RESUMOS DOS TRABALHOS APROVADOS PARA O CONGRESSO

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Tema: Aspectos éticos, legais, culturais, sociais e econômicos sobre o acesso e o uso medicinal da cannabis e seus derivados

Código: 78130 - THERAPEUTIC USE OF CANNABIS: A SOCIOANTHROPOLOGICAL STUDY OF PHARMACOLOGY MANUALS.

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Resumo: Introduction: Cannabis plants have been incorporated to medical therapy in several countries over the last decades. They have been used in the treatment of various diseases, such as drug-resistant epilepsy, multiple sclerosis and chronic pain. The therapeutic use of cannabis suffers stigma and prejudice. It's necessary to analyze how the recent medicalization process with Cannabis has been presented in professional health training. Objectives: To analyze in pharmacology manuals, the diffusion of scientific information involving representations on the consumption of cannabis and its derivatives, from the official biomedical discourse directed to health professionals. Method: Documentary research with socioanthropological approach. Data source: three pharmacology manuals adopted by Brazilian universities: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition; Basic & Clinical Pharmacology, 13th edition and Clinical Pharmacology: Fundamentals of Rational Therapy, 4th edition. Keywords researched in these manuals, between August and September of 2018 were: Cannabis and cannabinoids. Results: Endocannabinoid system's and its receptors descriptions have been found in the central nervous system pharmacology chapters. Δ9-THC has been considered as the only natural cannabinoid. Pursuing control of the emesis, stimulation of appetite and treatment of pain, dronabinol and nabilone have been presented as therapeutic alternatives. The use of other cannabinoids and their use in other health conditions have not been presented. Cannabis is highlighted in chapters discussing drugs abuse and addiction. Conclusions: Cannabis therapeutic use has been little discussed in pharmacology manuals, which represent fundamental references in training of health professionals in our country. Manuals ignore specialized knowledge restricted to scientific journals, reproducing hegemonic medical-legal discourse that stigmatizes cannabis use, and disregarding lay knowledge of medicinal use. Considering scientific knowledge produced by human activity in its social and political insertion, is important to mention in educational materials, empirical evidence which has already been described about cannabis use in clinical practice in several countries. Thus, this would contribute to reduce stigma and influencing professionals conduct towards the use of this health technology.

Código: 78135 - DEMOCRACY, HEALTH AND PSYCHOACTIVES: (IM)PRECISIONS ON RES N.1/MARCH OF 2018 OF THE NATIONAL COUNCIL ON DRUGS POLICIES

Autores: DAVID GUZZO FAUSTINO / Guzzo, D. / UNIVERSIDADE DE BRASÍLIA;

Resumo: The purpose of this research is to observe the continuities and descontinuities of the normative content of brazilian public health policies for individuals and communities related to the harmful use of Drugs. I will compare official documents from 2002-2016, analyzed by Teixeira (et al, 2016), to more recent documents from July/2016-2018. With the n. 2.197/2004 ordinance of the Ministry of Health, Brazil had been moving towards a more autonomist approach in the public health for individuals who harmfully use drugs. Teixeira has conducted an exquisite documental analysis of 22 official letters from 2001 to 2016, of which 8 have put harm reduction as the most adequate strategy. On the other hand, the legal review promoted by Ministry of Justice sustains that prevention, promotion and treatment must be based on scientific evidences, notwithstanding its absolute contrary position to drugs legalization. The Resolution considers specially, the overwhelmingly opposing position of the Brazilian population regarding drug legalization initiatives. In fact, the Ministry is unaware of much of the legal accommodation previously articulated, expressly suggesting the "promotion of abstinence" as a strategy for expanding and reorganizing health care services. Drug policies in Brazil, specially health public policies, have been relocated by the competent federal institutions during the time under consideration. This understanding comes from the distinctly process of moral and pathological reclamation towards the political policies about drugs, precisely noted in the rhetoric inflection of health-related norms. Using documental analysis, it was possible to note that all of the documents presented conflictive semantic fields. They also present overlapping considerations regarding the previous legal corpus. The prefix -re is frequently mentioned as in immediate reorientation, realignment, reorganization, outlining a (re)vision movement. Preferring abstinence over other strategies, it consolidates the central role of private partners, which have been recurrently subject at political agenda. The RES/n.1/2018/CONAD, specially considered in this research, suggests the vulnerability of political participation mechanisms, not rarely observed in the elaboration of the previous legislation, as well as the importance of holding institutions accountable.

Código: 78096 - PRO ENTOURAGE AND AGAINST SYNTHETIC DISCOURSES: CANNABIS EXTRACTION EQUIPMENT IMPORTANCE

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Resumo: Introduction This research started aiming at the non-human actors articulated by cannabis media groups in Brazil. After entering the first Cannabis group, several statements became evident. Phrases like "We hate the Industry," or "Cannabis synthetics are bad." are common at Cannabis Brazilian Associations (CBA) media groups. A research question was created to identify the source of such discontent with the Industry. The research question is which are the discourses from Brazilians Cannabis Entrepreneurs? The discourses found are 1) pro entourage effect and 2) against synthetic Cannabis. All entrepreneurs articulate the discourse pro entourage effect; however, BCA is against synthetic cannabis medicine. The non-human actor that is not present at BCA discourse is extraction equipment. This central research finding is that BCA is against synthetics production due to its lack of financial and legal support for equipment purchasing. Objective The primary objective was to identify discourses articulated by Brazilians Cannabis Entrepreneurs. Method The research used ANT controversies mapping (Latour, 2012) to identify the mediating actors present at Brazilians entrepreneurs. During six months the researcher interacted with seven associations media groups, six international Cannabis companies and with twelve professionals witch intent to explore the Cannabis Business in Brazil. The analysis was conducted comparing Brazilian associations discourses with entrepreneurs discourses (foreigners companies and Brazilians professionals). Results The principal mediator actors found was ANVISA, Genetics, Licenses, oil, Cannabinoids, THC, CBD, extraction equipment, technical knowledge. There are two discourses identified. The first discourse proposes the entourage effect as primordial for health treatments. The second discourse purposes to maintain flowers for recreational purposes and use the rest of the Cannabis plant to produce isolated cannabinoids. All groups accept the entourage effect discourse; however, Brazilian Cannabis Associations does not accept isolating cannabinoids. Conclusions Brazilian Cannabis Associations discourse is pro entourage effect and against the cannabinoids isolation due to its lack of financial and legal access to extraction equipment. References Latour, B. (2005). Reassembling the social: An introduction to actor-network-theory. Oxford: Oxford University Press.

Tema: Educação sobre aplicação medicinal de canabinoides

Código: 78127 - THE SIDE EFFECTS STATUS QUO: CANNABIS VERSUS PRESCRIPTION DRUGS. WHY DO WE SAY NO TO THE FIRST AND YES TO THE SECOND?

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Resumo: Medical Cannabis (MC) is growing. Its side effects are not. So how come healthcare actors are still very hesitant in prescribing MC? Despite the massive and growing body of evidence in favor of MC, Physicians and especially veterinarians still tend to act with extreme awareness on prescribing it, often opting for regular (and often harmful) prescription drugs. The reluctancy of those professionals are due to the potential undesirable side effects of cannabis which can be summarised as dizziness, euforia, dry mouth, dry and/or red eyes and, in some cases of high dosing: mild motor incoordination, temporary memory impairment and sedation. Such awareness is usually a good thing since every drug could potentially deliver health risks. Conversely, the same level of precaution is not seen among the medical community concerning the side effects of regular prescription drugs such as, for example, opioids and glucocorticoids by far the most commonly used drugs for pain management alone or combined. Opioids such as tramadol and codeine have severe and even life-threatening side effects that includes: nausea, vomiting, dry mouth, constipation, dizziness. At high doses, it leads to blood pressure decrease, colapse, coma, seizures and even death by inhibiting the respiratory control center. Glucocorticoids are very well known to cause gastrointestinal bleeding and perforation, ulcer and severe immunosuppression. Those are listed as commonly observed in any prescribing information for those drugs. Also, many regular prescription drugs have potential life-risks leading to death, which is physically impossible when it comes to Cannabis. In fact, every single research to determine the DL50 of Cannabis and cannabinoids in mammals other then small rodents failed in achieving that goal since they were unable to get any individual killed at any given dose. It is by now very safe to state that Cannabis is a most non-harmful, non-toxic drug for medical purposes. Even those side effects from Cannabis are all seen among opioids, glucocorticoids, plus several others. Since the very same side effects are already present in almost any other given medicine, and since it lacks the severe side effects of these prescription drugs, with very high frequency of prescription and usage, what does it take for healthcare professionals finally shift their first-choice medicine in prol of Cannabis-based treatments instead of traditional "high side effects risk therapies?

Tema: Pesquisa básica sobre o sistema endocanabinoide

Código: 76860 - SYNERGISM AND ADDITIVITY BETWEEN CANNABINOIDERGIC, OPIOIDERGIC AND ADRENERGIC SYSTEMS IN THE ENDOGENOUS MODULATION OF PHERIPHERAL INFLAMMATORY NOCICEPTION.

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Resumo: Pain is of medical concern worldwide, with relevant economic and social impacts, markedly represented by 30% of individuals affected at least once in life. Relevant comprehension of pain mechanisms was achieved by Pharmacology, being shown that peripheral inflammatory nociception is controlled by endogenous cannabinoidergic, opioidergic and adrenergic systems. Diverse combinations of pharmacological antagonists of representative GPCRs of these systems (CB1R, MOR and α2C, respectively) are shown to elicit hyperalgesic responses in an algesimeter adapted from Randall & Sellito (1957), even in the absence of inflammation by carrageenan-λ. To confirm synergism, addictive isoboles were constructed for binary combinations of agonists and isobolographic analysis showed strong synergistic or additive interactions. Molecular synergism characterization by immunohistochemistry in glabrous hindpaw skin and L3-L5 dorsal root ganglia revealed the presence of the three GPCRs on primary sensory neurons (PSN), and a proximity ligation assay (Duolink® Sigma) is being performed to characterize the occurrence of GPCR heterodimers and their correlation with the observed synergism. These results reinforces the hypothesis of a tonic control of peripheral pain, mediated by different endogenous analgesic systems, which act synergistically, possibly due to GPCR heterodimers formation in PSN plasma membrane.

Código: 78129 - EVALUATION OF THE NEUROPROTECTIVE PROPERTY OF NON-PSYCHOACTIVE CANNABINOIDS IN TWO IN VITRO NEUROTOXICITY MODELS: RELEVANCE FOR ITS THERAPEUTIC USE IN NEURODEGENERATIVE DISEASES

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Resumo: In the last years, the identification of phytocannabinoids from Cannabis sativa L. phytocannabinoids), the characterization of the endocannabinoid system in the brain and its neuromediators triggered an exponential growth in the study of the beneficial effects of the plant and its isolated components. Tetrahydrocannabinol (THC) is the most studied phytocannabinoid due to its psychoactive properties, while cannabidiol (CBD) and cannabigerol (CBG), without psychotropic effects, have been less investigated. In Cannabis these compounds are found in their acid form, known as cannabidiolic acid (CBDA) and cannabigerolic acid (CBGA). CBD has vast therapeutic potential, while the therapeutic properties of CBG and the corresponding acids are less well-known. Several studies indicate that cannabinoids could have neuroprotective activity, e.g., attenuate the progression of neurodegenerative diseases. Since oxidative stress and mitochondrial damage are key mechanisms involved in the pathogenesis of these diseases, and the structural characteristics of CBG and CBD and their acids are associated with a high antioxidant capacity, we hypothesized that these compounds are effective neuroprotector agents. We studied the neuroprotective potential of CBD, CBG, CBDA and CBGA (Phytoplant Research) in primary cultures of cerebellar granule neurons (CGN) against neuronal death induced by neurotoxins which elicit oxidative stress and mitochondrial alteration, hydrogen peroxide, H2O2 and rotenone, respectively. Different pre-incubation times were applied. The cell survive was evaluated morphologically and using the MTT method. If the neuroprotective property was mediated by 5-HT1A receptor or CB1-R and CB2-R was also assessed. Results indicate that CBD and CBG show a neuroprotective effect in CGN, which was much clearer when they were 1 h pre-incubated before both insults. While CBGA did not show neuroprotective action, CBDA elicited neuroprotection in rotenone paradigm but at only at a high concentration and after 24 h pre-incubated. Decarboxylation of CBDA seems to be a condition for its neuroprotection activity. A partial involvement of the 5-HT1A receptor was detected for CBG but not for CBD. The contribution of CB1-R and CB2-R remains under study. Our data will contribute to the comprehension of the biological effects of cannabinoids and to the development of new therapeutic strategies for neurodegenerative diseases.

Código: 77591 - ENDOCANNABINOID SYSTEM IN THE MODULATION OF NEUROPATHIC PAIN

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Resumo: INTRODUCTION: Peripheral neuropathic pain results from injury to some component of the primary sensory neurons. It is part of a complex syndrome that affects thousands of people. Pain is an expression of a poorly adaptive plasticity that leads to the generation of ectopic action potentials and facilitating the transmission of the nerve impulse. This impulse is passive to be modulated by endogenous analgesic systems. AIM: To evaluate the participation of the endogenous cannabinoid system during the neuropathic pain. METHODS: Male Wistar rats, weighing 180 g, were used for sciatic nerve constriction (CCI) surgery as described by Benett and Xie (Pain 33:87, 1988), which consist of the placement of 4 loose ligatures on the sciatic nerve. The groups were: Operated (OP) treated with the antagonist and treated with antagonist vehicle, false-operated wired, false-operated wireless, and those who was not submitted to any surgical procedure, however, they were treated with the antagonist or its vehicle. It was used 5 animals per group. The algesimetric test used was the mechanical paw pressure test described by Randall and Selitto (Arch. Int. Pharmacodynamics 111: 409, 1957) which measures the nociceptive threshold in grams (g). Measurements were made daily during 15 days to evaluate the kinetics of neuropathic pain. CB1 (AM251, 80 µg/paw) and CB2 (AM630 100 µg/paw) cannabinoid receptor antagonists were given intraplantarlly. One-way and two-way ANOVA followed by Bonferron□s test was used ($p < 0.05$). Research approval by the committee for Ethics in Animal Experimentation (CEUA/UFMG) 173/2014. RESULTS: The neuropathic pain kinetics showed that on day 1 there was hypoalgesia, followed on day 6 by moderate hyperalgesia which increased until day 10 and kept constantly until the end of the experiment. After injection of CB1 (AM251) and CB2 (AM630) receptor antagonists, it was found that they induced a worse hyperalgesia compared to the control group on days 1, 5, 6 and 12 after CCI. The exception was AM630, which on day 1 and day 12 did not cause nociceptive threshold reduction. CONCLUSION: Results showed the participation of the cannabinoid system in the modulation of neuropathic pain controlling, in a selective way, along of neuropathic hyperalgesia. FINANCIAL SUPPORT: CNPq, CAPES and FAPEMIG.

Código: 77492 - EVALUATION OF THE ANTINOCICEPTIVE EFFECT OF CANNABIDIOL (CBD) IN NEUROPATHIC PAIN AND THE ENDOGENOUS MECHANISMS INVOLVED IN THIS EVENT

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Resumo: Introduction: Cannabidiol (CBD) is one of the most abundant non-psychoactive components of the Cannabis plant and several works showed its potential as an anti-inflammatory drug. CBD classic mechanism is the agonism of 5-HT1A and TRPV1 receptors and it is believed that these pharmacological targets are responsible for most of its effects. However, works from other research groups have shown other possible target receptors for CBD, especially related to its potential as an analgesic drug. Possibly, it might induce analgesia through activation of the endocannabinoid system and subsequent activation of endogenous pathways that culminate with potassium channel opening and hyperpolarization. Aim: The aim of this study was to investigate the endogenous mechanisms involved in the antinociception induced by CBD in a model of neuropathic pain. Methods: Sciatic constriction surgery was performed in male Swiss mice weighing 30-35 g. CBD was injected intraperitoneally and the other drugs were injected subcutaneously in the right hind paw. Evaluation of the nociceptive response was performed using a mechanical paw pressure test. CBD was injected daily from 11º until the 21º day after surgery, and the algesimetric pharmacological experiments were performed on the 21º day. All animal experiments were approved by the ethics committee under the number of protocol CEUA nº: 57/2017. Results: CBD induces antinociception in a dose-dependent manner with the highest dose of 20 mg/Kg promoting complete reversion of the nociceptive response in neuropathic mice, and chronic treatment with CBD for 10 days does not alter the antinociceptive response measured. The selective antagonists of 5-HT1A, TRPV1, CB1 and CB2 receptors dose-dependently reversed the antinociception induced by CBD. Nonselective inhibition of NOS enzymes also dose-dependently reversed CBD-induced antinociception. Interestingly, guanylyl cyclase was not involved in this event since its inhibition did not alter the analgesic effect mediated by CBD. Blockade of KATP channels dose-dependently reversed the analgesia induced by CBD. Conclusion: CBD promotes analgesia through activation of 5-HT1A, TRPV1, CB1 and CB2 receptors with subsequent activation of the NOS enzymes, culminating with ATP sensitive potassium channels activation and hyperpolarization of nociceptive neurons in neuropathic mice. Chronic CBD treatment does not induce antinociceptive tolerance.

Código: 78131 - INVESTIGAÇÃO DA PARTICIPAÇÃO DO SISTEMA ENDOCANABINOIDE NO PREJUÍZO DO COMPORTAMENTO SOCIAL EM RATOS EXPOSTOS A STATUS EPILEPTICUS NEONATAL

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Resumo: Status epilepticus (SE), uma condição aguda caracterizada por crises repetitivas ou em curso, pode produzir consequências deletérias a longo prazo. Dados prévios demonstraram que ratos Wistar submetidos à SE neonatal apresentaram comportamento autístico, caracterizado por baixa preferência por novidade, déficit na discriminação social e comportamento estereotipado. Utilizamos este modelo animal para o transtorno do espectro autista (TEA) para investigar um possível papel do sistema endocanabinoide na etiologia do TEA. Ratos Wistar machos foram submetidos a SE no nono dia de vida por injeção de pilocarpina (380 mg / kg); os animais controles receberam salina 0,9% (0,1 mL / 10g). Em P60 ambos os grupos foram injetados com JZL195 (0,01 mg / kg), inibidor das enzimas FAAH e MAGL, catalisadoras de anandamida (AEA) e 2-AG, agonistas endógenos de receptores CB1. Após duas horas, os animais foram submetidos a testes comportamentais que avaliaram memória social e interesse por novidade social.Ao fim dos testes, foram extraídos tecidos de estruturas da via mesocorticolímbica: hipocampo, córtex pré-frontal, estriado e amígdala. O material extraído foi utilizado para análise da expressão gênica do gene CNR1 (por RT-PCR) e quantificação de receptores CB1 (por ELISA). No teste de memória social, animais controle tratados com JZL, quando apresentados à novidade social, mostraram menos interesse em investigar a novidade social ($F(1,18)=5,481$; $p=0,03$), sem prejuízo da capacidade de discriminação ($F(1,18)=9,807$; $p=0,0058$); animais experimentais tratados com JZL não apresentaram diferença significativa no tempo de investigação da novidade social ($F(1,17)=2,509$; n.s.). O tratamento com JZL interferiu especificamente no tempo de investigação do grupo controle em todas as sessões ($F(1,175)=0,6686$; $p<0,0001$). No teste de sociabilidade, o tratamento com JZL reduziu o tempo de investigação dos animais controle ($F(1,19)=4,863$; $p=0,04$) e afetou a preferência por novidade social ($t(20)=3,356$; $p<0,01$); o JZL não afetou o tempo de investigação dos animais experimentais ($F(1,19)=0,001$; n.s.). A PCR-RT não indicou diferença na expressão do RNAm do receptor CB1 nas estruturas analisadas. A quantificação por Elisa apontou menor concentração de CB1 no hipocampo de experimentais ($U=2000$; $p=0,03$).Nossos resultados sugerem que o sistema endocanabinoide participa da modulação de comportamento social e que existe alteração neurobiológica dessa circuitaria no TEA.

Código: 77590 - EVALUATING THE EFFECTS OF CB1 AND CB2 ANTAGONISTS ON HUMAN OLIGODENDROCYTES BY PROTEOMIC ANALYSIS: IMPLICATIONS IN SCHIZOPHRENIA

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Resumo: Introduction: Endocannabinoids are crucial neuromodulators of many brain functions, and the interest in the modulation of endocannabinoid signaling has increased since the discovery of CB1 and CB2 receptors. Several studies have associated changes in ligands and receptors of the endocannabinoid system with psychiatric disorders, such as schizophrenia. However, the molecular pathways and biological processes involved in cannabinoid effects on this disorder are not completely understood. Some studies, including from our group, have shown the involvement of oligodendrocytes (OLDs - the myelinating cells of the central nervous system) in the pathophysiology of schizophrenia. Other demonstrated the potential effects of cannabinoids in OLDs. Objective: Our aim was to investigate the effects of AM251 and AM630, CB1 and CB2 antagonists respectively, on the proteome of a human oligodendrocyte cell line (MO3.13 cells). Therefore, we seek to contribute to the understanding of the role of the endocannabinoid system in oligodendrocytes, and its possible implications in schizophrenia. Methods: The cells were treated with AM251 (1µM) and AM630 (1µM) for 8 hours. Proteins were extracted, digested and prepared for shotgun proteomic analyses using liquid chromatography coupled to mass spectrometry (LC-MS/MS). Afterwards, the raw data were processed and quantified using Progenesis QI for proteomics (Waters) and analyzed using in silico systems biology tools. Results: In total, 3935 proteins were identified and quantified. We found that AM251 affected the expression of 1482 proteins (489 upregulated and 993 downregulated) and AM630 modulated 1415 (482 upregulated and 933 downregulated). Of these, 1189 are modulated by both antagonists, and are related mainly to metabolism (especially of aminoacids and derivatives), immune system (mainly neutrophil degranulation and cytokine signaling), post-translational protein modification (mostly asparagine N-linked glycosylation, deubiquitination and neddylation), signal transduction, celular response to stress, axon guidance, and membrane trafficking of vesicle mediated transport. Moreover, the number of proteins modulated by these antagonists is higher when compared to the modulation induced by CB1 and CB2 agonists. Conclusion: Taken together, these findings may contribute to understand the effects of CB1 and CB2 antagonists on human oligodendrocytes, and its possible implications in the pathophysiology and treatment of schizophrenia.

Código: 78134 - EFFECTS OF CANNABINOIDS ADMINISTRATION IN HUMAN ASTROCYTES REVEALED BY PROTEOMICS

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Resumo: Introduction: Endocannabinoids are crucial neuromodulators of several brain processes, and the interest in the modulation of endocannabinoid signaling has increased since the discovery of its receptors (CB1 and CB2). Hence, there is much interest in understanding the effects of cannabinoids present in Cannabis sp, Δ9-tetrahydrocannabinol (Δ9-THC) which is psychotomimetic and cannabidiol (CBD) which has antipsychotic effects, on brain cells, such as neurons, oligodendrocytes and astrocytes. Astrocytes are the most abundant glial cell type in the nervous system and are integral functional components of synapses, establishing functional tripartite synapses, processing synaptic information and regulating synaptic function. Several studies have supported that the endocannabinoid system contributes to the interaction that occurs in synapses. However, the molecular pathways and biological processes involved in cannabinoid effects on astrocytes function are not fully understood. Objective: Our aim was to investigate the effects of CBD and WIN 55,212-2 (WIN55) - to mimic Δ9-THC effects- on the proteome of astrocytes derived from Neural Stem Cells (NSC) derived from Human Induced Pluripotent Stem Cells (hiPSC). Therefore, we aim to contribute to the understanding of the effects of the administration of exogenous cannabinoids in astrocytes. Methods: The cells were treated with CBD (2,5µM) or WIN55 (2,5µM) for 8 hours. Proteins were extracted, digested and prepared for shotgun proteomic analyses using liquid chromatography coupled to mass spectrometry (LC-MS/MS). Afterwards, the raw data were processed and quantified using Progenesis QI for proteomics (Waters) and analyzed using in silico systems biology tools. Results: In total, 246 proteins were identified and quantified. We found that CBD affected the expression of 40 proteins and they are related mostly to translation initiation, mRNA processing, glycolysis, and cell-cell adhesion. The treatment with WIN55 modulated 10 proteins and they are mainly related to protein targeting to membrane, transcription, mRNA catabolic process and translation initiation. Conclusion: Although preliminary, these findings may help elucidate the cellular effects of phyto or synthetic cannabinoids on human astrocytes.

Código: 77597 - CELL DEATH INDUCED BY CANNABINOIDS IS DEPENDENT ON P2X7 NUCLEOTIDE RECEPTOR IN EMBRYONIC RETINAL CELL CULTURES.

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Resumo: P2X7 receptors are involved with retinal new born neurons cell death (Anccasi et al. Purinergic Signal. 9(1):15-29, 2013). CB1 and CB2 receptors are important for a wide range of physiological phenomena in the brain, between them calcium currents, neurotransmission, neuroplasticity and neuroprotection (Schwitzer et al, Neural Plast. 2016; 2016). This work aims to investigate the actions of cannabinoids on the proliferation, death and calcium signal on chick retinal cells in culture treated with ATP and ADP. Cultures of retinal cells were obtained from the White-Leghorn chicken embryos at E7. Cells were seeded on culture dishes (3100 cells/mm2) and cultured for 24 hours at 37°C in a humidified atmosphere of 95% air/5% CO2. Immunofluorescence microscopy revels that both CB1 and CB2 receptors are expressed on nestine, β-tubulin III and 2M6 positive cells. In order to verify cell proliferation, incorporation of [3H]-thymidine assay was realized. Treatment with 0.5 µM WIN 55,212-2, a non selective CB1 and CB2 agonist, for 24 hours inhibited ~ 84.14% (n=5) of ATP-induced cell proliferation. In the same way, 50 µM URB 602, a MAGL inhibitor, an enzyme that hydrolyzes 2-arachidonoylglicerol, inhibited ~ 75% (n=03) of ADP-induced cell proliferation. To evaluate cell viability, cultures in E7C1 were treated with increasing concentrations of WIN 55.212-2 (0.5; 1.0 and 5.0 µM) for 24 hours and submitted to the cell viability assay (MTT). WIN 55,212-2 reduced cell viability. Cell death induced by WIN 55,212-2 was completely reverted by 1 µM AM251 and 1µM AM630, CB1 and CB2 antagonist receptor, respectively. Using 5 mM fura-2 as calcium probe, the addition of 50 mM KCl induced ~77% of calcium increase only in neurons, while 1 mM ATP has no effect. However, KCl was not able to increase the calcium signal in cultures treated with 0.5 µM WIN 55,212-2 24h, while 1 mM ATP induced ~37.5% of calcium increase only in Müller glial cells. At least 2600 cells were analyzed (n = 3). Finally, cultures in E7C1 were treated with 100 nM A438079, a selective antagonist of P2X7 receptors, plus 1 µM WIN 55,212-2 for 24 hours, and submitted to the cell viability assay (MTT). A438079 completely inhibited the cell death induced by WIN 55,212-2. These data together suggest that cannabinoids, through CB1 and CB2 receptors, inhibits ATP/ADP-induced cell proliferation, induce Müller glial cell differentiation and P2X7 dependent cell death.

Código: 76449 - EXPERIMENTAL ISCHEMIA/REPERFUSION MODEL IMPAIRS ENDOCANNABINOID SIGNALING AND NA+/K+ ATPASE EXPRESSION AND ACTIVITY IN KIDNEY PROXIMAL TUBULE CELLS

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Resumo: LLC-PK1 cells, an immortalized epithelial cell line derived from pig renal proximal tubules, express all the major players of the endocannabinoid system (ECS) such as CB1, CB2 and TRPV1 receptors, as well as the main enzymes involved in the biosynthesis and degradation of the major endocannabinoids named 2-arachidonoylglycerol, 2-AG and anandamide, AEA. Here we investigated whether the damages caused by ischemic insults either in vitro using LLC-PK1 cells exposed to antimycin A (an inductor of ATP-depletion) or in vivo using Wistar rats in a classic renal ischemia and reperfusion (IR) protocol, lead to changes in AEA and 2-AG levels, as well as altered expression of genes from the main enzymes involved in the regulation of the ECS. Our data show that the mRNA levels of the CB1 receptor gene were downregulated, while the transcript levels of monoacylglycerol lipase (MAGL), the main 2-AG degradative enzyme, were upregulated in LLC-PK1 cells after IR model. Accordingly, IR was accompanied by a significant reduction in the levels of 2-AG and AEA, as well as of the two endocannabinoid related molecules, oleoylethanolamide (OEA) and palmitoylethanolamide (PEA) in LLC-PK1 cells. In kidney cortex homogenates, only AEA levels were significantly decreased. In addition, we found that in both the in vitro and in vivo model IR caused a reduction in the expression and activity of the Na+/K+ ATPase. These changes were reversed by the CB1/CB2 agonist WIN55,212, in a CB1-receptor dependent manner in the in vitro and in vivo IR model. In conclusion, the ECS and Na+/K+ ATPase are down-regulated following IR in LLC-PK1 cells and rat kidney. We suggest that CB1 agonists might represent a potential strategy to reverse the consequences of IR injury in kidney tissues.

Código: 77602 - EFFECTS OF CB1 AND CB2 AGONISTS IN THE PROTEOME OF A HUMAN OLIGODENDROCYTE CULTURE

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Resumo: Background: The endocannabinoid system seems to play an important role in glial cells regulation, especially associated to differentiation and neuronal survival. Specifically, cannabinoids affect the function of oligodendrocytes (OLDs) that are responsible for myelination in the central nervous system. Studies have shown that cannabinoid treatment increased proliferation and maturation of OLDs precursor cells [1,2], suggesting a potential effect on demyelination processes. However, the molecular pathways involved are still not fully understood. Aim: Analyzing the effect of cannabinoids agonists ACEA (CB1 agonist) and HU308 (CB2 agonist) on the proteome of human OLDs in culture, in order to identify proteins differentially expressed by these treatments as well biochemical pathways and biological systems involved. Methods: OLDs (MO3.13) were treated with 1µL of ACEA or HU308 for 8 hours. Next, cells were harvested, proteins were extracted and peptides generated by trypsin digestion. Peptides were analyzed using a large-scale proteomic tool, which consists of two-dimensional liquid chromatography coupled to mass spectrometry. Proteins were identified, quantified, and evaluated in silico systems biology tools such as STRING, DAVID and Reactome. Results: For both treatments, we indentified 2976 proteins. ACEA regulated the expression of 132 proteins, being 38 upregulated and 94 downregulated. These were mostly involved in the cellular transport, mRNA metabolic processes, RNA binding, metabolism of RNA, cell cycle and signal transduction. Curiously, treatment with HU308, affected only 29 proteins, being 16 upregulated and 13 downregulated, mainly involved in the function of RNA binding, cell cycle and extracellular exosome. Conclusion: Combining in vitro models with proteomic analysis is analternative tool to elucidate molecular pathways of involved in the CB1 or CB2 activation. Interestingly, both drugs affected cell cycle, which is in line with the fact that activation of cannabinoid receptors play role in proliferation and differentiation processes. Finally, these preliminary results can bring a deeper understanding of the cannabinoid function in OLDs. Reference: 1. Molina-Holgado E. et al. Journal of Neuroscience. 2002, 22(22), 9742-9753 2. Gomez O et al. British journal of pharmacology. 2011, 163(7), 1520-1532 Acknowledgement: FAPESP (grant 2018/03673-0) and SAE/UNICAMP (01-P-55/2018)

Código: 77585 - ROLE OF ENDOCANNABINOID SYSTEM IN ARIPIPRAZOLE-INDUCED PERIPHERAL ANTINOCICEPTION

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Resumo: Introduction: Aripiprazole has a peripheral analgesic component; however, the mechanism involved in this effect is not fully established. Therefore, the aim was to obtain pharmacological evidences for the involvement of cannabinoid system in the peripheral antinociceptive effect induced by aripiprazole. Methods: To induce hyperalgesia, mice paws were treated with intraplantar prostaglandin E2 (PGE2, 2 μg) injection. Nociceptive thresholds were measured, using the mice paw pressure test. All drugs were given locally into the right hindpaw of Swiss male mice weighing 30-35 g, with n = 4 animals per group. Results: Aripiprazole induced an antinociceptive effect in a dose-dependent manner and the highest dose was (100 μg/paw). This dose was blocked by CB1 and CB2 cannabinoid receptor antagonists AM251 (40, 80 and 160 μg/paw) and AM630 (100, 200 and 400 μg/paw), respectively. Administration of fatty acid amide hydrolase inhibitor, MAFP (0.5 μg/paw) and monoacylglycerol lipase inhibitor, JZL184 (3.8 μg/paw), was able to potentiate the peripheral antinociception effect induced by aripiprazole (25 μg/paw). Moreover, the same effect was observed with the anandamide uptake inhibitor, VDM11 (2.5 μg/paw). Conclusion: The results suggest that aripiprazole induces peripheral antinociceptive effect through cannabinoid system activation. Financial support and acknowledgments: CNPq (Nº 448283/2014-0), FAPEMIG and CAPES. Research approval by the Committee for Ethics in Animal Experimentation (CEUA, UFMG) under the protocol number 109/2011.

Código: 77525 - CANNABINOID-INDUCED PROTEOMIC CHANGES IN A HUMAN OLIGODENDROCYTE CULTURE

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Resumo: Background: Several studies have shown the potential effects of cannabinoids in the glial cells, such as oligodendrocytes (OLDs), which are responsible for myelinating axons. Increasing interest in the understanding of the dysfunction of OLDs and potential drugs (i.e. cannabinoids) to prevent white matter deficits have been observed. Studies have shown the role of cannabidiol (CBD) and CB1/CB2 agonists in proliferation, survival, differentiation of OLDs. However, mechanisms involved in these functions are not fully understood. Aim: Investigating pathways and biological processes modulated by WIN55,212-2 (WIN55) and CBD on the human oligodendrocyte culture (MO3.13). Methods: We evaluated the proteome of MO3.13 cells treated with 1µl of WIN55 or CBD for 8h. Proteins were extracted, digested, and processed using a state-of-the-art LC-MS/MS system. Quantitative proteomics was employed in a label-free fashion. Differentially expressed proteins between the cannabinoids and vehicle were analyzed using in silico systems biology tools (String, Reactome and David Database). Results/Discussion: We identified and quantified 2976 and 2295 proteins in WIN55 and CBD treated cells respectively. We found that WIN55 affected the expression of 170 proteins (68 upregulated and 102 downregulated) and CBD modulated the expression of 71 proteins (29 upregulated and 42 downregulated). Proteins modulated by CBD are involved mainly in protein targeting, translational processes, glycolysis, intracellular protein transport, and mRNA metabolic process. WIN55 affected mRNA metabolic process, SRP-dependent cotranslational protein targeting to membrane, nucleic acid metabolic process, cytoplasmic transport, translational processes, and amide biosynthetic process. Although we observed common pathways in the WIN55 and CBD treatments, some of the modulated pathways were drug-specific. For instance, protein heterodimerization activity, lamellipodium, and NIK/NF-kappaB for WIN55-treatment, and mitochondrion for cells treated with CBD. Conclusion. Although preliminary, these results may initiate future hypothesis-driven studies to reveal the mechanisms and pathways involved with WIN55 and CBD effects on OLDs and possible implications for demyelinating disorders. Acknowledgement: FAPESP (grants 2017/18242-1and 2018/03673-

Código: 77605 - CB1 AND CB2 RECEPTORS: WHAT'S THE ROLE OF THE ENDOCANNABINOID SYSTEM IN AUTISM SPECTRUM DISORDERS?

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Resumo: The endocannabinoid (EC) system is composed by arachidonic acid derived molecules such as N-arachidonoylethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG), their cannabinoid receptors (CB1 and CB2) and the enzymes responsible for EC degradation which are N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) and fatty acid amide hydrolase (FAAH), both degrading AEA, and diacylglycerol lipase enzyme (DAG), responsible for 2-AG degradation. CB1 receptors are expressed in central and peripheral nervous system, mostly in cerebellum, hippocampus and the basal ganglia, while the CB2 receptors are restricted to immune system cells. Both of those systems have showed to be involved in Autism Spectrum Disorders (ASD) pathophysiology. According to American Psychiatry Association, ASD is a group of neurodevelopmental disorders characterized by persistent social communication and interaction impairments. Patients present altered phosphorylation of CB1 receptors, which reduced NAPE-PLD enzyme and consequently reduced AEA, a possible explanation for social symptoms. ASD is associated as well with immune system dysregulation. CB2 is increased in peripheral blood mononuclear cells, enhancing Th1 and Th2 response and resulting in an imbalance of immunoglobulin levels, increase in cytokines levels and disruption of the immune system. Translational researches involving AEA hydrolysis inhibitors, CB1 receptor agonists and FAAH inhibitors show prominent results in increasing modulation of CB1 receptors and thus improving social symptoms. Those findings indicate that endocannabinoid system should be considered as target option for autism pharmacological therapy.

Tema: Pesquisa em animais sobre aplicações medicinais de canabinoides

Código: 77598 - CANNABIDIOL REDUCES MORTALITY, RECRUITMENT OF INFLAMMATORY CELLS AND INTESTINAL INJURY IN MURINE GRAFT-VERSUS-HOST DISEASE

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Resumo: Graft versus host disease (GVHD) is an illness secondary to allogeneic bone marrow transplant, that leads to a generalized inflammation in the host, causing damage to several organs. Therefore Cannabidiol (CBD), a cannabinoid known to modulate inflammatory response, with no psychotropic effect, emerges as a possible treatment to GVHD. Objectives: This study evaluates the effect of CBD treatment in the inflammatory response of mice submitted to experimental GVHD. Methods: GVHD was induced in Balb/c mice by the transplant of 1x10^7 bone marrow cells and 3x10^7 splenocytes from C57BL/6 mice. GVHD-mice were treated with CBD (30 mg/Kg) every 24h, from the day of disease induction and in the following 15 days. After transplant, mortality was assessed daily. Inflammatory response was evaluated in the 6th day after GVHD induction in the intestine and liver. Histopathological analysis, quantification of cytokines/chemokines (ELISA) and flow cytometry were performed. Results and Discussion: CBD 30mg/Kg was able to reduce intestinal injury, assessed by histopathological score. Levels of TNF-α, IFN-γ, CCL2 and CCL3 were also reduced, corroborating with flow cytometry, in which CBD did not reduce the number of lymphocytes, except in FoXP3+ population, with displayed a increase when compared to the control group. These results elucidate why CBD did not reduce GVHD s anti-tumoral effect (GVL), but still protects the host against GVHD inflammation. Conclusion: CBD treatment reduced mortality of GVHD mice, decreasing intestinal inflammation, injury and increasing FoxP3+. Therefore, CBD is a potential treatment for GVHD. More research is needed in order to elucidate CBDs mechanisms.

Código: 78132 - CANNABIS-OIL AS ADJUNCTIVE TREATMENT FOR INTERVERTEBRAL DISC DISEASE (IVDD) WITH PARAPLEGIA IN A FRENCH BULLDOG: A CASE-REPORT

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Resumo: A six year old spayed female french bulldog, named ‘P‘, was adopted by ‘ O with known history of injury resulting in Intervertebral Disc Disease (IVDD) - TL (T12) hemivertebrae and kyphosis (scoliosis), leading to hindlimb paraplegia with deep pain sensation on pelvic limbs. Initial exam was performed on February 5th, 2018. The chronic spinal injury led to extremely hypertonic muscles of the shoulder girdle with bilateral trigger points throughout several muscle groups, hyperactive reflex with hyperesthesia to superficial digital palpation and atrophy of hindlimb muscles with spasticity inhibiting normal flexion/extension. Prior to initial exam, P has received prednisone, ondansentron, cephalexin, enrofloxacin, carprofen with no improvement in P s condition or life quality. P then transitioned to an integrative modality therapy of massage, low level laser therapy, and acupuncture. Until March, P had only minor improvements in hyperesthesia and spasticity in response to integrative modality therapy (video 1). The pace of progression was restricted by P s degree of hyperesthesia as any attempt to progress to rehabilitation exercise, deeper massage or more advanced acupuncture techniques resulted in 8-12 h of muscle soreness, lethargy and mental exhaustion. On April 17th, O initiated Cannabis therapy with a 4:1 CBD:THC ratio (8 mg CBD : 2 mg THC / 1 ml) isolate in an MCT oil base, target dose of 0.5 ml, and weekly integrative therapy. Immediate and significant improvements were accomplished in hyperesthesia, ability to progress in massage and acupuncture techniques with absence of muscle soreness or lethargy. O reported increased wellbeing of P so rehabilitation exercises were added. One month into cannabinoid therapy, P exhibited impressive improvement on spasticity and was able to sit and stand on her own (video 2). By September P was able to sustain her own body on the hindlimbs (video 3). The analgesic and anti-inflammatory proprieties of CBD and THC may have contributed to the progress seen here. Cannabinoids are also known for maintaining bone remodelling at balance, thus enhancing IVDD treatment and quality of life. The results shown here supports the ideia that cannabinoids can be useful in conditions such as IVDD and pave the way for alternative non-toxic management with Cannabis-based medicine in contrast to glucocorticoids and/or nonsteroidal anti-inflammatory drugs both typical potent inducers of gastrointestinal bleeding and ulcers in dogs.

Código: 77588 - ANXIOLYTIC AND ANALGESIC EFFECT: THE SYNERGY OF CANNABIDIOL IN BENEFIT OF THE CHRONIC PAIN, ON THE CCI MODEL IN RATS

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Resumo: Chronic pain is often accompanied by emotional and cognitive disorders. These dysfunctional changes or imbalance aversive/motivational circuits probably contribute to the challenges of treating neuropathic pain. Considering the neurochemistry of nociceptive modulation, the cannabinoid system is an important endogenous system participating in the circuitry painful sensitivity. In this perspective, the cannabidiol (CBD) is considered to be a promising strategy for the treatment of neuropathic pain. Our study aimed to evaluate the systemic effect of CBD (3 days) on rats submitted to sciatic nerve constriction (CCI) and nociceptive tests (TN). For this study were used 30 rats (220 g) Wistar (CEUA FORP-USP nº 2018.1.103.58.5). The animals were submitted to surgical procedure (CCI or false operated/SHAM) on day zero, and the development of neuropathy was accompanied during 3 weeks by nociceptive tests (von Frey, hot plate and acetone). On the 24th day, the animals were submitted to the open field test and under CBD. Nociceptive tests were performed on the 25th day, after 3 days treatment with CBD. The two-way ANOVA test was used, followed by the Bonferroni test, $p < 0.05$. The results showed that sub-chronic treatment with doses of 3 and 10 mg/kg i.p. obtained anesthetic effect of CBD in nociceptive tests, that evaluated the sensory components-discriminating painful sensitivity: (i) von Frey ($F (5, 20) = 37.9$; $P < 0.0001$), (ii) acetone ($F (5, 20) = 142$; $P < 0.0001$) and (iii) hot plate ($F (5, 20) = 27$; $P < 0.0001$). Also in the open field test both doses showed modulation of the behavior of the anxiolytic type ($F (2, 24) = 3.53$; $P = 0.0455$) CCI groups and treated with CBD, compared with other groups (NAIVE, Vehicle and SHAM treated with CBD). This preliminary result corroborates with the literature on the effects of painkillers and anti-anxiety drugs CBD, and that this combination offers favorable prospects for better treatment of neuropathic pain. FAPESP (2018/06877-5); CAPES-PROEX, CNPq.

Código: 77604 - HEMOPRESSIN PEPTIDE FRAGMENT DECREASES THE EPILEPSY SYMPTOMS IN ZEBRAFISH AND MICE MODELS

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Resumo: The World Health Organization estimates that approximately 50 million people around the world suffer from epilepsy, neurological disorder that is characterized by recurrent seizures and memory loss, and it is estimated that one-third of patients do not respond to the available treatments, stimulating the search for more effective treatments. In the 19th century, an anticonvulsant effect was observed for Cannabis sativa, and more recently, similar effects were reported using cannabinoid receptor 1 (CB1) agonists that reduces the intensity and frequency of seizures. Our group characterized hemopressin (Hp) as the first peptide with CB1 pharmacological inverse agonist activity. Here, we investigate the therapeutic potential of an Hp shorter peptide fragment (sHp) in both zebrafish (Danio rerio) and C57BL/6 mice model of epilepsy, respectively, induced by pentylenetetrazole (PTZ) and pilocarpine. Adult zebrafish (n=20) were divided into two groups: 1) control, treated solely with PTZ (11 mM for 20 min) and 2) experimental, treated with sHp (10 µM for 10 min) and then with PTZ (11 mM for 20 min). Behavior footage was recorded and manually analyzed showing a significant decrease ($p<0.05$) in the erratic movements, number of spasms and sinking in the animals treated with the sHp. The epileptic behavior induced by PTZ was reduced while not completed ceased by sHp. In mice, sHP was administrated orally (500 µg/Kg) and increase ($p<0.002$) the period for the first epileptic seizure compared to control saline or cannabidiol (30 mg/kg, i.p.). A reduction in mice death was also significantly reduced following sHp treatment. These data suggest that sHp should be further investigated for the treatment of epileptic seizures and other neurologic diseases involving the endocannabinoid system. Financial support: FAPESP, CNPq, CAPES, Remer, Villaça and Nogueira and Proteimax Biotechnology LTDA.

Código: 77530 - CANNABIDIOL PRESENTS ANTICONVULSANT ACTIVITY IN A CHRONIC PROTOCOL OF EPILEPTIC SEIZURES

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Resumo: Epilepsies are neurological disorders characterized by the presence of epileptic seizures. The Wistar Audiogenic Rat (WAR) is a rodent strain selected in the early 1990s in which animals are capable of developing epileptic seizures in response to intense sound (110 dB) stimulation (called audiogenic seizures). The initially midbrain-dependent seizures, give rise to forebrain-dependent seizures through a process called limbic recruitment along the chronic protocol of audiogenic seizures (audiogenic kindling, AuK). Cannabidiol (CBD) is a prominent compound present in Cannabis plants and has been implicated in seizure treatment in both humans and animal models. However, little is known about CBD effects on chronic protocols of epilepsies. Thus, the aim of this study was to verify the potential CBD anticonvulsant and antiepileptogenic effects in a chronic protocol of epileptic seizures. WARs and Wistars (control strain) were submitted to AuK protocol (20 acoustic stimulations, twice a day). Animals were placed in an acrylic box and sound was applied for one minute, or until the development of tonic seizures. CBD (25 mg/kg; i.p.) treatment was initiated 24h. before the first stimulus and was maintained along the AuK protocol CBD was administered 1h before each acoustic stimulation (two times/day). Animal behaviour was analysed for until three minutes (min.): 1 min. before, 1 min. during stimulus (or until tonic seizures), and 1 min. after stimulus. After the 20º stimulus, animal were divided into two groups: (1) continuous CBD treatment and (2) interrupted CBD treatment, and two days after the 20º stimulus, animals were submitted to a rebound stimulation. Chronic CBD pre-treatment was capable of reducing brainstem seizure index ($p<0,05$) and prevented limbic ($p<0,05$) seizures. No WAR with continuous CBD treatment presented limbic seizures on 21º stimulus, whereas 20% of WARs with interrupted CBD treatment exhibited limbic seizures on the rebound stimulus. No Wistar presented any type of seizure, confirming the specificity of acoustic stimulations to generate seizures only in WARs.CBD was capable of reducing brainstem seizure severity and prevented limbic recruitment. Additionally, these findings suggested that the continuous CBD treatment is important to protect animals from future limbic seizures. Acknowledgements: INCT-Translational Medicine, FAPESP, CAPES, CNPq, FAEPA.

Tema: Pesquisa em humanos sobre aplicações medicinais de canabinoides

Código: 77601 - SAFETY AND TOLERABILITY OF CANNABIDIOL AS A TREATMENT FOR BIPOLAR DEPRESSION: REPORT OF PRELIMINARY RESULTS.

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Resumo: Introduction: Given the overall lack of effective treatments for bipolar depression and the burden of illness associated with depressive symptoms, the validation of new treatment options is highly needed. In this context, the endocannabinoids system stands out as an important treatment target in bipolar disorder and a pathway for new molecules discovery. The endocannabinoids system consists of endogenous ligands and receptors proposed to be involved in neuroimmune functions, in psychosis and in mood and related disorders. Cannabidiol (CBD) is a cannabinoid derived from Cannabis sativa with clinical and pre-clinical evidences that suggest a potential role to treat neurologic, inflammatory and psychiatric conditions. CBD acts on endocannabinoids receptors; regulates glutamatergic receptors; inhibits the intracellular degradation of the endocannabinoid anandamide and indirectly enhances its signaling. CBD showed safety and tolerable profile in previous humans studies. Objective: We aim to investigate the efficacy, safety and tolerability of cannabidiol 300mg/day as a treatment of bipolar depression. Methods: A double blind, randomized, placebo-controlled trial of the use of cannabidiol as an adjunctive therapy to mood stabilizers in bipolar depression. Fifty participants will receive 01 capsule of cannabidiol 150mg per day and fifty will receive 01 capsule of placebo per day in an RCT fashion for a period of 12 week. After 6 weeks of trials, those participants who do not meet the criteria to response to treatment will receive 02 capsules per day until the endpoint (week 12). All patients will remain in treatment as usual for the duration of trial. Patients will be assessed at baseline using the MINI. The affective symptoms will be evaluated through Montgomery-Åsberg Depression Rating Scale and Young Mania Rating Scale. The evaluation of side effects will be according Udvalg for Kliniske Undersogelser side effects rating scale. Results: All patients included to date maintained treatment as planned and there were no withdrawals. There were no psychotic episodes induced as well as no manic switch. In addition, there were no severe side effects associated to the intervention. Conclusion: We conclude from these preliminary results that CBD is a safe and tolerable treatment for bipolar disorder, which is in accordance with other studies in other illnesses. However, it is not possible to draw definitive conclusions since the study is still ongoing.

Tema: Pesquisa em humanos sobre aplicações medicinais de canabinoides

Código: 78123 - FARMACANNABIS: EFFECTIVENESS OF NEUROLOGICAL DISORDERS TREATMENT OF PEDIATRIC AND ADOLESCENT PATIENTS WITH CANNABIS EXTRACTS - PRELIMINARY EVALUATION

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Resumo: Introduction: The therapeutic use of Cannabis extracts (CE) has been regulated in several countries. This study monitors patients under 18 years old with drug resistant epilepsy. However, the effectiveness and safety profile of CE and if therapeutic responses are related to the levels of cannabidiol (CBD) and tetrahydrocannabinol (THC) are unknown. Objectives: To describe the sociodemographic, clinical and pharmacotherapeutical profile of patients using EC analyzed by the Farmacannabis project. To investigate if the effects reported by the patients' parents are related of CBD and THC levels in CE. Method: Descriptive study, based on data sources: (i) self-administered questionnaires answered by the patients' parents; (ii) laboratory clinical parameters about patients' conditions; (iii) cannabinoids content in CE. The data were presented in absolute frequencies. Results: Patients (children/adolescent) with drug resistant epilepsy, with or without autism (n=15); females (n=7) and males (n=8); 14 from Southeast and 1 from Northeast Brazilian region; 5 patients are treated by the Public Health System, 5 by Private Health System. Women are the legal responsible for the patients, 7 with college degree and 5 with high school. Due to the lack of response, some results do not totalize 15. Before CE treatment, one patient did not use any anticonvulsant, and the others used up to 8. After starting use, 11 patients reduced to up to 5 anticonvulsants, 2 stopped using, and 3 used only the CBD for the crises control. Six patients used handmade CE, 8, the imported, and 1, both. After use, seizures episodes decreased in 7 patients. Conclusions: There is no established therapeutic protocol for medical use of cannabis, nor consolidated information on the sociodemographic, pharmacotherapeutic and clinical profile of the patients. The limitations identified were the lack of CE s standardization, the perception inconsistency of the clinical conditions by the parents and the difficulty of evaluating parameters effectiveness, due to different clinical situations, which reflect a multivariate scenario for this analysis. Reformulating the questionnaires and conducting face-to-face interviews with parents can minimize the limitations. The results of the study may contribute to the elaboration of guidelines and future health actions.

Código: 76681 - THE USE OF CANNABIDIOL AS AN ADDITIONAL TREATMENT FOR REFRACTORY EPILEPSY: A NEW PERSPECTIVE BASED ON A BRAZILIAN RETROSPECTIVE STUDY

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Resumo: Summary: Introduction: The treatment of refractory epilepsy in childhood is a challenge in medical practice. The authors describe their experience with the use of cannabidiol (CBD) in patients with seizures refractory to conventional drugs. Objective: The aim of the study was to assess the effects of treatment with CBD, as well as its tolerability and side effects. Methods: A descriptive, retrospective study was conducted on 24 patients between 1 and 45 years old diagnosed with uncontrolled epilepsy. Patients were already under treatment with the maximum therapeutic dosage of antiepileptic drugs when the additional treatment with CBD was proposed. Doses varied from 2.5mg/kg/day to 14mg/kg/day (with an average dosage of 6.3mg/kg/day). The data were collected through review of medical records and periodic medical visits. Results: A decrease of 80% of seizures rate were noted in 14 patients (58.2%), of which 10 patients (41.6%) had a reduction in seizures rate between 80-99% and 4 patients showed no seizure at all (16.6%). In those patients who were hospitalized for status epilepticus, there was a reduction in the number of hospitalizations and it was possible to reduce antiepileptic drugs polytherapy in about 70% of the cases. In addition, other neurological benefits were observed from the treatment with CBD, such as improvements in cognition, language, interaction, temper and motor development. There were no observable relevant adverse side effects or toxicological effects. On the other hand, in the analysis of our study, we found that 4 patients (16.6%) showed an increase in seizures number, of which 1 went through status epilepticus and, thus, had the CBD treatment removed (a patient with a structural focal epilepsy). Conclusion: Based on these results, it was concluded that CBD represents a promising alternative for epileptic patients that have shown unsatisfactory response to available conventional treatments.

Tema: Produção industrial de canabinoides, cannabis e seus derivados para fins medicinais

Código: 76628 - EDAFOCLIMATIC CONDITIONS FOR THE DEVELOPMENT OF CANNABIS SPP.: A REVIEW

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Resumo: This paper presents a review of the literature on edaphoclimatic conditions for the development of plants of the genus Cannabis. Data on the physiology of the plant and its relationship with the photoperiod, temperature and humidity, water demand and the cycle length in Growing Degree Days (GDD) and days after showning were reviewed. The ideal temperature for development is between 29ºC and 35ºC when CO2 is injected. For cultivation without CO2 injection, a temperature below 35ºC is recommended. The ideal average temperature is 21ºC, varying between 15ºC and 29ºC. Temperatures below 10ºC reduce plant growth. The minimum temperature for leaf appearance is 1ºC, and 2.5ºC for canopy establishment. The best physiological responses of the plants are obtained with relative air humidity between 40% and 65%. The best development occurs in crops that are located at approximately 400m altitude, and regions located above 1000m are not recommended. The duration of the cycle can vary from 110 to 120 days, and the floral initiation lasts from three weeks to one month. There are, also, authors that adopt average cycles of 150 days. Plants have a demand from 1900 to 2000 GDD between the period of germination and maturation (development) of the fibers, and between 2700 and 3000 GDD until complete seed development. The most vigorous growth goes from the twentieth day after germination to the sixth week, for an average cycle of 115 days. At this stage, the plant does not tolerate water deficit and until its end, it requires approximately 75% of the total water demanded during its entire cycle. During the flowering and grain production phase, the plant responds favorably to moderate water stress. It is estimated that the total water demand is around 400mm for an average cycle of 110 days. Other authors reported higher water consumption, varying between 445 and 805mm. The total crop evapotranspiration (ETc) recorded was 445 mm for a cycle of 120 days. There are not many restrictions on soil types except physical impediments to root growth and aeration. In most varieties of Cannabis spp. the phenological phase change is induced by the photoperiod. It takes between eight and twelve hours dark for flowering, according to the variety. The varieties of Cannabis ruderalis are an exception because reproduction is regulated by physiological maturation.

Código: 76629 - MODELING TO DETERMINE THE DURATION OF THE CYCLE, DATE OF PLANTATION AND HARVEST OF CANNABIS SPP.

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Resumo: The objective of this work was to develop an algorithm to estimate the dates of planting, flowering and harvest of Cannabis spp. The inputs of the model are the geographic location of the site, the monthly average temperature data, the growing degree days (GDD) in the vegetative and total period, and the basal temperature for the crop. The exits are the dates of planting (Xp), flowering (Xf) and harvest (Xc). Grain maturation was considered as the end of the cycle. The algorithm was developed in R. To calculate Xp, for the varieties of Cannabis spp. sensitive to the photoperiod, the reference date was the day of the year in which induction occurs at the beginning of flowering. As the minimum dark hours that induce this process can vary between 8 and 12 hours, depending on the variety, the value of 12 hours was used as the criterion for calculating Xf. Considering the necessity of GDD demanded during the vegetative phase, a regressive sum was taken, from Xf, to estimate Xp. To determine the date of harvest (Xc), from Xp a progressive sum of growing degree days was made until reaching the total thermal demand required for the variety to complete its cycle. In order to standardize the data of both hemispheres, as well as to frame the complete cycle within one agricultural year, the date from which the day begins to have more than 12 hours of light was adopted as "zero time" (To), beginning of the growing season. The calculation of day-degrees for the crop was done considering the average temperature of the day and the basal temperature of the plant. In order to determine the average daily temperature throughout the year, the data of the average monthly temperatures of the climatological normals were used. Due to the differences in altitude and latitude and, consequently, climatic conditions between the sites, the algorithm showed a variation in the cycle length of Cannabis spp., as well as dates of planting, beginning of flowering and harvesting. For cultivars with accumulated 2700 growing degree days demand, in the city of Cabrobó (PE) the cycle duration forecast is 170 days, while for Boa Vista (RR) the duration would be 155 days. This predictive model can help in making more assertive decisions regarding the cultivation of Cannabis spp. for medicinal and industrial purposes, when compared to the determination of the crop cycle based only on the number of days after sowing.

Código: 78124 - HARLE-TSU CANNABIS STRAIN: STUDIES OF RAW MATERIAL PREPARATION AND CANNABINOIDS SEPARATION BY SUPERCRITICAL FLUID EXTRACTION

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Resumo: Plants from Cannabis genus have more than 50 phytocannabinoids, the most well-know are cannabidiol (CBD), tetrahydrocanabinol (THC) and their acid forms, tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), besides other terpenoids compounds. In Brazil, the control of seizures with CBD rich extracts motivated the sanitary regulation of importation of Cannabis products registered in USA as food supplement, but didn't guarantee access and therapeutic quality. To improve the access to pharmaceutical products derived from Cannabis is essential to study the chemical profile of specimens cultivated in Brazil and the extractive processes for pharmaceutical active ingredient (PAI) production. Our goals were standardization raw material preparation and development the cannabinoids separation by supercritical fluid extraction (SFE). Harle-Tsu Cannabis strain (HT) specimen was cultivated indoor and after harvest the fresh flowers were separated from the steams and dry at 40ºC for up to 15 hours in a forced convection oven. Desiccation and cannabinoids content were evaluated. Dry flowers were homogenized by crushing and using in the next steps. The cannabinoids profile was analyzed by GC-MS and five cannabinoids quantified by HPLC-DAD. Decarboxylation technique was studied in triplicate for each condition of temperature (100°C up to 120°C) and time (1 up to 5 hours). The relation CBDA and CBD was used to evaluate the decarboxylation rate. Cannabinoids extraction by SFE was made in a Top Industries, Multi Solvent Lab, a fixed temperature and three different pressure values were tested in a pilot experiment and the optimal pressure based on recovery and organoleptic characteristic were selected. The optimal conditions were applied to vegetable specimen in replicates (four times) with varying amounts of raw material (between 10 and 24 grams). Vegetable specimen showed hemp profile, CBD:THC (10:1) with mean CBD content 7%. The condition 40°C for 15 hours was adequate for dry vegetable specimen and the conditions heating 5 hours at 110° and 120° showed CBDA/CBD decarboxilation rates 0.06 (94%) and 0.04 (95%), respectively. The method of cannabinoids separation by SFE shows recovery mean 86% and a gold yellow coloring resin was obtained. With 71 g of raw material from HT were produced 6.8 g of resin and 3.7 g of CBD. Brazil has technological potential to produce RM, PAI and Cannabis extracts with pharmaceutical quality.

Código: 78128 - HIGH PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR CANNABINOIDS QUANTIFICATION IN CANNABIS PRODUCTS FORMULATED IN OILY VEHICLES

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Resumo: Brazilian National Heath Surveillance Agency (ANVISA) authorized personal importation of CBD-rich Cannabis extracts for medicinal purpose in 2015. On the other hand, the cost of importing medical cannabis products is high and emerges the handmade products and clandestine market with products of unknown composition that are frequently used by children with serious neurological diseases. In order to monitor the Cannabis products used in medical treatments the objectives of this work were to develop and validate a High Performance Liquid Chromatography coupled to Photodiodo Array (HPLC-PDA) method for cannabinoids quantification in oily vehicles. The sample preparation was performed by dilution of the matrix with methanol:hexane (9:1 v/v) containing diazepam as internal standard and ultrasound extraction. Five cannabinoids (tetrahydrocannabinol-THC, tetrahydrocannabinolic acid-THCA, CBD, cannabidiolic acid-CBDA, cannabinol-CBN) was separate in reversed phase in a C18 column in gradient mode with methanol and ammonium formate buffer. The method was validated with blank matrix of mix oils (olive, coconut, and MCT oil) according to ANVISA guidelines and was applied to Cannabis products formulated in oily vehicles and resins donated by patients (N=111; 78 artisanal products and 33 imported CBD-rich extracts). The cannabinoids were separated in 21 min with good resolution. The calibration curve showed $r2 \geq 0.99$ for all analytes. The limit of detection was 0.01 for all analytes and the limits of quantification were 0.11 for THC, 0.13 for CBD and 0.12 for THCA, CBDA and CBN. The repeatability and intermediate precision values were within those established by ANVISA regulation. The method was selective for THC, THCA, CBD, CBDA and CBN in five types of oils and glycerin. The samples showed great variation in physical and organoleptic characteristics. The cannabinoids contents in artisanal Cannabis products showed high variance in composition and was identified THC-rich extracts (THC between 0.73 and 44.9 mg/mL for oily vehicles and 28.3 and 348.5 mg/g for resins), CBD-rich extracts (CBD between 1.0 and 10.5 mg/mL) and extracts with traces of cannabinoids (THC $\leq$ 0.9 mg/mL and CBD $\leq$ 0.3 mg/mL). Imported CBD-rich extracts in oily vehicles and resins showed CBD concentration between 13.2 and 284.9 mg/mL and 105.0 and 189.3 mg/g, respectively. The national products were not compatible with imported products.

Código: 78126 - MICROBIOLOGICAL QUALITY ASSESSMENT OF CANNABIS: FROM PLANT TO MEDICINAL EXTRACT

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Resumo: The National Sanitary Surveillance Agency (ANVISA) of Brazil authorized the importation of Cannabis extracts in 2015 and rich CBD products has been used in medical treatment, especially by children with epilepsy. The ANVISA□s regulation does not guarantee the access and many responsible for patients are cultivating and producing their own extracts or acquiring in the unregulated market. As well as imported food supplements, these products do not have quality control required for medicines and the microbiological contamination is a risk in the treatment, for instance, infections and fever can trigger seizures. To minimize the risks of treatment patients are being accompanied by a university extension project and vegetable specimens and products from Cannabis are being analyzed. The microbiological quality was evaluated based on Brazilian Pharmacopoeia 5th edition □ second supplement (2017) with total count of aerobic bacteria and fungi, and pathogen research. The microbiological analysis were applied to Cannabis products (28 imported and 47 artisanal extracts, n=75) and 27 samples collected in three artisanal preparation observed by project, A, B at patient houses and C at university. Flowers, and dry extracts (called kief) and oil extracts, 9 samples and 3 replicates from artisanal preparations, showed different microbiological contamination profiles. The preparation A shows absence of bacteria in all samples and high number of fungi (1,0 x 106 CFU/g) with presence of Aspergillus flavus, Aspergillus parasiticus and Aspergillus brasiliensis; B shows high number of bacteria in the flower and dry extract (1,2 x 105 CFU/g): Escherichia coli, Staphylococcus aureus, Enterobacter cloacae and Enterobacter gergoviae, besides the presence of fungi in the 3 stages (1,0 x 105 CFU/g): Aspergillus flavus and Aspergillus parasiticus; and C shows presence of bacteria in flower and dry extract (1,0 x 103 CFU/g): Enterobacter cloacae and Cedaceae davisae, and absence of fungi at all stages (flower, dry and oily extract). According Brazilian Pharmacopoeia, A and B preparation presented quality deviations and C presented microbial load within the recommended limits. Other Cannabis products showed mibrobiological contamination in 17.9% and 19.1% of imported and artisanal samples, respectively. Good practices of cultivation, harvesting and production should be adopted and the conditions of use and storage of the products should be improved to avoid microbial contamination.

Código: 78125 - MORPHOLOGICAL CHARACTERIZATION OF THREE VARIETIES OF CANNABIS CULTIVATED BY PATIENTS IN RIO DE JANEIRO, BRAZIL

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Resumo: The history of plants of the genus Cannabis is closely linked to the human evolution. Cultivation techniques influenced a great number of varieties and cultivars. Depends on fiber quality and chemical composition, varieties are used in textile market or recreational and medicinal market. Although the medicinal use of Cannabis in Brazil is increasing, access to quality products depends on the standardization of raw material. Many patients are cultivating, they start with imported seeds from bank seeds and then reproduced plants by cutting and replanted again (cloning). To describe specimens cultivated by patients will be a means of prospecting varieties that may be standardized for pharmaceutical production. Therefore the objective of this work was to present the morphological characteristics of three varieties of Cannabis cultivated by patient attended by Farmacannabis project, a university extension project that monitors cannabis treatments and provides pharmaceutical support in the production of cannabis extracts. The varieties Harle-Tsu, Painkiller and Mazar were documented with the use of digital cameras and dissected using a stereomicroscope and manual magnifying glass. The parameters evaluated for comparison were: (1) plant architecture, (2) foliar and leaf morphology, (3) morphology and dressing of female bracts and flowers, (4) arrangement of female flowers in inflorescences. The morphology of the regular leaves of the Harle-Tsu and Painkiller varieties are quite similar, while the basal lobes of the Mazar leaves are very short, making them distinct from the others. The leaves near the base of the Harle-Tsu inflorescences are covered by secretory trichomes, while those of Painkiller and Mazar show sparse distribution of these trichomes. Harle-Tsu and Mazar bracts are completely covered by secretory trichomes. While Harle-Tsu and Mazar bracts are long, Mazar bracts are very short. Although Harle-Tsu and Painkiller flowers are similar, Mazar flowers are arranged in groups of four in the axes of the inflorescences. The specimens showed different morphological characteristics and increasing the studied population will be possible to establish botanical identification parameters for the quality control of raw material.