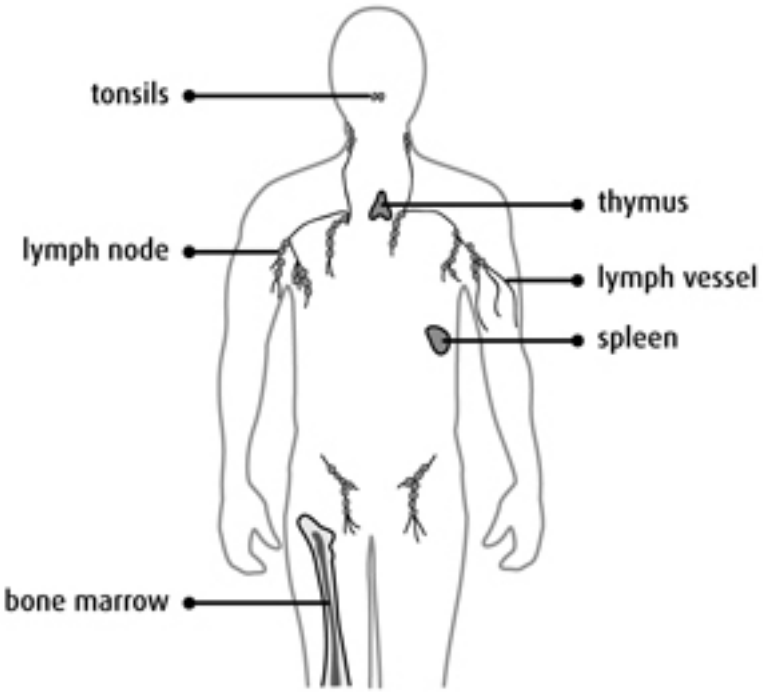
Lymphoma

Excerpt from www.cancer.ca:

Hodgkin lymphoma is cancer that starts in the lymphocytes, the cells of the lymphatic system. The lymphatic system works with your immune system to help your body fight infection and disease. The lymphatic system is made up of a network of lymph vessels (which are a little like veins), lymph nodes and the lymphatic organs (such as the spleen, thymus, tonsils and bone marrow).

Lymph is a clear, yellowish fluid that contains *lymphocytes*. Lymphocytes are special white blood cells that help fight infection. *Lymph nodes* are small bean-shaped glands. Clusters of lymph nodes are found in your neck, underarms, chest, abdomen and groin. The lymph nodes filter out waste, bacteria and unwanted cells, including cancer cells, as the lymph passes through them. *Lymphatic vessels* collect lymph from different tissues throughout the body, filter it through the lymph nodes and return it to the bloodstream.

Hodgkin lymphoma can begin in almost any part of the body. It usually starts in a group of lymph nodes in one part of the body – most often the neck – and grows in a predictable, orderly way from one lymph node group to the next. Eventually, it can spread to almost any tissue or organ in the body through the lymphatic system or the bloodstream.



Non-Hodgkin lymphoma is a cancer that starts in the lymphocytes, the cells of the lymphatic system. The lymphatic system works with other parts of your immune system

to help your body fight infection and disease. The lymphatic system is made up of a network of lymph vessels (which are a little like veins), lymph nodes and the lymphatic organs (such as the spleen, thymus, tonsils and bone marrow).

Lymph is a clear, yellowish fluid that contains *lymphocytes*. Lymphocytes are special white blood cells that help fight infection. They develop in the bone marrow from immature cells (called *stem cells*). There are two kinds of lymphocytes:

- *B-cells* stay in the bone marrow or lymphatic organs until they mature.
- *T-cells* move to the thymus gland to mature.

Lymph nodes are small bean-shaped glands. Clusters of lymph nodes are found in your neck, underarms, chest, abdomen and groin. Lymph nodes filter out waste, bacteria and unwanted cells, including cancer cells, as the lymph passes through them. *Lymphatic vessels* collect lymph from different tissues throughout the body, filter it through the lymph nodes and return it to the bloodstream.

Non-Hodgkin lymphoma develops when a lymphocyte, either a B-cell or T-cell, becomes abnormal. It can begin in almost any part of the body and can form tumours. It usually starts in a group of lymph nodes in one part of the body, most often the neck. Eventually, it can spread to almost any tissue or organ in the body through the lymphatic system or the bloodstream.

There are over 30 types of non-Hodgkin lymphoma. The cells of the different types look different under a microscope, and they develop and spread differently (for example, slowly or aggressively). The way the abnormal cells develop and spread depends on the type of lymphocyte the lymphoma started in. Most types of non-Hodgkin lymphoma develop from B-cells. It is important for your doctor to find out which type of non-Hodgkin lymphoma you have so you can get the treatment that works best for that type.

Lymphoma

Volume 579, Issue 30, 19 December 2005, Pages 6885-6889

Cannabinoid receptor ligands mediate growth inhibition and cell death in mantle cell lymphoma

Edited by Lukas Huber

Jenny Flygare[a], Kristin Gustafsson[a], Eva Kimby[b], Birger Christensson[a] and Birgitta Sander[a,]
[a]Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Karolinska University Hospital Huddinge, F-46, SE-141 86 Stockholm, Sweden
[b]Department of Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden
Received 7 September 2005; revised 4 October 2005; accepted 9 November 2005. Available online 29 November 2005.

Abstract

We have earlier reported overexpression of the central and peripheral cannabinoid receptors CB1 and CB2 in mantle cell lymphoma (MCL), a B cell non-Hodgkin lymphoma. In this study, treatment with cannabinoid receptor ligands caused a decrease in viability of MCL cells, while control cells lacking CB1 were not affected. Interestingly, equipotent doses of the CB1 antagonist SR141716A and the CB1/CB2 agonist anandamide inflicted additive negative effects on viability. Moreover, treatment with the CB1/CB2 agonist Win-55,212-2 caused a decrease in long-term growth of MCL cells in culture. Induction of apoptosis, as measured by FACS/Annexin V–FITC, contributed to the growth suppressive effect of Win-55,212-2. Our data suggest that cannabinoid receptors may be considered as potential therapeutic targets in MCL.

doctorbob@cannabuzz.net

Anandamide is an endogenous inhibitor for the migration of tumor cells and T lymphocytes

Journal	Cancer Immunology, Immunotherapy
Publisher	Springer Berlin / Heidelberg
ISSN	0340-7004 (Print) 1432-0851 (Online)
Issue	Volume 53, Number 8 / August, 2004
Category	Original Article
DOI	10.1007/s00262-004-0509-9
Pages	723-728
Subject Collection	Biomedical and Life Sciences
SpringerLink Date	Thursday, March 18, 2004

Jan Joseph[1], Bernd Niggemann[1], Kurt S. Zaenker[1] and Frank Entschladen[1]

(1) Institute of Immunology, Witten/Herdecke University, Stockumer Str. 10, 58448 Witten, Germany

Received: 26 September 2003 **Accepted:** 27 January 2004 **Published online:** 18 March 2004

Abstract Cell migration is of paramount importance in physiological processes such as immune surveillance, but also in the pathological processes of tumor cell migration and metastasis development. The factors that regulate this tumor cell migration, most prominently neurotransmitters, have thus been the focus of intense investigation. While the majority of neurotransmitters have a stimulatory effect on cell migration, we herein report the inhibitory effect of the endogenous substance anandamide on both tumor cell and lymphocyte migration. Using a collagen-based three-dimensional migration assay and time-lapse videomicroscopy, we have observed that the anandamide-mediated signals for $CD8^+$ T lymphocytes and SW 480 colon carcinoma cells are each mediated by distinct cannabinoid receptors (CB-Rs). Using the specific agonist docosatetraenoylethanolamide (DEA), we have observed that the norepinephrine-induced migration of colon carcinoma cells is inhibited by the CB_1-R. The SDF-1–induced migration of $CD8^+$T lymphocytes was, however, inhibited via the CB_2-R, as shown by using the specific agonist JWH 133. Therefore, specific inhibition of tumor cell migration via CB_1-R engagement might be a selective tool to prevent metastasis formation without depreciatory effects on the immune system of cancer patients.

Keywords Anandamide - Cannabinoid receptors - Cell migration - T lymphocytes - Tumor cells

The FASEB Journal Express Article doi:10.1096/fj.02-1129fje
Published online July 3, 2003

Cannabinoid Receptor-Mediated Apoptosis Induced by *R*(+)-Methanandamide and Win55,212-2 Is Associated with Ceramide Accumulation and p38 Activation in Mantle Cell Lymphoma

1. Kristin Gustafsson,
2. Birger Christensson,
3. Birgitta Sander and
4. Jenny Flygare

+ Author Affiliations

1. *Karolinska Institutet, Department of Laboratory Medicine, Division of Pathology, Karolinska University Hospital Huddinge, Stockholm, Sweden*

1. **Address correspondence to:**
   Birgitta Sander, Department of Laboratory Medicine, Division of Pathology, Karolinska University Hospital Huddinge, F-46, SE-14186 Stockholm, Sweden. E-mail: birgitta.sander@ki.se

Abstract

We have recently shown that cannabinoids induce growth inhibition and apoptosis in mantle cell lymphoma (MCL), a malignant B-cell lymphoma that expresses high levels of cannabinoid receptor types 1 and 2 (CB_1 and CB_2). In the current study, the role of each receptor and the signal transduction triggered by receptor ligation were investigated. Induction of apoptosis after treatment with the synthetic agonists *R*(+)-methanandamide [*R*(+)-MA] and Win55,212-2 (Win55; (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo-[1,2,3-*d*,*e*]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone) was dependent on both cannabinoid receptors, because pretreatment with *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboximide hydrochloride (SR141716A) and *N*-((1*S*)-endo-1,3,3-trimethyl bicyclo heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide) (SR144528), specific antagonists to CB_1 and CB_2, respectively, abrogated caspase-3 activity. Preincubation with the inhibitors 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1*H*-imidazole (SB203580) and 4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1*H*-imidazole (SB202190) showed that phosphorylation of MAPK p38 was implicated in the signal transduction leading to apoptosis. Treatment with *R*(+)-MA and Win55 was associated with accumulation of ceramide, and pharmacological inhibition of ceramide synthesis de novo prevented both p38 activation and mitochondria depolarization assessed by binding of 3,3′-dihexyloxacarbocyanine iodide ($DiOC_6$). In contrast, the pancaspase inhibitor z-Val-Ala-Asp(Ome)-CH_2F (z-VAD-FMK) did not protect the mitochondrial integrity. Taken together, these results suggest that concurrent ligation of CB_1 and

CB_2 with either *R*(+)-MA or Win55 induces apoptosis via a sequence of events in MCL cells: accumulation of ceramide, phosphorylation of p38, depolarization of the mitochondrial membrane, and caspase activation. Although induction of apoptosis was observed in both MCL cell lines and primary MCL, normal B cells remained unaffected. The present data suggest that targeting CB_1/CB_2 may have therapeutic potential for the treatment of mantle cell lymphoma.

http://molpharm.aspetjournals.org/content/70/5/1612.short

Anandamide Induces Apoptosis in Human Cells via Vanilloid Receptors

EVIDENCE FOR A PROTECTIVE ROLE OF CANNABINOID RECEPTORS* (Neuroblastoma and Lymphoma)

1. Mauro Maccarrone,
2. Tatiana Lorenzon,
3. Monica Bari,
4. Gerry Melino and
5. Alessandro Finazzi-Agrò‡

+ Author Affiliations

1. *From the Department of Experimental Medicine and Biochemical Sciences, University of Rome Tor Vergata, Via di Tor Vergata 135, I-00133 Rome, Italy*

Next Section

Abstract

The endocannabinoid anandamide (AEA) is shown to induce apoptotic bodies formation and DNA fragmentation, hallmarks of programmed cell death, in human neuroblastoma CHP100 and lymphoma U937 cells. RNA and protein synthesis inhibitors like actinomycin D and cycloheximide reduced to one-fifth the number of apoptotic bodies induced by AEA, whereas the AEA transporter inhibitor AM404 or the AEA hydrolase inhibitor ATFMK significantly increased the number of dying cells. Furthermore, specific antagonists of cannabinoid or vanilloid receptors potentiated or inhibited cell death induced by AEA, respectively. Other endocannabinoids such as 2-arachidonoylglycerol, linoleoylethanolamide, oleoylethanolamide, and palmitoylethanolamide did not promote cell death under the same experimental conditions. The formation of apoptotic bodies induced by AEA was paralleled by increases in intracellular calcium (3-fold over the controls), mitochondrial uncoupling (6-fold), and cytochrome *c* release (3-fold). The intracellular calcium chelator EGTA-AM reduced the number of apoptotic bodies to 40% of the controls, and electrotransferred anti-cytochrome *c* monoclonal antibodies fully prevented apoptosis induced by AEA. Moreover, 5-lipoxygenase inhibitors 5,8,11,14-eicosatetraynoic acid and MK886, cyclooxygenase inhibitor indomethacin, caspase-3 and caspase-9 inhibitors Z-DEVD-FMK and Z-LEHD-FMK, but not nitric oxide synthase inhibitor*N*ω-nitro-l-arginine methyl ester, significantly reduced the cell death-inducing effect of AEA. The data presented indicate a protective role of cannabinoid receptors against apoptosis induced by AEA via vanilloid receptors.

Anandamide (arachidonoylethanolamide, AEA)[1] belongs to an emerging class of endogenous lipids including amides and esters of long chain polyunsaturated fatty acids and collectively indicated as “endocannabinoids” (1). In fact, AEA has been isolated and

characterized as an endogenous ligand for cannabinoid receptors in the central nervous system (CB1 subtype) and peripheral immune cells (CB2 subtype). AEA is released from depolarized neurons, endothelial cells and macrophages (2), and mimics the pharmacological effects of Δ^9-tetrahydrocannabinol, the active principle of hashish and marijuana (3). Recently, attention has been focused on the possible role of AEA and other endocannabinoids in regulating cell growth and differentiation, which might account for some pathophysiological effects of these lipids. An anti-proliferative action of AEA has been reported in human breast carcinoma cells, due to a CB1-like receptor-mediated inhibition of the action of endogenous prolactin at its receptor (4). An activation of cell proliferation by AEA has been reported instead in hematopoietic cell lines (5). Moreover, preliminary evidence that the immunosuppressive effects of AEA might be associated with inhibition of lymphocyte proliferation and induction of programmed cell death (PCD or apoptosis) has been reported (6), and growing evidence is being collected that suggests that AEA might have pro-apoptotic activity, both *in vitro* (7) and *in vivo* (8). This would extend to endocannabinoids previous observations on Δ^9-tetrahydrocannabinol, shown to induce PCD in glioma tumors (8), glioma cells (9), primary neurons (10), hippocampal slices (10), and prostate cells (11). However, the mechanism of AEA-induced PCD is unknown. The various effects of AEA in the central nervous system and in immune system (reviewed in Refs.1-3), as well as its ability to reduce the emerging pain signals at sites of tissue injury (12), are terminated by a rapid and selective carrier-mediated uptake of AEA into cells (13), followed by its degradation to ethanolamine and arachidonic acid by the enzyme fatty acid amide hydrolase (FAAH) (14). Recently, we showed that human neuroblastoma CHP100 cells and human lymphoma U937 cells do have these tools to eliminate AEA (15). Therefore, these cell lines were chosen to investigate how AEA and related endocannabinoids induce apoptosis and how the removal and degradation of AEA are related to this process. The existence of a neuroimmune axis appears to be confirmed by the finding that endocannabinoids elicit common responses in these two cell types.

Mol Cancer Res. 2009 Jul;7(7):1086-98. doi: 10.1158/1541-7786.MCR-08-0361.

Potentiation of cannabinoid-induced cytotoxicity in mantle cell lymphoma through modulation of ceramide metabolism.

Gustafsson K, Sander B, Bielawski J, Hannun YA, Flygare J.

Source

Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet and Karolinska University Hospital Huddinge, Stockholm, Sweden.

Abstract

Ceramide levels are elevated in mantle cell lymphoma (MCL) cells following treatment with cannabinoids. Here, we investigated the pathways of ceramide accumulation in the MCL cell line Rec-1 using the stable endocannabinoid analogue R(+)-methanandamide (R-MA). We further interfered with the conversion of ceramide into sphingolipids that promote cell growth. Treatment with R-MA led to increased levels of ceramide species C16, C18, C24, and C(24:1) and transcriptional induction of ceramide synthases (CerS) 3 and 6. The effects were attenuated using SR141716A, which has high affinity to cannabinoid receptor 1 (CB1). The CB1-mediated induction of CerS3 and CerS6 mRNA was confirmed using Win-55,212-2. Simultaneous silencing of CerS3 and CerS6 using small interfering RNA abrogated the R-MA-induced accumulation of C16 and C24. Inhibition of either of the enzymes serine palmitoyl transferase, CerS, and dihydroceramide desaturase within the de novo ceramide pathway reversed ceramide accumulation and cell death induced by R-MA treatment. To enhance the cytotoxic effect R-MA, sphingosine kinase-1 and glucosylceramide synthase, enzymes that convert ceramide to the pro-proliferative sphingolipids sphingosine-1-phospate and glucosylceramide, respectively, were inhibited. Suppression of either enzyme using inhibitors or small interfering RNA potentiated the decreased viability, induction of cell death, and ceramide accumulation induced by R-MA treatment. Our findings suggest that R-MA induces cell death in MCL via CB1-mediated up-regulation of the de novo ceramide synthesis pathway. Furthermore, this is the first study were the cytotoxic effect of a cannabinoid is enhanced by modulation of ceramide metabolism.

PMID: 19609004 [PubMed - indexed for MEDLINE] PMCID: PMC3077284

Semin Cancer Biol. 2011 Nov;21(5):313-21. doi: 10.1016/j.semcancer.2011.10.004. Epub 2011 Oct 20.

The role of cannabinoid receptors and the endocannabinoid system in mantle cell lymphoma and other non-Hodgkin lymphomas.

Wasik AM, Christensson B, Sander B.

Source

Division of Pathology, Department of Laboratory Medicine, Karolinska Institutet and Karolinska University Hospital Huddinge, SE 141 86 Stockholm, Sweden. agata.wasik@ki.se

Abstract

The initiating oncogenic event in mantle cell lymphoma (MCL) is the translocation of cyclin D1, t(11;14)(q13;q32). However, other genetic aberrations are necessary for an overt lymphoma to arise. Like other B cell lymphomas, MCL at some points during the oncogenesis is dependent on interactions with other cells and factors in the microenvironment. The G protein coupled receptors cannabinoid receptors 1 and 2 (CB1 and CB2) are expressed at low levels on non-malignant lymphocytes and at higher levels in MCL and other lymphoma subtypes. In this review we give an overview of what is known on the role of the cannabinoid receptors and their ligands in lymphoma as compared to non-malignant T and B lymphocytes. In MCL cannabinoids mainly reduce cell proliferation and induce cell death. Importantly, our recent findings demonstrate that cannabinoids may induce either apoptosis or another type of programmed cell death, cytoplasmic vacuolation/paraptosis in MCL. The signalling to death has been partly characterized. Even though cannabinoid receptors seem to be expressed in many other types of B cell lymphoma, the functional role of cannabinoid receptor targeting is yet largely unknown. In non-malignant B and T lymphocytes, cannabinoid receptors are up-regulated in response to antigen receptor signalling or CD40. For T lymphocytes IL-4 has also a crucial role in transcriptional regulation of CB1. In lymphocytes, cannabinoid act in several ways - by affecting cell migration, cytokine response, at high doses inhibit cell proliferation and inducing cell death. The possible role for the endocannabinoid system in the immune microenvironment of lymphoma is discussed.

PMID: 22024769 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/22024769

Studies of cannabinoid receptor 1 in mantle cell lymphoma

Gustafsson, Kristin
Date: 2008-12-12
Location: 9Q Månen, Karolinska Institutet
Time: 09.30
Department: Institutionen för laboratoriemedicin / Department of Laboratory Medicine

Abstract:

Mantle cell lymphoma (MCL) is a malignant B-cell lymphoma that affects older individuals and has a male predominance. MCL has one of the worst prognoses among lymphomas and currently there is a search for a curative therapy. This thesis focuses on the possibility to induce cannabinoid receptor mediated cell death in MCL and other malignant lymphomas. * The effects of cannabinoids on cell fate were investigated in MCL cell lines and patient samples. Nanomolar doses of cannabinoids did not induce growth of MCL cells. Instead, micromolar doses induced cell death and decreased viability and growth of MCL cells expressing the cannabinoid receptors CB1 and CB2 while control cells lacking expression of CB1 remained unaffected. Interestingly, at micromolar doses the cannabinoid receptor agonist anandamide and the antagonist SR141716 additively decreased viability. * Signaling in MCL after treatment with the cannabinoids Win55 and methanandamide was investigated. The signaling was mediated via both CB1 and CB2 since blocking with nanomolar doses of antagonists prevented apoptosis. The signaling was mediated via de novo synthesis of the second messenger ceramide which caused phosphorylation of the MAP-kinase p38. This was followed by a disruption of the mitochondrial membrane potential and subsequently apoptosis. Signaling via the CB1 and CB2 receptors in MCL led to cell death while normal B-cells were spared. * The expression of cannabinoid receptors in other B-cell lymphomas was investigated. Using quantitative real-time PCR it was found that 80% of the selected lymphoma samples expressed CB1 and/or CB2. The expression was confirmed at protein level by Western Blot and immunohistochemistry. Further, methanandamide treatment induced cell death in B-CLL cell lines. Importantly, we showed that methanandamide treatment reduced tumor burden in a MCL xenograft mouse model. Thus the cannabinoid system could be a potential target in malignant lymphoma. * The ceramide metabolism in connection to cannabinoid treatment was studied. Pharmacological inhibition of the enzymes serine palmitoyl transferase, ceramide synthase or dihydroceramide desaturase prior to cannabinoid treatment led to disruption of ceramide synthesis and cell death in MCL. An upregulation of ceramide synthase 3 and 6 mRNA was observed after treatment with cannabinoids. Moreover, the effect of cannabinoid treatment on viability and cell death was potentiated by inhibiting the ceramide metabolizing enzymes sphingosine kinase-1 and glucosylceramide synthase. In conclusion, MCL and a large percentage of other B-cell lymphomas express functional cannabinoid receptors that can mediate cell death specifically in malignant cells. Cannabinoid receptor mediated cell death in MCL could be potentiated by modulation of ceramide metabolism.

https://publications.ki.se/xmlui/handle/10616/38032?locale-attribute=en

Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease

. Robert J. McKallip, Catherine Lombard, Michael Fisher, Billy R. Martin, Seongho Ryu, Steven Grant, Prakash S. Nagarkatti, and Mitzi Nagarkatti

+

Author Affiliations

. [1] From the Departments of Microbiology and Immunology, Pharmacology and Toxicology, and Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond.

Abstract

In the current study, we examined whether ligation of CB2 receptors would lead to induction of apoptosis in tumors of immune origin and whether CB2 agonist could be used to treat such cancers. Exposure of murine tumors EL-4, LSA, and P815 to delta-9-tetrahydrocannabinol (THC) in vitro led to a significant reduction in cell viability and an increase in apoptosis. Exposure of EL-4 tumor cells to the synthetic cannabinoid HU-210 and the endogenous cannabinoid anandamide led to significant induction of apoptosis, whereas exposure to WIN55212 was not effective. Treatment of EL-4 tumor-bearing mice with THC in vivo led to a significant reduction in tumor load, increase in tumor-cell apoptosis, and increase in survival of tumor-bearing mice. Examination of a number of human leukemia and lymphoma cell lines, including Jurkat, Molt-4, and Sup-T1, revealed that they expressed CB2 receptors but not CB1. These human tumor cells were also susceptible to apoptosis induced by THC, HU-210, anandamide, and the CB2-selective agonist JWH-015. This effect was mediated at least in part through the CB2 receptors because pretreatment with the CB2 antagonist SR144528 partially reversed the THC-induced apoptosis. Culture of primary acute lymphoblastic leukemia cells with THC in vitro reduced cell viability and induced apoptosis. Together, the current data demonstrate that CB2 cannabinoid receptors expressed on malignancies of the immune system may serve as potential targets for the induction of apoptosis. Also, because CB2 agonists lack psychotropic effects, they may serve as novel anticancer agents to selectively target and kill tumors of immune origin.

http://bloodjournal.hematologylibrary.org/content/100/2/627.long

Int J Cancer. 2008 Sep 1;123(5):1025-33. doi: 10.1002/ijc.23584.

Expression of cannabinoid receptors type 1 and type 2 in non-Hodgkin lymphoma: growth inhibition by receptor activation.

Gustafsson K, Wang X, Severa D, Eriksson M, Kimby E, Merup M, Christensson B, Flygare J, Sander B.

Source

Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet and Karolinska University Hospital Huddinge, F-46, SE-14186 Stockholm, Sweden.

Abstract

Endogenous and synthetic cannabinoids exert antiproliferative and proapoptotic effects in various types of cancer and in mantle cell lymphoma (MCL). In this study, we evaluated the expression of cannabinoid receptors type 1 and type 2 (CB1 and CB2) in non-Hodgkin lymphomas of B cell type (n = 62). A majority of the lymphomas expressed higher mRNA levels of CB1 and/or CB2 as compared to reactive lymphoid tissue. With the exception of MCL, which uniformly overexpresses both CB1 and CB2, the levels of cannabinoid receptors within other lymphoma entities were highly variable, ranging from 0.1 to 224 times the expression in reactive lymph nodes. Low levels of the splice variant CB1a, previously shown to have a different affinity for cannabinoids than CB1, were detected in 44% of the lymphomas, while CB1b expression was not detected. In functional studies using MCL, Burkitt lymphoma (BL), chronic lymphatic leukemia (CLL) and plasma cell leukemia cell lines, the stable anandamide analog R(+)-methanandamide (R(+)-MA) induced cell death only in MCL and CLL cells, which overexpressed both cannabinoid receptors, but not in BL. In vivo treatment with R(+)-MA caused a significant reduction of tumor size and mitotic index in mice xenografted with human MCL. Together, our results suggest that therapies using cannabinoid receptor ligands will have efficiency in reducing tumor burden in malignant lymphoma overexpressing CB1 and CB2.

PMID: 18546271 [PubMed - indexed for MEDLINE]