REVIEW ARTICLE

Different Views on the Relationship between Cannabinoids and Cancer

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ABSTRACT

Vidinský B., Gál P., Mojžiš J.: Different Views on the Relationship between Cannabinoids and Cancer
Cannabinoids are the major active components of the most widely used illegal drug – marihuana. They have a long history of medicinal use. However, they are still a controversial topic in oncological praxis. Cannabinoids play a role in different organs of the human body, and they are an integral part of the newly described endocannabinoid system, which regulates several body functions. The important function of endocannabinoids which is related to cancer is the regulation of cell cycle and cell survival pathways. This review presents three different views on the relationship between cannabinoids and cancer. First, in the treatment of adverse symptoms of oncological therapy – nausea and vomiting inhibition, appetite stimulation, pain relief, mood modulation and muscle stiffness relieving. Second, in the late 1990s, three possible mechanisms of antitumour action were identified – apoptosis induction, direct cell cycle arrest and angiogenesis and metastasis inhibition. Phase I/II of clinical trials are being carried out in Spain, studying the effects of local administration of tetrahydrocannabinol on the growth of glioblastoma multiforme. Third, the results of the most recent study focused on the relationship between cannabinoids use and cancer risk showed no significant correlation between increased cancer incidence and cannabinoids use, no matter how much cannabis is used. It is important to establish the relationship between marihuana use and cancer risk with regard to the debate on the advantages and risks of medicinal cannabinoids use and the impact on public health.
Key words: cannabinoids, endocannabinoid system, palliative therapy, tumor growth regulation, cancer risk.

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The medical significance of cannabinoids has been known for 4000 years, but their role in medicine is still controversial (1). There exist two types of cannabinoids, i.e. exogenous – contained essentially in the plant cannabis sativa (which the popular "leisure drug" marihuana is made from) and endogenous, which are integral part of the tissues of most vertebrae within endocannabionoids system (ECS) (2). It is estimated that all around the world about 3.5 % of the population above the age of 15 take marihuana from non-medical purposes (3). The number of publications concerning cannabinoids (CB) in the database http://www.ncbi.nlm.nih.gov/entrez/query.fcgi in the year 1989 was about 250 new contributions a year, while during the year 2004 more than 1100 recent works appeared. That evidences an enormous public interest in this topic. The crucial year for the whole CB research progress was the year 1990, when the first specific CB receptor – cannabinoid receptor 1 (CB1R) was described (4). Recently both scientists and the lay community have obtained more information about the relationship between cancer and CB. First, there is the application of CB in palliative care for cancer. From September 2003 this has been recommended in oncological practice for the symptomatic treatment in radio- and chemotherapy of cancer. The principal advantages are antiemetic effects, appetite stimulation and analgesia. Actually the medical use of CB is legal in Holland and Canada (3). The second possible relationship between CB and cancer is the direct anticancer therapy, which is actually in the preclinical research phase. The research teams of Professor Manuel Guzman in Madrid and of Professor Vincenzo Di Marzo in Naples, within the Endocannabinoid Research Group, are most involved here. Professor Guzman's group, which has an extraordinary position in the world, co-operates with the University Hospital Tenerife in performing clinical evaluations of phase I/II concerning the impact of the local administration of delta-9-tetrahydrocannabinol (THC – principal effective substance of marihuana) on the recurrent growth of glioblastoma multiforme. This clinical study was approved by Spanish public health minister in the year 2003 (5). The third debated relationship is the possible CB impact on the cancer genesis and progress.

Our review is aimed at symptomatic treatment in cancer therapy, molecular physiology accented on mechanisms of the cell cycle regulation, and the pro- and anti-tumor effects of CB.

ENDOCANNABINOID SYSTEM

The plant CB, like THC and the synthetic analogues, acts on the organism by means of specific cell surface receptors which are normally filled by endogenous ligands – endocannabinoids (ECB). They form ECS (6) together with receptors, specific proteins of the synthesis and degradation and of the re-uptake system. This relatively recently developed system has been investigated since 1990, when CB_1R was for the first time identified in the brain cortex of rats (4). In the year 1993 the cannabionoid receptor 2 (CB_2R) was first described in human promyelocyte leukemic cells (HL-60) (7). Currently other receptors are being discussed. So-called non-CB_1, non-CB_2 receptors. CB_1R are predominantly located in CNS in pre-

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synaptic neurons such as in immune and reproductive system cells, digestive tract, lung, eye and vessels. CB_2R are mainly associated with immune system cells – tonsils, spleen, macrophages and lymphocytes (B lymphocytes, Nκ-cells). Cannabinoid receptors (CBR) are among the group of transmembrane proteins linked with G-proteins, especially with the type $G_{i/o}$. One of the most investigated ECB is amide of arachidonic acid and ethanolamine – anandamide (AEA) and ester of arachidonic acid and glycerol – 2-arachidonoyl glycerol (2-AG). N-arachidonoyl dopamine is one of the most recently described ECB, which is also a potential vanilloid type receptor agonist (TRPV1 – transient receptor potential vanilloid type 1). These are functionally associated with ECS (6). The ECB cycle is best investigated in CNS (Fig. 1, p. 455). Many regulatory functions of ECS in different systems of organism are described in current scientific literature (2, 8, 9), but in the presented work we focus on the function of cell cycle regulation and cell survival and the role in the process of carcinogenesis.

SYMPTOMATIC THERAPY IN TREATMENT OF CANCER

CB have been known for their palliative effect in oncology since 1970, but in spite of that they are clinically utilized only to a limited extent. Some possible applications are known, for instance nausea and vomiting inhibition, appetite stimulation, pain relief, mood modulation, muscle weakness inhibition and muscular spasticity relaxation (10). The antiemetic effect is mediated by CB_1R located in the myenteric and submucous plexus of stomach, duodenum and the large intestine. CB_1R agonists (for instance synthetic analogue of THC Nabilon and Dronabilon) induce blockade of acetylcholine release and thus the inhibition of digestive tract motility. CB_1R are also situated in the dorsal vagal complex of brain stem, where it is located in the centre of vomiting (11). So far the antiemetic effect is the most frequently used indication in oncological practice. Randomized clinical studies have demonstrated this significantly additive or synergic effect in combination with prochlorperazine (12). Frequent phenomena in oncological patients are weight lost and anorexia, potentially leading to cachexia. Results of the clinical studies of phase III have proved appetite stimulation after per oral administration of synthetic THC in the daily dose of 5.0 mg in patients with an advanced form of cancer (10). Double blinded, placebo controlled clinical studies showed the analgetic effect of CB in patients with severe form of pain in cancer, which is resistant to classic analgetics, and they improved appetite and mood as well (3). Influence on mood has not so far been carefully based on clinical studies. It was detected that Nabilon could reduce depression and anxiety (10). From September 2003 CB are officially applied in Holland for medical purposes and in this short term it was demonstrated that the most frequent indication of prescription is chronic pain, muscle spasticity and cramps, but only 8 % of all patients treated by CB were oncological patients (12). During recent years scientists have also concentrated on the possibility of direct CB effect on tumors and thus on inhibition (5) or growth stimulation, and on the adverse effect in medical or more often non-medical CB use (13).

ANTITUMOR EFFECTS OF CANNABINOIDS

The antitumor effects were first established in the year 1975. The dose related tumor growth reduction after Dronabinol administration (14). Since then nobody was involved in this issue until the late 1990s, when at almost the same time two large teams around Professor Guzman and Professor Di Marzo began to concentrate on and investigate this area. Antitumor effects are predominantly mediated by CB_1R and CB_2R signal transduction. TRPV1 receptor is the most important of the non-CBR signal pathways for tumor growth regulation. For a clear overview the cell signal transduction of CB can be divided into six groups (15, 16) (Fig. 2, p. 455):

1. adenylylcyclase regulation;
2. ion channel regulation (CB_1R dependent and non-dependent mechanisms):
   a) ion channel modulation by proteinkinase A (PKA),
   b) potassium ion chanel activation,
   c) inhibition of voltage gaited calcium channels L, N and P/Q;
3. regulation of intracellular calcium – increase after proteinkinase C (PKC) activation by releasing from intracellular store;
4. mitogen activated proteinkinase (MAPK) regulation – these kinases have the principal role in cellular growth, transformation and apoptosis. Their activation is usually linked with thyrosinkinase receptors, other so far not well-investigated pathways are presumed in CB.
5. Immediate impact of genes of early response, protein synthesis regulation.
6. NO metabolism regulation – increase of NO synthase activity.

CB_1R and CB_2R have 44 % general homology and 68 % homology in transmembrane segment (7). In CB_2R the effect mediated by ion channel regulation has not so far been proved. At present three possible mechanisms of CB antitumor effect are known (Tab. 1, p. 455):

1. apoptosis induction (17, 18),
2. direct arrest of cell growth (19, 20),
3. angiogenesis and metastasis inhibition (21–23).

INDUCTION OF APOPTOSIS

Apoptosis can principally proceed in two ways: external – the binding of ligand on Fas receptor or TNFR (tumor necrosis factor receptor) and subsequently the caspase cascade activation, or internal – after the release of the protein Bcl-2 from Apaf-1 (apoptosis protease factor-1) on external surface of mitochondrial membrane the cytochrome c is released from mitochondrias and activates the caspase cascade (24).

Velasco and coworkers (25) assume the principal role in antitumor CB activity without ceramide level increases in two ways. The first is ceramide increase by the activation of sfingomyelinase (SMase), which is associated with TNFR by FAN protein (factor associated with activation of neutral sfingomyelinase) and the sfingomyeline is split (SM – short term generation). The second one is the synthesis *de novo* by induction of serinpalmitoyltransferase (SPT – long term generation). Ceramide subsequently activates Raf1/MAP kinase cascade, whose increased activation is generally considered as a proliferation trigger (Fig. 2), but long-term activation induce the cell cycle arrest and apoptosis (17). This mechanism has been successfully confirmed in the trials both *in vivo* and *in vitro* in the treatment of glioblastoma multiforme. However, the dual effect of CB on glial cells and glial tumors, conditioned by different capacity of these cells to synthesize ceramide, is evidenced – CB prevent apoptotosis in glial cells and induce apoptotosis in glioma cells (5).

Ellert-Miklaszewska and coworkers (26) detected that after CB_1R activation Raf1/MAP kinase cascade and serine/threonin protein kinase cascade PI3K/Akt are inhibited. They are functionally linked by pro-apoptotic protein of Bcl-2 family (Bad protein), which is the essential protein responsible for apoptosis triggering after CB_1R activation. This effect was demonstrated *in*

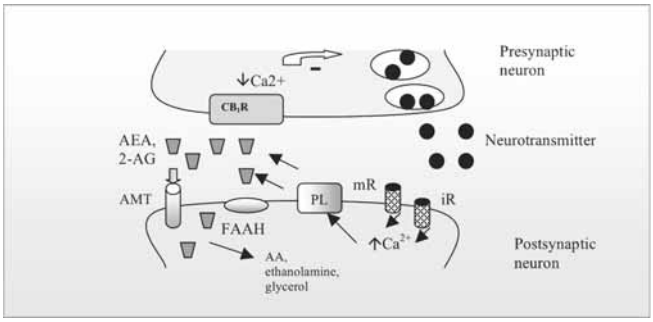

Fig. 1. A simplified outline of the endocannabinoid system operation in the CNS. The ECB biosynthesis occurs in the postsynaptic neuron based on demand; thus no storage in any reserve vesicle occurs. The stimuli for the synthesis are predominantly unknown; what is known is the fact that there is an increase of the cytosolic calcium (following the stimulation of the ionotropic receptors (iR) and of metabotropic receptors (mR)), catalyzing the enzymatic processes of the phospholipid splitting (PL) of the cell membranes, the synthesis of the ECB – AEA, 2-AG is a consequence thereof, subsequently being combined with the target molecules – being mostly the CB1R, where they are extracellularly combined with the presynaptic neuron. Here they modulate the detachment of neurotransmitters and thus have the effect of being a retrograde messenger. Following the intermediating of the effect, the ECB are inactivated intracellularly, where they like the lipophil agents partly get by diffusion and partly through a selective anandamide membrane transporter (AMT). The degradation mostly occurs intracellullarly through the integral membrane protein –fatty acid amide hydrolase (FAAH) to the arachidon acid (AA), glycerol and ethanolamine (6, 10).

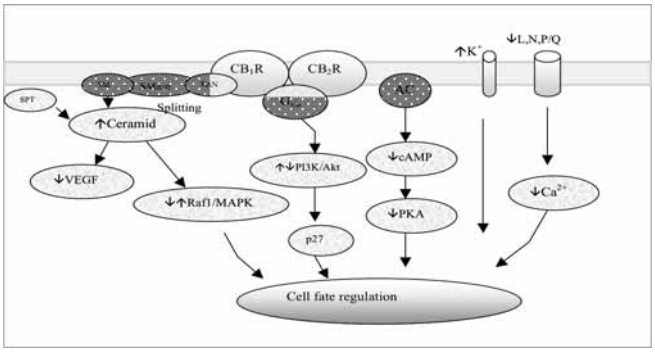

Fig. 2. The signal transduction in the cell participating in the cell fate regulation following the CB stimulation. After the combination with the CBR agonist, in particular the Gi/o protein activation (even if the effect on the Gs protein has been shown, too) and the inhibition of the enzyme adenylylcyclase (AC) occurs. The intracellular cAMP level decreases, also followed by the PKA activity with results in the main changes in the cell activity. In addition, there is also the inhibition of the stress regulated calcium channels. The path of the Raf1/MAPK cascade activation is intermediated through the increase in the level of the secondary lipid of the ceramide messenger. Another important way of regulating the cell cycle is the fosfatidylinozitol-3-kinese (PI3K)/Act of the survival pathway, the activation of which results in the glial cells for the cell survival and in the gliomas for the apoptose. Both pathways are associated with the CBR (25). Further description see the text.

Tab. 1. Sensitive tumors to growth inhibition induced by cannabinoids

Type of Tumor	Type of Experiment	Effect	Mechanism of action	List of Literature Resources
Gliomas	*in vivo*, *in vitro*	A, C, Z,	CB_1R, CB_2R	18, 23, 26
Breast cancer	*in vitro*	BC in S- faze, G_1/S	CB_1R	19, 20
Prostate Cancer	*in vitro*	A, BC, C	CB_1R, CB_2R	20, 32
Carcinoma of the cervix	*in vitro*	A	VR_1	33
Leukemia /Lymphomas	*in vivo*, *in vitro*	A, Z	CB_2R,	24, 34, 35
Skin Cancer	*in vivo*, *in vitro*	A, C, Z	CB_1R, CB_2R	21
Thyroid Gland Cancer	*in vivo*, *in vitro*	BC in G_1/S, Z, C, M	CB_1R	28,29
Colon Cancer	*in vitro*	I	COX-2	36

A – Apoptosis, Z – Reduction of tumor size, C – Inhibition of angiogenesis , BC – Blocking of cell cycle, M – Inhibition of metastases, I – Induction of cell death, but of neither apoptosis nor necrosis

vitro on glioma cells C6.

External and internal pathways of apoptosis act to a different degree on the apoptosis induction after CBR stimulation. In leukemic Jurkat cells the internal pathway is more preferred, while the external pathway can facilitate apoptosis by the activation of the internal pathway (24).

CELL CYCLE ARREST

CB_1R were identified in multipotent neural progenitor cells in the human brain in adults. This supports the theory of ECS involvement in the regulation of neural cell death and survival. The CB_1R activation facilitates cell proliferation and the formation of neurospheres (27), but the CB effect on tumor cells and cell cycle appears to be completely inverse, which is the basis of the current theory of dual effect of CB (5). The CB_1R activation blocks the cell cycle between the phases G1 and S, which has been demonstrated on mammary cells (19). The accurate mechanism is not fully clarified. The involvement of PKA (inhibition) and thus Raf1/MAPK cascade activation and subsequent reduction of two specific receptors for growth factors, prolactin and neutrophin, are assumed. This fact was also proved on mammarian and prostate tumor cells after administration of micromolar concentration of AEA and 2-AG, where cell cycle was arrested in the phase S (20). The cell cycle arrest at the G1/S transition was documented in thyroidal cells as well (28).

INHIBITION OF ANGIOGENESIS AND METASTASIS

The principal condition for tumor growth and metastasis is the formation of new vessels. Inhibition of their formation can reduce these processes. Functional analysis of gliomas (22) and skin carcinomas (21) in mice demonstrated that the vessels had become small and ineffective after administration of cannabionoids. These changes were associated with the reduction of proangiogenic factors (VEGF – vascular endothelial growth factor). Moreover, the migration and survival of endothelial cells decreased by way of

CB_1R, exposed on vessels endothelia (22). The inhibition of matrix metalproteinase-2, which is responsible for extracellular substance transformation, growth of new vessels and metastasis, appeared as well. These results partially explain why a decrease of metastasis in lung cancer in mice after CB administration occurred (29).

PROCARCINOGEN EFFECTS

Clinical studies investigating the relation between marihuana use and cancer incidence have only limited credibility, because marihuana is mostly used by smoking. In that process many similar carcinogens as in tobacco smoking are inhaled. At the same time most CB users smoke tobacco cigarettes as well. The results of the most recent clinical study were presented in June, 26, 2005 at the congress of International Society of Cannabinoid Research in Florida and simultaneously published in the journal Alcohol. The group of Professor Donald Tashkin, which has been involved in possible pro carcinogen effects of marihuana use for many years, analyzed 1209 cases of cancer (611 lung, 403 oral cavity and pharynx, 90 larynx, 108 oesophagus). The control group had similar socio-demographic characteristic. The medical history of the family, alcohol and tobacco use, alimentation habits, environmental factors and different other socio-demographic impacts were taken in account, and the result was that marihuana smoking was not associated with increased cancer incidence independently from the quantity of used cannabis. So the increased cancer incidence in tobacco smoking was proved with the dose dependency. Tashkin points out, however, that larger clinical studies, meta-analysis and larger cohorts of patients are necessary for the maximization of statistical accuracy and detection of causes of different results (30). Detection of any relationship between marihuana use and cancer risk is important when considering the advantages and risks of medical use of CB and in order to clarify the impact of marihuana use on the public health.

The risk of cancer incidence after exposition to CB may be more accurately explained by experimental studies eliminating other factors. Currently two mechanisms are discussed that can take part in cancer growth induction: direct impact on cell survival (13) and immunosupression of anticancer immunity (31).

Hart and coworkers (13) proved that after exposition to different synthetic and natural CBR agonists epidermal growth factor receptor (EGFR) was transactivated (mediated by tumor necrosing factor alpha converting enzyme) and subsequently activation increase of two signal pathways significant for cell survival – Raf1/MAPK and PI3K/Akt cascade occurred. It leads in the increased proliferation of glioblastoma and lung tumor cell lines after the administration of 100–300 $nmol.l^{-1}$ of THC. Inversely, the administration of micromolar concentrations ended up with pro apoptotic effect. It follows that CB have probably dual effect on cellular proliferation, depending on the dose. To utilize the antiproliferation effects of CB local administration is probably necessary, as was documented in the clinical study in glioblastomas (5). Other trials especially *in vivo* are necessary for application of this knowledge in clinical practice.

McKallip and coworkers (31) proved that mammarian cells with only low quantity of CBR were resistant to CB administration. Moreover these cells, after application in the bodies of mice, manifested an increased growth and raised formation of metastasis in lung after treatment by CB. This effect was partially explained by the suppression of anticancer immunity response mediated by CB_2R. This effect was fully reversed by administration of CB_2R antagonist. During the treatment by lower doses of CB (25 $mg.kg^{1}$) the level of Th_2 cytokines – interleukin-4 and interleukin-10 increased as well as the level of interferon gamma. Balance between pro-inflammation cytokines Th_1 and Th_2 was shifted in favor of Th_2 cytokines. This effect is desirable in chronic inflammatory processes yet not in tumor processes. During the treatment by doses of CB (50 $mg.kg^{-1}$) levels of these pro-inflammation cytokines decreased. The authors explain the immunosuppressive effect by the direct induction of apoptosis in immune cells.

CONCLUSION AND CLINICAL APPLICATION

CB proves relatively low toxicity. LD_{50} reached several 100 $mg.kg^{-1}$ in some animal species. Death from CB overdose has not been proved in humans. Infarct induction is possible by affecting the vessels exposing CBR, but only in pathologically altered heart (1). Psychoactive effects considerably limit medical use of CB in oncology, whether for symptomatic treatment in chemo- and radiotherapy or directly in tumor death induction. These are mediated by CB_1R and thus the possible future is joined with the use of selective CB_2 agonists. The growth inhibition of gliomas (18) and skin carcinomas (21) has already been proved by the use of selective agonists of CB_2R *in vitro* and *in vivo*. It is also possible to utilize the non-psychoactive CB that do not predominantly act over CBR, for instance ajulemic acid. Other alternative may be a local increase of CB in tumor site by selective blockage of degradation, successfully demonstrated in animal models (10). The local CB administration in tumor seems to be the most favorable and it is actually aimed in the clinical research of phase I/II in Spain.

CB may become an efficient cancer medicament in the future because of the direct effects on tumor growth as well as palliative effect in symptomatic treatment in oncological therapy.

Abbreviations

AA – arachidonic acid
AC – adenylylcyclase
AEA – arachidonyl ethanol amine - anandamide
2-AG – 2-arachidonoyl glycerol
Apaf-1 – apoptosis protease factor-1
cAMP – cyklic adenosine monophosphate
CB_1R – cannabinoid receptor 1
CB_2R – cannabinoid receptor 2
CBR – cannabinoid receptor
CNS – central nervous system
ECS – endocannabinoid system
ECB – endocannabinoids
EGFR – epidermal growth factor receptor
FAN – factor associated with neutral sfingomyelinase activation
iR – ionotrope receptor
MAPK – mitogen of activovated protein kinase
mR – metabotrope receptor
PL – phospholipids
SMase – sfingomyelinase
SM – sfyngomyelin
SPT – serinpalmitoyltransferase
PKA – proteinkinase A
PKC – proteinkinase C
VEGF – vascular endothelial growth factor
THC – delta-9-tetrahydrocannabinol
TNFR – tumor necrosis factor receptor
TRPV1 – transient receptor potential vanilloid type 1 – vanilloid receptor

LITERATURE

1. **Grotenhermen, F.:** Cannabinoids. Curr. Drug Targets CNS Neurol. Disord., 2005, 4, pp. 507-530.
2. **Vidinský, B., Gál, P., Toporcer, T., Mojžiš, J.:** Cannabinoids and the human organism – what is new? Lek. Obz., 2005, 54, pp. 382-385.

3. **Hall, W., Christie, M., Currow, D.:** Cannabinoids and cancer: causation, remediation, and palliation. Lancet Oncol., 2005, 6, pp. 35-42.
4. **Matsuda, L. A., Lolait, S. J., Brownstein, M. J. et al.:** Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature, 1990, 346(6284), pp. 561-564.
5. **Velasco, G., Galve-Roperh, I., Sanchez, C. et al.:** Hypothesis: cannabinoid therapy for the treatment of gliomas? Neuropharmacology, 2004, 47, pp. 315-323.
6. **Bisogno, T., Ligresti, A., Di Marzo, V.:** The endocannabinoid signalling system: biochemical aspects. Pharmacol. Biochem. Behav., 2005, 81, s. 224-238.
7. **Munro, S., Thomas, K. L., Abu-Shaar, M.:** Molecular characterization of a peripheral receptor for cannabinoids. Nature, 1993, 365(6441), pp. 61-65.
8. **Kvasnička, T.:** Endocannabinoids—the new option in the treatment of metabolic syndrome and in smoking cessation. Čas. Lék. čes., 2005, 144, pp. 81-84.
9. **Rodriguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F. J. et al.:** The endocannabinoid system: physiology and pharmacology. Alcohol, 2005, 40, pp. 2-14.
10. **Guzman, M.:** Cannabinoids: potential anticancer agents. Nat. Rev. Cancer, 2003, 3, pp. 745-755.
11. **Di Carlo, G., Izzo, A. A.:** Cannabinoids for gastrointestinal diseases: potential therapeutic applications. Expert. Opin. Investic. Drugs., 2003, 12, pp. 39-49.
12. **De Jong, F. A., Engels, F. K., Mathijssen, R. H. et al.:** Medicinal cannabis in oncology practice: still a bridge too far? J. Clin. Oncol., 2005, 23, pp. 2886-2891.
13. **Hart, S., Fischer, O. M., Ullrich, A.:** Cannabinoids induce cancer cell proliferation via tumor necrosis factor alpha-converting enzyme (TACE/ADAM17) – mediated transactivation of the epidermal growth factor receptor. Cancer Res., 2004, 64, pp. 1943-1950.
14. **Munson, A. E., Hartus. L. S., Friedman, M. A. et al.:** Antineoplastic activity of cannabinoids. J. Natl. Cancer Inst., 1975, 55, pp. 597-602.
15. **Howlett, A. C., Barth, F., Bonner, T. I. et al.:** International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev., 2002, 54, pp. 161-202.
16. **Demuth, D. G., Molleman, A.:** Cannabinoid signalling. Life Sci., 2005, 16 (v tlači).
17. **Galve-Roperh, I., Sanchez, C., Cortes, M. L. et al.:** Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. Nat. Med., 2000, 6, pp. 313-319.
18. **Sanchez, C., de Ceballos, M. L., del Pulgar, T. G. et al.:** Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor. Cancer Res., 2001, 61, pp. 5784-5789.
19. **De Petrocellis, L., Melck, D., Palmisano, A. et al.:** The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. Proc. Natl. Acad. Sci. U S A, 1998, 95, pp. 8375-8380.
20. **Melck, D., De Petrocellis, L., Orgando, P. et al.:** Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation. Endocrinology, 2000, 141, pp. 118-126.
21. **Casanova, M. L., Blazquez, C., Martinez-Palacio, J. et al.:**Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. J. Clin. Invest., 2003, 111, pp. 43-50.
22. **Blazquez, C., Casanova, M. L, Planas, A. et al.:** Inhibition of tumor angiogenesis by cannabinoids. FASEB J., 2003, 17, pp. 529-531.
23. **Blazquez, C., Gonzalez-Feria, L., Alvarez, L. et al.:** Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas. Cancer Res., 2004, 64, pp. 5617-5623.
24. **Lombard, C., Nagarkatti, M., Nagarkatti, P. S.:** Targeting cannabinoid receptors to treat leukemia: role of cross-talk between extrinsic and intrinsic pathways in Delta9-tetrahydrocannabinol (THC)-induced apoptosis of Jurkat cells. Leuk. Res., 2005, 29, pp. 915-922.
25. **Velasco, G., Galve-Roperh, I., Sanchez, C. et al.:** Cannabinoids and ceramide: two lipids acting hand-by-hand. Life Sci., 2005, 77, pp. 1723-1731.
26. **Ellert-Miklaszewska, A., Kaminska, B., Konarska, L.:** Cannabinoids down-regulate PI3K/Akt and Erk signalling pathways and activate proapoptotic function of Bad protein. Cell Signal., 2005, 17, pp. 25-37.
27. **Aguado, T., Monory, K., Palazuelos, J. et al.:** The endocannabinoid system drives neural progenitor proliferation. FASEB J., 2005, 19, pp. 1704-1706.
28. **Bifulco, M., Laezza, C., Portella, G. et al.:** Control by the endogenous cannabinoid system of ras oncogene-dependent tumor growth. FASEB J., 2001, 15, pp. 2745-2747.
29. **Portella, G., Laezza, C., Laccetti, P. et al.:** Inhibitory effects of cannabinoid CB1 receptor stimulation on tumor growth and metastatic spreading: actions on signals involved in angiogenesis and metastasis. FASEB J., 2003, 17, pp. 1771-1773.
30. **Hashibe, M., Straif, K., Tashkin, D. P. et al.:** Epidemiologic review of marijuana use and cancer risk. Alcohol, 2005, 35, pp. 265-275.
31. **McKallip, R. J., Nagarkatti, M., Nagarkatti, P. S.:** Delta-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. J. Immunol., 2005, 174, pp. 3281-3289.
32. **Sarfaraz, S., Afaq, F., Adhami, V. M., Mukhtar, H.:** Cannabinoid receptor as a novel target for the treatment of prostate cancer. Cancer Res., 2005, 65, pp. 1635-1641.
33. **Contassot, E., Tenan, M., Schnuriger, V. et al.:** Arachidonyl ethanolamide induces apoptosis of uterine cervix cancer cells via aberrantly expressed vanilloid receptor-1. Gynecol. Oncol., 2004, 93, pp. 182-188.
34. **Herrera, B, Carracedo, A., Diez-Zaera, M. et al.:** p38 MAPK is involved in CB2 receptor-induced apoptosis of human leukaemia cells. FEBS Lett., 2005, 579, pp. 5084-5088.
35. **McKallip, R. J., Lombard, C., Fisher, M. et al.:** Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. Blood, 2002, 100, pp. 627-634.
36. **Patsos, H. A., Hicks, D. J., Dobson, R. R. et al.:** The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase-2. Gut, 2005, 54, pp. 1741-1750.

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COMMENTARY

On the article by B. Vidinský, P. Gál and J. Mojžíš "Different Views on the Relationship between Cannabinoids and Cancer"

The article refers to a very topical and at the same time delicate subject. The authors have succeeded in creating a very good overview of all principal medical aspects related to the topic, while in my opinion avoiding in appropriate fashion the non-medical aspects. However, I regard it as necessary to outline at least some of them in the commentary and to recall at the same time that in this research area our country has a rich tradition as well as current activities.

In the introduction to the article the authors note a quotation from the work of Grotenhermen et al. (1) that the topic of the article is controversial in contemporary medicine. I do not share completely share this view. On the contrary; this topic does not evoke many controversies from medical point of view, and the results of current research as well as historical experience clearly indicate this. This topic is only controversial in terms of non-medical impact from political, legal, criminological, economic and other perspectives. It is only due to these factors that the topic tend to be viewed by some as delicate, in medicine too. This is, incidentally, a classic example of how the "evidence-based" approach can be eased out and replaced by other attitudes. By the way, it is interesting from a historic perspective that the period when hemp drugs became illegal, is regarded in addictology as the period with a significantly dominant moralist approach or model. Medicine succumbed more or less to this supposed "controversy" and thus was deprived of an important perspective on treating substances for many decades; it has yet to recover fully. The authors of the article, for example, remark that it is not so long since the medical use of CB was authorized in Canada and Holland. It is important to say that the Canadian political establishment in particular experienced very difficult diplomatic and media pressure from the United States of America. Unbelievable situations between both states occurred, concerning every conceivable approach except the professional one. Canada finally made its own decision, and medical research was fortunately enabled. It is certainly interesting that even the European Union did not avoid the pressure of USA, and it still faces frequent (mostly medically easy to challenge and more or less ideological) critics merely for having an open attitude towards this field of medical research and research concerning the drug policy.

Considering non-medical cannabis use, mentioned by the authors several times in the article, it is important to note that in the Czech Republic more than 1.7 million people have had experience with cannabis, and estimates of regular users range from 300 000 to 400 000 (for more detail see 2, 3). In this context the use patterns are, however, the essential point. They are crucial precisely from the research perspective in relation to different risk levels of genesis and progression of oncologic diseases. In spite of cardinal attention drawn to smoking (whether marihuana cigarette, joint, classic or water pipe, etc), a significant group of users combine or even prefer peroral application and add different products from cannabis to meals or drinks. Thus it is that in the last years the so-called vaporisers have appeared on the market (sold legally in retail chains) enabling inhalation of psychoactive substances without burning the dry matter. However, unfortunately we do not have at out disposal practical research results of the last use pattern in relation to risks of cancer – though it can merely be theoretically supposed that this use pattern might not be associated with a significant risk of the onset of cancer. Possible impacts on public health are wildly discussed in face of the steadily raising popularity of cannabis, especially among young people in the whole EU (4). Different EU countries try different innovations in approach to this group of addictive substances (5, 6). So far only one fact is evident – actual instruments of drug policy do not seem to be effective on impacting this trend anywhere in the world (see also 7).

In the year 2004 the monothematic number of the journal Addictology dealt with the history and presence of CB research (8). Our country has a long tradition in the field of cannabis research, founded in modern history by Professor Jan Kabelík, who investigated the antibacterial effects of cannabinoid extracts, by Professor Zdeněk Krejčí engaged in the same topic and of course by professor František Šantavý as well. The last two figures mentioned deserve recognition for, among other things, isolating and identifying the substance responsible for antibacterial effects, which they called canabidiol acid (9). Their legacy is acknowledged by one of the most significant contemporary scientist in this area, Dr. Lumír Hanuš, participating in 1992 on discovery of anandamid – substance binding on cannabinoid receptors (this discovery was published in the journal Science in the very same year). Extraordinary results in preclinical research are also being studied by the team lead by Professor Alexandra Šulcová at the Medical Faculty of Masaryk University in Brno. The team directed by Dr. Michal Miovský in Prague is engaged in the research of psychosocial associations of non-medical use of cannabis.

I am delighted that Časopis lékařů českých (Journal of Czech doctors) is presenting an article that contributes to the discussion of such a difficult topic as the application of substances contained in cannabis. Rapid progress in further basic and applied medical research on this field seems possible, and we may in the future expect interesting results in the area of research into technical hemp, namely in perspective of alternative sources of energy, beast feeding etc.

LITERATURE

1. **Grotenhermen, F.:** Cannabinoids. Curr. Drug Targets CNS Neurol. Disord., 2005, 4, pp. 507-530.
2. **Miovský, M., Šťastná, L., Řehan, V.:** Actual overview of cannabinoid drug use in the Czech Republic in perspective of scholar and population studies. Psychiatrie, 2004a, 3, pp. 194-199. Czech.

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3. **Miovský, M., Šťastná, L., Řehan, V.:** Indicators of risky behaviour in context of hemp drug use. Psychiatrie, 2004b, 4, pp. 280-285. Czech.
4. **EMCDDA:** Extended annual report on the state of the drugs problems in the European Union. Lisboa, EMCDDA, 2000–2004.
5. **EMCDDA**:. Illicit drug use in the EU: legislative approaches. Lisboa, EMCDDA, 2005.
6. **Loo, M. et al.:** Cannabis Policy, Implementation and Outcomes. Santa Monica/ Arlington/ Pittsburgh, Rand Europe, 2003.
7. **Radimecký, J.:** Marihuana and law „Legal status of cannabis". Lecture for members of Czech Parliament. (Source: http://wtd.vlada.cz/urad/urad_postaveni.htm, 24. 5. 2003, 23:32). Czech.
8. **Journal Addictology** (Adiktologie) No. 4/2004 – special monothematic issue about cannabis and cannabis use (website: www. adiktologie.cz.).
9. **Hanuš, L.:** Editorial. Adiktologie, 2004, 2, pp. 457-460.

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On the article by B. Vidinsky, P. Gál, J. Mojžiš "Different Views on the Association between Cannabinoids and Cancer"

The synoptic article of the Slovak pharmacologists provides a summary of current knowledge regarding the mechanisms of the anti-cancer cannabinoid effect and of their clinical application in the treatment of pain and vomiting in patients with a tumor disease. Based on the data, a certain contradiction may be detected between the large amount of the cannabinoid theoretical findings and their relatively restricted clinical application in the treatment of the oncology patients. A similar situation is also found in other spheres of a potential therapeutic cannabinoid application with an impact on the other regulatory mechanisms of the organism, for example on pain, inflammation, appetite for food, immunity system and muscular functions. Undoubtedly this is in connection with the psychotropic marihuana alcaloid effects leading to its being misused and accompanied by a number of side-effects (1, 2). Based on these reasons, many legislative measures have been established which have an influence on both clinical and pre-clinical research of these agents, their production, distribution, clinical evaluation and prescription. The national regulatory authorities are not unanimous; however, they mostly concur that the clinical assessment of these agents may be possible, in particular in connection with serious chronic diseases (for example, Acquired Immunodeficiency Syndrome and tumor disease) , where there is absence of a corresponding alternative treatment.

Currently the delta-9-tetrahydrocannabinol, also called the THC or the Dronabinol, is produced as a medicament in Canada and in the US. In addition to these countries, a synthetically variety, nabilon, is also produced in the UK. Their application has been permitted only by some regulatory authorities, usually they have been included in specific curative programs ("Orphan Drugs"). Usually they are indicated for treatments of anorexia and of body wasting of the patients with the Acquired Immunodeficiency Syndrome. They have been further applied for the nausea and vomiting decrease induced by emetogeneous cytostatics, which cannot be managed by the usual medicines.

The psychotropic effects, such as dizziness, euphoria, somnolence, distress, impaired concentration ability, increased risk of psychotic conditions, present the main current disadvantage of the cannabinoid therapeutic application. Similarly undesirable cardiovascular effects (heart rhythm disorder, hypotension or hypertension) may be of a serious character and gastro-intestinal symptoms (nausea, vomiting, abdominal pains) are also quite frequent. Sometimes the patients are requesting the cannabinoid treatment very strongly, which may even give rise to judicial proceedings on the subject (3).

The development of new derivatives and forms of medicines intended for oral application or as an oral spray has been initiated in order to avoid the ill-effects of marihuana smoking on the respiratory system. Cannabinoids with restricted psychotropic activities (Cannabidiol, Cannabinol) have been produced. As for Europe, cannabinoids have so far been evaluated clinically in Germany, Finland, Great Britain, Belgium, France and Spain. Concurrently, there are six clinical studies available in the clinical evaluation section of the database Pub Med (www.pubmed.gov). These are focused on the effect on the spasticity with the interspersed cerebrospinal sclerosis, on chronic painful conditions with tumors and with fibromyalgia. The existing pre-clinical research studies also indicate the possibility of further therapeutic application, in particular in the treatment of the neurodegenerative conditions, for example such as Alzheimer Disease, Parkinson's Disease and Huntington's Disease, potentially also depression, osteoporosis, obesity, glaucoma and rheumatoid arthritis. It is therefore obvious that medical cannabinoid application in oncology, but also in other spheres of therapeutic utilization, has not been settled unequivocally yet. The contribution of theoretical research into cannabinoids and their receptors is indisputable. However, the potential therapeutic usage will have to be interpreted with enormous thoroughness, and it must always be accompanied with current evaluation of both their positive and also potential negative effects, and this always in connection with the current options on treatment of the basic illness in question.

REFERENCES

1. **Nešpor, K., Csémy, L., Zima, T.:** Marijuana's Ill-Effects In the Course of Some Years. Čas. Lék. čes., 2004, 143, pp. 490-491.
2. **Thomson** MICROMEDEX® Healthcare Series.127, 2006.
3. **Okie, S.:** Medical Marijuana and the Supreme Court. N. Engl. J. Med., 2005, 353, pp. 648-651.

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