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Constitutive and visna virus induced expression of class I and II major histocompatibility complex antigens in the central nervous system of sheep and their role in the pathogenesis of visna lesions

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Expression of major histocompatibility complex (MHC) antigens was studied in the brains of 10 healthy sheep 2 months to 5 years old and 13 sheep infected with visna virus by intracerebral inoculation and killed one and 6 months post infection (p.i.). In healthy sheep there was prominent expression of class I, mainly on endothelial cells but also detected on ependyma, choroid plexus and in the leptomeninges. Class II expression was sparse. It was observed on perivascular cells, in choroid plexus, leptomeninges and on microglial cells in the white matter. No definite increase with age in the constitutive expression of class I and II was observed, confirming that we are dealing with a true constitutive expression. In visna-infected sheep a considerable induction of MHC antigens on microglia was observed, which correlated with severity of lesions and was mainly found in or adjacent to inflammatory infiltrates of the white matter. Increase in class II antigen expression was detected in all sheep but class I only in sheep with the most severe lesions 6 months p.i., an indication of a higher threshold for induction of class I than class II antigens on microglia. Few cells expressed viral antigens, indicating that direct immune-mediated destruction of infected cells plays a minor role in evolution of lesions. Since the preferential induction of MHC antigens on microglia in the white matter correlated with the lesion pattern, activated microglia may play a considerable role in the pathogenesis of lesions.

Keywords: Visna, ovine lentiviral infection, encephalitis, major histocompatibility complex antigens, immunohistochemistry

Introduction

Visna, a meningoencephalomyelitis of sheep, is caused by the visna strain of maedi-visna virus, the prototype lentivirus [32]. The virus is related to the human immunodeficiency virus type-1 (HIV-1) [34] and causes a systemic infection in sheep [27]. The host–virus interactions in visna show several features similar to those observed in early stages of infection with HIV-1 [11,28]. The main target cells in infection with visna virus are as in HIV-1 infection, monocytes/macrophages [23] but lymphocytes are in contrast to infection with HIV-1 apparently not permissive for visna virus and the infection does not cause an overt immunodeficiency.

The initial pathological alterations in the central nervous system (CNS) in visna are meningitis, periventricular

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inflammation and infiltration of the choroid plexus. The inflammation spreads to the white matter and may cause a prominent leukoencephalitis sometimes accompanied by liquefaction necrosis and secondary myelin-breakdown [10]. Occasionally at late stages of infection plaques of primary demyelination are observed [8]. The inflammatory infiltrates consist mainly of lymphocytes with some admixture of macrophages and plasma cells.

Sheep infected with visna virus mount a fairly good humoral and a variable cellular immune response [27,38]. The immune response does not clear the host of the infection, which persists throughout the life-span of the host. We have found evidence that the CNS lesions are immune-mediated and that the damaging immune response is apparently directed against viral antigens [28]. The cell-mediated immune response seems to play a key role with CD8 and CD4 positive lymphocytes as the main effector cells [38,43].

As CD8 positive lymphocytes recognize antigen presented by major histocompatibility complex (MHC) class I molecules and CD4 positive lymphocytes recognize antigen presented by MHC class II molecules, knowledge of their expression in the CNS is of importance for understanding of the immunopathological mechanisms in visna. Since expression of MHC class molecules has, except for our pilot study [38] and a study on class II expression on macrophages in the brain in visna [43], not been studied in the CNS of sheep, we explored in detail by immunohistochemistry expression of MHC class I and II molecules in the CNS. Brains of healthy sheep of different age were studied to establish the distribution and level of constitutive expression, an important parameter for understanding the intitial interaction of the immune response and the CNS in visna-infected sheep and a necessary baseline for the evaluation of induction of MHC molecules by infection with visna virus. For that purpose brains of sheep infected by intracerebral infection of visna virus were studied at different time points post-infection (p.i.) and the expression of MHC molecules was compared with the character and severity of pathological lesions.

Materials and methods

Animals and infection

To study constitutive expression of class I and II antigens, the brains of 10 normal, outbred Icelandic sheep from two months to 5 years old were removed immediately after exsanguination under Vetenarcol (Veterenaria AG, Zürich, Switzerland) anaesthesia.

To study the visna virus induced expression of class I and II antigens 13 outbred Icelandic sheep were infected with a biological [9] or molecular clone [3] of visna virus by intracerebral inoculation [31]. Five sheep were killed and examined 1 month and eight sheep 6 months p.i. The establishment of infection was confirmed by virus isolation and serology (data not shown).

The left half of the brain was fixed by immersion in 4% formaldehyde in PBS for histopathological evaluation of lesions and and 2–5 blocks were frozen immediately for immunohistochemistry.

Histology

Nine blocks from each brain were cut at standard levels, embedded in paraffin and sections cut at 3–5 μm thickness. The sections were stained with haematoxylin & eosin and Klüver-Barrera for myelin. Selected sections were stained for axons according to Bodian's method. The severity of lesions was graded on a scale of 0–6 [27,39].

Immunohistochemistry

For immunohistochemistry two to five blocks from each brain were embedded in OCT medium (Tissue-Tek, Miles, USA) and frozen on dry ice or in liquid nitrogen. The two blocks included cerebral cortex, centrum semiovale, corpus striatum, lateral ventricle and sometimes choroid plexus. The additional blocks included cerebellum, brain stem, 4th ventricle and sometimes choroid plexus. Cryostat sections were cut at a thickness of 4–6 μm, mounted on gelatin coated glass slides and air-dried for 20 min. After some testing the following fixation methods were used:

(i) For staining with antibodies against class II antigens sections were fixed in acetone for 5 min at room temperature (RT).

(ii) For staining with antibodies against class I antigens sections were fixed in absolute alcohol for 10 min at 4 °C.

The following antibodies were used: mouse monoclonal antibodies (mABs) against sheep class I, clone SBU I, 41–19; [12] and class II, clone SBU II, 28–1; [29] antigens (Center for Biotechnology, University of Melbourne, Australia). Selected sections were also

stained for class II with mouse mABs, clone A32 (a generous gift from Dr W.R. Hein, Basel Institute for Immunology, Switzerland), clone vpm 36 and for class I with clone vpm 19 (a generous gift from John Hopkins, University of Edinburgh, UK). These antibodies were used undiluted. Selected sections were stained with mouse mABs against sheep CD4- and CD8-positive lymphocytes (Center for Biotechnology, University of Melbourne, Australia), rabbit antihuman von Willebrand factor, a marker for endothelial cells, anti-CD68, clone EBM11, a marker for macrophages (Dako AS, Denmark) and with mouse mABs against the p25 core protein of visna virus [9].

The immunolabelling was done according to the peroxidase–antiperoxidase (PAP) procedure [19] and/or Streptavidin-Biotin (Dako AS, Denmark) method according to instructions of the manufacturer. Controls for immunolabelling included substitution of the primary antibody by buffer or an unrelated antibody.

Results

Constitutive expression of MHC antigens

Constitutive expression of MHC class I antigens was very prominent, whereas class II antigen expression was sparse. Class I antigen was mainly detected in association with vessels and was especially prominent in cortex and other grey matter areas, whereas vessel-associated expression of class II was discrete and similar in grey and white matter (Figure 1). The pattern of the immunostaining differed in that staining for class I revealed a continuous ribbon-like pattern, very similar to that observed with staining with antibody to von Willebrand factor, whereas the vessel-associated expression of class II was discontinuous (Figure 1). The class II positive cells appeared to be perivascular in location and the pattern of staining was comparable with that obtained by staining with an antimacrophage antibody (Figure 1). Class I antigen was also detected on scattered perivascular cells.

In the choroid plexus class I and II antigens were detected on numerous cells in the stroma, i.e. elongated spindle-shaped or with ramified cytoplasmic processes and rounded to oval cells. By staining with antimacrophage antibody several positive cells of a round shape were detected (Figure 1). In sections stained for class I antigens the staining of cells in the stroma was to a considerable extent obscured by a prominent ribbon-like staining of vessels (Figure 1). Neither class I nor II antigens were detected on choroidal epithelial cells. Class I expression was detected on ependymal cells (Figure 1) in an irregular and patchy distribution, whereas staining for class II was negative.

In the leptomeninges both class I and II expression was detected. Class I expression was somewhat more pronounced, but the morphology of class I and II positive cells was similar to that observed in the choroid plexus. The antigen-positive cells were irregularly distributed in the meninges, some were in the adventitia of large vessels and some spindle-shaped elongated cells were closely applied to the surface of the brain, sometimes extending alongside vessels into the cortex.

A sparse and weak expression of class II was detected on glial elements in the white matter, which according to morphological critera were microglial cells (Figure 2). The class II positive cells were irregularly distributed in small foci in both cerebellar and cerebral white matter. Class I expression was not observed on microglia and neither class I nor II were detected on astrocytes, oligodendroglia or neurons.

The constitutive expression of class I and II antigens was found in all sheep studied. Except for some individual variation in class II expression on microglia the pattern and extent was similar in sheep of various ages.

Visna infected sheep: pathology and expression of MHC antigens

Typical CNS lesions were found in all cases, i.e. periventricular inflammation, frequently extending into adjacent white matter, inflammatory infiltrates of choroid plexus and meningitis. Myelin breakdown, partly of primary, partly of secondary type was observed in cases with the most severe lesions. The inflammatory infiltrates consisted mainly of CD4- and CD8-positive lymphocytes with some admixture of macrophages and plasma cells. The severity of lesions showed considerable variation, i.e. from grade 0.5–4.5 (data not shown).

Expression of class I MHC antigens in the neuroparenchyma was mainly observed on vessels and showed the same pattern and comparable extent in cortex and other grey matter areas as in normal sheep. There was a moderate increase in their expression on vessels in the white matter immediately adjacent to periventricular inflammatory infiltrates. In the inflammatory foci the

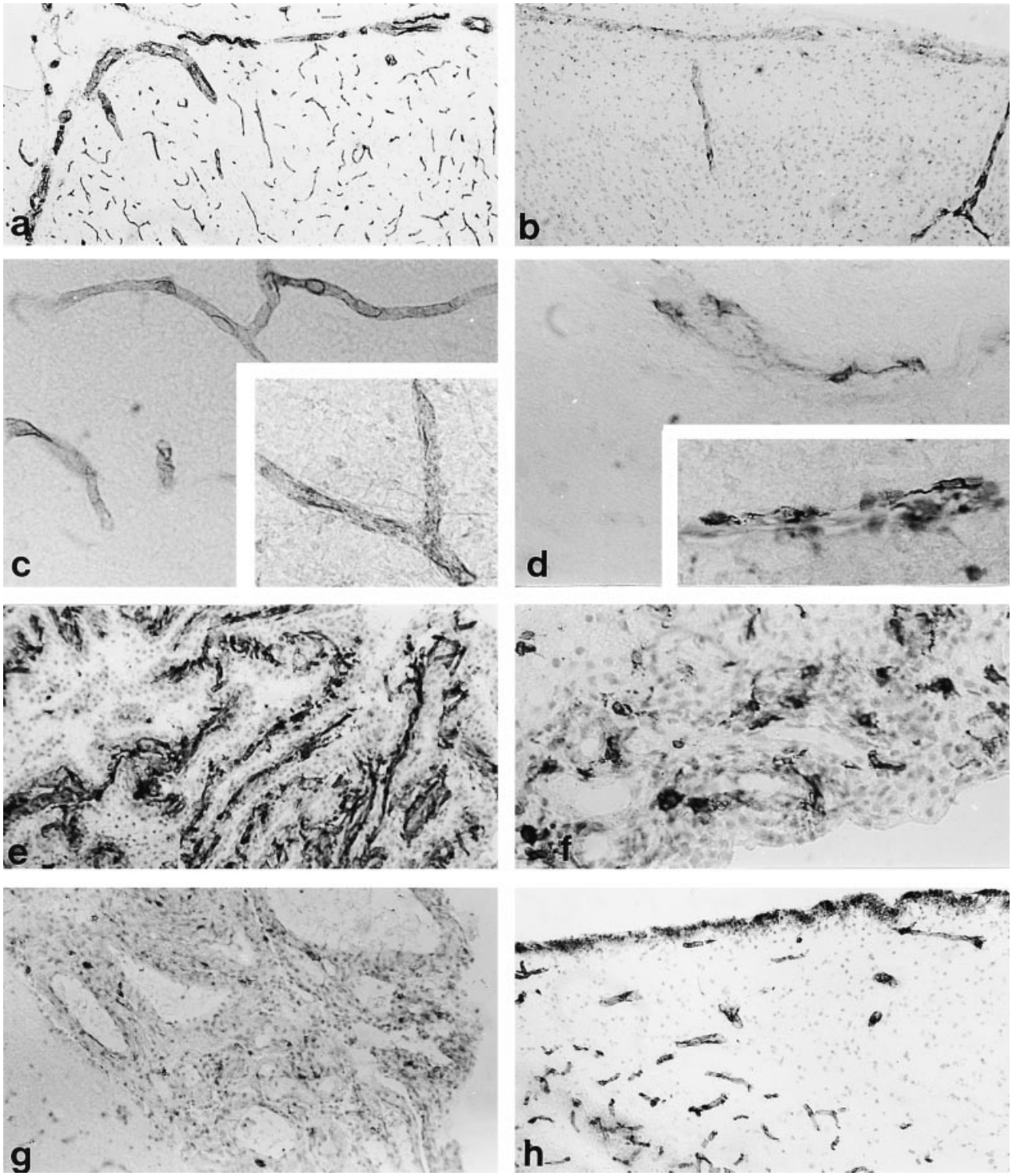

Figure 1. Immunostaining. Constitutive expression of MHC class I and II antigens: **a,** Class I expression on vessels in cerebral cortex, ×40; **b,** Class II expression on vessels in a corresponding area, haematoxylin counterstain, ×40; **c,** Higher magnification of vessel-associated class I expression in cerebral cortex, ×200. Inset: Endothelial staining with antivon Willebrand factor, ×320; **d,** Vessel-associated expression of class II. Inset: Perivascular cells stained with antimacrophage antibody, H. counterstain, ×320. **e,** Class I expression in choroid plexus, H. counterstain, ×80; **f,** Class II expression in choroid plexus, H. counterstain, ×200; **g,** Staining with antimacrophage antibody. Several positive cells in choroid plexus, H. counterstain, ×80; **h,** Class I expression on ependyma and vessels, H. counterstain, ×80.

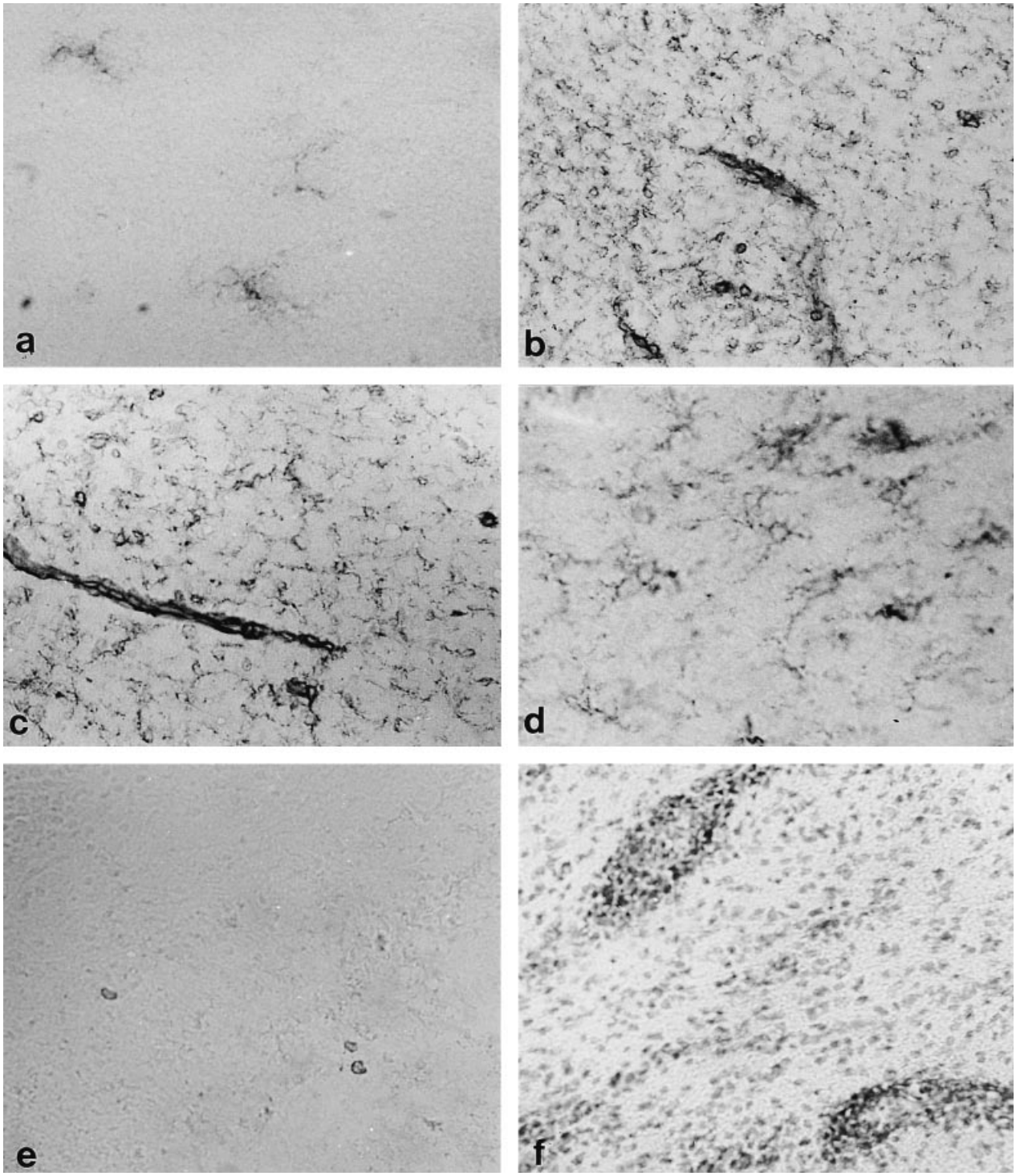

Figure 2. Immunostaining. **a,** Constitutive expression of class II on microglia in the white matter, × 380; **b,** and **c,** Visna-induced expression of class II (**b**) and class I (**c**) on microglia in the white matter adjacent to periventricular inflammation, × 200; **d,** higher magnification of class II positive microglia, × 380; **e,** 3 cells positive for visna viral antigen in periventricular inflammation, × 200; **f,** Haematoxylin staining of a corresponding area, × 200.

expression of class I antigens on resident cells was difficult to evaluate due to expression of class I on inflammatory cells in areas with diffuse infiltration or perivascular cuffing. In the meninges and choroid plexus increased expression was observed but this was mainly due to expression on rounded cells apparently inflammatory cells. The choroidal epithelial cells were negative. The ependyma was for the most part desquamated.

Expression of class I was not observed on glial cells in sheep killed 1 month p.i., but in five out of eight sheep killed 6 months p.i. class I antigen was detected on microglia (Figure 2). This expression was in general weak and mainly found in the white matter immediately adjacent to periventricular inflammatory infiltrates. In one case, however, with the most severe CNS lesions class I antigen expression was also observed on microglia in the deepest layers of cortex adjacent to inflammatory reaction in the subcortical white matter. The extent of expression of class I antigen on microglia correlated with the severity of CNS lesions.

Expression of class II MHC molecules was moderately increased on perivascular cells in the white matter immediately adjacent to periventricular inflammation. In the case with the most severe pathological lesions, increased expression was detected on vessels in the cortex, where the pattern was different, i.e. more ribbon-like, indicating an expression on endothelial cells. Ependyma was for the most part desquamated but in parts small clusters of class II antigen positive cells were detected. Except for expression on inflammatory cells in choroid plexus and leptomeninges, class II antigen expression was similar to that observed in healthy sheep.

A very marked increase of class II expression on microglial cells was observed in all sheep. This was especially prominent in sheep showing the most pronounced pathological lesions. This increase was most prominent in or adjacent to the periventricular inflammation (Figure 2) but extended far into the white matter even to subcortical areas in the gyri in cases with higher lesion grades. In sheep examined 6 months p.i. focal expression of class II antigens was observed in the white matter at some distance from the periventricular inflammation. In these foci either no or very sparse infiltration of inflammatory cells was detected. Although the main impact of class II expression was found in the white matter some expression of class II was detected in the basal part of cortex adjacent to inflammation in the subcortical white matter and in the superficial part of cortex adjacent to inflammatory infiltrates in the leptomeninges.

Neither class I nor class II antigens were detected on cells that could definitely be identified as astrocytes, oligodendroglia or neurons.

By staining with a monoclonal antibody for the core protein p25 of the visna virus, only few and scattered antigen-positive cells were detected in most cases. They were almost exclusively found in the periventricular inflammatory infiltrates (Figure 2).

Discussion

Constitutive expression of MHC molecules

We did not detect an age-dependent increase of MHC antigen expression, which suggests that we are dealing with true constitutive expression. Our results differ from reports on an increased expression of MHC with age in humans [30,33,36] and rats [26], but the apparent discrepancy may due the fact that our findings are based on relatively young animals.

The main pattern and extent of constitutive expression of MHC antigens in the CNS of sheep is similar to that described in other species [13,33,37,40,41]. There is, however, apparently some variation in the extent of MHC antigen expression and types of positive cells and in some studies, constitutive expression of either class I or II or both was not detected [15,17,22]. This may be due species variation but possibly also reflect methodical difficulties in the detection of MHC molecules, which depends on several factors such as the type and length of fixation, *post mortem* intervals and some clinical parameters such as accompanying systemic disorders [20]. In the present study we used healthy sheep 2 months to 5 years old that had been kept in the laboratory and never showed signs of intercurrent diseases. The brain was removed immediately after death and snap frozen and the type and length of fixation optimized.

The pattern of vessel-associated MHC antigen expression observed in our study, i.e. class I mainly on endothelial cells and class II on perivascular cells, is in accord with light microscopic and/or ultrastructural studies in rats [35,40,41] and humans [13,20,33,37]. The MHC antigen positive perivascular cells are according to our results by staining with a macrophage marker of the monocyte/macrophage lineage and may constitute a subset of microglia [16,18].

In sheep we did detect a similar pattern of MHC antigen expression on microglia, in meninges and choroid plexus as has been described in other species [13,20,35,40].

Induced expression of MHC molecules in visna

The main difference between normal and visna infected sheep was a very distinct upregulation of MHC class I and II molecules on parenchymal microglia in the white matter, which is similar to observations on class I and/or II expression induced by HIV-1 [1,5,15] and other viral infections in humans and rodents [2,17,22,41].

The expression of MHC molecules correlated with the grade of histological lesions and was most pronounced in or adjacent to inflammatory infiltrates, which are mainly composed of T-lymphocytes. Cytokines secreted by inflammatory cells and activated microglia [21] probably play a major role in the induction of MHC antigens. A unique IFN induced by interaction between lymphocytes and visna virus infected macrophages, which has been reported to induce class II molecules on macrophages in the CNS of goats infected with the related caprine-arthritis encephalitis virus, may also contribute [24,43]. The main localization of the MHC class I and II expression in the white matter is consistent with the drainage pattern of the interstitial fluid in the brain [42]. An interesting finding is that our results show that there is a higher threshold for the induction of class I than class II antigens on microglia. Thus induction of class I was first detected 6 months p.i. and only in five out eight sheep with the most severe lesions.

Pathogenesis of CNS lesions

The character of the pathological lesions in the CNS, as well as their severity was similar to that previously described in sheep infected with these biological [9] and molecular clones [3] of the visna virus.

The initiation and progression of lesion development in visna, when put in context with constitutive and induced MHC antigen expression and productively infected cells, may be envisaged as follows: latently infected monocytes may by 'Trojan horse' mechanism [14] carry infection into the CNS by migrating into the CSF through the choroid plexus as suggested in HIV-1 infection [7]. Upon differentiation to macrophages they sustain an active replication of the virus [6,43] and interact with the choroid plexus, meninges and ependymal lining, inducing meningitis, choroiditis and periventricular inflammation. An additional mechanism of lesion development may be disruption of the blood–brain barrier and influx of inflammatory cells through interaction of CD8 or CD4 positive lymphocytes and endothelial and/or perivascular cells coexpressing MHC class I and II molecules and viral antigen, a mechanism proposed for CNS lesions in dengue fever [25] and consistent with reports on productive infection of endothelial cells *in vitro* [43] and *in vivo* [9]. Once within the CNS compartment, activated CD8-and CD4-positive lymphocytes may kill target cells, i.e. productively infected cells expressing MHC antigens, by cytotoxic mechanisms or delayed hypersensitivity reaction. Since, however, relatively few cells are productively infected according to our present and earlier findings [9] compared with the extent of lesions in the CNS other more indirect mechanisms may play a considerable role, e.g. cytokines, superoxide and reactive nitrogen intermediates and proteases released by inflammatory cells but also activated microglia [4,5,21]. The activation of the microglia predominantly in the white matter coincides with the topography of lesions, i.e. the leukoencephalitis, indicating that they may play an important role in the progression of lesions.

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