Towards a neurobiological view of depression

van Buel, Erin

General Introduction

1

Major Depressive Disorder

Major Depressive Disorder (MDD) is a serious illness with disabling consequences for those affected. MDD is currently the second leading cause of disability worldwide [1]. Reduction of disability associated with MDD could be achieved by the development of better treatment strategies, the improvement of diagnostic methods, and the identification of successful preventive measures. A thorough understanding of the etiology and pathophysiology of depression is crucial for all of these options.

Symptoms and subtypes

Major Depressive Disorder (MDD) is a highly heterogeneous disease mainly characterized by a depressed mood and/or a loss of interest or pleasure. Box 1 summarizes the DSM-IV-TR criteria for diagnosis of MDD [2]. When looking at these criteria, it is easy to see that individual symptom profiles may differ considerably.

Attempts have been made to identify MDD subtypes based on symptom profile. The most common subtypes are melancholic, atypical, and psychotic depression [3]. Melancholic depression is characterized by persistent anhedonia that is unreactive to positive events. Atypical depression is associated with preserved mood reactivity, hypersomnia, increased appetite and weight, leaden paralysis, and interpersonal rejection sensitivity [4]. Psychotic depression is accompanied by psychotic symptoms, such as delusions and/or hallucinations.

Pathophysiology

The pathophysiology of MDD is complex. Over the last decades, different hypotheses have been put forward. For instance, MDD has been suggested to be related to monoaminergic dysfunctions, stress, HPA axis overactivity, decreased neurogenesis and neuroplasticity, and inflammatory processes.

Box 1: DSM-IV-TR criteria for the diagnosis of Major Depressive Disorder

At least five of the following symptoms should be present during a two- week period, with at least one of the symptoms being either criterion 1 or 2

1. depressed mood
2. anhedonia (a loss of interest or pleasure)
3. changes in appetite or weight
4. insomnia or hypersomnia
5. psychomotor agitation and retardation
6. loss of energy or fatigue
7. feelings of worthlessness or guilt
8. impaired concentration or indecisiveness
9. thoughts of death or suicidal ideation

Although there is evidence for all of these hypotheses, it has been proven difficult to define one single abnormality that is common to all MDD patients. One of the reasons might be the heterogeneous nature of this disorder, which might reflect heterogeneity in pathophysiology [5]. Rather than defining depression by alterations in a single biological system, it is important to keep in mind that complex interactions exist between these systems and therefore abnormalities in one system may influence other biological systems as well. Probably, there are individual differences in the extent to which specific biological mechanisms are affected, with some mechanisms being more prominent in certain subsets of patients, while other mechanisms may be more prominent in others [5].

One could question if MDD itself should be viewed as one specific disorder, or as a collective term defining a set of disorders with partly overlapping symptomatology. The latter view is supported by evidence indicating that certain symptom profiles may be linked to specific biological abnormalities. For example, atypical depression has been associated with metabolic dysregulation and inflammation, while HPA axis abnormalities are more common in patients with melancholic depression [6].

Biomarkers for depression

A biomarker can be defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [7]. Biomarkers may include hormones, proteins, and genetic markers at the level of DNA and RNA, but also structural and functional alterations that can be visualized with imaging techniques.

The use of biomarkers for MDD may be threefold:

1. Biomarkers may aid diagnosis of MDD. The heterogeneity of symptoms (see box 1) and symptomatic overlap with other psychiatric or somatic disorders may complicate MDD diagnosis. Biomarkers that could help differentiate between MDD and other disorders would be very useful.
2. Biomarkers may be used as an early indicator of treatment response. Most antidepressant treatments have a delayed onset of action. Meanwhile there is no delay in the onset of side effects. Biomarkers that show an early change in case of treatment response could aid in the decision to continue or stop treatment.
3. Biomarkers may identify MDD subtypes and assist treatment choice. Individual differences in the presence or absence of certain biomarkers may reflect individual differences in the biological mechanisms underlying MDD. The underlying biological abnormalities may influence the chance of success of different treatment strategies.

Attempts at identifying suitable biomarkers for MDD have so far been unsuccessful due to failure of biomarkers to reach sufficient sensitivity and specificity [5]. One reason for this failure might lie in the heterogeneous nature of MDD. Individual differences in the biological mechanisms that are affected in MDD patients will likely result in individual differences in the expression of

potential biomarkers. Therefore, it is questionable if one single biomarker can accurately reflect disease state in MDD patients. The use of a combination of biomarkers reflecting different potential pathophysiological processes may be more successful, and might add the benefit of identifying the extent of biological abnormalities in different domains in the individual patients. Future research should therefore be directed at the identification of such combinations of MDD biomarkers. Chapter 2 reviews in detail the current state of scientific knowledge regarding potential biomarkers for depression and gives indications for future research.

Treatment options

The usual treatment for MDD consists of antidepressant medication and/or psychotherapy. Although reasonably effective, there is a relatively large subset of MDD patients that does not respond to these therapies. In addition, their delayed onset of action despite early presence of side effects may limit treatment motivation.

Psychotherapy

Many different types of psychotherapy exist. Two types that are commonly used in the treatment of MDD are cognitive behavioral therapy, which aims at altering thinking and behavioral patterns, and interpersonal therapy, which focuses on the patient's interpersonal relationships [8]. Overall, psychotherapy is equally effective as antidepressant drugs in reducing depressive symptoms. It has been suggested that psychotherapy may have inferior efficacy compared to antidepressant drugs in the treatment of severe depression, but this claim is insufficiently supported by the available scientific literature [8]. Psychotherapy may be prescribed alone or in combination with antidepressant drugs.

Pharmaceutical antidepressants

Pharmaceutical antidepressants can be roughly divided into three categories: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective serotonin and/or noradrenalin reuptake inhibitors (SSRIs, SNRIs, NRIs). All categories are more or less equally effective, although some types of drugs may have a superior effect in certain subtypes of depression. For example, TCAs may have a superior effect in melancholic depression, while MAOIs may be more effective in atypical depression [4].

The MAOI iproniazid, which was originally used for the treatment of tuberculosis, was first discovered to have antidepressant effects in the early 1950s [9]. Soon other MAOIs were developed for the treatment of MDD. MAOIs inhibit the enzyme monoamine oxidase (MAO), thereby preventing the breakdown of monoamine neurotransmitters [9,10]. The first MAOIs irreversibly bound to both MAO isoforms (MAO-A and MAO-B). Although effective in the treatment of MDD, their potentially serious side effects limited their clinical use. These side effects include serious drug interactions, including serotonin syndrome when combined with serotonergic drugs, and potentially fatal hypertensive crises due to interaction with tyramine-containing foods [10,11]. More recently, MAOIs have been developed that bind MAO reversibly and/or are selective for specific MAO isoforms (MAO-A or MAO-B), resulting in increased safety and therefore increased clinical applicability [10].

TCAs were first introduced in the late 1950s. They are believed to act primarily by blocking reuptake of the monoamine neurotransmitters serotonin and noradrenalin in the synaptic cleft [11]. TCAs have many side effects, including blurred vision, dry mouth, constipation, urinary retention, hypotension, tachycardia, dizziness, and sedation. These side effects are believed to be mainly related to their antagonistic properties at the muscarinic, α1-adrenergic, and histaminergic H1 receptors [11]. Side effects typically occur before the onset of clinical improvement and may limit motivation to continue treatment. However, the severity of side effects may reduce over time. When overdosed, TCAs have cardiotoxic effects, which may result in death [11].

In response to the potentially fatal consequences of TCA overdose, drugs have been developed that selectively inhibit the reuptake of serotonin (selective serotonin reuptake inhibitors; SSRIs), noradrenalin (noradrenalin reuptake inhibitors; NRIs), or both (serotonin and noradrenalin reuptake inhibitors; SNRIs). These drugs lack the antagonistic properties at the muscarinic, adrenergic, and histaminergic receptors that are found in TCAs [11]. Therefore, they have a milder side effect profile. Because their toxic dose is higher than for TCAs, they are considered safer. These drugs are currently considered the first line treatment for MDD.

Although up to 80% of patients benefit to some extent from antidepressant drugs, only around 50% demonstrate complete remission of symptoms [12]. In patients that do not sufficiently respond to antidepressant drugs and/or psychotherapy alternative treatment options can be considered. Electroconvulsive therapy (ECT) is often applied in patients that have failed to respond to multiple antidepressant treatment strategies.

Electroconvulsive therapy

Electroconvulsive Therapy (ECT) involves the induction of seizures via electrodes placed on the patient's scalp. A single ECT session may alleviate symptoms for some time, but to induce a lasting clinical improvement repeated ECT sessions should be applied. Typically, ECT is given two to three times per week, with a total number of treatments of 4 – 40, depending on the patient's improvement in symptoms.

A historical perspective on electroconvulsive therapy

The notion that psychiatric disorders may be cured by the induction of seizures has been around for centuries. Reports of induction of convulsions by camphor in order to cure "lunacy" date back as far as the 16th century [13]. In the late 1920s and early 1930s several physicians suggested a potential biological antagonism between epilepsy and schizophrenia, providing the rationale for convulsion-based treatment of schizophrenia. Intrigued by these observations, the Hungarian psychiatrist Ladislaus von Meduna experimented with different seizure-inducing substances and eventually developed metrazol-induced shock therapy, which became popular throughout Europe as a treatment for schizophrenia [14].

Because of the unpleasant side effects and potential danger associated with metrazol injections, scientists Ugo Cerletti and Lucio Bini investigated the possibility of inducing seizures via electrical stimuli, resulting in the introduction of electroconvulsive therapy in 1938 [14]. Although originally developed for the treatment of schizophrenia, the antidepressant potential of this new treatment strategy was soon recognized.

Several modifications to the ECT protocol have been introduced to increase the therapy's safety and tolerability. Most notable were the introduction of the muscle relaxant succinylcholine in the 1950s and the increasing use of short- acting anesthetics in the decades after the introduction of ECT [14,15], which reduced serious side effects such as bone fractures and significantly increased clinical applicability. In addition, modifications to the stimulus waveform and the placement of the electrodes were found to reduce cognitive deficits associated with ECT [14].

With the introduction of pharmaceutical antidepressants in the 1950s the use of electroconvulsive therapy declined. The reputation of ECT as a barbaric treatment further contributed to this decline [14]. However, due to the failure of antidepressant drugs to induce clinical improvement in about 50% of MDD patients and the relative efficacy of ECT in treatment-resistant MDD, ECT has again gained in popularity over the past two decades.

Current use of electroconvulsive therapy: indications, efficacy and side effects

Although often used as a last resort, ECT is a highly effective treatment for MDD. Numerous studies have compared the efficacy of antidepressant drugs to that of ECT. A meta-analysis of the literature including 18 trials and a total of 1144 participants has demonstrated a significant superior effect of ECT compared to pharmacotherapy [16]. As relapse rates are high, continuation ECT and/or pharmacotherapy is often prescribed to prevent recurrence of depressive symptoms [17,18].

The main indication for ECT is failure to respond to multiple types of antidepressant drugs. ECT induces remission of depressive symptoms in roughly 50% of patients suffering from so-called treatment-resistant depression [19]. In addition, due to its quick onset of clinical improvement, ECT may be prescribed in patients at high risk of committing suicide [20]. Finally, ECT may be considered in patients that cannot tolerate the side effects of antidepressant drugs [21,22].

Side effects of ECT are usually relatively mild compared to those of pharmaceutical antidepressants and include postictal disorientation, headaches, muscle aches, nausea and fatigue [13,23]. These side effects are directly related to ECT sessions and usually subside within hours to days after a session. A more problematic side effect is amnesia, which may be both anterograde and retrograde [13]. While anterograde amnesia is usually limited to the weeks directly following ECT, retrograde amnesia may be more persistent. Usually, ECT-induced retrograde amnesia mainly concerns events in the weeks to months prior to ECT and improves within months after discontinuation of ECT. However, in some cases severe long-lasting retrograde amnesia can occur dating back years prior to ECT [13]. Although rare, the possibility of prolonged severe amnesia is a major impediment in the prescription of ECT.

Cellular and molecular mechanisms underlying the antidepressant effects of ECT

The mechanisms underlying the antidepressant effects of ECT are currently a matter of intense investigation. A quick literature search will prove that ECT induces a myriad of effects in diverse biological systems. These effects include, but are not limited to, proliferation of neurons and glial cells, angiogenesis, increased synaptic plasticity, neuroprotective effects, normalization of HPA axis activity, altered functionality of monoaminergic systems, immune system modulation, and restoration of GABA/glutamate balance. However, the extent to which each of the many actions of ECT contributes to its antidepressant effects is unclear.

A complicating factor in ECT research is the lack of animal models for depression with sufficient face, construct, and predictive validity [24]. In addition, there is a lack of consensus regarding the validity of behavioral tests measuring depressive-like symptoms in rodents [24]. Consequently, most preclinical studies have been performed in healthy rodents and thus the results can only theoretically be linked to ECT's antidepressant effects. Direct proof of the necessity of certain ECT-related effects at the cellular and molecular levels for the reduction of symptoms of depression would greatly contribute to our understanding of this therapy. To achieve this, the use of animal models for depression would be crucial. We therefore believe future research should focus on the cellular and molecular effects of ECS in relation to the behavioral effects in animal models for depression. In addition, the development of depression models with improved face, construct, and predictive validity would offer unique opportunities for studying the mechanisms underlying the behavioral effects of ECS as well as other antidepressant treatment strategies, and would be highly valuable to MDD research in general.

Overview of the thesis

The overall aim of this thesis is to investigate potential biomarkers for depression and to study the molecular mechanisms underlying depression and the antidepressant effects of ECT.

Chapter 2 reviews the current state of knowledge regarding biomarkers for depression and elaborates on methods for the discovery of new biomarkers. In addition, this chapter gives an overview of different hypotheses for the pathophysiology of depression and their relation to individual biomarkers. Finally, the potential use of combinations of biomarkers is discussed.

Chapter 3 describes a large scale clinical study in MDD patients and matched control subjects aiming at the development of a biomarker-based test for depression. This study investigates a large panel of potential blood and urine biomarkers for depression. A statistical method is used to identify combinations of biomarkers that might together have sufficient sensitivity and specificity to be used in a clinical setting.

Chapter 4 reviews the effects of ECT on two systems that are regularly associated with depression: the neurotrophic system and the immune system, and discusses cross-links between these systems. In addition, a hypothesis is given that aims to explain both the neurotrophic and immunological aspects of ECT.

Chapter 5 describes the effects of ECS in a modified Chronic Social Defeat mouse depression model with increased construct validity. Special attention is given to potential cognitive effects of ECS in this model and their relation to molecular changes in the brain.

Chapter 6 investigates the effects of chronic ECS on brain reactivity to an inflammatory lipopolysaccharide (LPS) stimulus and neuroinflammation-related changes in depression-like behavior.

In *Chapter 7* the effects of ECS on migration of peripheral immune cells towards the brain are studied in mice that have been transplanted with GFP-positive bone marrow, giving rise to GFP-positive peripheral immune cells.

Chapter 8, the general discussion, gives a summary of the outcomes of all chapters and puts them into perspective of the scientific literature.

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[1]University of Groningen, University Medical Centre of Groningen,
University Centre of Psychiatry, Groningen, The Netherlands.

[2]Department of Molecular Neurobiology, Behavioural & Cognitive Neuroscience,
University of Groningen, Groningen, The Netherlands.

[3]Department of Nuclear Medicine & Molecular Imaging,
University of Groningen, Groningen, The Netherlands