Možne interakcije med kanabinoidi in estrogeni pri pogostih boleznih

Potential interactions between cannabinoids and estrogens in common diseases

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Izvleček

Pred kratkim so odkrili prve molekularne povezave med kanabinoidnim sistemom in estrogeni. Preučevanje medsebojnega učinkovanja je zanimivo predvsem zato, ker bi lahko privedlo do novih farmakoterapevtskih pristopov, zlasti pri boleznih, kjer sta oba molekularna sistema vpletena v patofiziologijo bolezni. Članek predstavlja pregled vloge kanabinoidnega sistema in estrogenov pri osteoporozi, aterosklerozi in raku ter potencialne koristi medsebojne povezave obeh sistemov pri farmakoterapiji teh bolezni.

Po obsežnem pregledu literature utemeljeno sklepamo na verjetno součinkovanje med kanabinoidnim sistemom in estrogeni, vendar ustreznih neposrednih študij na molekularnem nivoju v literaturi nismo zasledili. Z rezultati nedavne lastne raziskave na primarnih kulturah človeških osteoblastov smo prvi pokazali na morebitno molekularno součinkovanje med navedenima sistemoma.

Abstract

Molecular associations between the cannabinoid system and estrogens have recently been discovered. This research field is particularly interesting because it could lead to new pharmacotherapeutic approaches, especially in diseases where both molecular systems contribute to the pathophysiology. This paper presents an overview of the role of the cannabinoid system and estrogens in osteoporosis, atherosclerosis and cancer, and discusses the potential benefits of the modulating both systems in the pharmacotherapy of these diseases.

Although an extensive literature review points to likely interactions between the cannabinoid system and estrogens, appropriate molecular studies have not yet been carried out. Our recent results in primary human osteoblasts are the first to demonstrate a possible interaction between the two systems at a molecular level.

Potrebne so nadaljnje raziskave, ki bodo natančno preučile molekularno součinkovanje ter koristnosti in varnost posameznih kombinacij estrogenov in kanabinoidov v patogenezi oz. farmakoterapiji osteoporoze, ateroskleroze, rakavih in drugih pogostih obolenj.

Further studies are needed to carefully examine molecular interactions as well as the efficacy and safety of various combinations of estrogens and cannabinoids in the pathogenesis and pharmacotherapy of osteoporosis, atherosclerosis, cancer and other common diseases.

CANNABINOID SYSTEM

Cannabinoid research began in 1964 with the identification of Δ9–tetrahydrocannabinol (Δ9–THC) and, until 1980, it was believed that the effects of cannabinoids were the result of non–specific interactions with cell membranes. The identification of cannabinoid receptors profoundly changed this early view of how cannabinoids interact with cells. It soon became clear that the effects of cannabinoids in the human body are a consequence of their binding to cannabinoid receptors 1 and 2 (CB1 and CB2). It was also discovered that cannabinoids can activate other receptors, including the vanilloid type 1 receptor (TRPV1) and the G–protein coupled receptors GPR18, GPR55 and GPR119 (1).

CB1 and CB2 receptors belong to the family of G–protein coupled receptors. Their activation results in inhibition of adenylyl cyclase and activation of mitogen–activated protein kinases p42/44 , p38, c–Jun N–terminal kinase and activator protein 1, as well as in increased membrane permeability for calcium ions (2–5).

Although both CB1 and CB2 receptors are expressed in the peripheral and central nervous systems, CB1 receptor expression is much more pronounced and many of the psychoactive effects of non–selective cannabinoids can be attributed to their activation of CB1 receptors. CB2 receptor expression, on the other hand, is higher in atherosclerotic plaques, bone tissue, the large intestine in chronic inflammatory diseases, the synovial fluid in rheumatoid arthritis, demyelinating lesions in multiple sclerosis, the immune system, gastrointestinal mucosa and biopsies of endometriosis (1, 6, 7).

ESTROGENS IN THE HUMAN BODY

Three estrogens are present in significant quantities in the plasma of human females: 17β–estradiol, estrone and estriol. The estrogenic potency of 17β–estradiol is 12 times higher than that of estrone and 80 times higher than that of estriol, making the total estrogenic efficiency of 17β–estradiol many times that of the other two together. 17β–Estradiol is the principal estrogen secreted by the ovaries; small amounts of estrone are also secreted, but most of the circulating estrone is formed in peripheral tissues from androgens (8).

Estrogens bind to estrogen receptors alpha (ERα) and beta (ERβ), which are nuclear transcription factors involved in the regulation of many complex physiological processes. Modulation of estrogen receptors is currently being considered for the prevention and treatment of a wide variety of pathological conditions, including osteoporosis, metabolic and cardiovascular diseases, inflammation, neurodegeneration, and cancer (9). A third, G–protein coupled estrogen receptor (GPER), has recently been discovered, although its functional role is still unclear (10).

INTERACTION BETWEEN THE ENDOCANNABINOID SYSTEM AND ESTROGENS

Interaction between the endocannabinoid system and estrogens is a growing area of interest because of the discovery of associations at a molecular level. Previous studies have shown that 17β–estradiol increases the expression of CB2 receptors in osteoclasts in vitro as well as the expression of CB1 receptors in human colon cancer (11, 12). In the brain, 17β–estradiol regulates

CB1 receptor expression in a region–dependent manner, providing a possible explanation for gender–related differences in sensitivity to the central effects of cannabinoids (13). Recently, selective estrogen modulators (raloxifene, bazedoxifene, lasofoxifene) were discovered to act as inverse CB2 agonists; this finding indicates that estrogens could have a direct effect on cannabinoid receptors (14). However, the importance of this interaction in the human body has not yet been clearly understood and needs further research.

In the present article we will review potential roles of the endocannabinoid system and estrogens, as well as interactions between the two, in the pathogenesis of three common diseases: osteoporosis, atherosclerosis and cancer. Understanding interactions between the two systems, especially, could lead to new pharmacotherapeutic approaches.

CANNABINOIDS AND ESTROGENS IN OSTEOPOROSIS

Bone remodeling is critical for maintaining the integrity of bone structure. During a lifetime, bones undergo three phases: a phase of rapid skeletal growth and increasing bone mineral density, a sustenance phase, and a phase of predominant bone resorption causing bone loss. The bone remodeling process is influenced by many factors, including estrogens and the endocannabinoid system. Imbalances in bone remodeling mechanisms cause one of the most common degenerative diseases in developed countries, osteoporosis (15). It is estimated that over 200 million people worldwide suffer from osteoporosis. The costs to health care services in the European Union due to osteoporotic complications are already considerable and, if current trends continue, the costs are predicted to double by 2050 (16).

Osteoblasts are influenced by estrogens at both a cellular and molecular level. Estrogens bind to nuclear estrogen receptors in osteoblasts and act as transcription factors, modulating expression of specific deoxyribonucleic acid sequences (DNA) (17). For example, estrogens increase collagen I and osteoprotegerin gene expression (18). Some evidence suggests inhibitory effects of estrogens on osteoblast apoptosis (19).

Compared with CB1 receptors, CB2 receptors have been reported to have significantly higher expression in osteoblasts, osteoclasts and osteocytes (20). Selective CB2 agonists/antagonists may therefore regulate bone remodeling. Importantly, selective CB2 receptor ligands are not generally psychoactive, making them more suitable for potential clinical use (21). The TRPV1 receptor is also considered to be important in the pathogenesis of osteoporosis; the role of the GPR55 receptor in bone formation has not yet been extensively studied (7, 22).

Treatment with 17β–estradiol led to increased expression of CB2 receptors on osteoclasts (11). In our recent study in primary human osteoblasts, we tested the hypothesis that 17β–estradiol could also influence CB2 receptor expression in osteoblasts. Our preliminary results indicate a possible synergistic interaction between 17β–estradiol and a selective CB2 antagonist/inverse agonist (23).

CANNABINOIDS AND ESTROGENS IN ATHEROSCLEROSIS

Atherosclerosis is a leading cause of death in developed and developing countries. The pathophysiology underlying atherosclerosis is a combination of endothelial cell dysfunction and vascular inflammation, accompanied by a build–up of lipids, cholesterol and calcium within the tunica intima. Together, these can result in plaque formation, thrombosis and cardiovascular insufficiency (6).

High expression of CB1 and CB2 receptors in atherosclerotic plaques indicates an important role for the endocannabinoid system in atherosclerosis (6). CB1 receptors are associated with cardiovascular risk factors such as obesity and dyslipidemia and CB1 agonists have been shown to be harmful since they increase the amount of reactive oxygen species (ROS) and induce apoptosis of endothelial cells in coronary arteries (24, 25). On the other hand, in an

animal model of atherosclerosis, CB1 antagonists have proved useful; they reduced accumulation of oxygenated LDL in macrophages, reduced inflammatory reactions in small blood vessels, decreased proliferation of smooth muscle cells in vessel walls and consequently delayed disease progression (24). CB2 receptors have also been proven to have a significant role in the pathogenesis of atherosclerosis. Δ9–THC, a non–selective CB1 and CB2 agonist, administered in a mouse model, slowed the progression of atherosclerotic plaques. This effect was nullified by subsequent administration of a selective CB2 antagonist (26). CB2 agonists reduce accumulation of lipids in human foam cells (27). Cannabinoids also lower expression of the CD36 receptor, which promotes the release of pro–inflammatory cytokines and increases its own expression (28).

Increased incidence of cardiovascular incidents in postmenopausal women suggests that estrogens play an essential protective role against cardiovascular diseases. Menopause creates unhealthy changes in plasma lipoprotein levels that can be reversed by postmenopausal estrogen replacement therapy (29). Studies have shown that estrogens are important for normal cell proliferation in blood vessels. When physiological angiogenesis is lacking or insufficient, a setting is created for various cardiovascular diseases (30). Estrogens regulate lipid and cholesterol levels and may provide protection by increasing plasma high density lipoprotein levels (31). On the other hand, estrogens may modulate inflammatory responses within vascular cells, cause stem cell death and may also be involved in the development of hypertrophy (32). Estrogens may also have antioxidant effects that can attenuate the oxidation of lipids and low density lipoprotein by macrophages in the early stages of atherosclerosis, reactions that lead to foam cell formation and atherogenesis (33, 34). 17β–estradiol can lower the activity and expression of vascular nicotinamide adenine dinucleotide phosphate oxidase, a potent source of ROS (35). ERα stimulation leads to endothelial dysfunction and diminishes basal nitrogen oxide (NO) release. ERβ receptors, on the other hand, mediate the cardioprotective effects of 17β–estradiol through modulation of ion channel expression and calcium–handling proteins (36). Activation of the GPER receptor also increases endothelial release of NO (37).

Current evidence suggests that a combination of a selective CB1 antagonist or a selective CB2 agonist with an estrogen may provide an effective treatment for atherosclerosis. As discussed above, estrogens could influence the expression of both CB1 and CB2 receptors and could also possibly interact directly with cannabinoid receptors. To the best of our knowledge, appropriate studies on the interaction between cannabinoids and estrogens in the pathogenesis of atherosclerosis have not yet been performed.

CANNABINOIDS AND ESTROGENS IN CANCER

Cancer represents a group of diseases that are defined by uncontrolled proliferation of pathological cells with the potential to invade and spread to other parts of the body. Cancer is a major public health problem, with more than 14.1 million new cases globally in 2012. The financial costs of cancer are enormous and have been estimated at $1.16 trillion per year worldwide (38).

Cannabinoids have inhibitory effects on the proliferation and survival of tumor cells. They affect apoptosis, proliferation, migration, adhesion and invasion of carcinoma cells. Breast carcinomas are associated with increased expression of CB1 and CB2 receptors (39). In vitro studies show that the inhibitory effects of cannabinoids on the proliferation of carcinoma cells is mediated via CB1 receptors and that the inhibitory effects on migration are mediated via CB2 receptors (40, 41). In a mouse model, Δ9–THC decreased the growth of breast carcinoma cells, decreased cell proliferation and inhibited angiogenesis; these effects are probably mediated by CB2 receptors (39). In colorectal tumor cells, apoptotic and antiproliferative effects are mediated by CB1 receptors; down–regulation of these receptors could thus promote carcinogenesis. CB2 receptors may also play a role in these processes, depending on the cell line tested (42).

Long term use of estrogens is known to promote carcinogenesis, especially in breast and endometrial cancers (43). Estrogens or estrogen metabolites stimulate production of intracellular ROS that modify DNA, interfere with DNA repair mechanisms and slow down damage repair, leading inevitably to accumulation of mutations (44, 45). In vitro studies revealed that estrogens can increase the invasiveness and mobility of MCF7 and T47D breast cancer cell lines (46). Estrogens can also interfere with drug treatment since they limit the ability of paclitaxel to induce apoptosis in breast cancer cells (47). Conversely, clinical and experimental studies have indicated an anti–proliferative action of estrogens in colon cancer (48). It seems likely that 17β–estradiol is able to interact with polyamines and growth factors required for cell proliferation in colon cancer (49, 50).

It has been proven that selective estrogen receptor modulators can act as inverse CB2 agonists and can influence expression of cannabinoid receptors (14). A combination of a cannabinoid and a selective estrogen receptor modulator may inhibit estrogen–induced carcinogenesis more potently than either agent alone and a combination of an estrogen with a CB1 modulator could be beneficial in colorectal cancer.

CONCLUSION

This review shows that the endocannabinoid system and estrogens may be more closely associated than previously thought. Further studies into the exact nature of these interactions are needed and could lead to the development of new pharmacological approaches for osteoporosis, atherosclerosis and cancer.

A possible synergistic interaction between 17β–estradiol and a selective CB2 antagonist/inverse agonist in osteoblasts has been observed and could lead to a new therapeutic option in osteoporosis.

A selective CB1 antagonist or a selective CB2 agonist together with an estrogen could be an interesting combination for the prevention or treatment of advanced atherosclerosis.

Different combination treatments should be considered for different cancers. In estrogen–dependent cancers, a combination of a cannabinoid and a selective estrogen receptor modulator may inhibit carcinogenesis. In colorectal cancer, a combination of an estrogen and a CB1 modulator may be more beneficial. All of the proposed combinations would, however, need to be tested for efficiency and safety in preclinical and further clinical studies.

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