Journal of Affective Disorders 208 (2017) 22–32

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness

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ARTICLE INFO

Keywords:
Antidepressants
Antimicrobials
Dysbiosis
Depression
Gut microbiota

ABSTRACT

Objectives: The first drug repurposed for the treatment of depression was the tuberculostatic iproniazid. At present, drugs belonging to new classes of antidepressants still have antimicrobial effects. Dysbiosis of gut microbiota was implicated in the development or exacerbation of mental disorders, such as major depressive disorder (MDD). Based on the current interest in the gut-brain axis, the focus of this narrative review is to compile the available studies regarding the influences of gut microbiota in behavior and depression and to show the antimicrobial effect of antidepressant drugs. A discussion regarding the possible contribution of the antimicrobial effect of antidepressant drugs to its effectiveness/resistance is included.
Methods: The search included relevant articles from PubMed, SciELO, LILACS, PsycINFO, and ISI Web of Knowledge.
Results: MDD is associated with changes in gut permeability and microbiota composition. In this respect, antidepressant drugs present antimicrobial effects that could also be related to the effectiveness of these drugs for MDD treatment. Conversely, some antimicrobials present antidepressant effects.
Conclusion: Both antidepressants and antimicrobials present neuroprotective/antidepressant and antimicrobial effects. Further studies are needed to evaluate the participation of antimicrobial mechanisms of antidepressants in MDD treatment as well as to determine the contribution of this effect to antidepressant resistance.

Abbreviations: ACTH, adrenocorticotropic hormone; BDNF, Brain-derived neurotrophic factor; CCL2, , Chemokine (C-C Motif) Ligand 2); CMS, chronic mild stress; CNS, central nervous system; COX 2, cyclooxygenase 2; GABA, gamma-aminobutyric acid; GF, germ-free; GLT1, glutamate transporter 1; HC, healthy controls; HPA, hypothalamic-pituitary-adrenal; IFN-γ, gamma interferon; IgA, Immunoglobulin A; IgM, Immunoglobulin M; iNOS, inducible nitric oxide synthase (iNOS); JB-1, lactobacillus rhamnosus; LPS, lipopolysaccharide; MAO, Monoamine-oxidase; MAOI, Monoamine-oxidase inhibitor; MDD, Major depressive disorder; MIC, minimum inhibitory concentrations; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NMDA, N-methyl –D- aspartate; PGE2, prostaglandin 2; SPF, specific pathogen free; TCA, tricyclic antidepressants; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha

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http://dx.doi.org/10.1016/j.jad.2016.09.012
Received 27 May 2016; Received in revised form 13 September 2016; Accepted 18 September 2016
Available online 28 September 2016
0165-0327/

1. Introduction

Major depressive disorder (MDD) is a common and recurrent psychiatric illness associated with significant morbidity and social burden (Nemeroff, 2007). In 2010, the Global Burden Study (GBD) considered MDD the 19th most prevalent disease in the world and the second leading cause of disability (Ferrari et al., 2013; Vos et al., 2012). The major consequence of MDD is suicide, a public-health problem (Jenkins, 2002). Also, depression has been associated with increased risk of severe chronic diseases, such as atherosclerotic heart disease and stroke (Clarke and Currie, 2009). Therefore, these findings emphasize the relevance of depression as a public-health problem and the implementation of effective interventions to reduce its burden.

The first drug used for depression treatment was iproniazid in the 1950s. The choice of this drug was based on its euphoric effects in tuberculosis patients (López-Muñoz and Alamo, 2009). At that moment, the discovery of iproniazid antidepressant effects was especially important because it could relegate Ugo Cerletti's electroconvulsive therapy, the only antidepressant treatment available with significant rates of effectiveness, but used only in highly specific cases (López-Muñoz and Alamo, 2009). Subsequently, it was demonstrated that iproniazid was a monoamine-oxidase (MAO) inhibitor, particularly MAO-A. The role of MAO-A is to convert biogenic (e.g. serotonin and catecholamines) and sympathomimetic (e.g. tyramine and benzylamine) amines into deaminated products (Johnston, 1968). This discovery led to the development of the first class of antidepressants, the MAO inhibitors (MAOIs). Examples of this class include tranylcypromine and phenelzine. Subsequently, the prototype antidepressant molecule, desmethylimipramine, was developed (Ban and Lehmann, 1962). The development of imipramine gave rise to the tricyclic antidepressants (TCAs), a class of drugs whose mechanism of action involves the inhibition of noradrenaline and serotonin reuptake by neurons (Raisman et al., 1979). Later on, the monoamine serotonin was related to the pathophysiology of depression (Lapin and Oxenkrug, 1969). Based on this discovery, the first family of psychoactive drugs with a rational design, the serotonin-specific re-uptake inhibitors (SSRIs) was developed (Altamura et al., 1988). Fluoxetine was thus the first SSRI synthesized, quickly becoming one of the most prescribed antidepressants in the world (Altamura et al., 1988; López-Muñoz and Alamo, 2009). Therefore, thanks to the discovery and subsequent therapeutic use of TCAs and MAOIs, in the 1960s, the monoaminergic theories of depression were developed (López-Muñoz and Alamo, 2009).

Despite the development of different classes of antidepressant drugs, still today delayed onset of action and high rates of drug resistance are the major limitations of antidepressant therapy. These limitations may possibly be related to other mechanisms, than monoamines deficiency, involved in the pathophysiology of depression. Vis-a-vis, oxidative/nitrosative stress, neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis, neurogenesis/neurotrophins and ion channels have been important approaches for research in this field (Bakunina et al., 2015; Castrén and Rantamäki, 2010; Iijima et al., 2010; Maes, 2011; Moylan et al., 2014). More recently, on the basis of the important evidences about the role of gut microbiota in the regulation of behavior and in the pathophysiology of several mental disorders, among them depression, the gut-brain axis and its regulation has been subject of many studies (Foster and McVey Neufeld, 2013).

Dysbiosis refers to an altered balance of the gut microbiota. Indeed, dysbiosis is characterized by decreases in commensal bacteria, most notably the phyla Bacteroidetes and Firmicutes, including the clinically relevant *Faecalibacterium prausnitzii* and increases in adherent/invasive *Escherichia coli* (Jones et al., 2014). This gut microbiota imbalance is also observed in patients suffering from intestinal and extra-intestinal disorders, i.e. allergy, asthma, metabolic syndrome, cardiovascular disease, and obesity (Carding et al., 2015). Interestingly, both intestinal and extra-intestinal disorders are comorbidities of MDD (Filipovic and Filipovic, 2014; Mayer et al., 2001).

Based on iproniazid antidepressant effects, it is not surprisingly that, at present, drugs belonging to new classes of antidepressants still have antimicrobial effects. In this regard, the antimicrobial effects of antidepressants range from weak to strong depending on the drug (Munoz-Bellido et al., 2000a). For instance, several new antidepressant drugs such as sertraline, fluoxetine, escitalopram and older drugs such as tranylcypromine and imipramine present antimicrobial effects (Lieb, 2004; Munoz-Bellido et al., 2000a). Conversely, β-lactams and tetracyclines also have potential antidepressant properties (Mello et al., 2013; Miyaoka et al., 2012). However, some antimicrobials, such as fluoroquinolones, have also been associated with neuropsychiatric adverse events and mood dysregulation, including depression (Ahmed et al., 2011; Grassi et al., 2001), manic (Bhalerao et al., 2006) and anxiety disorders (Kaur et al., 2016; Rollof and Vinge, 1993).

Thus, in the light of: i) the involvement of dysbiosis in depression and its comorbidities, ii) the antimicrobial effect of some antidepressant drugs and iii) the evidences for antidepressant effect of some antimicrobial agents; this review aims to compile the studies regarding the influences of gut microbiota in behavior and depression as well as to give evidences of antimicrobial effect of antidepressant drugs. We aim to further discuss the possible contribution of the antimicrobial effect of antidepressant drugs to its effectiveness/resistance.

2. Methods

For this narrative review, articles published in English from November 1984 to February 2016 were searched in relevant web datasets (PubMed, SciELO, LILACS, PsycINFO, and ISI Web of Knowledge). Search terms included combinations of the following: “MDD and gut microbiota”; “MDD and dysbiosis”; “behavior and germ-free animals”; “behavior and gut microbiota”; “antimicrobials and antidepressant activity”; “antidepressants and antimicrobial activity”. Two authors (AJMCF and DM) performed independent search of the articles. Four authors selected the relevant articles (DM, CNSS, AJMCF and JQ). Observational, experimental studies in humans and animal models and literature reviews were considered in the search. Inclusion criteria were pre-specified as the following: i) behavioral alterations induced by gut microbiota dysbiosis; ii) effects of stress and depression in gut microbiota, iii) original studies (in vitro and in vivo) and review papers presenting the antimicrobial effect of antidepressants and vice versa and iv) originality and the overall methodological quality of the studies. An exclusion criterion was being a conference abstract. The search retrieved 181 articles, 120 of which were selected.

3. Results

3.1. Gut microbiota and depression

3.1.1. Gut microbiota composition

The human gut contains a complex ecosystem, called intestinal microflora, consisting of a wide range of bacteria (Gerritsen et al., 2011). Studies have estimated that the intestinal microflora has at least 1800 bacterial genera and over 40,000 species of these microorganisms, which together possess about 100 times more genes than the human genome (Forsythe et al., 2010). Recently, the structure of the microbial flora has been better elucidated. Despite the presence of many phyla of bacteria in the gut, the most prominent are the Firmicutes and Bacteriodes. These phyla comprise 70–75% of the gut microbiota with a Firmicutes/Bacteriodetes ratio of 10.9 in adult individuals (Mariat et al., 2009).

The composition of the gut microbiota varies among individuals (Gerritsen et al., 2011; Mariat et al., 2009). Indeed, the gut microbiota is an extremely dynamic entity, influenced by factors such as genetics, age, diet, metabolism, geography and stress (Mariat et al., 2009;