Journal of Affective Disorders 240 (2018) 6–16

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review article

Poor evidence for putative abnormalities in cerebrospinal fluid neurotransmitters in patients with depression versus healthy non-psychiatric individuals: A systematic review and meta-analyses of 23 studies

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ARTICLE INFO

Keywords:
Depression
Neurotransmitter
Pathophysiology
Systematic review
Meta-analyses

ABSTRACT

Background: Although investigated for decades, surprisingly no systematic review has ever been published on monoamines concentrations in cerebrospinal fluid (CSF) in major depressive disorder (MDD) versus healthy individuals (HC).

Methods: We did a systematic review and meta-analyses according to the PRISMA Statement based on comprehensive database searches for studies on CSF biomarkers of monoamines and their precursor and/or metabolites, and glutamine, glutamate and GABA in MDD versus HC. Risk of bias was systematically assessed.

Results: A total of 23 studies were included. Statistically significantly decreased levels between MDD and HC were found regarding CSF 5-HIAA (n = 2/13 (15%)), HVA (n = 2/11 (18%)), MHPG (n = 1/8 (13%)), and GABA (n = 2/4 (50%)), while increased levels were reported regarding NE (n = 1/2 (50%)), MHPG (n = 1/8 (13%)) and DOPEG (n = 1/1 (100%)). A majority of the studies found no statistically significant differences between MDD and HC regarding CSF 5-HIAA, HVA, NE, MHPG, glutamine, glutamate and GABA. Meta-analyses showed: 5-HIAA (−3.85, −8.89, 1.19, 0.14), HVA (−18.02, −30.99, −5.04, 0.01), MHPG (0.11, −2.96, 3.17, 0.95) and GABA (−33.20, −51.79, −14.62, 0.00) (mean difference, lower 95% CL, upper 95% CL, p-value). Most studies were influenced by risk of bias mainly due to small sample sizes, and not considering potential confounders as age, gender, severity of depression, body height and position during lumbar puncture, analytics of biomarkers and medication.

Conclusion: The evidence for CSF 5-HIAA, HVA, NE, MHPG, DOPEG and GABA being related to the pathophysiology of MDD is poor. Future controlled studies of monoamines or metabolites should validate the null i.e., that the concentrations of these compounds are not abnormal in MDD.

1. Introduction

The neurobiological mechanisms in depression are still largely unknown. The diagnosis of MDD largely depends on the clinical interview (Smith et al., 2013; Ogawa et al., 2015) and no established biochemical marker is available for everyday use in the clinical setting. The identification of objective biological markers that represent pathophysiologic processes could possibly provide biological targets for the development of individual prevention strategies and new treatments (Mossner et al., 2007).

The human brain, the most complex of all organs, contains 100 billion neurons and 10 times as many glial cells. As the brain develops, neurons migrate and differentiate in response to chemical, 'micro-environmental' stimuli such as receptor-mediated signals from

Abbreviations: N, Number; SD, Standard deviation; P, Patients; C, Controls; M, Male; F, Female; dMDD, depressed Major Depressive Disorder; rMDD, remitted Major Depressive Disorder; NA, Not Applicable; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-A, Hamilton rating scale for Anxiety; HAM-D, Hamilton rating scale for Depression; CGS, Clinical Global Severity; SSI, Scale for Suicidal Ideation; RDC, Research Diagnostic Criteria; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; ICD, International Statistical Classification of Diseases and Related Health Problems; SCID, Structural Clinical Interview for DSM; GABA, γ-Aminobutyric acid; 5-HT, 5-hydroxytryptamine/Serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, Homovanillic acid; NE, Norepinephrine; DOPEG, dihydroxyphenylethylene glycol; MHPG, 3-methoxy-4-hydroxyphenylglycol= HMPG, 4-hydroxy-3- methoxyphenylglycol; TCA, Tricyclic Antidepressiva

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https://doi.org/10.1016/j.jad.2018.07.031
Received 13 December 2017; Received in revised form 28 May 2018; Accepted 11 July 2018
0165-0327/

neurotransmitters (Mossner et al., 2007). In the adult nervous system, neurotransmitters are discrete intercellular signaling devices that mediate communication between cells in complex neural circuitries (Lauder, 1988). Since cerebrospinal fluid (CSF) is in contact with the interstitial fluid in the central nervous system (CNS) and is mostly segregated from the peripheral circulation by the blood-brain barrier, CSF reflects molecular dynamics in the brain (Strittmatter, 2013).

Since 1957 when Arvid Carlsson demonstrated that dopamine was a neurotransmitter in the brain levels of neurotransmitter precursors and metabolites have been measured in CSF to access central neurochemical function (Carlsson et al., 1957). A major area of interest has been in the field of monoamine neurotransmitter metabolism, especially the indoleamine serotonin (5-HT) and the catecholamines dopamine (DA), and norepinephrine (NE) (Bottiglieri et al., 2000). Most of the serotonergic, noradrenergic and dopaminergic neurons are located in midbrain and brainstem nuclei and project to large areas of the entire brain. This anatomy suggests that monoaminergic systems are involved in the regulation of a broad range of brain functions, including mood, attention, reward processing, sleep, appetite, and cognition (Hasler, 2010). This had led to the monoamine hypothesis of affective disorders which implicates that depression is associated with a relative deficiency of brain monoamines (McLeod and McLeod, 1971). While multiple neurotransmitter systems appear dysregulated in MDD, the greatest amount of empirical research has focused on the role of impairments in central monoaminergic function and serotonergic dysfunction (Kaddurah-Daouk et al., 2012; Sher et al., 2003).

Further, melatonin occurs through hydroxylation, decarboxylation, acetylation and a methylation starting with L-tryptophan. Melatonin has been discussed controversially with respect to affective disorders (De Crescenzo et al., 2017; Wetterberg, 1999).

There is growing evidence that increased glutaminergic and decreased γ-aminobutyric acid (GABA) transmission, combined with alterations in the glutamine/glutamate cycle, are also implicated in the pathophysiology of MDD (Sanacora et al., 2012). Glutamate mediates the majority of excitatory transmission in the brain and functions as an excitatory neurotransmitter in the nervous system. It is possible that excitatory transmission plays a central role in mediating the complex emotional/cognitive changes associated with depression (Sanacora et al., 2012). GABA mediates the majority of inhibitory transmission and GABA deficit associated with MDD has found increasing support (Mann et al., 2014; Roy et al., 1991). The hypothesis of reduced GABAergic activity in mood disorders may complement the monoamine deficiency hypothesis, proposing that the balance between multiple neurotransmitter systems may be altered in MDD.

Although monoamines concentrations in CSF have been investigated in MDD for more than half a century, surprisingly, there is no newer systematic review published on monoamines concentrations in CSF in patients with MDD compared with healthy control individuals (HC)

1.1. Aims of the study

The aim of this systematic review is to identify studies including data concerning monoamines and their precursor and/or metabolites in the CSF in patients with MDD versus healthy control persons (HC). Differences between study findings will be explored descriptively by investigating whether concentrations of the various monoamines concentrations in CSF may be explained by or vary with age, gender, severity of depression, body height, the body position (sitting or lying) of participants during the lumbar puncture procedure, measure methods for analysing biomarkers and medication. Furthermore, mean differences in biomarker levels will be explored in meta-analyses.

2. Matrial and methods

This review includes a literature search using PubMed (MEDLINE)-database in order to systematically identify relevant literature concerning the relationship between CSF biomarkers and depression compared with HC groups.

2.1. Studies

Studies were selected if the sample included a group of adult patients with a diagnosis of MDD and a HC group. A minimum of 10 patients in each group should be included in the study. Data regarding participants with bipolar disorders (i.e. bipolar depression) or disorders other than unipolar depression was excluded. Studies including neurological patients as a control group were also excluded. None of the participants in the HC group used any significant medication, otherwise they were excluded. If the same results were reported twice, only the study firstly published study was included.

2.2. Outcome measures

Studies were included if the biomarker was measured in CSF. Studies of depression measuring potential biomarkers in plasma or detected biomarkers in brain regions using Proton Magnetic Resonance Spectroscopy were excluded.

2.3. Search methods for identification of studies

The systematic search was conducted on November 2017 using the following search syntax: *(depressi* OR "depressive disorder" OR "depressive disorder, major") AND "cerebrospinal fluid"*

The title for each article, and the abstract and full-text when necessary, was reviewed. The PubMed advanced search builder lead to the identification of 2220 related articles in the MEDLINE database ranging from 1966–2017. The following process was used to search and screen articles for relevance against aforementioned criteria:

a) Studies with insufficient data were excluded
b) Non-English language and non-human articles were manually removed
c) Titles and abstracts were screened for meeting inclusion and exclusion criteria
d) The remaining articles were then screened in full text.

In addition, cross-references were searched from identified papers.

The identified articles were divided in four groups: 'neuroamines', 'hormones', 'neuroproteins', and 'others' .

2.4. Meta-analyses

Meta-analysis of 5-HIAA, HVA, MHGP and GABA were performed using the random effects model as described in (Borenstein et al., 2011). Meta-analyses were performed with R Statistical software version 3.4.4 (R Core Team, 2018) and the rmeta-package (Thomas, 2018) in particular.

3. Results

A total of 2220 publications were identified, and 23 publications satisfied all the inclusion and exclusion criteria as illustrated by Fig. 1. Design and sample characteristics, outcome measures (CSF levels in the included participants with MDD versus HC) and study results are summarized in Tables 1–4. For Forrest plots, see Supplementary Material.

In the identified studies, a majority of the data concerned the monoamines serotonin (5-HT), dopamine, and norepinephrine (NE), and their metabolites. Overall, 17 publications reported data concerning the monoamines 5-HT (Hou et al., 2006) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Kaddurah-Daouk et al., 2012; Sher