ORIGINAL ARTICLE

# Biogenic Amine Metabolites and Thiamine in Cerebrospinal Fluid in Heredo-Degenerative Ataxias

*M.I. Botez and S.N. Young*

**ABSTRACT:** ***Background:*** The aims of the present study were: i) to measure levels of the dopamine metabolite homovanillic acid (HVA), the serotonin metabolite 5-hydroxindoleacetic acid (5HIAA) and precursor tryptophan, as well as the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) and thiamine in the cerebrospinal fluid (CSF) of patients with Friedreich's ataxia (FA), olivopontocerebellar atrophy (OPCA), and the autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSAC), as compared with sex- and age-matched control subjects. ***Patients and methods:*** CSF amine related compound levels and thiamine results were compared in 40 FA, 44 OPCAand nine ARSAC patients with those of 94 sex- and age-matched subjects. Neuroimaging (CT scans and single photon emission computed tomographies i.e. SPECT) were carried out in all patients and controls. Genetic studies were conducted on OPCApatients. CSF amine related compounds were measured by high performance liquid chromatography, whereas CSF thiamine levels were measured by a microbiological method. ***Results:*** FA patients had significantly lower CSF HVA, 5HIAA and thiamine values than control patients and a trend for lower MHPG levels. In OPCA patients, CSF HVA, MHPG and thiamine values were markedly lower whereas CSF 5HIAA values showed only a trend towards lower levels; in ARSAC patients only thiamine and HVA CSF values were lower than those in control subjects. ***Conclusion:*** After presenting the relationships between neurochemical findings on one side, the degree of ataxia, the degree of cerebellar atrophy and the SPECT findings on the other, the authors concluded that replacement and neuroprotective clinical trials in these patients would have to include two or three drugs because the neurotransmitter deficiencies are multiple.

**RÉSUMÉ: Métabolites d'amines biogènes et thiamine du liquide céphalorachidien dans les ataxies hérédo-dégénératives.** ***Introduction:*** Les buts de cette étude étaient de mesurer les niveaux d'acide homovanillique (HVA), un métabolite de la dopamine, d'acide 5-hydroxindoleacétique (5HIAA) , un métabolite de la sérotonine, et de son précurseur, le tryptophane, ainsi que du 3-méthoxy-4-hydroxyphényléthylène glycol (MHPG), un métabolite de la noradrénaline et de la thiamine dans le liquide céphalorachidien (LCR) de patients atteints d'ataxie de Friedreich (AF), d'atrophie olivopontocérébelleuse (OPCA) et d'ataxie spastique autosomale récessive de Charlevoix-Saguenay (ARSAC) et de les comparer à ceux de sujets contrôles appariés pour le sexe et l'âge. ***Patients et méthodes:*** Les niveaux de composés reliés aux amines du LCR et les résultats de thiamine ont été comparés chez 40 patients atteints d'AF, 44 d'OPCAet neuf d'ARSAC à ceux de 94 sujets contrôles appariés pour le sexe et l'âge. Des examens de neuroimagerie (CT scan et tomographie à émetteur gamma i.e. SPECT) ont été effectués chez tous les patients et les contrôles. Les patients atteints d'OPCA ont également subi des tests génétiques. Les composés reliés aux amines du LCR ont été mesurés par chromatographie à haute pression en phase liquide et les niveaux de thiamine ont été mesurés par une méthode microbiologique. ***Résultats:*** Les patients atteints d'AF avaient des valeurs de HVA, de 5HIAAet de thiamine du LCR significativement plus basses que les sujets contrôles et une tendance à des niveaux plus bas de MHPG. Chez les patients atteints d'OPCA, les valeurs de HVA, de MHPG et de thiamine du LCR étaient beaucoup plus basses, alors que les valeurs de 5HIAAdu LCR avaient seulement une tendance à être plus basses; chez les patients atteints d'ARSAC, seulement les valeurs de thiamine et de HVA du LCR étaient plus basses que celles des sujets contrôles. ***Conclusions:*** Les auteurs présentent les relations entre les observations neurochimiques d'une part et le degré d'ataxie et d'atrophie cérébelleuse et les observations de neuroimagerie d'autre part et ils concluent que les essais thérapeutiques de remplacement et de neuroprotection chez ces patients devraient inclure deux ou trois médicaments à cause des déficits multiples en neurotransmetteurs.

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Measurements of the levels of biogenic amine metabolites in cerebrospinal fluid (CSF) have been carried out in patients with various degenerative disorders. In Friedreich's ataxia (FA) and olivopontocerebellar atrophies (OPCA), most studies have involved only a few patients (less than 10).[1,2] Furthermore, the groups of patients studied were often heterogenous and included various cerebellar pathologies.[1,3]

The relationships between brain amines and motor and non-motor behaviours involved in the clinical picture of heredo-degenerative ataxias have been investigated in both experimental animals[4-8] and humans.[9-11] The data from these studies have lead

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to small clinical trials of a number of different compounds in cerebellar degenerative diseases but no marked clinical improvement has been demonstrated.[12]

In a previous study, we found low levels of thiamine in the CSF of patients with heredo-degenerative ataxias.[13] This is relevant to possible alterations of biogenic amines because of experimental[14,15] and clinical[9,16,17] data linking thiamine deficiency with a lowering of both serotonin and noradrenaline, particularly in the cerebellum.

The aims of the present study were: i) to measure levels of the dopamine metabolite homovanillic acid (HVA), the serotonin metabolite 5-hydroxindoleacetic acid (5HIAA) and precursor tryptophan, as well as the noradrenaline metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) in the CSF of patients with three well-defined heredo-degenerative ataxias, i.e. FA, OPCAand the autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSAC), as compared with sex- and age-matched control subjects; ii) to look at the relationship between CSF amine metabolite levels and thiamine concentration, and; iii) to investigate whether there is a relationship between the levels of thiamine and amine metabolites in CSF and the degree of ataxia and of cerebellar atrophy, as measured by computed tomography (CT) scans and magnetic resonance imaging (MRI), and blood flow, as measured by the single-photon emission computed tomography (SPECT).

## Methods

### Patients and controls

Ninety-three patients suffering from heredo-degenerative ataxia (40 FA, 44 OPCAand nine ARSAC) were compared with 94 sex- and age-matched subjects who underwent spinal tap either for lumbar disc herniation or negative clinical investigation for other neurological disease.

Some patients were enrolled from the Ataxia Clinic of Hôpital Hôtel-Dieu de Montréal, in order of presentation at the outpatient clinic. Others were referred by the Canadian Association of Friedreich's ataxia and recruited from the entire province of Québec. X-ray, CT and MRI studies were carried out in all patients before their inclusion in the study. Those showing central (i.e. ventricular dilatation) and cortical (i.e. cortical sulci dilatation) atrophies according to previously-defined radiological criteria[18,19] were excluded, so that only patients with clearly identified cerebellar damage were included in this study. Others excluded were OPCA patients with even mild parkinsonian signs, as assessed by reinforcement methods.[20] Finally, epileptics, alcoholics, patients with medical diseases in evolution, and patients taking medications which could interfere with the metabolism of biogenic amines, were excluded. Also, those taking vitamins, as well as those with dietary deficiencies, were excluded from the present study. Dietary deficiencies were determined on the basis of a dietary assessment by a dietician, and on the basis of plasma vitamin levels. The patients gave informed consent to participate in the study, which was approved by the Research Ethics Board of the hospital.

All FA adult patients included in this study fulfilled the diagnostic criteria of Harding.[21] Genetic studies were undertaken in the OPCApatients in the laboratory of Dr. Guy Rouleau at the Montréal General Hospital.[22] These studies allowed us to classify the autosomal dominant OPCApatients into two groups: those with SCA1 in which the locus is on chromosome 6p, and those with SCA2 in which the locus is on chromosome 12q.

Patients with ARSAC fulfilled the diagnostic criteria of Bouchard et al[23] and were originally from Charlevoix-Saguenay county in the province of Québec.

### Clinical assessment

Besides the routine clinical neurological examination, the degree of ataxia in the upper and lower limbs was assessed as mild to moderate or severe following previously established criteria.[19] Ataxia in OPCA patients was assessed for both upper and lower limbs. In FA patients it was done only for the upper limbs, because they were already paraplegic **(see below)**.

The degree of cerebellar atrophy was assessed as mild to moderate or severe by inspection of the films by the neuroradiologist[19] using previously defined radiological criteria.[18,24,25].

Crossed cerebello-cerebral diaschisis was initially described using SPECT in patients with unilateral cerebellar infarcts.[26-30] In a previous study, out of 15 OPCA patients with marked reductions in cerebellar hexamethylpropyleneamine oxime (HMPAO) uptake, 11 had bilateral fronto-parietal HMPAO hypoperfusion in spite of a normal CT scan at the supratentorial level.[28] Therefore we carried out SPECT studies in all our patients in order to establish the metabolic effects at a distance from the anatomical (cerebellar) gross macroscopic damage. The method was fully described in our previous papers.[28,31]

### Biochemical measures

All patients underwent routine laboratory tests. CSF was collected by lumbar puncture on fasting patients between 8:00 a.m. and 9:30 a.m.

Thiamine status was determined solely on the basis of CSF levels, without taking into account the plasma levels. This was done for two reasons, namely: i) in a previous study[13] we showed that in heredo-degenerative ataxias, plasma vitamin levels are normal whereas CSF thiamine levels are low. In this study the important variable is the amount of vitamin available to the brain; and ii) low plasma levels due to borderline deficiencies might be corrected by improved nutrition during a short stay in the hospital, but recovery of CSF levels would take longer.

Thiamine levels were determined by the microbiological method, in duplicate, using Lactobacillus fermenti.[32] When low values of thiamine were found, an additional incubation was carried out with added thiamine to check that no inhibitors of bacterial growth were present.[33] Using this method of verification, the normal values of CSF thiamine in our laboratory are higher than 24 ng/ml. This is in good agreement with levels reported by Baker and Frank,[32] and by Rindi et al.[34]

Tryptophan, 5HIAA, HVA and MHPG were measured in CSF using high performance liquid chromatography with fluorometric and electrochemical detection.[35,36] All of the biochemical analyses were done blind to the clinical assessment.

### Statistics

From a pool of 101 control subjects, three control groups were matched by age and sex with patient groups by an independent researcher not involved directly in the study. Thus, the three control groups differed slightly because of the



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somewhat different age and sex profiles of the three patient groups.

The sex ratios of the patients and the controls were compared using a $X^2$ test. Differences in length of illness between the patients were assessed using an analysis of variance (ANOVA) for parallel groups. Finally, the CSF values between the patients and the controls were evaluated using a 2 by 3 ANOVA.

Similarly, a 2 by 2 ANOVA was used to compare values from the FA and OPCA patients, including the degree of cerebral atrophy, the degree of ataxia and the presence or absence of diaschisis.

For all the variables, the critical level of significance was set at five per cent.

## Results

### Clinical measures

All but six of the FApatients were confined to a wheelchair; all had paraplegia and a bilateral cerebellar and upper motor neuron syndrome as revealed by Babinski sign. Thirty-one had dorso-lumbar scoliosis, 39 had polyneuropathies, nine were diabetics and nine had cardiomyopathies. Twenty-eight FA patients had mild-moderate, and 12 severe, ataxias of the upper limbs.

Of the OPCA patients, 20 had autosomal dominant OPCA, corresponding to form 3 from the classification of Huang and Plaitakis,[37] in whom the SCA1 locus maps on chromosome 6p, and 24 patients had autosomal dominant OPCAcorresponding to form 5 n of Huang and Plaitakis, in whom the SCA2 locus maps on chromosome 12q.[22] This latter form is characterized by slow ocular saccades.[38] There were no biochemical differences between the two variants (data not shown).

All OPCA patients were able to walk; 14 had a mild ataxia, 14 had a moderate ataxia, and the remaining 12 had severe cerebellar ataxias. Twelve had polyneuropathies, while four had bilateral or unilateral plantar extensor response.

The nine patients with ARSAC had the classical clinical picture: spastic paraparesis with ataxia of gait, dysarthria, distal muscle wasting, posterior column signs.[23] Six had polyneuropathies and in eight patients the sensory action potentials in the lower limb were absent. All patients, except for

**Table 1:** CSF Neurochemical Findings in Patients with Heredo-Degenerative Ataxias

| Variables | | Friedreich's ataxia | OPCA | ARSAC |
|---|---|---|---|---|
| Sex ratio M/F | Patients | 23/17 | 21/23 | 2/7 |
| | Controls | 20/20 | 22/22 | 3/7 |
| Age (years) | Patients | 29.0±0.9 | 43.8±1.9 | 38.0±3.2 |
| | Controls | 31.2±1.1 | 43.4±1.9 | 39.6±3.4 |
| Lenght of the ilness (years) | Patients | 18.7±1.0 | 15.0±1.6 | 33.0±5.7 |
| HVA | Patients | 31.4±2.4** | 31.3±2.4** | 27.8±4.7** |
| | Controls | 51.2±4.3 | 51.7±3.1 | 63.3±13.3 |
| Tryptophan | Patients | 493±28** | 430±22 | 368±40 |
| | Controls | 405±19 | 406±20 | 346±21 |
| 5HIAA | Patients | 18.5±1.7** | 21.3±2.3 | 19.1±4.2 |
| | Controls | 25.7±2.0 | 26.2±l.9 | 24.1±2.6 |
| MHPG | Patients | 7.84±0.42 | 7.70±0.44* | 6.60±1.0 |
| | Controls | 9.06±0.54 | 9.13±0.38 | 9.01±1.1 |
| Thiamine | Patients | 26.4±1.6** | 23.6±1.8** | 15.2±1.44** |
| | Controls | 34.6±1.7 | 32.7±1.5 | 33.1±1.7 |

* $p < 0.05$, ** $p < 0.01$ when contrasting mean values of the patients with those of their respective controls.
Except for sex ratio, all values are means±SE in ng/ml.

**Table 2.** Relationships between the Degree of Ataxia and CSF Neurochemical Findings

| Variables | Friedreich's ataxia | | OPCA | |
|---|---|---|---|---|
| | Mild-moderate ataxia (15M, 13F) | Severe ataxia (8M, 4F) | Mild-moderate ataxia (11M, 12F) | Severe ataxia (10M, 11F) |
| Age (years) | 27.6±1.2 | 29.6±1.1 | 42.3±2.9 | 45.4±2.5 |
| HVA | 33.9±3.0 | 25.5±3.8 | 34.2±2.9 | 28.2±3.9 |
| Tryptophan | 465±32 | 558±50 | 421±19 | 440±41 |
| 5HIAA | 20.5±2.2 | 14.1±2.3 | 23.9±3.9 | 18.2±2.1 |
| MHPG | 7.50±0.53 | 8.49±0.66 | 7.73±0.57 | 7.69±0.71 |
| Thiamine | 26.1±1.8 | 27.0±3.2 | 25.6±2.7 | 21.4±2.5 |

CSF neurochemical values are expressed as mean±SE in ng/ml.



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**Table 3:** Relationships between the Degree of Cerebellar Atrophy on CT Scans or MRI and the CSF Neurochemical Findings

| Variables | Friedreich's ataxia | | OPCA | |
|---|---|---|---|---|
| | Mild-moderate (16M, 12F) | Severe cerebellar atrophy (7M, 5F) | Mild-moderate (11M, 12F) | Severe cerebellar atrophy (10M, 11F) |
| Age (years) | 29.3±1.2 | 28.3±1.2 | 45.4±29.3 | 42.0±2.4 |
| HVA | 33.5±3.0 | 26.5±4.0 | 31.6±3.3 | 31.0±3.6 |
| Tryptophan | 501±36 | 475±38 | 418±32 | 443±29 |
| 5HIAA | 20.0±2.2 | 14.7±2.1 | 19.3±3.4 | 23.3±3.2 |
| MHPG | 7.84±0.51 | 7.84±0.75 | 7.68±0.54 | 7.74±0.73 |
| Thiamine | 27.6±2.0 | 23.6±2.2 | 25.6±2.8 | 21.2±2.2 |

CSF neurochemical values are expressed as mean±SE in ng/ml.

**Table 4:** Relationships between SPECT Studies and the CSF Neurochemical Findings

| Variables | Friedreich's ataxia | | OPCA | |
|---|---|---|---|---|
| | No diaschisis (13M, 13F) | Diaschisis (I0M, 4F) | Nodiaschisis (I0M, 14F) | Diaschisis (11M, 9F) |
| Age (years) | 28.9±1.2 | 29.1±1.5 | 41.8±2.4 | 46.1±3.0 |
| HVA | 26.8±2.1 | 39.9±5.2 | 25.9±3.0 | 37.8±3.4 |
| Tryptophan | 470±33 | 535±50 | 435±37 | 423±19 |
| 5HIAA | 17.0±2.0 | 21.5±3.1 | 16.1±1.9 | 27.2±4.1 |
| MHPG | 7.38±0.48 | 8.70±0.77 | 6.91±0.54 | 8.60±0.69 |
| Thiamine | 25.6±1.7 | 27.8±3.2 | 21.7±2.4 | 26.0±2.8 |

CSF neurochemical values are expressed as mean±SE in ng/ml.

one in a wheelchair, were able to walk. Characteristic retinal striation found in ARSAC was evident in four patients.

### Amine metabolites and thiamine

FA patients had significantly lower CSF HVA, 5HIAA and thiamine values than control patients and had a trend for lower MHPG levels (Table 1). In OPCA patients, CSF HVA, MHPG and thiamine values were significantly lower, while 5HIAA values showed only a trend towards lower levels. In ARSAC patients (Table 1), thiamine and HVA had mean values less than half that in control subjects.

While biochemical values did not differ between patients with mild-moderate ataxia and those with severe ataxia in each disorder (Table 2), taking FA and OPCA patients together, those with severe ataxia had lower HVA levels ($F_{1,80} = 4.02$, $p<0.05$). For CSF 5-HIAA there was only a trend for those with severe ataxia to have lower levels that those with mild-moderate ataxia ($F_{1,78} = 3.18$, $p<0.075$), while MHPG and thiamine did not differ with severity.

While age ($F_{1,80} = 0.16$) and levels of HVA ($F_{1,80} = 0.99$), tryptophan ($F_{1,80} = 0.12$), 5HIAA($F_{1,78} = 0.01$) or MHPG ($F_{1,74} = 0.001$) did not differ between those with mild-moderate and severe cerebellar atrophy, there was a trend for CSF thiamine levels to be lower in patients with severe atrophy ($F_{1,80} = 3.49$, $p<0.075$) (Table 3).

As mentioned above, some patients with heredo-spinocerebellar ataxias display a reverse cerebello to basal ganglia to frontoparietal diaschisis, i.e. a bilateral reduced HMPAO uptake at the supratentorial level despite a normal CTscan or MRI at the basal ganglia or cortical levels.[28] Table 4 shows values for age and the biochemical variables in FA and OPCA patients who were divided into two groups: one with no cerebellar to basal ganglia to cortical diaschisis and the other with diaschisis. Patients with diaschisis tended to be older than those without diaschisis ($F_{1,80} = 3.35$, $p<0.075$), and had higher CSF levels of HVA ($F_{1,80} = 14.3$, $p<0.001$), 5HIAA ($F_{1,80} = 8.09$, $p<0.01$), and MHPG ($F_{1,74} = 5.78$, $p<0.05$) than those with no diaschisis. Thiamine levels did not differ either with diagnosis ($F_{1,79} = 1.35$) or with diaschisis ($F_{1,79} = 1.42$).

Covariance analyses did not show any relationship between CSF thiamine on one hand and CSF amine metabolites on the other.

## Discussion and conclusion

Our results are consistent with those from a variety of small studies that found low CSF HVA in patients with FA[2,39,40] OPCA[1,2] and in multiple system atrophy which encompasses the overlapping syndromes of OPCAand striatonigral degeneration, accompanied in many cases by autonomic failure.[3] In post-mortem studies, mild to moderate striatal dopamine loss is a common but not constant feature of OPCA.[41] However, in OPCA patients having moderate to marked striatal dopamine reduction, no parkinsonian symptoms were observed, which was explained by the fact that the degree of dopamine loss did not attain a critical threshold. Our OPCA patients also did not exhibit any



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parkinsonian signs in spite of the significant reduction of CSF HVA.

The exact role of dopamine in heredo-degenerative ataxias remains uncertain. Dopaminergic innervation of the cerebellum has been documented,[42,43] although levels are low, but animal work supports a relationship between the cerebellum and striatum. Rats given the neurotoxin 3-acetylpyrdine, which causes degeneration of the olivocerebellar system, also have low levels of dopamine in the striatum.[44] In our study, OPCAand FA patients with severe ataxias had significantly lower CSF HVA values than those with mild-moderate ataxias (Table 2). Therefore, low CSF HVA is presumably secondary to changes in the cerebellum. SPECT findings showed that both FA and OPCA patients with cerebello to basal ganglia to cortical diaschisis have higher CSF HVA values than those without diaschisis, in whom the reduced cerebellar HMPAO uptake was limited to the cerebellar anatomic damage (Table 4). In crossed cerebellar to cerebral diaschisis, at the subcortical level, we found that remote reduced HMPAO uptake involved the basal ganglia but not the thalamus,[27,28] a result confirmed in other laboratories.[29,30] At the cortical level, diminution of HMPAO uptake is more pronounced in the frontal lobe and less so in the parietal lobe. The significance of these findings remains to be elucidated.

Kish et al[45] found normal serotonin but elevated 5HIAA levels in cerebellar cortex of patients with OPCA. Strazielle et al[46] found normal serotonin levels but evidence of degeneration of serotonin neurons in the brains of lurcher mutant mice, which are a model of OPCA. The decline in CSF 5HIAA we found is not as striking as that reported by Trouillas et al[40] but is in agreement with our preliminary findings.[2] In our FA patients, CSF 5HIAAvalues were lower than in the OPCApatients, which could be explained by the additional involvement of the brain stem. Thus, the low CSF 5HIAA may have been due to degeneration of serotonin neurons but the tendency for CSF 5HIAA and HVA levels to be correlated may have also contributed to this lowering.[47]

We found low CSF MHPG values in our OPCApatients, with a trend to low values in FA patients (Table 1), although levels in ARSAC patients were normal. Our data are consistent with those of Kish et al[48] who found a 40% decrease of noradrenaline in the cerebellum of 15 patients with dominantly inherited OPCA. While the noradrenergic system in the human cerebellum has been fully documented,[49] its possible role in cerebellar ataxias is not clear, although Watson and Elligott[50] found that cerebellar noradrenaline depletion is associated with impaired acquisition of specific locomotor tasks in rats.

In a previous study, we found normal blood thiamine but low CSF thiamine in FA and OPCA patients.[13] In the present study, we found severe CSF thiamine deficiency in all three groups of patients. Animal studies indicate the importance of thiamine in the cerebellum. In rats, the cerebellum, medulla and pons have the highest thiamine turnover rate in the central nervous system[34,51,52] and these are the first regions to develop lesions due to thiamine deficiency.[53] In the present study when FA and OPCA patients were analyzed together (Table 3), patients with severe cerebellar atrophy had significantly lower CSF thiamine values than those with mild-moderate atrophies but other variables were not specifically related to low thiamine levels. However, thiamine deficiency is associated with degeneration of serotonin neurons in rats[14,54] and we found that three out of five alcoholic patients with low CSF thiamine concentrations also had low CSF 5HIAA. When the patients were treated with thiamine, CSF 5HIAA was markedly increased in those three patients.[16] Thiamine deficiency also lowers brain noradrenaline in rats and CSF MHPG in humans,[9,10] although no effects on dopamine have been reported. Therefore, some of the lowering of CSF 5HIAAand MHPG may have been secondary to thiamine deficiency.

Various replacement therapies have been tried in heredo-degenerative ataxias. The serotonin precursor, D-L-5-hydroxytryptophan, has produced variable results,[55-57] while the serotonin$_{1A}$ agonist buspirone has achieved some success in patients with OPCAand cerebellar cortical atrophy.[58,59] We have used the dopamine releaser amantadine hydrochloride in both FA and OPCA. Improvement was mild in FA but striking in OPCA patients.[60,61] Given that amantadine can block NMDA receptors[62,63] and can prevent NMDA receptor-mediated neurotoxicity,[64] this may have contributed to its action. Thiamine has not been tested, but probably should be. If it has an effect, some combination of thiamine with potentiation of serotonin and dopamine function may be best for symptom alleviation.

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