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AARHUS UNIVERSITY

Behavioural and molecular effects induced by Cannabidiol in animal models of depression

Efeitos comportamentais e moleculares induzidos pelo Canabidiol em modelos animais de depressão

GABRIELA PANDINI SILOTE

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Doctoral thesis presented to the Graduate Program of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirão Preto (University of São Paulo, Brazil) and Faculty of Health (Aarhus University, Denmark) to obtain the double PhD degree.

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Supervisor: Prof. Sâmia R. L. Joca Wegener

Co-supervisor: Prof. Gregers Wegener

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SUMMARY

SILOTE, G. P. Behavioural and molecular effects induced by Cannabidiol in animal models of depression. 2021. 296f. Thesis (Doctoral). School of Pharmaceutical Sciences of Ribeirão Preto – University of São Paulo, Ribeirão Preto, 2021.

Introduction: Major depressive disorder (MDD) is a chronic and severe psychiatric disorder, which is more prevalent in women. Cannabidiol (CBD) is a compound isolated from the plant Cannabis sativa L., which produces an antidepressant-like effect in animal models. However, only a few studies investigated the effect of such compounds in females, and it is unclear the influence of gender on CBD effects. The antidepressant effect induced by CBD involves the activation of BDNF-TrkB-mTOR signaling in the hippocampus and prefrontal cortex, an effect also demonstrated for ketamine. **Aims:** The present study aimed to: investigate the influence of strain and gender of mice in CBD antidepressant-like effects (Study 1A); investigate CBD effects in male and female FSL rats, tested at different time points (Study 1B); investigate the molecular mechanisms involved in CBD and ketamine antidepressant effect in the prefrontal cortex (PFC) and hippocampus of FSL rats (Study 2). **Methods:** Study 1: Adult male and female Swiss and C57BL/6 mice and adult male and female FSL and Flinders Resistant Line (FRL) rats were used. Mice received the systemic injection with CBD (3, 10, and 30 mg/kg, i.p.), imipramine (IMIP; 20 mg/kg, i.p.) or vehicle 30 minutes before the elevated plus maze (EPM) and tail suspension test (TST). FSL rats were treated with CBD (10, 30, and 60 mg/kg, i.p.), S-ketamine (15 mg/kg, i.p.) or vehicle, 1 or 2 hours before the open field test (OFT) and forced swim test (FST). An independent experiment was conducted with female FSL rats that received S-ketamine (10, 15, and 20 mg/kg, i.p.) or vehicle 1h before OFT and FST to select ketamine effective dose. Study 2: Adult male FSL and FRL rats received intraperitoneal treatment with CBD (30 mg /kg), S-Ketamine (15 mg/kg) or vehicle (Saline and Tween 80 3%), 1h before behavioral tests in the OFT (5 min) and FST (5 min). Immediately after the behavioral tests, the PFC, dorsal hippocampus (DH), and ventral (VH) were dissected. To investigate the molecular mechanisms involved in the antidepressant-type effect induced by CBD and S-Ketamine, the analysis of gene expression (Fluidigm) and synaptosome protein levels by WB were performed on PFC, DH, and VH for the glutamatergic, neurotrophic signaling and synaptic plasticity. **Results:** Study 1A: CBD produced an antidepressant-like effect in male, but not in female Swiss mice in the TST. Furthermore, CBD did not induce any significant effect in C57BL/6 mice, both males and females. Study 1B: Surprisingly, in FSL rats, CBD (30 mg/kg) induced a depressive-like effect in females 1 hour after the treatment, but an antidepressant-like effect after 2 hours. In males, CBD (30 mg/kg) produced an antidepressant-like effect 1 hour after the injection; no effect could be observed following 2 hours. Ketamine induced a significant antidepressant-like effect in female FSL rats submitted to FST 1 hour after the injection (15 and 20 mg/kg). Study 2: We replicated the behavioural results from Study 1B, the injection of CBD and ketamine reduced the immobility time in FSL rats exposed to FST, which reinforces our findings. There was no correlation between the CBD blood levels and the immobility exhibited in the FST. In the molecular analysis, the effect of CBD was associated with increased expression of the EAAT3, Nr2a, Nr2b, BDNF transcript in the PFC. In contrast, ketamine effect was associated with downregulation in VEGF and sortilin levels and increased protein levels of Nr2b, Nr2a and pGluR1 (S831) in the same region. However, in DH, CBD increased the levels of VEGF and Nr2b and decreased the expression of Sort1 and pGluR1 (S831), and ketamine reduced the expression of pGluR1 (S831) and increased the

levels of Nr2b protein. In VH, CBD reduced the expression of mGluR5 and pGluR1 (S831 and S845) and increased the expression of GluR2, and ketamine reduced the levels of pGluR1 (S831) in the same limbic region. **Conclusion:** Based on the present findings, we conclude that CBD effects can be influenced by species, strain, gender, and time of administration. The molecular mechanisms involved on CBD antidepressant-like effect involves the regulation of the neurotrophic and glutamatergic signaling pathway in the PFC, DH and VH. In contrast, the effect of ketamine seems to involve mainly the restoration of normal glutamatergic function in the limbic brain areas.

Keywords: Cannabidiol; S-ketamine; gender; FSL/FRL rats; mice; forced swim test; gene expression; synaptosome.

RESUMO

SILOTE, G. P. **Efeitos comportamentais e moleculares induzidos pelo Canabidiol em modelos animais de depressão.** 2021. 296f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2021.

Introdução: O transtorno depressivo maior (TDM) é um transtorno psiquiátrico crônico e grave, mais prevalente em mulheres. O canabidiol (CBD) é um composto isolado da planta *Cannabis sativa L.*, que produz um efeito antidepressivo em modelos animais. No entanto, apenas alguns estudos investigaram o efeito de tais compostos em fêmeas, e ainda não está claro sobre a influência do sexo nos efeitos do CBD. O efeito antidepressivo induzido pelo CBD envolve à ativação da via de sinalização do BDNF-TrkB-mTOR no hipocampo e no córtex pré-frontal (PFC), efeito também demonstrado para a ketamina. **Objetivos:** O presente estudo teve como objetivo: investigar a influência da linhagem e do sexo de camundongos no efeito tipo-antidepressivo do CBD (Estudo 1A); investigar os efeitos do CBD em ratos FSL machos e fêmeas, testados em diferentes momentos (Estudo 1B); investigar os mecanismos moleculares envolvidos no efeito antidepressivo do CBD e da ketamina no PFC e no hipocampo de ratos FSL (Estudo 2). **Métodos:** Estudo 1: Foram utilizados camundongos adultos machos e fêmeas das linhagens Swiss e C57BL/6 e ratos e ratas adultos FSL e Flinders Resistant Line (FRL). Os camundongos receberam a injeção sistêmica com CBD (3, 10 e 30 mg/kg, ip), imipramina (IMIP; 20 mg/kg, ip) ou veículo 30 minutos antes do labirinto em cruz elevado (EPM) e teste de suspensão da cauda (TST) Os ratos FSL foram tratados com CBD (10, 30 e 60 mg/kg, ip), S-ketamina (15 mg/kg, ip) ou veículo, 1 ou 2 horas antes do teste de campo aberto (OFT) e teste de natação forçada (FST). Um experimento independente foi conduzido com ratas FSL que receberam S-ketamina (10, 15 e 20 mg/kg, i.p.) ou veículo 1h antes de OFT e FST para selecionar a dose eficaz de ketamina. Estudo 2: Ratos adultos FSL e FRL receberam tratamento intraperitoneal com CBD (30 mg/kg), S-ketamina (15 mg/kg) ou veículo (solução salina e Tween 80 3%), 1h antes dos testes comportamentais no OFT (5 min) e FST (5 min). Imediatamente após os testes comportamentais, o PFC, o hipocampo dorsal (HD) e o ventral (VH) foram dissecados. Para investigar os mecanismos moleculares envolvidos no efeito do tipo antidepressivo induzido por CBD e S-ketamina, a análise da expressão gênica (Fluidigm) e dos níveis de proteína do sinaptossoma por WB foram realizadas no PFC, DH e VH para a sinalização glutamatérgica, neurotrófica e plasticidade sináptica. **Resultados:** Estudo 1A: o CBD produziu um efeito tipo-antidepressivo em camundongos Swiss machos, mas não em fêmeas no TST. Além disso, o CBD não induziu nenhum efeito significativo em camundongos C57BL / 6, tanto machos quanto fêmeas. Estudo 1B: Surpreendentemente, em ratas FSL, o CBD (30 mg/kg) induziu um efeito do tipo-depressivo 1 hora após o tratamento, mas efeito do tipo-antidepressivo após 2 horas. Nos ratos, o CBD (30 mg/kg) produziu um efeito tipo- antidepressivo 1 hora após a injeção; nenhum efeito pode foi observado após 2 horas. A ketamina induziu um efeito antidepressivo significativo em ratas FSL submetidas ao FST 1 hora após a injeção (15 e 20 mg/kg). Estudo 2: Nós replicamos os resultados comportamentais do Estudo 1B, a injeção de CBD e ketamina reduziram o tempo de imobilidade em ratos FSL expostos ao FST, o que reforça os nossos achados. Não houve correlação entre os níveis sanguíneos de CBD e a imobilidade exibida no FST. Na análise molecular, o efeito do CBD foi associado ao aumento da expressão do transcrito de EAAT3, Nr2a, Nr2b, BDNF no PFC. Em contraste, o efeito da ketamina foi associado a uma downregulation em VEGF e sortilina e aumento nos níveis protéicos de Nr2b, Nr2a e pGluR1 (S831) na mesma região. No entanto, no DH, o CBD

elevou os níveis de VEGF e Nr2b e diminuiu a expressão de Sort1 e pGluR1 (S831), e a ketamina reduziu a expressão de pGluR1 (S831) e aumentou os níveis de proteína Nr2b. No VH, o CBD reduziu a expressão de mGluR5 e pGluR1 (S831 e S845) e aumentou a expressão de GluR2, e a ketamina reduziu os níveis de pGluR1 (S831) na mesma região límbica. **Conclusão:** Com base nos presentes achados, concluímos que os efeitos do CBD podem ser influenciados pela espécie, linhagem, sexo e tempo de administração. No PFC, a análise molecular revelou que o CBD modula principalmente o BDNF e a via de sinalização glutamatérgica, enquanto a ketamina regula as moléculas associadas à neurotransmissão glutamatérgica, VEGF e vias de sinalização da sortilina. No entanto, para a DH, o CBD regula a Sortilina, VEGF, sistemas glutamatérgicos e ketamina regulados exclusivamente a neurotransmissão glutamatérgica.

Palavras-chave: Canabidiol; S-ketamina; gênero; Ratos FSL / FRL; teste de natação forçada; expressão gênica; sinaptossoma.

RESUMÉ

SILOTE, G. P. **Adfærdsmæssige og molekylære effekter induceret af Cannabidiol i dyremodeller for depression.** 2021. 296f. PhD afhandling. School of Pharmaceutical Sciences of Ribeirão Preto - University of São Paulo, Ribeirão Preto, 2021.

Indledning: Depression er en kronisk og alvorlig psykiatrisk lidelse, som er mere udbredt hos kvinder. Cannabidiol (CBD) er et kemisk stof isoleret fra planten *Cannabis sativa L*., som producerer en antidepressiv-lignende virkning i dyremodeller. Imidlertid har kun få studier undersøgt effekten af sådanne forbindelser hos kvinder, og det er uklart hvilken indflydelse køn har på den mulige effekt af CBD. Den antidepressive effekt induceret af CBD involverer aktivering af BDNF-TrkB-mTOR-signaleringskaskaden i hippocampus og præfrontale cortex, en effekt, der også er vist for ketamin. **Formål**: Dette studium havde til formål at: undersøge indflydelsen af stamme og køn hos mus på CBD antidepressiva-lignende effekter (Undersøgelse 1A); undersøge CBD-effekter hos FSL-hanrotter, testet på forskellige tidspunkter (Studie 1B); undersøge de molekylære mekanismer, der er involveret i effekten af CBD og ketamin antidepressiv-lignende effekter i præfrontale cortex (PFC) og hippocampus hos FSL rotter (Studie 2). **Metoder**: Undersøgelse 1: Voksne Swiss og C57BL/6-mus samt voksne FSL- og Flinders Resistant Line-rotter (begge køn) blev brugt. Mus modtog en systemiske injektion med CBD (3, 10 og 30 mg/kg, ip), imipramin (IMIP; 20 mg/kg, ip) eller vehikel 30 minutter før Elevated Plus Maze (EPM) og Tail Suspension Test (TST). FSL-rotter blev behandlet med CBD (10, 30 og 60 mg/kg, ip), S-ketamin (15 mg/kg, ip) eller vehikel 1 eller 2 timer før open field test (OFT) og Forced Swim Test (FST). Et uafhængigt eksperiment blev udført med FSL-hunrotter, der modtog S-ketamin (10, 15 og 20 mg / kg, i.p.) eller vehikel 1 time før OFT og FST, for derigennem at vælge effektiv ketamin dosis. Undersøgelse 2: Voksne FSL- og FRL-hanrotter fik intraperitoneal behandling med CBD (30 mg/kg), S-ketamin (15 mg/kg) eller vehikel (saltvand og Tween 80 3%), 1 time før adfærdstest i OFT (5 min) og FST (5 min). Umiddelbart efter adfærdstestene blev PFC, dorsal hippocampus (DH) og ventral (VH) dissekeret. For at undersøge de molekylære mekanismer, der er involveret i den antidepressiv-lignende effekt induceret af CBD og S-ketamin, blev der foretaget en analyse af genekspression (Fluidigm) og synaptosomprotein-niveauer ved hjælp af Western Blot på væv fra PFC, DH og VH. Proteiner og gener indenfor glutamaterg, neurotrofiske signalering og synaptisk plasticitet blev udvalgt. **Resultater**: Undersøgelse 1A: CBD producerede en antidepressiv-lignende virkning hos hanner, men ikke hos Swiss hunmus i TST. Endvidere inducerede CBD ikke nogen signifikant effekt i C57BL/6-mus, både hanner og hunner. Undersøgelse 1B: CBD (30 mg/kg) inducerede hos FSL-rotter en depressiv-lignende virkning i hunner 1 time efter behandlingen, men en antidepressiv-lignende virkning efter 2 timer. I hanner producerede CBD (30 mg/kg) en antidepressiv-lignende virkning 1 time efter injektionen; ingen virkning kunne observeres efter 2 timer. Ketamin inducerede en signifikant antidepressiv-lignende virkning hos FSL-hunrotter, i FST 1 time efter injektionen (15 og 20 mg/kg). Undersøgelse 2: Vi replikerede adfærdsmæssige resultater fra undersøgelse 1B, injektion af CBD og ketamin reducerede immobilitetstiden i FSL-rotter i FST. Der var ingen sammenhæng mellem CBD-blodniveauerne og immobiliteten i FST. I molekylæranalysen var effekten af CBD forbundet med øget ekspression af EAAT3,

Nr2a, Nr2b, BDNF-transkript i PFC. I modsætning hertil var ketamineffekten forbundet med nedregulering i VEGF- og sortilinniveauer og øgede proteinniveauer af Nr2b, Nr2a og pGluR1 (S831) i samme region. Imidlertid øgede CBD i DH niveauerne af VEGF og Nr2b og nedsatte ekspressionen af Sort1 og pGluR1 (S831), og ketamin reducerede ekspressionen af pGluR1 (S831) og øgede niveauerne af Nr2b-protein. I VH reducerede CBD ekspressionen af mGluR5 og pGluR1 (S831 og S845) og øgede ekspressionen af GluR2, og ketamin reducerede niveauerne af pGluR1 (S831) i samme limbiske region. **Konklusion**: Baseret på de nuværende fund konkluderer vi, at effekterne af CBD kan påvirkes af art, stamme, køn og administrationstidspunkt. De molekylære mekanismer, der er involveret i den antidepressiv-lignende virkning af CBD involverer regulering af den neurotrofiske og glutamatergiske signalvej i PFC, DH og VH. I modsætning hertil synes effekten af ketamin hovedsageligt at involvere glutamaterg funktion i de limbiske hjerneområder.

Nøgleord: Cannabidiol; S-ketamin; køn; FSL / FRL rotter; mus; tvungen svømmetest genekspression; synaptosom.

1 INTRODUCTION

1.1 Major Depressive Disorder (MDD)

1.1.1 Diagnosis and epidemiology

Major depressive disorder (MDD) is a mood disorder that affects 322 million people worldwide, according to the World Health Organization (WHO, 2017a, 2017b). The prevalence varies across the different countries, raging in between 3 to 6%. In Brazil, about 11 million people are affected by depression, corresponding to 5.8% of the population (WHO, 2017a). Unfortunately, depression is a severe, chronic, debilitating, and disabling psychiatric disorder, which significantly impact the social, physical, and occupational aspects of the life of affected individuals (KUEHNER, 2017; KYU et al., 2018; OTTE et al., 2016; WHO, 2017a). This results in several years lived with disability, and considerable global burden of diseases, making MDD one of the leading cause of disability worldwide (information published in January 2020 and accessed in September 2020: https://www.who.int/news-room/fact-sheets/detail/depression). MDD increases the risk of suicide and produces an enormous social and economic impact on society (WHO, 2017a). MDD is twice more prevalent in women than in men, but the mechanisms involved in gender differences are still unknown (OTTE et al., 2016; WHO, 2017a).

Given the subjectivity and complexity of the symptoms observed in depression, firm diagnostic criteria are necessary to guarantee the correct diagnosis. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders from the American Psychiatric Association (DSM-5, APA) established that MDD is defined by the presence of five or more symptoms, including one of the core symptoms, depressed mood or loss of interest (anhedonia), accompanied by other symptoms not related to other medical conditions for at least two weeks (APA, 2013). The current diagnostic criteria for MDD are described in Table 1.

Table 1. Diagnostic criteria for MDD disorder, according to DSM-5 (APA, 2013).

	Symptoms	Frequency
Core symptoms	1. Depressed mood (feels sad, empty, hopeless) and, in children and adolescents, irritable mood evidenced by subjective report or observation made by the others.	Most of the day, nearly every day
	2. Anhedonia (a reduction in interest or pleasure in the activities).	Most of the day, nearly every day
Other symptoms	3. Weight disturbances, considerable weight loss when not dieting, weight gain (more than 5% in one month), or increase or decrease appetite.	Nearly every day
	4. Insomnia or hypersomnia.	Nearly every day
	5. Psychomotor agitation or retardation .	Nearly every day
	6. Fatigue or loss of energy.	Nearly every day
	7. Feelings of worthlessness or excessive or inappropriate guilt.	Nearly every day
	8. Decreased ability to think or concentrate, or indecisiveness.	Nearly every day
	9. Thoughts of death (not just fear of dying), suicide ideation with or not a specific plan, or a suicide attempt or a detailed plan.	Recurrent

1.1.2 Etiology

The etiology of MDD is complex and multifactorial, and it results from the interactions between environmental factors (e.g. stress exposure), genetic/epigenetic factors, and personality traits (CASPI et al., 2003; KENDLER; GARDNER, 2016; OTTE et al., 2016). The stress from chemical, physical, or psychological origin triggers several physiological and behavioral responses to promote adaptation to the new internal or external demands. However, prolonged and intense exposure to stress can lead to excessive exposure to mediators of the stress response and can potentially impair adaptation to the aversive environment, allowing the development of physical and emotional disorders, such as depression (KENDLER; GARDNER, 2016; KENDLER; KARKOWSKI; PRESCOTT, 1999; KENDLER et al., 1995; MAHAR et al., 2014; POST, 1992; RAVINDRAN et al., 1995). In line with that, it has been suggested that exposure to a stressful event may precipitate the first depressive episode in 60% of cases, with less importance of the environmental factor for the

following episodes, thus suggesting that the depressive episode itself can sensitize the organism for the development of new episodes (POST, 1992). Different stressful life events in adulthood, such as unemployment, exposure to violence, financial insecurity, chronic health problems, divorce, and grief can increase the risk of MDD development, (KENDLER; GARDNER, 2016; KENDLER et al., 1995; KESSLER, 1997). Moreover, exposure to traumatic events in childhood (psychological neglect, physical and sexual violence, exposure to domestic violence, or separation from the parents) can also increase the likelihood of developing MDD later in life (DUBE et al., 2001; KESSLER et al., 2010; KIM et al., 2020; STARR et al., 2020; WANG, 2020)(ENTRINGER; BUSS; WADHWA, 2017; STEIN et al., 2014).

The core response to stress involves the activation of the hypothalamic-pituitary-adrenal (HPA) axis (HERMAN et al., 2016; NICOLAIDES et al., 2014; RUSSELL; LIGHTMAN, 2019). During the exposure to stress, corticotrophin-releasing factor (CRF) is released in the paraventricular nucleus of the hypothalamus (PVN), which leads to the release of adrenocorticotropic hormone (ACTH) from the pituitary, triggering the secretion of cortisol (corticosterone in rodents) by the adrenal cortex. Glucocorticoids act through activation of MR and GR receptors, which then mobilizes energy resources and prepares the body to face a stressful situation (HERMAN et al., 2016; NICOLAIDES et al., 2014; RUSSELL; LIGHTMAN, 2019). In healthy individuals, the HPA axis activation is limited through negative feedback, which involves the activation of GR localized in the PVN, prefrontal cortex (PFC) and hippocampus (HPC) (HERMAN et al., 2016; NICOLAIDES et al., 2014; OTTE et al., 2016; RUSSELL; LIGHTMAN, 2019). Under chronic stress exposure, this feedback mechanism can become impaired, due to down-regulation of GR receptors, for example, resulting in dysregulation of the HPA axis activation, which has been associated with the development of MDD (HERMAN et al., 2016; OTTE et al., 2016; RUSSELL; LIGHTMAN, 2019; STARR et al., 2020).

The interaction between environmental factors and the genetic background seems to play an essential role in the etiology of depression (KENDLER; GARDNER, 2016; KENDLER et al., 1995; WICHERS et al., 2009, 2007). Indeed, genetic vulnerability accounts for ~35%-40% of depression (SULLIVAN; NEALE; KENDLER, 2000). Accordingly, previous studies have shown that first-degree relatives of patients with major depression were at three times higher risk of developing MDD (GESCHWIND; FLINT, 2015). Furthermore, a large-scale study with monozygotic and dizygotic twin estimated 38% heredity for MDD (KENDLER et al., 2006). Several genetic mutations have been implicated in the

pathophysiology of depression and in response to antidepressant treatment, including: BDNF, HTR1A, HTR2A, COMT, CLOCK, SLC6A4, SLC6A3, SLC6A2, and TPH, although they have only moreate role in vulnerability to depression (FLINT; KENDLER, 2014). It is thought that MDD development involves the participation of several genes producing small effects that contribute to the phenotype exhibited. These genes have important roles in brain neurochemistry and neurplasticity and can, therefore, impact stress adaptation and disease vulnerability.

Not only genetic, but also epigenetic factors have proven to be important in vulnerability to stress and depression neurobiology. As the current work did not focus on epigenetics, a comprehensive discussion lies beyond the scope of this text, and has been reviewed elsewhere (NESTLER, 2014; PARK et al., 2019; PENNER-GOEKE; BINDER, 2019). Briefly, epigenetics is a dynamic process derived from the interaction between gene x environmental factors that affects the remodeling and function of chromatin, resulting in altered gene expression and protein translation without changing the base sequence of deoxyribonucleic acid (DNA) s (HOLLIDAY, 2006; NESTLER et al., 2016). Many epigenetic mechanisms, including phosphorylation, acetylation, deacetylation, methylation and demethylation in the histone tails and DNA methylation, are modified by stress exposure and antidepressant treatment (HOLLIDAY, 2006). Growing evidence has identified an association between epigenetics alterations with aetiology of major depressive and treatment response (ROBISON et al., 2013; TALAROWSKA, 2020; VIALOU et al., 2013).

1.2 Animal models of depression

Animal models of depression play an essential role in exploring the mechanisms involved in the pathophysiology of MDD and in investigating novel potential compounds for its treatment (NESTLER; HYMAN, 2010; WANG et al., 2018). However, there are some symptoms (such as recurrent thoughts of death or suicide, or excessive guilt) and psychological concepts (like low self-esteem and the ability to perceive the future) which are impossible to model in rodents (CRYAN; SLATTERY, 2007). Despite these limitations, the use of animal models of depression remains as important experimental tools to understand the molecular mechanisms and new treatment options of depression.

Based on the etiology involved in depression, animal models may involve different approaches, such as genetic alterations, pharmacological manipulation, environmental

challenges (stress), and brain injuries. These manipulations induce physiological and behavioral changes in animals, which are attenuated by effective antidepressant treatment (HAO et al., 2019; NESTLER; HYMAN, 2010; PLANCHEZ; SURGET; BELZUNG, 2019). Animal models based on environmental manipulation usually consist of exposing animals to uncontrollable stressors that trigger physiological and behavioral changes similar to the ones observed in depressed patients, such as hypercortisolemia, anhedonia, and cognitive deficits (HAO et al., 2019; PLANCHEZ; SURGET; BELZUNG, 2019; STREKALOVA et al., 2011). Exposure to stress in adulthood, such as chronic unpredictable mild stress (CUMS), learned helplessness (LH), social defeat, or early in life (maternal separation) can induce behavioral changes that can reflect different aspects of MDD symptomatology: sucrose preference (anhedonia), social interaction (sociability), novelty-induced suppressed feeding (anxiety), forced swimming test (despair, helpless), amongst others (DUMAN, 2010; NESTLER; HYMAN, 2010; PLANCHEZ; SURGET; BELZUNG, 2019; SÖDERLUND; LINDSKOG, 2018; WANG et al., 2018). Of note, the Forced Swim Test (FST) and the Tail Suspension Test (TST) were originally developed to assess the behavioral changes produced by exposure to an inescapable stressful situation that could be attenuated by antidepressant treatment and, despite increasing criticism, they remain widely used tests to investigate both stress and antidepressant effects (COMMONS et al., 2017; CRYAN; MOMBEREAU; VASSOUT, 2005; CRYAN; VALENTINO; LUCKI, 2005; DUMAN, 2010; NESTLER; HYMAN, 2010).

It has been a consensus that animal models of depression do not represent all the complexity underlying the human condition (GURURAJAN et al., 2019; HAO et al., 2019; MONTEGGIA; HEIMER; NESTLER, 2018; PLANCHEZ; SURGET; BELZUNG, 2019), and itmay be difficult to model a human situation where the diagnosis is solely based on phenomological observations and not biological correlates. Nevertheless, the animal models are useful tools that allows for the evaluation of behavioral endpoints that resemble depression, allowing us to study its neurobiology and treatment. It is therefore, crucial that any given animal model of depression would fulfill or partly fulfill specific validity criteria, classified as following: 1) Homological validity; 2) Pathogenic validity; 3) Mechanistic validity; 4) Face validity; 5) Predictive validity (BELZUNG; LEMOINE, 2011), See deatials in Table 2. The “ideal model” would fulfill all of these criteria, but since only some aspects of illness can be modeled in animals, it is important to take into consideration the limitations of each model when interpreting their results (BELZUNG; LEMOINE, 2011; GURURAJAN et al., 2019).

Table 2. Validity criteria for animal models of psychiatry disorders (BELZUNG; LEMOINE, 2011).

Validity Criteria	Description
1. ***Homological validity***	Proper choice of strain and species of animal to understand the disease (Species and strain validity).
2. ***Pathogenic validity***	The similarity of processes leading to disease identical to humans (Ontopathogenic and triggering validity).
3. ***Mechanistic validity***	Cognitive or biological mechanisms underlying the disorder are identical in humans and animals.
4. ***Predictive validity***	The aetiological factors and therapeutic agents are identical to the human condition (Induction and remission validity).
5. ***Face validity***	The similarity of observable behaviours or biological outcomes (Ethological and biomarker validity) in humans and animals.

The FST, developed by Porsolt and colleagues in 1977, (PORSOLT; LE PICHON; JALFRE, 1977; PORSOLT; BERTIN; JALFRE, 1978), has been widely used to detect novel antidepressant compounds and understand the biological brain substrates involved in depression (BORSINI; MELI, 1988; CRYAN; MOMBEREAU, 2004; CRYAN; MOMBEREAU; VASSOUT, 2005; CRYAN; VALENTINO; LUCKI, 2005). It consists of submitting the rodent to inescapable stress (swimming in a cylinder filled with water), which triggers active behaviors oriented to escape followed by the prevalence of an immobile posture (BOGDANOVA et al., 2013; PORSOLT; LE PICHON; JALFRE, 1977; PORSOLT; BERTIN; JALFRE, 1978). There are differences in the protocol depending on the species of rodent used (CRYAN; VALENTINO; LUCKI, 2005; PORSOLT; BERTIN; JALFRE, 1978; SLATTERY; CRYAN, 2012). The majority of clinically effective antidepressant drugs reduce immobility and increase or prolong the active escape behaviours (climbing and swimming) during the test (DETKE; JOHNSON; LUCKI, 1997; DETKE; RICKELS; LUCKI, 1995; PORSOLT; LE PICHON; JALFRE, 1977). The advantages of the FST are the following: a) the low cost; b) ease to execute the method; c) high sensitivity to screening the efficiency of antidepressants with strong predictive validity (BOGDANOVA et al., 2013; CRYAN; SLATTERY, 2007; HAO et al., 2019; PLANCHEZ; SURGET; BELZUNG, 2019).

The tail suspension test (TST) is another important test for detecting potential antidepressant drugs with the same construct as the FST (STERU et al., 1985). In this test, the mice are subjected to an inescapable stressful situation (hung by their tail), and after a

struggling period, they assume an immobile response. However, if treated with antidepressant drugs, the immobility is decreased, resulting in more escape-oriented behaviours (CRYAN; MOMBEREAU; VASSOUT, 2005; STERU et al., 1985). Despite the similarities with the FST, it is noteworthy that the TST has the following advantages: a) avoid any possible complications induced by hypothermic exposure in FST; b) it is a useful tool to study genetically modified mice with compromised motor activity; c) increased sensibility to detect SSRIs treatments; d) the animal is immobile faster, but cannot remain at this posture for an extended period (CRYAN; MOMBEREAU; VASSOUT, 2005). However, both TST and FST have been criticized for detecting the antidepressant effect after acute drug administration, unlike depressed patients who need chronic treatment to show the therapeutic effect (CRYAN; MOMBEREAU; VASSOUT, 2005). Despite both FST and TST exhibit the same construct, evidence indicates different neural substrates' activation in the tests (RENARD et al., 2003). Even though they have important limitations in terms of vailidity, the FST and TST remain the most widely tests to study the stress effects associated to depression and the screening of promising antidepressant substances.

In addition to the models based on exposure to stress, models resulting from genetic manipulation have also become important experimental tools to investigate depression neurobiology and treatment. Behavioral changes associated with depression have been observed in transgenic animals which present mutations in genes associated to neuroplasticity, such as BDNF and TrkB, and serotonin signalling (5-HT1A receptors SERT), amongst others (COWEN; EDITORS, 2013; PLANCHEZ; SURGET; BELZUNG, 2019). Genetic models can also result from selective breeding, such as the Flinders Sensitive Line (FSL) rats, which were developed to investigate the mechanisms involved in resistance to anticholinesterase agents, organophosphates, specifically to diisopropyl fluorophosphate (DFP; OVERSTREET et al., 1988). However, these rats present altered sensitivity to cholinergic agonists, what is also observed in depressive patients (OVERSTREET; RUSSELL, 1982, 1984; OVERSTREET et al., 2005; OVERSTREET; WEGENER, 2013; RISCH et al., 1980). Besides that, it was evidenced that this rat strain has several characteristics resembling depression, such as disrupted sleep pattern (BENCA et al., 1996), low body weight (OVERSTREET, 1993, 2002), reduced appetite (BUSHNELL; LEVIN; OVERSTREET, 1995), psychomotor retardation (OVERSTREET, 1986; RUSSELL et al., 1982) and significant sensitivity/vulnerability to stress (OVERSTREET, 1986; OVERSTREET et al., 1986).

It is important to note that subchronic treatment (14 days) with classical antidepressants (including SSRI, SNRI, MAOI, and TCA) is normally required to induce a pronounced antidepressant-like effect in FSL rats, which is an advantage when compared to other rats lines exposed to FST (OVERSTREET et al., 1995, 2005; OVERSTREET; KEENEY; HOGG, 2004; OVERSTREET; WEGENER, 2013; PUCILOWSKI et al., 1993; SCHILLER et al., 1992). However, treatment with Ketamine (KET) and other potential fast-acting antidepressant substances can modify the behavioural response of FSL rats in the FST after acute administration (DU JARDIN et al., 2018, 2016; LIEBENBERG; JOCA; WEGENER, 2014). (DU JARDIN et al., 2016)(SANCHEZ; ASIN; ARTIGAS, 2015). The use of FSL rats has, thus, significantly contributed to the understanding of the participation of gene x environment interaction in the aetiology of depression and investigation of new potential antidepressants.

1.3 Neurobiological hypotheses for MDD

Multiple hypotheses regarding the underlying pathophysiology of MDD exist, which does not necessarily exclude – but rather supplement each other. Some of the more established hypotheses will be presented briefly below.

1.3.1 Monoaminergic hypothesis

The discoveries about the mechanism of action of antidepressant drugs in the sixties set the first biological basis for the neurobiology of MDD, the ‘Monoaminergic Hypothesis of depression’. This hypothesis was mainly based on the following observations: 1) Drugs that inhibit the metabolism of monoamines, such as monoamine oxidase (MAO), promotes mood improving effects (ZELLER et al., 1952); 2) Tricyclic drugs, such as imipramine, which were able to block the reuptake of monoamines also induced antidepressant effects in humans (AXELROD et al., 1961; AXELROD; INSCOE, 1963; AXELROD; WHITBY; HERTTING, 1960; HERTTING; AXELROD; GORDON, 1961; KUHN, 1958); 3) Reserpine, a drug used as antihypertensive medication inhibits monoamine storage in vesicles and depletes them from the synapse, induces depressive episodes in some patients (LEMIEUX; DAVIGNON; GENEST, 1956); 4) Imipramine reverses the effects of reserpine and the administration on psychostimulant amphetamines induced transient mood elevating effects e (BUNNEY;

DAVIS, 1965; COPPEN et al., 1967; LEMIEUX; DAVIGNON; GENEST, 1956; SCHILDKRAUT, 1965). Based on that, the monoaminergic hypothesis postulated that MDD results from a reduction in the monoamines levels in the synaptic cleft in important limbic brain regions and the antidepressant effect would be associated to the restoration of the levels of these neurotransmitters (COPPEN, 1967; COPPEN et al., 1967; SCHILDKRAUT, 1965).

However, the basis of the monoaminergic hypothesis has been challenged, due to several limitations. Of note, the mood elevating effect induced by antidepressant drugs are only observed after several weeks of treatment, usually 4 to 6 weeks, even though the blockage of the monoamine transporter or MAO inhibition reaches the steady-stage within a few hours or days after injection (BLIER; DE MONTIGNY, 1983; BLIER; LISTA; DE MONTIGNY, 1993; BLIER; CHAPUT; DE MONTIGNY, 1988; BLIER; WARD, 2003). To explain this latency for the antidepressant effect, it was proposed that the acute treatment with antidepressants promotes a rapid increase of 5-HT levels in the synaptic cleft and subsequent activation of 5HT1A receptors located in the cell bodies of serotoninergic neurons in raphe nuclei, inhibiting the neuronal firing and diminishing 5-HT release in target limbic regions. The chronic treatment promotes desensitization and/or downregulation of somatodendritic 5-HT1A auto-receptors, allowing the recovery of neuronal firing and consequent increased release of monoamines in limbic structures, which coincides with the therapeutic effect of the drugs (BLIER; EL MANSARI, 2013; HAMON; BLIER, 2013). Therefore, signaling through post-synaptic 5-HT1A heteroreceptors in the PFC and hippocampus (HPC) after chronic antidepressant treatment would be associated with the antidepressant action (ALTIERI et al., 2013; GARCIA-GARCIA; NEWMAN-TANCREDI; LEONARDO, 2014). Other serotonin and noradrenalin receptors are known to be up or down-regulated after chronic antidepressant treatment, as reviewed by (KÖHLER et al., 2016).

In support of the monoaminergic theory, several genetic mutations in genes related to monoamines have been implicated in the pathophysiology of depression and in response to treatment, such as HTR1A, HTR2A, COMT, MAOA, 5HTTLPR/SLC6A4, DAT/SLC6A3, NET/SLC6A2, TPH1, TPH2 (FLINT; KENDLER, 2014). However, monoamine depletion in healthy patients did not produce depressive symptoms, but it impaired the treatment response in depressed patients (RUHÉ; MASON; SCHENE, 2007). Thus, monoamines certainly play an important modulatory role in mood regulation and are still the main target of the available pharmacological treatment in MDD (CIPRIANI et al., 2018; MAFFIOLETTI et al., 2020; SRAMEK; MURPHY; CUTLER, 2016). Nevertheless, it is important to consider that monoaminergic antidepressant also induce several changes in different neurotransmitter

systems, especially after chronic administration, which point to additional mechanisms involved in the antidepressant effect (BALLESTEROS-ZÉBADÚA; MANJARREZ-MARMOLEJO; FRANCO-PÉREZ, 2013; LAMMERS et al., 2000; MARTÍNEZ-TURRILLAS; DEL RÍO; FRECHILLA, 2007; MARTINEZ-TURRILLAS; FRECHILLA; DEL RÍO, 2002; PRATT; BOWERY, 1993) . The non-monoaminergic mechanisms have been the source of intense investigation in the past decades as a way to better understand depression neurobiology and identify novel and more effective pharmacological treatments.

1.3.2 Glutamatergic hypothesis

Glutamate is the major excitatory neurotransmitter and widely distributed in the mammalian brain, with an essential physiological role in synaptic plasticity, learning, and memory. Its action occurs through the interaction with two superfamilies of receptors located pre and postsynapticly, including the ionotropic receptors (AMPA, NMDA, Kainate) and the metabotropic receptors (mGluR) (MURROUGH; ABDALLAH; MATHEW, 2017a; NICIU; KELMENDI; SANACORA, 2013). Once released in the synaptic cleft, glutamate is reuptaken by excitatory amino acid transporters 1, 2, and 3 (EAAT1, 2, and 3) which limit its action (MURROUGH; ABDALLAH; MATHEW, 2017b; WATKINS; PEI; NEWBERRY, 1998).

The excess of glutamate has been implicated in excitotoxic damage, neurodegeneration and impairments in the synaptic integrity (MURROUGH; ABDALLAH; MATHEW, 2017b; NICIU; KELMENDI; SANACORA, 2013; PEREIRA; HIROAKI-SATO, 2018; SANACORA; TRECCANI; POPOLI, 2012). Patients diagnosed with MDD present high glutamate levels in the serum (ALTAMURA et al., 1995; KIM et al., 1982), cerebrospinal fluid (LEVINE et al., 2000), and brain (HASHIMOTO; SAWA; IYO, 2007; MCEWEN et al., 2012a; SANACORA et al., 2004), which have implicated glutamate in the neurobiology of MDD. Accordingly, chronic treatment with antidepressant drugs normalizes excessive brain glutamate levels induced by stress exposure and modulates the expression of glutamate receptors (POPOLI et al., 2013; TOKARSKI et al., 2008). Thus, the investigation of potential new antidepressant drugs that act in the glutamatergic system seems has been intensively studied in the past three decades.

In fact, drugs that modulate the glutamatergic system have shown promising effects in depression treatment. In 1990, Trullas and Skolnick were the first to report that the

administration of NMDA receptor antagonists produced an antidepressant-like effect in the FST (TRULLAS; SKOLNICK, 1990). In this initial study, and later several other studies it was shown that systemic administration of NMDA antagonists induce a behavioral response similar to those induced by antidepressant drugs in animals submitted to different animal models (BURGDORF et al., 2013; LI et al., 2010b; MAENG et al., 2008; MOSKAL et al., 2014; SHIRAYAMA; HASHIMOTO, 2017). Furthermore, injection with NMDA antagonist into a specific brain area related to depression, such as PFC and HPC, also produced an antidepressant-like effect, thus implicating dysfunctional glutamatergic signaling in this brain regions in depression neurobiology (FUKUMOTO et al., 2017a; FUKUMOTO; IIJIMA; CHAKI, 2016; PADOVAN; GUIMARÃES, 2004; PEREIRA et al., 2015; PHAM et al., 2017).

Clinical studies also show that the infusion of a subanesthetic dose of a non-competitive NMDA antagonist, namely KET exerts robust rapid (within 2 h following administration) and sustained antidepressant effects, both in humans and in animal models (BERMAN et al., 2000) (AUTRY et al., 2011; FRANCESCHELLI et al., 2015; FUKUMOTO et al., 2017a; KOIKE; IIJIMA; CHAKI, 2011; LI et al., 2010a; LIEBENBERG; JOCA; WEGENER, 2014; MAENG et al., 2008). Recently, an intranasal formulation of s-ketamine was approved by the FDA in treating treatment resistant depression (FDA, 2019). The antidepressant effect induce by ketamine and its molecular mechanism will be discussed in subsequent section 1.4.2 and also in the study 2. Furthermore, recently, other drugs that modulate the NMDA receptor activity are under investigation as fast-acting antidepressant drugs, such as Rapastinel, AV-101, NRX-1074 (for review see (MURROUGH; ABDALLAH; MATHEW, 2017a).

1.3.3 Inflammation hypothesis

Accumulating evidence has associated increased inflammatory response to MDD neurobiology (BRUNO et al., 2020; MILLER; RAISON, 2016). The immune hypothesis proposes that chronic exposure to stress is associated with the activation of the inflammatory response and leads to increased levels of proinflammatory cytokines, especially interleukin 1 beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alfa (TNF-α), and interferon (INF), which can modulate brain neurochemistry and neuroendocrine responses, ultimately leading to behavioral changes (BRUNO et al., 2020; MILLER; RAISON, 2016).

In line with this hypothesis, administration of inflammatory cytokines or their inducers (for example, endotoxin or typhoid vaccination) causes depressive symptoms in healthy patients (BONACCORSO et al., 2002; CAPURON et al., 2002; HARRISON et al., 2009; REICHENBERG et al., 2001). In addition, individuals affected by chronic inflammatory diseases (rheumatoid arthritis, lupus erythematosus, influenza virus infection) often present depression as a comorbidity (MEIJER; ZAKAY-RONES; MORAG, 1988; SPARKS et al., 2020), and the blockade of cytokines or inflammatory signaling reverses the depressive symptoms in patients (ABBOTT et al., 2015; KÖHLER et al., 2014, 2015; SUN et al., 2017; TYRING et al., 2006). However, the modulatory effect of antidepressant drugs in immune response is still controversial (KUBERA; BASTA-KAIM; PAPP, 1995; MUSSELMAN et al., 2001; WEIZMAN et al., 1994).

Furthermore, a growing body of evidence has shown that the activation of the immune system can play a modulatory role in the HPA axis (FELGER et al., 2016; MILLER; RAISON, 2016), promotes changes in the neurochemical profile (FELGER; LI; MARVAR, 2013; KORTE-BOUWS et al., 2019; MAES, 1995; MAES et al., 1994; SPERNER-UNTERWEGER; KOHL; FUCHS, 2014; ZOLLER et al., 2012), alterations in neurotrophin signaling (CARLOS et al., 2017; KENIS et al., 2011; LOTRICH; ALBUSAYSI; FERRELL, 2013; MILLER; RAISON, 2016; RAGE; SILHOL; TAPIA-ARANCIBIA, 2006; TONG et al., 2008), and impairment of neuroplastic mechanisms (HAYLEY, 2014; WU et al., 2012; YIRMIYA; GOSHEN, 2011), leading to the development of major depression.

1.3.4 Neuroplastic hypothesis

Neuroplasticity is a crucial adaptive function of the brain to perceive, assess, adapt, and select the appropriate response to internal and external stimuli. This response occurs through different mechanisms, including alterations in dendritic function, synaptic remodeling, long-term potentiation, dendritic arborization, synaptogenesis, and neurogenesis (DUMAN et al., 2000, 2016a; MANJI; DREVETS; CHARNNEY, 2001). This brain function plays an essential role in memory, cognition, learning, and stress adaptation (DUMAN et al., 2016a; PITTENGER; DUMAN, 2008; PRICE; DUMAN, 2020). Brain-derived neurotrophic factor (BDNF) is considered a key neurotrophin responsible for neuronal survival, growth, and differentiation of neurons, and regulation of the synaptic plasticity (DINIZ et al., 2018; PARK; POO, 2013). The neuroplasticity hypothesis postulates that the development of MDD

results from the impairments in neurotrophin signaling and subsequently in neuroplasticity processes, which would be restored by treatment with antidepressants (CASTRÉN, 2005).

Imaging studies revealed that depressed patients present reduced hippocampus (HPC) and frontal cortex regions, important limbic areas related to depression (DREVETS, 2001, 2000; DREVETS; PRICE; FUREY, 2008; HORNE; NORBURY, 2018; TAE et al., 2011; WU et al., 2018). Moreover, postmortem studies have revealed smaller size and density of neurons and lower synapses in the PFC of depressed subjects (DREVETS, 2000; KANG et al., 2012). Besides, the morphological alterations are accompanied by reduced levels of BDNF (DUNHAM et al., 2009; GUILLOUX et al., 2012; KAREGE et al., 2005a, 2005b; KOBAYASHI et al., 2005; RAY et al., 2011; SEN; DUMAN; SANACORA, 2008; SHIMIZU et al., 2003). However, the treatment with several antidepressant classes prevents or normalizes these morphological deficits (CASTRÉN; ANTILA, 2017; CASTRÉN, 2005), accompanied by the increased BDNF levels (SEN; DUMAN; SANACORA, 2008; SHIMIZU et al., 2003). The volume reduction extension is correlated with the duration of disorder, time of treatment, and the severity of depression (DUMAN et al., 2016b).

Corroborating with the clinical findings, in animals, exposure to inescapable stress reduced BDNF levels in brain regions related to depression, the PFC and HPC (DUMAN; MONTEGGIA, 2006; LARSEN et al., 2010; SMITH et al., 1995), causing atrophy, and the loss of neurons and glial cells in these brain region (DUMAN; AGHAJANIAN, 2012; MCEWEN et al., 2012b). Furthermore, rodents exposed chronically to glucocorticoids presented decreased synaptic number and function and atrophy in neurons located in limbic structures (LIU; AGHAJANIAN, 2008; MAGARIÑOS; MCEWEN, 1995) and diminished BDNF levels in the same structure (LI et al., 2019). Chronic, but not acute, antidepressant treatment restores the the impairment of synaptic plasticity (ARDALAN et al., 2020; CASTRÉN; ANTILA, 2017; LI et al., 2010b; TRECCANI et al., 2019) and also increased BDNF and TrkB receptor levels in the HPC (AUTRY; MONTEGGIA, 2012; CASTRÉN; ANTILA, 2017; DUMAN; MONTEGGIA, 2006; NIBUYA; MORINOBU; DUMAN, 1995). However, fast-acting antidepressants, such as ketamine, produces rapid increases in BDNF levels and the dendritic arborization in the HPC (LI et al., 2010b). Since the selective loss of BDNF in HPC attenuates the antidepressant effect produced by monoaminergic antidepressant drugs (desipramine and escitalopram) and the fast-acting antidepressant KET (ADACHI et al., 2008; AUTRY et al., 2012), BDNF-TrkB signaling is considered necessary for the antidepressant effect.

The interaction between BDNF and its receptor TrkB activates its intracellular cascades that regulate neuronal survival, development, and differentiation, playing a fundamental role in the neuroplasticity process (CASTRÉN; ANTILA, 2017; CUNHA; BRAMBILLA; THOMAS, 2010a). The detailed discussion about the interaction between BDNF and TrkB is described elsewhere (CASTRÉN; KOJIMA, 2017; CUNHA; BRAMBILLA; THOMAS, 2010b).

Furthermore, it is noteworthy that the impairment of neuroplastic and synaptogenesis mechanisms resulting from a complex interaction between the other factors involved in the neurobiology of depression, such as monoaminergic neurotransmission imbalance (MAFFIOLETTI et al., 2020; PEREIRA; HIROAKI-SATO, 2018), increased levels of glutamate (MURROUGH; ABDALLAH; MATHEW, 2017a; NICIU; KELMENDI; SANACORA, 2013), the activation of HPA axis (MCEWEN et al., 2012a), immune response activation (BRUNO et al., 2020; MILLER; RAISON, 2016) and neurotrophin signaling (CASTRÉN; ANTILA, 2017; CASTREN; VOIKAR; RANTAMAKI, 2007; CASTRÉN; KOJIMA, 2017; CASTRÉN; RANTAMÄKI, 2010; DUMAN; DEYAMA; FOGAÇA, 2019).

1.3.5 Conclusion

Although many hypothesis have been postulated about depression neurobiology, there is no unifying theory that can explain such a complex and heterogenous disorder. Dysfunctions in different pathways and neurotransmitter systems could explain the diversity set of symptoms presented by depressed patients. Therefore, each of the hypothesis can represent an oversimplification of one of the dysfunctions associated with MDD.

1.4 Pharmacological treatment of MDD

As mentioned a variety of current treatment options exist for treatment of MDD. However, none of them are able to relieve the symptoms in more than 60-70% of the patients, and only 25-30% of the patients achieve remission. Below, a brief summary of the established treatment options for MDD is listed.

1.4.1 Monoaminergic antidepressants

The discovery of the first antidepressant occurred by serendipity. The tuberculosis patients with simultaneous diagnose of depression treated with iproniazid reported a general improvement in the mood (ZELLER et al., 1952). In the same period, imipramine was synthesized from the chemical modifications in the structure of the antipsychotic agent, chlorpromazine, that was ineffective for psychosis but displayed a remarkable improvement of depression symptoms after chronic treatment for 1 to 6 weeks (AXELROD et al., 1961; AXELROD; INSCOE, 1963; AXELROD; WHITBY; HERTTING, 1960; KUHN, 1958). The elucidation of the mechanism of action for both drugs revealed that iproniazid acts inhibiting the enzyme monoamine oxidase (MAO) (ZELLER et al., 1952), and imipramine blocks the reuptake of noradrenaline and 5-HT (tricyclic antidepressant (TCA), increasing the monoamines levels in the brain (AXELROD et al., 1961; AXELROD; INSCOE, 1963; AXELROD; WHITBY; HERTTING, 1960; HERTTING; AXELROD; GORDON, 1961). Due to due to the lack of selectivity in their action, both drugs cause several significant side effects (MAFFIOLETTI et al., 2020; PEREZ-CABALLERO et al., 2019). Subsequently, the search for new antidepressants with similar mechanisms of action was initiated, and more selective compounds were developed, including the selective serotonin reuptake inhibitor (SSRI), selective noradrenaline reuptake inhibitors (SNRI), and serotonin and norepinephrine reuptake inhibitor (SNRI), resulting in safer compounds with fewer side effects (MAFFIOLETTI et al., 2020; PEREZ-CABALLERO et al., 2019). The SSRI and SNRI are considered the first choice pharmacological treatment of depression nowadays (CIPRIANI et al., 2018; MAFFIOLETTI et al., 2020).

Although monoaminergic antidepressants are effective to treat depression, these compounds have several limitations, including a latency to initiate the therapeutic effect (4 to 6 weeks) (CIPRIANI et al., 2018), and low-efficacy rates, in which 40-50% of the patients respond partially or do not respond to treatment (CIPRIANI et al., 2018; KEKS et al., 2007; OTTE et al., 2016). Furthermore, at the begging of the treatment, the conventional antidepressants may worsen depression or induce suicidal ideation (CIPRIANI et al., 2018; OTTE et al., 2016). In fact, it is fundamental to understand the pathophysiology enrolled in the disorder to investigate new substances with potential antidepressant effects. In particular, compounds with rapid onset of action and effective in individuals who do not respond to currently available treatments.

1.4.2 Ketamine

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate glutamate receptor (NMDA; KOHRS; DURIEUX, 1998; WHITE et al., 1980), commonly used as a dissociative anesthetic in humans. In the begging of 2000, Berman et al. (BERMAN et al., 2000) were the first to reveal that the infusion of a subanesthetic dose of ketamine exerts robust rapid (within 2 h following administration) and sustained antidepressant effect lasting for 3 days in the depressed patient (BERMAN et al., 2000). Subsequent clinical studies evidenced similar rapid and sustained (7 days on average) antidepressant effect in patients (CUSIN et al., 2016; DIAZGRANADOS et al., 2010; FREEMAN et al., 2020; GHASEMI et al., 2013; KRYSTAL et al., 1994; O'BRIEN et al., 2019; RODRIGUES et al., 2020; ZARATE et al., 2006; ZARATE JR et al., 2012). Moreover, ketamine exerts an antidepressant effect in treatment-resistant depression patients and reduces suicide ideation (DIAZGRANADOS et al., 2010; MURROUGH et al., 2015; O'BRIEN et al., 2019; RODRIGUES et al., 2020). In this sense, ketamine opens a new era for the treatment of depression with a fast-acting antidepressant class, with non-monoaminergic mechanism.

Besides, preclinical studies have described similar findings. A single injection of ketamine produces a rapid and sustained antidepressant-like effect in several animal models of depression, including chronic unpredictable mild stress (CUMS), learned helplessness (LH), social defeat, forced swim test (FST), and tail suspension test (AUTRY et al., 2011; FUKUMOTO et al., 2017b; KOIKE; IIJIMA; CHAKI, 2011; LI et al., 2010a; MAENG et al., 2008; PHAM et al., 2017; SUN et al., 2016). Ketamine can also produce an antidepressant-like effect in genetic animal models depression, FSL, and Wistar-Kyoto rats, as well as treatment-resistant models (DU JARDIN et al., 2016; LIEBENBERG; JOCA; WEGENER, 2014; PEREIRA et al., 2019; SOWA et al., 2019). Corroborating with prior clinical findings, ketamine induces an antidepressant-like effect which lasts for 7 days in different paradigms (AUTRY et al., 2011; FUKUMOTO et al., 2014, 2017b; LIEBENBERG; JOCA; WEGENER, 2015; MAENG et al., 2008; TRECCANI et al., 2012; ZANOS et al., 2019). In this sense, preclinical studies are essential tools that allow us to investigate the ketamine antidepressant effect mechanisms and possibly translate those findings to humans.

The molecular mechanism responsible for ketamine antidepressant effect is complex. It involves multiple the antagonism of the NMDA receptor localized on GABAergic interneurons promoting glutamate release in synaptic cleft, which activates α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor. Once activated the AMPA receptor leads the release BDNF, which activates its receptor tropomyosin related kinase B

(TkB) signaling pathway, activating mammalian target of rapamycin (mTOR) other downstream molecules, resulting synaptogenesis and synaptic plasticity induction. The detailed molecular mechanism involved in ketamine antidepressant effect is reviewed elsewhere (DUMAN; SANACORA; KRYSTAL, 2019; PHAM; GARDIER, 2019; ZANOS; GOULD, 2018), and also elaborated on in the discussion of study 2 later in this thesis.

Notwithstanding, ketamine can induce undesirable side-effects, such as abuse and addiction (WHITE; WAY; TREVOR, 1982). Among which, the main side effects psychotomimetic effects, such as delusions, hallucinations, dissociative or extracorporeal effects (feeling of being outside the body), and vivid dreams (DIAZGRANADOS et al., 2010; JANSEN, 2000; KRYSTAL et al., 1994; SHORT et al., 2018; SINGH et al., 2016; WHITE; WAY; TREVOR, 1982; ZARATE et al., 2006), that can produce abuse, which, therefore, would limit its use in depressed patients. Therefore, it is still fundamental to develop new therapeutic approaches with antidepressant effects similar to those produced by ketamine (fast and sustained).

1.4.3 Cannabidiol

The *Cannabis sativa L.* (cannabis) is a plant that has been used for medical and religious purposes by several civilizations in the world for thousands of years (ZUARDI, 2006). The use of cannabis in medicine by ancient Chinese was reported in the pharmacopeia around 2.700 B.C. (TOUW, 1981). Notably, in India, folk medicine reported cannabis preparation with flowers and resin to treat anxiety, mania, hysteria, and depression thousands of years before the Christian era (RUSSO, 2005). Beyond the medicinal use, the plant is widely used for recreational purposes because of its psychoactive properties, including the alteration of conscious perception, euphoria, and relaxation (RUSSO, 2005). Thereby, the medicinal use spread gradually worldwide, first to the Middle East and Europe in the 18th century, reaching Africa and America later. Indeed, the actual introduction of cannabis for medical propose occurred in the 19th century from William B. O'Shaughnessy, who described the cannabis preparations, methodically investigated its toxic effect on animals and the therapeutic effect on humans different diseases (O'SHAUGHNESSY, 1843). In the first decade of the 20th century, there was a decline in the plant's use for therapeutic purposes due to the difficulty to replicate the effects, variable efficacy of different sample of the plant (ZUARDI, 2006). The active compounds were still unknown, and the extract has varying

concentration and potency, which produce considerable side effects (ZUARDI, 2006). Advances in isolation techniques allowed to isolate the cannabinoids present in plant extracts in the 1940s (ADAMS; HUNT; CLARK, 1940; GAONI; MECHOULAM, 1964; MECHOULAM; SHVO, 1963) and to identify endogenous receptors and ligands, leading to the identification of the endocannabinoid system in the central nervous system (CNS). Understanding the molecular basis and the endocannabinoid system's role has increased scientific interest in exploring the potential effect of cannabinoids.

The endocannabinoid system is constituted by two G protein-coupled receptors (GPCR), cannabinoid type 1 and 2 receptors (CB1 and CB2), two main endogenous ligands arachidonoyl ethanolamide (AEA, anandamide) and 2-arachidonoylglycerol (2-AG) that acts in the receptors; the enzymes involved in the endocannabinoid biosynthesis and degradation, AEA (other N-acylethanolamines) are respectively synthesized and hydrolyzed by N-acylphosphatidylethanolamine (NAPE)-specific phospholipase D-like hydrolase (NAPE-PLD) and fatty acid amide hydrolase (FAAH)(CRAVATT et al., 1996; OKAMOTO et al., 2004). Whereas 2-AG, diacylglycerol lipase α (DAGLα), and DAGLβ catalyze the biosynthesis, and monoacylglycerol lipase (MAGL) is responsible for its hydrolysis (BISOGNO et al., 2003; DINH et al., 2002). Besides, the endocannabinoids may act through orphan GPCR 55, known as GPR55 receptor (LAUCKNER et al., 2008; PERTWEE, 2007; RYBERG et al., 2007) and vanilloid receptor, transient receptor potential cation channel subfamily V member 1 (TRPV1) (BISOGNO et al., 2001; CRISTINO et al., 2006; ROSS, 2003).

The endocannabinoid belongs to the class of atypical neurotransmitters. Thus, the neurotransmitter is not stored in vesicles; however, it is synthesized in the postsynaptic neuron on demand, in response to physiological neuronal depolarization. Once the neurotransmitter is released in the synaptic cleft, it may act as a CB1 agonist located in a presynaptic neuron, in a retrograde manner. The receptor is coupled with G inhibitory protein resulting in the inhibition of neuronal depolarization modulating neurotransmitter releases, mainly glutamate and GABA(AZAD et al., 2008; HÄRING et al., 2007; HERMANN; LUTZ, 2005; KANO et al., 2009; MOROZOV; TORII; RAKIC, 2009). Endocannabinoids can also act on CB2 receptors located in the glial cells in the central nervous system, which modulates the release of cytokines participating in the synaptic activity and pruning (CRISTINO; BISOGNO; DI MARZO, 2020; DI MARZO, 2018).

Abnormalities in the endocannabinoid neurotransmission have been implicated in the pathophysiology of stress-related disorders, such as anxiety and MDD (MICALE et al.,

2013; NAVARRETE et al., 2020). Post mortem study revealed that CB1 receptor expression was reduced in the anterior cingulate cortex (ACC) of the depressed patient (KOETHE et al., 2007). In the same way, the 2-AG blood levels were reduced in women diagnosed with depression (HILL et al., 2008). Similarly, non-treated depressed patients present low basal serum levels of AEA and 2-AG (HILL et al., 2009). In contrast, patients treated with SSRI have increase plasmatic levels of AEA and 2-AG (ROMERO-SANCHIZ et al., 2019). Similar to the clinical findings, knockout mice for CB1 receptors exhibit a depressive- and anxiety-like phenotype in different behavioural tests (MARTIN et al., 2002). Also, the systemic administration of the CB1 agonist receptor produces an antidepressant-like effect in rats submitted to FST (BAMBICO et al., 2007). In addition, the MAGL inhibitor, JZL194, has similar antidepressant effects in CUMS (ZHANG et al., 2015).

The plant Cannabis sativa L. has over 100 different phytocannabinoids, and the Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) are the two most studied compounds. Δ^9-THC is the primary psychoactive substance responsible for the effect produce by the cannabis, which was isolated and the chemical structure elucidated in the 1964s (GAONI; MECHOULAM, 1964), while CBD a non-active compound isolated in the early 1940s, and the chemical structure determined in 1963 (ADAMS; HUNT; CLARK, 1940; MECHOULAM; SHVO, 1963). In the beginning, curiously, CBD was considered a non-active cannabinoid, but later studies revealed that CBD produces the opposite behavioral effect induced by Δ9-THC on anxiety and psychotic symptoms in healthy patients (MARTIN-SANTOS et al., 2012; ZUARDI et al., 1982). THC acts through agonism of CB1 and CB2 receptors, facilitating the endocannabinoid action (GROTENHERMEN, 2003).

Differently from THC, the molecular mechanism involved in the CBD effect has not been fully elucidated. It is known that CBD acts through several molecular targets and is not restricted only to the endocannabinoid system. It seems that CBD modulates the endocannabinoid system acting as CB1 and CB2 receptors allosteric modulators, AEA uptake inhibitor, FAAH inhibitor, TRPV1 agonist, and GPR55 antagonist, as well as the in serotoninergic, opioidergic, adenosinergic neurotransmission systems, and modulating the inflammatory signaling, as presented in Table 3.

Table 3. Main pharmacological targets for Cannabidiol.

Biological System	***Target***	***References***
eCBD	CB1 receptor antagonist	(CAMPOS et al., 2013; FOGAÇA et al., 2018)
	CB2 receptor inverse agonist	(CAMPOS et al., 2013; FOGAÇA et al., 2018)
	FAAH inhibitor	(BISOGNO et al., 2001; CAMPOS et al., 2013; FOGAÇA et al., 2018; LEWEKE et al., 2012; PETROSINO et al., 2018)
	AEA uptake inhibitor	(BISOGNO et al., 2001; CAMPOS et al., 2013; FOGAÇA et al., 2018; LEWEKE et al., 2012; PETROSINO et al., 2018)
	TRPV1 agonist	(BISOGNO et al., 2001; DE GREGORIO et al., 2018; FONSECA; CORREIA-DA-SILVA; TEIXEIRA, 2018; PETROSINO et al., 2018)
	TRPA1 agonist	(DE PETROCELLIS et al., 2008)
	TRPM8 antagonist	(DE PETROCELLIS et al., 2008)
	TRPV2 agonist	(EUBLER et al., 2018; NABISSI et al., 2015; QIN et al., 2008)QIN et al., 2008; NABISSI et al., 2015;EUBLER et al., 2018.
	GPR55 antagonist	(CHERIF et al., 2015; WALSH et al., 2015)WALSH et al., 2015; CHERIF et al., 2015.
Serotonin	*5-HT1A agosnist*	(CAMPOS; FERREIRA; GUIMARÃES, 2012; DE GREGORIO et al., 2018; FOGAÇA et al., 2014; GOMES; RESSTEL; GUIMARÃES, 2011; MYERS et al., 2018; RESSTEL et al., 2009; RUSSO et al., 2005; SARTIM; GUIMARÃES; JOCA, 2016; ZANELATI et al., 2010)
	5-HT2A agonist	(LONG et al., 2012; PELZ et al., 2017; RUSSO et al., 2005)RUSSo et al., 2005; LONG et al., 2012; PELZ et al., 2017
	5-HT3 agonist	(XIONG et al., 2011)

	Tryptophan degradation inhibitor	(JENNY et al., 2009)
Opioid	Mu- opioid ligand	(KATHMANN et al., 2006; RODRÍGUEZ-MUÑOZ et al., 2012; VIUDEZ-MARTÍNEZ et al., 2018)
	Delta- opioid allosteric modulator	(KATHMANN et al., 2006)
	Sigma-opioid ligand	(RODRÍGUEZ-MUÑOZ et al., 2012)
Adenosine	Adenosine uptake inhibitor and indirect A2A agonist	(CARRIER; AUCHAMPACH; HILLARD, 2006; LIOU et al., 2008; MIJANGOS-MORENO et al., 2014; OLÁH et al., 2014; PANDOLFO et al., 2011)
Dopamine	Dopamine uptake inhibitor	(MURILLO-RODRÍGUEZ et al., 2011; PANDOLFO et al., 2011; ROSSIGNOLI et al., 2017)
Other	PPARγ agonist	(GIACOPPO et al., 2017; HIND; ENGLAND; O'SULLIVAN, 2016; VALLÉE et al., 2017)
	GABAA positive allosteric modulator	(BAKAS et al., 2017; LONG et al., 2012)
	α7 nicotinic acetylcholine antagonist	(MAHGOUB et al., 2013)
	Regulator of intracellular calcium	(DRYSDALE et al., 2006; RYAN et al., 2009)
	iNOS inhibitor	(ESPOSITO et al., 2006)
	NF-κB inhibitor	(ESPOSITO et al., 2006)
	COX-1 and 2 inductor	(WHEAL et al., 2014)

A growing body of evidence has indicated that CBD shows promising effects in several psychiatric disorders, including anxiety (CRIPPA et al., 2011; GUIMARÃES et al., 1990; MOREIRA; AGUIAR; GUIMARÃES, 2006; SOARES et al., 2010; ZUARDI et al., 1982, 2017), psychosis (MOREIRA; GUIMARÃES, 2005; ROTTANBURG et al., 1981; ZUARDI; ANTUNES RODRIGUES; CUNHA, 1991), epilepsy (CRIPPA et al., 2016; DO VAL-DA SILVA et al., 2017; GOBIRA et al., 2015), and major depression (LINGE et al., 2016; SALES et al., 2018b, 2018a; ZANELATI et al., 2010). In the last years, CBD was approved by Food and Drug Administration (FDA) for the treatment of severe forms of epilepsy, Lennoux-Gastaut syndrome, and Dravet syndrome (FDA, 2018), and also approved National Health Surveillance Agency (ANVISA) a corresponding FDA agency in Brazil for the same purpose (CONSELHO FEDERAL DE MEDICINA, 2016).

Despite its proven efficacy in other conditions, CBD effects in depression remains controversial a largely unexplored. For the first time, our group investigated whether the acute systemic treatment with CBD produced an antidepressant effect in male Swiss mice exposed to a test predictive for antidepressant compounds, the FST. The results revealed that the acute administration with CBD reduces the immobility time in the test, similar to the established antidepressant imipramine (ZANELATI et al., 2010). Interestingly, the behavioural response produced by CBD was counteracted by the pre-treatment with 5-HT1A antagonist receptor (WAY100635) (ZANELATI et al., 2010). For the first time, this study suggested an antidepressant-like effect induced by CBD and evidenced the involvement of 5-HT1A receptor in the CBD effect. A subsequent study corroborated these findings, showing an antidepressant-like response in Swiss mice exposed to FST and TST after acute administration even at a higher dose (200 $mg.kg^{-1}$) (EL-ALFY et al., 2010).

In addition, it was evidenced that CBD is also effective after the repeated treatment in Swiss mice and Wistar rats exposed to TST and FST (RÉUS et al., 2011; SCHIAVON et al., 2016). Altogether, these findings reinforce that CBD produces antidepressant effects after acute or repeated administration, in both mice and rats. However, varying effects in the effective doses are observed and there is not systematic investigation of CBD effects in different strain to assess possible differences, which can be a source of variability.

Other studies have been evidenced promised antidepressant-like effect of CBD in rodents exposed to different paradigms, including the learned helplessness (LH) (SALES et al., 2018b), the olfactory bulbectomy (OBX) (LINGE et al., 2016), and the chronic unpredictable mild stress (CUMS; (GÁLL et al., 2020; XU et al., 2019). Interestingly, for Wistar rats, only the chronic treatment with CBD (for 28 days) reversed the behavioural response induced by CUMS, not the acute administration (GÁLL et al., 2020). Notably, CBD produced antidepressant and pro-hedonic responses in the genetic rat model based on selective breeding, the Flinders Sensitive Line (FSL; Sales et al., 2018; Shbiro et al., 2019), and the Wistar-Kyoto rats (SHBIRO et al., 2019; SHOVAL et al., 2016). Strikingly, CBD produced the antidepressant effect in both males and females Wistar-Kyoto rats, but only in male FSL rats. Interestingly, it appears that the effectiveness of CBD depends on the gender and strain of rodent selected. However, the present study evaluated only one dose of CBD (30 mg.kg-1), which it is difficult to conclude about the effect of CBD in female rats. Additional studies are necessary to address this question.

Importantly, CBD promotes rapid antidepressant effect in OBX and LH models (LINGE et al., 2016; SALES et al., 2018b), in contrast to conventional monoaminergic

antidepressants, which require chronic treatment, indicating that it may be a fast-acting antidepressant. Furthermore, our group showed for the first time that CBD promotes an antidepressant effect that lasts for one week after a single injection (SALES et al., 2018b), thus suggesting a sustained antidepressant-like effect similar which have been demonstrated for KET (LI et al., 2010b; MAENG et al., 2008). Besides, the serotoninergic system appears to be crucial for the CBD effect, as previously shown for ketamine also (DU JARDIN et al., 2018, 2017; FUKUMOTO et al., 2017a). Accordingly, the co-administration of sub effective doses of CBD with fluoxetine (SSRI) produced a synergic antidepressant-like effect in mice exposed to FST. However, the previous depletion of 5-HT following with PCPA (serotonin synthesis inhibitor) abolished the CBD antidepressant effect (SALES et al., 2018a). Corroborating with the findings, the antidepressant effect observed with CBD treatment in the OBX model was accompanied by increased levels of 5-HT in the ventromedial PFC. However, the previous administration with 5-HT1A antagonist receptor (WAY100635) attenuated the behavioral and neurochemical response induced by CBD (LINGE et al., 2016).

Interestingly, the sub chronic administration of CBD (during 14 days) in diabetic rats reversed the behavioral deficits and increased 5-HT levels in HPC and PFC (CHAVES et al., 2020). Furthermore, the site-specific injection of CBD into limbic brain regions related to depression, including dorsal HPC and ventromedial PFC resulting in an antidepressant effect in FST (SARTIM; GUIMARÃES; JOCA, 2016; SARTIM et al., 2018). The behavioral effect produced by intra-mPFC injection was countered by previous treatment with 5-HT1A (SARTIM; GUIMARÃES; JOCA, 2016). Indeed, the results show the relevance of serotoninergic neurotransmission on mPFC for the CBD behavioral effect. Altogether, these results indicated that CBD effects depend on the intact function of serotonin signaling in limbic brain regions. Further investigations are necessary to understand the mechanism involved in the effect.

Based on the above findings, presented in full in Table 4, it is possible to conclude that CBD produces an antidepressant-like effect in different paradigms, using distinct rodent strains and species. Furthermore, the regimen of treatment did not influence the final observed outcome of CBD (acute, repeated treatment (14 days) or chronic (28 days)). However, the antidepressant effect in female animals is still unclear and warrants further investigations based on epidemiologic data about MDD prevalence. Moreover, it is essential to determine the molecular mechanism involved in the effect of CBD to develop the most effective antidepressant compounds.

Table 4. Preclinical evidence regarding the antidepressant effect produced by CBD (Modified from SILOTE et al., 2019).

Reference	Animal	Age	Origin	Dose	Route	Test	Effect
ZANELATI et al., 2010	Male Swiss mice	n.s.	Natural	30 mg/kg	i.p.	FST	Antidepressant effect
				3, 10 and 100 mg/kg	i.p.	FST	No effect
EL-ALFY et al., 2010	Male Swiss Webster mice	8 weeks	Natural	200 mg/kg i.p.	i.p.	FST	Antidepressant effect
	Male Swiss Webster mice	8 weeks		20 and 100 mg/kg i.p.	i.p.	FST	No effect
	Male DBA/2	8 weeks		20, 100 and 200 mg/kg i.p.	i.p.	TST	No effect
RÉUS et al., 2011	Male Wistar rats	8 weeks	n.s.	30 mg/kg (Acute)	i.p.	FST	Antidepressant effect
				15 and 60 mg/kg (Acute)	i.p.	FST	No effect
				30 mg/kg (Repeated - 14 days)	i.p.	FST	Antidepressant effect
				15 and 60 mg/kg (Repeated - 14 days)	i.p.	FST	No effect

CAMPOS et al., 2013	Male C57BL/6J mice (CUS)	12 weeks	Natural	30 mg/kg (Repeated - 14 days)	i.p.	EPM and NSF	Anti-stress effect
	HiB5 cells	-	Natural	100 nM	culture medium	Immunofluorescence microscopy	Neural progenitor proliferation
					culture medium	Flow citometry	Increase neural progenitor cell in S phase cells
SCHIAVON et al., 2016	Male Swiss albino mice	5-6 weeks	Natural	3 and 10 mg/kg (Acute)	i.p.	TST	Antidepressant effect
				30 mg/kg (Acute)	i.p.	TST	No effect
				3 and 30 mg/kg (Repeated - 15 days)	i.p.	TST	Antidepressant effect
LINGE et al., 2016	Male C57BL6 mice (Olfatory bulbectomy)	12 weeks	Natural	50 mg/kg (Acute)	i.p.	OFT	Antidepressant effect
				50 mg/kg (Repeated- 7 days)	i.p.	OFT	Antidepressant effect
					i.p.	SPT	Prohedonic effect
SHOVAL et al., 2016	Wistar-Kyoto rats	13 weeks	Natural	30 mg/kg	oral (food pellet)	SPT	Prohedonic effect
				15 and 45 mg/kg	oral (food pellet)	SPT	No effect

SARTIM; GUIMARÃES; JOCA, 2016	Male Wistar rats	n.s.	Natural	10, 30 and 60 nmol/0.2 ul/side	intra-PL mPFC	FST	Antidepressant effect
				45 and 60 nmol/0.2 ul/side	intra-IL mPFC	FST	Antidepressant effect
				30 nmol/0.2 ul/side	intra-IL mPFC	FST	No effect
BREUER et al., 2016*.	Male Swiss mice	n.s.	Natural	HUF101: 3 mg/kg	i.p.	FST	Antidepressant effect
				HUF101: 1 and 10 mg/kg	i.p.	FST	No effect
				HUF103: 3 and 10 mg/kg	i.p.	FST	Antidepressant effect
				HUF103: 1 mg/kg	i.p.	FST	No effect
FOGAÇA et al., 2018	Male C57BL6 mice (CUS)	8-9 weeks	Natural	30 mg/kg (Repeated - 14 days)	i.p.	EPM and NSF	Anti-stress effect
SARTIM et al., 2018	Male Swiss mice	7-8 weeks	Natural	10 nmol/0.2 ul/side	intra-dHPC	FST	Antidepressant effect
				30 and 60 nmol/0.2 ul/side	intra-dHPC	FST	No effect
				10 mg/kg	i.p.	FST	Antidepressant effect

SALES et al., 2018b	Male Swiss mice	8 weeks	Natural	10 mg/kg	i.p.	FST	Rapid antidepressant effect
				10 mg/kg	i.p.	FST	Sustained antidepressant effect
				7 and 30 mg/kg	i.p.	FST	No effect
	Male Wistar rats	n.s.	Natural	300 nmol/ul	i.c.v.	FST	Antidepressant effect
				50 and 150 nmol/ul	i.c.v.	FST	No effect
				30 mg/kg	i.p.	LH	Rapid antidepressant effect
				10 mg/kg	i.p.	LH	No effect
	Male FSL and FRL rats	n.s.		10 and 30 mg/Kg	i.p.	FST	Rapid antidepressant effect
SALES et al., 2018a	Male Swiss mice	8 weeks	Natural	10 mg/kg	i.p.	FST	Antidepressant effect
				3 and 7 mg/kg	i.p.	FST	No effect
DE MORAIS et al., 2018	Male Wistar rats	n.s.	n.s.	30 mg/kg (Acute)	i.p.	FST	Antidepressant effect
	Male Wistar rats (diabetic)	n.s.		0.3, 3, 10, 30 and 60 mg/Kg (Acute)	i.p.	FST	No effect
				30 mg/Kg (Subchronic; 3	i.p.	FST	Antidepressant effect

				injections 24,5 and 1h before FST)			
				0.3, 3, 10 and 60 mg/Kg (Subchronic; 3 injections 24,5 and 1h before FST)	i.p.	FST	No effect
SHBIRO et al., 2019	Male and Female Wistar Kyoto rats	70 days	n.s.	30 mg/kg	Oral (food pellet)	FST	Antidepressant effect
						SPT	Prohedonic effect
	Male FSL rats			30 mg/kg	Oral (food pellet)	FST	Antidepressant effect
	Female FSL rats			30 mg/kg	Oral (food pellet)	FST	No effect
XU et al., 2019	Male ICR mice (SPF; Animals submitted to CMS 4 weeks)	6 weeks	Natural	10 mg/kg (1 inj./week - 4 weeks)	i.v.	FST	Antidepressant effect
				100 mg/kg (1 inj./week - 4 weeks)	oral	FST	Antidepressant effect
				10 mg/kg (1	oral	FST	No effect

				inj./week - 4 weeks)			
GÁLL et al., 2020	Male Wistar rats (Animals submitted to CMS 4 weeks)	n.s.	Natural	10 mg/kg	i.p.	SPT	Prohedonic effect
SALES; GUIMARÃES; JOCA, 2020	Male Swiss mice	8 weeks	Natural	3, 7 and 10 mg/kg	i.p.	FST	No effect
				10 mg/kg	i.p.	FST	Antidepressant effect
CHAVES et al., 2020	Male Wistar rats (Diabetic)	n.s.	Synthetic	3 and 10 mg/kg (Repeated - 14 days)	i.p.	FST	No effect
				30 mg/kg (Repeated - 14 days)	i.p.	FST	Antidepressant effect

Abbreviations: EPM- Elevated plus maze; FRL rats - Flinders Resistant Line; FSL rats - Flinders Sensitive Line; FST- Forced swim test; HPC - Hippocampus; IBA1 – Ionized calcium binding adaptor molecule 1; i.c.v - intracerebroventrcular; i.p. - intraperiatoneal; intra-dHPC - Intra-dorsal hippocampus; intra-IL mPFC- infralimbic medial prefrontal cortex: intra-PL mPFC- prelimbic medial prefrontal cortex; LH - Learned helplessness; n.s. - not specified; NSF - Novelty supressed feeding; OFT - Open field test; PFC - Prefronal cortex; SPF – Specific-pathogen-free; SPT - Sucrose preference test; TST - Tail suspension test; * Fluorinate cannabidiol.

2 OVERALL CONCLUSION

In summary, our findings indicate that sex, strain, species, and chosen time of the administration may interfere with the behavioural response produced by CBD in rodents exposed to animal models of depression. In mice, CBD produced an antidepressant-like effect only in male Swiss mice in the TST. CBD did not significantly affect in female Swiss mice and both sexes of C57BL/6 mice in the test. However, in female FSL rats, CBD produced a dual effect, an antidepressant-like effect 2 hours after the injection, but at 1 hour, a depressive-like effect. In males FSL rats, CBD produced an antidepressant-like effect 1 hour after the injection and no effect at 2 hours. Besides, we confirm that KET has an antidepressant-like effect in female FSL rats. These findings point out that it is necessary to consider gender, strain, rodents species chosen, compound chemistry, exposure to a previous stressful condition, and behavioural test to plan the most appropriate experimental design when evaluating new potential drugs.

In addition, we investigated the molecular mechanisms involved on CBD and ketamine antidepressant effect of FSL rats in the limbic regions implicated with depression (PFC, DH and VH). Contrary to our expectations, CBD and KET did not share a common molecular expression pattern in the genes and proteins examined. For the PFC, CBD mainly modulates the BDNF and glutamatergic signaling pathway, while ketamine regulates the molecules associated with glutamatergic neurotransmission, VEGF and sortilin signaling pathways. However, for DH, CBD regulates the Sortilin, VEGF, glutamatergic systems, and ketamine regulated exclusively by glutamatergic neurotransmission. Our results suggest that CBD effect involved the restoration of glutamatergic dysfunction and facilitating the neurotrophic signaling pathway, which triggers neuronal survival and neuroplasticity. On the other hand, the effect of ketamine seems to involve only the restoration of normal glutamatergic function in the limbic brain areas. However, further investigations are necessary to elucidate the molecular mechanisms that participate in the behavioural response.

Notably, it was evidenced that FSL rats have several changes in the neurotrophic signaling, glutamatergic, neurotransmission, and synaptic proteins in the limbic brain regions (PFC, DH, and VH) compared to FRL rats. Thus, our findings reinforce that FSL is a validity genetic animal model to study the pathophysiology of depression and

investigate promising antidepressant compounds and their molecular mechanisms involved in the effect.

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