Genetic testing for cannabinoid use

Testes genéticos para uso de canabinoides

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ABSTRACT

BACKGROUND AND OBJECTIVES: Cannabis is the most popular and consumed illicit drug in the world, it has about 540 bioactive phytocannabinoids, including tetrahydrocarbinol (THC) and cannabidiol (CBD). The therapeutic potential of phytocannabinoids has been the subject of many studies in recent decades for many medical situations, including the management of chronic pain. The advent of pharmacogenetics currently allows the indication of the Cannabis dose to be evaluated individually. The objective of this work was to carry out a survey of the literature on the medicinal use of Cannabis and the application of pharmacogenetics in this therapy.

CONTENTS: THC and CBD phytocannabinoids are the most abundant and researched. In the endocannabinoid system there are compounds similar to phytocannabinoids, cell receptors and metabolism enzymes. All these molecules are secreted from genes, which may have individual genetic polymorphisms that determine the modulation of the endocannabinoid system, and consequently impact the patients' therapeutic response.

CONCLUSION: The existence of genetic tests for the prior assessment of the patients genetic profile in order to avoid side effects and to have more assertiveness in the indication of the cannabis product is an important tool to increase adherence to cannabis treatment.

Keywords: Cannabis, Genetic variation, Medical marijuana, Pharmacogenetics, Polymorphism, Single nucleotide.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A cannabis é a droga ilícita mais popular e consumida no mundo, possuindo cerca de 540 fitocanabinoides bioativos, entre eles o tetra-hidrocarbinol (THC) e o canabidiol (CBD). O potencial terapêutico dos fitocanabinoides tem sido alvo de muitos estudos nas últimas décadas para muitas situações médicas, incluindo o manejo da dor crônica. O advento da farmacogenética permite que atualmente a indicação da dose de cannabis seja avaliada individualmente. O objetivo deste estudo foi realizar um levantamento da literatura sobre o uso medicinal da cannabis e a aplicação da farmacogenética nessa terapia.

CONTEÚDO: Os fitocanabinoides THC e CBD são os mais abundantes e pesquisados. No sistema endocanabinoide, existem compostos similares aos fitocanabinoides, receptores celulares e enzimas de metabolismo. Todas essas moléculas são secretadas a partir de genes que podem possuir polimorfismos genéticos individuais determinantes para a modulação do sistema endocanabinoide e, consequentemente, impactam a resposta terapêutica do paciente.

CONCLUSÃO: A existência de testes genéticos para avaliação prévia do perfil genético do paciente a fim de evitar efeitos colaterais e ter mais assertividade na indicação do produto de cannabis é uma importante ferramenta para aumentar a aderência ao tratamento com cannabis.

Descritores: Cannabis, Farmacogenética, Maconha medicinal, Nucleotídeo único, Polimorfismo, Variação genética.

INTRODUCTION

Pharmacogenetics is the study of how individual genetic variability impacts an individual's response to a particular drug. Single nucleotide polymorphisms (SNPs), responsible for genetic and phenotypic variability, have been associated with different therapeutic and adverse responses in treatments with various drugs and with cannabis. Thus, the determination of SNPs can identify which phytocannabinoid is best suited to a particular patient, and which specific dosage to bring therapeutic benefits with low risk or even absence of side effects, which makes the treatment much more effective and with greater adherenc[1-14].

The genes containing the SNPs specific to cannabis pharmacogenetics can be divided into membrane receptor genes, transport genes, genes to enzymes involved in cannabinoid metabolism, genes involved in the biosynthesis and bioactivation of endogenous cannabinoids, and genes for cannabinoid-related cellular processes[13].

Thus, previous genetic evaluation regarding the use of cannabis can allow a great assertiveness for the prescription, promoting

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HIGHLIGHTS
- There are questions about adverse effects and risk of addiction associated with cannabis use.
- Evaluation of genetic polymorphisms related to cannabis use is a reality.
- Pharmacogenetics allows assertiveness in cannabis prescribing.

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better management and efficiency of the treatment, with a decrease in intoxication risks or in administration of sub-optimal doses for a certain individual, besides suggesting the best route of administration[12-14].

The present study's objective was to conduct a survey of the literature on medicinal use of cannabis and the application of pharmacogenetics to this therapy.

CONTENTS

Brief history

200 years ago, pain medicine already knew about and made use of morphine, a potent painkiller naturally obtained from opium, which is extracted from poppy. Due to the large amount of opioid prescriptions for chronic pain management in recent decades, opioid overdose has claimed 69,000 lives annually, and another 15 million people are considered addicted to opioids worldwide. Due to analgesic effects of active ingredients and secondary metabolites of cannabis, its medicinal use, especially in the control of chronic pain, linked or not to malignant tumors, has been increasingly discussed in counterpoint to the opioid prescription crisis[6,11,15-17].

Until the early 20th century, cannabis use was common among Chinese, Mexicans, Arabs, and Afro-descendants, i.e., among socially discriminated minorities. In addition, cannabis competed with the powerful cotton textile industry for clothing, and also with the tobacco and alcohol industry. Thus, cannabis came to be seen as a drug that should be combated. In 1925, cannabis was included by the Geneva Convention as a dangerous and illicit drug, while tobacco and alcohol remained legal[3].

It was not until the 1960s that chemical structure, isolation, purification, and synthesis of CBD and THC were obtained. Pharmacological experiments with the cannabinoids extracted from cannabis were performed between the 1940s and 1950s, as well as the first tests with synthetic cannabinoids, demonstrating the power of each type of cannabinoid in different animal species, especially its psychotropic effect[18].

PHYTOCANNABINOIDS

Although there are more than 500 phytochemicals in cannabis, the fat-soluble phytocannabinoids THC, CBD and their precursors are the most abundant molecules in cannabis variants and therefore both have been widely investigated[1]. Depending on the cannabis species and strain, there is a higher concentration of either one phytocannabinoid. In general, *Cannabis sativa* produces more THC and *Cannabis indica* has a higher concentration of CBD[3,19].

THC is the main psychoactive molecule in cannabis, with a wide variation in concentration according to the cannabis species, which has an important impact on those who use it medicinally. The effects of THC are related to mood swings and psychopathological symptoms, such as anxiety, panic or paranoia, as well as producing audiovisual changes and negatively impacting memory[3,18].

On the other hand, CBD, the second most present molecule in cannabis, has no psychoactive effect and, if administered in conjunction with THC, diminishes the psychoactive effects promoted by THC. CBD is a molecule of wide interest due to its therapeutic potential, for not being psychoactive and having few side effects.

As for its therapeutic potential, CBD has been used in Brazil for treatment of psychiatric or neurodegenerative diseases, besides having analgesic, antitumor and immunosuppressive actions[3]. However, in legal trade purchased cannabis, the presence of THC has increased from 4% to 12% in the last 25 years, while the proportion of CBD in relation to THC has been decreasing[5,7]. In different presentations of cannabis, there has been a difference in THC concentration increase, while the concentration of CBD has not changed over the last decades[19].

ENDOCANNABINOID SYSTEM

The endocannabinoid system comprises endogenous phytocannabinoid-like molecules and their precursors, the enzymes responsible for synthesis and degradation of endocannabinoids, and the cell membrane receptor system. The discovery of this system had a great impact on cannabinoid research, because research started to study not only phytocannabinoids from cannabis and synthetic cannabinoids, but also endocannabinoids and what are the physiological and pathological events that promote the release and metabolism of these molecules, besides their role in health and disease[15,18].

Endogenous ligands of the endocannabinoid system are derived from arachidonic acid and ethanolamine, namely anandamide or N-araquidonoiletanolamine (AEA) and 2-araquidonoilglycerol (2-AG). While AEA is similar to THC, 2-AG is similar to CBD, and is more prevalent than AEA. Besides these two, three other endocannabinoids have been described, all derived from the degradation of arachidonic acid. The metabolic enzymes responsible for the synthesis and degradation of endocannabinoids include diacylglycerol lipase α and β isoenzymes, fatty acid amide hydrolase, monoacylglycerollipase, and N-acylphosphatidylethanolamine-selective phospholipase D[2-4,15].

The main G protein-coupled cell membrane receptors that are part of endocannabinoid system are called CB1 and CB2, with 44% homology between them. CB1 is encoded by *CNRI* gene, located on chromosome 6q14-15, and is extremely conserved between species. CB2 is encoded by the *CNR2* gene and is located on chromosome1p36[11]. The highest concentrations of CB1 and CB2 receptors are in central nervous system (CNS) and immune system cells, respectively.

CB1 receptors are very present in hippocampus, cerebral cortex, cerebellum, and basal ganglia. CB1 neurochemical structure is very similar to that of opioid receptors and is believed to modulate the nociceptive process in the brain. CB2 receptor, on the other hand, is found in higher concentration in sensory neurons of dorsal root ganglion and spinal cord, areas known to be sites of intense nociceptive integration. Outside CNS, cannabinoid receptors are involved in antinociceptive pathways by noradrenergic signaling[1,2,4,15].

In addition to CB1 and CB2 receptors, two more receptor genes involved in the endocannabinoid system, *TRPV1* and *GPR55*,

have been described. *TRPV1* is on chromosome 17p13[2] and encodes a transient receptor with potential subfamily V member 1 action for CBD. THC does not bind to *TRPV1* receptors, but CBD does. Binding of CBD metabolites simultaneously at the CB2 and *TRPV1* receptors is necessary for *ABCB1* gene expression, related to phytocannabinoid transport. When there was binding only on CB2 or *TRPV1* receptors, there was no signaling for *ABCB1* gene, showing that only joint binding on the two receptors is capable of initiating the metabolization process[20].

GPR55 gene is located on chromosome 6 in the human species and encodes the G protein-coupled receptor with 319 amino acids and seven hydrophobic domains, presenting a structure similar to that found in cannabinoid receptors, and is even considered a new subtype of cannabinoid receptor that does not bind to CB1 and CB2[21,22].

There is evidence in animal model studies of other possible cell membrane receptors that are involved in cannabinoid signaling, however these have not yet been properly identified[21].

Endocannabinoid system modulates the neurological hormone system in a retrograde manner, regulating many neurobiological processes, with a key role in homeostasis, hunger sensation, anxiety, emotions, depression, neurogenesis, neuroprotection, reward system, learning, memory, pain sensation, fertility, gestation, and pre- and postnatal development[1,2,15].

The tissue concentration of endocannabinoids and its receptors increases in some conditions, such as multiple sclerosis, chronic pain, cancer, schizophrenia, post-traumatic stress, intestinal and cardiovascular diseases, causing a reduction in the severity of symptoms or slowing the progression of the condition. In other situations, such as female infertility, obesity, brain damage after heart attack, septic shock, cystitis, and gastrointestinal alterations, there is also an increase in the endocannabinoid system, but in this case leading to unwanted effects, and there are no studies on the clinical relevance of such effects yet[15,18]. Thus, due to the multiple functions linked to endocannabinoid system, its modulation has been the subject of studies to benefit dozens of medical conditions[15].

PHYTOCANNABINOID METABOLISM

In the process of phytocannabinoid metabolism, there are reports still being studied of membrane-associated proteins for the transport of these molecules. At least two proteins from *ABC* transporter gene family are involved in extra- and intracellular transport of cannabinoids, *ABCB1* and *ABCG2*. These proteins are involved in multidrug resistance, especially *ABCB1*. *SLC6A4* gene and *COMT* gene also produce cannabinoid cellular transport proteins[13].

The fat-soluble phytocannabinoids THC and CBD are metabolized in the liver for elimination via feces and urine. Products of natural origin, such as cannabis, are known to have their effect modulated by cytochrome P450 enzymes and uridine diphosphate (UDP) glucuronosyltransferase (UGT).

In humans the enzyme proteins of cytochrome P450 gene family include 57 functional genes and 58 more pseudogenes. Cytochrome P450 family enzymes act in a variety of phase 1 metabolic reactions, including the metabolism of steroids, drugs, and xenobiotics. Phytocannabinoids are metabolized primarily by enzymes produced by cytochrome P450, such as CYP 2C9 and CYP 2C19 enzymes, with genes on chromosome 10, and CYP 3A4 enzyme, with genes on chromosome 7.

CYP 2C9 enzyme metabolizes about 15% of all clinically relevant drugs, including opioids and THC. CYP 2C19 enzyme is involved in about 2% of drug metabolism. CYP 3A4 enzyme is involved in the metabolism of THC and also of CBD[13,23]. Phytocannabinoids and metabolites of THC are able to inhibit a good part of cytochrome P450 enzymes[24].

UGT complex enzymes are located in endoplasmic reticulum of liver, kidneys, and upper aerodigestive tract cells, being most present in liver. They comprise four subfamilies, UGT1, UGT2, UGT3, and UGT8, comprising a total of 22 enzymes essential to the reaction that catalyzes the binding of metabolized molecules to glyburonic acid in phase 2 detoxification. This reaction allows the molecules to become water soluble to facilitate excretion by urine and feces. UGT family enzymes are critical for metabolism and clearance of endogenous and exogenous compounds, including steroid hormones, bile acids, bilirubin, fatty acids, carcinogens, and therapeutic drugs, and are responsible for 15% of the drugs metabolism[24-26].

UGT1A1, UGT1A3, UGT1A9 enzymes, all on chromosome 2, and the enzyme UGT2B7, on chromosome 4, are involved in metabolization and detoxification of phytocannabinoids[13]. Recently it has been shown that phytocannabinoids, especially CBD, are able to inhibit many of UGT enzymes (mainly UGTs1A6, 1A9, 2B4 and 2B7), suggesting that deleterious effects of cannabis may be more likely to occur in patients with reduced renal or hepatic function[24].

CANNABIS PHARMACOGENETICS

Pharmacogenetics studies the variations in response to drugs according to the patient's genetic makeup[14]. The knowledge of proteins and other molecules involved in reception, transport, action and metabolism of cannabinoids leads to a list of candidate genes to check for SNPs that can influence therapeutic responses and especially adverse reactions in cannabis treatments[13,27].

In the topics already described, were mentioned the main constituent genes of endocannabinoid system and also of phytocannabinoid metabolizing system.

In the endocannabinoid system, the cell membrane receptors CB1 and CB2, encoded by *CNR1* and *CNR2* genes, besides being the main responsible for endocannabinoid cell signaling, are also activated with phytocannabinoids. *CNR1* is so far the gene with highest number of SNPs described for risk of cannabis dependence and risk of mood swings due to abstinence. Carriers of these SNPs have higher or lower risk of dependence and withdrawal crisis, depending on the unique individual combination[1,13,28]. *CNR2* gene also has polymorphisms described that promote altered receptor function[13].

To date, there are no reports of polymorphisms in *TRPV1* membrane receptor gene associated with cannabis. As for the *GPR55* gene, also a membrane receptor, a polymorphism has

been described that is associated with an increased risk of anorexia nervosa[13].

The opioid receptor gene *OPRM1* has a polymorphism that contributes to individual response to cannabis and to serum THC levels[29].

The phytocannabinoid transporter genes, extra and intracellular, *ABCB1* and *ABCG2*, involved in resistance to drugs, in addition to *SLC6A4* and *COMT* genes, have polymorphisms, some associated with cannabis metabolism. The SNP present in *ABCB1* gene is responsible for modulating THC serum levels in chronic cannabis users[13,30]. In *COMT* gene, a variant increases the risk of schizophrenia in the carrier and also promotes a greater adverse effect on cannabis use[27,31,32].

As for the metabolization of phytocannabinoids, the main genes involved are from cytochrome P450 family *CYP 2C9*, *CYP 2C19* and *CYP 3A4* and from UGT family, *UGT1A1*, *UGT1A3*, *UGT1A9* and *UGT2B7*. Certainly, there are other genes involved in the various signaling pathways involving the metabolization of more than 500 phytocannabinoids, but not all have been discovered yet[13].

Genetic variants in the genes encoding these cytochrome P450 enzymes have been evaluated with regard to altered enzyme function. A relevant number of functional haplotypes have been identified in cytochrome P450 genes, resulting in phenotypes whose frequencies vary according to ethnic group. An alteration in *CYP 2C9* enzyme activity, originating from a SNP, impacts one of the THC conversion steps, reducing THC metabolization by up to 70% when compared to the wild allele carrier[33]. *CYP 3A4* gene has also been described as a causal factor for lower enzyme activity in THC metabolization[13].

Genetic markers of pharmacokinetics, involving cytochrome P450 genes, are important tools to define the optimal dose of the drug in question, or in the case of cannabis, to help define the best concentrations of THC and CBD that should be used in a given individual. Patients with high rate of metabolization need higher doses, while patients with low metabolism need lower doses[13,16].

UGT enzymes are critical for phytocannabinoid detoxification, and UGT expression and activity are regulated by very precise processes at various cellular levels[25]. *UGT1A* gene presents polymorphisms that are variable according to ethnicity, impacting bilirubin and estrogen levels[34], also impacting THC metabolism[35].

Besides SNPs in genes involved in the endocannabinoid system, there are also specific SNPs to predict which individuals are likely to develop cannabis addiction. In such cases, the genomes of thousands of cannabis users have been compared with the genomes of non-users in order to find allele frequencies that could relate to cannabis addiction[1,10,36,37]. Other genome wide analyses have assessed tolerance and risk behaviors for habits such as smoking, alcoholism, and sex addiction, and found hundreds of SNPs associated with higher risks of addiction and higher tolerance to the drug administered[38].

Genetic variants may also be present in psychological and psychiatric factors that may be associated with cannabis use, such as anxiety, depression, mood disorders, schizophrenia, bipolar disorder, and psychoses. SNPs already identified for all of these conditions can be previously evaluated prior to therapeutic cannabis use to identify genetic susceptibility for a particular psychological or psychiatric condition[2,5,7,8,10,31,32,37,39-43]. Individuals with sleep disorders and insomnia also have SNPs that may predict changes in cannabis use[44]. It is even possible to predict the risk of obesity with cannabis use according to the SNP of *FTO* gene[45].

SNPs evaluation is certainly a useful tool for prediction of adverse reactions and unwanted risks in patients who need to perform therapeutic use of cannabis. Through a simple buccal swab and collection tube with a liquid that preserves DNA, cells are obtained for genetic variants analysis[4,14].

CONCLUSION

Cannabis treatment is very different from an allopathic therapy, as finding the right dose of cannabis for a patient is challenging, as there are numerous factors involved in the process, such as weight, age, stage and type of disease, sensitivity to cannabis, cannabinoid pharmacology, various plant options with different concentrations of active ingredients and various routes of administration, as well as the patient's individual genetics and metabolism.

In Brazil, there are already tests that evaluate individual SNP--type genetic variants involved in endocannabinoid system and other genes that may be associated with adverse effects of cannabis on the body.

Performing these tests prior to medical cannabis use allows the physician to prescribe cannabis in a much safer, individualized and personalized manner to the patient, drastically reducing the risk of addiction and unwanted symptoms after use, as well as promoting more safety and therapeutic efficacy in the choice of cannabis product that will be used.

The customization of medicine with application of predictive genetic testing is already a reality and should be used as an important tool for patients who have an indication for therapeutic cannabis use, considerably improving treatment adherence.

AUTHORS' CONTRIBUTIONS

Ciro Dresch Martinhago

Data Collection, Conceptualization, Project Management, Research, Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Validation

Rafael Moraes de Albuquerque Pessoa

Statistical Analysis, Funding Acquisition, Writing - Review and Editing

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