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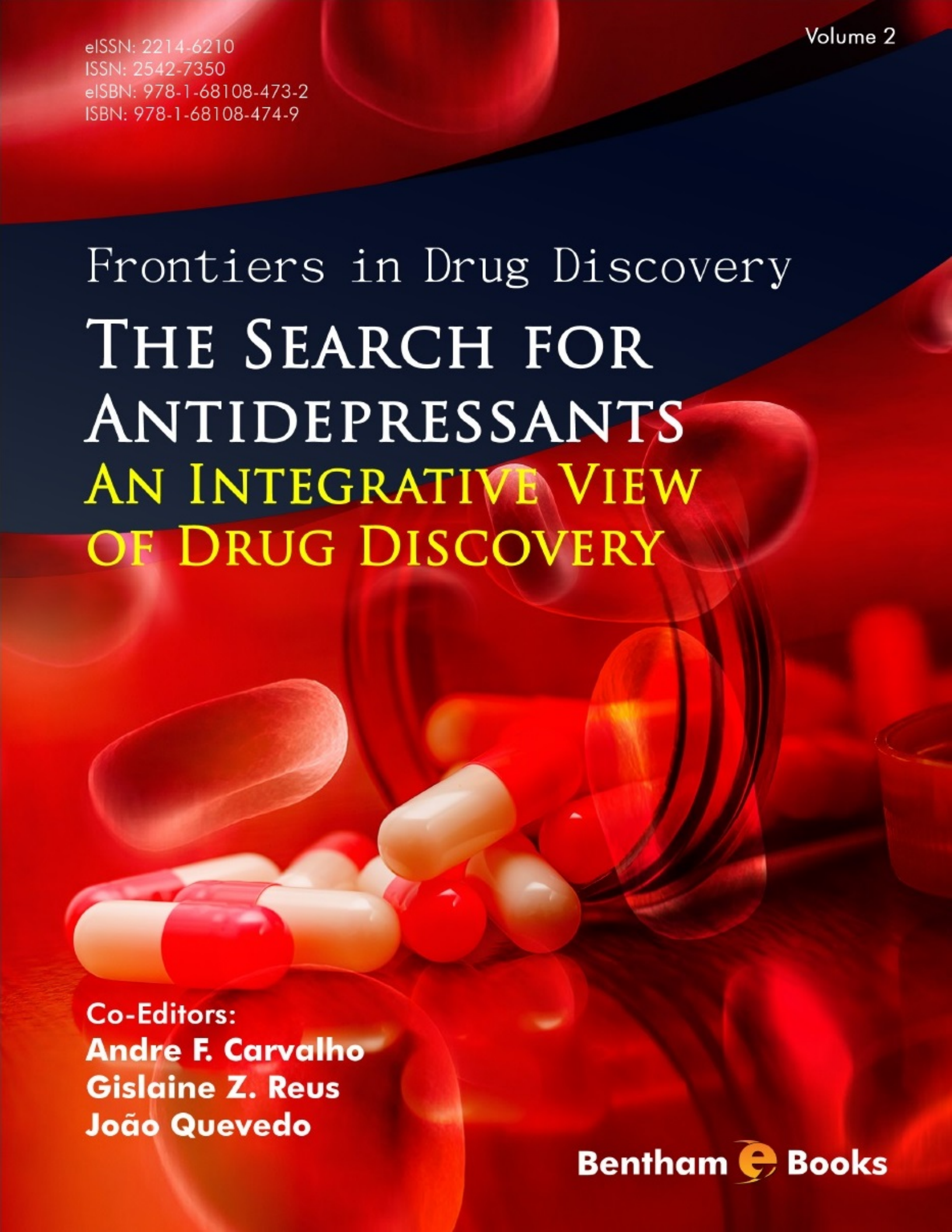
Volume 2

Frontiers in Drug Discovery

The Search for Antidepressants

An Integrative View of Drug Discovery



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Frontiers in Drug Discovery

(Volume 2)

(The Search for Antidepressants - An Integrative View of Drug Discovery)

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CONTENTS

The Search For Novel Antidepressants

In spite of the undeniable progress of Psychiatry over the past 60 years, and hundreds of new molecules having been tested for the treatment of mental disorders, the pharmacological treatment of depression is far from being satisfactory. In the last decades, no significant paradigm shifts in the psychopharmacology of mood disorders have occurred, mostly because the development of novel antidepressant agents is limited by our limited understanding of the pathophysiology of the illness. In this context, Andre F. Carvalho, Gislaine Z. Reus, and João Quevedo have devoted their talent and effort to provide us with a crisp summary of the past, present, and future treatment options for the management of depression that will please both preclinical and clinical investigators in neuropsychopharmacology. This e-jewell, rather than e-book, (and its printed version) gathers prominent researchers in basic and clinical psychopharmacology, authoring thoughtful chapters on exciting topics such as animal models, optogenetics, endophenotypes, repurposing, cognitive dysfunction, biomarkers, oxidative stress, and the microbiota-brain axis, which are outstandingly relevant for understanding the current approach to the pathopshysiology of mood disorders. Modern and traditional treatment targets, such as glutamate receptors, monoamine-oxidase-A, intracellular signaling pathways, and new avenues based on the comorbidity between depression and metabolic syndrome, neuropeptides, or herbal remedies are also part of this comprehensive text which starts with a wonderful chapter on innovative solutions for the development of new antidepressant drugs. I personally enjoyed reading it and learnt much from it. In difficult times such as ours, when social and methodological hurdles are challenging our ability to translate scientific progress into true impactful innovation in this field, the reading of this book fuels fresh air into the community of scientists, clinicians, and perhaps informed patients who await answers or at least better questions for the understanding and management of depression.

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PREFACE

This eBook was conceived after an invitation by the Bentham Science Publishers due to the necessity to review novel antidepressant alternatives.

The prevalence of people with major depressive disorder (MDD) has increased drastically worldwide. In addition, many patients do not respond to classic antidepressant treatments. However, in the last years, new strategies have been studied in experimental and clinical approaches.

The development of novel treatment of MDD would decrease the morbidity and mortality, and consequently the economic burden associated with hospital. Some of these new treatment alternatives are associated with a fast antidepressant effects and low side effects compared to classical treatments. Several studies indicate that pathological mechanisms involved with MDD development are not only based on monoaminergic system, but also with metabolic disturbances, inflammation and a decrease in protein involved with neuroplasticity.

This eBook aims to contribute to an integrated understanding concerning innovative alternatives to treat MDD. It is based on cutting edge research and the outcome will shed light on the most appropriate approach to treat resistant-treatment MDD patients. It gathers a wide range of topics on the subject and includes several chapters with original material.

Authors and co-authors represent a multidisciplinary team that includes scientists and professors with a vast experience in the area, from different universities and research institutions. It is an attempt to encourage the implementation of alternative approaches to the classic antidepressants for humans.

The eBook is organized in fourteen chapters: the general introduction is followed by a review devoted to experimental models, optogenetics therapy, the role of healthy human volunteers, monoamine oxidase-A, repurposed drugs, glutamatergic compounds, cognition, oxidative and nitrosative stress, melatoninergic pathway, neuropeptides, gut microbiota, metabolic disturbances, and plant-based drugs.

Ultimately, we would like to thank all authors that have actively contributed to this eBook, and all people that someway helped us to bring it to daylight, including our family, friends, students and colleagues.

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CHAPTER 1

Innovative Solutions to the Development of Novel Antidepressants

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Abstract: Major depression is a serious problem of today's society affecting approximately 14.8 million American adults, or about 6.7 percent of the U.S. population age 18 and older in a given year. In the last decades neuroscientists have focused their efforts to understand depression and find adequate antidepressant treatments. Despite antidepressant drug treatment patients continue to experience low remission rates and some patients are treatment-resistant. Furthermore, current antidepressant drugs display a slow onset of action and clinical benefits are evident only after several weeks of treatment. Most of the marketed antidepressant drugs target the brain monoaminergic systems, *i.e.*, serotonin (5-HT), noradrenaline (NA) and dopamine (DA) sharing common mechanisms of action. Thus, new therapeutic approaches are needed. The purpose of the following manuscript is to take a journey starting from the discovery of the first antidepressant drug to the recent exciting advances in antidepressant therapeutic approaches. In particular, we summarize the discovery of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs), dual acting/multi-target antidepressants and ketamine. We also discuss novel therapeutic targets such as glutamate, gamma-aminobutyric acid (GABA), neuropeptides, immune system- and brain-gut axis-related targets among others. Finally, we examine the efficacy and safety of non-pharmacological therapeutic approaches for treatment-resistant patients such as electroconvulsive therapy, transcranial magnetic stimulation, magnetic seizure therapy, transcranial direct current stimulation, deep brain stimulation and vagus nerve stimulation.

Keywords: Antidepressant, DBS, ECT, Ketamine, MAOI, Multimodal, NASSA, NDRI, SARI, SNRI, SSRI, TCA, TMS, VNS.

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INTRODUCTION

At some point in our life, some individuals may have experienced a general low frame of mind, felt deeply sad or miserable in response to a specific stress or shock. Feeling 'sad' is a natural response to stressful or bad events of everyday life. However, when 'sadness' is persistent it could develop into a 'malignant sadness' or into depression. Depression is a serious mental health problem that interferes with everyday life over long periods of time. According to the Diagnostic and Statistical manual of Mental disorders version V (DMS-V) [1], depression is diagnosed when at least 5 core symptoms listed in Table **1** have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (i) depressed mood or (ii) loss of interest or pleasure. In the US, the economic burden associated with depression was estimated to reach $210.5 billion in 2010 [2] and the World Health Organization (WHO) has predicted that by the year 2030, depression will be the second leading cause of disease burden worldwide, preceded only by human immunodeficiency virus (HIV) [3]. Despite, the high impact of depression on today society, current antidepressant treatments have important shortcomings relative to the therapeutic needs of depressed patients (Fig. **1**; Table **2**). Thus, antidepressant drug efficacy is typically observed only after several weeks of treatment and approximately 30-40% of patients do not respond to any antidepressant therapy. Furthermore, antidepressant drug treatments induce modest clinical improvement with only a minority of patients achieving full remission [4]. Given this huge unmet need, enormous resources from the scientific world (public and private) have been as is being devoted to the search for novel and better antidepressant treatments. The aim of this review is to summarize the currently available antidepressant therapies (drug and non-drug) and discuss the future directions for antidepressant research.

1. MONOAMINERGIC ANTIDEPRESSANTS

The 1960's represent the golden age for the antidepressant drug discovery and market entries (Fig. **1**). The first antidepressants introduced in the market, iproniazid and imipramine, were discovered thanks to the perceptiveness of some brilliant scientists and were not initially developed to treat depression. Indeed, before the discovery of the first antidepressants, depression was thought of as a sympthomatological manifestation of personal internal conflicts that did not need pharmacological treatment [16].

Depressed individuals were supposed to resolve their personal conflicts to find out the roots of their inner problems and any drug treatment was highly discouraged. Depression was not considered as a biological illness. The discovery of the first

antidepressants unraveled the biological foundations of depression.

Table 1. DMS-V Criteria for Diagnosis of Major Depression.

i. depressed mood most of the day, nearly every day, as indicated by either subjective report (*e.g.*, feels sad or empty) or observation made by others (*e.g.*, appears tearful).
ii. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
iii. significant weight loss when not dieting or weight gain (*e.g.*, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
iv. insomnia or hypersomnia nearly every day
v. psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
vi. fatigue or loss of energy nearly every day
vii. feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
viii. diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
ix. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

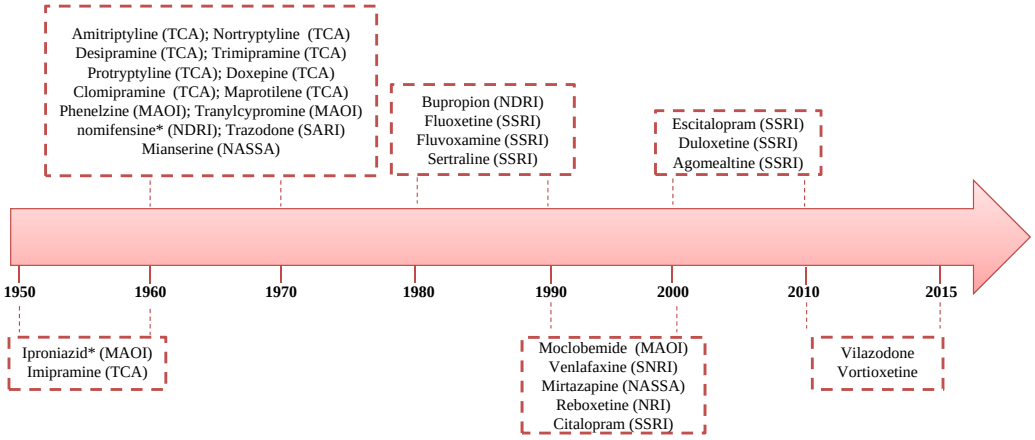

Fig. (1). Schematic representation of the chronology for the discovery of drugs for the treatment of major depression. * withdrawn from the market. Abbreviations: TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake Inhibitors; SNRI, serotonin–noradrenaline reuptake inhibitor; SARIs, serotonin antagonist and reuptake inhibitors; SNRI, serotonin-noradrenaline reuptake inhibitor; NDRI, noradrenaline-dopamine reuptake inhibitors; SARI, serotonin-2 antagonist and reuptake inhibitor; NASSA, noradrenergic and specific serotonergic antidepressant; MASSA, melatonin agonist and selective serotonin antagonist.

CHAPTER 2

Animal Models of Depression: Current Status and Perspectives

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Abstract: Considering the high prevalence of depressive disorders, its social burden and the limitations of currently available antidepressant treatments, animal models of depression aiming at better understanding the neurobiology of this psychiatric disorder and the development of target therapies are essential tools. Although these models fail to mimic all the aspects of this complex psychiatric disorder they have significantly contributed to the development of the field in psychiatry. In this chapter, we summarize the main models of depression that are currently used to assess depression-like phenotypes in rodents. Existing models of depression include stress-based, pharmacological and genetic models, which are evaluated in this chapter in relation to their construct, face and predictive validity as well as their contribution to our understanding of neurobiological mechanisms involved in depression and antidepressant responses.

Keywords: animal models, antidepressants, behavior, construct validity, depression, face validity, genes, inflammation, predictive validity, rodents, stress.

GENERAL CONSIDERATION IN EXPERIMENTAL MODELING DEPRESSION

Despite the high prevalence of depression and its severe global and individual impact, the pathophysiology of this psychiatric disorder is still not completely understood, which makes challenging the conception of an accurate valid animal model of depression. Moreover, some of the hallmark features of depression are subjective feelings (*e.g.* guilt, suicidality and sad mood) and assessing emotional components in animals is an underdeveloped field of research. While particular

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aspects of depression are likely to be purely human features, some signs of the depressive disorder have been successfully translated to behaviors that are assessable in laboratory animals. For example, measures of helplessness, anhedonia, behavioral despair and other neurovegetative alterations such as changes in sleep, sexual and appetite patterns can be easily evaluated in animal models, and in numerous occasions improved with antidepressant treatment.

Several animal models of depression are available, and each one attempts to resemble a particular aspect of this complex illness. Ideally, an animal model should fulfill three main criteria: i) to have similar causative conditions to the human disease (etiological or construct validity), ii) to reproduce in animals symptom profiles comparable to the clinical depression (face validity) and iii) to produce identical antidepressant treatment responses to that seen in the human disease (predictive validity) [1, 2]. These criteria help to compare models against each other, but each one of these models has basic weaknesses [3]. Construct validity is difficult to examine, since the multifactorial etiology of depression is not understood. The current diagnostic systems for depression rely upon presenting symptoms and do not adequately reflect relevant neurobiological alterations to support the modified behavioral patterns. Face validity for models of depression comprises alterations in mood (hard to investigate in animals), cognitive changes, alteration in libido, appetite and body weight, dysregulation of hypothalamic-pituitary-adrenal axis (HPA), sleep disturbances, and decreased motivation to seek and experience pleasurable experiences (anhedonia) [3, 4]. Predictive validity requires an accurate reflection of the temporal aspects of a clinical response to antidepressants, which classically involves a time delay in onset of action. However, classical antidepressant treatments are ineffective or partially effective for many patients [4].

Therefore, several useful animal models of depression have been established but, so far, none of these models perfectly replicate the different depressive phenotypes observed in humans [4].

STRESS-BASED TESTS AND MODELS OF DEPRESSION

Forced Swimming Test and Tail Suspension Test

The forced swimming test (FST) and the tail suspension test (TST) predictive models of depression are based on acute inescapable stressors that may induce feelings of helplessness in the rodents. Porsolt *et al*. [5] originally proposed the FST as a primary drug screening procedure in rodents. In this test, mice or rats are forced to swim in a narrow cylinder while the amount of time spent without making any movements is measured. After an initial period (2-3 min) of vigorous activity, the animals cease attempts to escape and adopt a characteristic immobile

posture (floating in the water making only movements necessary to balance the body and keep their heads above water). Immobility was thus given the name "behavioral despair", a phenomenon that has been associated with the human depressive state. The administration of clinically effective antidepressants as well as non-pharmacological treatments including electroconvulsive shock, paradoxical sleep deprivation, transcranial magnetic stimulation and environmental enrichment, produces a reduction in the duration of the immobility in this test [5 - 8].

The FST, besides being ease of use and inexpensive, is very reliable across laboratories. Moreover, this test has high specificity in detecting novel drugs, since it may be capable of identifying antidepressants undetectable with other tests, such as iprindole, nomifensine and mianserin (atypical antidepressants) [9]. Importantly, an alternative version of the FST separates active behaviors into two distinct categories: climbing (with vertical movement of the forepaws) and swimming (with horizontal movement throughout the swim chamber) [10 - 12]. This modified version of FST helps to determine whether a novel pharmacological agent predominantly activates catecholaminergic or serotonergic neurotransmitter systems, since climbing behavior is sensitive to drugs with selective effects on catecholamine transmission and swimming behavior is sensitive to serotonin-selective antidepressants [13].

The TST, introduced by Steru *et al*. [14] as a new model for detecting antidepressant activity, is conceptually related to the FST; however, in this test immobility is induced by suspending the mouse by the tail. Therefore, animals are subjected to inescapable stress of being suspended by their tail while duration of immobility is assessed. The test usually takes 6 min and, similar to FST, after initial escape-oriented movements, mice rapidly become immobile [14]. If antidepressant treatments or other therapeutic interventions, such as physical activity, are applied prior to the test, mice will actively persist engaging in escape-directed behaviors, reducing the immobility scores compared to vehicle-treated animals [14, 15].

An evident advantage of the TST is the possibility to identify a broad spectrum of antidepressants regardless of their underlying mechanism of action. The test is economical, methodologically simple and easily amenable to automation, permitting evaluating a greater number of animals simultaneously. No unusual post-experimental treatment (rubbing down, maintenance in a warmed environment) is necessary and it is more sensitive to lower doses of drugs, with clear dose response association [11]. Another important advantage of the TST is that it is not confounded by stressful hypothermia as occurs in the FST. On the other hand, the TST is restricted to mice and strains that do not tend to climb their

CHAPTER 3

Potential Role of Optogenetics for The Development of Novel Antidepressants

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Abstract: The need for novel antidepressants is growing with the rate of depression diagnoses. Until recently, systems level analyses of brain physiology have been largely unavailable or outcomes have been overgeneralized to large subsets of neurons in depression. Optogenetics, promoting the use of genetic tools to control light-activated proteins in cells, provides neuroscientists with the ability to specifically control distinct circuits and cell subtypes in order to determine their roles in depression symptomology. This technique affords control at the systems, cellular, and molecular levels. Defining the sub-circuits, mediating depression symptomology through optogenetic studies, can provide information on the brain circuits and cell subtypes to potentially target with electrical and pharmacological therapeutics and treat depression symptoms.

Keywords: Acetylcholine, Depression, Dopamine, Epigenetics, Gene Expression, Glutamate, G-Protein Coupled Receptors, Neural Inhibition, Neural Stimulation, Opsins, Optogenetics, Optopharmacology, Stress Models.

INTRODUCTION

Depression is one of the leading causes of disability worldwide with far reaching social and economic effects on individuals and society. In the United States alone, 6.9% of all adults have experienced at least one episode of major depression [1]. The disorder comes with a heavy economic burden [2] and symptoms are psychologically debilitating. Common symptoms of depression include depressed mood, lethargy, anhedonia, weight disturbances, insomnia, and fatigue [3]. At its worst, depression can lead to suicide. Understanding the underlying neurobiological factors that drive depression symptomology is essential for the well-being of human kind. Fortunately, the past 10 years have seen an expansion

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in new technologies to discover and treat maladaptive behavioral symptoms caused by depression.

Pharmacological treatments for depression have greatly expanded [4]. However, pharmacological antidepressant treatments are often ineffective for all patients [5]. Often multiple treatments are used in combination and up to 30% of patients fail to display remission [6]. Further, common antidepressant targets are found throughout both the central and peripheral nervous system leading to complicating factors and unwanted side-effects [7]. Many of these therapies target well-studied neurotransmitters (*e.g.*, serotonin, dopamine, norepinephrine, *etc*.), with aims of balancing monoamine signaling within the brain [8]. These neurotransmitters are involved in motivation, emotion, and reward related circuity [9 - 12] and play a key role in balancing neurological firing within regions known to be involved in depression symptomology and complex behaviors. Unfortunately, the biological mechanism of these antidepressants is still largely unknown. Optogenetics, the use of genetic tools to control light-activated proteins in cells, holds the potential to dissect these specific maladaptive effects within the brain by restoring normal function of these neurotransmitters and cells in a circuit, temporal, and cell-type specific manner [11, 13 - 15]. Furthermore, research focused on stimulating or inhibiting these modulatory inputs to specific brain regions may prove useful in determining the action of antidepressants.

It is clear that depression manifests itself through dynamic changes in a multitude of brain regions, thus a wide variety of approaches are necessary to identify underlying neurobiological mechanisms that mediate depression symptomology. While human studies have examined brain activity and connectivity in mood disorders, these studies lack cell-type specific resolution, thus making it extremely difficult to parse out individual sub-circuit dysfunction in depression. An explosion in new neuroscience technologies to manipulate and observe brain function in discreet neurons and microcircuits holds promise for answering these questions. In particular, optogenetics has the capability of probing depression-associated brain circuits to refine our understanding of function and enhance the specificity of treatment strategies. Spatial, temporal, and genetic specificity, along with the variety of tools used both *in vivo* and *ex vivo* will aid in determining the underlying neurobiological mechanisms of depression symptomology. Utilizing these findings could encourage and support the development of novel antidepressant treatments that target these circuits and cells.

Animal Models to Investigate Depression Symptomology

Preclinical animal models of depression rely on stressors to produce depressive-like endophenotypes since stress has been highly implicated as a major cause in

the development of depression [16]. While it has been argued that mild acute stressors are beneficial for memory and mental function, repeated or high intensity stressors produce maladaptive behavioral outcomes. Discrete behavioral paradigms aim to produce stress in different manners and are critically evaluated on their distinct etiology. Stress models utilize naturalistic or non-naturalistic stressors or both in order to induce symptoms. Often, stressors aim to produce anhedonia, the central and most defining symptom of depression [16]. However, other behavioral outcomes often co-vary with anhedonia severity, including reduced motivation, helplessness, weight loss/gain, comorbid anxiety, and impaired social function. Based on numerous factors including stress severity, number of stressors, and types of stress, distinct types of depression models may function better to dissect circuitry underlying specific depression outcomes. Due to the temporal and cellular specificity of optogenetic strategies, optogenetics functions well in understanding distinct behaviors at specific time points during or after stressors and their relation to underlying circuitry and signaling.

NEUROSCIENCE METHODS TO ALTER BRAIN ACTIVITY WITHIN NEURAL CIRCUITS: A CASE FOR OPTOGENETICS

Of all the current neuroscience methodologies, optogenetics provides the greatest specificity for manipulating specific cell types. Other methods often lack temporal, spatial, cell-type specificity, and reversibility. The location of illumination, the expression pattern and spread of the constructs, and the specific promoter garner the benefits of spatial specificity. Optogenetic studies utilize genetically targeted viruses with cell-type specific promoters and/or transgenic mice to specifically express optogenetic constructs in the neuronal subtypes. Further, temporal specificity is achieved through the activation of constructs specifically during illumination. Spatial and temporal specificity are characteristics used to dissect the role of circuits, cells, and molecules in awake and behaving mice. These qualities achieve precise stimulation or inhibition of specific cell-types and circuits within the brain during behavior.

Activation of brain regions can be achieved by direct magnetic or electrical stimulation within these areas. In cases of treatment resistant depression, doctors may rely on brain stimulation. Historically somatic stimulation interventions such as electroconvulsive therapy (ECT) have been utilized for patients not responsive to drugs [17]. While effective, this method of stimulation is non-specific, even with respect to regional specificity, thus it is unclear which brain circuits ECT is effected. Alternative methods were developed to avoid this methodology such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS). These strategies have proven effective in a number of brain regions. High frequency prefrontal cortical stimulation using repetitive TMS has alleviated depression

CHAPTER 4

The Relevance of Studies in Healthy Human Volunteers for The Development of Novel Antidepressants: Exploring Endophenotypes

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Abstract: Comparisons between normal individuals and patients are fundamental to improving our pathophysiological models of psychiatric disorders and promoting the development of new treatments. These comparisons are possible by focusing on the basic constituents of human behavior at different levels of organization. This chapter discusses the advantages of exploring psychophysiological, neurophysiological, and psychophysical strategies for the identification of endophenotypes shared by patients with different diagnosis and normal individuals. An integrative but experimentally viable approach to cognitive functions like attention, emotions, decision making, balance control, and social cognition is discussed. The use of new methodologies based on virtual reality for functional studies are also presented. The objective is to demonstrate that the search for new drugs, the improvement of diagnostic systems, and the identification of new endophenotypes are simultaneous and inseparable processes. The efficiency of this search depends on a close integration of pharmacological, cognitive, and neurophysiological strategies in clinical and experimental investigations.

Keywords: Anxiety, Attention, Balance, Diagnostic criteria, Endophenotypes, Evoked potentials, Normality, Psychophysiology, Psychiatric diagnosis, Social cognition, Virtual reality.

1. WHY STUDY NORMALS

The development of new drugs is not the outcome of a series of logical steps that starts with the identification of a new disease and culminates with the design and

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synthesis of a new molecule. Serendipity is usually the rule and, not rarely, the observation of unexpected effects of a new drug can suggest new ways to cluster symptoms in new syndromes [1, 2]. For example, the proposal of considering panic disorder as a separate diagnostic category was initiated in 1959 when Donald Klein was observing patients with depressive-anxiety symptoms treated with imipramine, a new tricyclic compound. The peculiar action of this new drug on anxious symptoms was suggested by the nurses' observation that patients reduced their trips to the nursing station to complain about being sick or dying, and that they were more independent and capable of walking around the hospital by themselves [3, 4]. The observation of this previously unexpected effect lead to a revision of diagnostic criteria and provided new evidences for the study of pathophysiology of anxiety.

This example illustrates the idea that sometimes, the discovery of a treatment can precede the identification of a disease. Clinical observation is still an important mechanism for therapeutic development and the study of drug actions on normal individuals or in patients with diverse conditions remains fundamental to the psychopharmacology progress. This dialectic process is possible because diseases are not a natural occurring phenomena but rather a classificatory decision carried out by specialists with the objective of developing a common language for a reliable communication. Even dependent on consensus, medical diagnosis is not a mere question of opinion. The decision about the pathological character of a given set of symptoms does not depend on the mere variation from the norm, but it involves a judgment about the consequences of having such characteristics in terms of quality and expectancy of life. Moreover, the dependency upon human judgment does not imply in lack of objectivity, as well demonstrated by other biological disciplines. For example, Ross [5] pointed out that "The concept of a biological species similarly has no clear-cut natural boundary. Nevertheless, biologists do not conclude from this that species is an arbitrary and non-scientific concept".

The distinction between normal and pathological behavior can also be compared with the partition of a territory between two countries. National borders are of institutional nature, dependent on collective consensus but they are also dependent on physical elements. Mutual frontiers are usually based on natural points of references like rivers. The existence of geographical markers does not validate the idea of nations but gives them a physical expression. The necessity of separating nations comes first and the choice of a geographical accident to perform this function comes later [6].

Therefore, the study of patients and non-patients is essential to: 1) define demarcatory criteria between them; 2) identify objective markers as reference for

such separation (as we shall discuss ahead, this step is essentially the search for biological markers or endophenotypes); 3) establish possible mechanisms to explain how biological mechanisms interact with psychological, cultural, and social instances in modulating the clinical expressions and prognosis of mental disorders; and 4) search for treatments or strategies to modify the natural history of conditions considered as pathological.

When focusing our attention on biological mechanisms it is important to keeping in mind that the understanding of the impact of diseases over individual's life requires a broader perspective.

For example, the diagnosis of malnutrition can be made based on objective biological criteria but physiological models alone do not inform all details of disease pathophysiology. Low food ingestion is not associated to a primarily metabolic or genetic dysfunction but rather to social or environmental factors. Drugs and supportive measures may be necessary for dealing with very severe cases but the whole strategy for treat and preventing malnutrition must involve social, cultural, and political interventions.

2. THE LIMITATIONS OF CURRENT MENTAL DISORDERS DIAGNOSTIC CRITERIA: FROM DSM TO THE RESEARCH DOMAIN CRITERIA

Despite its undeniable development in recent decades, current psychiatric nosology is still provisory and heterogeneous. Conditions with strong biological determinants like dementias coexist with other conditions dependent upon sociocultural determinants like Compulsive Buying Disorder [7].

This characteristic gives a general aspect of imprecision to psychiatric diagnosis as a whole. This state of affairs can be explained by the descriptive character of contemporary diagnostic systems like the Diagnostic and Statistical Manual of Mental Disorder (DSM) and the International Classification of Diseases (ICD).

The limitations of such approach are clear even for those directly involved in the revision of these diagnostic systems. For example, David Kupfer, head of the DSM-5 (*Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders),* stated that "The problem that we've had in dealing with the data that we've had over the five to 10 years since we began the revision process of DSM-5 is a failure of our neuroscience and biology to give us the level of diagnostic criteria, a level of sensitivity and specificity that we would be able to introduce into the diagnostic manual" (quoted from [8]).

CHAPTER 5

Monoamine Oxidase-A: A Valid Target for the Management of Depression

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Abstract: Monoamine oxidase enzyme has been developed as a valid target for the treatment of depression. The development of selective and reversible type of monoamine oxidase-A inhibitors still remains a challenge to medicinal chemists pursuing the research towards the search of innovative chemotypes for the management of depressive states. The present chapter focuses on the history of MAO-A inhibitors, structure and biochemistry of MAO-A. It also covers challenges involved in the drug development of MAO-A inhibitors.

Keywords: Adrenaline, Chees effect, Depression, FAD/Dopamine, Inhibitor binding cavity, MAO-A, MAO-B, Moclobemide, Tranylcypromine.

INTRODUCTION

Antidepressants are the drugs used for treating mental disorders accompanied by the depression state. Depressed mood is typically associated with low energy or fatigue, feeling guilt, poor concentration, loss of interest in life and sleep disturbances [1]. The depressive state mainly arises from a dysfunction of neurogenic amines such as serotonin (5-hydroxytryptamine) [5-HT] noradrenaline [NA] and dopamine [DA]. A general strategy employed is the blockade of 5-HT/NA transporters or inhibition of monoamine oxidases (MAOs) by increasing the concentrations of extracellular transmitters which would reappear to the normal level of neurotransmission [2]. In the treatment of depressive mood,

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monoamine oxidase inhibitors (MAOIs) were the first clinically used agents. This family of drugs has been through ups and downs over the last decades due to various side effects and non-selective inhibition [3].

History of MAO-A Inhibitors

In 1952, the psychiatrist Jean Delay firstly explained the antidepressant potential of isoniazid (INH), a hydrazine derivative used as a first line drug for tubercular treatment [4]. From the light of Jean Delay research, Albert Zeller *et al.* also reported N'-isopropyl isonicotinohydrazide as an effective inhibitor of mitochondrial MAO in the same year [5]. Tranylcypromine, was the initially marketed monoamine oxidase inhibitor (MAOI) dissimilar to hydrazine structure and was synthesized in 1948 by Dr. Burger from Smith, Kline and French Laboratories. The MAOI potential of this molecule was corroborated ten years later [6 - 8]. This non hydrazine derivative did not posses the side effects associated with first-generation MAOIs [9]. In 1964, Tranylcypromine withdrawn from the U.S. pharmaceutical market due to the occurrence of hypertensive crisis, but within a short period of time it was reintroduced again at the request of clinicians as the due benefits outweighed its risks. In the middle of the eighties tranylcypromine and Phenelzine [hydrazine derivative] together accounted for 90% of the MAOIs prescribed [10]. In 1968, J. P. Johnston, at the Research Laboratory of May & Baker Ltd., United Kingdom identified that MAO exist in two forms MAO-A and MAO-B, in which MAO-A is preferably associated with depressive disorders in the rat brain [11].

The first generation MAOIs such as iproniazid, phenelzine and tranylcypromine irreversibly inhibited both MAO-A and MAO-B [12]. This opened up the search for novel selective MAO-A inhibitors and allows MAO-B to remain active and exercise its metabolizing action on certain substances, such as the tyramine ingested with food, and whose failure to disaminate could lead to hypertensive crises [13]. This amplified the momentum for the discovery of reversible and selective inhibitors of MAO-A (RIMA) [14, 15]. The minimum criteria in the drug development process of inhibitors of MAO-A should pass the blood-brain barrier [BBB] and have efficient antidepressant properties excluding cheese effect [16]. Moclobemide is a well-known MAO-A selective reversible inhibitor that has antidepressant and anxiolytic effects. It appears to be as effective as other antidepressants giving positive results for cases of refractory depression [17]. However the search for new class of selective and reversible type of MAO-A inhibitors have still greater therapeutic value for the management of depressive states.

Mechanism of Enzymatic Action of MAO

Monoamine oxidase enzymes are mitochondrial membrane bound flavoproteins which contain flavin adenine dinucleotide (FAD) as a redox active cofactor [18]. They are covalently bound to cysteine at the 8-α position of the isoalloxazine ring [19]. The MAO enzyme consists of two isoforms that are encoded by separate genes, MAO-A and MOA-B which share approximately 70% of sequence identity at amino acid level, but differ in their selectivity for substrates and inhibitors [20]. The structure around the FAD evidenced to be virtually identical in both MAO-A and MAO-B [21]. Monoamine oxidase enzyme mainly catalyzes the oxidative deamination of biogenic amines. The substrate of this enzyme includes primary, secondary and tertiary amines. Initially imines are formed by transfer of the equivalent of two hydrogen atoms from amines to the covalently bound FAD cofactor. The reduced flavin is re-oxidized by oxygen, producing hydrogen peroxide (H_2O_2). The imine product rapidly hydrolyzes to the aldehyde releasing ammonia (Fig. **1**) [22]. The reaction is coupled to the cofactor FAD re-oxidation by molecular oxygen, which produces hydrogen peroxide. This side product is supposed to contribute to oxidative stress which represents a hallmark of neurodegenerative diseases [23]. MAO inhibition decreases the breakdown of monoaminergic neurotransmitters by increasing the levels of these amines in the brain. Thus, monoamine oxidase inhibitors (MAOIs) have been developed and used as antidepressants. They are also useful to decrease the breakdown of remaining dopamine when it is depleted in Parkinson's disease [24].

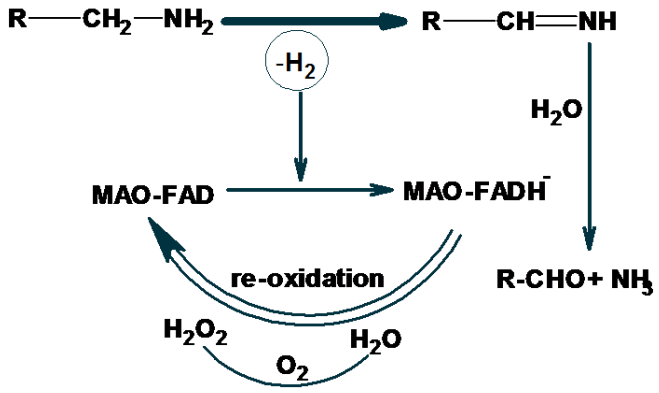

Fig. (1). Catalytic mechanism of MAO.

For *in vitro* studies, serotonin is used as a selective MAO-A substrate and β-phenylethylamine is used for MAO-B. Kynuramine for MAO-A and benzylamine for MAO-B are used as substrates in spectrophotometric assays but are oxidised by both enzymes albeit with different efficiencies [25].

CHAPTER 6

Repurposed Drugs: A Shortcut to the Discovery of Novel Antidepressants?

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Abstract: Drug repurposing aims to find new therapeutic indications for existing drugs in the market. Because the process of discovering a new pharmacological compound with desired clinical effectiveness is challenging, drug repurposing is being increasingly utilized in many areas. To address the unmet needs and limitations of treating depressive disorders with available treatments, many pharmacological agents are being investigated for antidepressant efficacy. For example, there have been some promising results with repurposing agents targeting acetylcholinergic and glutamatergic neurotransmission, as well as modulating immune system. Furthermore, anti-glucocorticoid agents also suggested to have possible antidepressant activity. In this chapter, we summarize the results from studies on the repurposing for treating depression of various agents, and search for perspectives on treatment strategies for depression beyond approved antidepressants.

Keywords: Acetylcholine, Antidepressant, Anti-inflammatory, Celecoxib, Depression, Glutamate, Ketamine, Mecamylamine, Metyrapone, Mifepristone, Repurposing, Scopolamine.

INTRODUCTION

There is a long-standing history of drug repurposing in the treatment of depression. For example, mitochondrial monoamine oxidase (MAO) inhibitor iproniazid [1] was originally developed to treat tuberculosis in the early 1950's by Hoffman-La Roche laboratories. However, iproniazid was noted for its antidepressant effects in psychiatric populations: patients evinced greater vitality and demonstrated a gradual increase in social activity [2]. Subsequently, MAO

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inhibitors became the first class of pharmacological agents approved for the treatment of depression [3]. Tricyclic antidepressants (TCAs) were also discovered serendipitously. After the success of chlorpromazine (*i.e.* the first antipsychotic drug for the treatment of schizophrenia) Hafliger and Schinder investigated the antipsychotic properties of imipramine (*i.e.* the first TCA) by modifying the classic antihistamine structure of chlorpromazine. Although imipramine did not possess antipsychotic properties, it produced a marked antidepressant effect [4]. Following the development of MAO inhibitors and TCAs, newer antidepressants including the selective serotonin reuptake inhibitors (SSRIs), and serotonin and noradrenaline reuptake inhibitors (SNRIs) were developed based on the monoamine hypothesis of depression.

Conventional antidepressants, with the exception of agomelatine, are mechanistically similar to TCAs and target the monoamine system. Newer antidepressants, including SSRIs, SNRIs and atypical antidepressants (*e.g.* mirtazapine), have improved side-effect profiles but are no more effective than MAO inhibitors and TCAs. In other words, most currently available antidepressants have a limited set of mechanisms, which may partly contribute to the inadequate remission rates found in contemporary clinical trials. Moreover, for more than two decades, the SSRIs and SNRIs have been the most commonly prescribed classes of antidepressants [5]; and the development of new antidepressant drug has reached a plateau [5]. There remains an unmet need for the development of novel antidepressants with novel mechanisms of action.

Limitations in the development of pharmacological agents for depression include the heterogeneous patho-etiology of depressive disorders, safety/tolerability and antidepressant efficacy. For example, there are two major uncertainties in novel drug discovery [6]. The first is safety; to which toxicity and pharmacokinetic properties of new drugs are related. The second is efficacy; to which biological pathway and pharmacodynamics properties of new drugs are related. Moreover, antidepressant efficacy studies are extremely expensive (they involve chronic treatment of at least hundreds of patients) and are notoriously risky (large placebo response effects cause many trials to fail) [7]. This increases the threshold for a pharmaceutical or biotechnology company to embark on a trial of any antidepressant, especially one with a new bona fide (and therefore riskier) mechanism. The uncertainty of novel drug development is often mitigated by eliminating some of the unknown elements [8]. For example, a pharmacological agent on the market has already demonstrated to be safe and well tolerated in clinical populations [9] and its mechanism of action has been investigated [10]. Hence, repurposing of existing drugs would be a desirable alternative strategy for discovering novel antidepressants at a lower overall cost [5, 11].

In this chapter, we review extant literature from both pre-clinical and clinical studies on repurposing drugs for the treatment of depression with an overarching aim to summarize various treatment strategies for managing depressive disorders beyond approved antidepressants.

ACETYLCHOLINERGIC AGENTS

The cholinergic hypothesis of depression was proposed more than three decades ago [12]: Janowsky *et al*. posited that depression is associated with hyperactivation of the cholinergic system and decreased activity of the noradrenergic system. Since its conceptualization more than three decades ago, several lines of evidence have supported the foregoing hypothesis. For example, observations of elevated levels of the acetylcholine precursor choline in the brains of depressed subjects and the normalization of central choline levels with remission [13, 14] are directionally consistent with the cholinergic hypothesis of depression.

In pre-clinical models of depression, manipulation of the cholinergic system has been reported to induce the development of depression-like behavior. For example, rats selectively bred to show increased sensitivity to the centrally active acetylcholine esterase (AchE) inhibitor diisopropyl fluorophosphates (Flinders Sensitive Line, FSL) exhibited greater scores on the measures of depression-like behavior (*e.g.* reduced locomotor activity, reduced body weight, increased REM sleep and cognitive deficits) [15]. Overstreet and Russell [16] reported increased acetylcholine levels in the brains of FSL rats as well as greater numbers and enhanced function of high affinity nicotine acetylcholine receptors (AchRs) [17, 18]. FSL rats also exhibited greater behavioral depression including immobility in the forced swim test (FST), poor performance in the avoidance task, and decreased sugar and water consumption, indicative of stress-induced anhedonia [15, 19, 20].

In clinical populations, Janowsky *et al*. [21] reported that in subjects with an underlying affective disorder, treatment with physostigmine, the blood-brain barrier permeable acetylcholine esterase inhibitor, decreased manic and increased depressive symptoms. In healthy subjects, physostigmine has been reported to induce symptoms of dysphoria, depression, anxiety and irritability [22]. Taken together, these observations in human subjects and in animal models suggest that hyperactivity of the cholinergic system can contribute to the pathophysiology of depression.

There are two main classes of acetylcholine receptors; muscarinic (mAChR) and nicotinic receptors (nAChR). Muscarinic receptors are metabotropic receptors that activate ion channels via G-protein coupling [23] and belong to a multigene

CHAPTER 7

Ketamine and Glutamatergic Compounds: Exploring Biomarkers and Mechanisms Related to Rapid Antidepressant Action

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Abstract: Over the last two decades, several studies have shown the role that the glutamatergic system plays in the pathophysiology of major depressive disorders (MDD). This theory is supported mainly by the fact that glutamatergic modulators have revealed antidepressant effects in animal models as well as in clinical trials. Many of these compounds have been created to be tested as antidepressants. However, there are many other compounds used in the treatment of non-depressive illnesses that have subsequently been discovered to possess antidepressant properties, one such example being ketamine. Ketamine is an antagonist of the N-methyl-D-aspartate receptor, and it has shown to improve the symptoms of patients with MDD, including refractory depression. Laboratory studies have mainly investigated the mechanism of action responsible for the rapid and prolonged antidepressant effects presented by NMDA modulators. This chapter will focus on studies which have demonstrated the antidepressant effects of ketamine, as well as other glutamatergic modulators. Data from experimental studies and clinical trials have also been included, and these will demonstrate the biomarkers and mechanisms of action involved behind the effects of fast acting antidepressants.

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Keywords: Biomarkers, D-Cycloserine, Fast antidepressant, Glutamatergic modulators, Glutamatergic system, Ketamine, Major depressive disorder, Memantine, N-methyl-D-aspartate, Scopolamine, Sleep deprivation.

1. INTRODUCTION

1.1. Depression

Major depressive disorder (MDD) is one of the most common mental disorders in modern society, with a worldwide prevalence of approximately 17% [1]. Despite extensive research, the neurobiology of MDD remains poorly understood due to a lack of biomarkers, relatively low rates of heritability, and the heterogeneity of precipitating factors, including stress [1, 2]. Depressive syndrome is generally characterized by a low mood, anhedonia, a loss of interest in daily activities as well as other well described symptoms, and is associated with severe consequences including suicide and an increased risk of cardiovascular events [3]. The human cost of this illness is highlighted by the fact that suicide is now the third highest cause of death in individuals aged 15 to 24 years [4]. The treatment of MDD has historically focused on monoamine modulation, largely owing to the unexpected discovery that tricyclic antidepressants and monoamine oxidase inhibitors preferentially inhibited the reuptake and breakdown of dopamine, norepinephrine, and serotonin, respectively [5]. However, even this class of therapy failed to address the basic limitations of current antidepressants [6]. The first major limitation is that current antidepressants are effective in less than 50% of patients [7]. Secondly, these drugs can take weeks or even months to produce a therapeutic response, and are only moderately effective, thus leaving more than one-third of depressed individuals resistant to drug treatments [8]. Thirdly, almost all of current antidepressants induce a wide spectrum of adverse reactions [6]. These significant drawbacks mean that the search for novel, rapid and efficacious medications for the treatment of MDD, including resistant MDD, continues. In light of these difficulties, the glutamatergic system is receiving more attention as one of the potential targets of novel therapeutic agents for the treatment of mood disorders [9, 10].

Glutamate is the major excitatory neurotransmitter in the brain, and growing evidence indicates that there are abnormalities in the glutamatergic system of patients with mood disorders [11]. Researchers are working to develop medications that act within the glutamatergic system, which may lead to a breakthrough in the pursuit of more effective measures to treat mood disorders [12]. Thus, in this chapter we will highlight recent findings related to potential novel antidepressants, which mainly target the N-methyl-D-aspartate (NMDA)

receptors within the glutamatergic system.

1.2. Glutamatergic System

Glutamate (Glu) is an essential and abundant amino acid that performs various functions within the brain, most notably acting as an excitatory neurotransmitter and precursor of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) [9, 13]. Under normal conditions, Glu plays a prominent role in synaptic plasticity, learning and memory, but in pathological situations it is known to be a potent neuronal excitotoxin, triggering either rapid or delayed neurotoxicity [9]. To prevent neuronal cell death from excessive glutamate, there are a number of receptors and reuptake mechanisms on both neurons and astrocytes that regulate glutamatergic neurotransmission [14]. After its release from presynaptic neurons, glutamate interacts with adaptor molecules such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate and NMDA receptors, which all belong to postsynaptic ionotropic glutamate receptors (iGluRs) [6]. These receptors have ion channels with selective conductance to calcium and sodium. Once activated, there is an influx of cations, favoring the depolarization of the neuron [15]. Moreover, the metabotropic glutamate receptors (mGluRs), which begin their signal transduction cascade through G protein coupling, are located on presynaptic and postsynaptic neurons [6, 16]. In addition to this, the released glutamate is recycled by surrounding glial cells via the excitatory amino acid transporters (EAATs), converted to glutamine, then transported back to presynaptic neurons where glutamine is reconverted to glutamate [17 - 19].

NMDA receptors (NMDARs) are a subclass of the excitatory, ionotropic L-glutamate neurotransmitter receptors [20]. They are important for normal brain function, being both primary candidates for the molecular basis of learning and memory, and in the establishment of synaptic connections during the development of the central nervous system (CNS) (Fig. **1**) [21]. NMDARs are tetrameric structures of seven subunits including at least one obligatory subunit, GluN1, and varying numbers of a family of GluN2 (GluN2A-D) or GluN3 (GluN3A-B) subunits, with multiple binding sites including those binding to glutamate, polyamine, magnesium, and glycine [22]. They are also coupled to ion channels, specifically, sodium, potassium and calcium channels [6]. The pharmacological regulation of NMDARs depends on unique combinations of subunit-specific binding sites. While NMDARs channels can conduct sodium and calcium, NMDA channels are blocked by magnesium under physiological conditions [22]. This block is relieved by cellular depolarization, which plays a critical role in synaptic plasticity, particularly in long-term potentiation (LTP). Still, removal of magnesium requires depolarization of the postsynaptic neuron, which typically

CHAPTER 8

Novel Antidepressant Targets for Cognitive Dysfunction in Major Depressive Disorder

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Abstract: Cognitive dysfunction in MDD represents one of the most frequent residual symptoms persistently following the achievement of symptomatic remission. Moreover, emerging evidence indicates that significant cognitive deficits occur early in the course of the disorder and may persist during affective remission. Cognitive impairment lowers the likelihood of achieving the functional recovery. Conventional antidepressant treatments exert a beneficial yet unsatisfactory effect on cognitive dysfunction in MDD. As a consequence, the recognition of treatments capable of specific cognitive improvements is an unmet need. Vortioxetine, a multimodal antidepressant, has cognitive enhancing properties that seem to occur independently of affective improvement. Several routes of research are evaluating the potential of several pharmacological and non-pharmacological interventions in improving cognitive performance. Agents under investigation include lisdexamfetamine, glutamatergic modulators, erythropoietin, anti-inflammatory agents as well as nutraceuticals, such as omega-3-polyunsaturated fatty acids, S-adenosyl-methionine and melatonin. Moreover, neuromodulatory, psychological and biobehavioural approaches provided preliminary encouraging results. However, further investigations are warranted to confirm these findings and to evaluate the potential pseudo-specificity of these approaches.

Keywords: Antidepressant, Anti-inflammatory agents, Cognitive deficits, Cognitive dysfunction, Cognitive remediation, Erythropoietin, Ketamine, Lisdexamfetamine, Major Depressive Disorder, Melatonin, Neuromodulation, Omega-3-polyunsaturated fatty acids, Physical exercise, S-adenosyl-methionine, Treatment, Vortioxetine.

INTRODUCTION

Major depressive disorder (MDD) is recognized as a chronic and disabling

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disorder, associated with high morbidity and mortality. It has been estimated that MDD affects more than 150 million people worldwide and is a leading cause of disability-related years loss [1]. Approximately only up to one-third of individuals with MDD achieve symptomatic remission following an antidepressant treatment and a significant proportion of them continue to exhibit residual symptoms that prevent the achievement of functional recovery [2, 3]. A growing body of evidence indicates that cognitive dysfunction is a strong mediator of psychosocial functioning [4, 5]. Some evidence indicates that workplace performance is related to cognitive deficits to a greater extent than to overall affective symptomatology [6]. A greater impairment in neurocognitive performance predicts a lower probability of functional remission [7].

A widespread cognitive impairment with small to moderate effect sizes has been documented in MDD, encompassing the domains of attention, processing speed, executive functions, working memory and learning [8, 9]. Cognitive deficits may be recognized not only during the symptomatic phases of the disorder, but often persist after remission [10] and can be observed in the early phases of the disorder in young adults and adolescents as well [11]. Consequently, cognitive impairment has been acknowledged as a discrete dimension in MDD, instead of a simple epiphenomenon of depressive severity [12]. Moreover, reduced cognitive flexibility appears to be reduced in unaffected relatives of individuals with MDD, suggesting that neurocognitive deficits may represent familiar trait markers not associated with the onset of depression [13].

There is a unanimous consensus that efficacy of conventional antidepressant on cognitive dysfunction is sub-optimal. A systematic review and meta-analysis indicates that the use of antidepressants is associated with small positive effects on certain domains including memory and psychomotor speed but not on executive functions [14]. There is some evidence that antidepressants targeting the serotoninergic and the noradrenergic systems may exert a more beneficial effect on cognitive impairment as compared to those targeting only the serotoninergic system (selective serotonin reuptake inhibitors, SSRIs) [15]. For instance, beneficial effects on cognitive performance have been documented with serotoninergic-noradrenergic reuptake inhibitors (SNRIs) (duloxetine), independently of improvements in the depressive symptoms' severity [16]. Importantly, while pharmacotherapy appear to exert a limited benefit on cognitive functioning, no specific pattern of improvement can be consistently demonstrated in particular domains [17]. Moreover, until recently, the interpretation of literature in the field has been limited by the over-representation of subjects aged over 65 in the majority of studies assessing cognition in MDD [18]. Lastly, it should also be noted that the use of conventional antidepressant may also account for cognitive complaints in adults with MDD in partial or full remission [19]. For instance,

tricyclic antidepressants may exert detrimental effects on executive functions and memory due to well-known anticholinergic properties [20].

Recently, some experts argue that 'cognitive remission' may become a novel therapeutic objective for MDD more closely related to functional recovery than the current definition of remission [12]. Nevertheless, this remains a clear unmet need in the treatment of MDD [14, 17]. Recently, the search for therapeutic agents for cognitive dysfunction of MDD has been an area of increasing research interest.

Vortioxetine is a novel multi-modal antidepressant with 5-HT3 and 5-HT7 receptor antagonistic properties, 5-HT1A receptor agonism, 5 HT-1B receptor partial agonism. In addition, vortioxetine inhibits the 5-HT transporter. Randomized placebo-controlled trials (RCTs) assessing vortioxetine effects on cognitive performance have provided encouraging results. Vortioxetine showed a significant superiority over placebo in improving executive functioning in adults aged 18-65 [21, 22]. Path-analysis indicated that the pro-cognitive potential of vortioxetine was partly attributable to the direct effect of treatment and not simply driven by the improvement in depressive symptoms' severity.

Notwithstanding the exact mechanisms leading to cognitive dysfunction in MDD remain elusive, it has been posited that neuroprogressive mechanisms including, but not limited to, immune-inflammatory alterations, changes in tryptophan catabolite (TRYCAT) pathway, abnormalities in glutamatergic neurotransmission, impaired neurotrophic support, as well as oxidative and nitrosative stress (O & NS) and aberrations in energy metabolism might be involved [23 - 25]. Novel compounds targeting these pathways have been tested or deserve future attention as pro-cognitive agents. Moreover, non-pharmacological strategies, including neuromodulation as well as psychological and biobehavioural interventions (*e.g.*, cognitive remediation and physical exercise) provided promising results [26, 27]. Here we review novel treatment strategies showing preliminary evidence of cognitive enhancement in MDD (Fig. **1**).

PHARMACOLOGICAL TREATMENTS

Lisdexamfetamine Dimesilate

Lisdexamfetamine dymesilate (LDX) is a pro-drug of d-amphetamine approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults. LDX antidepressant properties have been tested in a RCT involving adults with non-psychotic MDD and residual depressive symptoms receiving escitalopram [28]. Augmentation treatment for 6 weeks with LDX resulted in greater reductions in depressive symptoms on the Montgomery-Asberg

CHAPTER 9

Oxidative and Nitrosative Stress, Immune Inflammation and Trptophan Catabolites in Driving Melatonergic Pathway Alterations in Depression: Treatment Implications

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Abstract: In this chapter we review the interactions of oxidative and nitrosative stress (O&NS), immune-inflammation, tryptophan catabolites (TRYCATs) and suboptimal mitochondrial functioning in driving changes in the melatonergic pathways in major depressive disorder (MDD). We propose that such interactive biological processes provide a framework for the development of a number of novel pharmaceutical and nutriceutical treatment targets, with relevance to a classification of MDD that is based on biological underpinnings rather than on subjective phenomenology.

Keywords: Inflammation, Major depressive disorder, Mitochondria, Nitrosative stress, Oxidative stress, Tryptophan catabolites.

INTRODUCTION

There have been many classifications of depression, ranging from psychoanalytic and cognitive to the biological, with the latter emphasizing the decreased levels of serotonin and alterations in neuronal activity. Such classical conceptualizations still carry considerable influence in clinical practise. However, more recent research on depression's biological underpinnings have highlighted changes in oxidative and nitrosative stress (O&NS) and immuno-inflammatory pathways, with consequences for alterations in tryptophan catabolites (TRYCATs), such as kynurenine (kyn) and kynurenic acid (KYNA), which, in turn, can change neuronal activity [1]. The differential expression of such neuroregulatory TRYCATs in different brain regions, would then be expected to change the

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patterning of inter-area neuronal activity [1]. An important aspect of such increases in TRYCATs activity that is driven by inflammatory cytokines and stress induction of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) respectively, is that tryptophan is diverted from serotonin synthesis to the production of neuroregulatory TRYCATs. Such driving down of serotonin levels by O&NS and pro-inflammatory cytokines links these processes to the plethora of data associating decreased serotonin with major depressive disorder (MDD). However, decreased serotonin has wider biological relevance to the etiology, course and treatment of MDD, with serotonin acting as a necessary precursor for the melatonergic pathways, including the production of N-acetylserotonin and melatonin.

In this chapter we look at these interconnected changes in MDD, linking to the genesis, course and treatment of this still poorly conceptualized disorder. Firstly, we review the data on alterations in O&NS in MDD.

Oxidative and Nitrosative Stress in Depression

O&NS

Decreased levels of endogenous anti-oxidants and anti-oxidant enzymes are a common finding in MDD patients and animal models of depression. Pro-inflammatory cytokines as well as the metabolic challenging of mitochondria leads to the generation of free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as superoxide, peroxynitrite, hydrogen peroxide and nitric oxide (NO). Evolutionary forces have acted to incorporate ROS and RNS into normal, physiological processes, perhaps particularly in response to the plasticity required for environmental adaptation. Given that ROS and RNS can produce toxic and damaging effects, their utilization in normal processing has to be counterbalanced by antioxidant defenses. As such, ROS and RNS, either when in excess, or when anti-oxidant defenses are compromised, lead to their damaging effects *via* reactions with, and damaging effects upon, membranes and DNA. Antioxidants, such as vitamin C, vitamin E, coenzyme Q10 (CoQ10) and glutathione (GSH) afford protection against ROS and RNS induced free radicals, with antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPX) also neutralizing ROS/RNS, reviewed in [1].

O&NS occurs when the oxidant/antioxidant ratio is raised, leading to an array of damaging processes, such as peroxynitrite driven lipid peroxidation, which damages membrane lipids and DNA, as well as contributing to protein nitrosative damage, reviewed in [1]. Dysfunction to key cellular processes may follow, contributing to an increased likelihood of apoptosis. ROS and RNS are highly

produced by mitochondria and, in the absence of adequate anti-oxidant defences, can lead to sup-optimal mitochondrial functioning, leading to deficits in mitochondrial cellular energy production.

Such increases in O&NS that are driven by ROS and RNS are relevant to the etiology, course and treatment of many medical conditions, including inflammatory bowel disease [2], multiple sclerosis (MS) [3], Parkinson's disease [4] and Alzheimer's disease (AD) [5], as well as MDD [6]. The association of increased rates of MDD in such neurodegenerative disorders is suggested not to arise as a disentangled comorbidity, but rather by O&NS, as well as a related increases in immune-inflammation and TRYCATs, being the biological underpinnings of MDD that contribute not only to cognitive dysfunction in MDD [7], but also to the etiology and course of these neurodegenerative conditions [8]. Neuroprogression is a recent term to emerge in this context, indicating that the neurodegenerative processes that are normally associated with disease such as AD and MS, may also be evident in MDD, although with less intensity [9].

O&NS and MDD

The oxidant/anti-oxidant imbalance seems an inherent feature of MDD [10] with an increase in this ratio correlating with cognitive dysfunction in MDD, including when associated with other medical conditions [11]. Depression is associated with increased mRNA and protein levels of myeloperoxidase [12], the pro-inflammation associated cyclooxygenase-2 (COX-2) [13], malondialdehyde [14] and inducible nitric oxide synthase [15], especially in patients with recurrent MDD episodes. Increased ROS and O&NS in MDD patients, *versus* controls, shows MDD patients to have more DNA breaks, alkali-labile sites, and oxidative DNA damage [16], possibly as a consequence of genetic suboptimal DNA repair systems [17]. More studies must be conducted to elucidate the role of DNA damage and repair in depression.

Antidepressant treatments can decrease ROS, RNS and O&NS [18], further supporting the role of O&NS in MDD. Likewise data derived from preclinical studies of depression also indicate increased levels of ROS and O&NS, with stress induced depression in rodents being driven by NADPH Oxidase-derived superoxide and ultimately hydrogen peroxide [19], reviewed in [1]. Such an accumulation of data highlights the relevance of O&NS in MDD, with implications for processes of cellular ageing and neuroprogression, as indicated by decreased telomere lengths in the oligodendrocytes of MDD patients [20].

IMMUNE-INFLAMMATORY PROCESSES AND MDD

Increased levels of immune-inflammation and pro-inflammatory cytokines are

CHAPTER 10

Novel Non-Monoaminergic Antidepressants: Focus on Neuropeptides

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Abstract: Major depressive disorder (MDD) is a common illness representing a social problem worldwide, that is predicted to become the second cause of disability in 2020 by the World Health Organization (WHO), with a heavy economic burden for the western societies.

The discovery of the first-generation antidepressants, *i.e.*, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), followed by selective serotonin reuptake inhibitors (SSRIs), dual-acting serotonin/norepinephrine reuptake inhibitors (SNRIs) and a few others, improved significantly the treatment and the prognosis of MDD, besides promoting the investigation of its possible biological mechanisms. However, the long latency of therapeutic effect, the presence of relevant side effects and the treatment's resistance are still major problems in MDD management. For those reasons, the pharmacological treatment of MDD is still far from being satisfactory, without any significant paradigm shifts in the psychopharmacology of MDD occurring in the last decades. More recently, other mechanisms, besides monoamines' modulation, have been explored in the attempt to discover novel and effective antidepressants. To date, a number of novel compounds acting on neuropeptide receptors have been developed and tested in both animals and humans with different results. In this chapter, we will provide a short overview of the main neuropeptides, from their biochemical and molecular characteristics to preclinical and clinical evidence in MDD.

Keywords: Antidepresants, Depresion, Galarin, Neuropeptide, Neuropeptide Y, Oxytocin, Substance P, Vasopression.

INTRODUCTION

Every year millions of subjects develop major depressive disorder (MDD) that is one of the most common psychiatric disorders [1]. MDD is considered one of the most invalidating medical diseases and the World Health Organization (WHO)

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has estimated that it will become the second cause of disability worldwide in 2020 [2]. Pharmacological treatment of MDD has been developed from the 1950s, when two compounds, iproniazide and imipramine, were found to improve the depressive symptoms. Iproniazide and imipramine are, respectively, an inhibitor of the monoamine oxidases (MAOs), catabolic monoamines' enzymes, and an inhibitor of the reuptake of serotonin (5-HT) and norepinephrine (NE). Thereafter, the enhancement of monoamine neurotransmission was considered the underlying mechanism of action of antidepressants and led to the development of the so-called *monoamine deficiency hypothesis* postulating that MDD would be resulting from impairments of the monoamine systems [3]. Along this line, MAO inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were developed that represented a successful strategy of MDD treatment [3]. However, the increasing bulk of investigations soon showed that the monoamine hypothesis was insufficient to explain the whole picture of MDD and could not account for the delayed latency of therapeutic effect, so that it was modified to include pre- and postsynaptic receptor changes [4]. In the course of the 70s and the 80s, selective serotonin (5-HT) reuptake inhibitors (SSRIs) and 5-HT/norepinephrine reuptake inhibitors (SNRIs), with a more specific mechanism of action and with less severe side effects profile were developed and successfully introduced into the clinical practice. In any case, even SSRIs and SNRIs provoke side effects, possibly invalidating, such as sexual dysfunctions, weight gain, anxiety, and sleep disorders that constitute an important cause of discontinuation. Moreover, their latency of therapeutic effect is not different from that of MAOIs or TCAs, and still one third of MDD patients remains treatment-resistant. From a theoretical point of view, a future generation of antidepressants should lack these unmet clinical needs and overcome the main adverse effects [3 - 5]. For these reasons, new pharmacological approaches have been developed in order to improve the management and the outcome of MDD. The development of triple monoamine reuptake inhibitors or the augmentation with other pharmacological selective antagonists of the 5-HT_{1A} or 5-HT_{2A} could trigger a faster and stronger clinical efficacy paralleled by an increase of the clinical effect and/or a decrease of the side effects [6, 7]. Another current approach is focused on other non-monoamine molecular mechanisms, potentially involved in the pathophysiology of MDD [8 - 11] and, in particular, on neuropeptides. Neuropeptides are small protein-like molecules produced by neurons to communicate each other, which act as neurotransmitters or co-transmitters through the binding to specific metabotropic or G-protein-coupled receptors. In general, they can be considered modulators of monoaminergic neurotransmission. The main ones are substance P (SP), corticotropin-releasing factor (CRF), neuropeptide Y (NPY), vasopressin (VP) and oxytocin (OT), galanin (Gal) and melanin-concentrating hormone (MCH) [12]. Neuropeptides seems to be crucial in the regulation of the response to

stressful stimuli and in the modulation of the stress system. In fact, the sensitivity to stress and the "resilience" in coping might be respectively increased and decreased by a combination of genetic abnormalities, early stressful experiences and exposure to traumatic, unpredictable stressors [13]. Mood and anxiety disorders are included amongst the so-called stress-related disorders, as a series of investigations demonstrated that those psychiatric syndromes are accompanied by alterations of the stress system [14]. One of the most known and studied biological correlates of MDD is the hyperactivity of the hypothalamic-pituitar--adrenal (HPA) axis with impairment of the physiological negative feedback mechanism [15]. Amygdala, hippocampus and prefrontal cortex are the brain structures that mainly regulate the HPA axis through several central neuropeptides [10]. Some neuropeptides (CRF and VP) might be, however, related to the development of MDD pathophysiology even independently from the HPA axis [16 - 19]. During the last years, some novel compounds acting on neuropeptides or their receptors have been developed and tested in both animal models and in MDD patients and, particularly, antagonists of neurokinin (NK) 1 and CRF1 receptors that appear promising. In this chapter we will present a short, but comprehensive overview of the available data on some novel non-monoaminergic compounds and their possible use in MDD.

Substance P

Tachykinins are neuropeptides involved in the regulation of peripheral autonomic functions, including blood pressure, respiration, micturition and gastrointestinal motility, and central functions like drinking behavior and food intake, mood, anxiety, aggression, pain, learning and memory [20]. The most important ones are substance P (SP) and neurokinin (NK) A. Generally, SP acts as co-transmitter with monoamines, such as 5-HT [20, 21]. Tachykinins bind to three different G-protein coupled receptors (NK1R, 2 and 3) with NK1R showing the highest affinity for SP [20]. It has been shown that some NK1R antagonists nay behave as antidepressants through the modulation of monoaminergic systems. Not surprisingly, some evidence indicates that SP innervation may reach monoamine neurons that may express NK1Rs. Further, brain regions regulating affective behaviors and neurochemical response to stress have been demonstrated to express NK1Rs [21]. Direct data of tachykinin alterations in depressed patients are limited to the report of higher SP cerebrospinal fluid (CSF) levels and lower orbitofrontal cortex NK1R density [22 - 24]. Aprepitant (MK-869) is one NK1Rs antagonist tested at 300 mg/day in a six-week trial involving 200 MDD patients and comparing it to paroxetine (20 mg/day) or placebo. The results showed that both paroxetine and aprepitant were effective on both depressive and anxious symptoms and superior over placebo [22]. The compound L-759274, another NK1R antagonist, showed a significantly greater improvement of HRSD scores

CHAPTER 11

Novel Antidepressant Drugs: Exploring Neurotrophins and Intracellular Signaling Pathways

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Abstract: This chapter is aimed to critically review the current literature focusing on alternative treatment strategies using novel antidepressant compounds in major depression. Major depression and stress-related disorders are associated with relevant brain changes such as loss of dendritic spines and synapses, dendritic atrophy as well as a reduction of glial cells (both in number and size) of specific brain areas such as the hippocampus and prefrontal cortex. There are several intracellular pathways (such as cyclic adenosine monophosphate pathway, Wnt/ß-Catenin pathway, and mTOR pathway) that are supposed to be involved in causing major depression. Immune/inflammatory altered pathways have been also hypothesized as one of the most relevant mechanisms implicated in the pathophysiology of major depression. Antidepressant treatment is associated with a substantial induction of neuroplasticity mechanisms reversing the pathological effects of depression and stress-related disorders. The non-competitive NMDA receptor antagonist ketamine may be defined as one of the most intriguing therapeutic options for the treatment of patients with major depressive disorder and treatment-resistant depression. Ketamine is associated with a rapid and sustained glutamate burst stimulating the BDNF-mTORC1 cascade leading to acute synaptogenic action in specific brain areas. Scopolamine, a non-selective M receptor antagonist, the effect of which is dependent on glutamate, may be identified as another rapid-acting antidepressant compound associated with induced mTORC1 and synapse formation. In addition, microRNAs (miRNAs), which regulate gene expression by targeting the three prime untranslated region of genes, have been shown to play a significant role in neurogenesis. Exploring miRNAs effects may help to develop new

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molecular strategies aimed to modulate the expression of certain genes with an interesting potential in the antidepressant field.

Keywords: Antidepressant medications, Chronic stress, Glutamatergic alterations, Immune / inflammatory abnormalities, Inflammatory pathway, Intracellular pathways, Neurotrophins, Neuroplasticity, Neurogenesis, Serotonergic system.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common and disabling psychiatric conditions associated with a significant disability, and functional impairment worldwide [1 - 3]. Patients with MDD often experience a variety of psychiatric symptoms, such as depressed mood, loss of interests, anhedonia, feelings of helplessness which are significantly associated with suicidal behavior and also despair, anxiety, agitation and irritability [4].

Although multiple medications are now available to treat this complex disorder [5], more than 20% of MDD patients treated with traditional antidepressant drugs do not recover completely. Above all, they are affected by treatment-resistant depression (TRD) [6].

For more than forty years, both clinicians and researchers have tried to depict a satisfactory model, which may explain the most relevant mechanisms underlying the pathophysiology of this condition as well as reliable criteria for response and remission after treatment [7]. Resistance to commonly used antidepressant medications mainly targeting the reuptake or breakdown of monoamines reflects the intriguing complexity of MDD pathogenesis. To add further complexity to this condition, most MDD patients also need long-term treatment in order to regain stable conditions and avoid relapses [8, 9]. Although several reports revealed that a number of different molecular changes are related to both chronic stress and major depression, the most relevant molecular and cellular dysfunctions associated with MDD are poorly understood till date. Both preclinical and clinical evidence reported that chronic stress [10, 11] and MDD [12, 13] may induce changes in intracellular signaling, gene expression, neuronal structure, and functions in the brain regions associated with mood regulation, and neurocognitive functions.

Herein, we will first focus briefly on the current knowledge about neurotrophins, monoaminergic systems, and intracellular pathways, the dysfunctions of which are mainly involved in MDD pathogenesis.

Over the last two decades, studies aimed to identify the therapeutic action of

available antidepressant medications have focused predominantly on the synthesis, reuptake, and metabolism of 5-HT and its receptor binding sites; However, 5-HT neurotransmission at pre- and postsynaptic sites is regulated by both receptors and specific intracellular signal transduction pathways [14].

Further additional investigation of the main signaling molecules underlying synaptic plasticity, chronic stress, and major depression will undoubtedly offer new horizons in the development of novel therapeutic interventions. Under this purview, we have been motivated to delineate currently proposed assumptions regarding the pathophysiology of MDD together with the most recently investigated molecular targets concerning the development of novel antidepressant drugs.

THE ROLE OF NEUROTROPHINS IN THE PATHOPHYSIOLOGY OF MAJOR DEPRESSION

Although an appreciable number of evidence over the last 20 years demonstrated the active involvement of different intracellular signaling pathways in chronic stress and major depression, the exact molecular changes preceding cellular remodeling events are still poorly understood. To date, studies suggested that neurotrophic factors are able to play a fundamental role in neuronal development (*e.g.,* growth, differentiation, and survival), and neuroplasticity mechanisms [15 - 19]. It has been reported that neuronal atrophy, cell loss, and altered tissue volume in specific brain areas are significantly associated over time with major depression and that higher the number of depressive episodes, higher the level of cellular/molecular impairment. Chronic stress is associated with a significant reduction in hippocampal neurotrophins levels as well [20]. These findings support the hypothesis that long-term effects of stress/depression are mediated by the deficiency of adequate neurotrophins according to the so called “neurotrophic hypothesis of depression” [21]. Based on this theory, altered neurotrophic signaling is one of the most relevant contributing factors in the pathophysiology of major depression and neuroplasticity related events, which are usually induced after 3-4 weeks of treatment with conventional antidepressant medications [15, 22, 23].

It has been demonstrated that adult hippocampal neurogenesis is regulated by several neurotrophic factors such as brain-derived-neurotrophic factors (BDNF), insulin-like growth factor I (IGF-I), and vascular endothelium growth factor (VEGF-B) [24 - 27]. Some of the common alterations, which may be found in MDD, seem to be directly linked to the reduced BDNF hippocampal levels [21, 28 - 30].

Both the decreased BDNF production and reduced cortical dendritic branching

CHAPTER 12

Shared Pathophysiology between Depression, Obesity and Metabolic Disturbances: Novel Antidepressant Targets?

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Abstract: The prevalence of obesity and related metabolic disorders is largely the result of poor dietary choices and excessive caloric intake. Consumption of palatable, energy-rich foods can lead to obesity and increase the risk of depression. Depression not only impairs the quality of life of obese individuals but also increases the associated risks of obesity and hinders motivation to seek out and adhere to weight loss strategies. In turn, certain forms of depression are closely linked with overeating, promoting an adverse cycle of depressed mood, comfort-food seeking and further weight gain. This chapter provides an overview of the metabolic, immune and neural processes that accompany increased adiposity and obesity and their impact on mood and the development of depression. In this context, potential treatments for the alleviation of depression co-morbid with obesity are discussed.

Keywords: Anhedonia, Animal models, Cortisol, Depressive-like behaviours, Diabetes, Diet-induced obesity, Drug treatment, Inflammation, Insulin, Leptin, Polyunsaturated fatty acids, Reward, Stress.

I. INTRODUCTION

The consequences associated with obesity and poor nutrition have become a worldwide concern. According to the *World Health Organization*, more than 3.4 million people die each year from health problems stemming from overweight and

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obesity [1]. This number is far from subsiding. The proximity, low cost and ease of accessibility of foods with high caloric density takes center stage of this epidemic. Sweet and fatty energy-rich foods are rewarding and our strong preference for these foods is posited to have evolved to maximize growth and survival [2, 3]. A state of positive energy balance develops when energy intake surpasses energy expenditure, resulting in the storage of excess calories. Indeed, the coupling of over-nutrition with reduced physical activity has led to a doubling in obesity rates since 1980 [1]. This increase is largely due to individuals in developing countries adopting similar lifestyle habits evident in North America: excessive intake of sugars, fats and processed foods and increased sedentarity [4] [5].

Conditions such as cardiovascular disease, cancer, type 2 diabetes and metabolic syndrome are typical ramifications of obesity [6]. Although less recognized, mood disorders account for a significant proportion of obesity comorbidities. Depression is a multifactorial disease that represents a major global health burden [7]. Several lines of evidence highlight a positive correlation between obesity and the development of depressive symptoms. Obesity and the metabolic syndrome are both strong predictors of the onset of depression [8, 9]. Moreover, the significance of weight gain in the link between obesity and depressed mood is suggested by the negative correlation between body mass index (BMI) and emotional state [10, 11]. Of key significance however, the risk of depression in obese individuals appears to depend on metabolic dysfunctions [12, 13]. Obese individuals characterized as metabolically healthy (normal blood pressure, insulin sensitivity, inflammatory and lipid profiles) are much less susceptible to developing depression [12, 13]. Finally, the association between obesity and depression is bidirectional [14]. As adaptations in the neural circuitry controlling emotional state can develop with weight gain and obesity, depressed mood can also lead to overeating to compensate for a reduced affective state [15 - 17]. Thus, the complex interface between emotions, food choice and eating behaviour can contribute to a vicious cycle whereby mood impairments can drive poor eating habits and further weight gain [18].

There is a physiological basis underlying the relationship between obesity and depression [19]. At the core of the problem lies alterations in the communication between metabolic tissues and the brain that perturbs signalling in the neural network controlling mood. Reviewed in greater detail in preceding chapters, the circuitry controlling emotions and mood regulation largely resides in corticolimbic and midbrain regions nuclei including the prefrontal cortex (PFC), nucleus accumbens (NAc), dorsal striatum, amygdala, hippocampus and ventral tegmental area (VTA) [20]. Dopamine (DA) release in corticolimbic sites plays a central role in the control of motivated behaviour and mood and is well-

implicated in the neuroplastic responses to palatable food intake, weight gain and associated changes in metabolic signals [20, 21]. DA interacts with opioids, serotonin and endocannabinoids in corticolimbic regions and receives input from hypothalamic nuclei that direct energy homeostasis by controlling food intake and energy expenditure [22].

The aim of this chapter is to present an overview of the current status of our knowledge of the biological processes contributing to depressive symptomatology in obesity. The stress axis and alteration in glucocorticoid function in both obesity and depression will be reviewed. Next, a significant part of the discussion is dedicated to growing evidence for the role of the inflammatory processes common to obesity and depression and their impact on neurotransmission and neural plasticity. This will be followed by an overview of the principal peripherally-derived metabolic hormones and nutrients that modulate mood. The chapter will conclude with a review of both available and promising pharmacotherapies for the alleviation of depression co-morbid with obesity.

II. STRESS, OBESITY AND DEPRESSION

By definition, stress is a response to stimuli that involves perception, appraisal, and arousal [23]. Physiological reactions to stress involve actions in the nervous, endocrine and immune systems [24 - 26]. Stress can have a positive or a negative impact on health, depending on the manner by which the individual controls and adapts to it. Typically, stressful situations trigger an instant 'fight-or-flight' reaction to either confront or escape from the stressor [27]. This can be as simple as avoiding predators (negative stressor), thus providing a means of survival [27]. However, prolonged or recurrent stress can lead to health problems.

Stress plays a major role in the control of food intake [28]. Prolonged, moderate stress increases intake of high-fat and/or -sugar foods and, consequently, the accumulation of fat mass [28]. Chronic stress exposure can potentiate sensitivity to reward and motivation to obtain palatable 'comfort' foods [18], in part due to increased compulsivity for food [29]. Psychological and physiological stressors can alter communication between the brain and periphery by modulating hypothalamic-pituitary-adrenal axis (HPA) function. The HPA axis plays an important role in the control of energy homeostasis [30] and HPA impairments are associated with both visceral obesity and depression susceptibility as well as depressive-like behaviours in rodent models [31].

HPA Activity, Obesity and Depression

Once activated, the HPA axis induces a cascade of hormonal release events

CHAPTER 13

The Development of Novel Antidepressants: Focus on Plant-based Drugs

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Abstract: Depression is a world-wide health problem that currently affects approximately 16% of the population in the United States alone. As one of the most common psychiatric disorders, it can be quite debilitating, and is certainly a major financial burden. With current medications suffering from major shortcomings that include slow onset of action, poor efficacy, and unwanted side effects, the search for new and improved antidepressants is ever increasing. Many patients may seek complementary and alternative medicine (CAM) remedies to evade the financial burden, adverse effects, or because of cultural or religious beliefs. Thus these remedies offer a valuable resource for the discovery of new and improved antidepressant medications. This chapter provides an overview of the current knowledge state regarding a variety of natural products commonly used in depression. Herbal medicines discussed have been used in clinical trials for the treatment of mild to moderate depression states include the popular St. John's wort, saffron, *Rhodiola*, lavender, *Echium*, and the Chinese formula banxia houpu. A comprehensive review of both clinical and preclinical aspects of each of the reviewed products is provided.

Keywords : Antidepressant-like action, Banxia houpu, Depression, Echium, Lavender, Plant constituents, Rhodiola, St. John's Wort, Saffron.

INTRODUCTION

Depression is a common psychiatric disorder that, according to the World Health Organization (WHO), affects approximately 350 million people worldwide [1]. In the United States, the National Comorbidity Survey Replication reported that 16.2% of the population experienced a major depressive disorder in their lifetime, with 6.6% having a depressive episode over the past year [2]. In addition, the study reported that women have a 1.7 to 2.7 times higher lifetime prevalence of

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depression as compared to men. Depression can occur at any age. However, adults between the ages of 18 to 29 years exhibit the highest rates of major depression. Symptoms of depression include emotional, physical, cognitive, as well as psychomotor symptoms. Emotionally, a depressive episode typically presents with a progressively reduced ability to experience pleasure, sad/depressed mood, and feelings of guilt and worthlessness that may also be accompanied by suicidal thoughts [3]. Physically, patients often complain of chronic fatigue, pain, sleep and appetite disturbances, and sometimes gastrointestinal and cardiovascular complaints [4, 5]. Cognitive symptoms vary from slow thinking, reduced concentration ability, and poor short-term memory, to reduced decision making ability and confusion [4]. Depression may also present with either psychomotor retardation or agitation, with the patient having slow movement and speech, or restless, purposeless, uncontrolled movements.

The specific diagnostic criteria for depression are defined by the Diagnostic and Statistical Manual of Mental Disorders (DMS-5) by the American Psychiatric Association in the U.S [6]. and non-European countries, and by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) issued by the World Health Organization, commonly used in Europe [7]. The DMS-5 categorized depressive disorders into four disorders: 1) Major Depressive Disorder, 2) Persistent Depressive Disorder, which includes both Dysthymia and chronic Major Depression in the revised DSM-IV, 3) Disruptive Mood Dysregulation, and 4) Premenstrual Dysphoric Disorder [6]. According to DMS-5, patients experiencing a major depressive episode manifest at least five of the following symptoms, and for at least two consecutive weeks, and nearly every day; 1) depressed mood most of the day, 2) loss of interest or pleasure, 3) sleep disturbance, 4) appetite/weight disturbance, 5) psychomotor retardation or agitation, 6) thoughts of guilt or worthlessness, and 7) recurrent suicidal thoughts or suicidal attempts. At least one symptom must be either depressed mood or loss of interest. Additionally, diagnosis of depressive disorders should be distinguished from secondary depression caused by other medical conditions [6].

The introduction of the classical antidepressants in the 1950s was based on the serendipitous discovery that depression is associated with the depletion of brain monoaminergic neurotransmitters; serotonin and norepinephrine. Such discovery led to the emergence of the monoamine hypothesis of depression and the development of monoamine oxidase and reuptake inhibitors as antidepressants [8]. Up to date, drugs based on the monoamine hypothesis constitute the major antidepressant drug classes. However, the monoamine hypothesis suffered from shortcomings that became evident following the use of antidepressants. Most prominent among these shortcomings is the therapeutic lag observed in depression patients. Despite the immediate increase in monoamine levels following

antidepressant administration, clinical effectiveness usually takes weeks [9, 10]. Such therapeutic delay led to further studies that revealed adaptive changes such as desensitization of norepinephrine and serotonin receptors are important contributors to the full therapeutic response to antidepressants [11]. After decades of research, the biological basis of depression still relies on the monoamine hypothesis. The hypothesis extended the monoamine deficiency in depression to include the dysregulation of serotonin, norepinephrine, and dopamine neurotransmitters [12, 13].

Because of the limitations of the monoamine hypothesis, the need for proper understanding of depression has intensified. Recent research has emphasized the potential role of brain derived neurotrophic factor (BDNF) in the mechanisms that underlie depressive disorders. BDNF plays a crucial role in the survival and differentiation of neurons. Studies have shown that elevated glucocorticoids resulting from chronic stress lead to downregulation of BDNF and might contribute to the etiology of depression. The reversal of BDNF dysregulation by long-term antidepressant treatment corroborates the role of BDNF in depressive disorders [13]. In addition, several research efforts have recently focused on the role of glutamatergic systems in depression. Yuksel and Ongur [14] reported a reduction in glutamate levels in various brain regions of patients with major depressive disorder. However, other studies did not observe the reduction in glutamate [15, 16]. Despite conflicting data, the current conclusion is that glutamate dysfunction possibly plays a role in major depressive disorder, but the direction of change can be different in various brain regions. Further studies are still needed to delineate the exact role if glutamate in mood depression.

Pharmacotherapeutic treatment of depression relies on the currently available antidepressants that are classified based on their mechanism of action into six categories: 1) selective serotonin reuptake inhibitors (SSRIs), 2) serotonin norepinephrine reuptake inhibitors (SNRIs), 3) norepinephrine and dopamine reuptake inhibitor (NDRI), 4) mixed serotonergic effects, 5) serotonin and α_2-adrenergic antagonist, and 6) monoamine oxidase inhibitors (MAOIs). Despite the availability of these therapeutic options, all of them suffer from major drawbacks. A major problem is the therapeutic lag, whereby it takes several weeks before these medications are clinically effective. In addition, about 30% of patients remain to be refractory to treatment despite various mono and polytherapy [13, 17, 18]. In addition, all current antidepressants are associated with a myriad of adverse effects that range from sexual dysfunction, weight gain, insomnia/sleep disturbance, cardiac effects, to anticholinergic effects and discontinuation syndrome [17, 19]. Such adverse effects, combined with a delayed therapeutic benefit, result in poor patient compliance. It is evident that current depression treatment suffers from several problems that impede proper therapeutic

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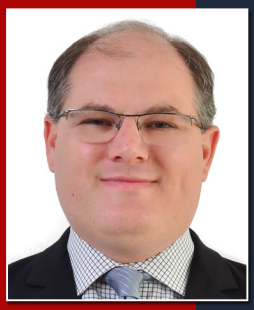
André F. Carvalho

André F. Carvalho, MD, PhD is associate professor of psychiatry and head of the Translational Psychiatry Research Group at the Faculty of Medicine of Federal University of Ceará (Brazil). He has been elected to the board of councilors of the International Society of Bipolar Disorders (ISBD) and is also the elected vice-chair of the section of private practice psychiatry of the World Psychiatric Association (WPA). He sits on the editorial board of several international peer-reviewed journals, including Psychotherapy and Psychosomatics. He has served as a peer-reviewer for several leading journals and funding agencies. He is an expert in mood disorders, psychiatric epidemiology, and evidence-based mental health. He is a sought after speaker in several national and international meetings.

Gislaine Z. Réus

Dr. Réus obtained degree in Biology and doctorate (Ph.D.) in Health Sciences from University of Southern Santa Catarina (UNESC), Brazil (2007 and 2011, respectively). Dr. Réus completed a Postdoctoral Fellowship at UNESC, Brazil (2014) and a Postdoctoral Fellowship at the Department of Psychiatry and Behavioral Sciences at The University of Texas Medical School at Houston, USA (2015). Currently, Dr. Réus is an assistant Professor at UNESC, Brazil. Dr. Réus works on behavior and neurochemical alterations of psychiatric disorders focusing on animal models of mood disorders, mainly major depressive disorders (MDD). In addition, Dr. Réus studies the relation between glutamatergic system and inflammation and MDD, and new therapeutic targets for MDD treatment. Dr. Réus has authored more than 90 peer-reviewed publications. Dr. Réus was awarded with "For Women in Science from ABC/ĹOreal/UNESCO" and "Samuel Gershon Awards for Junior Investigators from International Society for Bipolar Disorders". Dr. Réus has been also received travel grants from meetings focused in Psychiatry field.

João Quevedo



Dr. João Luciano de Quevedo concluded his M.D. in 1998, his residency training in Psychiatry in 2001 and his Ph.D. in Biological Sciences (Biochemistry) in 2002, all from the Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil. He is currently Professor of Psychiatry at the McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, Texas, USA. Over here he is Vice-Chair for Faculty Development and Outreach, Director of the Translational Psychiatry Program, and Director of the Treatment-Resistant Mood Disorder Program. Before move to Houston he was Dean at the University of Southern Santa Catarina Medical School, Criciúma, SC, Brazil, where he is still Adjunct Professor of Psychiatry. He is also a 1A research fellow (the highest level) of the National Council for Scientific and Technological Development (CNPq), Brazil; an affiliate member of the Brazilian Academy of Sciences (an award given to the most notable under 40 year-old researchers in Brazil), associate editor of the Revista Brasileira de Psiquiatria, and vice president of the Santa Catarina State Association of Psychiatry. He Is Director of the Continuous Medical Education Program in Psychiatry (PROPSIQ) of the Brazilian Association of Psychiatry. He is author of around 400 research papers (peer-reviewed) and 6 scientific books. He has been involved in research since 1994, while still in Medical School. As a medical student he was a research fellow in the laboratory of Prof. Ivan A. Izquierdo, the most important scientist in Brazil at that time. In 1996 he published his first research paper focused on the neurobiology of learning and memory, area to which he devoted himself until shortly after the completion of his Ph.D. He was gradually shifting their research interest to the neurobiology of psychiatric disorders, particularly mood disorders. His work in this area has been devoted to the development of animal models that are closer to the human clinical features, pathophysiology and treatment. Thus, Dr. João Luciano de Quevedo became a specialist in animal models of depression and bipolar disorder, making important contributions in understanding the pathophysiology of this disease. Importantly, his main findings are related to the role of oxidative stress and changes in brain energy