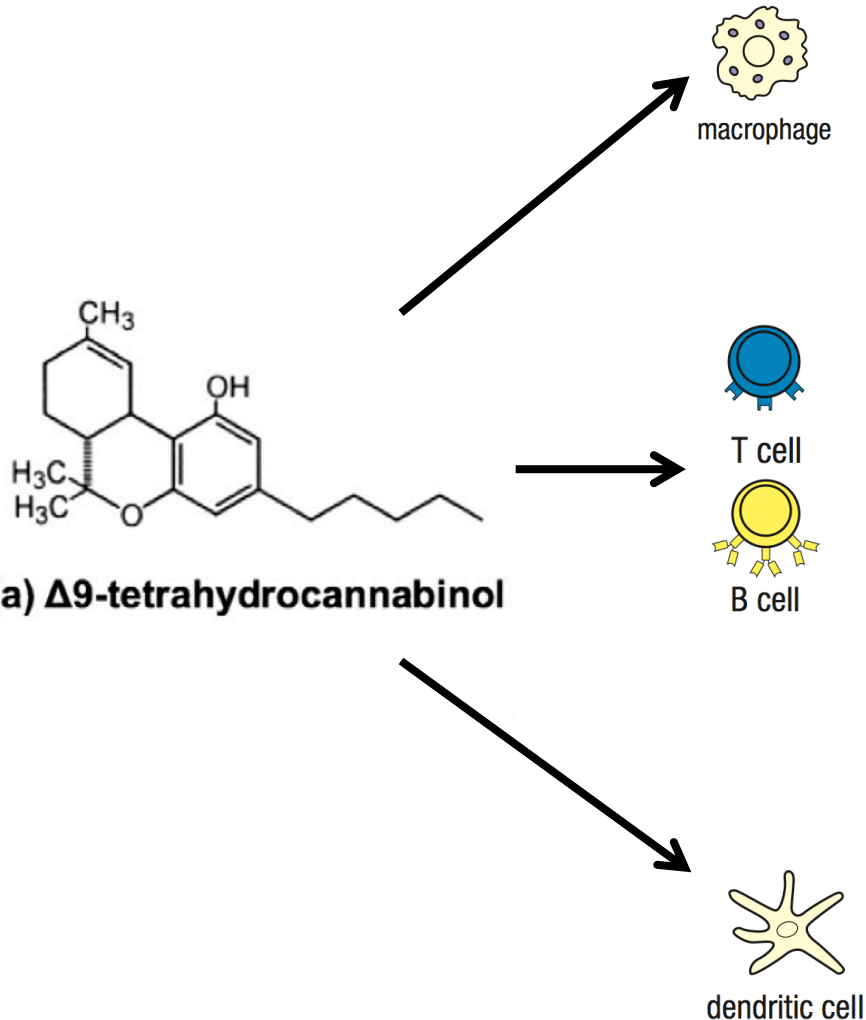
Cannabinoids and the immune system overview

- Immunomodulatory role depends on:
 - Type of cannabinoid
 - Type of immune cell
 - Dose administered
- Both stimulatory and immunosuppressive

Cannabinoids exert immunosuppressive properties through 4 main pathways:

1. Induction of apoptosis (cell death)
2. Inhibition of cell proliferation
3. Inhibition of cytokine and chemokine production
4. Induction of regulatory T cells

Immunomodulatory effects of THC

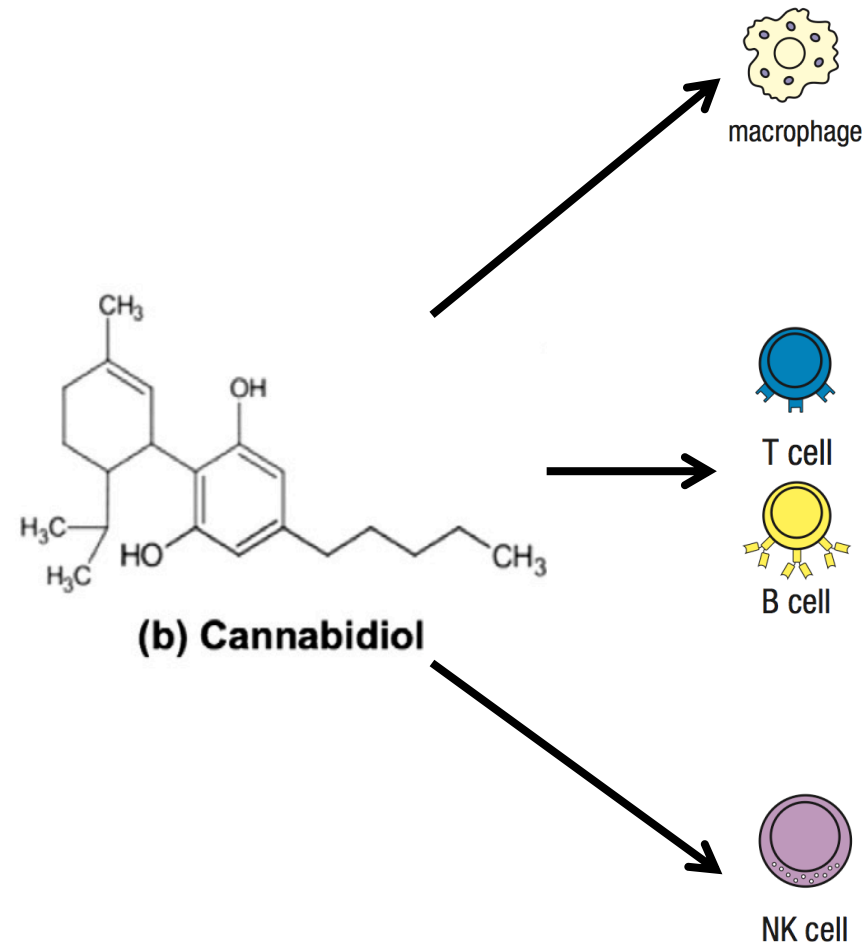


- Induces apoptosis
- M1 \rightarrow M2 phenotype
- Suppress cytokine/chemokine release

- Induces apoptosis (via CB2)
- Decreases proliferation
- Th1 (destructive) \rightarrow Th2 (protective)
- Increase Treg proliferation
- Suppress Ig levels

- Inhibits IL12 production
- Suppresses maturation

Immunomodulatory effects of CBD



- Inhibits phagocytosis
- M1 → M2 phenotype

- Induces apoptosis (via ROS production)
- Inhibits Th1 IL1, IL12, TNF α , INF γ release
- Enhances Th2 IL4, IL10 release

- Suppress cytotoxic function

Cannabinoids can have potent effects on immune cell cytokine production

Increase cytokine production

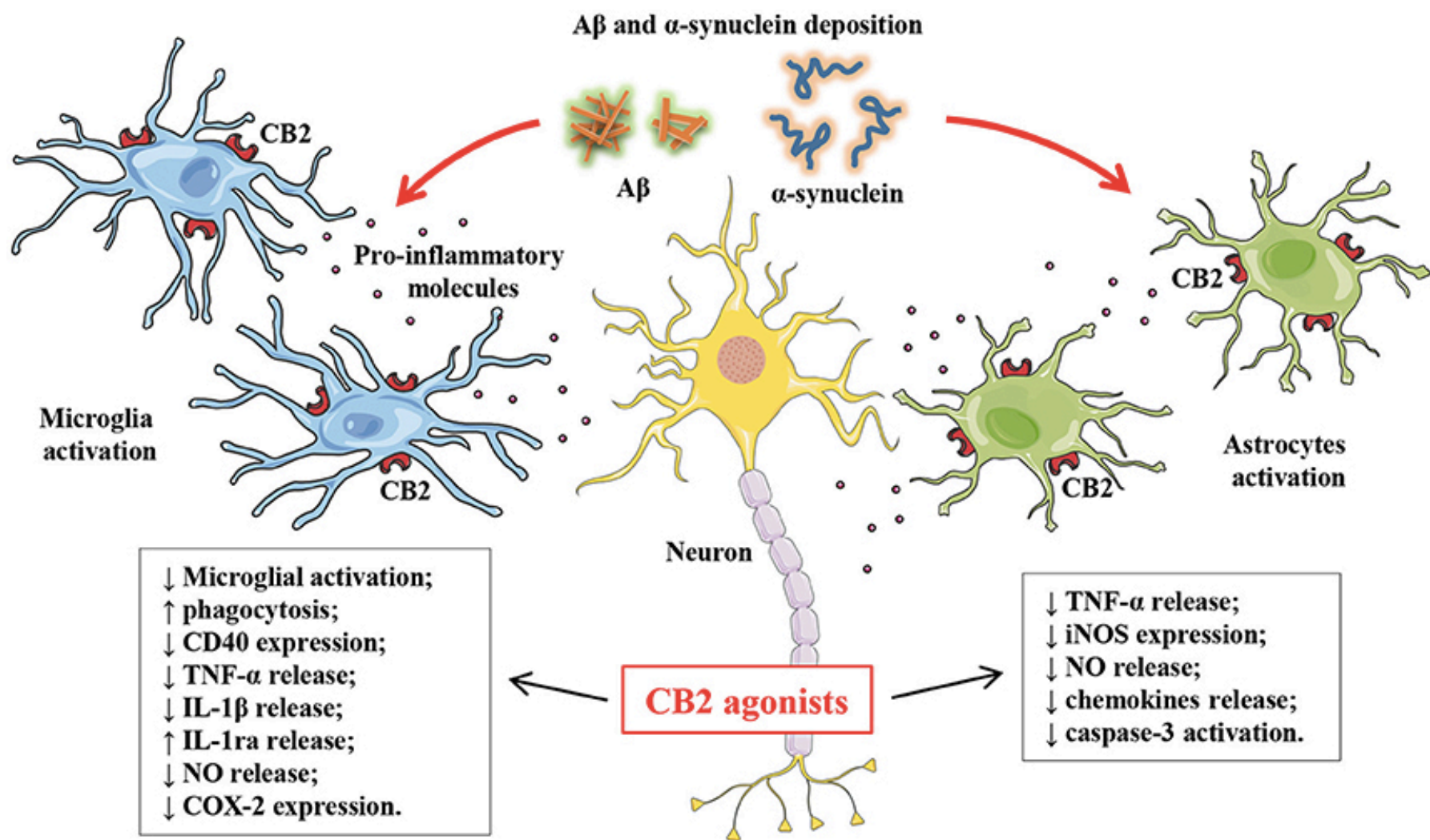
IL-1	In vitro mouse macrophages	THC
	In vivo mouse serum	THC
	In vitro mouse macrophages	THC
TNF	In vitro human monocytes	THC
	In vivo mouse serum	THC
	In vitro mouse macrophages	THC
IL-4	In vitro human T cell	THC
	dendritic cell co-culture	
IL-6	In vivo mouse serum	THC
IL-12	In vitro/ex vivo mouse macrophages	CBD

Decrease cytokine production

IFN- γ	Ex vivo mouse spleen	THC
	In vitro human NK cells	THC
	In vitro mouse splenocytes	THC
	In vitro human PBMC	THC/CBD
	In vitro human T cell	THC
TNF	dendritic cell co-culture	
	In vitro mouse splenocytes	THC
	Macrophage cell lines	THC
	In vitro human NK cells	THC
	In vitro human PBMC	CBD
IL-1	In vitro human NK cells	THC
	In vitro human PBMC	CBD
	In vitro mouse spleen	THC
	In vitro human T cells	THC/CBD
	In vitro/ex vivo mouse macrophages	CBD
IL-12	In vitro mouse splenocytes/macrophages	THC

Neurological implications

- ECS decreases neuronal cell damage during neuroinflammatory processes
- Neuronal CB1 attenuates oxidative stress
- CB2 on glia attenuates inflammation
 - Suppresses microglia activation
 - Inhibits release of neurotoxic factors



ECS and neurological conditions

	Alzheimer's Disease and Amyloid-β-Induced Neurotoxicity and Memory	Multiple Sclerosis (and Corresponding Experimental Models)	Amyotrophic lateral Sclerosis (SOD G93A Mice)	Parkinson's Disease	Huntington's Chorea
CB₁ Expression	Unchanged or decreased	Decreased (EAE); Decreased/Unchanged (CREAE, TMEV-IDD); Increased (MS)	Unchanged	Decreased early Increased late	Decreased early and late
CB₂ Expression	Increased	Increased (human MS)	Increased	No report	Increased in some models
Endocannabinoid levels	Increased early Decreased late	Decreased, unchanged, or increased in an acute phase (EAE); Increased (CREAE, TMEV-IDD)	Increased	Increased	Decreased early and late
Effect of CB₁ agonism	Beneficial on neurotoxicity	Beneficial on pain, spasticity and tremors	No effect	Beneficial on LID	No effect
Effect of CB₂ agonism	Beneficial on inflammation	Beneficial on inflammation	Beneficial	Beneficial on inflammation	Beneficial on inflammation
Effect of inhibition of endocannabinoid inactivation	Beneficial on neurotoxicity and amnesia only with early treatment	Beneficial on spasticity	Beneficial	Beneficial on LID	Beneficial but <i>via</i> TRPV1
Effect of CB₁ knock-out or antagonism	Beneficial on amnesia	Worsening on spasticity and tremors	Beneficial	Beneficial in the late phases, possibly also on LID	No report
Effect of CB₂ knock-out or antagonism	Beneficial on some hallmarks of gliosis	Worsening, or in some cases beneficial, on inflammation	Worsening	Worsening	Worsening

Conclusions

- Cannabinoids modulate the immune system
- Both THC and CBD impact the immune system
- The effect on the immune system is complicated and depends on a number of factors