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Cerebrospinal fluid monoamine metabolite concentrations in depressive disorder: A meta-analysis of historic evidence

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ABSTRACT

Altered monoaminergic functions have been implicated in the pathophysiology of depressive disorder. However, previously reported cerebrospinal fluid (CSF) monoamine metabolite concentrations in major depression have been inconsistent. We performed a meta-analysis of historic evidence to determine whether CSF monoamine metabolite levels were different between patients with depression and normal controls, and could be used as depression biomarkers. Relevant studies that investigated CSF 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in patients with depression and normal controls were identified in PubMed, Web of Science, PsycINFO, and Embase databases through September 5, 2017, using a synonymous search for *depression*, *CSF*, *normal*, *control*, and each monoamine metabolite name, and in the reference lists of the acquired articles. Obtained records were individually scrutinized for eligibility. Our search strategy identified 26 studies, including our own. We employed random effects modeling and adopted "Hedges's *g*" as an index of effect size. In the meta-analyses, no significant difference was observed in CSF 5-HIAA or MHPG levels between patients with depressive disorder and controls. In contrast, CSF HVA was significantly decreased in patients with depression (Hedges's $g = -0.30$, $P = 0.0000025$), and these results remained significant after patients with bipolar disorder were excluded (Hedges's $g = -0.37$, $P = 0.000061$). In the meta-regression, sex was significantly associated with the Hedges's g of CSF HVA ($Q = 4.41$, $P = 0.036$). This meta-analysis revealed that only CSF HVA, and not 5-HIAA or MHPG, levels were decreased in depressive disorder. The reduction in the CSF HVA concentration in patients with depression may guide future studies on depression and serve as a useful biomarker of depressive disorder.

1. Introduction

Depressive disorder is a common disease, with the global point prevalence estimated at 4.4% (Ferrari et al., 2013). The Global Burden of Disease Study 2015 reported that depressive disorder was the third largest cause of years lived with a disability (GBD, 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Although several biological mechanisms of depressive disorder have been proposed, such as monoamine deficiency, hypothalamic-pituitary-adrenal axis dysregulation, and chronic neuroinflammation, the pathophysiology of the disease remains elusive (Kunugi et al., 2015). Biochemical markers for depressive disorder usable in routine clinical settings have not yet been established.

Cerebrospinal fluid (CSF) contacts the brain interstitial fluid and is largely segregated from the peripheral circulation by the blood-brain barrier (Strittmatter, 2013); therefore, the CSF has been considered an ideal resource for biomarker research in diseases of the central nervous system (CNS) (Humpel and Hochstrasser, 2011). Numerous studies have attempted to identify CSF biomarkers for depressive disorder (Al Shweiki et al., 2017; Ditzen et al., 2012; Hashimoto et al., 2016; Hattori et al., 2015; Ishii et al., 2018; Kaddurah-Daouk et al., 2012; Ogawa et al., 2015; Sasayama et al., 2013; Wan et al., 2012). Within the framework of the classical monoamine hypothesis of depressive disorder pathogenesis (Coppen, 1967; Schildkraut, 1965), studies have focused on levels of 5-hydroxytryptamine (serotonin), dopamine, and noradrenaline in CSF. However, the CNS catabolic cycle mediated by enzymes, such as monoamine oxidases or catechol-*O*-methyltransferase, degrades serotonin, dopamine, and noradrenaline into 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), respectively (Asberg, 1997; Hyland, 2007; Scheinin, 1985). Therefore, 5-HIAA, HVA, and MHPG are used as surrogate markers for their parent monoamines and

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presumed to reflect monoaminergic neurotransmitter turnover in the brain (Bowers, 1974; Stanley et al., 1985; Wester et al., 1990). Indeed, monoamine metabolite concentrations in the CSF correlate with those in postmortem brains (Stanley et al., 1985).

We recently reported a case-control study (Yoon et al., 2017) in which we found significantly decreased CSF 5-HIAA and MHPG levels in patients with depressive disorder on antidepressant treatments, but not in antidepressant-free patients, compared with normal controls. CSF HVA levels in patients with moderate to severe depressive disorder showed significantly lower HVA levels than patients with mild to remitted depressive disorder and normal controls. We concluded that CSF HVA levels might be a useful marker for depressive disorder severity in clinical settings. However, the results of relevant previous investigations (Asberg et al., 1984; Berger et al., 1980; De Bellis et al., 1993; Ehnvall et al., 2003; Geracioti et al., 1997; Gerner et al., 1984; Hou et al., 2006; Jones et al., 1990; Kaddurah-Daouk et al., 2012; Kasa et al., 1982; Koslow et al., 1983; Little et al., 1999; Molchan et al., 1991; Oreland et al., 1981; Palaniappun et al., 1991; Post et al., 1973; Reddy et al., 1992; Roy et al., 1986, 1988, 1989; Sher et al., 2003, 2005, 2006; Sullivan et al., 2006a, 2006b; Swann et al., 1999; Westenberg and Verhoeven, 1988; Widerlöv et al., 1988) have been inconsistent.

We performed a meta-analysis of historic evidence to determine whether CSF monoamine metabolite levels were different between patients with depression and normal controls, and could be used as depression biomarkers. We also performed meta-regression analyses to test the possible relationships between CSF monoamine metabolite levels, and age and sex.

2. Material and methods

2.1. Study selection

Two researchers (S.O. and S.T.) conducted systematic searches for relevant studies published in the English language. All publications in the PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD, USA), Web of Science (Thomson Reuters, Corp, New York, NY, USA), PsycINFO (Ovid Technologies, Inc, New York, NY, USA), and Embase (Elsevier B.V., Amsterdam, Netherlands) databases through September 5th, 2017, were searched. The following search strings were used: *depression OR depressive OR depressed OR affective OR melancholia OR "mood disorder" OR "mood disorders"* (in titles); *("cerebrospinal fluid" OR CSF) AND (normal OR control OR controls OR healthy) AND (5-HIAA OR HVA OR "homovanillic acid" OR MHPG OR HMPG)* (in topics, abstracts, and keywords).

This strategy obtained 326 records, among which 158 were duplicates. However, no abstract data were available for some early studies. Therefore, we conducted an extensive manual search of the reference lists of the articles acquired in the automated database search. In this process, we obtained another 73 records, resulting in a total of 241 potentially eligible studies. In an initial screening, 58 non-English-language, review, or animal studies were excluded. The remaining 183 articles were scrutinized for eligibility, resulting in the exclusion of another 158 studies. Including our own data, the selection strategy produced 26 eligible studies (Fig. 1). The search was in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009).

Our own data were extracted from a study of Ogawa et al. (2015), which investigated CSF monoamine metabolite levels in drug-free patients and healthy controls. Several previous studies have employed "neurological controls", who may have disturbances in monoaminergic functions (Asberg et al., 1984). Therefore, we chose only studies that used normal (i.e., showing no psychiatric or neurological symptoms) subjects as controls. Psychotropic drugs affect CSF monoamine metabolite levels (Little et al., 1999); therefore, we omitted studies that did not describe the patients' medication status or used patients on psychotropic medication. We did include the study of Rudorfer et al. (1993) in the analyses even though their patients met the criteria of affective disorders with a seasonal pattern.

The quality of the selected studies was assessed by 2 researchers (S.O. and S.T.) using the checklist of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, which outlines recommendations for reporting observational studies (von Elm et al., 2007). According to Green et al. (Green et al. (2011), we ranked each study as having a low, medium, or high probability of reporting bias based on how many STROBE items were checked (the cutoff points were set at 33 and 66%). Studies classified as having a high possibility of reporting bias (i.e., with < 33% of the STROBE items checked) were excluded (Fig. 1). Eventually, 26 studies including our own were selected (Asberg et al., 1984; Berger et al., 1980; De Bellis et al., 1993; Ehnvall et al., 2003; Engström et al., 1999; Geracioti et al., 1997; Gerner et al., 1984; Jimerson et al., 1984; Jones et al., 1990; Kasa et al., 1982; Koslow et al., 1983; Molchan et al., 1991; Ogawa et al., 2015; Oreland et al., 1981; Palaniappun et al., 1991; Reddy et al., 1992; Roy et al., 1986, 1988; Rudorfer et al., 1993; Sher et al., 2003, 2005; Sjöström, 1973; Sullivan et al., 2006a, 2006b; Westenberg and Verhoeven, 1988; Widerlöv et al., 1988).

2.2. Data extraction

The sample sizes, mean monoamine metabolite values, and standard deviations (SDs) of both the patient and control groups were extracted from each study. Standard errors were converted into SDs. Six studies reported means and SDs for subgroups only (Jones et al., 1990; Roy et al., 1986, 1988; Sher et al., 2003, 2005; Sullivan et al., 2006b), for example, patients with or without a history of suicide attempts; therefore, we combined the data from the subgroups. We did not use any values obtained using the probenecid technique, which inhibits the active transport of acid monoamine metabolites from the brain and CSF to the bloodstream (Ebert et al., 1980).

Initially, we used all data, including those for patients with bipolar disorder, but subsequently excluded the bipolar patient data for unipolar-only analyses. For the latter, we used data from selected studies in which patients were diagnosed with "major depressive disorder" or "major depression", or studies that explicitly described depression polarity as "unipolar". We excluded the studies of Sher et al. (2003) and Ehnvall et al. (2003) from the unipolar-only analysis because of insufficient or ambiguous information on depression polarity.

Age and sex data, if available, were extracted from each study for meta-regression analyses.

2.3. Meta-analysis and meta-regression

We used the Comprehensive Meta Analysis software (version 3.3.070; Biostat, Englewood, NJ, USA) for both analyses. A forest plot analysis of all data was performed, followed by unipolar-only analysis. Sample characteristics (age, sex, diagnosis, and ethnicity) varied among studies; therefore, we employed random effects modeling according to the recommendation of Borenstein et al. (2010). We adopted "Hedges's *g*" (Hedges, 1981) as an index of effect size for the meta-analysis. Potential publication biases were assessed by funnel plots and Egger's regression analyses, and the significance of Egger's regression was set at a 2-tailed $P < 0.1$. We also assessed heterogeneity across studies using the Q test, and quantified the scale with I^2 values (0–25% = no publication bias, 25–50% = low, 50–75% = medium, and 75–100% = high) (Huedo-Medina et al., 2006; Rechetnikov and Maitra, 2009) in the forest plot analyses. For the meta-regression analysis, we adopted the Maximum Likelihood estimator. Hedges's *g* was set as the outcome variable, and age or sex was set as the explanatory variable, which were tested as potential estimators of variance between studies. We set the mean age and percent of males of total participants in each study as moderator variables. Results were deemed significant if