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Biomolecular aspects of depression: A retrospective analysis

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Abstract

Objective: The effects of psychological stress, oxidative stress, and chronic low grade inflammation on the neuro-immune connection have been implicated in the pathogenesis of depression. Thus, in the recent past, there has been a growing effort in determining the mechanism of this pathogenesis. While attempting to map out, this mechanism researchers and clinicians have searched for clinically relevant biomarkers for use in the diagnosis and for the assessment of those suffering from depression. In this study, we have performed a retrospective analysis of biomarkers with clinically relevant potentials, including peripheral catecholamines, chemokines, cytokines, and neurotransmitters.

Methods: The retrospective analysis was performed on data collected over a six-year period of time (July 2009 to July 2015), gathered from patients (N = 1399; Mage = 42, SD = 13; 71% female, 29% male) who submitted samples with complaints of feeling hopeless, worthless, isolated, alone, general sadness, overwhelmed, and/or a lack of interest in things they once enjoyed. The data collected consisted of quantitative values of urinary catecholamines and neurotransmitters (peripheral dopamine, epinephrine, histamine, kynurenic acid, norepinephrine, β-PEA, and serotonin), salivary hormones (peripheral cortisol and melatonin), and peripheral blood mononuclear cell secreted cytokines and chemokines (Interleukins 1β, 6, 8, 10, MCP-1, GCSF, and TNFα). Statistical and clinical significance was assessed by comparison with a control group (N = 2395; Mage = 42, SD = 13; 70% female, 30% male), calculating the percent mean difference, p value, and effect size (Cohen's ɗ) for each parameter between groups.

Results: The findings of this study suggested that, in a model of general depression, there is a dysregulation in the enzymatic production and degradation of catecholamines, neurotransmitters, hormones, and immunological proteins. A cycle of interaction was found between all of these biomolecules, where an increase or decrease in one marker could result in a stimulatory or inhibitory effect on others. The mechanism of this was proposed to occur through the interaction of psychological stress, inflammation, and oxidative stress pathways. All of these biomolecules were found to be significantly altered in the general depression group and are key components of the interaction between the neurological and immunological systems.

Conclusions: This study serves to further elucidate the role of biomolecules in the regulation of affective disorders, such as depression. Resulting in providing a network of clinically relevant biomarkers to objectively assess and monitor general depression.

1. Introduction

Depression is a serious medical illness and according to the National Health and Nutrition Examination Survey (NHNES) of 2005–2006, 5.4% of Americans 12 years of age and older experience some form of depression [1]. A more recent study by Pence et al. estimated that 12.5% of primary care patients have had major depressive disorder (MDD) within that year. They go on further to estimate that of those patients with MDD, 47% are clinically diagnosed, 24% are treated, with 9% having adequate treatment, and 6% experiencing remission [2]. These estimates illustrate the need for accurate diagnosis, treatment, and monitoring tools of depression.

The current diagnosis, treatment, and course of depression has long been assessed and monitored by subjective methods that evaluate a patient's propensity and severity of depression based on symptomology. The initial diagnosis is often self-reported by the patient and followed up with an evaluation by a practitioner, more specifically a physician or psychologist. This evaluation process usually consists of

Abbreviations: DA, dopamine; EP, epinephrine; HIST, histamine; KYNA, kynurenic acid; NE, norepinephrine; PEA, β-phenylethylamine; 5HT, serotonin; MEL, melatonin; CORT, cortisol; PBMCs, peripheral blood mononuclear cells; IL, interleukin; MCP-1, monocyte chemotactic protein 1; GCSF, granulocyte-colony stimulating factor; TNFα, tumor necrosis factor alpha.

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diagnostic screening questionnaires that can be self-rated or administered and rated by the practitioner. The most common subjective tool used by practitioners in the United States is the Diagnostic and Statistical Manual of Mental Disorders which is currently on the fifth edition (DSM-5). However, the correlation between self-rated scores and practitioner-rated scores has been found to be moderate to poor [3–5]. The lack of strong correlation could be explained by a misinterpretation on the practitioner's behalf, or by under- or over-reporting on the patient's behalf. Besides the possible disagreement between self-reporting and clinician-reporting, there is the possibility of depressive symptoms being associated with other psychological or physiological problems leading to the potential for misdiagnosis or ineffective treatment. These flaws are supported by the evidence of Pence et al. [2].

It is evident that relying solely on subjective evidence for diagnosis of depression and assessment of treatment efficacy is falling short and that the addition of clinically relevant, objective measurements are needed. It is the aim of this retrospective study to evaluate the biomolecular aspect of patients presenting with symptomatology attributed with major depressive episodes such as anxiety, hopelessness, aches and pains, fatigue, etc. As is suggested by the symptomology, depression can often have comorbidity not only with other psychological disorders, but physiological disorders as well. Many of these physiological disorders are associated with inflammatory conditions such as chronic fatigue syndrome, rheumatoid arthritis, inflammatory bowel disease, and cardiovascular disorders, among others [6]. The comorbidity with inflammatory conditions suggests that a connection between the neurological and immunological systems may play a key role in the pathogenesis of depression. This connection provides a key starting point to elucidate the mechanism of depression in regards to inflammation and stress. From this study, we intend to present a host of objective and clinically relevant biomarkers that can be measured from non-invasive samples including urine, saliva, and blood. The use of these objective markers in combination with a subjective evaluation, clinicians may be able to more accurately diagnose and more effectively treat depression.

2. Methods

2.1. Data sources

All data used in this study were obtained from de-identified, historical sample submissions measured and reported by the diagnostic laboratory Pharmasan Labs, Inc. (Osceola, WI). The sample submissions spanned a six-year period of time from July of 2009 to July of 2015. Samples were submitted for analysis for a variety of reasons, not solely for assessment and treatment of depression. All samples submitted were accompanied by a self-reported health history questionnaire. This health history questionnaire included previous and current diagnoses, current health issues, patient complaints, and current medications, supplements, or other treatments. Parameters analyzed in this study included the salivary hormones peripheral melatonin and peripheral cortisol; peripheral urinary neurotransmitters and catecholamines dopamine, epinephrine, histamine, kynurenic acid, norepinephrine, β-phenylethylamine, and serotonin; and the peripheral blood mononuclear cell secreted proteins interleukins (IL) 1β, 6, 8, and 10, monocyte chemotactic protein 1 (MCP-1), granulocyte-colony stimulating factor (GCSF), and tumor necrosis factor alpha (TNF α). All individuals gave their informed consent for anonymous use of their results for research purposes. The studies were performed following a protocol approved by the internal clinical ethics committee.

2.2. Salivary hormones

Subjects were restricted from drinking any liquids (except water), using nicotine, and taking any supplements or medications within twelve hours of sample collection. One hour prior to collection, subjects were restricted from eating, chewing gum, or brushing teeth. For cortisol specifically, the first sample was collected in the morning after waking, followed by three additional collections approximately five hours apart from each collection. Cortisol levels were measured by an electro-chemiluminescence immunoassay (ECLIA) kit manufactured by Roche and performed on the Cobas e601 analyzer (Roche Diagnostics; Indianapolis, IN). For melatonin specifically, samples were collected one hour after waking up for the day. Melatonin levels were measured using a radioimmunoassay (RIA) kit manufactured by IBL international (Tecan; Morrisville, NC). All saliva samples were stored frozen at −20 °C and assayed within one week of collection, but were determined stable up to one month.

2.3. Urinary catecholamines and neurotransmitters

Subjects were instructed to fast eight hours prior to going to bed, but were allowed to drink plain water and take supplements or medications normally. The morning of urine collection, subjects were required to fast and avoid drinking any liquids. The first morning urine was voided and two hours later, the second morning urine was collected for subsequent analysis. All urinary samples were stored frozen at −20 °C and assayed within one week of collection, but were determined stable up to two months. Urinary catecholamines and neurotransmitters were measured by competitive ELISA methods developed by Pharmasan Labs Inc. (Osceola, WI).

2.4. Peripheral blood mononuclear cell secreted proteins

Subjects were allowed to collect blood at any time of the day, from Monday through Thursday, without fasting. Blood was collected in acid-citrate dextrose vacutainer tubes (BD Biosciences; San Jose, CA) and shipped overnight. Samples were only considered for analysis if they were received within twenty-four hours of blood draw. Peripheral blood