Significantly lower levels of hypoxanthine and creatinine in the CSF of patients with schizophrenia
Abstract

Levels of hypoxanthine, xanthine, uric acid (UA), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and creatinine were measured in the cerebrospinal fluid (CSF) of 49 patients with schizophrenia and 21 healthy controls. Twenty-six of the patients were first admissions who had never received antipsychotic treatment. We found significantly lower levels of hypoxanthine in the CSF of the patients (p=0.02) – the mean±SD was 3.09±0.57 µmol/l for controls and 2.72±0.69 µmol/l for patients with schizophrenia. Female schizophrenics had significantly lower levels of creatinine in their CSF than controls (p=0.01) – the mean±SD was 3.04±0.56 µmol/l for female controls and 2.67±0.74 µmol/l for females with schizophrenia. There were also numerous positive correlations between the substances in the CSF. But these positive correlations between metabolites in the CSF need to be interpreted with caution as it could be caused by a similar grade of dilution.

The finding of lowered levels of hypoxanthine in schizophrenia is interesting in the light of the purine hypothesis of schizophrenia – which proposes that schizophrenia, at least in part, may be caused by an imbalance in adenosine signaling. But also because of the recent interest the xanthine-oxidase inhibitor, and hypoxanthine isomer, allopurinol has gained as an adjuvant treatment in schizophrenia.

Sammanfattning

Koncentrationen av hypoxantin, xantin, urat (UA), homovanillinsyra (HVA), 5-hydroxyindolacetat (5-HIAA) och kreatinin i cerebrospinalvätskan (CSF) uppmättes hos 49 patienter med schizofreni och hos 21 friska kontroller. Tjugosex av patienterna var nyinsjuknade och hade aldrig behandlats med antipsykotika. Vi fann signifikant lägre nivåer av hypoxantin i ryggmärgsvätskan hos patienterna (p=0.02) – medelvärdet±SD var 3.09±0.57 µmol/l hos kontrollgruppen och 2.72±0.69 µmol/l hos patienterna med schizofreni. Kvinnor med schizofreni hade signifikant lägre nivåer av kreatinin i sin ryggmärgsvätska jämfört med kvinnor i kontrollgruppen (p=0.01). Medelvärdet±SD var 3.04±0.56 µmol/l hos kvinnor i kontrollgruppen och 2.67±0.74 µmol/l hos kvinnorna med shizofreni. Vi fann också flera signifikanta positiva korrelationer mellan ämnen i ryggmärgsvätskan. Dessa fynd måste dock tolkas med stor försiktighet då det kan orsakas endast av en gemensam spädningsnivå.

Att patienter med schizofreni har lägre nivåer av hypoxantin isin ryggmärgsvätska är intressant med tanke på purinhypotesen – som föreslår att störningar i adenosinsignaleringen åtminstone till viss del kan liga bakom schizofreni. Nivåer av hypoxantin är också värda att studera då allopurinol, en hypoxantin-isomer och xantin oxidas-hämmare, har prövats och visat effekt i behandlingen av schizofreni.
Significantly lower levels of hypoxanthine and creatinine in the CSF of patients with schizophrenia

**Introduction**

Schizophrenia is one of the leading causes of morbidity in the world. According to the WHO schizophrenia is the 8th leading cause of Disability-Adjusted life years in people 15-44 years old. (1) It causes a lot of suffering for both patients and relatives – illustrated by the fact that active schizophrenia was ranked the health state with the highest disability weight in a recent Lancet article. (2) Despite many decades of research and hundreds of thousands of publications the pathophysiology of schizophrenia remains unclear and findings have often been discrete. These findings point towards a complex aetiology with hereditary and environmental factors interacting in promoting the disorder. (3)

Symptoms in psychotic disorders (including e.g. bipolar disorder and schizophrenia) can be classified into 5 categories: I) Positive symptoms – delusions and hallucinations II) Negative symptoms – encompassing lack of drive and motivation III) Cognitive impairment – loss of executive functions and memory difficulties IV) Manic symptoms V) Depressive symptoms. Schizophrenia is characterised by symptoms from the first three of these groups and differentiates itself from the other psychotic disorders through less affective dysregulation. (4) According to numerous models schizophrenia could be considered as a systemic disease which majorly affects the brain. A number of neurotransmitters have been found altered in the schizophrenic brain and both dopaminergic, serotonergic, glutamatergic, cholinergic and GABAergic models have been used to explain the diverse symptoms seen in schizophrenia. (5) Dopamine is the main target for current treatment in schizophrenia and all antipsychotics acts by blocking dopamine receptors. (4) Though relatively effective against the positive symptoms in schizophrenia they are ineffective against cognitive deficits and negative symptoms. (6) This is in line with increasing evidence that negative symptoms may be caused by a hypodopaminergic state in the prefrontal cortex (7) contrary to the hyperdopaminergic state in the basal ganglia which is thought to cause the positive symptoms. (8)

**Purines**

Purines have multiple biologically fundamental roles – they are a crucial component of cells DNA and RNA, they supply the cell with energy in the form of ATP and GTP. Beside this purine receptors are
evolutionary old and widely distributed in the human body – especially the nervous system. The diverse role of purine signalling can be understood by the fact that ATP functions as a cotransmitter in all nerves in the central and the peripheral nervous system. Purinergic receptors are classified into two types based on what substance acts as the main effector – P1 receptors (with adenosine as main effector) and P2 receptors (which reacts mainly on ATP). Adenosine has an important role as neuromodulator in the release of multiple other neurotransmitters. For example does the adenosine receptor A1 seem to inhibit the release of all classical neurotransmitters and the A2A-receptor interacts with the dopamine D2-receptor which is also the main target of antipsychotic medications. Nucleotide signalling is also present early in embryonic neurodevelopment and has numerous effects on neurogenesis, plastic remodelling and regeneration later in life.

A purinergic hypothesis of schizophrenia was first laid forward by Lara et al. in 2000. According to this theory an imbalance in the purinergic system would result in reduced adenosinergic activity which could explain for the imbalance in both dopaminergic and glutamatergic neurotransmission. It could also explain the neuro-immunological findings in schizophrenia. The hypothesis is mainly built upon the fact that allopurinol as adjuvant therapy significantly improved symptoms in patients with poorly responsive schizophrenia. Allopurinol – which is otherwise mostly used in the treatment of gout and hyperuricaemia – is a hypoxanthine isomer and acts as a xanthine oxidase inhibitor in the body thus reducing formation of uric acid. According to Brunstein et al. the first psychiatric symptom which was treated with allopurinol was aggressive behaviour in dementia. The idea came from the fact that Lesch-Nyhan disease, a disorder of purine metabolism, is characterised by mental retardation, self-mutilation and aggressive behaviour.

Attached to this study is a mapping of the purine metabolism from the impressive Kyoto Encyclopaedia of Genes and Genomes. Metabolites analysed in this study is marked on the map in red, adenosine in green and xanthine-oxidase, the therapeutic goal of allopurinol, in blue. The picture also illustrates the complexity of metabolomics research and all the possible genes that could play a role in shifting a transmitter balance.

**Two-hit model and dopamine**

Lara et al. present a two-hit model of schizophrenia which is consistent with the widely accepted neurodevelopmental model. They postulate that increased levels of adenosine pre- and perinatally have neurotoxic effects and can lead to defective neurodevelopment due to aberrant glutameric transmission. The increased concentrations of adenosine can also cause a loss of adenosine A1-receptors which leads to the hyper-dopaminergic state in young adults - due to loss of inhibition. This view is supported by an experiment where mice 3-14 days old treated with an A1 adenosine
receptor agonist caused a reduction in $A_1$ receptor expression. The treatment also caused white matter reduction, ventriculomegaly, axon volume reduction and neuronal loss(21) - a picture in some ways similar to findings in patients with schizophrenia.(22) The idea that $A_1$-receptor expression contribute to schizophrenia receives some support in a recent genetic study which link certain $A_1$ receptor gene (ADORA1) polymorphisms to the disorder.(23)

Adenosine, glutamate and inflammation
Apart from dopaminergic receptors adenosine also modulates glutamergic signalling in the brain which according to Boison et al.(15) could give an explanation to the altered glutameric transmission seen in schizophrenia. They propose that an altered adenosinergic signalling could inhibit NMDA-receptors (the main excitatory receptor of glutamate) in hippocampal regions which is believed to play a role in the cognitive symptoms seen in schizophrenia. This hypothesis gains some support from a recent study showing that transgenic mice with overexpression of adenosine kinase (the key enzyme of adenosine clearance) – leading to lower levels of adenosine – cause attentional impairments linked with schizophrenia.(24)

That there is an altered inflammatory response in schizophrenia is indicated by the strong negative correlation between schizophrenia and rheumatoid arthritis.(25) In light of the increasing interest in inflammations role in neuropsychiatric diseases purine signalling is also of interest since adenosine is a potent regulator of neutrophil and monocyte function as well as a vasodilator and anti-inflammatory agent.(26)

Previous findings
Hypoxanthine and xanthine are end products in the catabolism of adenosine. The concentrations of these metabolites in cerebrospinal fluid (CSF) have been shown to correlate with a number of psychiatric and neurologic diseases. One study found significantly increased levels of xanthine in patients with dementia of Alzheimers type(27) and both hypoxanthine and xanthine have also shown correlation to certain psychiatric variables in patients with major depressive disorder.(28)

Concentrations of purine metabolites in plasma have been studied by Yao et al.(29) which have shown significantly higher levels of xanthosine and lower levels of guanine in patients compared to healthy controls. It is however difficult to draw conclusions about the concentrations of these metabolites in the brain since plasma levels can be significantly lower than CSF-levels.(30) While Lara et al.(5) emphasizes purines regulatory and neurodevelopmental role Yao et al.(31) focus on the purine metabolisms role in the antioxidant defence system. Levels of purines have also been measured in urine without finding any significant differences between patients and controls.(32)
**Aim of this study**

The object of this study is to explore if there are differences in the concentrations of purine metabolites in the CSF of patients with schizophrenia and if these concentrations correlate with concentrations of monoamine metabolites. We expect to find similar correlations as in the above mentioned plasma studies.

**Method**

This study was carried out on data collected among schizophrenic patients at Uppsala University Hospital between 1980 and 1984.

Cerebrospinal fluid was collected by lumbar puncture and the levels of homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), xanthin, hypoxanthin, creatinine and uric acid (UA) were measured in 49 patients with schizophrenia diagnosed using DSM-III. Of these 26 were first admissions who had never received neuroleptic treatment and the remaining were patients in relapse and had been off antipsychotic medication for at least two weeks. The control group consist of 21 healthy volunteers without history of psychiatric disorder or family history of schizophrenia and took no regular medication (except for oral contraceptives in seven females).

The lumbar puncture was performed in a standardized way between 8 and 9 a.m. with the person in a sitting position. 18 ml of CSF was taken, immediately centrifuged at 1.000 g for 10 minutes at ambient temperature, decanted, well mixed and thereafter divided into 1 ml-aliquots. The sample was placed in -20°C within 20 minutes and in -80°C within 3 hours until assayed. There were no restrictions of physical activity or food intake before the procedure. The control subjects were, contrary to the patients, not hospitalized the night before the lumbar puncture.

The CSF was analysed for hypoxanthine, xanthine, creatinine and UA by means of a reversed phase high performance liquid chromatography (HPLC) using a UV-absorbance detector as described by Niklasson et al.(33) Assays for HVA and 5-HIAA were performed according to Swahn et al.(34) using a HPLC equipped with a multiple ion detector.

**Statistical analyses**

The statistical analyses were carried out using R Commander, an open source graphical interface of the R programming language for statistical computing. The two groups were compared in terms of sex, age, length and weight. We also checked if there were differences between the first admission patients and the relapse patients. Levels of metabolites were checked for non-normality using Shapiro-Wilk’s test with a confidence level of p<0.1. The distribution was also visually examined.
through histograms. Correlations between metabolite concentrations and physical characteristics (height, weight and age) were tested using Spearman rank-order on all the data, both patients and controls. Correlations between metabolites were checked using Pearson product moment or Spearman rank-order as appropriate of complete pairwise observations both in the patient group and in the control group. P-values of all metabolite correlations were adjusted using Holm’s method. Levels of metabolites were compared using Welch t test or Wilcoxon rank sum test as appropriate. Concentrations of metabolites were compared both between patients and controls and between patients without previous treatment and patients who previously had received neuroleptic drugs. To adjust for group differences in height, weight and sex an ANCOVA was carried out for each of the metabolites.

**Results**

A finding of lower levels of HVA and no difference in levels of HIAA in patients with schizophrenia has previously been reported from this patient material, why this is not discussed further here.(35)

There were no major differences between controls and schizophrenic patients in terms of age, weight or height. There was a larger proportion males in the patient group. (Data on weight and height were missing for 2 of the controls and 2 of the patients.)

| Table 1 – Comparison of age, weight, height and sex of patients and controls. |
| Age (years) | Weight (kg) | Height (cm) | Sex |
|__________|_________|___________|______|
| Mean | SD | n | Mean | SD | n | Mean | SD | n | Male | Female |
| Controls | 26.6 | 8.7 | 21 | 67.0 | 10.5 | 19 | 173 | 8.7 | 19 | 9 | 12 |
| Schizophrenics | 26.6 | 5.2 | 49 | 68.0 | 12.3 | 47 | 176 | 8.7 | 47 | 35 | 14 |

There were no major differences between first-episode patients and patients in relapse.

| Table 2 – Comparison of age, weight, height and sex in first episode patients and patients in relapse. |
| Age (years) | Weight (kg) | Height (cm) | Sex |
|__________|_________|___________|______|
| Mean | SD | n | Mean | SD | n | Mean | SD | n | Male | Female |
| First episode | 25.0 | 3.7 | 26 | 64.8 | 10.2 | 25 | 176 | 10.2 | 25 | 18 | 8 |
| Relapse | 28.5 | 6.0 | 23 | 71.7 | 13.6 | 22 | 176 | 7.0 | 22 | 17 | 6 |

Among the controls all metabolites except creatinine had normally distributed concentrations – p>0.1 in Shapiro Wilks normality test. But as can be seen in the histogram below creatinine was also
quite normally distributed. In the patient group all metabolite concentrations except HVA and UA were normally distributed according to Shapiro Wilks test. But as the histograms below indicate these were also quite normally distributed. We conclude that the data fit the normality assumption and that it can be compared using Welch two sample t-test.

![Histograms of metabolites](image)

Figure 1 – Histograms of the metabolites whose concentrations were non-normal according to Shapiro-Wilks normality test, p>0.1.

Correlations between metabolites and physical characteristics (age, weight and height) were calculated in both the patient group and the control group using Spearman rank-order between pairwise complete values (n=18-21 in the control group; n=46-49 in the patient group). In the control group there were significant correlations between height and urate (r_s=-0.50; p=0.03). In the patient group there were significant correlations between age and HVA, age and UA, height and HIAA, height and UA, weight and HIAA, and weight and UA. (see table 3)

Table 3 – Correlation between physical characteristics and metabolites in the patient group.
* = p<0.05, ** = p<0.01

<table>
<thead>
<tr>
<th>Correlation – Patients</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman rank-order</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIAA</td>
<td>-0.02</td>
<td>-0.39**</td>
<td>-0.45**</td>
</tr>
<tr>
<td>HVA</td>
<td>-0.34*</td>
<td>-0.24</td>
<td>-0.20</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>-0.07</td>
<td>-0.10</td>
<td>-0.21</td>
</tr>
<tr>
<td>Xanthine</td>
<td>-0.10</td>
<td>-0.08</td>
<td>-0.25</td>
</tr>
<tr>
<td>UA</td>
<td>0.37**</td>
<td>0.30*</td>
<td>0.30*</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-0.10</td>
<td>0.26</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Correlations between metabolites were calculated using Pearson product-moment with p-values adjusted using Holm’s method for complete pairs (n=20-21 in the control group and n=48-49 in the patient group). Among the controls there were significant positive correlations between HVA-
creatinine, HVA-xanthine, hypoxanthine-xanthine and creatinine-xanthine. (see table 4) In the patient group there were significant correlations between HIAA-HVA, HIAA-hypoxanthine, HIAA-xanthine, HVA-hypoxanthine, HVA-creatinine, HVA-xanthine, hypoxanthine-creatinine, hypoxanthine-xanthine and creatinine-xanthine. (see table 5)

Table 4 - Correlations between metabolites in the control group using Pearson R. P-values were adjusted using Holm's method. *=p<.05; **=p<.01

<table>
<thead>
<tr>
<th>Correlations controls</th>
<th>HIAA</th>
<th>HVA</th>
<th>Hypoxanthine</th>
<th>Xanthine</th>
<th>UA</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIAA</td>
<td>1.00</td>
<td>0.53</td>
<td>0.39</td>
<td>0.46</td>
<td>-0.09</td>
<td>0.28</td>
</tr>
<tr>
<td>HVA</td>
<td>0.53</td>
<td>1.00</td>
<td>0.27</td>
<td>0.70**</td>
<td>-0.08</td>
<td>0.63**</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>0.39</td>
<td>0.27</td>
<td>1.00</td>
<td>0.61**</td>
<td>0.15</td>
<td>0.41</td>
</tr>
<tr>
<td>Xanthine</td>
<td>0.46</td>
<td>0.70**</td>
<td>0.61**</td>
<td>1.00</td>
<td>0.04</td>
<td>0.88**</td>
</tr>
<tr>
<td>UA</td>
<td>-0.09</td>
<td>-0.08</td>
<td>0.15</td>
<td>0.04</td>
<td>1.00</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.28</td>
<td>0.63**</td>
<td>0.41</td>
<td>0.88**</td>
<td>0.08</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 5 - Correlations between metabolites in the patient group using Pearson R. P-values were adjusted using Holm's method. *=p<.05; **=p<.01

<table>
<thead>
<tr>
<th>Correlations Patients (Pearson R)</th>
<th>HIAA</th>
<th>HVA</th>
<th>Hypoxanthine</th>
<th>Xanthine</th>
<th>UA</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIAA</td>
<td>1.00</td>
<td>0.50**</td>
<td>0.62**</td>
<td>0.50**</td>
<td>-0.01</td>
<td>0.29</td>
</tr>
<tr>
<td>HVA</td>
<td>0.50**</td>
<td>1.00</td>
<td>0.59**</td>
<td>0.50**</td>
<td>-0.27</td>
<td>0.43*</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>0.62**</td>
<td>0.59**</td>
<td>1.00</td>
<td>0.75**</td>
<td>0.06</td>
<td>0.58**</td>
</tr>
<tr>
<td>Xanthine</td>
<td>0.50**</td>
<td>0.50**</td>
<td>0.75**</td>
<td>1.00</td>
<td>0.24</td>
<td>0.67**</td>
</tr>
<tr>
<td>UA</td>
<td>-0.01</td>
<td>-0.27</td>
<td>0.06</td>
<td>0.24</td>
<td>1.00</td>
<td>0.30</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.29</td>
<td>0.43*</td>
<td>0.58**</td>
<td>0.67**</td>
<td>0.30</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Using Welch two sample t-test we compared the concentrations of metabolites between patients and controls, and between first-episode schizophrenic patients and previously medicated patients.

There were no significant differences in metabolite concentrations between previously medicated and drug-naive patients.

There were no significant differences in levels of xanthin, creatinine or urate between patients and controls. (Differences in levels of HVA and HIAA in this material is reported elsewhere.(35)) Patients with schizophrenia had significantly lower levels of hypoxanthine in their CSF (t=2.37, p=0.02); the
mean±SD was 3.09±0.57 for controls and 2.72±0.69 for patients with schizophrenia. The differences were as large among the females as among the males.

To identify differences between the groups masked by differences in height, weight and sex an ANCOVA was carried out for all the metabolites. The expression used was ‘metabolite ~ height + sex + type + weight’. Doing this the difference in concentration of hypoxanthine between patients and controls remained significant (p=0.03). The ANCOVA also showed significantly lower levels of creatinine in the patient group compared to the control group when ruling out height, weight and sex differences (p=0.03). The difference in concentration is only seen among the females.

Figure 2 – Box plot and plot of means comparing levels hypoxanthine between patients and controls, and between males and females. The whiskers in the plot of means indicate standard errors.

Figure 3 – Boxplots and plot of means comparing levels of creatinine patients and controls, females and males, and between female patients and female controls. Whiskers in the plot of means indicate standard errors.
Doing a Welch Two Sample test we saw that the female patients have significantly lower levels of creatinine compared to female controls. \((t = 2.76 \ p = 0.01)\); the mean±SD was 3.04±0.56 for controls and 2.67±0.74 for patients with schizophrenia.

**Discussion**

**Hypoxanthine**

Significantly lowered levels of hypoxanthine in CSF in patients with schizophrenia have not previously been reported. Studies of plasma and urine have not found any differences between patients with schizophrenia and controls.\((29)\) (32) The cause of this finding is still a matter of speculation. Hypoxanthine is known to be a marker of disturbed energy metabolism in the brain. This is due to the fact that it reflects degradation of high energy phosphates (e.g. ATP)\((36)\) and can be increased more than 10-fold in case of ischemia.\((37)\) In a study of patients suffering a number of neurological diseases - multiple sclerosis, myelopathy, stroke, epilepsy and viral meningitis – one found 2-3 fold increases of hypoxanthine. Stover et al.\((36)\) interpreted this as a marker of glutamate-mediated excitotoxicity as glutamate cause increased ATP-consumption.

Hypoxanthine could possibly have a role in protecting the brain against hypoxic events. This has been shown through administration of hypoxanthine to rabbits subjected to hypoxia which significantly improved their brain recovery.\((38)\) Hypoxanthine may have this effect through inhibiting xanthine oxidase that may play a role in forming oxygen reactive compounds in case of metabolic stress. A deficiency in hypoxanthine may increase stress vulnerability and explain the therapeutic improvements reported by Brunstein et al.\((16)\) when complimenting treatment with allopurinol, a hypoxanthine isomer. It would be bold to draw conclusions about levels of adenosine from our data. Lower levels of hypoxanthine could either be a sign of less adenosine signalling and that it thus is less adenosine that can be metabolized to hypoxanthine; or it could be a sign of less degradation and thus higher concentrations of adenosine in the brain.

**Creatinine**

Lowered concentrations of creatinine in the CSF of patients with schizophrenia have previously been reported by Swahn et al.\((39)\) They have also showed that levels of creatinine increased with neuroleptic treatment. As opposed to this study they did not find any differences due to sex either in the control group or in the patient group. We do not have any good explanation for the difference seen, in this study, between males and females in the patient group. Creatinine may, just as
hypoxanthine, be an indicator of the brain's energy metabolism as it is formed when cells catabolize creatine-phosphate. CSF levels together with blood levels can be a measure of blood-brain barrier permeability\(^{(40)}\) – why blood samples taken at the time of the lumbar puncture would add an interesting aspect to this finding.

Contrary to Yao et al.\(^{(29)}\) this study showed no correlation between urate levels and levels of hypoxanthine or xanthine. Both of these findings need to be interpreted with caution as they may not properly represent levels of extracellular metabolite levels in the brain. \(^{(30)}\)\(^{(41)}\) It is also difficult to know whether a deviant concentration of a substance is caused by an altered transmitter turnover in the brain or an altered transport of the substance across the blood-brain barrier – which can be either a cause or an effect of the disease.

The fact that both this study and Yao’s study only found positive correlations between metabolites should lead to very careful interpretation of these findings as they can be solely a sign of degree of dilution. It is to be expected that a fluid with higher concentration of one protein have higher concentrations of other proteins as well. A negative correlation would be easier to interpret as a sign of metabolic interaction.

**Conclusion**

There were lowered concentrations of hypoxanthine and creatinine in cerebrospinal fluid in patients with schizophrenia compared to controls. There were also numerous positive correlations between metabolite concentrations. Both these findings may be due to a more diluted CSF in patients with schizophrenia. The finding of lowered levels of hypoxanthine in schizophrenia is interesting in the light of the purine hypothesis of schizophrenia. But also because of the recent interest the xanthine-oxidase inhibitor allopurinol has gained as an adjuvant treatment in schizophrenia.

Future research needs to validate these findings making use of the progress seen in metabolomic biochemistry methods in the last 20 years. It would be interesting to study the metabolomic profile of persons with high risk of schizophrenia to identify differences between those who do not develop and those who do develop schizophrenia. The purinergic hypothesis of schizophrenia offers a new approach in understanding the symptoms of schizophrenia – how it develops and possibilities for new treatments. However – many parts of the theory still needs to be proved: for example could PET with radioligand-studies explore if there is lower concentrations of A1 adenosine receptors in patients with schizophrenia, and adenosine modulating medication needs to prove its place in schizophrenia treatment.
Referenser


35. Lindström LH. Low HVA and normal 5HIAA CSF levels in drug-free schizophrenic patients compared to healthy volunteers: Correlations to symptomatology and family history. Psychiatry Res. 1985 Apr;14(4):265–73.


