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Caspase-1 levels in biological fluids from patients with multiple sclerosis and from patients with other neurological and non-neurological diseases

Abstract

In multiple sclerosis (MS), pathological white matter damage in the central nervous system is sustained by immune-inflammatory response. Caspase-1 plays a pivotal role in immune-mediated inflammation, as it regulates the cellular export of IL-1beta and IL-18. We carried out a preliminary in vitro study of the

kinetics of extracellular caspase-1 release. We then measured caspase-1 levels in paired serum and cerebrospinal fluid (CSF) samples of 75 MS patients, 15 healthy subjects, and patients with other neurological diseases. Paired synovial fluid and serum samples of patients with juvenile idiopathic arthritis, and paired sputum and serum samples of asthma patients were also studied. Mean serum caspase-1 concentrations did not differ between groups. Caspase-1 was detected in the CSF of patients with acute, but not stable, MS [7.5 ± (SEM) 0.9 pg/ml; test's sensitivity, 56% and specificity, 100%]. Its levels correlated with pleocytosis. The highest mean caspase-1 levels were found in the arthritic synovial fluids (945.5 ± 126.6 pg/ml, which correlated with erythrocyte sedimentation rate), and in the sputum samples (370.1 ± 71.0 pg/ml, which correlated with the number of macrophages in the sputum). On condition that caspase-1 is determined in the fluids pertaining to the disease-specific inflammatory sites, its level is a reliable marker of ongoing immune-inflammatory response. The enzyme measurement in CSF can also help define state-trait in MS.

Full text

INTRODUCTION

Caspase-1, formely IL-1beta converting enzyme (ICE) [1], belongs to a family of proteases (caspases), which cleaves substrates at sites with aspartate in the P1 position. Caspases can activate a signalling cascade that leads to cell apoptosis [2]. However, caspase-1 is more involved in inflammation than in apoptosis. Caspase-1 yields to the active form of IL-1beta [1], and activates the so-called IFN-gamma-inducing factor (IL-18) [3], a fundamental polypeptide in the induction of Th1 cells along with IL-12 [4]. Th1 cells induce IL-1beta production upon intermonocyte contact [5], thus yielding a reverberating circuit. IFN-gamma, in turn, strongly activates monocytes, increases their antigen-presenting capacity, and stimulates the production of proinflammatory cytokines [6]. Finally, monocytes from caspase-$1^{-/-}$ mice export neither IL-1alpha nor IL-1beta, and only diminished amounts of IL-6 and TNF-alpha [7]. All these data indicate that caspase-1 can trigger both innate and adaptive immunity, by exploiting the functional potentialities of IL-1beta and IL-18 on lymphocytes and monocytes.

Th1 response, which is typical of diseases in which macrophages are the main effectors of pathological damage, is characterised by release of IFN-gamma and IL-2 by T lymphocytes, and IL-1beta by monocyte/macrophages [1]. Multiple sclerosis (MS) is a chronic-inflammatory, immune-mediated disease of the central nervous system (CNS), in which non-antigen specific lymphocytes and macrophages are ultimately responsible for demyelination and axonal loss [8]. Therefore, Th1 response, together with the correlated proinflammatory cytokines, fosters the pathogenic processes that lead to MS lesions, although MS cannot be considered a prototypical Th1 disease [8]. Caspase-1 is likely to play a pivotal role in the regulation of these processes.

We had previously studied the modifications of caspase-1 mRNA levels in MS [9] and in its animal model, experimental autoimmune encephalomyelitis (EAE) [10]. The aim of the present study was to determine extracellular caspase-1 levels in biological fluids in MS and in other neurological and non-neurological inflammatory diseases. The latter diseases include juvenile idiopathic arthritis, a clear-cut Th1-type inflammatory disease, and asthma, a Th2-type disease in which, however, IFN-gamma is a pathogenetically important cytokine [11]. Our aim was to evaluate the possible practical use of circulating caspase-1 levels as an inflammatory marker of disease. Caspase-1 acts intracellularly. Given the scarcity of information about circulating caspase-1, we carried out a preliminary *in vitro* study of the kinetics of intracellular production and extracellular-released concentrations of the enzyme. To this end, we used THP-1 cells, which constitutively produce caspase-1.

PATIENTS AND METHODS

Cell culture

THP-1 cells were cultured in RPMI-1640, supplemented with 10% FBS, 2 mM L-glutamine, 100 mug/ml streptomycin, and 100 U/ml penicillin, in 5% CO_2 at 37° C. Stimulation of the cells is not required to produce caspase-1 [12]. Before the culture, the cells were synchronised by serum deprivation for 24 hours. Flasks, with approximately 20 x 10^6 cells/flask, were processed at time 0, or at 24 hours, at 48 hours, or at 72 hours, to obtain supernatants and cell lysates.

Preparation of THP-1 cell lysates

Cytosolic extract of THP-1 cells were prepared as previously described [12]. The cells were washed in PBS, then suspended in a hypotonic buffer (25 nM HEPES, pH 7.5, 5 mM $MgCl_2$, 1 mM EDTA), and broken with a homogeniser with proteinase inhibitors (PMSF, pepstatin, leupeptin). After centrifugation, 6 mM EDTA was added to the supernatant, which was, in turn, sequentially centrifuged to remove granules and microsomal membranes. The supernatant was dialyzed overnight at 4° C against 25 mM HEPES, pH 7.5, 10% sucrose, 0.1% CHAPS, and 2 mM DTT, and stored at - 80° C.

Patients with MS

Paired serum and CSF samples were obtained from 75 patients with relapsing-remitting MS, 25 in an active, and 50 in a stable phase of the disease [54 females, 21 males; mean ± SD age, 38 ± 11 years (range, 23-64); mean disease duration, 8 ± 7 years (range, 0.5-23); mean EDSS [13], 2.5 ± 1.6 (range, 0.5-6.0)]. All the patients: a) had definite MS [14]; b) were not under chronic therapy with immunomodulatory drugs (various formulations of IFN-beta or glatiramer acetate); c) had not received immunosuppressive agents for at least 3 months before the study; and d) were studied within two weeks of the onset of symptoms (acute MS), or at least 2 months after the end of an exacerbation (stable MS). Exacerbations had one or other, or both, of the following characteristics: one or more new symptoms; worsening of pre-existing symptoms, where the worsening lasted more than 24 hours but less than 4 weeks, and excluded any sign of spontaneous improvement.

Control groups

Normal and neurological controls consisted in 15 orthopaedic patients without inflammatory disease, who underwent epidural anaesthesia; 10 patients with non-inflammatory neurological diseases (Alzheimer's disease, 5; Parkinson's disease, 3; amyotrophic lateral sclerosis, 2); and 10 patients with other inflammatory neurological diseases (Guillain-Barre syndrome, 5; HIV-1 encephalitis, 3; HSV-1 encephalitis 2).

Non-neurological controls included paired serum and synovial fluid (SF) of 18 children with juvenile idiopathic arthritis [15]. All patients had active disease defined, in accordance with the presence of synovitis upon examination. SF samples, collected at the time of intra-articular steroid injection, were kept on

ice, centrifuged at 4° C (1,000 g for 10'), and the supernatants centrifuged again (10,000 g for 10').

Sputum samples were taken, by means of a standard procedure [16], from 13 asthma patients [17], 8 of whom also suffered from atopy. In five of the latter, peripheral blood samples were available. All the patients were in a chronic phase of the disease, and were not under corticosteroid therapy.

Routine analyses

Erythrocyte sedimentation rate (ESR) and serum C reactive protein were determined. CSF analysis included cell count, isoelectric focusing for the search for oligoclonal immunoglobulin bands, and the evaluation of blood-brain barrier permeability and of intrathecal IgG production [18]. The biological fluids were stored at - 70° C until tested.

ELISA for caspase-1

Caspase-1 was measured with a commercial ELISA, in accordance with the manufacturer's instructions (Bender MedSystems, Vienna, Austria). The kit employs a monoclonal antibody that recognises both the p45 precursor form and the enzymatically active p10:p20 complex of caspase-1. The kit includes a secondary, polyclonal anti-caspase-1 antibody (rabbit), and a peroxidase-linked, anti-rabbit IgG antibody. The detection limit was 5 pg/ml. Within-run coefficient of variation was 6.1%, and between-run 7.8%. Sera were tested undiluted, or post-diluted when necessary. SF samples were diluted 1:5 in sample diluent. Minor modifications were made to test caspase-1 concentrations in sputum and in CSF samples. Sputum samples were collected in dithiothreitol (Sputolysin, Calbiochem, San Diego, CA, USA, which, had been diluted 1:10 in H_2O, and then 1:2 in PBS, immediately before use), final concentration of 1:20. To obtain sample-specific standard curves, caspase-1 standards were diluted 1:20 in dithiothreitol for sputum enzyme determinations, or in a pool of CSF from healthy subjects with no inflammation for CSF measurements. The within- and between-run coefficient of variations for these modified tests did not exceed 10%.

Statistical analysis

Data are reported as means ± standard error (± SEM). The non-parametric Mann-Whitney U-test was employed for the comparison of the mean data between groups. Spearman rank correlation between quantitative variables was also used. A *p*-value lower than 0.05 was considered significant.

RESULTS

Figure 1 shows the parallelism between caspase-1 levels in the medium and in the THP-1 cell lysates. The intracellular production of the enzyme reached its maximum at 2 days, and decreased thereafter. LPS-stimulated monocytes showed similar parallelism and kinetics (data not shown).

Mean serum caspase-1 concentrations (values in pg/ml) did not differ between groups (healthy controls, 58.2 ± 10.2; MS, either acute, 76.7 ± 8.6, or stable 65.2 ± 7.0; non-inflammatory neurological diseases, 57.1 ± 10.4; other inflammatory neurological diseases, 78.2 ± 18.2; juvenile idiopathic arthritis, 341.0 ± 81.0; asthma, 72.2 ± 17.5). Caspase-1 was detectable (7.5 ± 0.8) in 14/25 CSF samples of acute MS patients, and not in those of stable patients (test's sensitivity, 56%, and specificity, 100%). These CSF levels correlated with pleocytosis (Figure 2), but not with the indexes of blood-brain barrier permeability, or intrathecal immunoglobulin synthesis. Detectable CSF caspase-1 levels were also found in HIV-1 encephalitis (12.3 ± 2.6).

Mean caspase-1 levels in SF (945.5 ± 126.6) and sputum (370.1 ± 71.0) samples were higher than those in the respective sera ($p < 0.05$), without reciprocal correlation; SF levels correlated with ESR in juvenile idiopathic arthritis ($r = 0.53$, $p = 0.02$), and sputum levels with the number of macrophages in asthma ($r = 0.57$, $p = 0.04$). In juvenile idiopathic arthritis, serum C reactive protein levels tended to correlate with SF caspase-1 levels ($r = 0.45$, $p = 0.06$). Figure 3 summarises caspase-1 levels in the biological fluids from the groups studied. Eosinophils, whether in the peripheral blood of juvenile idiopathic arthritis patients, or in the sputum of asthma patients, showed a trend of inverse correlation with caspase-1 levels in the serum of the former group, and in the sputum in the latter group (data not shown).

DISCUSSION

We show that the intracellular, pro-inflammatory key-enzyme caspase-1 can be detected extracellularly in various biological fluids. In an *in vitro* study, we found that parallel increases in caspase-1 concentrations can be detected in both the supernatants and cell lysates of THP-1 cells. These findings indicate that the measurement of the extracellular caspase-1 levels is a reliable index for its intracellular concentration. The ELISA, we used for both the *in vitro* and *in vivo* studies, employs a capture antibody for caspase-1 that recognises both the inactive p45 precursor and the active p10:p20 complex. Therefore, we also attempted to measure caspase-1 levels, in our samples, with two functional assays to verify if what we measured with ELISA had biological activity too. Both the fluorometric and pro-IL-1beta cleavage assays, which measure the caspase-1 ability to cleave respectively a fluorogenic substrate, or the precursor of IL-1beta [12], failed to detect any enzymatic activity even in the samples with the highest caspase-1 levels measured with ELISA (data not shown). However, in monocytes, the inactive form of caspase-1 is largely predominant, both in unstimulated and even in stimulated cells [19]. Thus, the amount of bioactive caspase-1 extracellularly released by mononuclear cells in overt inflammatory diseases might represent a minor part of total caspase-1, or could be susceptible, once released, to rapid disactivation by proteinases. In any case, we show that both the bioassays used were not sensitive enough to detect active caspase-1 in biological fluids from patients with important inflammatory stigmata.

Caspase-1 was detectable at amounts of picogram/milliliter in the sera from healthy individuals. In inflammatory diseases, this enzyme selectively increased in the biological fluids, which "drained" the disease-specific inflammatory sites. Indeed, in MS, caspase-1 was detectable only in the CSF of active patients, and, in juvenile idiopathic arthritis and in asthma, its concentrations were higher in SF and in sputum than in serum. CSF lymphomonocytoids and sputum macrophages likely contributed to caspase-1 increases in acute MS and chronic asthma. Mean serum caspase-1 levels in the three above-mentioned pathologies did not differ from those in healthy controls. The fact that SF caspase-1 correlated with erythrocyte sedimentation rate in juvenile idiopathic arthritis indicates that the enzyme tends to fluctuate concordantly with a generic marker of inflammation.

In a longitudinal study on MS, we have previously demonstrated that a) caspase-1 mRNA levels in peri-pheral blood mononuclear cells were higher before

exacerbations, and b) the magnitude of the increase correlated with the number of new CNS lesions [9]. These findings suggest that caspase-1 influences early inflammatory events in MS. We supported this hypothesis with a study on EAE [10]. The timing of sample collection (before *vs* during exacerbations) may explain the difference between what we previously found at mRNA level [9] and the present data, where we found unmodified caspase-1 concentrations in serum, but detectable concentrations in the CSF, in acute MS. These CSF levels imply an up-regulation, *via* IL-18, of IFN-gamma production. IFN-gamma is a pro-inflammatory, MS-exacerbating cytokine [8]. However, we recently showed that IFN-gamma can protect mice from EAE by promoting the apoptosis of pathogenetic T cells through the TNFR1 pathway [20]. Taken together, our previous and present data indicate that caspase-1 might play a dual role in MS, firstly in the initiation of the immune-inflammatory response, and secondly in the limitation of both the extension and duration of the response. These findings also challenge the concept that to deactivate caspase-1 tout-court means to cure IL-1beta/IFN-gamma-mediated diseases.

Our data on high caspase-1 levels in the SF in juvenile idiopathic arthritis, and in the CSF in HIV-1 encephalitis, are consistent with the enzyme hyper-expression described at the level of the respective affected tissues [21, 22]. In asthma, the high enzyme levels we found in sputum confirm the notion that Th2-induced airway hyper-reactivity is not down-regulated by Th1 effectors that, in turn, are responsible for severe airway inflammation [23].

CONCLUSION

In conclusion, the determination of caspase-1 with ELISA can be considered as a reasonably easy-to-perform, laboratory support for the identification of non-specific, ongoing inflammatory processes, on condition that determination is performed on the biological fluid pertaining to the lesioned tissue. In MS, the determination of caspase-1 in the CSF defines active disease with maximal specificity. Improvements in the analytical sensitivity of the test are expected to improve diagnostic sensitivity.

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Figures

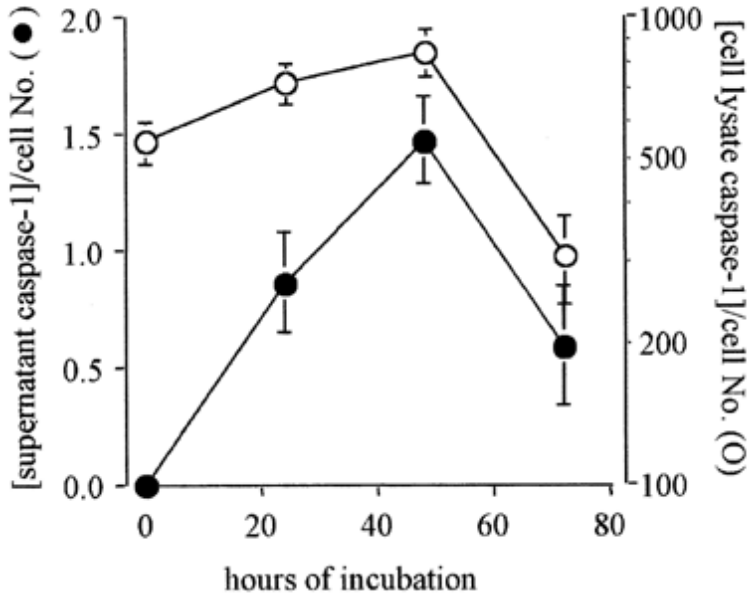


Figure 1

Caspase-1 is detectable in the supernatant of THP-1 cells (solid circles), and its amount is proportional to the intracellular concentration (open circles). THP-1 cells, once synchronised, were cultured unstimulated. Supernatant and cell lysate, obtained from one of the flasks at the various times, were tested in ELISA. Results are expressed as the ratio between caspase-1 concentration in either supernatant, or lysate, and number of the THP-1 cells. Values are the means of 2 experiments.

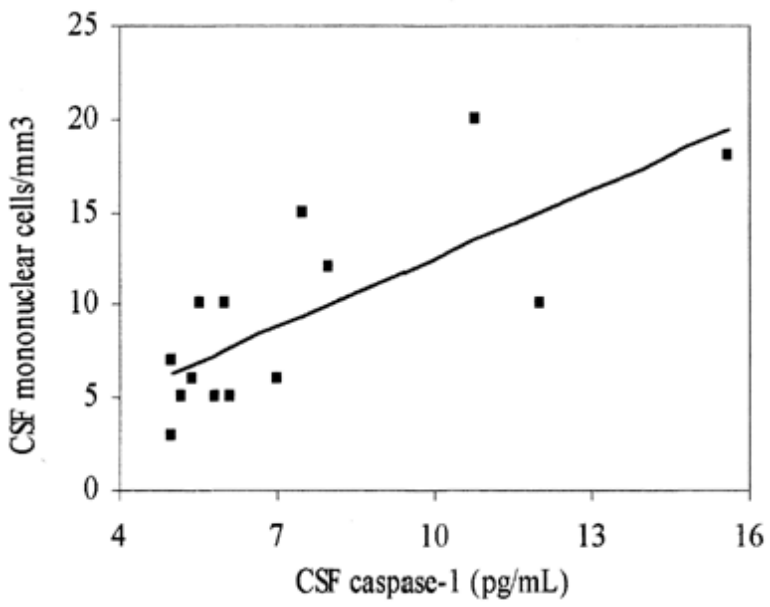


Figure 2
Caspase-1 concentrations *versus* mononuclear cells in the cerebrospinal fluid of patients with acute multiple sclerosis. The correlation was significant, r = 0.73, p = 0.004.

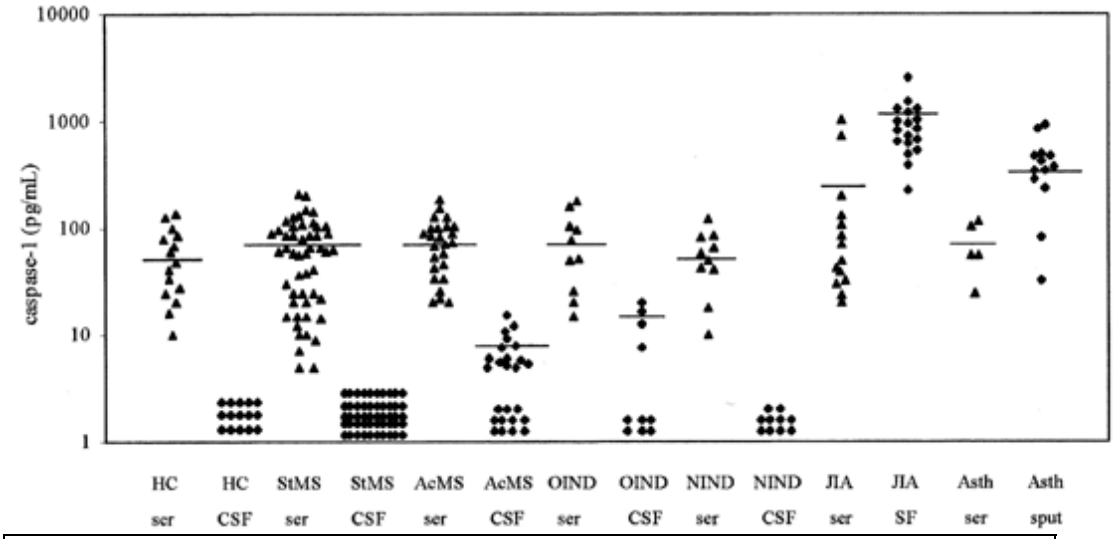


Figure 3
Caspase-1 concentrations in various biological fluids in multiple sclerosis (MS) patients and in controls. HC, healthy controls; StMS, stable MS; AcMS, acute MS; OIND, other inflammatory neurological diseases; NIND, noninflammatory neurological diseases; JIA, juvenile idiopathic arthritis; Asth, asthma; ser, serum; CSF, cerebrospinal fluid; SF, synovial fluid; sput, sputum. The test's detection limit was 5 pg/ml. Horizontal lines indicate mean values.

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CSF-1, tumour progression, metastasis, de-differentiation.

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IL-1beta, TNF-alpha, GM-CSF, neuron, mRNA, protein.

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