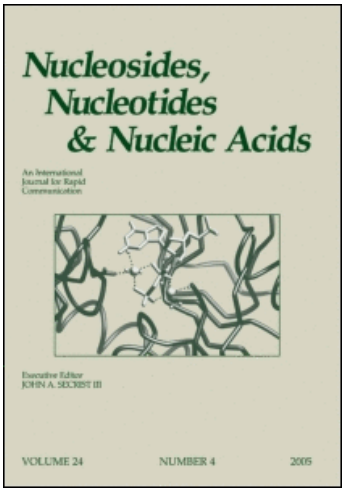

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Urate Oxidation in CSF and Blood of Patients with Inflammatory Disorders of the Nervous System

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ABSTRACT

Urate is largely excluded from the brain under non-inflammatory conditions (concentration gradient serum:CSF about 10:1), but increases markedly in Guillain–Barré Syndrome and bacterial meningitis. The oxidation product allantoin is normally not passively distributed between blood and cerebrospinal fluid (gradient 3:1) and increases 5-fold in CSF of patients with meningitis. Patients with multiple sclerosis had normal levels of urate and allantoin in blood and CSF.

Key Words: Allantoin; Blood-brain barrier; Meningitis; Multiple sclerosis; Urate.

INTRODUCTION

Several types of disorder of the nervous and central nervous system (CNS), including bacterial meningitis, Guillain–Barré Syndrome (GBS) and multiple sclerosis (MS), are linked to inflammatory processes. In the case of idiopathic paresis of the facial nerve (facial palsy), inflammation is generally thought to be involved (Table 1). Furthermore, meningitis and MS are accompanied by disturbances of the blood-brain barrier (BBB), and the blood-nerve barrier (BNB) is affected in GBS and facial palsy (Table 1).

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Table 1. Characteristics of neurological diseases investigated in the present study with respect to urate metabolism (BCSFB = blood-cerebrospinal fluid barrier, BNB = blood-nerve barrier).

Disease	Facial palsy	Guillain–Barré syndrome	Multiple sclerosis	Bacterial meningitis
Inflammation	(+) (facial nerve)	+ (spinal roots and peripheral nerves)	+ (brain and spinal cord)	+++ (CSF)
BCSFB/BNB	(+)	++	(+)	+++
Disturbance	(BNB and, to some degree, BCSFB)	(BNB and BCSFB)	(BCSFB)	(BCSFB)
Oxidative stress	Unknown	+	+	+++

Inflammation should give rise to enhanced oxidative stress in the nervous system, causing changes in the levels of antioxidants and formation of characteristic degradation products in the cerebro-spinal fluid (CSF). Urate is considered to be an important neuroprotective antioxidant in man, a specific product of oxidation being allantoin.[1,2] To evaluate the relative magnitude of cerebral oxidative stress, the levels of urate and allantoin were compared quantitatively in CSF and blood serum of controls (patients with non-inflammatory neurological conditions, such as migraine and tension-type headache), and patients suffering from bacterial meningitis, facial palsy, GBS or MS. Especially the latter were of interest, because this neurological disease has been associated with low levels of urate in serum and CSF.[3,4] Determinations in both compartments, blood and CSF, subserved the purpose of evaluating the integrity of the BBB.

MATERIALS AND METHODS

All samples were obtained primarily for diagnostic purposes after patients gave informed consent. Samples of blood serum and CSF were deproteinated with perchloric acid and the supernatants employed for determination of urate and allantoin by high pressure liquid chromatography, details of which have been given previously.[1,5]

RESULTS

The levels of urate in serum were within the normal physiological range of 200–400 μM for the control, facial palsy and GBS groups (see Table 2) and, unexpectedly, also in the case of the patients with MS. Patients with bacterial meningitis tended to have slightly lower serum urate levels, but this was not statistically significant.

Patients with an intact blood-brain barrier obviously exclude urate from the cerebral compartment (CSF/serum concentration ratio approx. 0.14 in controls). However, the levels of urate differed in CSF of the various groups, with significantly higher values found in the samples from patients with GBS (2 fold rise) and meningitis (4–5 fold rise). Again, patients with MS did not differ significantly from controls.

Table 2. Levels of urate and allantoin in CSF and serum, and the ratio of CSF vs. serum concentrations.

Controls (26)	Facial palsy (11)	Guillain–Barré syndrome (18)	Multiple sclerosis (18)	Bacterial meningitis (15)
Urate [μM]				
CSF: 25 ± 15	29 ± 14	52 ± 47*	18 ± 7	125 ± 87[#]
Serum: 214 ± 80	288 ± 113	236 ± 111	238 ± 63	196 ± 126
Ratio: 0.14 ± 0.13	0.10 ± 0.04	0.54 ± 1.38*	0.08 ± 0.04	1.2 ± 1.7[#]
Allantoin [μM]				
CSF: 7.5 ± 4.0	5.3 ± 3.0	11.8 ± 8.2	6.8 ± 4.4	41.3 ± 18.9[‡]
Serum: 22 ± 11	20.1 ± 8.6	26 ± 16.8	21.3 ± 10.7	53.4 ± 22.5[‡]
Ratio: 0.41 ± 0.26	0.34 ± 0.26	0.7 ± 0.7	0.39 ± 0.28	1.1 ± 1.4[#]

Mean values ± SD.
*$p < 0.05$ vs. control and MS (Kruskal–Wallis One Way ANOVA on Ranks).
[#]$p < 0.05$ vs. all except GBS.
[‡]$p < 0.05$ vs. all other groups.

As listed in Table 2, the distribution of urate between serum and CSF was quite distinctive: low CSF values in controls, facial palsy and MS (about 10–30 μM, i.e., 10–15% of the serum levels), moderately elevated levels in GBS (about 50 μM, corresponding to a mean distribution ratio between CSF and serum of about 0.5), and very high levels, almost at equillibrium with serum, in meningitis (distribution ratio slightly above 1). However, 5 of the 15 patients with bacterial meningitis had CSF urate levels even exceeding those of serum. Thus, at least some of the CSF urate had to be of central origin. This conclusion is supported by the absence of any correlation between CSF urate and serum urate in all groups. Thus, in meningitis and GBS, disruption of the BBB alone is not sufficient to cause an increase of CSF urate.

Allantoin was present in all samples tested (Table 2), controls having serum levels of 10–30 μM and significantly less in CSF (5–10 μM, $p < 0.05$). Levels of allantoin found in serum and CSF of patients with meningitis were 3–5 fold higher than in the three other groups. The mean distribution ratio of allantoin between CSF and serum increased significantly from 0.4 (controls) to 1.1 in meningitis, suggesting that the enhancement of oxidative processes was greater in the intra- than in the extracerebral compartment.

There was no correlation between CSF allantoin and serum allantoin in the control group ($r = 0.014$), and not even in the case of meningitis ($r = 0.12$), showing that allantoin is not passively distributed across the BBB. Surprisingly, CSF allantoin was also not correlated to CSF urate in controls ($r = 0.24$) and in meningitis ($r = 0.13$), demonstrating independence of urate oxidation from the ''substrate'' concentration. In other words, there is always sufficient urate present to cover oxidative reactions.

DISCUSSION

In conclusion, the brain relies relatively little on uric acid to protect itself from oxidative stress under normal conditions. In the special case of bacterial meningitis, and

perhaps also GBS, additional uric acid is recruited as antioxidant. Only some of this urate seems to stem from the blood compartment via passive leak; additional formation from catabolism of nucleotides, nucleosides and purine precursors within the cerebral compartment must also contribute to the rise in CSF levels. In accordance with the expectations based on the severity of oxidative stress in the various forms of neurological disorders investigated, more urate is associated with more of the oxidation product allantoin in the CSF on a group average basis. However, this does not hold true for individuals on an intragroup basis, presumably because CSF urate levels are multifactorially determined (passive leak, catabolic formation, oxidative degradation) and are always high enough to saturate oxidative reaction kinetics.[2] Finally, we were unable to substantiate the occurrence of low urate levels in MS: neither the serum nor the CSF urate level of MS patients was lower than in controls. This may have been due to the fact that our patients presented with relatively mild expression of disease (Expanded Disability Status Scale EDSS = 1.5–4.0).[4] Indeed, we saw no evidence for enhanced oxidative stress in the group.

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