

Supplementary Materials: A guide to targeting the endocannabinoid system in drug design

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1 **Table S1.** Diseases and disorders that could be treated by targeting ECS proteins.

Protein	Ligand type	Remarks	Evidence	References
Pain				
CB1	Agonist	Preferable CB1 peripheral agonists or CB1 PAMs		[1,2]
CB2	Agonist	Also CB2 PAMs	Well grounded	[3,4]
TRPV1	Antagonist			[5]
FAAH	Inhibitor			[6]
MAGL	Inhibitor			[7,8]
AEA reuptake proteins	Inhibitor			[9]
Seizures				
CB1	Agonist			[10]
MAGL	Inhibitor		Well grounded	[11]
AEA reuptake proteins	Inhibitor			[11]
ABHD6	Inhibitor			[11]
TRPV1	Antagonist			[11,12]
TRPV1	Agonist		Limited evidence	[13]
Anxiety				
CB1	Agonist			[14–16]
CB2	Agonist		Well grounded	[15,16]
FAAH	Inhibitor			[14,17]
MAGL	Inhibitor			[16]
TRPV1	Agonist			[15]
FAAH	Enhancer	FAAH in basolateral complex of amygdala	Limited evidence	[18]
CB1	Antagonist	CB1 in lateral habenula		[19]
Depression				
CB1	Agonist		Well grounded	[20]
FAAH	Inhibitor			[20,21]
MAGL	Inhibitor			[22]
CB2	Agonist			[20]
CB1	Antagonist	short-term	Limited evidence	[23,24]
CB2	Antagonist			[24]
Addiction				
CB1	Antagonist	Preferable neutral antagonist or peripheral antagonist/inverse agonist	Well grounded	[25,26]
CB2	Agonist			[27,28]
CB1	Agonist	CB1 in insula; systemic in withdrawal syndrome	Limited evidence	[29,30]
CB2	Antagonist			[28]
MAGL	Inhibitor	MAGL in insula		[29]
Cognitive functions				
FAAH	Inhibitor			[31]
MAGL	Inhibitor		Very complex topic, more reasearch needed	[32]
CB1	Antagonist			[33–35]

CB1	Agonist			[36,37]
CB2	Agonist			[32,37]
Neurodegeneration				
CB1	Agonist			[38–40]
MAGL	Inhibitor		Well grounded	[41,42]
FAAH	Inhibitor			[43]
CB2	Agonist			[38]
TRPV1	Agonist			[44]
GPR55	Agonist		Limited evidence	[40,45]
GPR55	Antagonist			[46]
CB1	Antagonist	Focal cortical dysplasia		[47]
Inflammatory and autoimmune diseases				
CB2	Agonist	Inflammatory diseases		[48–52]
CB2	Antagonist	Immunoparalysis, renal fibrosis		[53,54]
FAAH	Inhibitor		Well grounded	[55–57]
PPAR γ	Agonist			[51,52]
CB1	Antagonist	Systemic sclerosis, pulmonary fibrosis		[51,58]
CB1	Agonist			[59]
CB1	Antagonist			[60]
TRPV1	Agonist			[61]
TRPV1	Antagonist		Limited evidence	[62]
GPR55	Agonist			[50]
GPR55	Antagonist			[46]
MAGL	Inhibitor			[63]
Obesity				
CB1	Antagonist	Preferable peripheral antagonist/inverse agonist		[64–68]
CB2	Agonist		Well grounded	[69]
GPR55	Agonist			[70,71]
GPR18	Agonist		Limited evidence	[71]
Diabetes				
CB1	Antagonist	Preferable peripheral antagonist/inverse agonist		[72,73]
CB2	Agonist		Well grounded	[74,75]
GPR119	Agonist			[76]
GPR55	Agonist		Limited evidence	[77,78]
Hepatic diseases				
CB1	Antagonist		Well grounded	[79,80]
CB2	Agonist			[81]
GPR119	Agonist		Limited evidence	[82]
Hypertension				
CB1	Agonist	Peripheral agonist		[83,84]
FAAH	Inhibitor		Well grounded	[85,86]
Atherosclerosis				
CB1	Antagonist			[87]
CB2	Agonist		Well grounded	[88]
MAGL	Inhibitor			[89]
GPR55	Agonist		Limited evidence	[90]
PPAR α	Agonist			[90]
Myocardial dysfunctions				
CB2	Agonist	Deleterious effect in myocardial infraction		[91,92]
			Limited evidence	

TRPV1	Agonist			[83]
MAGL	Inhibitor			[93]
Cancer				
CB1	Agonist			[94,95]
CB2	Agonist			[94,96]
GPR55	Antagonist		Well grounded	[97–100]
TRPV1	Agonist			[101,102]
FAAH	Inhibitor			[102,103]
MAGL	Inhibitor			[104–107]
NAAA	Inhibitor		Limited evidence	[108]
Respiratory disorders				
CB1	Agonist		Well grounded	[109]
Gastroenterology				
CB1	Agonist	Emesis and nausea, anorexia, malnutrition	Well grounded	[110]
CB2	Agonist			[110–112]
FAAH	Inhibitor		Limited evidence	[112]
MAGL	Inhibitor			[112]
GPR55	Antagonist			[113]
Osteology				
CB1	Antagonist		Well grounded	[114,115]
CB2	Agonist		Limited evidence	[114]
TRPV1	Antagonist			[114]
Reproductive system				
CB1	Antagonist	Potential use in erectile dysfunctions, preferable peripheral antagonist/inverse agonist	Limited evidence	[116]
Dermatology				
CB1	Agonist	Anti-fibrotic effect, hair growth		[117,118]
CB1	Antagonist	Anti-inflammatory	Well grounded	[117,118]
CB2	Agonist	Anti-acne, anti-seborrhea effect		[117,118]
CB2	Antagonist	Anti-dryness, anti-inflammatory, anti-fibrotic effect		[117,118]
eCB reuptake proteins	Inhibitor	In conditions with inflammation and dryness	Limited evidence	[119]
Genetic disorders				
CB1	Antagonist	Duchenne muscular dystrophy	Limited evidence	[120]

2 **Table S2.** Possible indications for activation or inhibition of the proteins of ECS.

Protein	Ligand type	Indication	Risk	References	
CB1	Agonist	Pain		[1,2]	
		Seizures		[10]	
		Anxiety		[14–16]	
		Depression		[20]	
		Withdrawal syndrome	Addiction		[30]
		Neurodegenerative disorders	Cognitive impairment		[38–40]
		Spasticity in multiple sclerosis	Weight gain		[121]
		Hypertension	Erectile dysfunction		[83,84]
		Cancer			[94,95]
		Asthma			[109]
		Emesis and nausea			[110,122]
		Anorexia and weight loss			[123]
		Duchenne muscular dystrophy			[120]
	Antagonist	Addiction			[25,26]
		Cognitive impairment			[33–35]
		Systemic sclerosis			[51]
		Pulmonary fibrosis	Anxiety		[58]
		Obesity	Depression		[64–68]
		Diabetes	Nausea		[72,73]
Nonalcoholic steatohepatitis				[79]	
Atherosclerosis			[87]		
CB2	Agonist	Pain		[3,4]	
		Anxiety		[15,16]	
		Addiction		[27,28]	
		Neurodegenerative disorders		[38]	
		Inflammation		[48–50]	
		Rheumatoid arthritis		[48]	
		Atherosclerosis		[88]	
		Systemic sclerosis		[51,52]	
		Obesity		[69]	
		Diabetes		[74,75]	
		Cancer		[94,96]	
	Inflammatory bowel disease		[112]		
	Emesis and nausea		[110,111]		
	Osteoporosis		[114]		
Antagonist	Immunoparalysis			[54]	
	Renal fibrosis			[53]	
FAAH	Inhibitor	Pain		[6]	
		Anxiety		[14,17]	
		Depression		[20,21]	
		Cognitive impairment	Seizures		[31]
		Neurodegenerative disorders	Neurological disorder		[43]
		Inflammation	Disbalance in the kidney redox system		[55–57]
		Hypertension	Disbalance in phospholipid metabolism		[85,86]
		Cancer			[102,103]
		Inflammatory bowel disease			[112]
MAGL	Inhibitor	Pain		[7,8]	
		Seizures		[11]	
		Tourette syndrome		[124]	
		Anxiety		[16]	
		Depression		[22]	

		Cognitive impairment		[32]
		Neurodegenerative disorders		[41,42]
		Cancer		[104–107]
		Inflammatory bowel disease		[112]
TRPV1	Agonist	Anxiety		[15]
		Neurodegenerative disorders		[44]
		Hypertension	Seizures	[125,126]
		Cancer	Aggravating pulmonary arterial hypertension	[101,102]
		Emesis and nausea		[111]
	Osteoporosis		[114]	
	Antagonist	Pain	Hyperthermia	[5,7]
		Seizures		[11,12]
PPAR γ	Agonist	Systemic sclerosis		[51,52]
GPR18	Agonist	Obesity	Liver and kidney damage	[71]
GPR55	Agonist	Neurodegenerative disorders		[40,45]
		Inflammation		[50]
		Obesity	Liver and kidney damage	[70,71]
		Diabetes		[77,78]
	Atherosclerosis		[90]	
		Antagonist	Neurodegenerative disorders	
		Cancer		[97–100]
GPR119	Agonist	Diabetes		[76]
		Dyslipidemia		[82]
		Nonalcoholic steatohepatitis		[82]
ABHD6	Inhibitor	Seizures		[11]
AEA reuptake proteins	Inhibitor	Pain		[9]
		Seizures		[11]
		Skin inflammation		[119]

3 Abbreviations

4 The following abbreviations are used in the Supplementary Materials:

- 5
- ABHD6 α/β hydrolase domain 6
 - AEA N-arachidonylethanolamine (anandamide)
 - CB1 cannabinoid receptor type 1
 - CB2 cannabinoid receptor type 2
 - eCB endocannabinoid
 - FAAH fatty acid amide hydrolase
 - GPR18 G protein-coupled receptor 18
 - 6 GPR55 G protein-coupled receptor 55
 - GPR119G protein-coupled receptor 119
 - MAGL monoacylglycerol lipase
 - NAAA N-acylethanolamine acid amidase
 - PAM positive allosteric modulator
 - PPAR α peroxisome proliferator-activated receptor α
 - PPAR γ peroxisome proliferator-activated receptor γ
 - TRPV1 transient receptor potential vanilloid type 1 channel

7 References

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