Supplementary Table S2: Effect of cannabinoids on NK function

Ligand	Putative CTs	Experimental model	Effect in NK cell	Reference
Endocannabinoids				
AEA (10 μM)	CB1, CB2: partial agonist GPR55: agonist GPR18: full agonist TRPV1: agonist	Primary human uNK cells	Administration enhances IFNγ and TNFα production by NK cells	26
PEA (1200mg /day)	GPR55: agonist	Primary human NK cells	Administration increased circulating NK cells	135
2-AG (1 μM)	CB1: Full agonist CB2: partial agonist GPR55: agonist	KHYG-1 cell line	2-AG act as a chemotactic stimulus, enhancing NK cell migration	27
Phytocannabinoids				
CBD (2.5 mg/kg/day)	GPR18: partial agonist GPR55: antagonist CB1: antagonist CB2: antagonist TRPV2: activation	Primary murine circulating NK cells	Increases the total and percentage NKT cells and NK cells	117
CBD (5 mg/kg/day))		Primary murine circulating NK cells	No effect in the total numbers of NK and NKT	117
CBD (1 - 20 μM)		Cytokine-induced killer (CIK) CD3+CD56+ NKT cells. Activation of peripheral mononuclear cells with IFNγ, IL1b and antiCD3 antibodies.	Protective effect of CBD against spontaneous lysis in vitro. Enhanced NKT cells number at 1 μM. Cytotoxicity of NKT cells against myeloid cells was not affected at low, but inhibition at high CBD concentration.	28
CBD		Primary human NK cells	Diminishes the production of cytokines, perforins and granzymes caused by the activation of GPR55 by O-1602	31
Δ9-THC (1-20 μg/mL)	CB1, CB2: partial agonist GPR55: agonist GPR18: full agonist TRPV2: activation	Primary murine splenic NK cells. YAC-1 lymphoma cells as targets.	Inhibits the cytotoxic activity against target cells	122
Δ9-THC (1-20 μg/mL)		Primary murine splenic NK cells. YAC-1 lymphoma cells as targets.	Inhibits the cytotoxic activity against target cells	121
Δ9-THC (1-20 μg/mL)		Primary human NK cells	Inhibits the cytotoxic activity against K562 target cells	123
Δ9-THC (1-10 μg/mL)		Primary murine splenic NK cells	Inhibits the cytotoxic activity against YAC-1 target cells Inhibition of proliferation	116
		KHYG-1 cell line	Inhibits NK response to chemotactic stimulus	27
Δ9-THC (15 mg/kg)		Primary murine splenocytes Pure NK population was not isolated	Decreased cytolysis of tumor YAC-1 cells co-cultivated with splenocytes	120
Synthetic Cannabinoids				
ACEA (5-20 μM)	CB1 agonist	Primary human NK cells	No effect on NK cell cytotoxicity against target cells.	126
AM251	CB1: antagonist/inverse agonist	Primary murine NK cells	Enhances NK population	146
CP-55940 (0.2-0,4 mg/kg)	CB1, CB2: full agonist GPR55: agonist	Primary murine NK cells	Inhibits the cytotoxicity against YAC-1 target cells	124
CP55940 (0.2 mg/kg)		Primary murine NK cells	inhibits NK cytotoxic activity	121
GW833972A	CB2 agonist	Primary human NK cells	No effect on NK cell cytotoxicity against target cells, in contrast to effect on CD8+ cells	126
JWH133 (0-50 μM)	CB2: full agonist	Primary murine NK cells	Decreases number of NK cells	118
O-1602	GPR55, GPR18: agonist	primary human NK cells	Increases CD69 activation marker expression, potentiates target cell – dependent degranulation and death of target cells, potentiates production of granzyme B, IFN-γ and TNF-α after stimulation with IL-2 and IL-12	31
SR144528 (1 μM)	CB2: antagonist	KHYG-1 cell line	Inhibits the migration	27
SMM-189	SB2 inverse agonist	Murine model of colitis	Decreases numbers of NK cells in the spleen	147
SR141716 (0.3–40 μM)	CB1: antagonist GPR55: partial agonist	Primary human NK cells	Enhances NK cell-mediated cytotoxicity against U251 glioma cells	148
SR144528 (10 mg/kg)	CB2 antagonist	Primary murine NK cells	Does not affect effector function	120
WIN55212-2 (10–100 μM)	CB1, CB2: full agonist	Primary murine NK cells	Increases cytotoxicity against PL12 and MP2 target cells increases the production and secretion of IFN-γ	149
WIN55212-2 (0.5 mg/kg)		Primary murine NK cells	Increases number of NK cells	150