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Endocannabinoid system, pharmacogenomics and response to therapy

"Conceivably, plasma and tissue endocannabinoids may represent reliable diagnostic markers of reproduction and pregnancy outcomes..."

Cannabinoids are the active constituents in marijuana, while endocannabinoids (eCBs) are the natural, endogenous marijuana-like substances found in animals and humans [1]. Recent advances in cannabinoid research indicate the existence of an elaborate and previously unknown but ubiquitous eCB system (ECS), whose fundamental role in human development, health and disease is unfolding. The ECS includes eCBs, their degrading enzymes, such as fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MGL), the known cannabinoid receptors – CB1-Rs and CB2-Rs – which are activated by eCBs and phytocannabinoids, the active constituents in marijuana [1]. ECBs, are abundant in the testis and uterus for their reproductive function, and are present in breast milk, not only to stimulate appetite, but also for the growth and development of the newborn. It has also been discovered that the ECS is involved in regulating oogenesis, embryo oviduct transport, blastocyst implantation, placental development and pregnancy outcomes and in sperm survival, motility, capacitation and acrosome reaction [2]. Conceivably, plasma and tissue eCBs may represent reliable diagnostic markers of reproduction and pregnancy outcomes, and in the functional state of human sperm. Another major breakthrough in cannabinoid research was the discovery that specific genes in human chromosome 6 and 1, encoding two distinct cannabinoid receptors (CB1-R and CB2-R, respectively), are activated by eCBs, cannabinoids and marijuana use. This new knowledge on the biology of marijuana, from gene to behavior [3], and the surprising recent discoveries in cannabinoid genomics have transformed cannabinoid research into mainstream science [4]. These remarkable advances and new understanding have been achieved owing to the availability of specific molecular tools and technology, which indicate

that the cellular, biochemical and behavioral responses to marijuana use are encoded in our genes [3,4]. Much of this progress in cannabinoid genomics is providing genetic variants and mutations in the ECS that deepen our understanding of cannabinoid pharmacogenomics. Such recent advances in understanding the biological actions of marijuana, cannabinoids and eCBs are unraveling the genetic basis of marijuana use, with functional implication for cannabinoid pharmacotherapy [3,4].

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"...drugs that are targeted to different aspects of [the endocannabinoid system] are already benefiting cancer patients and those with AIDS and metabolic syndromes."

With the promise of personalized medicine, the availability of cannabinoid pharmacogenomic tests can be utilized to determine an individual's response to natural or synthetic cannabinoid drugs, which will allow individually tailored cannabinoid therapies that target the different components of the ECS. Based on new knowledge of the genetic basis of marijuana, cannabinoid and eCB action, individuals can be identified that respond to cannabinoid therapy, for example in post-traumatic stress disorder, nausea and emesis, anorexia and cachexia, tremor and pain associated with multiple sclerosis, neuropathic pain or drug dependency [4–6]. A number of variations in cannabinoid receptor genes have been associated with these and other disorders [4]. As cannabinoid receptors are encoded in our genes, cannabinoid pharmacogenomics holds promise in disorders associated with genetic risk factors in the ECS. Therefore, in the era of personalized medicine, cannabinoids may be beneficial in psychiatry and in other conditions of ECS disorders involving CB1-Rs, CB2-Rs, CBn-Rs, FAAH and MGL receptor genes. As a result of the ubiquitous distribution and the fundamental role that

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the ECS plays in the regulation of a number of human physiological processes, drugs that are targeted to different aspects of this system are already benefiting cancer patients and those with AIDS and metabolic syndromes [7].

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“In the era of personalized medicine, however, it may become possible to select only obese individuals who will benefit from cannabinoid pharmacotherapy...”
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It has traditionally been argued that the use of cannabis as medicine is limited by the mind-altering psychoactivity associated with smoking marijuana; therefore, synthetic ligands of the ECS and those that do not cross the blood–brain barrier are touted to have therapeutic applications. Thus, an emerging area of intensive preclinical research and development is the discovery of novel natural and synthetic ligands of the ECS, as reviewed recently [8]. These ligands are not yet in clinical use, but they could be potential pharmacotherapies for different types of pain, glaucoma, cancer, head trauma and neurodegenerative diseases, such as Parkinson’s and Alzheimer’s diseases, by targeting different components of the ECS. ECBs mimic the actions of exogenous cannabis, but *in vivo*, the cannabimimetic effects of eCBs are weak because of rapid degradation by their hydrolyzing enzymes, FAAH and MGL. Therefore, development of eCB-hydrolyzing enzyme inhibitors may be used to enhance the levels of eCBs in the brain and periphery without the use of cannabis. A number of such promising enzyme inhibitors are being tested for pain relief and in psychiatric disorders [9], but are a long way from clinical utility. To date, however, only the synthetic agonists, such as marinol, nabilone, dronabinol, sativex, cesamet and cannador, mimicking the actions of the active ingredients in marijuana, for example, Δ^9 -tetrahydrocannabinol and cannabidiol, and CB1-R antagonists, such as acomplia, which has been withdrawn from Europe, have been used for different indications in the clinic. Unfortunately, the use of acomplia, which was never approved by the US FDA, but was approved and used in Europe as an antiobesity medication, was short lived and withdrawn owing to its anxiety-, depression- and suicide-inducing side effects in some patients. In the era of personalized medicine, however, it may become possible to select only obese individuals who will benefit from cannabinoid pharmacotherapy based on results from

their pharmacogenomic tests. This will limit the use of targeting the ECS in individuals that are vulnerable to the potential side effects of depression and suicide.

The rapid pace in the identification of genetic variants and haplotypes in *CNR*, *FAAH* and *MGL* genes associated with obesity, autoimmunity and addiction phenotypes may help identify those specific targets in conditions of eCB dysfunction. For example, we and others have now shown that variants of the *CNR1* and *CNR2* genes are associated with a number of disorders and substance abuse vulnerability in diverse ethnic groups, including European–American, African–American and Japanese subjects [5,10,11]. Furthermore, variants of *CNR* genes co-occur with other genetic variations and share biological susceptibility that underlies comorbidity in a number of neuropsychiatric disorders [12]. Genetic polymorphisms in cannabinoid receptor *CNR1* and *CNR2* genes have been linked to psychiatric and immune system disorders, and similar SNPs in the eCB-degrading enzyme genes, *FAAH* and *MGL*, have also been associated with a number of neurological and autoimmune disturbances [4]. Pharmacogenomics is associated with the influence of genetic variation on drug response in patients by correlating gene expression or SNPs with a drug’s efficacy or toxicity. While current knowledge of cannabinoid pharmacogenomics is still at preliminary stages, soon treatment with cannabinoids will have the capacity to be optimized with respect to the individual’s genotype to maximize efficacy and reduce adverse reactions with the promise of individualized medicine. Some examples of polymorphisms in *CNR*, *FAAH* and *MGL* genes that are associated with psychiatric and autoimmune disorders include:

- The *CNR1* SNPs, rs1049353 and rs806379, and (AAT)_n repeats in the *CNR1* gene showed modest association between these *CNR1* polymorphisms and substance dependence restricted at AAT polymorphism in Caucasian populations [5,13];
- *CNR1* SNP rs1049353, a silent polymorphism that results in the substitution of ‘G’ to ‘A’ at nucleotide position 1359 in codon 435, causes protection from heroin addiction in Caucasians [14];
- *CNR1* SNPs (AAT)_n repeats in the *CNR1* gene was associated with attention-deficit hyperactivity disorder, post-traumatic stress

disorder, depression in Parkinson's disease, schizophrenia and with restricting and binging/purging anorexia nervosa [15–18];

- *CNR2* SNPs and haplotypes have been associated with human osteoporosis, bone mass changes, autoimmune disorders, alcoholism, depression and schizophrenia [4,6,11,19–21].

Although there is increasing evidence that genetic variants in the different components of the ECS are associated with some disorders [4–6,11,13–21], little information exists regarding *CNR* gene copy number variations and epigenetic events in diverse populations, and their use as predictive markers or clinical utility in cannabinoid pharmacotherapeutics remains to be demonstrated. Furthermore, there is growing interest in epigenetics and its potential role in human disorders. We are interested in studying whether changes in the ECS are associated with epigenetic mechanisms in cannabinoid-induced behavioral effects. Knowledge of epigenetic processes combined with individual genetic information may allow specific targeting of different components of the ECS in human health and disease.

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Conclusion & functional implication of eCB system pharmacogenomics & response to therapy

The discovery that specific genes in our chromosomes code for the cannabinoid receptors CB1-R and CB2-R that are activated by marijuana use, and the finding that the human body produces its own natural marijuana-like substances – eCBs – has a significant impact on health, disease and therapeutic potential, as reviewed recently [4]. Therefore, the various components and elements of the ECS, including the cannabinoid receptors and their genes, their endogenous ligands, for example 2-arachidonyl glycerol, their metabolizing and synthetic enzymes, and transporters of eCBs are potential pharmacogenetic and pharmacotherapeutic targets. We now know that the existence and ubiquitous distribution of the ECS throughout the entire human physiology makes the components of the ECS a target for therapeutic intervention

during cell development, immune disorders, in reproduction and digestion, appetite stimulation, and CNS function and dysfunction, such as mental illness and neurodegenerative diseases [4]. Others have demonstrated that cannabinoids and eCBs have some role in cancer cell growth and could be potential adjuncts or targets in the treatment of cancer [22]. Although marijuana has been used for recreation and as medicine for thousands of years, in recent years, there has been increased interest in legalizing marijuana for medicinal use in AIDS, cancer, obesity, multiple sclerosis and in other medical conditions where patients might benefit from the pharmacological effects [101]. It is important to mention that synthetic cannabinoids, such as dronabinol, marinol and nabilone, already have an established use as antiemetics in nausea and vomiting associated with cancer chemotherapy. The reported beneficial effects in cancer and AIDS patients might reflect improved weight gain, owing to the well-documented antiemetic and appetite-stimulating effects of cannabinoids. However, the potential drawback in the use of cannabis as medicine has been the psychoactivity induced by smoking marijuana and the potential for abuse and dependence. Knowledge regarding the role of pharmacogenetics in individual responses to cannabis, cannabinoids and eCBs may be exploited in reducing psychoactivity. Progress in cannabinoid genomics is providing new insights into genetic variables and mutations in the various components of the ECS that deepen our understanding of how to identify individuals that will respond to cannabinoid therapy, for example in multiple sclerosis and neuropathic pain. Thus, identifying ECS genetic variants and biomarkers are potential future therapeutic targets in the era of personalized medicine.

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