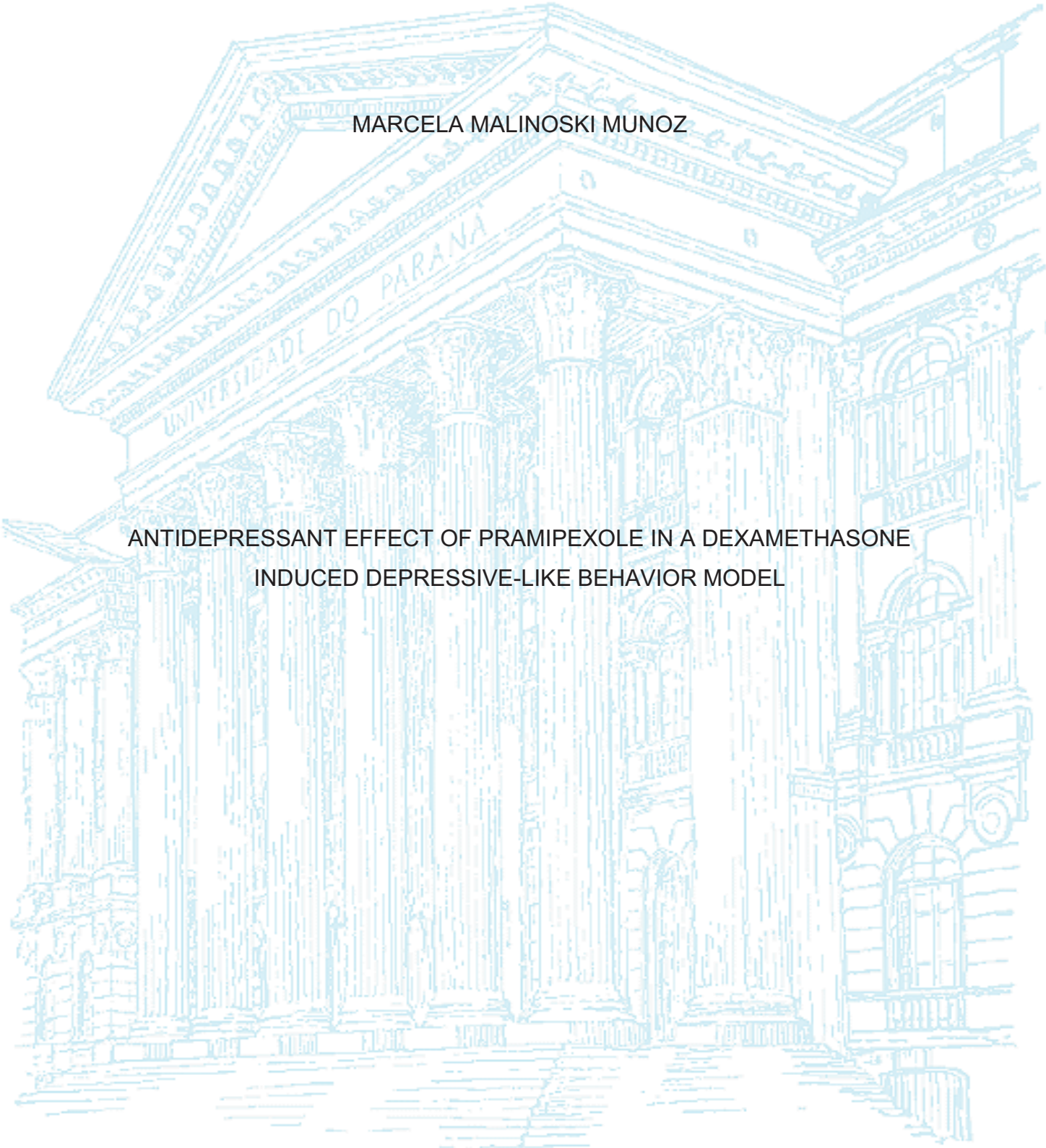
UNIVERSIDADE FEDERAL DO PARANÁ

MARCELA MALINOSKI MUNOZ




# ANTIDEPRESSANT EFFECT OF PRAMIPEXOLE IN A DEXAMETHASONE INDUCED DEPRESSIVE-LIKE BEHAVIOR MODEL

CURITIBA

2018

MARCELA MALINOSKI MUNOZ

# ANTIDEPRESSANT EFFECT OF PRAMIPEXOLE IN A DEXAMETHASONE INDUCED DEPRESSIVE-LIKE BEHAVIOR MODEL

Dissertação apresentada como requisito parcial à obtenção do grau de Mestre em Farmacologia, no Curso de Pós-Graduação em Farmacologia, Setor de Ciências Biológicas, Universidade Federal do Paraná.

Orientadora: Profª. Drª. Maria Aparecida Barbato Frazão Vital

CURITIBA

2018

Universidade Federal do Paraná. Sistema de Bibliotecas.
Biblioteca de Ciências Biológicas.
(Telma Terezinha Stresser de Assis –CRB/9-944)

Munoz, Marcela Malinoski
Antidepressant effect of pramipexole in a dexamethasone induced depressive like behavior model. / Marcela Malinoski Munoz. – Curitiba, 2018.
62 p.: il. ; 30cm.

Orientadora: Maria Aparecida Barbato Frazão Vital
Dissertação (Mestrado) - Universidade Federal do Paraná, Setor de Ciências Biológicas. Programa de Pós-Graduação em Farmacologia.

1. Depressão. 2. Dopaminérgicos. 3. Antidepressivos. I. Título. II. Vital, Maria Aparecida Barbato Frazão. III. Universidade Federal do Paraná. Setor de Ciências Biológicas. Programa de Pós-Graduação em Farmacologia.

CDD (20. ed.) 615.58

MINISTÉRIO DA EDUCAÇÃO
SETOR CIÊNCIAS BIOLÓGICAS
UNIVERSIDADE FEDERAL DO PARANÁ
PRÓ-REITORIA DE PESQUISA E PÓS GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO FARMACOLOGIA

# TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em FARMACOLOGIA da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **MARCELA MALINOSKI MUNOZ** intitulada: **Antidepressant effect of pramipexole in a dexamethasone induced depressive-like behavior model**, após terem inquirido a aluna e realizado a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de mestre está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

Curitiba, 17 de Agosto de 2018.

MARIA APARECIDA BARBATO FRAZÃO VITAL
Presidente da Banca Examinadora (UFPR)

JANAINA MENEZES ZANOVEL
Avaliador Interno (UFPR)

BRUNO JACSON MARTYNHAK
Avaliador Externo (UFPR)

## AGRADECIMENTOS

Primeiramente a Deus por ter me sustentado até aqui. Porque dEle, por Ele e para Ele são todas as coisas!

A minha família pelos conselhos, suporte e, sobretudo, por me apoiarem em todos os sonhos alçados ao longo da minha caminhada. Obrigada por não me deixarem desistir e me fazerem enxergar além das minhas próprias limitações.

A Profª Dra. Maria Vital pelo aceite em me orientar, pelos conselhos, pelos puxões de orelha e principalmente pela paciência.

Aos meus amigos e amigas por sempre me motivarem e levantarem o meu ânimo. Vocês são a família que eu escolhi ter.

Aos meus colegas de laboratório pelos conselhos, ajuda com os experimentos e paciência com os meus desabafos. Em especial à Joelle que me acompanhou em intermináveis experimentos.

Aos demais colegas, professores e funcionários do setor.

Aos funcionários do biotério, especialmente Luana e Gilmara pela gentileza com que sempre me trataram e constante disponibilidade em ajudar.

A cada um dos animais utilizados nos experimentos.

Aos membros da banca pela disponibilidade.

A UFPR por ter sido a minha casa nos últimos anos.

A CAPES pelo apoio financeiro.

A glória de Deus está nas coisas encobertas; mas a honra dos majestosos está em descobri-las!

(Provérbios 25:2)

## RESUMO

A depressão é um distúrbio psiquiátrico comum caracterizado por diversos sintomas debilitantes como a desesperança e a anedonia. Apesar de a fisiopatologia do distúrbio ainda não estar completamente elucidada, evidências demonstram a associação entre a depressão e disfunções do sistema dopaminérgico mesolimbico. Devido a isso, diversos estudos atuais têm buscado em fármacos que atuem nesse sistema novas alternativas terapêuticas para o tratamento da depressão. Nessa linha, o pramipexol – um agonista dos receptores dopaminérgicos D2/D3 – têm sido um foco de estudos pois, além da sua atividade direta nos receptores dopaminérgicos, esse medicamento também apresenta potencial neuroprotetor, anti-inflamatório e também de promover a liberação de fatores tróficos. Assim, com o objetivo de avaliar o efeito do pramipexol, os animais foram induzidos ao comportamento tipo-depressivo através do tratamento intraperitoneal com dexametasona (1 mg/kg) ou com o seu veículo por 21 dias e, em seguida, submetidas ao tratamento com o pramipexol no 21° e 22° dia. Nossos dados demonstraram que o modelo da dexametasona promoveu uma redução no peso e na locomoção dos animais. Além disso, também foi encontrada uma diferença estatisticamente significante entre os grupos dexametasona e veículo na preferência pela sacarose no 21° dia de tratamento e no tempo de imobilidade do teste de natação forçada, indicando um comportamento tipo-depressivo. Por sua vez, a administração repetida de pramipexol (1 mg/kg) foi capaz de reverter o comportamento tipo-depressivo induzido pela dexametasona no teste de natação forçada indicando um potencial para a droga no tratamento de distúrbios depressivos associados a altos níveis de glicocorticoides.



Palavras-chave: depressão maior; teste da natação forçada, agonista dopaminérgico; teste de preferência pela sacarose; antidepressivo.

## ABSTRACT

Major depressive disorder is a common psychiatric disease characterized by diverse debilitating symptoms that include hopelessness and anhedonia. Although the pathophysiology of depression has not been fully elucidated yet, it has been shown that there is a link between depression and an altered mesolimbic DA system function. Because of that, several current studies have investigated drugs that act in that system trying to find new therapeutic alternatives for depression treatment. In line with that, pramipexole – a D2/D3 dopaminergic receptors agonist – has received the attention of reserchers since it not only has a direct dopaminergic activity but also neuroprotective and antiinflamatory properties and the ability to promote the release of neurotrophic factors. Thus, with the goal of evaluating the effect of pramipexole, the animals were intraperitoneally treated for 21 days with dexamethasone (1 mg/kg) or its vehicle for depressive-like behavior induction and, after that, on day 21 and 22 with PPX. Our study showed that DEX treatment promoted a weight and locomotion reduction in treated animals. Also, there was a statistically difference between dexamethasone and vehicle groups only on day 21 in the sucrose preference test and in the immobility time in the forced swim test, indicating a depressive-like behavior.This state was reversed in the FST by the repeated PPX administration (1 mg/kg) indicating the drug potential in the treatment of depressive disorders associated with high glucocorticoid levels.



Key-words: major depressive disorder, forced swim test, dopaminergic agonist, sucrose preference test, antidepressant.

## LISTA DE FIGURAS

## LISTA DE ABREVIATURAS

5-HT – Serotonina

6-OHDA – 6-hidroxidopamina

BDNF – Fator neurotrófico derivado do cérebro

DA – Dopamina

DEX – dexametasona

DP – Doença de Parkinson

FST – Teste de natação forçada

GR – receptor glicocorticóide

HPA – hipotálamo-pituitária-adrenal

IP – Intraperitoneal

L-DOPA – Levodopa

LPS – Lipopolissacarídeo

MAO – enzima monoaminoxidase

MR – receptor mineralocorticóide

NA – Noradrenalina

NT – neurotransmissor

PPX – Pramipexol

SPI – Síndrome das Pernas Inquietas

SPT – Teste de preferência por sacarose

TCA – antidepressivo tricíclico

**SUMÁRIO**

# 1 INTRODUÇÃO

Globalmente, de acordo com dados do ano de 2015 publicados pela Organização Mundial de Saúde (OMS), a depressão atinge mais de 300 milhões de pessoas, o equivalente a 4,4% da população mundial (WHO, 2017; MILLER; RAISON, 2016). Além disso, a depressão frequentemente apresenta-se como uma condição recorrente associada a altos níveis de incapacidade funcional que afeta severamente a qualidade de vida do paciente acometido, podendo, em casos mais graves, inclusive levar ao suicídio (ALONSO et al., 2004; RENARD et al., 2010).

De acordo com a Associação Americana de Psiquiatria (2013), a depressão se caracteriza como um distúrbio no qual estão presentes sentimentos constantes e duradouros de tristeza, apatia, desespero, culpa e anedonia bem como sintomas físicos que se demonstram através da perda da motivação e interesse em atividades diárias. De maneira geral, os sintomas afetivos podem ser classificados em dois tipos principais: sintomas de afeto positivo e sintomas de afeto negativo. O afeto positivo geralmente encontra-se reduzido em pacientes com o distúrbio depressivo e inclui sentimentos de felicidade, interesse, energia, entusiasmo e autoconfiança. Ao contrário, o afeto negativo – usualmente elevado na depressão – se caracteriza por sentimentos subjetivos de angústia que se evidenciam por uma ampla gama de estados de humor negativos como o medo, ansiedade, irritabilidade, solidão, culpa e hostilidade (WATSON; TELLEGEN, 1985; WATSON et al., 1988).

O diagnóstico clínico da depressão maior pode ser realizado utilizando os critérios estabelecidos pelo Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-V), publicado pela Associação Americana de Psiquiatria. De acordo com este manual, o paciente pode ter o distúrbio diagnosticado quando apresentar ao menos cinco sintomas concomitantes pelo período mínimo de duas semanas. Esses sintomas incluem: humor deprimido na maior parte do dia (percebido pelo paciente ou por pessoas próximas), perda ou aumento significativo no peso e apetite, insônia ou hipersonia, agitação ou retardo psicomotor, fadiga, sentimentos de culpa ou inutilidade excessivos, redução da

capacidade de pensamento e concentração, pensamentos pessimistas e de morte recorrentes e prejuízo social. No entanto, para o diagnóstico definitivo da depressão maior, é indispensável que o humor deprimido ou a perda de interesse seja um dos sintomas experimentados do paciente (AMERICAN PSYCHIATRY ASSOCIATION, 2013).

Baseado na alta incidência da depressão na população mundial e nas consequências disso, inúmeros esforços da comunidade científica têm buscado elucidar não apenas o mecanismo fisiopatológico da doença como também encontrar novos tratamentos que sejam eficazes para esses pacientes. Partindo dessa ideia, esse trabalho procurou investigar o potencial antidepressivo do pramipexol – uma droga comumente utilizada no tratamento da doença de Parkinson – através de um modelo em ratos de comportamento tipo-depressivo induzido administração prolongada da dexametasona.

# 2 REVISÃO DE LITERATURA

## 2.1 DEPRESSÃO

### 2.1.1 Patogênese e Etiologia da depressão

A depressão é um distúrbio de natureza heterogênea e é provável que inúmeras vias distintas sejam capazes de levar ao distúrbio. Todavia, sabe-se que a interação entre suscetibilidades individuais e fatores ambientais é essencial para o seu desenvolvimento (SULLIVAN et al., 2000; RENARD et al., 2010).

Ao longo do tempo, diversas hipóteses foram formuladas a respeito da fisiopatologia dos distúrbios depressivos. Dentre elas, Schildkraut (1965) propôs que a depressão seria ocasionada pela redução da concentração de neurotransmissores monoaminérgicos em determinados locais do cérebro.

Essa teoria foi posteriormente redirecionada para a hipótese serotoninérgica da depressão, que afirma que a redução da síntese de serotonina (5-HT) e consequente hipoatividade serotoninérgica estaria diretamente associada ao desenvolvimento da depressão (PRAAG, VAN; KORF, 1971; OWENS; NEMEROFF, 1994). Entretanto, apesar do enfoque central dado ao papel da 5-HT e, em seguida, da noradrenalina (NA), pesquisas utilizando métodos farmacológicos, de neuroimagem e eletrofisiológicos em modelos humanos e animais da depressão têm oferecido suporte à função da dopamina (DA) na fisiopatologia do distúrbio depressivo (BUNNEY JR; DAVIS, 1965; SERRA et al., 1979; WILLNER, 1983a, 1983b; NUTT et al., 2007; BELUJON; GRACE, 2017). De fato, tanto a depressão como a anedonia têm sido associadas com uma redução da resposta estriatal à recompensa. Além disso, em pacientes depressivos com anedonia, exames de imagem têm demonstrado reduções significativas na ligação do transportador de dopamina em comparação a indivíduos saudáveis, sugerindo um *down-regulation* dos receptores ocasionado pela redução das concentrações de dopamina (BELUJON; GRACE, 2017).

Dessa maneira, partindo de novas informações, a partir dos anos 2000 houve a maior modificação da ideia monoaminérgica inicial. Surgiu então a hipótese da neuroplasticidade que integra os mecanismos de sinalização pós-receptor e os mecanismos de expressão gênica – incluindo a epigenética – com diversos outros processos como mecanismos sinápticos, neurotróficos e com a neurogênese. Portanto, essa hipótese propõe que a depressão é o resultado de um conjunto de readaptações cerebrais em resposta a estímulos internos e externos de diversas naturezas (Revisado por RACAGNI; POPOLI, 2008).

Dentro da hipótese da neuroplasticidade, uma área muito explorada no momento é a associação entre a inflamação, ativação da imunidade mediada por células e a depressão. Essa ligação partiu da observação inicial do denomidado comportamento doentio (*sickness behavior*), no qual um indivíduo acometido por uma enfermidade que promova respostas inflamatórias no organismo, também apresenta alterações comportamentais tipicamente encontradas em quadros depressivos como letargia, perda do apetite e humor

deprimido. Dessa maneira, essa teoria se embasa na existência de diversas características típicas da resposta inflamatória em grande parte dos pacientes depressivos. Isso inclui o aumento da expressão de citocinas inflamatórias e seus receptores, aumento de proteínas de fase aguda e moléculas solúveis de adesão no sangue periférico e no líquido cefalorraquidiano. Somado a isso, a descoberta de que as citocinas proinflamatórias interagem com diversos fatores fisiopatológicos que caracterizam a depressão como o metabolismo de neurotransmissores, funções neuroendócrinas, plasticidade sináptica e comportamento, bem como o fato de diversos medicamentos antidepressivos terem atividade anti-inflamatória, fornece ainda mais peso a essa hipótese (MAES, 1995, 2011; YIRMIYA et al., 2001; RAISON et al., 2006; MAES et al., 2011). Entretanto, outros autores ressaltam que a ativação do processo inflamatório não é um fator indispensável nem suficiente de forma isolada para produzir a síndrome atualmente definida como depressão e portanto a depressão não poderia ser considerada unicamente um distúrbio inflamatório (RAISON; MILLER, 2011).

Com efeito, estudos das últimas décadas têm demonstrado que a hiperatividade do eixo hipotalâmico-pituitária-adrenal (HPA), com consequente aumento dos níveis basais de cortisol, são os achados biológicos mais consistentes em alguns tipos de depressão (PARIANTE; LIGHTMAN, 2008). A ativação do eixo HPA não apenas regula funções corporais periféricas como metabolismo e imunidade, mas também possui acentuados efeitos no cérebro como a regulação da sobrevivência neuronal, neurogênese, aquisição de novas memórias e avaliação de eventos emocionais. De fato, estudos mostram que mesmo pacientes recuperados de quadros depressivos ainda apresentam níveis maiores de cortisol salivar do que os controles negativos (BHAGWAGAR et al., 2003). Esse aumento na concentração parece estar relacionado à redução do *feedback* negativo dos glicocorticoides endógenos que, ao se ligarem aos seus receptores (receptores glicocorticoides e mineralocorticoides) ao longo do eixo, deveriam atuar como potentes reguladores da síntese e liberação do fator liberador de corticotrofina (CRF) a partir do núcleo paraventricular e da pro-opiomelanocortina/ACTH na pituitária (CHAOULOFF, 2000; HEIM et al., 2000; PARIANTE; MILLER, 2001; PARIANTE; LIGHTMAN,

2008). Essa hipótese é reforçada pelos dados que mostram falhas no *feedback* negativo do eixo HPA em pacientes com o distúrbio depressivo submetidos ao teste de supressão pela dexametasona – um glicocorticoide sintético (CARROLL, 1980). Dessa forma, os achados sugerem que a hiperativação do eixo HPA descrita na depressão não é uma consequência da depressão e sim uma manifestação de anormalidades neurobiológicas – como uma redução no número ou na função dos receptores glicocorticoides (GR), por exemplo – que predisporia ao desenvolvimento da depressão (KLOET et al., 1998; PARIANTE, 2006; PARIANTE; LIGHTMAN, 2008; ANACKER et al., 2011).

Sabe-se também que um dos principais fatores de risco para o desenvolvimento da depressão maior é o estresse psicológico, sendo que grande parte dos episódios iniciais de depressão são precedidos por algum agente estressor identificável (KENDLER et al., 2000). Na verdade, situações de estresse promovem não apenas a elevação dos níveis basais de cortisol, mas também o aumento da produção de citocinas inflamatórias (BENOIT et al., 2001) e, unidos, ambos os fatores são capazes de reduzir a biodisponibilidade de serotonina devido ao aumento da expressão das enzimas da via das quinureninas, por exemplo (STRASSER et al., 2017). Nessa linha, é reconhecido que os processos inflamatórios contribuem para as alterações estruturais e funcionais no SNC que levam ao desenvolvimento da depressão (IWATA et al., 2013). Além disso, estudos mostram que citocinas inflamatórias são capazes de reduzir a função dos GR (PARIANTE et al., 1999). Portanto, em teoria, a resistência glicocorticoide nos tecidos alvo pode levar a ativação imune. De maneira análoga, a inflamação, por sua vez, é capaz de estimular a atividade do eixo HPA tanto pela ação direta das citocinas no cérebro como pela indução da resistência aos glicocorticoides, formando uma via interdependente entre processos que levam às alterações patológicas encontradas no distúrbio depressivo como a redução da concentração de neurotransmissores, atrofia de estruturas cerebrais como o hipocampo, redução da neurogênese e alterações na plasticidade neuronal (RAISON et al., 2006; SAVEANU; NEMEROFF, 2012; BOKU et al., 2018). Dessa forma, o estresse parece ser o *link* patológico que promove o gatilho entre a disfunção do eixo HPA, a inflamação e a depressão.

### 2.1.2 Tratamento

A primeira classe de medicamentos disponível para o tramento da depressão foi a dos inibidores da monoaminooxidase (MAOis). Os medicamentos desse grupo atuam inibindo de forma reversível ou irreversível a enzima MAO, responsável pelo metabolismo dos neurotransmissores NA, 5-HT e DA, promovendo um aumento geral na disponibilidade destes NT no SNC. Entretanto, apesar da sua grande eficácia terapêutica, é uma classe pouco utilizada em decorrência dos seus efeitos adversos potencialmente fatais (RIEDERER et al., 2004). Outra classe terapêutica é a dos antidepressivos tricíclicos (TCAs), que consistem em uma classe variada de drogas cujo principal mecanismo de ação é a inibição dos transportadores monoaminérgicos de membrana culminando no aumento da disponibilidade extracelular dos NT monoaminérgicos. Todavia, essa classe também apresenta uma gama de efeitos adversos que, em sua maioria, se devem ao variável antagonismo de receptores muscarínicos, adrenérgicos e histaminérgicos (THASE; KUPFER, 1996; RACAGNI; POPOLI, 2008; SARTORIUS et al., 2007).

Os principais medicamentos utilizados na atualidade são os chamados antidepressivos de segunda geração. Essa denominação inclui diversas classes de medicamentos como os inibidores seletivos da recaptação de serotonina (ISRS), inibidores seletivos da recaptação de serotonina e noradrenalina (ISRSN), inibidores da recaptação de noradrenalina (IRNA) e antidepressivos atípicos que, em geral, atuam como antagonistas de receptores serotoninérgicos. Devido ao fato de apresentarem efeitos adversos mais toleráveis, esses medicamentos foram substituindo os fármacos empregados anteriormente sem, entretanto, apresentar uma eficácia significativamente maior do que os TCAs. Além disso, um dos grandes problemas enfrentados na terapêutica da depressão é a latência de 2 a 4 semanas para o aparecimento da eficácia terapêutica e a falta de resposta de muitos pacientes ao tratamento com determinados fármacos (THASE; KUPFER, 1996; HOLLON et al., 2002; SARTORIUS et al., 2007; RACAGNI;

POPOLI, 2008a; CZÉH et al., 2016). Dessa maneira, conforme mencionado anteriormente, as terapias atuais ainda conferem muitas limitações ao tratamento da depressão, especialmente em relação a velocidade de início dos efeitos terapêuticos, tornando indispensável a busca por medicamentos mais eficazes, com ação mais rápida e com menos efeitos adversos (DERUBEIS et al., 2008).

Apesar do enfoque farmacoterapêutico, também são indicadas medidas não farmacológicas como as terapias cognitivas e comportamentais, a realização de exercícios físicos e, no caso de pacientes não responsivos ao tratamento medicamentoso convencional, a eletroconvulsoterapia (SACKEIM et al., 2001; HOLLON et al., 2002; SARTORIUS et al., 2007; DERUBEIS et al., 2008).

## 2.2 PRAMIPEXOL

O pramipexol (2-amino-4,5,6,7-tetrahidro-6-propil-amino-benzo-tiazol-dihidroclorido) é um potente agonista não-ergot que atua tanto em níveis pré como pós-sinápticos nos receptores dopaminérgicos da subfamília D2 (que inclui os receptores D2, D3 e D4) (MIERAU; SCHINGNITZ, 1992; MIERAU et al., 1995; BENNETT JR; PIERCEY, 1999). Seu uso nos Estados Unidos e na maioria dos países europeus foi aprovado no final da década de 90 como terapia única ou adjunta à levodopa para o tratamento dos sinais e sintomas da Doença de Parkinson e, posteriormente, seu emprego foi também aprovado para o tratamento da síndrome das pernas inquietas (SPI). Atualmente, é utilizado principalmente na SPI e como terapia inicial na Doença de Parkinson, sendo capaz de retardar por diversos anos o início do tratamento com a L-DOPA (AIKEN, 2007; ANTONINI; CALANDRELLA, 2011).

Esse medicamento apresenta baixa ligação às proteínas plasmáticas e é eliminado majoritariamente na sua forma inalterada pela urina (cerca de 90%). Tem uma meia-vida que pode variar de 8-12h e biodisponibilidade superior a 90%, sendo atingido o pico plasmático cerca de 2h após a

administração por via oral (WRIGHT et al., 1997). Devido ao metabolismo hepático inexpressivo, o pramipexol é considerado uma droga segura para pacientes com insuficiência hepática ou polimedicados, no entanto, reduções de doses são recomendadas para indivíduos com problemas renais ou que façam uso concomitante de drogas excretadas pelo transporte catiônico renal (AIKEN, 2007; ANTONINI; CALANDRELLA, 2011). É também considerado mais seguro que os agonistas dopaminérgicos ergot como a cabergolina e pergolida na ocorrência da doença cardíaca vascular restritiva (ANTONINI; POEWE, 2007).

No entanto, na análise de diversos estudos – apesar da sua relativa segurança – cerca de 9% dos pacientes que iniciam o tratamento com o PPX descontinuam o uso devido a efeitos adversos limitantes que incluem náuseas, dores de cabeça e sonolência (AIKEN, 2007). Além desses efeitos comuns, também podem ser encontrados efeitos mais graves que parecem ser associados ao efeito pronunciado do PPX sobre os receptores D3 como o aumento do risco de psicose e o aparecimento de comportamentos compulsivos como *punding,* apostas patológicas, compras, hiperfagia, desinibição e hipersexualidade. Esses efeitos adversos geralmente são dose-dependentes, ocorrendo em cerca de 30% dos pacientes que utilizam doses elevadas do PPX, e podem ser reduzidos consideravelmente pela adequação clínica da dosagem, todavia, em alguns casos, pode ser necessária a substituição da droga por outro agonista dopaminérgico (EVANS et al., 2004; KLOS et al., 2005; SANSONE; FERLAN, 2007; SALAS et al., 2009; KOLLA et al., 2010; AHLSKOG, 2011; MARUO et al., 2016).

Estudos animais tanto *in vitro* como *in vivo* propõem a existência de diversas propriedades neuroprotetoras do pramipexol que incluem a sua atividade antioxidante direta, a possível redução do estresse oxidativo, a capacidade de bloquear o poro de transição de permeabilidade mitocondrial, seu potencial anti-inflamatório e também sua capacidade de estimular a liberação de fatores tróficos (HALL et al., 1996; CASSARINO et al., 1998; ZOU et al., 1999; LEVANT et al., 1999; LE et al., 2000; PRESGRAVES et al., 2004; GU et al., 2004; JOYCE et al., 2004; PAN et al., 2005; SAYEED et al., 2006;

IZUMI et al., 2007; NAKAYAMA et al., 2009; FERRARI-TONINELLI et al., 2010; LI et al., 2010; LIEBERKNECHT et al., 2016; LUIS-RAVELO et al., 2017).

Além disso, diversos modelos animais de depressão demonstraram alterações no sistema dopaminérgico mesolímbico. Modificações na expressão de receptores dopaminérgicos nas estruturas límbicas foram observadas em diferentes modelos de comportamento tipo-depressivo como o desamparo aprendido e o estresse crônico moderado (PRUESSNER et al., 2004). Essas alterações parecem ser um reflexo da redução da liberação de dopamina na sinapse – conforme evidenciado pela redução na concentração do metabólito ácido homovanílico – bem como a redução da atividade dopaminérgica estriatal, também descrita em pacientes deprimidos em comparação aos controles saudáveis (BELUJON; GRACE, 2017). Aliado a essas observações da atuação do sistema dopaminérgico na depressão, experimentos utilizando alguns modelos do comportamento tipo-depressivo têm indicado o potencial do PPX na reversão destes comportamentos nos animais, (WILLNER et al., 1994; MAJ et al., 1997; BREUER et al., 2009; LIEBERKNECHT et al., 2016).

Em humanos, por sua vez, estudos têm demonstrado a eficácia do PPX no manejo da depressão associada à DP, da depressão unipolar e bipolar bem como na terapia adjunta para os pacientes refratários ao tratamento antidepressivo convencional (CORRIGAN et al., 2000; CASSANO et al., 2004; ZARATE et al., 2004; BARONE et al., 2006, 2010; LEMKE et al., 2006; AIKEN, 2007; PICILLO et al., 2009; MAH et al., 2011; ESCALONA; FAWCETT, 2017). Desta maneira, agonistas D3, como o pramipexol, parecem ser eficazes não apenas nos sintomas motores da DP, mas também nos sintomas não motores da doença – em particular, a depressão (MAJ et al., 2000; ANTONINI; CALANDRELLA, 2011).

Desta maneira, agonistas D2-D3, como o pramipexol, parecem ser eficazes não apenas nos sintomas motores da DP, mas também em outros distúrbios – em particular, a depressão (MAJ et al., 2000; ANTONINI; CALANDRELLA, 2011). Sugere-se que esta eficácia antidepressiva possa ocorrer em consequência da distribuição elevada de receptores do subtipo D3 nas regiões límbicas do encéfalo. Dentre os receptores da subfamília D2, o PPX apresenta afinidade cerca de 8x maior pelos receptores do subtipo D3 do

que pelos receptores D2 e D4 (GERLACH et al., 2003). O fármaco também parece apresentar uma baixa atividade nos receptores serotoninérgicos 5-HT1A e baixa afinidade pelos receptores 5-HT2A, 5-HT2B e pelo receptor dopaminérgico D1 o que também pode auxiliar no seu potencial antidepressivo (NEWMAN-TANCREDI *et al.*, 2002a; NEWMAN-TANCREDI *et al.*, 2002b; ANTONINI; POEWE, 2007). No entanto, ainda são necessários estudos a fim de que o mecanismo exato pelo qual o pramipexol exerce as suas atividades nos animais e pacientes avaliados seja elucidado.

## 2.3 MODELO ANIMAL DE DEPRESSÃO INDUZIDA POR DEXAMETASONA

O uso de modelos animais tem sido de grande valia para os avanços científicos obtidos nos últimos anos. Todavia, a fim de que um modelo apresente confiabilidade, alguns critérios devem ser respeitados. De acordo com Willner (1984), idealmente os modelos animais devem assemelhar-se às condições humanas apresentando similaridade entre os fenótipos comportamentais e perfis de sintomas clínicos (validade de face), resposta ao tratamento com as drogas efetivas clinicamente (validade preditiva) e características neurobiológicas equivalentes (validade construto).

Contudo, a depressão é um distúrbio multifatorial cujos mecanismos ainda não são plenamente esclarecidos e tanto os seus sintomas quanto as respostas ao tratamento podem variar diametralmente entre um paciente e outro – como exemplo, podemos citar os sintomas de insônia ou hipersonia, perda ou ganho de peso e agitação ou retardo psicomotor. Da mesma forma, é esperado que modelos individuais simulem determinados subtipos de sintomas, de acordo com as condições responsáveis pela sua indução (CZÉH et al., 2016).

Conforme mencionado anteriormente, os principais achados biológicos na depressão maior são a hiperativação do eixo HPA e o aumento dos níveis

basais de cortisol (HOLSBOER, 2000; PARIANTE; MILLER, 2001). Fundamentado nisso e no fato de que o estresse é um fator estimulante para a liberação de corticoides endógenos, a grande maioria dos modelos animais de depressão empregados atualmente envolvem respostas comportamentais a procedimentos estressantes como é o caso do desamparo aprendido, do teste da natação forçada e do estresse crônico moderado. Entretanto, os resultados obtidos a partir desses modelos nem sempre conseguem ser fielmente replicados por outros grupos. A inconsistência dos resultados entre os estudos pode estar relacionada com diferenças de procedimentos e mesmo com as variabilidades individuais de resposta ao estresse e, por esse motivo, buscaram-se alternativas para mitigar estes problemas (HARRIS et al., 1998; NIELSEN et al., 2000; VEENEMA et al., 2003; VOLLMAYR; HENN, 2003; BARDEN, 2004; ANISMAN; MATHESON, 2005; WILLNER, 2005; CASAROTTO; ANDREATINI, 2007). Apoiado no reconhecimento de que humanos expostos a terapias sistêmicas de duração prolongada com dexametasona – um glicocorticoide sintético com alta afinidade pelos GR – frequentemente são acometidos por modificações comportamentais semelhantes às encontradas em pacientes depressivos (CARPENTER; GRUEN, 1982; STANBURY; GRAHAM, 1998), foi demonstrado que a administração crônica de glicocorticoides é capaz de afetar a função do SNC reproduzindo alguns sintomas tipo-depressivos em roedores além de promover o aumento da expressão de genes relacionados ao estresse e a redução do volume hipocampal, outro achado característico nas análises de pacientes com o transtorno depressivo (BREMNER et al., 2000; MCEWEN, 2007; GOURLEY et al., 2008; TAYLOR et al., 2014; SKUPIO et al., 2015). Além disso, com a efetividade do tratamento antidepressivo, com frequência ocorre a normalização do eixo HPA anteriormente hiperativo possivelmente por intermédio do aumento da concentração celular do GR – tornando o sistema mais suscetível ao *feedback* inibitório do cortisol (PEPIN et al., 1989; BARDEN, 2004).

Portanto, o modelo de depressão pela administração crônica da dexametasona parece ser um modelo adequado visto que preenche quase que integralmente os critérios previamente organizados por Willner (1984).

# 3 OBJETIVOS

## 3.1 OBJETIVO GERAL

Investigar o efeito do Pramipexol no modelo animal de comportamento tipo-depressivo induzido pelo tratamento prolongado com dexametasona em ratos.

## 3.2 OBJETIVOS ESPECÍFICOS

- Analisar o efeito do tratamento prolongado com dexametasona no comportamento dos animais através dos testes de campo aberto e preferência pela sacarose.
- Avaliar, através do teste de natação forçada, o efeito do pramipexol no comportamento tipo-depressivo induzido pela dexametasona.

# 4 ARTIGO CIENTÍFICO

Os materiais e métodos, resultados e discussão do trabalho encontram-se no artigo científico a seguir.

Antidepressant-like effect of pramipexole in a dexamethasone-induced depressive-like behavior model

Marcela M. Munoz, Joelle de M. Turnes, Leonardo C. Souza, Eric L. R. Moura, Roberto Andreatini, Maria A. B. F. Vital

Pharmacology Department, Federal University of Parana, Brazil

## 4.1 ABSTRACT

Major depressive disorder is a common psychiatric disease characterized by diverse debilitating symptoms that include hopelessness and anhedonia. Because of that, several studies have sought new therapeutic alternatives for depression treatment, including the drug pramipexole, a D2/D3 dopaminergic receptors agonist. Although the pathophysiology of depression has not been fully elucidated yet, it has been shown that the systemic exposure to glucocorticoids, like dexamethasone, is capable of inducing some of the behavioral features of depression in humans and, thus, has been used as an animal model of the disease. Therefore, the present study investigated the effects of pramipexole in the depressive-like behavior induced by prolonged exposure to dexamethasone. The animals were intraperitoneally treated for 21 days with dexamethasone (1 mg/kg) or its vehicle. Our study showed that DEX treatment promoted a weight and locomotion reduction in treated animals. Also, there was a statistically difference between dexamethasone and vehicle groups only on day 21 in the sucrose preference test. In the forced swim test, animals who received DEX treatment showed a increase in the immobility time that, associated with de SPT result, indicates a depressive-like behavior. This state was reversed in the FST by the repeated PPX administration (1 mg/kg) indicating the drug potential in the treatment of depressive disorders associated with high glucocorticoid levels.

Key-words: major depressive disorder, forced swim test, dopaminergic agonist, sucrose preference test, antidepressant.

Abbreviations: MDD, major depressive disorder; PPX, pramipexole; DEX, dexamethasone; PFC, pre-frontal cortex; HPA-axis, hypothalamus-pituitary-adrenal axis; DST, dexamethasone supression test; FST, forced swim test; SPT, sucrose preference test; GR, glucocorticoid receptor; CNS, central nervous system; BDNF, brain-derived neurotrophic factor; LPS, lipopolissacaride; NO, nitric oxide; GMPc, cyclic guanosine monophosphate; D1R, Dopaminergic 1 receptor; D2R, Dopaminergic 2 receptor; 6-OHDA, 6-hidroxydopamine;

## 4.2 INTRODUCTION

Depression is a heterogeneous disorder affecting approximately 4,4% of the world population in 2015 (WHO, 2017). The disorder frequently presents as a recurrent condition with high levels of functional disability that affects the quality of life of the patient and also has a negative impact on people present in their social circle (Alonso et al., 2004; Gerhard et al., 2016; Krishnan and Nestler, 2008; Kupfer et al., 2012). According to the American Psychiatric Association (2013), depression is characterized as a disorder in which feelings of sadness, apathy, despair, guilt and anhedonia are constantly present, as well as physical symptoms that are demonstrated through decrease of cognition and memory, loss of motivation and a reduced interest in daily activities. Brain-imaging studies of patients with depressive disorder shows evidence of the existence of a dysregulation in the connectivity within pre-frontal cortex (PFC) networks and their target limbic regions and that those problems are responsible for the

disturbances in emotional, cognitive and autonomic regulation found in those patients (PRICE; DREVETS, 2010).

As a multifactorial disorder, current hypothesis suggest that several interactions between individual susceptibilities (genetic and environment predisposition) and stressful life events can lead to the onset of the depressive disorder (KESSLER, 1997; KENDLER et al., 2000; SULLIVAN et al., 2000; UCHIDA et al., 2017). Those interactions seems to be responsible for disturbances of key molecular pathways including the hypothalamus-pituitary-adrenal axis (HPA-axis), imune system, neurotransmitter systems, cell signaling, synaptic plasticity and neurogenesis (CHAOULOFF, 2000; PARIANTE; LIGHTMAN, 2008; RACAGNI; POPOLI, 2008b; DUMAN; AGHAJANIAN, 2012; DUMAN; LI, 2012; SAVEANU; NEMEROFF, 2012; SCHOENFELD; GOULD, 2012; UCHIDA et al., 2017).

Studies estimate that about 1% of the general population receives long-term systemic glucocorticoids. Since the middle of the 20th century, corticosteroids have been prescripted to treat common medical problems such as asthma, allergies and autoimmune diseases. However, such use, especially at high doses for extended periods, is associated with several systemic side effects that include diabetes, osteoporosis, cardiovascular disease, glaucoma, cataracts and also psychiatric disturbances (BROWN; CHANDLER, 2001; FARDET et al., 2015; MUNDELL et al., 2017). In addition to the findings that patients receiving chronic corticosteroids present psychiatric disturbances including depression, several studies in the last decades have shown that a significant amount of patients with some types of depressive disorder have high basal levels of cortisol due to HPA-axis hyperactivity (PARIANTE; MILLER, 2001; KELLER et al., 2017), and even in recovered patients with depression, it is still possible to find an increase in concentration of waking salivary cortisol compared to controls (BHAGWAGAR et al., 2003). This hyperactivity in depressive individuals is one of the most consistent findings in biological psychiatry and may be related to failures in HPA-axis negative feedback since most patients with depressive disorder have a bad response to the dexamethasone suppression test (DST) (CARROLL, 1980; FOUNTOULAKIS et al., 2008).

Based on the fact that stress is a stimulating factor for the release of endogenous corticoids, the vast majority of currently used animal models of depression involve behavioral responses to stressful procedures, such as, the learned helplessness, forced swim test and the chronic mild stress. However, the results obtained from those models can not always be faithfully replicated by other groups. The inconsistency of the results between studies may be related to differences in procedures and even with the individual variability of stress response and, therefore, alternatives were sought to mitigate these problems (HARRIS et al., 1998; NIELSEN et al., 2000; VEENEMA et al., 2003; VOLLMAYR; HENN, 2003; BARDEN, 2004; ANISMAN; MATHESON, 2005; WILLNER, 2005; CASAROTTO; ANDREATINI, 2007). Considering that humans exposed to long-term systemic therapies with dexamethasone - a synthetic glucocorticoid with high affinity for glucocorticoid receptor (GR) - are often affected by behavioral changes similar to those found in depressive patients (CARPENTER; GRUEN, 1982; STANBURY; GRAHAM, 1998), it has been demonstrated that chronic glucocorticoid administration is able to affect central nervous system (CNS) function by reproducing some depressive-like signs in rodents, in addition to promoting increased expression of stress-related genes and reduced hippocampal volume, another characteristic finding in the analysis of patients with the depressive disorder (BREMNER et al., 2000; MCEWEN, 2007; GOURLEY et al., 2008; TAYLOR et al., 2014; SKUPIO et al., 2015). Also, glucocorticoids acute and chronic administration are capable of modulate serotoninergic and dopaminergic systems and those systems are highly correlated with the depresive disorders (INOUE; KOYAMA, 1996; WRÓBEL et al., 2004).

Pramipexole (PPX) is a potent non-ergot agonist that acts at both pre and post-synaptic levels at dopaminergic receptors in the D2 subfamily (MIERAU; SCHINGNITZ,

1992; MIERAU et al., 1995; BENNETT JR; PIERCEY, 1999). Its use is approved both as a single therapy and as an adjunct to levodopa for the treatment of signs and symptoms of Parkinson's disease (PD) and also for the treatment of restless legs syndrome (Aiken, 2007; Antonini; Calandrella, 2011). However, several experiments using animal models of depressive-like behavior have indicated the potential of PPX in reversing these behaviors in animals. Among them, there is evidence of the reversal of anhedonia induced by moderate chronic stress in rats (WILLNER et al., 1994), the reduction of immobility time in the forced swim test in ACTH-treated rats (KITAGAWA et al., 2009), normalization of hyperlocomotion in olfactory bulbectomized rats (BREUER et al., 2009), the reversal of depressive-like behavior and increase of BDNF levels in the limbic structures in the pre-clinical model of PD induced by 6-OHDA (Berghauzen-Maciejewska et al., 2015, 2014) and, in a LPS-induced model, anhedonia and depressive-like behaviour were reversed after PPX treatment (LIEBERKNECHT et al., 2016). However, to our knowledge, there is no study so far demonstrating the efficacy of PPX in the model of depressive-like behavior induced by dexamethasone prolonged administration considering the dexamethasone modulating activity both in the dopaminergic and seratoninergic systems.

## 4.3. MATERIAL AND METHODS

### 4.3.1. Animals

Male Wistar rats from our breeding colony were used, weighing 290-330 g at the beginning of the treatment. The animals were randomly housed in groups of four to five in polypropylene cages with wood shavings as bedding and maintained in a temperature-controlled room (22 ± 2ºC) on a 12 h/12 h light/dark cycle (lights on at 7:00 AM). Before beginning any experimentation, the rats were allowed to acclimate to the environment and handling for at least 1 week. Experiments were performed during the light phase of the day. The animals had free access to water and food throughout the experiment. The studies were performed in accordance with the guidelines of the Committee on Care and Use of Experimental Animals Resources. The experimental protocol complied with the recommendations of Federal University of Parana and was approved by the University Ethics Committee (CEUA protocol # 1009/2016).

### 4.3.2. Drugs

#### 4.3.2.1 Dose-response curve in the FST (Experiment I)

Pramipexole (Biosintetica, Brazil) was dissolved in saline and injected intraperitoneally at 3 different doses, respectively: 1, 2, and 3 mg/kg. Saline injected animals served as controls. Additionally, imipramine treated animals (25 mg/kg i.p., dissolved in saline) served as “positive control” in the modified Forced Swim Test. The drugs doses were defined in accordance with articles published earlier (Ostadhadi et al., 2016; Schulte-Herbrüggen et al., 2012).

#### 4.3.2.2 Dexamethasone prolonged treatment (Experiment II)

Dexamethasone was purchased from EMS (Brazil), dissolved in saline solution in the concentration of 1 mg/mL, which was injected i.p (10-10:30 am) at a dose of 1 mg/kg for 21 days (KIM et al., 2015). The dexamethasone vehicle was injected in the control group. Pramipexole was dissolved in saline solution in the concentration of 0.3 mg/mL, which was injected i.p.three times on days 21 and 22 at a dose of 1 mg/kg, defined by the dose-response curve results. The pramipexole vehicle was injected in the control groups.

### 4.3.3. Behavioral evaluations

4.3.3.1 Open field test (OFT)
This test was used to determine motor alterations on days 7 and 14 of dexamethasone or vehicle treatment after a basal evaluation and on the day 22 to evaluate a possible motor effect of the tested drug (PPX). The apparatus consisted of a circular arena (97 cm diameter, 42 cm wall height) divided into three concentric circles and subdivided into 19 quadrants. The animals were gently placed in the center of the open field and allowed to freely explore the arena for 5 min. Two motor parameters were assessed through this test: locomotion frequency (i.e., the number of crossings from one quadrant to another) and rearing frequency (i.e., the number of times the animals stood on their hind paws). The open field apparatus was washed with a 5% water-alcohol solution before and between the open field tests to eliminate possible odors left by other animals (GOULD et al., 2009).

4.3.3.2 Modified forced swim test (FST)
This test was a modification of the method proposed by Porsolt et al. (1978) and Rénéric et al. (2002). This protocol was already validated in our lab in previous published data (SANTIAGO et al., 2010; BASSANI et al., 2014). The test was conducted in two sessions. In the training session, the rats were placed in a cylindrical tank that contained water at a temperature of 24 ± 1ºC at a depth of at least 30 cm for 15 min. In the next day (24 h after the training session), the rats were subjected to the test session which consisted of only 5 min. The animals received the drug treatment (PPX or vehicle) 23, 5 and 1h before the test. The test session was filmed for subsequent evaluation of the following parameters: immobility (i.e., absence of movement of the whole body of the animal, except for small movements necessary to keep its head above water), swimming (i.e., large movements with the forepaws that displaced water and were more than necessary to keep head above water) and climbing (i.e., vigorous movements of the forepaws in and out of the water, usually directed against the wall of the tank). The water was switched after each animal to avoid possible bias. This test was performed on day 22, one day after the last dexamethasone or vehicle injection.

4.3.3.3 Sucrose preference test (SPT)
Sucrose preference is frequently used as measure of anhedonia in rodents (Casarotto and Andreatini, 2007; Papp et al., 1991; Santiago et al., 2010). The animals were transferred into single housing cages with free access to food. Each rat was provided with two bottles of water, pre-weighed, on the extreme sides of the cage during the 24 h training phase to adapt the rats to drink from two bottles. After training, one bottle was randomly switched to contain 0,5% sucrose solution. The sum of water consumption and sucrose consumption was defined as the total fluid intake. The percentage of sucrose intake was calculated by using the following equation (% sucrose preference=sucrose intake×100/total intake). All the tests were carried out weekly for 24h, beginning with the basal test one week prior to the first dexamethasone exposure (to provide baseline values) and finishing 21 days after the treatment beginning. After the sucrose preference test, all the rats received free access and water.

4.3.4 Experimental design

4.3.4.1 Dose-response curve (Experiment I)
After one week of adaptation to the new environment, the animals were tested in the FST protocol as previously described. On day one, the rats were trained (training session) and each group received the first drug (PPX, IMIP or VEH) injection (i.p). On the test day, the drugs were administered 5h and 1h prior to the test as a repeated

treatment. The locomotor activity of animals was determined through the OFT, before the test session of the FST (Fig. 1). The experiments were filmed for posterior evaluation.

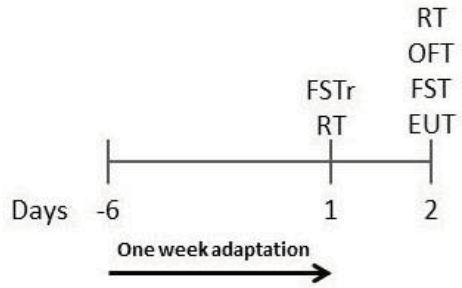



Fig 1. Experimental design (Experiment I). Abbreviations used: FSTr, forced swim test (training session); PPX, pramipexole treatment (PPX/IMIP/VEH); OFT, open field test; FST, forced swim test (test session); EUT, euthanasia;

4.3.4.2 Dexamethasone prolonged treatment (Experiment II)

Before the beginning of the experimental protocol, the rats were submited to the basal SPT. After that, the rats with more than 65% of sucrose preference were submited to the overall OFT and randomly distributed into two groups: dexamethasone (1 mg/kg) and vehicle (saline) that received the treatment for 21 consecutive days. Each animal was weighed at the beginning of the experimental protocol and every 2 days throughout the experimental protocol. After the beginning of drug treatment, the SPT was conducted on the 7th, 14th and 21th days and the OFT on the 7th, 14th and 22th days. After the last dexamethasone exposure, the animals were divided into four groups: vehicle+vehicle (control), dexamethasone+vehicle (dexamethasone), vehicle+ pramipexole (pramipexole), and dexamethasone+pramipexole (dex+ppx). On the 21th (training session) and 22th (test session) day after the first dexamethasone or vehicle exposure, the animals were tested using a modification of the method proposed by Porsolt et al. (1978) and Reneric et al. (2002) as validated before in our laboratory by Bassani et al. (2014) and Santiago et al. (2010). Thereafter, the animals were euthanized (Fig. 2).

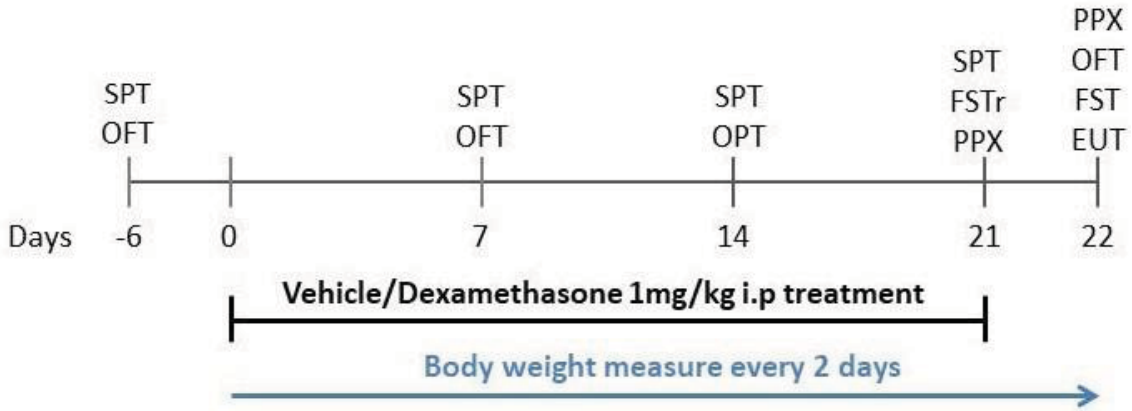



Fig 2. Experimental design (Experiment II). Abbreviations used: OFT, open field test; SPT, sucrose preference test; PPX, pramipexole treatment (PPX/VEH); FSTr, forced swim test (training session); FST, forced swim test (test session); EUT, euthanasia;

4.3.5 Statistics

Two-way ANOVA followed by Bonferroni *post hoc* test were performed to analyze the data from the body weight, total fluid intake, sucrose preference test and open field test. One-way ANOVA followed by Newman-Keuls *post hoc* test was performed to evaluate the forced swim test. The statistical analyses were performed using GraphPad

Prism, version 6.0. The error bars are reported as mean ± SEM of the mean. Significance level was set at P < 0.05.

## 4.4 RESULTS

### 4.4.1 Dose-response curve (Experiment I)

#### 4.4.1.1 Open field test

The locomotion frequency showed a statistically significant decrease in the 2 mg/kg and 3 mg/kg PPX groups and also for the imipramine 25 mg/kg group in comparison with the vehicle group. There was also a significant reduction on the imipramine group when compared with the PPX 1 mg/kg group as observed in the (Fig. 3A) [F(4, 34) = 5.739; P = 0.0012]. Rearing frequency did not present any significant change with the treatment [F (4, 34) = 1.194; P = 0.3311] (Fig. 3B) (n = 7-8/group).

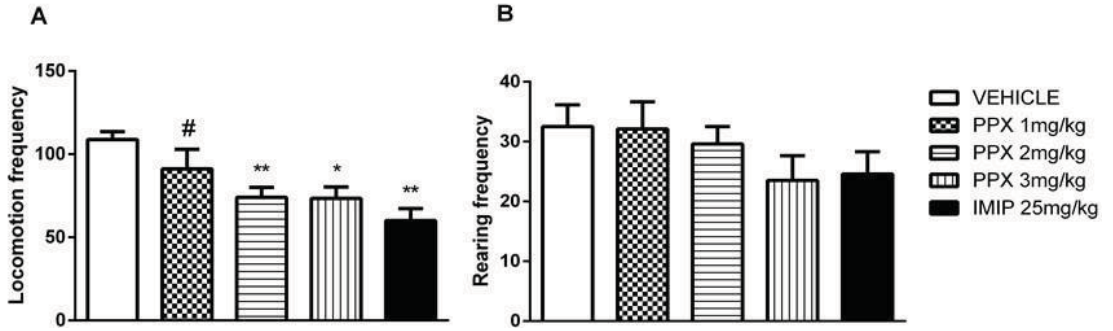



Fig 3. Effect of pramipexole treatment on locomotor activity in the open field test. (A) Locomotor frequency. (B) Rearing frequency. The data was expressed as mean ± S.E.M. *P < 0.05. **P < 0.01 in comparison with the negative control group and #P < 0.05 in comparison with the positive control group. One-way ANOVA followed by Newman-Keuls multiple comparisons *post-hoc* test.

#### 4.4.1.2 Forced swim test

In the immobility behavior, both PPX doses and imipramine were capable of producing a significant reduction in the immobility time [F(4, 34) = 214.4; P<0.0001] (Fig. 4A). There was a statistically significant difference in the climbing time between the PPX groups and the control group in all three PPX doses. The imipramine treatment also caused an increase in the climbing time [F (4,34) = 44.84; P<0.0001] (Fig. 4B). Also, in the swimming behavior, both PPX groups and imipramine group had an increase in the swimming time when compared with the control group [F(4,34) = 9.062; P<0.0001] (Fig. 4C). (n = 7-8/group).

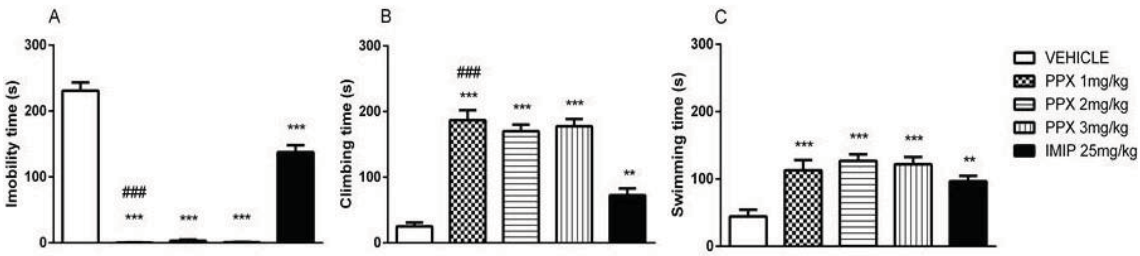



Fig 4. Effect of repeated pramipexole and imipramine treatment on time spent on each behavior in the forced swimming test. (A) Immobility time. (B) Swimming time. (C) Climbing time. The data was expressed as mean ± S.E.M. **P < 0.01. ***P < 0.001 in comparison with the negative control group and ###P < 0.001 in comparison with the positive control group. One-way ANOVA followed by Newman-Keuls multiple comparisons *post-hoc* test.

### 4.4.2 Dexamethasone prolonged treatment (Experiment II)

#### 4.4.2.1Body weight

Body weight was significantly reduced in the dexamethasone group from the 2nd to 22th day when compared with vehicle group ($P < 0.0001$; Fig.5) as indicated by the group [$F(1, 29) = 232.3$; $P < 0.0001$], time [$F(11, 319) = 105.9$; $P < 0.0001$] and interaction [$F(11, 319) = 372.9$; $P < 0.0001$] factors and also when compared with the same group in the beginning of the experimental protocol (n = 13-18/group).

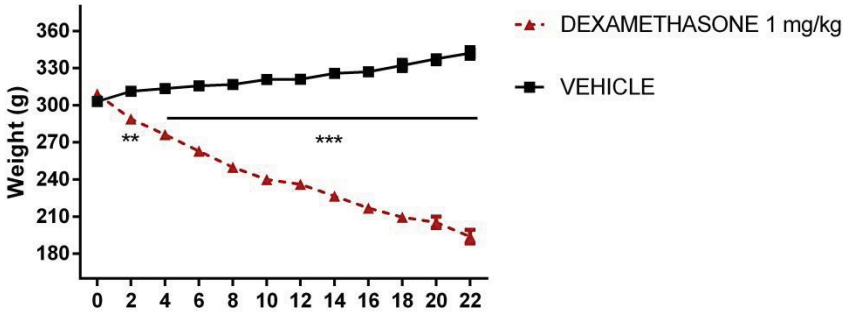



Fig 5. Effect of 21 days dexamethasone 1 mg/kg treatment on body weight. The data was expressed as mean ± S.E.M. **P < 0.01; ***P < 0.001 compared to vehicle (two-way ANOVA followed by Bonferroni *post-hoc* test).

#### 4.4.2.2 Sucrose preference test

There is a decrease in sucrose preference in the dexamethasone group on the 21th day when compared with the vehicle group ($P < 0.05$; Fig.6), as indicated by the time [$F(3, 93)=5.900$; $P=0.0010$] and interaction [$F(3, 93) = 4.628$; $P=0.0046$] factors but not by the group factor [$F(1, 31) = 0.001263$; $P=0.9719$] (n = 15-18/group).

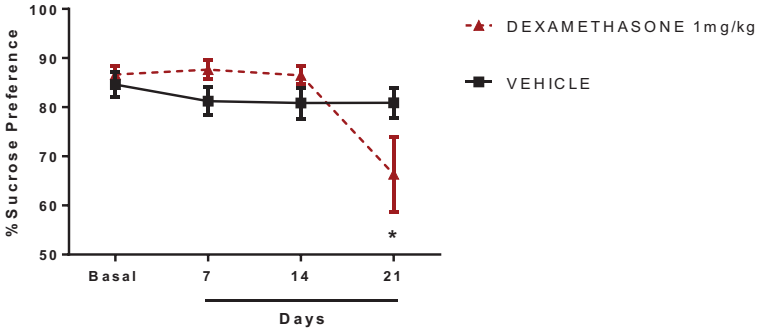



Fig 6. Effect of 21 days dexamethasone 1 mg/kg treatment on sucrose preference. The data was expressed as mean ± S.E.M. *P < 0.05, compared to vehicle group (two-way ANOVA followed by Bonferroni *post-hoc* test).

#### 4.4.2.3 Open field test

Locomotion frequency was significantly decreased in the dexamethasone group starting one week after the first dexamethasone injection and persisted throughout the entire experiment when compared with vehicle group ($P < 0.05$ on day 7 and $P < 0.0001$ on days 14 and 22; Fig.7A) as indicated by the group [$F(1, 29)=55.74$; $P < 0.0001$], time [$F(3, 87)=45.24$; $P < 0.0001$] and interaction [$F(3, 87)=7.223$; $P=0.0002$] factors. Rearing frequency was reduced in the dexamethasone group only in the last experimental day ($P < 0.001$; Fig 7B) as demonstrated by group [$F(1,29)=8.581$;

P=0.0066], interaction [F(3, 87)=5.634; P=0.0014] and time [F(3, 87)=75.22; P<0.0001] factors (n = 13-18/group).

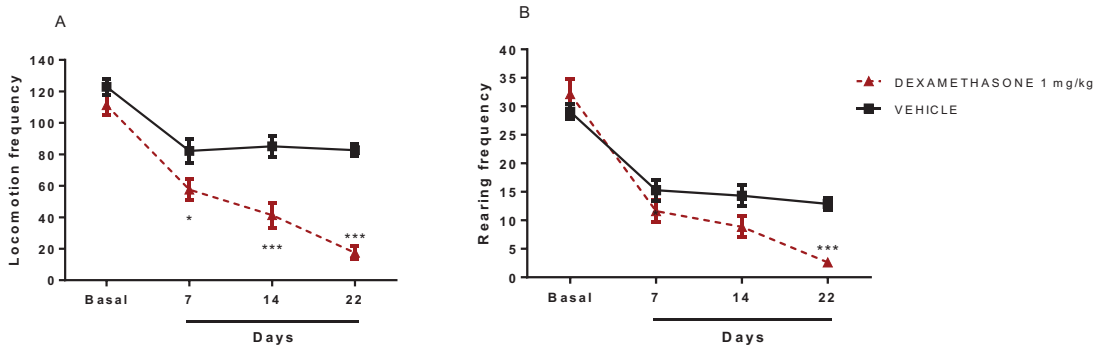



Fig 7. Effect of dexamethasone 21 days, 1 mg/kg treatment on behavior in the open field test. (A) Locomotor frequency. (B) Rearing frequency. The data was expressed as mean ± S.E.M. *P < 0.05. ***P < 0.001 (Two-way ANOVA followed by Bonferroni *post-hoc* test).

### 4.4.2.4 Open field test day 22: effect of PPX

Locomotion frequency was significantly reduced in the dexamethasone groups one day after the last dexamethasone exposure compared with controls (*P*<0.001; Fig. 8A). The PPX treatment neither reversed the dexamethasone effect neither change the locomotion frequency in the veh+ppx group [F(3, 27)=50.19; P<0.0001]. Rearing frequency was also reduced in the dexamethasone groups compared with controls (*P*<0.001; Fig. 8B). Again, PPX treatment did not reversed the reduction in rearing frequency caused by dexamethasone prolonged treament and did not change the frequency in the vehicle treated group as well [F(3, 27)=18.88; P<0.0001] (n = 6-9/group).

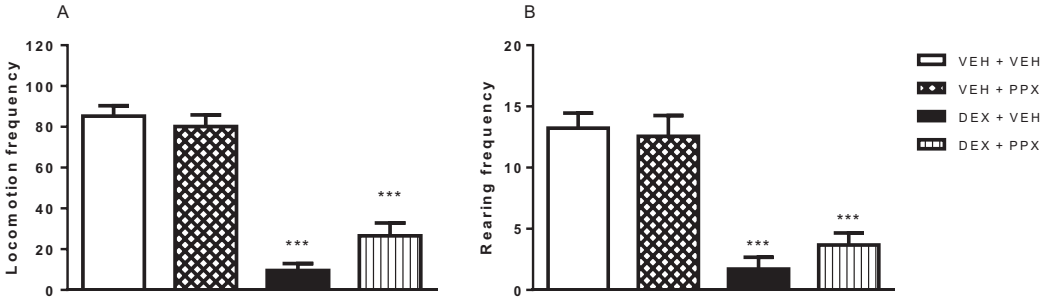



Fig 8. Effect of repeated pramipexole 1 mg/kg treatment on locomotor activity in the open field test after the dexamethasone 21 days, 1 mg/kg treatment. (A) Locomotor frequency. (B) Rearing frequency. The data was expressed as mean ± S.E.M. ***P < 0.001 compared with the veh+veh group. One-way ANOVA followed by Newman-Keuls multiple comparisons *post-hoc* test.

### 4.4.2.5 Forced swim test

Dexamethasone treatment increased immobility time compared with the control group (P<0.05) and the PPX treatment was capable of reducing significantly the immobility time in both groups (veh+ppx and dex+ppx) (P<0.001) [F(3, 27)= 125.1; P<0.0001] (Fig. 9A). A significant increase in climbing time was observed in both PPX treated groups compared with the veh+veh and the dex+veh groups (*P*<0.001) (Fig. 9B). Climbing time was similar in the veh+ppx and dex+ppx groups [F(3, 27)= 64.71; P<0.0001]. Except for the veh+ppx group compared with the dex+veh group (P<0.05), no other significant difference in swimming was observed between groups [F(3, 27)= 3.678; 0.0243] (Fig. 9C). (n = 6-9/group).

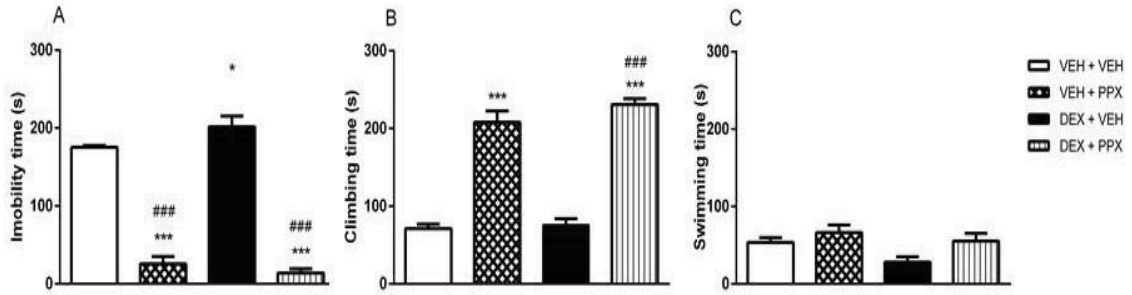



Fig 9. Effect of repeated pramipexole treatment on time spent on each behavior in the forced swimming test after the dexamethasone 21 days, 1 mg/kg treatment. (A) Immobility time. (B) Climbing time. (C) Swimming time. The data was expressed as mean ± S.E.M. *P < 0.05. ***P < 0.01 for comparisons with the veh+veh group and ###P < 0.001 for comparisons with the dex+veh group. One-way ANOVA followed by Newman-Keuls multiple comparisons *post-hoc* test.

## 4.5 DISCUSSION

Our results showed that the repeated PPX administration was capable of reversing the depressive-like behavior induced by the prolonged administration of dexamethasone.

First of all, we performed a dose-response curve (experiment I) in order to establish the PPX dose that would be used throughout the experiment. For this purpose, we used the modified Porsolt protocol in the FST for testing 3 different doses of PPX (1, 2 and 3 mg/kg) as well as the triclycic antidepressant imipramine (25 mg/kg) as a positive control. Our results showed that all three doses of PPX were capable of reduce the imobility time and increase the climbing time in the FST in comparison with both the control and the positive control group (IMIP group) but only the 1mg/kg dose did not change locomotor activity, evaluated by the open field test. The other two doses (2 and 3 mg/kg) resulted in a reduction in the locomotion frequency. Also, both IMIP and PPX groups presented an increase in swimming time.

The FST is an animal model primarily used to screen drugs with antidepressant activity based in the rodent's behavioral repertoire when exposed to a cylinder of water from which they can not escape. The test is based upon the tendency of the animals to, after moments of vigorous struggle, develop an immobile behavior in the test day after the exposure to a pre-test session – a behavioral pattern that is interpreted as a state of "behavioral despair" caused by the inescapable stress situation (PORSOLT et al., 1978; LUCKI, 1997; CRYAN et al., 2005; CASTAGNÉ et al., 2011). Despite several questions about the interpretation of this test, the rat FST presents an impressive sensitivity to a wide range of antidepressants drugs since the treatment with different antidepressant agents consistently decreases the time spent in immobility in the test session and drugs that are not antidepressant are not effective in the FST. The major problem is related to psychomotor stimulants which can reduce immobility time in the FST without beeing clinically effective as antidepressants. Due to this limitation, usually the OFT is employed prior to the FST in order to evaluate the effects of drugs on locomotion. If the drug do not enhance the locomotor activity, their effects may be considered selective to FST (BORSINI; MELI, 1988; CRYAN et al., 2005).

In light of this, we chose the smaller PPX dose since all 3 doses were able to reduce the depressive-like behavior evidenced by the imobility in the FST but only the 1mg/kg group did not show any motor alteration in the OFT. Based on previous data that demonstrated that the climbing behavior is related to NE and DA mechanisms, the swimming behavior to the 5-HT mechanisms (DETKE et al., 1997) and the immobile behavior to the decrease in NE and DA (SANTIAGO et al., 2010), our inicial results led us to believe that the PPX effect in the FST even after acute administration may not only exist due to dopaminergic mechanisms but also through serotoninergic mechanisms since it also increases the swimming time (CHERNOLOZ et al., 2009, 2012) and it has already been demonstrated that the PPX also has a slight activity in the 5-HT1A receptor (NEWMAN-TANCREDI; CUSSAC; AUDINOT; et al., 2002; NEWMAN-TANCREDI; CUSSAC; QUENTRIC; et al., 2002; ANTONINI; POEWE, 2007).

After the PPX dose definition, we started the prolonged dexamethasone (DEX) treatment for 21 days (experiment II) in order to induce a depressive-like behavior. Dexamethasone is a synthetic glucocorticoid with high potency and it is well known that long-term exposure to DEX can promote a prolonged activation of glucocorticoid receptors resulting in alterations in the central nervous system and development of a depressive-like state, behavioral alterations and increased expression of stress-related disorders genes in mice (SKUPIO et al., 2015).

Weight measures were performed every 2 days throughout the whole experiment II. The dexamethasone group demonstrated a significant weight loss consistent to earlier findings by Jahng et al. (2008) and Kim et al. (2015) demonstrating that dexamethasone has an anorexic effect, therefore, supressing food intake and weight gain in a dose-dependent manner by daily injections. That supression seems to be related to a prolonged increase in plasma leptin levels which, in short, reduces neuropeptide Y secretion by the hypothalamus promoting, in addition to food intake supression, an increase in energy expenditure resulting in body weight loss in rodents (SCHWARTZ et al., 1996, 2000).

Our results also showed that the sucrose solution preference was reduced on day 21 in animals receiving daily dexamethasone. This result reinforces the findings of other articles previously published where there were statistically significant reductions in the consumption of the sucrose solution after 21 days of dexamethasone treatment, an indicative of anhedonic-behaviour (KIM et al., 2015; SKUPIO et al., 2015). The sucrose preference test is a well establish model in rodents to evaluate the anhedonia which refers to a reduction of the ability to experience pleasure, which can be reflected in a minor interest in rewarding stimuli and pleasure events (PAPP et al., 1991; CASAROTTO; ANDREATINI, 2007; SANTIAGO et al., 2010; DER-AVAKIAN; MARKOU, 2012; SOUZA et al., 2018). The anhedonia is a core symptom of depression and it is possible related to a dysfunction in the reward and motivation systems (PIZZAGALLI, 2014). One may argue that the reduced sucrose preference showed on day 21 may be related to a motor impairment since the dexamethasone group presented a reduction in the locomotor frequency on the OFT, However, our data showed that although there is a significant difference on locomotion between groups since day 7, the reduction in the SPT only happened in the 21th day evidencing that the hipolocomotion does not seems to be related to the reduction in the sucrose preference. Therefore, despite

differences in methodology between laboratories such as sucrose preference test duration, previous water and food deprivation and sucrose solution concentration, as well as, differences in animal strains and dexamethasone doses, our results seems to confirm previous data demonstrating the ability of dexamethasone to induce a depressive-like behavior, suggested by an anhedonic state with reduced sweet preference, suporting the hypothesis that corticosteroids and HPA-axis dysfunction plays an important role in the neurobiology of depression (CASAROTTO; ANDREATINI, 2007; SIGWALT et al., 2011; KIM et al., 2015; SKUPIO et al., 2015). Thus, in view of the fact that several animal models of depression have shown weight loss and decreased sweet solution intake, seems plausible to suggest the common involvement of HPA axis dysregulation in its pathophysiologic mechanism.

In the OFT, the number of traveled squares was scored to assess locomotor activity and the number of rising on rear legs was scored to assess exploratory behavior. Our results showed that although animals started at the same basal level, the dexamethasone group presented a statistically significant reduction in locomotor frequency after day 7 of DEX treatment and that reduction was increased throughout the experiment. These findings agree with previous data that demonstrates that DEX after higher single dose or after lower dose given chronically reduces spontaneus locomotor activity and reduces hyperactivity induced by dopamine agonists in mice (WRÓBEL et al., 2005; TERADA et al., 2014; HU et al., 2015). However, there were also studies that did not show any locomotor alteration between DEX and control groups (KIM et al., 2015). The DEX animals also showed a reduction in the rearing frequency which suggests a reduction in the information-gathering activity. This behavior is sensitive to the cumulative time that the animal has spent in an environment, since it is well known that the animals develop a familiarity with the apparatus, as observed by the reduction in rearing-frequency as the environment becomes more familiar (CUMMINS; WALSH, 1976; LEVER et al., 2006; GOULD et al., 2009).

On day 22, immediately after the OFT, we performed the FST and the dexamethasone-treated group of animals displayed higher immobility time when compared to the control group which is usually interpreted, as mentioned earlier, as a state of “behavioral despair”. Although the DEX group presented a reduced locomotion frequency in the OFT, this dexamethasone-induced increase in immobility time may not be associated with motor alterations since a decreased locomotion in the OFT can be a consistent change related to a depression state, given that both psychomotor retardation and/or reduced motivation to explore are usually clinically observed (LEMKE et al., 2000; TYE et al., 2013). Also there were no significant differences between groups in the climbing behavior time which is a predictor parameter of motor activity in rat FST (LINO-DE-OLIVEIRA et al., 2005; VIEIRA et al., 2008; SIGWALT et al., 2011). It has been shown that dexamethasone treatment decreases adult hippocampal neurogenesis (KIM et al., 2004) and that 10-days dexamethasone administration in rats is capable of increasing the 5-HT2 receptor density in cerebral cortex and that this increase is also found in the post-mortem brain of suicides and depressed subjects (KURODA et al., 1993). Therefore, together with previous literature data that correlates the dexamethasone administration with central alterations similar with those found in human MDD patology and the anhedonia results found on day 21 in the SPT, the increased time spent in

immobility compared to controls seems to indicate a depressive-like behavior rather than simply a motor impairment.

In agreement with our hypothesis, the PPX repeated treatment was capable of reducing the time spent in the immobile behavior for both groups (DEX and VEH) without showing any effect in the rats locomotor activity, as showed by the OFT results imediately before the FST (day 22). This result also reinforces the dissociation between the reduced locomotor activity in the OFT and the time of immobility found in the FST. The reduction of immobility was accompanied by the increase in the time spent in climbing behaviour. Also, although there is not a statistically significant change in the swimming behavior with the PPX treatment, differently from the result we had found in the dose-response curve experiment, we can still observe a tendency of difference between the dex+veh and dex+ppx group. This result may be explained by the absence of DEX treatment in the dose-response curve experiment, since previous data have shown a reduction in the expression of 5-HT1A receptors in rat brain after treatment with glucocorticosteroids (ZHONG; CIARANELLO, 1995) and that the 5-HT1A receptors are under a tonic inhibitory control of corticosterone (CHAOULOFF, 1995, 2000). In this way, the difference in the results we found in the dose-response curve and after prolonged dexamethasone treatment seems to indicate that the increase in the swimming time caused by PPX may be related to a direct activity in those receptors and this response may have been affected by the glucocorticoid treatment. However, according to Ostadhadi et al. (2016), the PPX also has an indirect activity – through D2R activation – to inhibit nitric oxide synthesis, which has already been indicated by Cryan et al. (2005) and can also be associated with increases in the swimming time in the FST.

Glucocorticosteroids also have been reported to modulate dopamine metabolism at different levels. It has been shown that glucocorticoid excess changes the mRNA expression and distribution of D1R and D2R in cortico-striatal areas of rat forebrain and that the antidepressant treatment was capable of correcting the increased striatal levels of D1R and D2R (CYR et al., 2001; WRÓBEL et al., 2004). Despite this, according to Ostadhadi and coworkers (2016), the PPX activity in the FST seems to be only partially related to the direct activation of the D2 receptors (D2R), that could have been modulated by the DEX treatment, and also associated with the inibition, caused by the D2R activation, of the NMDA receptor and/or NO/GMPc synthesis.

In light of those, our results have shown that the dexamethasone model was able to mimic several features of depressive disorder and, despite the possible modulation of glucocorticoids in the dopaminergic and seratoninergic systems, the dopaminergic-agonist PPX have shown to be a promising drug in the reversal of depressive-like symptoms caused by glucocorticoids prolonged treatment.

## 4.6 CONCLUSION

The present study demonstrated that the prolonged dexamethasone administration was able to induce a depressive-like behavior as showed by the reduction in the sucrose preference and increased time spent immobile in the forced swim test. Despite the possible influence of dexamethasone on pramipexole targets, our data are in line with previously published data for the

pramipexole and demonstrated that the repeated treatment with the drug had a significant antidepressant-like effect in the FST as indicated by the increase in the climbing time and tendency of increased swimming time with consequent reduction in the immobility time.

## 4.7 ACKNOWLEDGMENTS

This work was supported by grants from National Counsel of Technological and Scientific Development and Coordination for the Improvement of Higher Education Personnel. The funding agencies had no further role in the study design, collection, analysis, and interpretation of the data, writing the report, or on the decision to submit the paper for publication. MABFV is recipient of a National Counsel of Technological and Scientific Development fellowship. The authors report no conflicts of interest.

## 4.8 REFERENCES

AHLSKOG, J. E. Pathological behaviors provoked by dopamine agonist therapy of Parkinson's disease. **Physiology & Behavior**, v. 104, n. 1, p. 168–172, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.physbeh.2011.04.055>. .

AIKEN, C. B. Pramipexole in Psychiatry: A Systematic Review of the Literature. **J. Clin Psychiatry**, v. 68, n. 8, p. 1231–1237, 2007.

ALONSO, J.; ANGERMEYER, M. C.; BERNERT, S.; et al. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. **Acta Psychiatrica Scandinavica**, v. 109, p. 38–46, 2004.

ANACKER, C.; ZUNSZAIN, P. A.; CARVALHO, L. A.; PARIANTE, C. M. The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? **Psychoneuroendocrinology**, v. 36, n. 3, p. 415–425, 2011. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.psyneuen.2010.03.007>. .

ANISMAN, H.; MATHESON, K. Stress, depression, and anhedonia: Caveats concerning animal models. **Neuroscience & Biobehavioral Reviews**, v. 29, p. 525–546, 2005.

ANTONINI, A.; CALANDRELLA, D. Pharmacokinetic evaluation of pramipexole. **Expert Opin. Drug Metab. Toxicol.**, v. 7, n. 10, p. 1307–1314, 2011.

ANTONINI, A.; POEWE, W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson ' s disease. **Lancet Neurology**, v. 6, n. September, p. 4–7, 2007.

BARDEN, N. Implication of the hypothalamic – pituitary – adrenal axis in the physiopathology of depression. **J Psychiatry Neurosci**, v. 29, n. 3, p. 185–193, 2004.

BARONE, P.; POEWE, W.; ALBRECHT, S.; et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. **Lancet Neurology**, v. 9, p. 573–580, 2010. Elsevier Ltd.

BARONE, P.; SCARZELLA, L.; MARCONI, R.; et al. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease. **J Neurol**, v. 253, p. 601–607, 2006.

BASSANI, T. B.; GRADOWSKI, R. W.; ZAMINELLI, T.; et al. Neuroprotective and antidepressant-like effects of melatonin in a rotenone-induced Parkinson's disease model in rats. **Brain Research**, v. 1593, p. 95–105, 2014.

BELUJON, P.; GRACE, A. A. Dopamine System Dysregulation in Major Depressive Disorders. **International Journal of Neuropsychopharmacology**, v. 20, n. 12, p. 1036–1046, 2017.

BENNETT JR, J. P.; PIERCEY, M. F. Pramipexole — a new dopamine agonist for the treatment of Parkinson's disease. **Journal of the Neurological Science**, v. 163, p. 25–31, 1999.

BENOIT, D.; ESA, L.; RALPH, G. The driving license examination as a stress model. Effects on blood picture, serum cortisol and the production of interleukins in man. **Life Sciences**, v. 68, p. 1641–1647, 2001.
BERGHAUZEN-MACIEJEWSKA, K.; KUTER, K.; KOLASIEWICZ, W.; et al. Pramipexole but not imipramine or fluoxetine reverses the “depressive-like” behaviour in a rat model of preclinical stages of Parkinson’s disease. **Behavioural Brain Research**, v. 271, p. 343–353, 2014. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2014.06.029>. .
BERGHAUZEN-MACIEJEWSKA, K.; WARDAS, J.; KOSMOWSKA, B. Alterations of BDNF and trkB mRNA Expression in the 6-Hydroxydopamine- Induced Model of Preclinical Stages of Parkinson ’ s Disease : An Influence of Chronic Pramipexole in Rats. **PLOS ONE**, p. 1–17, 2015.
BHAGWAGAR, Z.; HAFIZI, S.; COWEN, P. J. Increase in Concentration of Waking Salivary Cortisol in Recovered Patients With Depression. **Am J Psychiatry**, v. 160, n. October, p. 1890–1891, 2003.
BOKU, S.; NAKAGAWA, S.; TODA, H.; HISHIMOTO, A. Neural basis of major depressive disorder: Beyond monoamine hypothesis. **Psychiatry and Clinical Neurosciences**, v. 72, p. 3–12, 2018.
BORSINI, F.; MELI, A. Is the forced swimming test a suitable model for revealing antidepressant activity? **Psychopharmacology**, v. 94, p. 147–160, 1988.
BREMNER, J. D.; NARAYAN, M.; ANDERSON, E. R.; et al. Hippocampal Volume Reduction in Major Depression. **Am J Psychiatry**, v. 157, n. 1, p. 115–117, 2000.
BREUER, M. E.; GROENINK, L.; OOSTING, R. S.; et al. Antidepressant effects of pramipexole, a dopamine D3/D2 receptor agonist, and 7-OH-DPAT, a dopamine D3 receptor agonist, in olfactory bulbectomized rats. **European Journal of Pharmacology**, v. 616, p. 134–140, 2009. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2009.06.029>. .
BROWN, E. S.; CHANDLER, P. A. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. **Primary care companion J clin psychiatry**, v. 3, n. 1, p. 17–21, 2001. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/15014624%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC181154>. .
BUNNEY JR, W. E.; DAVIS, J. M. Norepinephrine in Depressive Reactions. **Arch Gen Psychiat**, v. 13, p. 483–494, 1965.
CARPENTER, W. T.; GRUEN, P. H. Cortisol’s Effects on Human Mental Functioning. **Journal of Clinical Psychopharmacology**, v. 2, n. 2, p. 91–101, 1982.
CARROLL, B. J. Dexamethasone suppression test in depression. **The Lancet**, p. 1249, 1980.
CASAROTTO, P. C.; ANDREATINI, R. Repeated paroxetine treatment reverses anhedonia induced in rats by chronic mild stress or dexamethasone. **European Neuropsychopharmacology**, v. 17, p. 735–742, 2007.
CASSANO, P.; LATTANZI, L.; SOLDANI, F.; et al. Pramipexole in treatment-resistant depression: an extended follow-up. **Depression and Anxiety**, v. 20, n. November, p. 131–138, 2004.
CASSARINO, D. S.; FALL, C. P.; SMITH, T. S.; BENNETT JR, J. P. Pramipexole reduces reactive oxygen species production in vivo and in vitro and inhibits the mitochondrial permeability transition produced by the parkinsonian neurotoxin methylpyridinium ion. **Journal of Neurochemistry**, v. 71, p. 295–301, 1998.
CASTAGNÉ, V.; MOSER, P.; ROUX, S.; PORSOLT, R. D. Rodent models of depression: Forced swim and tail suspension behavioral despair tests in rats and mice. **Current Protocols in Neuroscience**, , n. SUPPL.55, p. 1–14, 2011.
CHAOULOFF, F. Regulation of 5-HT receptors by corticosteroids: where do we stand? **Fundam Clin Pharmacol**, v. 9, p. 219–233, 1995.
CHAOULOFF, F. Serotonin, stress and corticoids. **Journal of Psychopharmacology**, v. 14, n. 2, p. 139–151, 2000.

CHERNOLOZ, O.; MANSARI, M. EL; BLIER, P. Sustained Administration of Pramipexole Modifies the Spontaneous Firing of Dopamine, Norepinephrine, and Serotonin Neurons in the Rat Brain. **Neuropsychopharmacology**, v. 34, p. 651–661, 2009.
CHERNOLOZ, O.; MANSARI, M. EL; BLIER, P. Long-term administration of the dopamine D3/2 receptor agonist pramipexole increases dopamine and serotonin neurotransmission in the male rat forebrain. **J Psychiatry Neurosci**, v. 37, n. 2, p. 113–121, 2012.
CORRIGAN, M. H.; DENAHAN, A. Q.; WRIGHT, C. E.; et al. COMPARISON OF PRAMIPEXOLE, FLUOXETINE, AND PLACEBO IN PATIENTS WITH MAJOR DEPRESSION. **Depression and Anxiety**, v. 65, n. February 1999, p. 58–65, 2000.
CRYAN, J. F.; VALENTINO, R. J.; LUCKI, I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. **Neuroscience and Biobehavioral Reviews**, v. 29, n. 4–5, p. 547–569, 2005.
CUMMINS, R. A.; WALSH, R. N. The Open-Field: A Critical Review. **Psychological Bulletin**, v. 83, n. 3, p. 482–504, 1976.
CYR, M.; MORISSETTE, M.; BARDEN, N.; et al. Dopaminergic activity in transgenic mice underexpressing glucocorticoid receptors: Effect of antidepressants. **Neuroscience**, v. 102, n. 1, p. 151–158, 2001.
CZÉH, B.; FUCHS, E.; WIBORG, O.; SIMON, M. Animal models of major depression and their clinical implications. **Progress in Neuropsychopharmacology & Biological Psychiatry**, v. 64, p. 293–310, 2016. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.pnpbp.2015.04.004>. .
DER-AVAKIAN, A.; MARKOU, A. The neurobiology of anhedonia and other reward-related deficits. **Trends in Neurosciences**, v. 35, n. 1, p. 68–77, 2012. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.tins.2011.11.005>. .
DERUBEIS, R. J.; SIEGLE, G. J.; HOLLON, S. D. Cognitive therapy vs. medications for depression: Treatment outcomes and neural mechanisms. **Nature Reviews Neuroscience**, v. 9, n. 10, p. 788–796, 2008.
DETKE, M. J.; JOHNSON, J.; LUCKI, I. Acute and Chronic Antidepressant Drug Treatment in the Rat Forced Swimming Test Model of Depression. **Experimental and Clinical Psychopharmacology**, v. 5, n. 2, p. 107–112, 1997.
DUMAN, R. S.; AGHAJANIAN, G. K. Synaptic dysfunction in depression: Potential therapeutic targets. **Science**, v. 338, n. 6103, p. 68–72, 2012.
DUMAN, R. S.; LI, N. A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. **Philosophical Transactions of the Royal Society B: Biological Sciences**, v. 367, n. 1601, p. 2475–2484, 2012. Disponível em: <http://rstb.royalsocietypublishing.org/cgi/doi/10.1098/rstb.2011.0357>. .
ESCALONA, R.; FAWCETT, J. Pramipexole in Treatment Resistant- Depression , Possible Role of Inflammatory Cytokines Modeling the Impact of Social Contact on Substance Use. **Neuropsychopharmacology**, v. 42, n. 1, p. 363, 2017. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/npp.2016.217>. .
EVANS, A. H.; KATZENSCHLAGER, R.; PAVIOUR, D.; et al. Punding in Parkinson's disease: Its relation to the dopamine dysregulation syndrome. **Movement Disorders**, v. 19, n. 4, p. 397–405, 2004.
FARDET, L.; PETERSEN, I.; NAZARETH, I. Monitoring of Patients on Long-Term Glucocorticoid Therapy. **Medicine**, v. 94, n. 15, p. 1–10, 2015. Disponível em: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-201504030-00006>. .
FERRARI-TONINELLI, G.; MACCARINELLI, G.; UBERTI, D.; BUERGER, E.; MEMO, M. Mitochondria-targeted antioxidant effects of S(-) and R(+) pramipexole. **BMC Pharmacology**, v. 10, n. 2, p. 1–6, 2010.
FOUNTOULAKIS, K. N.; GONDA, X.; RIHMER, Z.; FOKAS, C.; IACOVIDES, A. Revisiting the Dexamethasone Suppression Test in unipolar major depression: an

exploratory study. **Annals of General Psychiatry**, v. 7, n. 22, p. 1–9, 2008.
GERHARD, D. M.; WOHLEB, E. S.; DUMAN, R. S. Emerging treatment mechanisms for depression: focus on glutamate and synaptic plasticity. **Drug Discovery Today**, v. 21, n. 3, p. 454–464, 2016. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.drudis.2016.01.016>. .
GERLACH, M.; DOUBLE, K.; ARZBERGER, T.; LEBLHUBER, F. Dopamine receptor agonists in current clinical use : comparative dopamine receptor binding profiles defined in the human striatum. **Journal of Neural Transmission**, , n. 110, p. 1119–1127, 2003.
GOULD, T. D.; DAO, D. T.; KOVACSICS, C. E. The Open Field Test. **Mood and Anxiety Related Phenotypes in Mice**. p.1–20, 2009.
GOURLEY, S. L.; WU, F. J.; KIRALY, D. D.; et al. REGIONALLY-SPECIFIC REGULATION OF pERK1/2 MAP KINASE IN A MODEL OF ANTIDEPRESSANT-SENSITIVE CHRONIC. **Biol Psychiatry**, v. 63, n. 4, p. 353–359, 2008.
GU, M.; IRVANI, M.; COOPER, J. M.; et al. Pramipexole protects against apoptotic cell death by non-dopaminergic mechanisms. **Journal of Neurochemistry**, v. 91, n. 3, p. 1075–1081, 2004.
HALL, E. D.; ANDRUS, P. K.; OOSTVEEN, J. A.; ALTHAUS, J. S.; VONVOIGTLANDER, P. F. Neuroprotective effects of the dopamine D2/D3 agonist pramipexole against postischemic or methamphetamine-induced degeneration of nigrostriatal neurons. **Brain Research**, v. 742, p. 80–88, 1996.
HARRIS, R. B. S.; ZHOU, J. U. N.; YOUNGBLOOD, B. D.; et al. Failure to Change Exploration or Saccharin Preference In Rats Exposed to Chronic Mild Stress. **Physiology & Behavior**, v. 63, n. 1, p. 91–100, 1998.
HEIM, C.; NEWPORT, D. J.; HEIT, S.; et al. Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. **JAMA**, v. 284, n. 5, p. 592–597, 2000.
HOLLON, S. D.; THASE, M. E.; MARKOWITZ, J. C. TREATMENT AND PREVENTION OF DEPRESSION. **Psychological Science in the public interest**, v. 3, n. 2, p. 39–77, 2002.
HOLSBOER, F. The corticosteroid receptor hypothesis of depression. **Neuropsychopharmacology**, v. 23, n. 5, p. 477–501, 2000.
HU, W.; ZHANG, Y.; WU, W.; et al. Chronic glucocorticoids exposure enhances neurodegeneration in the frontal cortex and hippocampus via NLRP-1 inflammasome activation in male mice. **BRAIN, BEHAVIOUR, AND IMMUNITY**, p. 1–13, 2015. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.bbi.2015.09.019>. .
INOUE, T.; KOYAMA, T. Effects of acute and chronic administration of high-dose corticosterone and dexamethasone on regional brain dopamine and serotonin metabolism in rats. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, v. 20, p. 147–156, 1996.
IWATA, M.; OTA, K. T.; DUMAN, R. S. The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses. **Brain Behavior and Immunity**, v. 31, p. 105–114, 2013.
IZUMI, Y.; SAWADA, H.; YAMAMOTO, N.; KUME, T. Novel neuroprotective mechanisms of pramipexole, an anti-Parkinson drug, against endogenous dopamine-mediated excitotoxicity. **European Journal of Pharmacology**, v. 557, p. 132–140, 2007.
JAHNG, J. W.; KIM, N. Y.; RYU, V.; et al. Dexamethasone reduces food intake, weight gain and the hypothalamic 5-HT concentration and increases plasma leptin in rats. **European Journal of Pharmacology**, v. 581, p. 64–70, 2008.
JOYCE, J. N.; WOOLSEY, C.; RYOO, H.; BORWEGE, S.; HAGNER, D. Low dose pramipexole is neuroprotective in the MPTP mouse model of Parkinson's disease, and downregulates the dopamine transporter via the D3 receptor. **BMC Biology**, v. 2, n. 22, p. 1–12, 2004.
KELLER, J.; GOMEZ, R.; WILLIAMS, G.; et al. HPA Axis in Major Depression: Cortisol,

Clinical Symptomatology, and Genetic Variation Predict Cognition. **Mol Psychiatry**, v. 22, n. 4, p. 527–536, 2017.
KENDLER, K. S.; THORNTON, L. M.; GARDNER, C. O. Stressful Life Events and Previous Episodes in the Etiology of Major Depression in Women: An Evaluation of the "Kindling" Hypothesis. **Am J Psychiatry**, v. 157, n. August, p. 1243–1251, 2000.
KESSLER, R. C. THE EFFECTS OF STRESSFUL LIFE EVENTS ON DEPRESSION. **Annu. Rev. Psychol.**, v. 48, p. 191–214, 1997.
KIM, D.; LEE, S. H.; KIM, J. Y.; et al. Anorexia, anhedonia and depression in rats by chronic dexamethasone. **International Journal of Biosciences**, v. 6, n. 11, p. 32–41, 2015.
KIM, J. B.; JU, Y. J.; KIM, H. J.; et al. Dexamethasone inhibits proliferation of adult hippocampal neurogenesis in vivo and in vitro. **Brain Research**, v. 1027, p. 1–10, 2004.
KITAGAWA, K.; KITAMURA, Y.; MIYAZAKI, T.; et al. Effects of pramipexole on the duration of immobility during the forced swim test in normal and ACTH-treated rats. **Naunyn-Schmiedeberg's Archives of Pharmacology**, v. 380, n. 1, p. 59–66, 2009.
KLOET, E. R. D. E.; VREUGDENHIL, E.; OITZL, M. S.; PHARMACOLOGY, M.; AMSTERDAM, L. Brain Corticosteroid Receptor Balance in Health and Disease. **Endocrine Reviews**, v. 19, n. 3, p. 269–301, 1998.
KLOS, K. J.; BOWER, J. H.; JOSEPHS, K. A.; MATSUMOTO, J. Y.; AHLSKOG, J. E. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. **Parkinsonism and Related Disorders**, v. 11, n. 6, p. 381–386, 2005.
KOLLA, B. P.; MANSUKHANI, M. P.; BARRAZA, R.; BOSTWICK, J. M. Impact of Dopamine Agonists on Compulsive Behaviors: A Case Series of Pramipexole-Induced Pathological Gambling. **Psychosomatics**, v. 51, n. 3, p. 271–273, 2010.
KRISHNAN, V.; NESTLER, E. J. The molecular neurobiology of depression. **Nature**, v. 455, n. October, p. 894–902, 2008.
KUPFER, D. J.; FRANK, E.; PHILLIPS, M. L. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. **The Lancet**, v. 379, p. 1045–1055, 2012. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/S0140-6736(11)60602-8>. .
KURODA, Y.; MIKUNI, M.; NOMURA, N.; TAKAHASHI, K. Differential effect of subchronic dexamethasone treatment on serotonin-2 and B-adrenergic receptors in the rat cerebral cortex and hippocampus. **Neuroscience Letters**, v. 155, p. 195–198, 1993.
LE, W. D.; JANKOVIC, J.; XIE, W.; APPEL, S. H. Antioxidant property of pramipexole independent of dopamine receptor activation in neuroprotection. **J Neural Transm**, v. 107, p. 1165–1173, 2000.
LEMKE, M. R.; BRECHT, H. M.; KOESTER, J.; REICHMANN, H. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. **Journal of the Neurological Sciences**, v. 248, p. 266–270, 2006.
LEMKE, M. R.; WENDOR, T.; MIETH, B.; BUHL, K.; LINNEMANN, M. Spatiotemporal gait patterns during over ground locomotion in major depression compared with healthy controls. **Journal of Psychiatric Research**, v. 34, p. 277–283, 2000.
LEVANT, B.; LING, Z. D.; CARVEY, P. M. Dopamine D3 Receptors: Relevance for the Drug Treatment of Parkinson's Disease. **CNS Drugs**, v. 12, n. 6, p. 391–402, 1999.
LEVER, C.; BURTON, S.; O'KEEFE, J. Rearing on Hind Legs, Environmental Novelty, and the Hippocampal Formation. **Reviews in the Neurosciences**, v. 17, n. September, p. 111–133, 2006.
LI, C.; GUO, Y.; XIE, W.; et al. Neuroprotection of Pramipexole in UPS Impairment Induced Animal Model of Parkinson's Disease. **Neurochem Res**, v. 35, p. 1546–1556, 2010.
LIEBERKNECHT, V.; CUNHA, M. P.; JUNQUEIRA, S. C.; et al. Antidepressant-like effect of pramipexole in an inflammatory model of depression. **Behavioural Brain**

**Research**, 2016. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2016.11.007>. .
LINO-DE-OLIVEIRA, C.; LIMA, T. C. M. DE; CAROBREZ, A. D. P. Structure of the rat behaviour in the forced swimming test. **Behavioural Brain Research**, v. 158, n. 2, p. 243–250, 2005.
LUCKI, I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. **Behavioural Pharmacology**, v. 8, p. 523–532, 1997.
LUIS-RAVELO, D.; ESTÉVEZ-SILVA, H.; BARROSO-CHINEA, P.; et al. Pramipexole reduces soluble mutant huntingtin and protects striatal neurons through dopamine D3 receptors in a genetic model of Huntington's disease. **Experimental Neurology**, v. 299, n. June 2017, p. 137–147, 2017. Elsevier. Disponível em: <http://dx.doi.org/10.1016/j.expneurol.2017.10.019>. .
MAES, M. EVIDENCE FOR AN IMMUNE RESPONSE IN MAJOR DEPRESSION: A REVIEW AND HYPOTHESIS. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, v. 19, p. 11–38, 1995.
MAES, M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. **Progress in Neuro-Psychopharmacology and Biological Psychiatry**, v. 35, n. 3, p. 664–675, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.pnpbp.2010.06.014>. .
MAES, M.; LEONARD, B. E.; MYINT, A. M.; KUBERA, M.; VERKERK, R. The new ' 5-HT ' hypothesis of depression : Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to. **Progress in Neuropsychopharmacology & Biological Psychiatry**, v. 35, n. 3, p. 702–721, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.pnpbp.2010.12.017>. .
MAH, L.; JR, C. A. Z.; NUGENT, A. C.; et al. Neural mechanisms of antidepressant efficacy of the dopamine receptor agonist pramipexole in treatment of bipolar depression. **International Journal of Neuropsychopharmacology**, v. 14, p. 545–551, 2011.
MAJ, J.; ROGÓZ, W.; MARGAS, W.; KATA, M.; DZIEDZICKA-WASYLEWSKA, M. The effect of repeated treatment with pramipexole on the central dopamine D 3 system. **Journal of Neural Transmission**, v. 107, p. 1369–1379, 2000.
MAJ, J.; ROGOZ, Z.; KOŁODZIEJCZYK, K. The behavioural effects of pramipexole, a novel dopamine receptor agonist. **European Journal of Pharmacology**, v. 324, p. 31–37, 1997.
MARUO, J.; HARAGUCHI, Y.; TATEISHI, H.; et al. Abnormal behaviours during pramipexole treatment for Cotard's syndrome: a case report. **Psychogeriatrics**, v. 16, n. 4, p. 283–286, 2016.
MCEWEN, B. S. Physiology and Neurobiology of Stress and Adaptation : Central Role of the Brain. **Physiol Rev**, v. 87, p. 873–904, 2007.
MIERAU, J.; SCHINGNITZ, G. Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D2 receptor agonist. **European Journal of Pharmacology**, v. 215, p. 161–170, 1992.
MIERAU, J.; SCHNEIDER, F. J.; ENSINGER, H. A.; et al. Pramipexole binding and activation of cloned and expressed dopamine D2, D3 and D4 receptors. **European Journal of Pharmacology**, v. 290, p. 29–36, 1995.
MILLER, A. H.; RAISON, C. L. The role of inflammation in depression: From evolutionary imperative to modern treatment target. **Nature Reviews Immunology**, v. 16, n. 1, p. 22–34, 2016. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/nri.2015.5>. .
MUNDELL, L.; LINDEMANN, R.; DOUGLAS, J. Monitoring long-term oral corticosteroids. **BMJ open quality**, v. 6, p. 1–9, 2017. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/29450303%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5699140>. .

NAKAYAMA, H.; ZHAO, J.; EI-FAKHRANY, A.; et al. **NEUROPROTECTIVE EFFECTS OF PRAMIPEXOLE AGAINST TUNICAMYCIN-INDUCED CELL DEATH IN PC12 CELLS**. 2009.

NEWMAN-TANCREDI, A.; CUSSAC, D.; AUDINOT, V.; et al. Differential Actions of Antiparkinson Agents at Multiple Classes of Monoaminergic Receptor. II. Agonist and Antagonist Properties at Subtypes of Dopamine D2-Like Receptor and a1/a2-Adrenoceptor. **The Journal of Pharmacology and Experimental Therapeutics**, v. 303, n. 2, p. 805–814, 2002.

NEWMAN-TANCREDI, A.; CUSSAC, D.; QUENTRIC, Y.; et al. Differential Actions of Antiparkinson Agents at Multiple Classes of Monoaminergic Receptor. III. Agonist and Antagonist Properties at Serotonin, 5-HT1 and 5-HT2, Receptor Subtypes. **The Journal of Pharmacology and Experimental Therapeutics**, v. 303, n. 2, p. 815–822, 2002.

NIELSEN, C. K.; ARNT, J.; SA, C. Intracranial self-stimulation and sucrose intake differ as hedonic measures following chronic mild stress: interstrain and interindividual differences. **Behavioural Brain Research**, v. 107, p. 21–33, 2000.

NUTT, D.; DEMYTTENAERE, K.; JANKA, Z.; et al. The other face of depression, reduced positive affect: The role of catecholamines in causation and cure. **Journal of Psychopharmacology**, v. 21, n. 5, p. 461–471, 2007.

ORGANIZATION, W. H. **Depression and Other Common Mental Disorders: Global Health Estimates**. 2017.

OSTADHADI, S.; IMRAN, M. I.; NOROUZI-JAVIDAN, A.; DEHPOUR, A.-R. Antidepressant effect of pramipexole in mice forced swimming test: A cross talk between dopamine receptor and NMDA/nitric oxide/cGMP pathway. **Biomedicine & Pharmacotherapy**, v. 81, p. 295–304, 2016. Elsevier Masson SAS. Disponível em: <http://dx.doi.org/10.1016/j.biopha.2016.04.026>. .

OWENS, M. J.; NEMEROFF, C. B. Role of Serotonin in the Pathophysiology of Depression: Focus on the Serotonin Transporter. **Clin. Chem.**, v. 40, n. 2, p. 288–295, 1994.

PAN, T.; XIE, W.; JANKOVIC, J.; LE, W. Biological effects of pramipexole on dopaminergic neuron-associated genes: relevance to neuroprotection. **Neuroscience Letters**, v. 377, p. 106–109, 2005.

PAPP, M.; WILLNER, P.; MUSCAT, R.; STREET, O. C. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. **Psychopharmacology**, v. 104, p. 255–259, 1991.

PARIANTE, C. M. The glucocorticoid receptor: part of the solution or part of the problem? **Journal of Psychopharmacology**, v. 20, n. 4, p. 79–84, 2006.

PARIANTE, C. M.; LIGHTMAN, S. L. The HPA axis in major depression: classical theories and new developments. **Trends in Neurosciences**, v. 31, n. 9, p. 464–468, 2008.

PARIANTE, C. M.; MILLER, A. H. Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. **Biological Psychiatry**, v. 49, n. 5, p. 391–404, 2001.

PARIANTE, C. M.; PEARCE, B. D.; PISELL, T. L.; et al. The Proinflammatory Cytokine, Interleukin-1a, Reduces Glucocorticoid Receptor Translocation and Function*. **Endocrinology**, v. 140, n. 9, p. 4359–4366, 1999.

PEPIN, M.; BEAULIEU, S.; BARDEN, N. Antidepressants regulate glucocorticoid receptor messenger RNA concentrations in primary neuronal cultures. **Molecular Brain Research**, v. 6, p. 77–83, 1989.

PICILLO, M.; ROCCO, M.; BARONE, P. Dopamine receptor agonists and depression in Parkinson ' s disease. **Parkinsonism and related Disorders**, v. 15, p. S81–S84, 2009. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/S1353-8020(09)70841-7>. .

PIZZAGALLI, D. A. Depression, Stress, and Anhedonia: Toward a Synthesis and Integrated Model. **Annu. Rev. Clin. Psychol.**, v. 10, p. 393–423, 2014.

PORSOLT, R. D.; ANTON, G.; BLAVET, N.; JALFRE, M. Behavioural despair in rats: A new model sensitive to antidepressant treatments. **European Journal of Pharmacology**, v. 47, n. 4, p. 379–391, 1978.
PRAAG, H. M. VAN; KORF, J. Endogenous Depressions with and without Disturbances in the 5-hydroxytryptamine metabolism: A Biochemical Classification?*. **Psychopharmacologia (Berl.)**, v. 19, p. 148–152, 1971.
PRESGRAVES, S. P.; BORWEGE, S.; MILLAN, M. J.; JOYCE, J. N. Involvement of dopamine D2/D3 receptors and BDNF in the neuroprotective effects of S32504 and pramipexole against 1-methyl-4-phenylpyridinium in terminally differentiated SH-SY5Y cells. **Experimental Neurology**, v. 190, p. 157–170, 2004.
PRICE, J. L.; DREVETS, W. C. Neurocircuitry of Mood Disorders. **Neuropsychopharmacology**, v. 35, n. 1, p. 192–216, 2010. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/npp.2009.104>. .
PRUESSNER, J. C.; CHAMPAGNE, F.; MEANEY, M. J.; DAGHER, A. Dopamine Release in Response to a Psychological Stress in Humans and Its Relationship to Early Life Maternal Care : A Positron Emission Tomography Study Using [ 11 C ] Raclopride. **The Journal of Neuroscience**, v. 24, n. 11, p. 2825–2831, 2004.
RACAGNI, G.; POPOLI, M. Cellular and molecular mechanisms in the long-term action of antidepressants. **Dialogues in Clinical Neuroscience**, v. 10, n. 4, p. 385–400, 2008a.
RACAGNI, G.; POPOLI, M. Cellular and molecular mechanisms in the long-term action of antidepressants. **Dialogues in Clinical Neuroscience**, v. 10, p. 385–400, 2008b.
RAISON, C. L.; CAPURON, L.; MILLER, A. H. Cytokines sing the blues: inflammation and the pathogenesis of depression. **Trends Immunol.**, v. 27, n. 1, p. 24–31, 2006.
RAISON, C. L.; MILLER, A. H. Is depression an inflammatory disorder? **Current Psychiatry Reports**, v. 13, n. 6, p. 467–475, 2011.
RENARD, P.; MUÑOZ, C.; MILLAN, M. J. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. **Nature Reviews Drug Discovery**, v. 9, p. 628–642, 2010.
RÉNÉRIC, J. P.; BOUVARD, M.; STINUS, L. In the rat forced swimming test, chronic but not subacute administration of dual 5-HT/NA antidepressant treatments may produce greater effects than selective drugs. **Behavioural Brain Research**, v. 136, n. 2, p. 521–532, 2002.
RIEDERER, P.; LACHENMAYER, L.; LAUX, G. Clinical Applications of MAO-Inhibitors. **Current Medicinal Chemistry**, v. 11, p. 2033–2043, 2004.
SACKEIM, H. A.; HASKETT, R. F.; MULSANT, B. H.; et al. Continuation Pharmacotherapy in the Prevention of Relapse Following Electroconvulsive Therapy. **JAMA**, v. 285, n. 10, p. 1299–1307, 2001.
SALAS, R. E.; ALLEN, R. P.; EARLEY, C. J.; GAMALDO, C. E. A case of compulsive behaviors observed in a restless legs syndrome patient treated with a dopamine agonist. **Sleep**, v. 32, n. 5, p. 587–588, 2009.
SANSONE, R. A.; FERLAN, M. Pramipexole and compulsive masturbation. **Psychiatry**, v. 4, n. 9, p. 57–59, 2007. Disponível em: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20532122>. .
SANTIAGO, R. M.; BARBIEIRO, J.; LIMA, M. M. S.; et al. Depressive-like behaviors alterations induced by intranigral MPTP , 6-OHDA , LPS and rotenone models of Parkinson ' s disease are predominantly associated with serotonin and dopamine. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, v. 34, p. 1104–1114, 2010.
SANTIAGO, R. M.; ZAMINELLI, T.; BASSANI, T. B.; et al. The mechanism of antidepressant-like effects of piroxicam in rats. **Journal of Pharmacology and Pharmacotherapeutics**, v. 6, n. 1, p. 7–12, 2015.
SARTORIUS, N.; BAGHAI, T. C.; BALDWIN, D. S.; et al. **Antidepressant medications and other treatments of depressive disorders: a CINP Task Force**

**report based on a review of evidence**. 2007.
SAVEANU, R. V.; NEMEROFF, C. B. Etiology of Depression: Genetic and Environmental Factors. **Psychiatric Clinics of North America**, v. 35, n. 1, p. 51–71, 2012. Elsevier. Disponível em: <http://dx.doi.org/10.1016/j.psc.2011.12.001>. .
SAYEED, I.; PARVEZ, S.; WINKLER-STUCK, K.; et al. Patch clamp reveals powerful blockade of the mitochondrial permeability transition pore by the D2-receptor agonist pramipexole. **The FASEB Journal**, v. 21, n. 1, p. 1–22, 2006.
SCHILDKRAUT, J. J. THE CATECHOLAMINE HYPOTHESIS OF AFFECTIVE DISORDERS: A REVIEW OF SUPPORTING EVIDENCE. **The American Journal of Psychiatry**, v. 122, n. 5, p. 509–522, 1965.
SCHOENFELD, T. J.; GOULD, E. Stress, stress hormones, and adult neurogenesis. **Experimental Neurology**, v. 233, n. 1, p. 12–21, 2012. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.expneurol.2011.01.008>. .
SCHULTE-HERBRÜGGEN, O.; VOGT, M. A.; HÖRTNAGL, H.; GASS, P.; HELLWEG, R. Pramipexole is active in depression tests and modulates monoaminergic transmission, but not brain levels of BDNF in mice. **European Journal of Pharmacology**, v. 677, n. 1–3, p. 77–86, 2012. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2011.12.014>. .
SCHWARTZ, M. W.; SEELEY, R. J.; CAMPFIELD, L. A.; BURN, P.; BASKIN, D. G. Identification of Targets of Leptin Action in Rat Hypothalamus. **J. Clin. Invest.**, v. 98, n. 5, p. 1101–1106, 1996.
SCHWARTZ, M. W.; WOODS, S. C.; JR, D. P.; SEELEY, R. J.; BASKIN, D. G. Central nervous system control of food intake. **Nature**, v. 404, p. 661–671, 2000.
SERRA, G.; ARGIOLAS, A.; KLIMEK, V.; FADDA, F.; GESSA, G. L. CHRONIC TREATMENT WITH ANTIDEPRESSANTS PREVENTS THE INHIBITORY EFFECT OF SMALL DOSES OF APOMORPHINE ON DOPAMINE SYNTHESIS AND MOTOR ACTIVITY. **Life Sciences**, v. 25, p. 415–424, 1979.
SIGWALT, A. R.; BUDDE, H.; HELMICH, I.; et al. MOLECULAR ASPECTS INVOLVED IN SWIMMING EXERCISE TRAINING REDUCING ANHEDONIA IN A RAT MODEL OF DEPRESSION. **Neuroscience**, v. 192, p. 661–674, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.neuroscience.2011.05.075>. .
SKUPIO, U.; TERTIL, M.; SIKORA, M.; et al. BEHAVIORAL AND MOLECULAR ALTERATIONS IN MICE RESULTING FROM CHRONIC TREATMENT WITH DEXAMETHASONE: RELEVANCE TO DEPRESSION. **NEUROSCIENCE**, v. 286, p. 141–150, 2015. IBRO. Disponível em: <http://dx.doi.org/10.1016/j.neuroscience.2014.11.035>. .
SOUZA, L. C.; MARTYNHAK, B. J.; BASSANI, T. B.; et al. Agomelatine's effect on circadian locomotor rhythm alteration and depressive-like behavior in 6-OHDA lesioned rats. **Physiology & Behavior**, v. 188, n. December 2017, p. 298–310, 2018. Elsevier. Disponível em: <https://doi.org/10.1016/j.physbeh.2018.02.033>. .
STANBURY, R. M.; GRAHAM, E. M. Systemic corticosteroid therapy — side effects and their management. **Br J Ophthalmol**, v. 82, p. 704–708, 1998.
STRASSER, B.; SPERNER-UNTERWEGER, B.; FUCHS, D.; GOSTNER, J. M. Mechanisms of Inflammation-Associated Depression: Immune Influences on Tryptophan and Phenylalanine Metabolisms. **Inflammation-Associated Depression: Evidence, Mechanisms and Implications**. p.95–115, 2017.
SULLIVAN, P. F.; NEALE, M. C.; PH, D.; KENDLER, K. S. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. **Am J Psychiatry**, v. 157, n. 10, p. 1552–1562, 2000.
TAYLOR, W. D.; MCQUOID, D. R.; PAYNE, M. E.; et al. Hippocampus atrophy and the longitudinal course of late-life depression. **Am J Geriatr Psychiatry**, v. 22, n. 12, p. 1504–1512, 2014.
TERADA, K.; IZUMO, N.; SUZUKI, B.; KARUBE, Y.; MORIKAWA, T. Fluvoxamine moderates reduced voluntary activity following chronic dexamethasone infusion in mice via recovery of BDNF signal cascades. **NEUROCHEMISTRY INTERNATIONAL**, v. 69,

p. 9–13, 2014. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.neuint.2014.02.002>. .
THASE, M. E.; KUPFER, D. J. Recent Developments in the Pharmacotherapy of Mood Disorders. **Journal of Consulting and Clinical Psychology**, v. 64, n. 4, p. 646–659, 1996.
TYE, K. M.; MIRZABEKOV, J. J.; WARDEN, M. R.; et al. Dopamine neurons modulate neural enconding and expression of depression-related behaviour. **Nature**, v. 493, n. 7433, p. 537–541, 2013. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/nature11740>. .
UCHIDA, S.; YAMAGATA, H.; SEKI, T. Epigenetic mechanisms of major depression: Targeting neuronal plasticity. **Psychiatry and Clinical Neurosciences**, p. 1–16, 2017.
VECCHIA, D. D.; KANAZAWA, L. K. S.; WENDLER, E.; et al. Effects of ketamine on vocal impairment, gait changes, and anhedonia induced by bilateral 6-OHDA infusion into the substantia nigra pars compacta in rats: Therapeutic implications for Parkinson's disease. **Behavioural Brain Research**, v. 342, n. December 2017, p. 1–10, 2018. Elsevier. Disponível em: <https://doi.org/10.1016/j.bbr.2017.12.041>. .
VEENEMA, A. H.; MEIJER, O. C.; KLOET, E. R. DE; KOOLHAAS, J. M. Genetic Selection For Coping Style Predicts Stressor Susceptibility. **Journal of Neuroendocrinology**, v. 15, p. 256–267, 2003.
VIEIRA, C.; LIMA, T. C. M. DE; CAROBREZ, A. DE P.; LINO-DE-OLIVEIRA, C. Frequency of climbing behavior as a predictor of altered motor activity in rat forced swimming test. **Neuroscience Letters**, v. 445, n. 2, p. 170–173, 2008.
VOLLMAYR, B.; HENN, F. A. Stress models of depression. **Clinical Neuroscience Research**, v. 3, p. 245–251, 2003.
WATSON, D.; CLARK, L. A.; CAREY, G. Positive and Negative Affectivity and Their Relation to Anxiety and Depressive Disorders. **Journal of Abnormal Psychology**, v. 97, n. 3, p. 346–353, 1988.
WATSON, D.; TELLEGEN, A. Toward a Consensual Structure of Mood. **Psychological Bulletin**, v. 98, n. 2, p. 219–235, 1985.
WILLNER, P. Dopamine and Depression: A Review of Recent Evidente. I. Empirical Studies. **Brain Research Reviews**, v. 6, p. 211–224, 1983a.
WILLNER, P. Dopamine and Depression: A Review of Recent Evidente. II. Theoretical Approaches. **Brain Research Reviews**, v. 6, p. 225–236, 1983b.
WILLNER, P. The validity of animal models of depression. **Psychopharmacology**, v. 83, p. 1–16, 1984.
WILLNER, P. Chronic Mild Stress (CMS) Revisited: Consistency and Behavioural-Neurobiological Concordance in the Effects of CMS. **Neuropsychobiology**, v. 52, p. 90–110, 2005.
WILLNER, P.; LAPPAS, S.; CHEETA, S.; MUSCAT, R. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. **Psychopharmacology**, v. 115, p. 454–462, 1994.
WRIGHT, C. E.; SISSON, T. L.; ICHHPURANI, A. K.; PETERS, G. R. Steady-State Pharmacokinetic Pramipexole in Healthy Properties Volunteers. **Pharmacokinetics**, v. 37, p. 520–525, 1997.
WRÓBEL, A.; NOWAK, G.; OSSOWSKA, G.; DANILCZUK, Z.; WIELOSZ, M. EFFECT OF CHRONIC TREATMENT WITH DEXAMETHASONE ON BRAIN DOPAMINE RECEPTORS IN MICE. **Polish Journal of Pharmacology**, v. 56, p. 399–405, 2004.
WRÓBEL, A.; ZEBROWSKA-LUPINA, I.; WIELOSZ, M. Dexamethasone reduces locomotor stimulation induced by dopamine agonists in mice. **Pharmacological Reports**, v. 57, p. 451–457, 2005.
YIRMIYA, R.; POLLAK, Y.; BARAK, O.; et al. Effects of Antidepressant Drugs on the Behavioral and Physiological Responses to Lipopolysaccharide (LPS) in Rodents. **Neuropsychopharmacology**, v. 24, n. 5, p. 531–544, 2001.
ZARATE, C. A.; PAYNE, J. L.; SINGH, J.; et al. Pramipexole for Bipolar II Depression : A Placebo- Controlled Proof of Concept Study. **Biol Psychiatry**, v. 56, p. 54–60, 2004.

ZHONG, P.; CIARANELLO, D. Transcriptional regulation of hippocampal 5-HT1A receptors by corticosteroid hormones. **Molecular Brain Research**, v. 29, n. 94, p. 23–34, 1995.
ZOU, L.; JANKOVIC, J.; ROWE, D. B.; et al. Neuroprotection by pramipexole against dopamine- and levodopa-induced cytotoxicity. **Life Sciences**, v. 64, n. 15, p. 1275–1285, 1999.

## 5. CONCLUSÃO

O presente estudo demonstrou que o tratamento prolongado com a dexametasona é capaz de promover o aparecimento de comportamentos tipo-depressivos, conforme evidenciado pela redução na preferência pela sacarose bem como pelo aumento no tempo de imobilidade no teste da natação forçada O pramipexol, por sua vez, após o tratamento repetido, foi capaz de reverter o comportamento tipo-depressivo obtido no teste da natação forçada ao reduzir o tempo em que os animais passaram em imobilidade com o aumento do tempo nos comportamentos de escalada – intimamente ligado as concentrações de NA e DA – e natação. O resultado para o pramipexol, apesar de esperado devido aos dados da literatura, nos leva a propor hipóteses para estudos posteriores que elucidem o foco da provável conexão entre o eixo HPA com a inflamação e mecanismo pelo qual o pramipexol é capaz de exercer o seu efeito no modelo.

## REFERÊNCIAS

AHLSKOG, J. E. Pathological behaviors provoked by dopamine agonist therapy of Parkinson's disease. **Physiology & Behavior**, v. 104, n. 1, p. 168–172, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.physbeh.2011.04.055>. .

AIKEN, C. B. Pramipexole in Psychiatry: A Systematic Review of the Literature. **J. Clin Psychiatry**, v. 68, n. 8, p. 1231–1237, 2007.

ALONSO, J.; ANGERMEYER, M. C.; BERNERT, S.; et al. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. **Acta Psychiatrica Scandinavica**, v. 109, p. 38–46, 2004.

ANACKER, C.; ZUNSZAIN, P. A.; CARVALHO, L. A.; PARIANTE, C. M. The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? **Psychoneuroendocrinology**, v. 36, n. 3, p. 415–425, 2011. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.psyneuen.2010.03.007>. .

ANISMAN, H.; MATHESON, K. Stress, depression, and anhedonia: Caveats concerning animal models. **Neuroscience & Biobehavioral Reviews**, v. 29, p. 525–546, 2005.

ANTONINI, A.; CALANDRELLA, D. Pharmacokinetic evaluation of pramipexole. **Expert Opin. Drug Metab. Toxicol.**, v. 7, n. 10, p. 1307–1314, 2011.

ANTONINI, A.; POEWE, W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson ' s disease. **Lancet Neurology**, v. 6, n. September, p. 4–7, 2007.

BARDEN, N. Implication of the hypothalamic – pituitary – adrenal axis in the physiopathology of depression. **J Psychiatry Neurosci**, v. 29, n. 3, p. 185–193, 2004.

BARONE, P.; POEWE, W.; ALBRECHT, S.; et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. **Lancet Neurology**, v. 9, p. 573–580, 2010. Elsevier Ltd.

BARONE, P.; SCARZELLA, L.; MARCONI, R.; et al. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease. **J Neurol**, v. 253, p. 601–607, 2006.

BASSANI, T. B.; GRADOWSKI, R. W.; ZAMINELLI, T.; et al. Neuroprotective and antidepressant-like effects of melatonin in a rotenone-induced Parkinson's disease model in rats. **Brain Research**, v. 1593, p. 95–105, 2014.

BELUJON, P.; GRACE, A. A. Dopamine System Dysregulation in Major Depressive Disorders. **International Journal of Neuropsychopharmacology**,

v. 20, n. 12, p. 1036–1046, 2017.

BENNETT JR, J. P.; PIERCEY, M. F. Pramipexole — a new dopamine agonist for the treatment of Parkinson's disease. **Journal of the Neurological Science**, v. 163, p. 25–31, 1999.

BENOIT, D.; ESA, L.; RALPH, G. The driving license examination as a stress model. Effects on blood picture, serum cortisol and the production of interleukins in man. **Life Sciences**, v. 68, p. 1641–1647, 2001.

BERGHAUZEN-MACIEJEWSKA, K.; KUTER, K.; KOLASIEWICZ, W.; et al. Pramipexole but not imipramine or fluoxetine reverses the "depressive-like" behaviour in a rat model of preclinical stages of Parkinson's disease. **Behavioural Brain Research**, v. 271, p. 343–353, 2014. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2014.06.029>. .

BERGHAUZEN-MACIEJEWSKA, K.; WARDAS, J.; KOSMOWSKA, B. Alterations of BDNF and trkB mRNA Expression in the 6-Hydroxydopamine-Induced Model of Preclinical Stages of Parkinson ' s Disease : An Influence of Chronic Pramipexole in Rats. **PLOS ONE**, p. 1–17, 2015.

BHAGWAGAR, Z.; HAFIZI, S.; COWEN, P. J. Increase in Concentration of Waking Salivary Cortisol in Recovered Patients With Depression. **Am J Psychiatry**, v. 160, n. October, p. 1890–1891, 2003.

BOKU, S.; NAKAGAWA, S.; TODA, H.; HISHIMOTO, A. Neural basis of major depressive disorder: Beyond monoamine hypothesis. **Psychiatry and Clinical Neurosciences**, v. 72, p. 3–12, 2018.

BORSINI, F.; MELI, A. Is the forced swimming test a suitable model for revealing antidepressant activity? **Psychopharmacology**, v. 94, p. 147–160, 1988.

BREMNER, J. D.; NARAYAN, M.; ANDERSON, E. R.; et al. Hippocampal Volume Reduction in Major Depression. **Am J Psychiatry**, v. 157, n. 1, p. 115–117, 2000.

BREUER, M. E.; GROENINK, L.; OOSTING, R. S.; et al. Antidepressant effects of pramipexole, a dopamine D3/D2 receptor agonist, and 7-OH-DPAT, a dopamine D3 receptor agonist, in olfactory bulbectomized rats. **European Journal of Pharmacology**, v. 616, p. 134–140, 2009. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2009.06.029>. .

BROWN, E. S.; CHANDLER, P. A. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. **Primary care companion J clin psychiatry**, v. 3, n. 1, p. 17–21, 2001. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/15014624%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC181154>. .

BUNNEY JR, W. E.; DAVIS, J. M. Norepinephrine in Depressive Reactions.

**Arch Gen Psychiat**, v. 13, p. 483–494, 1965.

CARPENTER, W. T.; GRUEN, P. H. Cortisol's Effects on Human Mental Functioning. **Journal of Clinical Psychopharmacology**, v. 2, n. 2, p. 91–101, 1982.

CARROLL, B. J. Dexamethasone suppression test in depression. **The Lancet**, p. 1249, 1980.

CASAROTTO, P. C.; ANDREATINI, R. Repeated paroxetine treatment reverses anhedonia induced in rats by chronic mild stress or dexamethasone. **European Neuropsychopharmacology**, v. 17, p. 735–742, 2007.

CASSANO, P.; LATTANZI, L.; SOLDANI, F.; et al. Pramipexole in treatment-resistant depression: an extended follow-up. **Depression and Anxiety**, v. 20, n. November, p. 131–138, 2004.

CASSARINO, D. S.; FALL, C. P.; SMITH, T. S.; BENNETT JR, J. P. Pramipexole reduces reactive oxygen species production in vivo and in vitro and inhibits the mitochondrial permeability transition produced by the parkinsonian neurotoxin methylpyridinium ion. **Journal of Neurochemistry**, v. 71, p. 295–301, 1998.

CASTAGNÉ, V.; MOSER, P.; ROUX, S.; PORSOLT, R. D. Rodent models of depression: Forced swim and tail suspension behavioral despair tests in rats and mice. **Current Protocols in Neuroscience**, , n. SUPPL.55, p. 1–14, 2011.

CHAOULOFF, F. Regulation of 5-HT receptors by corticosteroids: where do we stand? **Fundam Clin Pharmacol**, v. 9, p. 219–233, 1995.

CHAOULOFF, F. Serotonin, stress and corticoids. **Journal of Psychopharmacology**, v. 14, n. 2, p. 139–151, 2000.

CHERNOLOZ, O.; MANSARI, M. EL; BLIER, P. Sustained Administration of Pramipexole Modifies the Spontaneous Firing of Dopamine, Norepinephrine, and Serotonin Neurons in the Rat Brain. **Neuropsychopharmacology**, v. 34, p. 651–661, 2009.

CHERNOLOZ, O.; MANSARI, M. EL; BLIER, P. Long-term administration of the dopamine D3/2 receptor agonist pramipexole increases dopamine and serotonin neurotransmission in the male rat forebrain. **J Psychiatry Neurosci**, v. 37, n. 2, p. 113–121, 2012.

CORRIGAN, M. H.; DENAHAN, A. Q.; WRIGHT, C. E.; et al. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. **Depression and Anxiety**, v. 65, n. February 1999, p. 58–65, 2000.

CRYAN, J. F.; VALENTINO, R. J.; LUCKI, I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. **Neuroscience and Biobehavioral Reviews**, v. 29, n. 4–5, p.

547–569, 2005.

CUMMINS, R. A.; WALSH, R. N. The Open-Field: A Critical Review. **Psychological Bulletin**, v. 83, n. 3, p. 482–504, 1976.

CYR, M.; MORISSETTE, M.; BARDEN, N.; et al. Dopaminergic activity in transgenic mice underexpressing glucocorticoid receptors: Effect of antidepressants. **Neuroscience**, v. 102, n. 1, p. 151–158, 2001.

CZÉH, B.; FUCHS, E.; WIBORG, O.; SIMON, M. Animal models of major depression and their clinical implications. **Progress in Neuropsychopharmacology & Biological Psychiatry**, v. 64, p. 293–310, 2016. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.pnpbp.2015.04.004>. .

DER-AVAKIAN, A.; MARKOU, A. The neurobiology of anhedonia and other reward-related deficits. **Trends in Neurosciences**, v. 35, n. 1, p. 68–77, 2012. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.tins.2011.11.005>. .

DERUBEIS, R. J.; SIEGLE, G. J.; HOLLON, S. D. Cognitive therapy vs. medications for depression: Treatment outcomes and neural mechanisms. **Nature Reviews Neuroscience**, v. 9, n. 10, p. 788–796, 2008.

DETKE, M. J.; JOHNSON, J.; LUCKI, I. Acute and Chronic Antidepressant Drug Treatment in the Rat Forced Swimming Test Model of Depression. **Experimental and Clinical Psychopharmacology**, v. 5, n. 2, p. 107–112, 1997.

DUMAN, R. S.; AGHAJANIAN, G. K. Synaptic dysfunction in depression: Potential therapeutic targets. **Science**, v. 338, n. 6103, p. 68–72, 2012.

DUMAN, R. S.; LI, N. A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. **Philosophical Transactions of the Royal Society B: Biological Sciences**, v. 367, n. 1601, p. 2475–2484, 2012. Disponível em: <http://rstb.royalsocietypublishing.org/cgi/doi/10.1098/rstb.2011.0357>. .

ESCALONA, R.; FAWCETT, J. Pramipexole in Treatment Resistant-Depression , Possible Role of Inflammatory Cytokines Modeling the Impact of Social Contact on Substance Use. **Neuropsychopharmacology**, v. 42, n. 1, p. 363, 2017. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/npp.2016.217>. .

EVANS, A. H.; KATZENSCHLAGER, R.; PAVIOUR, D.; et al. Punding in Parkinson's disease: Its relation to the dopamine dysregulation syndrome. **Movement Disorders**, v. 19, n. 4, p. 397–405, 2004.

FARDET, L.; PETERSEN, I.; NAZARETH, I. Monitoring of Patients on Long-Term Glucocorticoid Therapy. **Medicine**, v. 94, n. 15, p. 1–10, 2015. Disponível em:

<http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-201504030-00006>. .

FERRARI-TONINELLI, G.; MACCARINELLI, G.; UBERTI, D.; BUERGER, E.; MEMO, M. Mitochondria-targeted antioxidant effects of S(-) and R(+) pramipexole. **BMC Pharmacology**, v. 10, n. 2, p. 1–6, 2010.

FOUNTOULAKIS, K. N.; GONDA, X.; RIHMER, Z.; FOKAS, C.; IACOVIDES, A. Revisiting the Dexamethasone Suppression Test in unipolar major depression: an exploratory study. **Annals of General Psychiatry**, v. 7, n. 22, p. 1–9, 2008.

GERHARD, D. M.; WOHLEB, E. S.; DUMAN, R. S. Emerging treatment mechanisms for depression: focus on glutamate and synaptic plasticity. **Drug Discovery Today**, v. 21, n. 3, p. 454–464, 2016. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.drudis.2016.01.016>. .

GERLACH, M.; DOUBLE, K.; ARZBERGER, T.; LEBLHUBER, F. Dopamine receptor agonists in current clinical use : comparative dopamine receptor binding profiles defined in the human striatum. **Journal of Neural Transmission**, , n. 110, p. 1119–1127, 2003.

GOULD, T. D.; DAO, D. T.; KOVACSICS, C. E. The Open Field Test. **Mood and Anxiety Related Phenotypes in Mice**. p.1–20, 2009.

GOURLEY, S. L.; WU, F. J.; KIRALY, D. D.; et al. Regionally-specific regulation of perk1/2 map kinase in a model of antidepressant-sensitive chronic. **Biol Psychiatry**, v. 63, n. 4, p. 353–359, 2008.

GU, M.; IRVANI, M.; COOPER, J. M.; et al. Pramipexole protects against apoptotic cell death by non-dopaminergic mechanisms. **Journal of Neurochemistry**, v. 91, n. 3, p. 1075–1081, 2004.

HALL, E. D.; ANDRUS, P. K.; OOSTVEEN, J. A.; ALTHAUS, J. S.; VONVOIGTLANDER, P. F. Neuroprotective effects of the dopamine D2/D3 agonist pramipexole against postischemic or methamphetamine-induced degeneration of nigrostriatal neurons. **Brain Research**, v. 742, p. 80–88, 1996.

HARRIS, R. B. S.; ZHOU, J. U. N.; YOUNGBLOOD, B. D.; et al. Failure to Change Exploration or Saccharin Preference In Rats Exposed to Chronic Mild Stress. **Physiology & Behavior**, v. 63, n. 1, p. 91–100, 1998.

HEIM, C.; NEWPORT, D. J.; HEIT, S.; et al. Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. **JAMA**, v. 284, n. 5, p. 592–597, 2000.

HOLLON, S. D.; THASE, M. E.; MARKOWITZ, J. C. Treatment and prevention of depression. **Psychological Science in the public interest**, v. 3, n. 2, p. 39–77, 2002.

HOLSBOER, F. The corticosteroid receptor hypothesis of depression.

**Neuropsychopharmacology**, v. 23, n. 5, p. 477–501, 2000.

HU, W.; ZHANG, Y.; WU, W.; et al. Chronic glucocorticoids exposure enhances neurodegeneration in the frontal cortex and hippocampus via NLRP-1 inflammasome activation in male mice. **BRAIN, BEHAVIOUR, AND IMMUNITY**, p. 1–13, 2015. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.bbi.2015.09.019>. .

INOUE, T.; KOYAMA, T. Effects of acute and chronic administration of high-dose corticosterone and dexamethasone on regional brain dopamine and serotonin metabolism in rats. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, v. 20, p. 147–156, 1996.

IWATA, M.; OTA, K. T.; DUMAN, R. S. The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses. **Brain Behavior and Immunity**, v. 31, p. 105–114, 2013.

IZUMI, Y.; SAWADA, H.; YAMAMOTO, N.; KUME, T. Novel neuroprotective mechanisms of pramipexole, an anti-Parkinson drug, against endogenous dopamine-mediated excitotoxicity. **European Journal of Pharmacology**, v. 557, p. 132–140, 2007.

JAHNG, J. W.; KIM, N. Y.; RYU, V.; et al. Dexamethasone reduces food intake, weight gain and the hypothalamic 5-HT concentration and increases plasma leptin in rats. **European Journal of Pharmacology**, v. 581, p. 64–70, 2008.

JOYCE, J. N.; WOOLSEY, C.; RYOO, H.; BORWEGE, S.; HAGNER, D. Low dose pramipexole is neuroprotective in the MPTP mouse model of Parkinson's disease, and downregulates the dopamine transporter via the D3 receptor. **BMC Biology**, v. 2, n. 22, p. 1–12, 2004.

KELLER, J.; GOMEZ, R.; WILLIAMS, G.; et al. HPA Axis in Major Depression: Cortisol, Clinical Symptomatology and Genetic Variation Predict Cognition. **Mol Psychiatry**, v. 22, n. 4, p. 527–536, 2017.

KENDLER, K. S.; THORNTON, L. M.; GARDNER, C. O. Stressful Life Events and Previous Episodes in the Etiology of Major Depression in Women: An Evaluation of the "Kindling" Hypothesis. **Am J Psychiatry**, v. 157, n. August, p. 1243–1251, 2000.

KESSLER, R. C. The effects of stressful life events on depression. **Annu. Rev. Psychol.**, v. 48, p. 191–214, 1997.

KIM, D.; LEE, S. H.; KIM, J. Y.; et al. Anorexia, anhedonia and depression in rats by chronic dexamethasone. **International Journal of Biosciences**, v. 6, n. 11, p. 32–41, 2015.

KIM, J. B.; JU, Y. J.; KIM, H. J.; et al. Dexamethasone inhibits proliferation of adult hippocampal neurogenesis in vivo and in vitro. **Brain Research**, v. 1027, p. 1–10, 2004.

KITAGAWA, K.; KITAMURA, Y.; MIYAZAKI, T.; et al. Effects of pramipexole on the duration of immobility during the forced swim test in normal and ACTH-treated rats. **Naunyn-Schmiedeberg's Archives of Pharmacology**, v. 380, n. 1, p. 59–66, 2009.

KLOET, E. R. D. E.; VREUGDENHIL, E.; OITZL, M. S.; PHARMACOLOGY, M.; AMSTERDAM, L. Brain Corticosteroid Receptor Balance in Health and Disease. **Endocrine Reviews**, v. 19, n. 3, p. 269–301, 1998.

KLOS, K. J.; BOWER, J. H.; JOSEPHS, K. A.; MATSUMOTO, J. Y.; AHLSKOG, J. E. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. **Parkinsonism and Related Disorders**, v. 11, n. 6, p. 381–386, 2005.

KOLLA, B. P.; MANSUKHANI, M. P.; BARRAZA, R.; BOSTWICK, J. M. Impact of Dopamine Agonists on Compulsive Behaviors: A Case Series of Pramipexole-Induced Pathological Gambling. **Psychosomatics**, v. 51, n. 3, p. 271–273, 2010.

KRISHNAN, V.; NESTLER, E. J. The molecular neurobiology of depression. **Nature**, v. 455, n. October, p. 894–902, 2008.

KUPFER, D. J.; FRANK, E.; PHILLIPS, M. L. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. **The Lancet**, v. 379, p. 1045–1055, 2012. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/S0140-6736(11)60602-8>. .

KURODA, Y.; MIKUNI, M.; NOMURA, N.; TAKAHASHI, K. Differential effect of subchronic dexamethasone treatment on serotonin-2 and B-adrenergic receptors in the rat cerebral cortex and hippocampus. **Neuroscience Letters**, v. 155, p. 195–198, 1993.

LE, W. D.; JANKOVIC, J.; XIE, W.; APPEL, S. H. Antioxidant property of pramipexole independent of dopamine receptor activation in neuroprotection. **J Neural Transm**, v. 107, p. 1165–1173, 2000.

LEMKE, M. R.; BRECHT, H. M.; KOESTER, J.; REICHMANN, H. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. **Journal of the Neurological Sciences**, v. 248, p. 266–270, 2006.

LEMKE, M. R.; WENDOR, T.; MIETH, B.; BUHL, K.; LINNEMANN, M. Spatiotemporal gait patterns during over ground locomotion in major depression compared with healthy controls. **Journal of Psychiatric Research**, v. 34, p. 277–283, 2000.

LEVANT, B.; LING, Z. D.; CARVEY, P. M. Dopamine D3 Receptors: Relevance for the Drug Treatment of Parkinson's Disease. **CNS Drugs**, v. 12, n. 6, p. 391–402, 1999.

LEVER, C.; BURTON, S.; O'KEEFE, J. Rearing on Hind Legs, Environmental Novelty, and the Hippocampal Formation. **Reviews in the Neurosciences**, v. 17, n. September, p. 111–133, 2006.

LI, C.; GUO, Y.; XIE, W.; et al. Neuroprotection of Pramipexole in UPS Impairment Induced Animal Model of Parkinson's Disease. **Neurochem Res**, v. 35, p. 1546–1556, 2010.

LIEBERKNECHT, V.; CUNHA, M. P.; JUNQUEIRA, S. C.; et al. Antidepressant-like effect of pramipexole in an inflammatory model of depression. **Behavioural Brain Research**, 2016. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.bbr.2016.11.007>. .

LINO-DE-OLIVEIRA, C.; LIMA, T. C. M. DE; CAROBREZ, A. D. P. Structure of the rat behaviour in the forced swimming test. **Behavioural Brain Research**, v. 158, n. 2, p. 243–250, 2005.

LUCKI, I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. **Behavioural Pharmacology**, v. 8, p. 523–532, 1997.

LUIS-RAVELO, D.; ESTÉVEZ-SILVA, H.; BARROSO-CHINEA, P.; et al. Pramipexole reduces soluble mutant huntingtin and protects striatal neurons through dopamine D3 receptors in a genetic model of Huntington's disease. **Experimental Neurology**, v. 299, n. June 2017, p. 137–147, 2017. Elsevier. Disponível em: <http://dx.doi.org/10.1016/j.expneurol.2017.10.019>. .

MAES, M. Evidence for an immune response in major depression: a review and hypothesis. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, v. 19, p. 11–38, 1995.

MAES, M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. **Progress in Neuro-Psychopharmacology and Biological Psychiatry**, v. 35, n. 3, p. 664–675, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.pnpbp.2010.06.014>. .

MAES, M.; LEONARD, B. E.; MYINT, A. M.; KUBERA, M.; VERKERK, R. The new ' 5-HT ' hypothesis of depression : Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. **Progress in Neuropsychopharmacology & Biological Psychiatry**, v. 35, n. 3, p. 702–721, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.pnpbp.2010.12.017>. .

MAH, L.; JR, C. A. Z.; NUGENT, A. C.; et al. Neural mechanisms of antidepressant efficacy of the dopamine receptor agonist pramipexole in treatment of bipolar depression. **International Journal of**

**Neuropsychopharmacology**, v. 14, p. 545–551, 2011.

MAJ, J.; ROGÓZ, W.; MARGAS, W.; KATA, M.; DZIEDZICKA-WASYLEWSKA, M. The effect of repeated treatment with pramipexole on the central dopamine D 3 system. **Journal of Neural Transmission**, v. 107, p. 1369–1379, 2000.

MAJ, J.; ROGOZ, Z.; KOŁODZIEJCZYK, K. The behavioural effects of pramipexole, a novel dopamine receptor agonist. **European Journal of Pharmacology**, v. 324, p. 31–37, 1997.

MARUO, J.; HARAGUCHI, Y.; TATEISHI, H.; et al. Abnormal behaviours during pramipexole treatment for Cotard's syndrome: a case report. **Psychogeriatrics**, v. 16, n. 4, p. 283–286, 2016.

MCEWEN, B. S. Physiology and Neurobiology of Stress and Adaptation : Central Role of the Brain. **Physiol Rev**, v. 87, p. 873–904, 2007.

MIERAU, J.; SCHINGNITZ, G. Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D2 receptor agonist. **European Journal of Pharmacology**, v. 215, p. 161–170, 1992.

MIERAU, J.; SCHNEIDER, F. J.; ENSINGER, H. A.; et al. Pramipexole binding and activation of cloned and expressed dopamine D2, D3 and D4 receptors. **European Journal of Pharmacology**, v. 290, p. 29–36, 1995.

MILLER, A. H.; RAISON, C. L. The role of inflammation in depression: From evolutionary imperative to modern treatment target. **Nature Reviews Immunology**, v. 16, n. 1, p. 22–34, 2016. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/nri.2015.5>. .

MUNDELL, L.; LINDEMANN, R.; DOUGLAS, J. Monitoring long-term oral corticosteroids. **BMJ open quality**, v. 6, p. 1–9, 2017. Disponível em: <http://www.ncbi.nlm.nih.gov/pubmed/29450303%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5699140>. .

NAKAYAMA, H.; ZHAO, J.; EI-FAKHRANY, A.; et al. **NEUROPROTECTIVE EFFECTS OF PRAMIPEXOLE AGAINST TUNICAMYCIN-INDUCED CELL DEATH IN PC12 CELLS**. 2009.

NEWMAN-TANCREDI, A.; CUSSAC, D.; AUDINOT, V.; et al. Differential Actions of Antiparkinson Agents at Multiple Classes of Monoaminergic Receptor. II. Agonist and Antagonist Properties at Subtypes of Dopamine D2-Like Receptor and a1/a2-Adrenoceptor. **The Journal of Pharmacology and Experimental Therapeutics**, v. 303, n. 2, p. 805–814, 2002.

NEWMAN-TANCREDI, A.; CUSSAC, D.; QUENTRIC, Y.; et al. Differential Actions of Antiparkinson Agents at Multiple Classes of Monoaminergic Receptor. III. Agonist and Antagonist Properties at Serotonin, 5-HT1 and 5-HT2, Receptor Subtypes. **The Journal of Pharmacology and Experimental Therapeutics**, v. 303, n. 2, p. 815–822, 2002.

NIELSEN, C. K.; ARNT, J.; SA, C. Intracranial self-stimulation and sucrose intake differ as hedonic measures following chronic mild stress: interstrain and interindividual differences. **Behavioural Brain Research**, v. 107, p. 21–33, 2000.

NUTT, D.; DEMYTTENAERE, K.; JANKA, Z.; et al. The other face of depression, reduced positive affect: The role of catecholamines in causation and cure. **Journal of Psychopharmacology**, v. 21, n. 5, p. 461–471, 2007.

ORGANIZATION, W. H. **Depression and Other Common Mental Disorders: Global Health Estimates**. 2017.

OSTADHADI, S.; IMRAN, M. I.; NOROUZI-JAVIDAN, A.; DEHPOUR, A.-R. Antidepressant effect of pramipexole in mice forced swimming test: A cross talk between dopamine receptor and NMDA/nitric oxide/cGMP pathway. **Biomedicine & Pharmacotherapy**, v. 81, p. 295–304, 2016. Elsevier Masson SAS. Disponível em: <http://dx.doi.org/10.1016/j.biopha.2016.04.026>. .

OWENS, M. J.; NEMEROFF, C. B. Role of Serotonin in the Pathophysiology of Depression: Focus on the Serotonin Transporter. **Clin. Chem.**, v. 40, n. 2, p. 288–295, 1994.

PAN, T.; XIE, W.; JANKOVIC, J.; LE, W. Biological effects of pramipexole on dopaminergic neuron-associated genes: relevance to neuroprotection. **Neuroscience Letters**, v. 377, p. 106–109, 2005.

PAPP, M.; WILLNER, P.; MUSCAT, R.; STREET, O. C. An animal model of anhedonia: attenuation of sucrose consumption and place preference conditioning by chronic unpredictable mild stress. **Psychopharmacology**, v. 104, p. 255–259, 1991.

PARIANTE, C. M. The glucocorticoid receptor: part of the solution or part of the problem? **Journal of Psychopharmacology**, v. 20, n. 4, p. 79–84, 2006.

PARIANTE, C. M.; LIGHTMAN, S. L. The HPA axis in major depression: classical theories and new developments. **Trends in Neurosciences**, v. 31, n. 9, p. 464–468, 2008.

PARIANTE, C. M.; MILLER, A. H. Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. **Biological Psychiatry**, v. 49, n. 5, p. 391–404, 2001.

PARIANTE, C. M.; PEARCE, B. D.; PISELL, T. L.; et al. The Proinflammatory Cytokine, Interleukin-1a, Reduces Glucocorticoid Receptor Translocation and Function*. **Endocrinology**, v. 140, n. 9, p. 4359–4366, 1999.

PEPIN, M.; BEAULIEU, S.; BARDEN, N. Antidepressants regulate glucocorticoid receptor messenger RNA concentrations in primary neuronal cultures. **Molecular Brain Research**, v. 6, p. 77–83, 1989.

PICILLO, M.; ROCCO, M.; BARONE, P. Dopamine receptor agonists and depression in Parkinson ' s disease. **Parkinsonism and related Disorders**, v. 15, p. S81–S84, 2009. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/S1353-8020(09)70841-7>. .

PIZZAGALLI, D. A. Depression, Stress, and Anhedonia: Toward a Synthesis and Integrated Model. **Annu. Rev. Clin. Psychol.**, v. 10, p. 393–423, 2014.

PORSOLT, R. D.; ANTON, G.; BLAVET, N.; JALFRE, M. Behavioural despair in rats: A new model sensitive to antidepressant treatments. **European Journal of Pharmacology**, v. 47, n. 4, p. 379–391, 1978.

PRAAG, H. M. VAN; KORF, J. Endogenous Depressions with and without Disturbances in the 5-hydroxytryptamine metabolism: A Biochemical Classification?*. **Psychopharmacologia (Berl.)**, v. 19, p. 148–152, 1971.

PRESGRAVES, S. P.; BORWEGE, S.; MILLAN, M. J.; JOYCE, J. N. Involvement of dopamine D2/D3 receptors and BDNF in the neuroprotective effects of S32504 and pramipexole against 1-methyl-4-phenylpyridinium in terminally differentiated SH-SY5Y cells. **Experimental Neurology**, v. 190, p. 157–170, 2004.

PRICE, J. L.; DREVETS, W. C. Neurocircuitry of Mood Disorders. **Neuropsychopharmacology**, v. 35, n. 1, p. 192–216, 2010. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/npp.2009.104>. .

PRUESSNER, J. C.; CHAMPAGNE, F.; MEANEY, M. J.; DAGHER, A. Dopamine Release in Response to a Psychological Stress in Humans and Its Relationship to Early Life Maternal Care : A Positron Emission Tomography Study Using [ 11 C ] Raclopride. **The Journal of Neuroscience**, v. 24, n. 11, p. 2825–2831, 2004.

RACAGNI, G.; POPOLI, M. Cellular and molecular mechanisms in the long-term action of antidepressants. **Dialogues in Clinical Neuroscience**, v. 10, n. 4, p. 385–400, 2008a.

RACAGNI, G.; POPOLI, M. Cellular and molecular mechanisms in the long-term action of antidepressants. **Dialogues in Clinical Neuroscience**, v. 10, p. 385–400, 2008b.

RAISON, C. L.; CAPURON, L.; MILLER, A. H. Cytokines sing the blues: inflammation and the pathogenesis of depression. **Trends Immunol.**, v. 27, n. 1, p. 24–31, 2006.

RAISON, C. L.; MILLER, A. H. Is depression an inflammatory disorder? **Current Psychiatry Reports**, v. 13, n. 6, p. 467–475, 2011.

RENARD, P.; MUÑOZ, C.; MILLAN, M. J. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. **Nature Reviews Drug Discovery**, v. 9, p. 628–642, 2010.

RÉNÉRIC, J. P.; BOUVARD, M.; STINUS, L. In the rat forced swimming test, chronic but not subacute administration of dual 5-HT/NA antidepressant treatments may produce greater effects than selective drugs. **Behavioural Brain Research**, v. 136, n. 2, p. 521–532, 2002.

RIEDERER, P.; LACHENMAYER, L.; LAUX, G. Clinical Applications of MAO-Inhibitors. **Current Medicinal Chemistry**, v. 11, p. 2033–2043, 2004.

SACKEIM, H. A.; HASKETT, R. F.; MULSANT, B. H.; et al. Continuation Pharmacotherapy in the Prevention of Relapse Following Electroconvulsive Therapy. **JAMA**, v. 285, n. 10, p. 1299–1307, 2001.

SALAS, R. E.; ALLEN, R. P.; EARLEY, C. J.; GAMALDO, C. E. A case of compulsive behaviors observed in a restless legs syndrome patient treated with a dopamine agonist. **Sleep**, v. 32, n. 5, p. 587–588, 2009.

SANSONE, R. A.; FERLAN, M. Pramipexole and compulsive masturbation. **Psychiatry**, v. 4, n. 9, p. 57–59, 2007. Disponível em: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20532122>. .

SANTIAGO, R. M.; BARBIEIRO, J.; LIMA, M. M. S.; et al. Depressive-like behaviors alterations induced by intranigral MPTP , 6-OHDA , LPS and rotenone models of Parkinson ' s disease are predominantly associated with serotonin and dopamine. **Progress in Neuro-Psychopharmacology & Biological Psychiatry**, v. 34, p. 1104–1114, 2010.

SANTIAGO, R. M.; ZAMINELLI, T.; BASSANI, T. B.; et al. The mechanism of antidepressant-like effects of piroxicam in rats. **Journal of Pharmacology and Pharmacotherapeutics**, v. 6, n. 1, p. 7–12, 2015.

SARTORIUS, N.; BAGHAI, T. C.; BALDWIN, D. S.; et al. **Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence**. 2007.

SAVEANU, R. V.; NEMEROFF, C. B. Etiology of Depression: Genetic and Environmental Factors. **Psychiatric Clinics of North America**, v. 35, n. 1, p. 51–71, 2012. Elsevier. Disponível em: <http://dx.doi.org/10.1016/j.psc.2011.12.001>. .

SAYEED, I.; PARVEZ, S.; WINKLER-STUCK, K.; et al. Patch clamp reveals powerful blockade of the mitochondrial permeability transition pore by the D2-receptor agonist pramipexole. **The FASEB Journal**, v. 21, n. 1, p. 1–22, 2006.

SCHILDKRAUT, J. J. THE CATECHOLAMINE HYPOTHESIS OF AFFECTIVE DISORDERS: A REVIEW OF SUPPORTING EVIDENCE. **The American Journal of Psychiatry**, v. 122, n. 5, p. 509–522, 1965.

SCHOENFELD, T. J.; GOULD, E. Stress, stress hormones, and adult

neurogenesis. **Experimental Neurology**, v. 233, n. 1, p. 12–21, 2012. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.expneurol.2011.01.008>. .

SCHULTE-HERBRÜGGEN, O.; VOGT, M. A.; HÖRTNAGL, H.; GASS, P.; HELLWEG, R. Pramipexole is active in depression tests and modulates monoaminergic transmission, but not brain levels of BDNF in mice. **European Journal of Pharmacology**, v. 677, n. 1–3, p. 77–86, 2012. Elsevier B.V. Disponível em: <http://dx.doi.org/10.1016/j.ejphar.2011.12.014>. .

SCHWARTZ, M. W.; SEELEY, R. J.; CAMPFIELD, L. A.; BURN, P.; BASKIN, D. G. Identification of Targets of Leptin Action in Rat Hypothalamus. **J. Clin. Invest.**, v. 98, n. 5, p. 1101–1106, 1996.

SCHWARTZ, M. W.; WOODS, S. C.; JR, D. P.; SEELEY, R. J.; BASKIN, D. G. Central nervous system control of food intake. **Nature**, v. 404, p. 661–671, 2000.

SERRA, G.; ARGIOLAS, A.; KLIMEK, V.; FADDA, F.; GESSA, G. L. Chronic treatment with antidepressants prevents the inhibitory effect of small doses of apomorphine on dopamine synthesis and motor activity. **Life Sciences**, v. 25, p. 415–424, 1979.

SIGWALT, A. R.; BUDDE, H.; HELMICH, I.; et al. Molecular aspects involved in swimming exercise training reducing anhedonia in a rat model of depression. **Neuroscience**, v. 192, p. 661–674, 2011. Elsevier Inc. Disponível em: <http://dx.doi.org/10.1016/j.neuroscience.2011.05.075>. .

SKUPIO, U.; TERTIL, M.; SIKORA, M.; et al. Behavioral and molecular alterations in mice resulting from chronic treatment with dexamethasone: relevance to depression. **NEUROSCIENCE**, v. 286, p. 141–150, 2015. IBRO. Disponível em: <http://dx.doi.org/10.1016/j.neuroscience.2014.11.035>. .

SOUZA, L. C.; MARTYNHAK, B. J.; BASSANI, T. B.; et al. Agomelatine's effect on circadian locomotor rhythm alteration and depressive-like behavior in 6-OHDA lesioned rats. **Physiology & Behavior**, v. 188, n. December 2017, p. 298–310, 2018. Elsevier. Disponível em: <https://doi.org/10.1016/j.physbeh.2018.02.033>. .

STANBURY, R. M.; GRAHAM, E. M. Systemic corticosteroid therapy — side effects and their management. **Br J Ophthalmol**, v. 82, p. 704–708, 1998.

STRASSER, B.; SPERNER-UNTERWEGER, B.; FUCHS, D.; GOSTNER, J. M. Mechanisms of Inflammation-Associated Depression: Immune Influences on Tryptophan and Phenylalanine Metabolisms. **Inflammation-Associated Depression: Evidence, Mechanisms and Implications**. p.95–115, 2017.

SULLIVAN, P. F.; NEALE, M. C.; PH, D.; KENDLER, K. S. Genetic Epidemiology of Major Depression: Review and Meta-Analysis. **Am J Psychiatry**, v. 157, n. 10, p. 1552–1562, 2000.

TAYLOR, W. D.; MCQUOID, D. R.; PAYNE, M. E.; et al. Hippocampus atrophy and the longitudinal course of late-life depression. **Am J Geriatr Psychiatry**, v. 22, n. 12, p. 1504–1512, 2014.

TERADA, K.; IZUMO, N.; SUZUKI, B.; KARUBE, Y.; MORIKAWA, T. Fluvoxamine moderates reduced voluntary activity following chronic dexamethasone infusion in mice via recovery of BDNF signal cascades. **NEUROCHEMISTRY INTERNATIONAL**, v. 69, p. 9–13, 2014. Elsevier Ltd. Disponível em: <http://dx.doi.org/10.1016/j.neuint.2014.02.002>. .

THASE, M. E.; KUPFER, D. J. Recent Developments in the Pharmacotherapy of Mood Disorders. **Journal of Consulting and Clinical Psychology**, v. 64, n. 4, p. 646–659, 1996.

TYE, K. M.; MIRZABEKOV, J. J.; WARDEN, M. R.; et al. Dopamine neurons modulate neural enconding and expression of depression-related behaviour. **Nature**, v. 493, n. 7433, p. 537–541, 2013. Nature Publishing Group. Disponível em: <http://dx.doi.org/10.1038/nature11740>. .

UCHIDA, S.; YAMAGATA, H.; SEKI, T. Epigenetic mechanisms of major depression: Targeting neuronal plasticity. **Psychiatry and Clinical Neurosciences**, p. 1–16, 2017.

VECCHIA, D. D.; KANAZAWA, L. K. S.; WENDLER, E.; et al. Effects of ketamine on vocal impairment, gait changes, and anhedonia induced by bilateral 6-OHDA infusion into the substantia nigra pars compacta in rats: Therapeutic implications for Parkinson's disease. **Behavioural Brain Research**, v. 342, n. December 2017, p. 1–10, 2018. Elsevier. Disponível em: <https://doi.org/10.1016/j.bbr.2017.12.041>. .

VEENEMA, A. H.; MEIJER, O. C.; KLOET, E. R. DE; KOOLHAAS, J. M. Genetic Selection For Coping Style Predicts Stressor Susceptibility. **Journal of Neuroendocrinology**, v. 15, p. 256–267, 2003.

VIEIRA, C.; LIMA, T. C. M. DE; CAROBREZ, A. DE P.; LINO-DE-OLIVEIRA, C. Frequency of climbing behavior as a predictor of altered motor activity in rat forced swimming test. **Neuroscience Letters**, v. 445, n. 2, p. 170–173, 2008.

VOLLMAYR, B.; HENN, F. A. Stress models of depression. **Clinical Neuroscience Research**, v. 3, p. 245–251, 2003.

WATSON, D.; CLARK, L. A.; CAREY, G. Positive and Negative Affectivity and Their Relation to Anxiety and Depressive Disorders. **Journal of Abnormal Psychology**, v. 97, n. 3, p. 346–353, 1988.

WATSON, D.; TELLEGEN, A. Toward a Consensual Structure of Mood. **Psychological Bulletin**, v. 98, n. 2, p. 219–235, 1985.

WILLNER, P. Dopamine and Depression: A Review of Recent Evidente. I. Empirical Studies. **Brain Research Reviews**, v. 6, p. 211–224, 1983a.

WILLNER, P. Dopamine and Depression: A Review of Recent Evidente. II. Theoretical Approaches. **Brain Research Reviews**, v. 6, p. 225–236, 1983b.

WILLNER, P. The validity of animal models of depression. **Psychopharmacology**, v. 83, p. 1–16, 1984.

WILLNER, P. Chronic Mild Stress (CMS) Revisited: Consistency and Behavioural-Neurobiological Concordance in the Effects of CMS. **Neuropsychobiology**, v. 52, p. 90–110, 2005.

WILLNER, P.; LAPPAS, S.; CHEETA, S.; MUSCAT, R. Reversal of stress-induced anhedonia by the dopamine receptor agonist, pramipexole. **Psychopharmacology**, v. 115, p. 454–462, 1994.

WRIGHT, C. E.; SISSON, T. L.; ICHHPURANI, A. K.; PETERS, G. R. Steady-State Pharmacokinetic Pramipexole in Healthy Properties Volunteers. **Pharmacokinetics**, v. 37, p. 520–525, 1997.

WRÓBEL, A.; NOWAK, G.; OSSOWSKA, G.; DANILCZUK, Z.; WIELOSZ, M. Effect of chronic treatment with dexamethasone on brain dopamine receptors in mice. **Polish Journal of Pharmacology**, v. 56, p. 399–405, 2004.

WRÓBEL, A.; ZEBROWSKA-LUPINA, I.; WIELOSZ, M. Dexamethasone reduces locomotor stimulation induced by dopamine agonists in mice. **Pharmacological Reports**, v. 57, p. 451–457, 2005.

YIRMIYA, R.; POLLAK, Y.; BARAK, O.; et al. Effects of Antidepressant Drugs on the Behavioral and Physiological Responses to Lipopolysaccharide (LPS) in Rodents. **Neuropsychopharmacology**, v. 24, n. 5, p. 531–544, 2001.

ZARATE, C. A.; PAYNE, J. L.; SINGH, J.; et al. Pramipexole for Bipolar II Depression : A Placebo- Controlled Proof of Concept Study. **Biol Psychiatry**, v. 56, p. 54–60, 2004.

ZHONG, P.; CIARANELLO, D. Transcriptional regulation of hippocampal 5-HT1A receptors by corticosteroid hormones. **Molecular Brain Research**, v. 29, n. 94, p. 23–34, 1995.

ZOU, L.; JANKOVIC, J.; ROWE, D. B.; et al. Neuroprotection by pramipexole against dopamine- and levodopa-induced cytotoxicity. **Life Sciences**, v. 64, n. 15, p. 1275–1285, 1999.