A New Look on an Old Issue: Comprehensive Review of Neurotransmitter Studies in Cerebrospinal Fluid of Patients with Schizophrenia and Antipsychotic Effect on Monoamine’s Metabolism

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Neurotransmitters metabolism has a key role in the physiopathology of schizophrenia as demonstrated by studies measuring monoamine metabolites in patient’s cerebrospinal fluid (CSF) since the beginning of the antipsychotic use. This comprehensive review aims to understand the anomalies of CSF monoamines in schizophrenia and their correlation with clinical and paraclinical features. We also review the influence of antipsychotic treatment on CSF monoamines and discuss the connection with metabolic and inflammatory processes. Studies comparing CSF homovanillic acid (HVA) levels between patients and controls are miscellaneous, due to the heterogeneity of samples studies. However, low HVA is associated with more positive symptoms and a poorer outcome and negatively correlated with brain ventricle size. Based on humans and animals’ studies, antipsychotic treatments increase HVA during the first week of administration and decrease progressively over the time with a fall-off after withdrawal. 5-hydroxyindolacetic acetic acid levels do not seem to be different in the patient’s CSF compared to controls. Considering metabolic co-factors of neurotransmitters synthesis, there is evidence supporting an increase of kynurenic acid in the CSF of patients with schizophrenia. Few studies explore folate metabolism in CSF. Literature also emphasizes the relationship between folate metabolism, inflammation and monoamine’s metabolism. Those results suggest that the CSF monoamines could be correlated with schizophrenia symptoms and treatment outcome. However, further studies, exploring the role of CSF monoamines as biomarkers of disease severity and response to treatment are needed. They should assess the antipsychotic prescription, inflammatory markers and folate metabolism as potential confounding factors.

KEY WORDS: Neurotransmitters; Schizophrenia; Cerebrospinal fluid; Inflammation; Antipsychotic drug.

INTRODUCTION

Schizophrenia affects 1% of the population and leads to severe clinical conditions [1]. Treatment resistance occurs in almost 30% of patients and is responsible for more severe and chronic impairment [2]. In the 50’s, the discovery of the key role of dopamine in the physiopathology of schizophrenia was demonstrated by the efficacy of antipsychotic (i.e., D2 receptor-blocker) treatment [3]. Schizophrenia is a neurodevelopmental disease of unclear etiology for whom onset is related to a complex combination of genetic and environmental factors [4,5]. Among genetic factors, the latest Genome Wide Associations Studies (GWAS) put forward more than 100 loci associated with schizophrenia [6]. Several of the genes associated were related to dopamine receptors D2 (DRD2) and several glutamate associated receptors (GRIA1, GRIN2A, GRM3) [7]. Consistent with genetic studies, drugs known to increase dopamine transmission (amphetamine, L-Dopa) induced schizophrenia like symptoms in controls and exacerbate psychotic symptoms in patients [8]. Conversely, all antipsychotic drugs used in schizophrenia act via blocking of dopamine D2 receptors [9]. Regarding
glutamate involvement, the hypothesis arose from the psychotic effect of drug acting via N-Methyl-D-Aspartate (NMDA) antagonism [10]. More recently, functional brain imaging studies underpinned that schizophrenic patients have activity of the NMDA receptors [10]. Together, these data saw the emergence of two complementary theories based on dopaminergic and/or glutamatergic dysregulation in schizophrenia.

Thus, the central roles of monoamines in schizophrenia pathophysiology were emphasized and biological measures, including lumbar puncture, were conducted in order to directly explore the monoamines metabolism in patients. However, no clear biomarkers have been identified yet, and diagnosis and treatment are only guided by clinical arguments. These data have also motivated research on a biological marker of treatment response as a key issue in schizophrenia.

The synthesis of the three monoamines (Serotonin [5-HT], Noradrenalin [Na], and Dopamine [Da]) is mainly driven from tryptophan, which is an essential amino acid (i.e., only available from exogenous supply) and tyrosine. Dopamine will act on different post-synaptic dopamine receptors (D1-D5) or on a D2 presynaptic axonal, (which decrease dopamine release and neurotransmission). Dopamine can also be reuptaken through dopamine transporters into the presynaptic neuron. Finally, different enzymes, such as catechol-O-methyl-transferase (COMT), monoamine oxidase A (MAO-A), or monoamine oxidase B (MAO-B) will metabolize dopamine into a final metabolite, homovanillic acid (HVA). Dopamine can also be metabolized into noradrenaline by the dopamine hydroxylase. Noradrenalin is finally catabolized into 3-Methoxy-4-hydroxyphenylglycol (MHPG or MOPEG) [11].

Serotonin is produced from tryptophan by the tryptophan hydroxylase. It acts on the 5-HT receptors on the pre and postsynaptic neurons, and can also be recaptured in the pre-synaptic neuron. Serotonin is catabolized into 5-hydroxyindolamine acetic acid (5-HIAA) by the aldehyde deshydrogenase and the MAO [11].

The synthesis and degradation of monoamines are closely intricated with the metabolism of folates and pterins. Indeed, Methyltetrahydrofolate (MTHF) and Tetrahydrobiopterin (BH4) are cofactors of tryptophan hydroxylase and tyrosine hydroxylase, and contribute to the synthesis of the three monoamines [12]. Interestingly, it has been demonstrated that low folate levels was linked with a higher risk of schizophrenia, while the heterozygous mutation MTHFR 677 C→T is associated with a lower response to antipsychotic treatment [13]. This mutation is leading to a folate deficiency in CSF, which can drastically decrease dopamine synthesis [14]. It has also been suggested that MTHF-related hyperhomocysteinemia could be linked to cognitive deficits [15] in schizophrenia, and therefore associated with poorer outcome. BH4 is derived from neopterin, an enzyme activated by inflammatory cytokines [16]. BH4 is also implicated in the synthesis of kynurenic and kynurenic acid (KYN). KYN is, like serotonin, derived from tryptophan and has antagonist properties on the NMDA receptors. Those glutamate receptors are supposed to have a key role in the physiopathology of schizophrenia [17] (for an overview of monoamine’s metabolism; Fig. 1). In the past years, numerous studies have been published about the role of inflammation in both the onset of schizophrenia and its treatment resistance (for review, see [16]). While the exact mechanism between inflammation and schizophrenia has not been yet fully explained, recent findings showed that blood brain barrier might be dysfunctional in patients [18]. Moreover, inflammatory cytokines have been found elevated in the CSF of patients with schizophrenia. Anti-inflammatory properties of antipsychotic drugs have also been demonstrated [19]. Those data have led researchers to propose the use of immunomodulatory drugs as a putative treatment [20,21]. Some authors [21] have suggested that chronic inflammation could influence neurotransmitter synthesis by the inhibition of BH4 and the activation of indolamine 2,3 dioxygenase (IDO), leading to a defect in monoamine metabolism and KYNA synthesis [22].

Direct assessment of dopamine and serotonin is not easy, albeit theoretically possible [23] and plasma levels of HVA and 5-HIAA are not considered as relevant, being influenced by the peripheral metabolism [24]. Moreover, direct study of a patient’s brain tissue is not possible for obvious ethical reasons. In consequence, assessment of monoamine’s metabolism can only be made by lumbar punctures, allowing direct quantitative analysis of catabolites of dopamine and serotonin (HVA et 5-HIAA) but also pterins (neopterin and BH4). The assessment of CSF monoamines can be challenging in usual practice. Most psychiatrists are not trained to lumbar puncture. This could explain the relative lack of large clinical studies in the last twenty years in this field. However, CSF mono-
Fig. 1. Overview of monoamine’s metabolism. Tyrosine and Tryptophan are metabolized into the three monoamines (dopamine, noradrenalin, and serotonin). Tetrahydrobiopterin and Tetrahydrofolate are co-factors of the synthesis of L-DOPA and 5-OH tryptophan, which are the precursors of Dopamine and serotonin, respectively. Dopamine is catabolized into Homovanillic acid, or metabolized into noradrenalin which is transformed into 3-Methoxy-4-hydroxyphenylglycol. Serotonin is catabolized into 5-hydroxyindolamine acetic acid. Inflammatory processes influence monoamine’s metabolism by stimulating neopterin. IL-1B inhibits BH4, while IDO inhibits tryptophan hydroxylase and stimulates the kynurenin pathway. (1) Tyrosine Hydroxylase; (2) Tryptophan Hydroxylase; (3) Catecholamine-O-Methyl Transferase (COMT) and Monoamine Oxidase (MAO); (4) 6-Pyruvotetrahydropterin Synthase (PTPS) and Sepiapterin Reductase (SR); (5) Aldehyde Deshydrogenase and MAO; (6) Methionine Synthase; (7) Methyltetrahydrofolate Reductase (MTHFR). NH2TP, dihydroneopterin triphosphate; BH2, Dihydrobiopterin; BH4, Tetrahydrobiopterin; TRP, Tryptophan; DOPA, Dopamin; NA, Noradrenaline; 5-HT, serotonin; MHPG, 3-Methoxy-4-hydroxyphenylglycol; HVA, Homovanillic acid; 5-HIAA, 5-hydroxyindolamine acetic acid.

*aCan be measured in CSF.

Fig. 2. Flowchart of article selection process.
aminos are a key part in the understanding of schizophrenia’s physiopathology, being at the crossroad of several mechanisms implicated in this disease. This comprehensive review aims to synthesize CSF studies on monoamine metabolism in schizophrenia, and the influence of the antipsychotic medication.

**METHODS**

Researches have been conducted by two independent clinicians on PubMed on October 2nd, 2018 (Fig. 2). The first research was conducted with the following MeSH terms: [homovanillic acid] OR [vanillylmandelic acid] OR [5-hydroxyindolamine acetic acid] OR [kynurenine] OR [kynurenic acid] OR [quinolinic acid] AND [CSF] AND [schizophrenia] OR [psychosis]. The articles pertinence was assessed based on the abstracts and/or the full-texts. We selected 28 articles and the key messages were summarized.

The second research, conducted with the terms [homovanillic acid] OR [vanillylmandelic acid] OR [5-hydroxyindolamine acetic acid] OR [kynurenine] OR [kynurenic acid] OR [quinolinic acid] AND [antipsychotic] OR [neuroleptic]. The articles pertinence was assessed based on the abstracts and/or the full-texts. We selected 43 articles and the key messages were summarized.

The following MeSH terms (serotonin OR nor-epinephrine OR dopamine) were not used, in order to narrow the research results to articles that explore specifically central monoamine metabolism.

**RESULTS**

**Clinical Studies of CSF Neurotransmitters**

Six clinical studies CSF HVA and CSF5-HIAA in patients with schizophrenia and control subjects (Table 1).

Two studies find no difference in HVA, 5-HIAA and MHPG between patients with schizophrenia and healthy controls [25,26]. Bjerkensted et al. [27] finds reduction of HVA in patients, compared to controls, but no difference in 5-HIAA. To note, 50% of the patients are admitted for a first episode, and are therefore naïve of treatment. Another study from this cohort [28] shows a lower CSF HVA in the first episode and drug naïve patients with schizophrenia, compared to controls. Two other studies with drug free patients find low CSF HVA compared to healthy volun-

**Correlations with Morphological Imagery Studies**

The diminution of cerebral volume and the enlargement of the cerebral ventricles in schizophrenia is one of the most replicated findings [1]. Studies correlating CSF monoamines levels and cerebral ventricle size in patients with schizophrenia find a negative correlation with HVA and HVA/5-HIAA ratio [26,32]. Houston and colleagues [33] also find that the size of the third ventricle is negatively correlated with CSF HVA levels in schizophrenia. They suggest that this correlation may result from a progressive and time-dependent atrophy of dopaminergic neurons. However, a study measuring CSF HVA levels in adolescent patients with schizophrenia find a negative correlation between ventricle-brain ratio and CSF HVA [34]. It seems to indicate that a negative correlation between ventricle size and CSF HVA is present at an early stage of the disease.

In sum, CSF HVA level seems to be inversely correlated with ventricle size, at any stage of schizophrenia. This negative correlation is also found with 5-HIAA [26], in particular in adolescents with schizophrenia [34]. Mechanisms underpinning those results are not clear. All these studies are made with computed tomography-scan, and to our knowledge, no recent work linked cerebral imagery and CSF monoamines, using more precise imaging techniques (e.g., structural magnetic resonance imaging or functional imagery).

**Correlations with Disease Severity and Treatment Outcome**

Homogenizing on disease severity or treatment response might reduce the heterogeneity of monoamines results in CSF. Early reports show that low CSF 5-HIAA is
| First author | Journal/Year | Study type | Design | Sample size | Age, mean (yr) | Sex ratio, M/F | Treatment (for patients with recurrent episodes) | Clinical features (first onset or recurrent episodes) | Result |
|--------------|--------------|------------|--------|-------------|---------------|--------------|----------------------------------|----------------------------------|---------|
| Berger et al. [25] | American Journal of Psychiatry/1980 | Comparative study | Compared CSF monoamines in patients with schizophrenia, depression and healthy controls | 7 patients with schizophrenia, 14 controls | 36.3 (patients) 31.6 (controls) | Only males | Treatment stopped 2 weeks before | Recurrent episodes | No difference found |
| Nybäck et al. [26] | Psychiatry Research/1983 | Comparative study | Compared CSF monoamines in patients with schizophrenia under treatment and healthy controls | 26 patients with schizophrenia, 43 controls | 28 (patients) 27 (controls) | 2.6/1 (patients) 1/1 (controls) | Treatment stopped 3 weeks before | 12 first episode patients 14 patients with recurrent episode | No difference found |
| Bjerkenstedt et al. [27] | British Journal of Psychiatry/1985 | Comparative study | Compared CSF monoamines in patients with schizophrenia and healthy controls | 37 patients with schizophrenia, 65 controls | 28 (patients) 32.6 (controls) | 1.4/1 (patients) 3/1 (controls) | Treatment stopped 2 weeks before | 50% of first episode | HVA low (approximatively - 33%) in CSF of patients with schizophrenia |
| Lindström [29] | Psychiatry Research/1985 | Comparative study | Compared CSF monoamines in patients with schizophrenia and healthy controls | 40 patients with schizophrenia, 21 controls | 27.4 (patients) 25.1 (controls) | 2/1 (patients) 1/1.3 (controls) | Treatment stopped 2 weeks before | 21 first episode patients 19 patients with recurrent episodes | HVA low (approximatively - 20%) in CSF of patients with schizophrenia, no influence of pre existing treatment |
| Wieselgren et al. [30] | Psychiatry Research/1998 | Comparative/prospective study | Compared CSF monoamines in drug-free patients with schizophrenia and healthy controls, made correlation with disease outcome | 90 patients with schizophrenia, 47 controls | 27.3 (patients) 27.1 (controls) | 2/1 (patients) 1/2 (controls) | Treatment stopped 2 weeks before | 50 first episode patients 40 patients with recurrent episodes | HVA low (approximatively - 20%) in CSF of patients with schizophrenia |
| Miller et al. [28] | Biological Psychiatry/1996 | Comparative study | Compared CSF 5-HIAA and DOPAC in untreated patients with schizophrenia and controls | 21 patients with schizophrenia, 18 controls | 30.1 (patients) 39.2 (controls) | 2.5/1 (patients) 2/1 (controls) | First episode patients | First episode patients | No difference found |
| Nikkilä et al. [31] | Neuropsychobiology/2002 | Comparative study | Compared CSF Neopterin in patients with schizophrenia and controls | 11 patients with schizophrenia | 31 (patients and controls) | 1/1.2 (patients) 1.6/1 (controls) | Treatment stopped 3 months before | 6 first episodes patients 5 patients with recurrent episodes | No difference found |

CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindolamine acetic acid; DOPAC, 3,4-Dihydroxyphenylacetic acid; HVA, homovanillic acid.
correlated with both negative symptoms and delusions [35,36]. On the other hand, low CSF HVA is also correlated with positive symptoms [35]. A 28-year longitudinal study [37] shows that low CSF HVA/5-HIAA ratio was associated with a greater risk of suicide, but do not consider symptom’s severity as a confounding factor to interpret that result. In another report on a five-year longitudinal study [30], a low CSF HVA/5-HIAA quotient at baseline is correlated to a poorer outcome. Three different studies find on the contrary that a low HVA/5-HIAA ratio in CSF predicted a good response to clozapine [38-40] (for a review see also [41]).

The response to antipsychotic seems also linked with kinetic changes in CSF monoamines. HVA/5-HIAA ratio increases more in patients showing short-term improvement after haloperidol prescription [42]. Another study [43] finds that HVA rising from baseline to 4 weeks after the beginning of treatment is a predictor of poor outcome. This result is partially replicated [44], CSF HVA and 5-HIAA augmentation being inversely correlated with both positive and negative symptoms.

In sum, monoamine’s levels, especially the HVA/5-HIAA ratio, seems to be negatively correlated to treatment’s outcome, except for clozapine. Furthermore, an early kinetic change in that ratio appears to be a good predictor of treatment response.

**Effect of Antipsychotic Treatment on CSF Monoamines**

Considering the importance of monoamine metabolism in the pathophysiology of schizophrenia, many studies were led to assess the effect of antipsychotic treatment on CSF NT.

**Animal studies**

We summarize the studies on animals (all the studies presented below were done on rats) on the effect of antipsychotics. We separate them in two groups (i) immediate (i.e., in the first days of administration) effect of neuroleptics on HVA, (ii) effect of chronic administration (i.e., after one month of administration).

**Initial phase of antipsychotic administration: increase of HVA**

After administration of antipsychotic, HVA production increase. This increase seems to be dose and product-dependent: Haloperidol ≥ fluphenazine > loxapine > trifluoperazine > thiothixene > molindone > clopenthexol > chlorpromazine > thioridazine > clozapine > sulpiride [49-54]. The intensity and duration of HVA increase might also be region-dependent. Indeed, it is more important in the striatum compared to olfactory tubercle and limbic regions and more important in the caudate compared to the prefrontal cortex [50,52,55-58].

In synthesis, considering the drug and the regional brain area, early after administration in animals:

- Risperidone increases 3,4-Dihydroxyphenylacetic acid (DOPAC, an intermediate catabolite of DA) and DOPAC/DA ratio in the striatum, but less than haloperidol. Moreover, it increases the 5-HIAA/5-HT ratio in the hippocampus [59].
- Aripiprazole does not modify dopamine levels but increases moderately DOPAC and HVA and reduces 5-HIAA in the striatum and the medial prefrontal cortex [60].
- Olanzapine increases more notably DA, HVA, and DOPAC in striatum and medial prefrontal cortex, without modifying 5-HT and 5-HIAA [61].
- Clozapine increases DA, DOPAC, and HVA concentrations in mesocortical prefrontal cortex, but causes no changes in the nucleus accumbens and striatum, hence its specific action on the mesocortical DA pathway [62]. Another study shows different results, as acute administration of clozapine increases HVA,
HVA/DA ratio, and DOPAC in the striatum, and decreases DOPAC in other brain regions [63].

**Chronic phase after continued antipsychotic administration: HVA decreases**

After an initial augmentation, chronic (i.e., superior to 1 month) administration of antipsychotic in rats is associated with HVA decrease [61,64,65]. It is suggested that the augmentation could be driven by an initial enhancement of DA metabolism due to D2-blocking, especially in the prefrontal cortex [66] associated with the enhancement of DA firing. This hypothesis is supported by the augmentation of DA in the substantia nigra, even after chronic administration [65]. The HVA decreases with a tolerance mechanism set up in the prefrontal cortex, underpinned by a D2 receptor proliferation and a decrease of initial DA firing [54]. This diminution of DA firing does not appear after 21 day of clozapine administration [66-68]. Exploring more specifically those kinetic changes, HVA decreases more in the caudate nucleus versus the limbic region [67,69]. In monkeys, it has been suggested that this decrease could be associated with tardive dyskinesia [67,68].

Besides, decrease of HVA seems specific to the antipsychotic used: within a week for chlorpromazine, within two weeks for clozapine [69]. A study comparing HVA levels in rats after 3 weeks of olanzapine or aripiprazole shows increased HVA in CSF [60,61]. On the other hand, eight-month treatment with long-acting fluphenazine is associated with HVA increase in the striatum [70].

In sum, chronic administration of antipsychotics results in a dose-dependent increase of HVA in the striatum in the first month followed by a progressive decrease. This normalization could be explained by tolerance mechanisms. The heterogeneity of results by antipsychotics suggests that this mechanism could be influenced by specific receptor profiles. The results are presented in Table 2.

**Human studies**

After four weeks of antipsychotic, an HVA augmentation is observed [42,71-74]. Only two studies [43,75] show no significant difference. Another group of studies describe the evolution of CSF HVA on a larger time window (8 weeks). After an augmentation in the first 4 weeks, they show a diminution of HVA levels [76,77]. No difference is found on CSF 5-HIAA levels. Quetiapine and Olanzapine are responsible for an elevation of CSF HVA after 4 and 6 weeks respectively, without difference on 5-HIAA [44,78]. Interestingly, studies on clozapine do not find difference in HVA levels after 4 weeks of treatment [39,79].

A third group of studies assess the effect of antipsychotic withdrawal on CSF monoamines. They find a global decrease of both HVA and 5-HIAA [80-82] correlated with increased symptoms [83]. This effect is more important in the CSF of less severe patients [84].

Few studies investigated the effect of antipsychotic on CSF 5-HIAA levels: while haloperidol [72] and quetiapine [44] enhance 5-HIAA levels in CSF after 2 and 4 weeks of treatment, those levels remain unchanged after 4 weeks of sulphiride and chlorpromazine [76,77]. No difference were observed after 5 weeks of haloperidol [42], 6 weeks of olanzapine [78], and clozapine decreases CSF 5-HIAA levels after 3 weeks of treatment.

In sum, based on animals and humans’ studies CSF HVA seems to be increased in the first weeks of treatment. After one month, CSF HVA normalizes, perhaps longer with second generation antipsychotics. It is unclear how antipsychotic prescription modifies CSF 5-HIAA. Human studies show that antipsychotic withdrawal induced a fall of both CSF HVA and 5-HIAA, correlating with symptoms worsening. The results are presented in Table 3.

**DISCUSSION**

Is CSF Monoamines Level Different in Schizophrenia? Can It Be Used as a Biomarker of Severity?

Studies on CSF monoamines in schizophrenia are published for more than fifty years. It appears that no evident difference can be drawn between schizophrenia and controls. Several limitations should be considered: (i) In most of these studies, neuroleptic medication is stopped several weeks before the lumbar puncture, which, as we have seen, lead to an underestimation of CSF HVA. (ii) The lack of data on other CSF or plasmatic measurement that could influence CSF monoamines level. In particular, none of this study investigates MTHF levels in plasma or CSF. Indeed, MTHF has a major role in monoamine’s metabolism and could thus influence their CSF levels [85]. Furthermore, inflammatory processes could also influence monoamine synthesis [21], and none of the study as-
Table 2. Articles assessing antipsychotic effect on CSF monoamines in animal

| First author        | Journal/Year                  | Design                                                                 | Sample size                                                                 | Age, mean (yr) | Sex ratio, M/F | Treatment        | Clinical features (first onset or recurrent episodes) | Result                                                                 |
|---------------------|-------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------|----------------|-----------------|--------------------------------------------------------|------------------------------------------------------------------------|
| Kahn et al. [42]    | Archives of general psychiatry/1993 | Assessment of CSF HVA and 5-HIAA level at baseline and after 5 weeks of treatment | 16 patients with schizophrenia, 3 with schizo affective disorder             | 43.1           | Males inpatients | Haloperidol     | Recurrent episodes                                     | HVA increased by approximatively 50%, no change in 5-HIAA levels       |
| Nikisch et al. [44] | Journal of Clinical Psychopharmacology/2010 | Assessment of CSF HVA and 5-HIAA level at baseline and after 4 weeks of treatment | 22 patients with schizophrenia                                               | 35.9           | 1.75/1         | Quetiapine Norquetiapine                              | 14 patients with first episode, 8 patients with recurrent episode      | In the quetiapine group, HVA and 5-HIAA increased by approximatively 35%, no difference in the norquetiapine group |
| Szymanski et al. [39] | Psychopharmacology/1993         | Assessment of CSF HVA and 5-HIAA level at baseline and after 3 weeks of treatment | 17 patients with schizophrenia, 2 patients with schizo affective disorder   | 29.5           | 2/1            | Clozapine       | Recurrent episodes                                     | No difference                                                          |
| Sedvall et al. [71] | Journal of Psychiatric Research/1974 | Assessment of CSF HVA level at baseline and after 12 days of treatment | 34 patients with schizophrenia                                               | 30 (males)     | 1/2            | 3 antipsychotics                                      | HVA increased by approximatively 250%                                  |
| Rüther et al. [72]  | Pharmacopsychiatry/1976        | Assessment of CSF HVA and 5-HIAA level at baseline and after 5 and 15 days of treatment | 26 patients with schizophrenia                                               | 33.1           | 1.2/1          | Haloperidol     | Recurrent episodes                                     | HVA and 5-HIAA increased by approximatively 250% at day 5, by 75% at day 15 |
| Wode-Helgodt et al. [73] | Acta Psychiatrica Scandinavica/1977 | Assessment of CSF HVA level at baseline and after 2 and 4 weeks of treatment | 43 patients with schizophrenia                                               | 28 (males)     | 1/1.5          | Chlorpromazine                                         | HVA increased at week 2 by approximatively 50% and decreased near baseline at week 4 |
| Doran et al. [74]   | Biological Psychiatry/1989     | Assessment of CSF HVA level at baseline and after 3 weeks of treatment | 14 patients with schizophrenia                                               | 28.0           | 1/1            | Fluphenazine                                            | Recurrent episodes                                                    | HVA increased                                                          |
| Sharma et al. [75]  | Psychiatry Research/1989       | Assessment of CSF HVA level at baseline and after 5 weeks of treatment | 17 patients, 11 with schizophrenia                                           | 31.9           | 1.1/1          | Trifluoperazine                                         | Recurrent episodes                                                    | No difference                                                          |
Table 2. Continued

| First author | Journal/Year | Design | Sample size | Age, mean (yr) | Sex ratio, M/F | Treatment | Clinical features (first onset or recurrent episodes) | Result |
|--------------|--------------|--------|-------------|----------------|----------------|-----------|------------------------------------------------------|--------|
| Alfredsson et al. [76]/Härnryd et al. [77] (2 articles in the same journal issue about the same cohort) | Acta Psychiatrica Scandinavica/1984 | Assessment of CSF HVA and 5-HIAA level at baseline and during 8 weeks of treatment | 50 patients with schizophrenia | From 18 to 43 years | 1/1 | Sulpiride Chlorpromazine | Recurrent episodes | HVA increased approximately by 200% at week 2, then decreased at week 4 and returned to baseline at week 8. No change in 5-HIAA levels |
| Scheepers et al. [78] | Neuropsychopharmacology/2001 | Assessment of CSF HVA and 5-HIAA level at baseline and after 6 weeks of treatment | 21 patients with schizophrenia, 2 with schizoaffective disorder | 31.0 | Males inpatients | Olanzapine | Recurrent episodes | HVA increased approximately by 50%. No change in 5-HIAA levels |
| Gerlach et al. [79] | Psychopharmacologia/1975 | Assessment of CSF HVA and 5-HIAA level at baseline and after 3 weeks of treatment | 8 patients with schizophrenia | 39.1 | Males inpatients | Haloperidol Clozapine | Recurrent episodes | HVA decreased approximately by 30% in patients with clozapine, and increased by approximately 30% in patients with haloperidol. |
| Bagdy et al. [80] | Psychiatry Research/1984 | Assessment of CSF HVA 2 weeks after withdrawal in chronically treated patients | 15 patients with schizophrenia | — | Males inpatients | Chlorpromazine | Recurrent episodes | HVA decreased after withdrawal |
| Perényi et al. [81] | Acta Psychiatrica Scandinavica/1985 | Assessment of CSF HVA 2 weeks after withdrawal in chronically treated patients | 14 patients with schizophrenia | 43.4 | 3.75/1 | 5 antipsychotics | Recurrent episodes | HVA decreased after withdrawal; decrease was more important for patients with clinical deterioration |
| Sharma et al. [43] | Biological Psychiatry/1993 | Assessment of CSF HVA at baseline and after 4 weeks of treatment | 15 patients with schizophrenia, 4 with schizoaffective disorder | 29.3 | 1.3/1 | Various antipsychotic drugs (mean Chlorpromazine equivalent 1,118 mg) | Recurrent episodes | No difference |

CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindolamine acetic acid; HVA, homovanillic acid.
| First author | Journal/Year | Animal | Design | Treatment | Main result |
|--------------|--------------|--------|--------|-----------|-------------|
| Chang et al. [49] | Psychopharmacology/1988 | Rat | Assessment of HVA level in prefrontal cortex and caudate of rats 24 hours after administration | 12 antipsychotics | HVA increased by 300% for all antipsychotics, with haloperidol > fluphenazine > loxapine > trifluoperazine > thiathiene > molindone > clopenthixol > chlorpromazine > metoclopramide > thioridazine > clozapine > sulpiride |
| Stawarz et al. [50] | Psychopharmacologia/1975 | Rat | Assessment of HVA level in striatum and limbic forebrain of rats 2 hours after administration | 5 antipsychotics | HVA increased by all antipsychotics, with Haloperidol > pimozide > chlorpromazine > thioridazine > clozapine |
| Pugsley et al. [51] | Canadian Journal of Physiology and Pharmacology/1976 | Rat | Assessment of HVA level in striatum and olfactory tubercle of rats 3 hours after administration | Butaclamol | HVA increased by 300% |
| Wiesel et al. [52] | European Journal of Pharmacology/1975 | Rat | Assessment of HVA level in striatum and olfactory tubercle of rats 1.5 hours after administration | 4 antipsychotics | HVA increased by haloperidol > chlorpromazine > thioridazine and clozapine |
| Bowers et al. [53] | European Journal of Pharmacology/1982 | Rat | Assessment of HVA level in caudate and cortex at different time after the first administration | Haloperidol | HVA increased in caudate and cortex after 2 days (between by 200 and by 300%, depending on brain region) then returned to baseline after 10 days of administration |
| Rastogi et al. [54] | General Pharmacology/1982 | Rat | Assessment of HVA level in striatum at different time after the first administration | Haloperidol, chlorpromazine | HVA increased (approximately by 50%) in striatum after 1.5 hours then decreased below baseline (approximately 30%) after 20 days of administration |
| Scatton et al. [55] | Brain Research/1977 | Rat | Assessment of HVA level in striatum and retina at different time after the administration | Haloperidol Sulpiride | HVA increased in striatum after 1.5 hours then decreased after 11 days of administration. Increase was more important in striatum |
| Bowers et al. [56] | European Journal of Pharmacology/1984 | Rat | Assessment of HVA level in cortex and striatum of rats 3 hours after the first administration | 5 antipsychotics | Thioridazine, haloperidol, fluphenazine, and metoclopramide increased HVA levels in caudate more than in pre-frontal cortex. Sulpiride and clozapine produced greater increases in HVA in pre-frontal cortex |
| Bowers [57] | Psychopharmacology/1986 | Rat | Assessment of HVA level in cortex and striatum of rats at different time after the first administration | 3 antipsychotics | Haloperidol, sulpiride and fluphenazine increased HVA 3 hours after administration, and HVA decreased after 10 days of chronic administration |
| Watanabe et al. [58] | European Journal of Pharmacology/1999 | Rat | Assessment of HVA level in cortex and striatum of rats in the 5 hours after the first administration | Sertindole | HVA increased by 300% by sertindole after 5 hours |
| Antoniou et al. [59] | European Neuropsychopharmacology/2000 | Rat | Assessment of 5-HIAA level in hippocampus of rats 48 hours after administration or after 21 day administration | Haloperidol Risperidone | No change in 5-HIAA levels after acute and chronic administration. 5-HIAA/SHT was elevated by both drugs after acute administration |
| Jordan et al. [60] | European Journal of Pharmacology/2004 | Rat | Assessment of HVA level in cortex and striatum of rats at different time after the first administration | Aripiprazole Olanzapine | Antipiprazole increased HVA after acute chronic administration. Olanzapine increased HVA after acute administration but this increase was reversed after chronic administration |
| Arjona et al. [61] | Behavioural Brain Research/2004 | Rat | Assessment of HVA level in cortex and striatum of rats at different time after the first administration | Olanzapine | Olanzapine increased HVA (400%) in both regions after acute administration, but this increase was reversed after 30 days of chronic administration |
| Hernandez et al. [62] | Pharmacology, Biochemistry, and Behavior/1995 | Rat | Assessment of HVA level in cortex and striatum of rats at different time after the first administration | Clozapine | Clozapine increased HVA levels in acute administration, but not after chronic administration in prefrontal cortex. No changes were measured in striatum |
| Haleem et al. [63] | Medical Science Monitor/2002 | Rat | Assessment of HVA level in cortex and striatum 1 hour after administration | Clozapine | Clozapine increased HVA in striatum, but not in prefrontal cortex |
| First author   | Journal/Year | Animal | Design | Treatment          | Main result                                                                                                                                                                                                 |
|---------------|--------------|--------|--------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clow et al.   | European Journal of Pharmacology/1980 | Rat    | Assessment of HVA level on striatum at different time after the first administration | Trifluoperazine Thioridazine Haloperidol Fluopenitol | HVA increased by 250% 2 weeks after administration, then returned to baseline after one month  
In animals with acute treatment, HVA increased in striatum, but not in substantia nigra. Inverse effect was observed in animals with chronic treatment  
After 21 days, HVA increased in cortex but was similar to baseline in striatum, except for clozarline-treated animals, who had elevated HVA levels in striatum |
| Nicolaou     | European Journal of Pharmacology/1980 | Rat    | Comparison between HVA levels in substantia nigra and striatum in animals with acute vs. chronic treatment | Haloperidol Fluopenitol | HVA decreased in striatum after chronic administration in monkeys with dyskinesia, compared with those without dyskinesia  
HVA increased after acute administration  
After two weeks, clozapine-treated animals showed a reduction of HVA levels in caudate |
| Mefford et al. | Brain Research/1988 | Rat    | Assessment of HVA level in cortex and striatum at day 21 after daily administration | 4 antipsychotic | HVA increased in striatum after chronic administration of chlorpromazine but not haloperidol. 5-HT/5-HIAA ratio decreased in amygdala and thalamus |
| Shannak et al. [67] | Advances in Biochemistry and Psychopharmacology/1980 | Monkey | Assessment of long term (17 month) effect on HVA and 5-HIAA levels on different brain region | Chlorpromazine Haloperidol | HVA increased in striatum after chronic administration of chlorpromazine but not haloperidol. 5-HT/5-HIAA ratio decreased in amygdala and thalamus |
| Gunne et al. [68] | Journal of Clinical Psychiatry/1985 | Monkey | Comparison between HVA levels between monkeys with or without tardive dyskinesia after chronic (years) administration | Fluphenazine Haloperidol | HVA increased after acute administration  
After two weeks, clozapine-treated animals showed a reduction of HVA levels in caudate  
HVA level was increased compared to baseline in the fluphenazine-treated animals |
| Bowers et al. [69] | European Journal of Pharmacology/1976 | Rabbit | Assessment of HVA level in caudate and thalamus at different time after the first administration | 3 antipsychotics | HVA increased after acute administration  
After two weeks, clozapine-treated animals showed a reduction of HVA levels in caudate  
HVA level was increased compared to baseline in the fluphenazine-treated animals |
| See et al. [70] | Brain Research Bulletin/1992 | Rats | Assessment of HVA level in caudate and nucleus accumbens after nine months of chronic administration | Fluphenazine Haloperidol | HVA increased after acute administration  
After two weeks, clozapine-treated animals showed a reduction of HVA levels in caudate  
HVA level was increased compared to baseline in the fluphenazine-treated animals |

CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindolamine acetic acid; HVA, homovanillic acid.
sessed inflammatory markers with monoamine metabolism.

Our review also suggests that low CSF HVA, could be correlated with clinical features, such as positive symptoms. Those results can lead to the hypothesis that perturbed CSF monoamines levels (i.e., low CSF HVA and low HVA/5-HIAA) could be both a marker of severity and a negative predictor of treatment response. This hypothesis can be supported by the fact that CSF HVA seems to be inversely correlated to the cerebral ventricle size, which has been found enlarged in patients with poor outcome [86]. Future studies are needed in order to assess the differences in monoamines CSF between responder and non-responders to antipsychotic treatment.

How Can the Antipsychotic Action on CSF be Modeled?

There is a good concordance between animal and human studies about CSF HVA and antipsychotic effects (Fig. 3). Indeed, an augmentation of HVA levels in CSF in the first week (with both first and second-generation antipsychotics), normalization after 8 weeks, and a brutal decrease in case of treatment withdrawal. A first hypothesis is that D2-blocking increases the catabolism of dopamine, leading to HVA augmentation in CSF [34]. After a few weeks (2−4 weeks) the normalization could be explained [77] by an up-regulation in the striatal D2 receptors. A second explanation proposes [82] that D2-blocking increased the dopamine release in the striatum (responsible for the majority of HVA production) [87] followed by normalization after a few weeks. This augmentation of CSF HVA seems to be correlated to treatment response [44]. We make a third hypothesis of this biphasic evolution, and suppose that antipsychotic drugs could also have an influence on biopterin and neopterin. However, because 5-HIAA level does not seem to be affected by neuroleptics, and since no data is available on an antipsychotic effect on CSF biopterin or neopterin have been found, this hypothesis can not be verified.

To note, the specific profile of CSF HVA response to clozapine could be explained [39] by the specific serotonin-dopamine interactions profile of this drug (i.e., 5-HT2A blockade leading to pro-dopaminergic action). This ac-

Fig. 3. Overview of monoamine’s metabolism and the antipsychotic effect on CSF HVA. Antipsychotics influence monoamine’s metabolism by stimulating HVA production after its instauration. Withdrawal provokes a decrease in HVA level. Antipsychotic prescription should be considered as a confounding factor as well as inflammatory processes and folate metabolism when monoamine’s assessment is performed. (1) Tyrosine Hydroxylase; (2) Tryptophan Hydroxylase; (3) Catecholamine-O-Methyl Transferase (COMT) and Monoamine Oxidase (MAO); (4) 6-Pyruvotetrahydropterin Synthase (PTPS) and Sepiapterin Reductase (SR); (5) Aldehyde Deshydrogenase and MAO; (6) Methionine Synthase; (7) Methyltetrahydrofolate Reductase (MTHFR). NH2TP, dihydroneopterin triphosphate; BH2, Dihydrobipterin; BH4, Tetrahydrobipterin; TRP, Tryptophan; DOPA, Dopamine; NA, Noradrenaline; 5-HT, serotonin; MHPG, 3-Methoxy-4-hydroxyphenylglycol; HVA, Homovanillic acid; 5-HIAA, 5-hydroxyindolamine acetic acid. *Can be measured in CSF.
tion on the 5HT receptor is not specific of clozapine, being one the main mechanisms of second-generation antipsychotics.

Our review does not support the hypothesis of an isolated dysfunction of monoamines metabolism in schizophrenia, as it has been formulated by the first studies on this field [35,71]. However, the antipsychotic treatments disturb CSF monoamines in a time-dependent matter. Influence of antipsychotic drugs could have been a major bias for the interpretation of CSF monoamines. All those considerations encourage assessing monoamines in CSF more frequently in patients with schizophrenia, and to consider the confounding factors we cited: (i) measurement of inflammatory processes (ii) assessment of folate metabolism, specifically the presence of c677t MTHFR mutation (iii) control of antipsychotic treatment.

Moreover, the importance of the lumbar punctures’ quality, and specifically its standardization (i.e., CSF sample used to investigate neurotransmitters metabolism should always be taken at the same moment of the puncture), the concentration of monoamine metabolites is also influenced by a cranio-caudal gradient [88].

Our literature review is comprehensive; thus, it might be useful to perform a meta-analysis of the relationship between CSF monoamines levels and treatment response or schizophrenia subtype, in order to consider the heterogeneity of the study we reviewed.

Further studies on this field could help finding the missing link between inflammatory processes, folate metabolism and antipsychotic effect on the disease course (Fig. 3).

CONCLUSION

As research of a biomarker plays a crucial role in the treatment of schizophrenia, studies on monoamines metabolites in CSF reveals that those levels could be correlated to disease severity and to specific clinical features. While the antipsychotic treatment seems to provoke changes in CSF HVA, further studies should consider the antipsychotic treatment as a potential confounding factor, and consider the central place of neurotransmitters metabolism in metabolic and inflammatory processes involved in schizophrenia.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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