Bladder Cancer

Excerpt from www.cancer.ca:

Bladder cancer is a malignant tumour that starts in the cells of the bladder. Malignant means that it can spread, or metastasize, to other parts of the body.

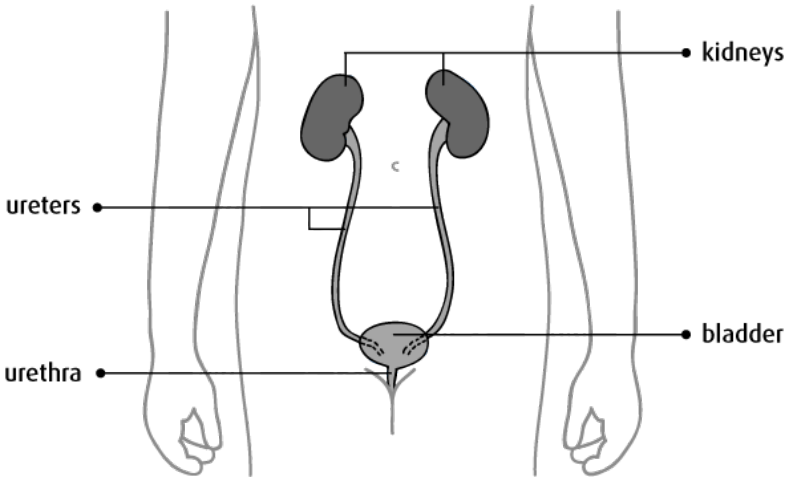
The bladder is part of the urinary system. It is a hollow, balloon-shaped organ with a flexible, muscular wall. The bladder stores urine. Urine is made by the kidneys, where it collects in the renal pelvis. It passes to the bladder through 2 tubes called ureters. Urine passes from the bladder and out of the body through a tube called the urethra.

Cells in the bladder sometimes change and no longer grow or behave normally. These changes may lead to benign conditions such as a urinary tract infection. They can also lead to benign tumours, such as papilloma or a fibroma. Benign conditions and tumours are not cancerous. But in some cases, changes to bladder cells can cause bladder cancer.

Most often, bladder cancer starts in cells of the urothelium (also called the transitional epithelium). The urothelium lines the inside of the bladder, ureters, urethra and renal pelvis. It is made up of transitional cells, or urothelial cells. Cancer that starts in transitional cells is called transitional cell carcinoma, or urothelial carcinoma. Transitional cell carcinomas make up more than 90% of all bladder cancers. When the cancer is only in the urothelium, it is called superficial bladder cancer. If the cancer spreads into the muscle wall of the bladder, it is called invasive bladder cancer.

Rare types of bladder cancer can also develop. These include squamous cell carcinoma and adenocarcinoma. Transitional cell carcinoma can also start in the renal pelvis or ureters, but this is less common.

Location of the Bladder



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Functional role of cannabinoid receptors in urinary bladder

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Abstract

Cannabinoids, the active components of Cannabis sativa (maijuana), and their derivatives produce a wide spectrum of central and peripheral effects, some of which may have clinical applications. The discovery of specific cannabinoid receptors and a family of endogenous ligands of those receptors has attracted much attention to the general cannabinoid pharmacology. In recent years, studies on the functional role of cannabinoid receptors in bladder have been motivated by the therapeutic effects of cannabinoids on voiding dysfunction in multiple sclerosis patients. In this review, we shall summarize the literature on the expression of cannabinoid receptors in urinary bladder and the peripheral influence of locally and systemically administered cannabinoids in the bladder. The ongoing search for cannabinoid-based therapeutic strategies devoid of psychotropic effects can be complemented with local delivery into bladder by the intravesical route. A greater understanding of the role of the peripheral CB_1 and CB_2 receptor system in lower urinary tract is necessary to allow the development of new treatment for pelvic disorders.

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TRPV2 activation induces apoptotic cell death in human T24 bladder cancer cells: a potential therapeutic target for bladder cancer.

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Abstract

OBJECTIVES:

To investigate the functional expression of the transient receptor potential vanilloid 2 (TRPV2) channel protein in human urothelial carcinoma (UC) cells and to determine whether calcium influx into UC cells through TRPV2 is involved in apoptotic cell death.

MATERIAL AND METHODS:

The expression of TRPV2 mRNA in bladder cancer cell lines (T24, a poorly differentiated UC cell line and RT4, a well-differentiated UC cell line) was analyzed using reverse transcriptase-polymerase chain reaction. The calcium permeability of TRPV2 channels in T24 cells was investigated using a calcium imaging assay that used cannabidiol (CBD), a relatively selective TRPV2 agonist, and ruthenium red (RuR), a nonselective TRPV channel antagonist. The death of T24 or RT4 cells in the presence of CBD was evaluated using a cellular viability assay. Apoptosis of T24 cells caused by CBD was confirmed using an annexin-V assay and small interfering RNA (siRNA) silencing of TRPV2.

RESULTS:

TRPV2 mRNA was abundantly expressed in T24 cells. The expression level in UC cells was correlated with high-grade disease. The administration of CBD increased intracellular calcium concentrations in T24 cells. In addition, the viability of T24 cells progressively decreased with increasing concentrations of CBD, whereas RT4 cells were mostly unaffected. Cell death occurred via apoptosis caused by continuous influx of calcium through TRPV2.

CONCLUSIONS:

TRPV2 channels in UC cells are calcium-permeable and the regulation of calcium influx through these channels leads directly to the death of UC cells. TRPV2 channels in UC cells may be a potential new therapeutic target, especially in higher-grade UC cells.

http://www.ncbi.nlm.nih.gov/pubmed/20546877

Cannabinoids Induce Cancer Cell Proliferation via Tumor Necrosis Factor α-Converting Enzyme (TACE/ADAM17)-Mediated Transactivation of the Epidermal Growth Factor Receptor

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Abstract

Cannabinoids, the active components of marijuana and their endogenous counterparts were reported as useful analgetic agents to accompany primary cancer treatment by preventing nausea, vomiting, and pain and by stimulating appetite. Moreover, they have been shown to inhibit cell growth and to induce apoptosis in tumor cells. Here, we demonstrate that anandamide, Δ^9-tetrahydrocannabinol (THC), HU-210, and Win55,212-2 promote mitogenic kinase signaling in cancer cells. Treatment of the glioblastoma cell line U373-MG and the lung carcinoma cell line NCI-H292 with nanomolar concentrations of THC led to accelerated cell proliferation that was completely dependent on metalloprotease and epidermal growth factor receptor (EGFR) activity. EGFR signal transactivation was identified as the mechanistic link between cannabinoid receptors and the activation of the mitogen-activated protein kinases extracellular signal-regulated kinase 1/2 as well as prosurvival protein kinase B (Akt/PKB) signaling. Depending on the cellular context, signal cross-communication was mediated by shedding of proAmphiregulin (proAR) and/or proHeparin-binding epidermal growth factor-like growth factor (proHB-EGF) by tumor necrosis factor α converting enzyme (TACE/ADAM17). Taken together, our data show that concentrations of THC comparable with those detected in the serum of patients after THC administration accelerate proliferation of cancer cells instead of apoptosis and thereby contribute to cancer progression in patients.

Introduction

Cannabinoids have been used in medicine for more than a century. Recently interest in their therapeutic value has been fuelled by suggestions to apply these drugs in cancer treatment to improve analgesia and to relieve insomnia (1) . Because of their neuroprotective properties, cannabinoids have also been proposed to be useful drugs for the therapy of neurodegenerative diseases like Parkinson‘s disease, Huntington disease, and multiple sclerosis (2) . Orally applicable Δ^9-tetrahydrocannabinol (THC; Dronabinol, Marinol) and its synthetic derivative Nabilone (Cesamet) have been approved by the United States Food and Drug Administration to stimulate the appetite of patients with AIDS and to reduce the nausea of cancer patients undergoing chemotherapy (1 , 3 , 4) .

Moreover, recent investigations propose that drugs activating the endogenous cannabinoid system might be used in cancer therapy to slow down or block cancer growth (4) . The endogenous cannabinoid anandamide (AEA) acts antiproliferatively in MCF-7, EFM-19, T47D, and DU145 cells (5) . Interestingly, cannabinoid-induced inhibition of proliferation in breast cancer cells

Furthermore, depending on drug concentration, the timing of drug delivery, and cellular context, cannabinoids may either inhibit or stimulate the function of immune cells. Although high concentrations of cannabinoids block immune cells, Derocq *et al*. (8) demonstrated proliferation in human B cells after cannabinoid stimulation at nanomolar concentrations (6, 7, 8) . In addition, murine hematopoietic cells depend on AEA for normal growth in serum-free medium (9) .

THC, the endogenous cannabinoid AEA and synthetic cannabinoids like HU-210 and Win55,212-2 interact with specific G protein-coupled receptors (GPCRs). Two subtypes of the cannabinoid receptors, CB1 and CB2, have been cloned and characterized (10 , 11) . The CB1 receptor, which is responsible for the well-known psychotropic effects of cannabinoids, is highly expressed in the central nervous system, but lower levels are also present in immune cells and peripheral tissues including testis, whereas the CB_2 receptor is predominantly expressed in immune cells (12, 13, 14) . Both cannabinoid receptors are coupled to heterotrimeric $G_{i/o}$-proteins and activate the mitogen-activated protein kinases (MAPK) extracellular signal-regulated kinase (ERK)1/2 and p38 as well as the Akt/PKB survival pathway (5 , 15) . Extensive research efforts have addressed the question how cannabinoids induce MAPK activation. Thus far, the accumulation of ceramides after cannabinoid stimulation has been implicated in the induction of the ERK/MAPK signal, whereas other reports suggested intracellular ceramide levels not to be required for cannabinoid-induced MAPK activation (5 , 12) . Previously we and others have shown that a wide variety of GPCR agonists leads to the activation of MAPK via transactivation of the epidermal growth factor receptor (EGFR) (16, 17, 18, 19) . This mechanistic concept involves the proteolytic processing of a membrane-spanning proEGF-like growth factor by a zinc-dependent metalloprotease of the ADAM family (18, 19, 20, 21) .

The aim of this study was to identify critical elements that link the cannabinoid receptors to activation of the ERK/MAPK and the Akt/PKB pathway. Hence, we tested whether cannabinoid receptors transactivate the EGFR in cancer cell lines, thereby activating downstream mitogenic signaling events.

Our results demonstrate that treatment of NCI-H292 (lung cancer), SCC-9 (squamous cell carcinoma), 5637 (bladder carcinoma), U373-MG (glioblastoma), 1321N1 (astrocytoma), and A498 (kidney cancer) cells with cannabinoids such as THC, AEA, HU-210, and Win55,212-2 leads to rapid EGFR tyrosine phosphorylation, phosphorylation of the adaptor protein Src homology 2 domain-containing (SHC), and downstream activation of ERK1/2 and Akt/PKB. EGFR transactivation is specifically mediated by cannabinoid-induced cleavage of proAmphiregulin (proAR) and/or proHeparin-binding epidermal growth factor-like growth factor (proHB-EGF) at the cell surface by tumor necrosis factor α-converting enzyme (TACE/ADAM17). Importantly, THC induced EGFR- and metalloprotease-dependent cancer cell proliferation. Thus, this cross-communication of CB1/CB2 receptors and the EGFR provides a molecular explanation of how cannabinoid receptors are linked to MAPK and Akt/PKB activation in a wide variety of human cancer cell lines.

In the light of these results, the use of cannabinoids in cancer therapy has to be reconsidered, because relatively high concentrations of THC induce apoptosis in cancer cells, whereas nanomolar concentrations enhance tumor cell proliferation and may, therefore, accelerate cancer progression in patients.

http://cancerres.aacrjournals.org/content/64/6/1943.long