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Immunophenotypic features of epiplexus cells and their response to interferon gamma injected intraperitoneally in postnatal rats

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ABSTRACT

The expression of major histocompatibility complex (MHC) antigens (class I and II), type 3 complement receptor (CR3) and leucocyte common antigen (LCA) was examined in epiplexus cells in rats of different ages. The cells exhibited intense immunoreactivity with the monoclonal antibody OX-42 which recognizes CR3 receptors. In early postnatal rats (1 d), the immunolabelled cells were mostly round but with increasing age (7 wk), they assumed a ramified or elongated form. The expression of LCA marked by the monoclonal antibody OX-1 followed a similar staining pattern. Class I MHC antigen expression was also demonstrated in some epiplexus cells using the monoclonal antibody OX-18 but they were less numerous than the OX-42 or OX-1 positive cells. Only sporadic OX-6 positive cells were observed in postnatal rats but they showed a marked increase in number in adult rats, suggesting an upregulation of class II MHC antigens with age. The expression of MHC class II antigens was vigorously elevated in postnatal rats receiving 6 successive intraperitoneal (i.p.) injections of interferon gamma (IFN-γ). In these animals, a large number of intensely stained OX-6 positive epiplexus cells were observed. These were mostly elongated or ramified with long processes. The immunostaining of epiplexus cells with OX-18 was also enhanced after IFN-γ injections but the expression of CR3 and LCA appeared to be unaffected. It is concluded that the expression of MHC class I and II antigens on epiplexus cells is upregulated and induced respectively after successive i.p. injections of IFN-γ into postnatal rats. The transformation of epiplexus cells from a predominantly round to a ramified form after application of IFN-γ suggests an activation of their functional activities involved in phagocytic activity, self-recognition and antigen presentation.

Key words: Choroid plexus; major histocompatibility antigens; complement receptor; leucocyte common antigen; lymphokines.

INTRODUCTION

The origin, nature and function of epiplexus cells associated with the choroid plexus have been the subject of many investigations since the first description of the cell type of Kolmer (1921). While much is known about their primary function as phagocytes (Carpenter et al. 1970; Hosoya & Fujita, 1973; Chamberlain, 1974; Allen, 1975; Sturrock, 1978, 1979, 1983, 1988; Ling, 1979, 1981, 1983; Ling et al. 1985, 1988; Maxwell & McGadey, 1988; Kaur et al. 1990; Maxwell et al. 1992; Lu et al. 1993*a*, *b*), little is known of their immunophenotypic features. This study was therefore undertaken to characterise the immunohistochemical properties of epiplexus cells in rats of different ages. We sought to determine if they display surface antigens, including complement type 3 receptors (CR3), leucocyte common antigen (LCA) and major histocompatibility complex (MHC) antigens known to be present on monocyte-derived cells. A further objective was to ascertain whether the expression of these surface antigens, if they were demonstrable on epiplexus cells, would be altered when treated with interferon gamma (IFN-γ) by intraperitoneal (i.p.) administration. This is because IFN-γ is known to be a potent inducer of MHC antigens, especially class II, for cells in brain both in vitro (Sasaki et al. 1989; De Groot et al. 1991) and in vivo (Steiniger & van der Meide, 1988; Vass & Lassmann, 1990). Our earlier studies (Lu et al.

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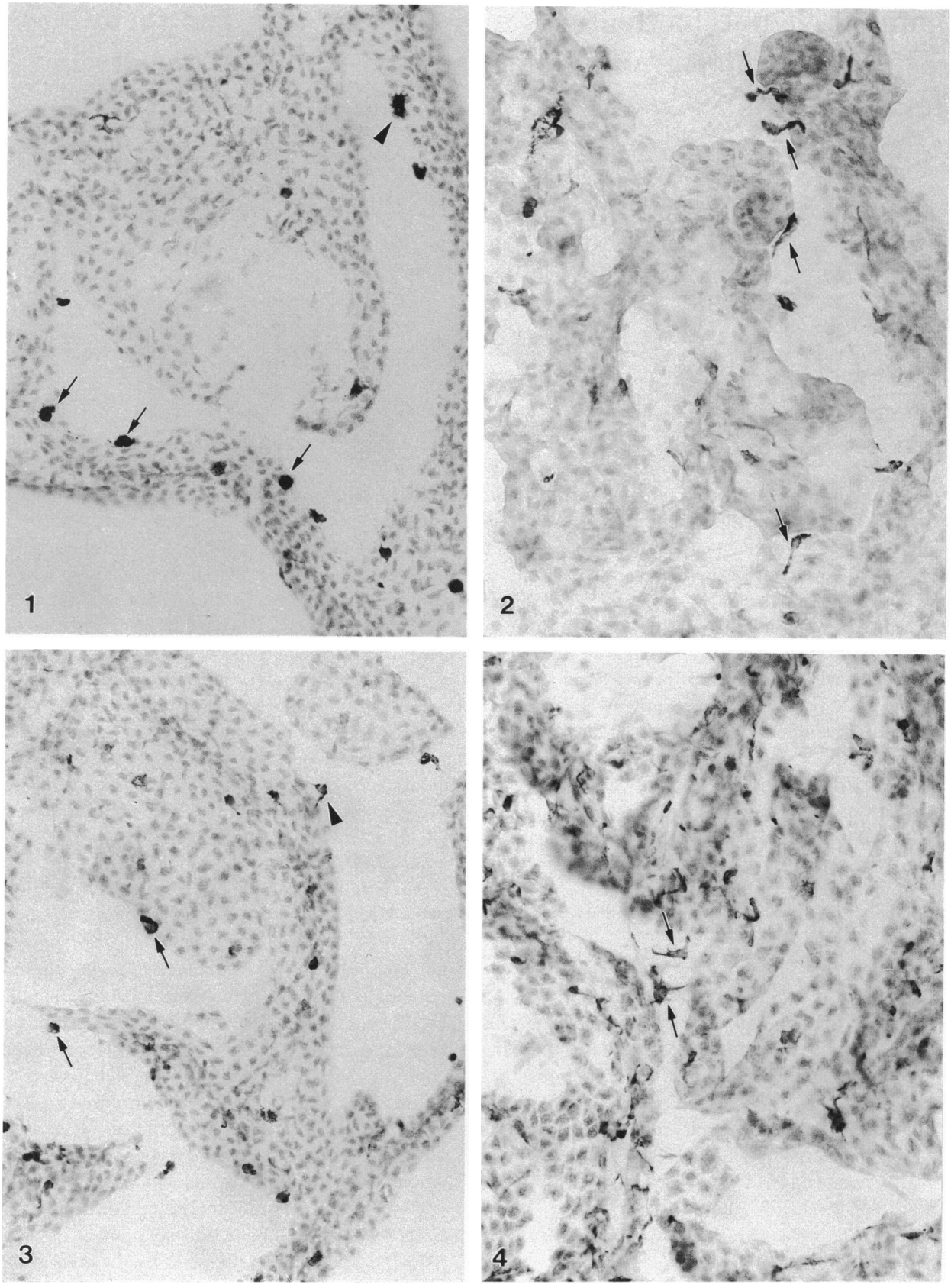


Fig. 1. OX-42 positive epiplexus cells (arrows) on the choroid plexus in the lateral ventricle in a 1-d-old rat. The stained cells are mostly round but a few display short stout processes (arrowhead).

Fig. 2. OX-42 positive epiplexus cells (arrows) in the lateral ventricle in a 7-wk-old rat. The stained cells are ramified or elongated.

1993*a*, *b*) had shown that foreign substances such as rhodamine isothiocyanate and horseradish peroxidase when introduced intraperitoneally readily cross the blood-cerebrospinal fluid (CSF) barrier to be taken up subsequently by the epiplexus cells. It was with this premise that IFN-γ was administered by i.p. injection in the hope that it would gain access to the CSF where the epiplexus cells would be exposed to and stimulated by the lymphokine.

MATERIALS AND METHODS

A total of 41 Wistar rats of either sex was used in this study. They were divided into 2 groups. (1) Normal immunohistochemistry: 16 rats aged 1, 7, 14 d and 7 wk were used. (2) IFN-γ injection: this group consisted of 25 rats aged 1 d. Under ether anaesthesia, the rats were given single daily i.p. injection of 10 μl of rat recombinant IFN-γ (10^5 U in 1 ml sterile distilled water; Gibco BrL, 3283 SA) for 3 or 6 consecutive days. Control rats received injections of an equal volume and frequency of sterile distilled water. The rats were killed 3 and 6 d after the 1st injection.

Under ether anaesthesia, rats from both groups were perfused with Ringer's solution until the liver and lungs were clear of blood. This was followed by an aldehyde fixative composed of a mixture of periodate-lysine-paraformaldehyde containing 2% paraformaldehyde according to the method of McLean & Nakane (1974). The perfusion lasted for 10–15 min. After perfusion, the brain was removed and was fixed in a similar fixative for another 2 h. The brain was kept in 0.1 M phosphate buffer containing 10% sucrose overnight at 4 °C. Frozen serial sections of the cerebrum which included the 2 lateral ventricles containing choroid plexus were cut at 40 μm and rinsed in phosphate-buffered saline (PBS). The sections were then incubated for 18–20 h at room temperature using one of the following monoclonal antibodies: OX-1 (Sera-Lab MAS 026b), OX-42 (Sera-Lab MAS 370b), OX-18 (Sera-Lab MAS 101b) and OX-6 (Sera-Lab MAS 043b) diluted 1:100 with PBS for the detection of leucocyte common antigens (LCA), complement type 3 receptors (CR3) and major histocompatibility complex (MHC) class I and II (Ia), respectively. Subsequent antibody detection was carried out by using the Vectastain ABC-kit (PK-4002, Vector Laboratories, Burlingame, CA) against mouse IgG (rat adsorbed) with 3,3′-diaminobenzidine (DAB, Sigma, 5637) as a peroxidase substrate, and intensified with nickel ammonium sulphate. The sections were counterstained with 1% methyl green, dehydrated and mounted in Permount.

RESULTS

Immunohistochemistry of epiplexus cells in normal rats

The epiplexus cells on the surface of the choroid plexus were strongly labelled with OX-42 in rats of different ages (Figs 1, 2). In 1-d-old rats, the majority of the immunostained cells were round although a few possessed short stout processes (Fig. 1). In 7-d-old rats, some of the stained cells became ramified or elongated. In 14-d-old rats, more ramified cells bearing a variable number of processes were observed. With advancing age, i.e. in 7-wk-old rats, the ramified or elongated epiplexus cells prevailed (Fig. 2).

The results with OX-1 paralleled those with OX-42. Epiplexus cells stained with OX-1 (Figs 3, 4) were observed in rats of different ages but their immunoreactivity was weaker when compared with the OX-42 positive cells.

The epiplexus cells in different aged rats also exhibited OX-18 immunoreactivity. In early postnatal (1 d) rats, the OX-18 positive cells were almost exclusively round (Fig. 5) but with increasing age, they assumed a ramified or elongated form (Fig. 6). The stained cells were less numerous than those stained with OX-42 or OX-1.

With OX-6, immunolabelled epiplexus cells was extremely rare in postnatal (1, 7 d) and developing (14 d) rats (Fig. 7). However, in adult rats (7 wk), there was a marked increase in the number of OX-6 positive cells (Fig. 8). They were generally ramified or elongated and their number was comparable to that of OX-42 or OX-1 positive cells of the corresponding age group.

Administration of IFN-γ

Three successive i.p. injections of IFN-γ. Following 3 successive i.p. injections of IFN-γ into 1-d-old rats, the number of OX-18 and OX-6 positive cells showed

Fig. 3. OX-1 positive epiplexus cells on the choroid plexus in a 1-d-old rat. The stained cells (arrows) are mostly round but a few display short stout processes (arrowhead) resembling the OX-42 positive cells illustrated in Figure 1.

Fig. 4. Choroid plexus in the lateral ventricle in a 7-wk-old rat. The ramified or elongated epiplexus cells (arrows) residing on the epithelium are strongly reactive with OX-1.

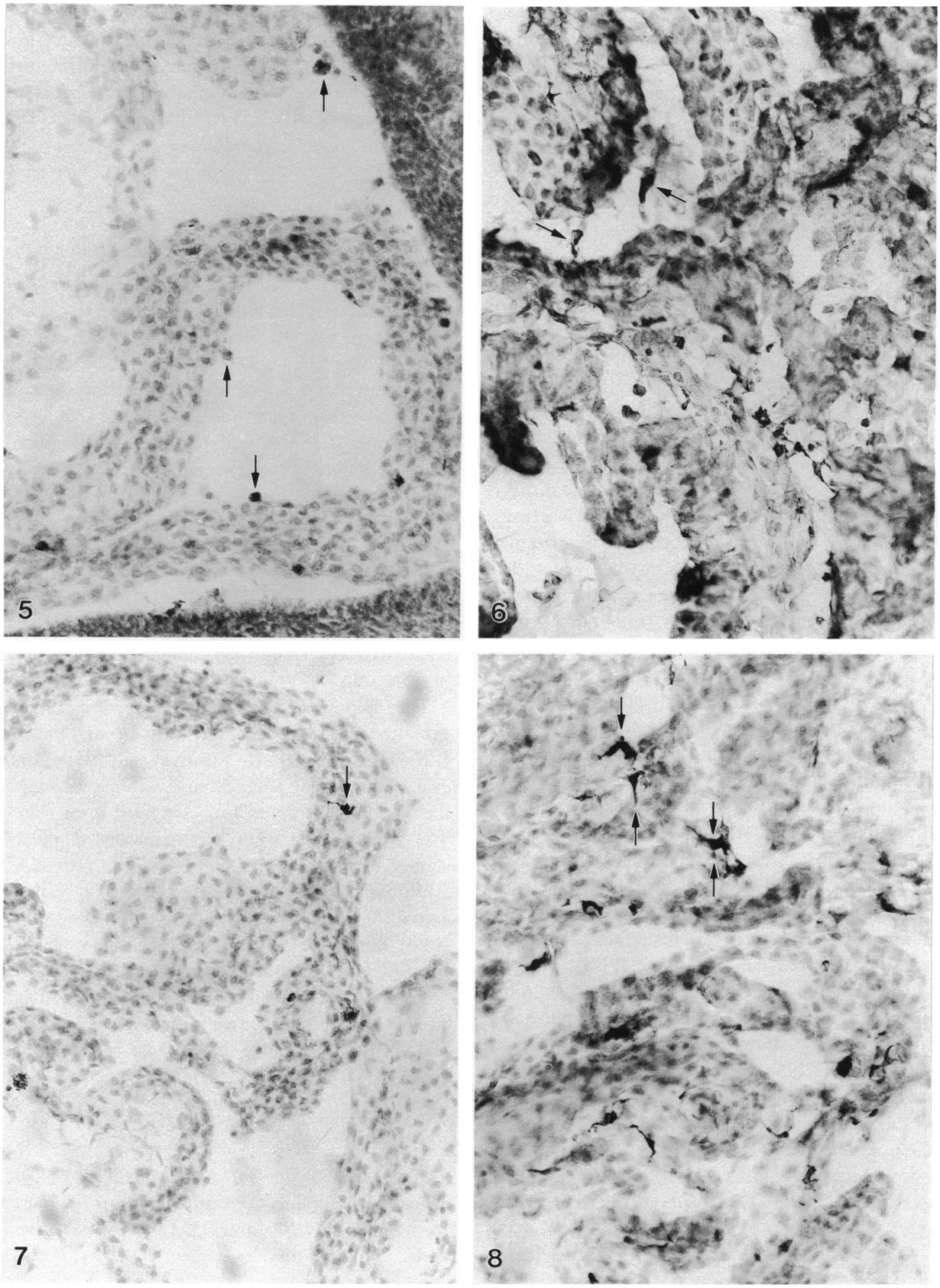


Fig. 5. Epiplexus cells (arrows) in a 1-d-old rat immunostained with OX-18. Note that the stained cells are round.

Fig. 6. Several ramified or elongated epiplexus cells (arrows) stained with OX-18 in a 7-wk-old rat.

Fig. 7. An epiplexus cell (arrow) immunostained with OX-6 in a 1-d-old rat.

Fig. 8. A few epiplexus cells (arrows) are immunostained with OX-6 in a 7-wk-old rat. All the stained cells are ramified or elongated.

a moderate increase. In the control rats, the number of the stained epiplexus cells was comparable to that of the normal animals. The immunostaining of epiplexus cells with OX-42 or OX-1 both in experimental and control rats showed no noticeable difference from that of the normal rats.

Six successive i.p. injections of IFN-γ. With OX-18, immunopositive epiplexus cells of the control rats were randomly distributed on the choroid plexus and they were mostly rounded (Fig. 9). Following 6 successive i.p. injections of IFN-γ, the number of the intensely stained cells appeared to have increased (Fig. 10). The stained cells became elongated and more ramified (Fig. 10). In addition, the blood vessels in the choroid plexus stroma were also intensely stained (Fig. 11).

With OX-6, only sporadic immunoreactive cells were observed on the choroid plexus in control rats (Fig. 12). Following IFN-γ injections, a large number of OX-6 positive epiplexus cells were observed on the choroid plexus (Fig. 13). Most of the intensely stained epiplexus cells were elongated or ramified, bearing long branching processes (Figs 13–15). Stromal macrophages in the connective tissue were also stained (Figs 13–15).

With OX-42, the epiplexus cells were strongly stained both in control (Fig. 16) and IFN-γ injected rats (Fig. 17); most of the stained cells were round. The immunoreactivity and the external morphology of the epiplexus cells in both groups of rats did not show any obvious difference.

Epiplexus cells were also intensely stained with OX-1 both in control (Fig. 18) and IFN-γ treated rats (Fig. 19). The number of immunoreactive epiplexus cells and their external morphology in the control rats (Fig. 18) were comparable to that of IFN-γ treated rats (Fig. 19).

DISCUSSION

The concept that the normal brain is an immunologically privileged site is no longer tenable. This is because the expression of MHC antigens has been demonstrated on microglia in normal human brain (Hayes et al. 1987) and also on the same cell type in inflammation (Weinstein et al. 1990; Mucke & Oldstone, 1992), experimental allergic encephalomyelitis (Vass et al. 1986), grafts (Poltorak & Freed, 1989; Finsen et al. 1991), experimentally induced neurodegeneration (Akiyama et al. 1988; Streit et al. 1989; Morioka & Streit, 1991; Kaur & Ling, 1992), neurodegenerative disorders such as multiple sclerosis (Woodroofe et al. 1986) and Alzheimer's disease (McGeer et al. 1987, 1993), and after treatment with IFN-γ (Steiniger & van der Meide, 1988; Sethna & Lampson, 1991; DeGroot et al. 1991; Colton et al. 1992). In contrast to the brain parenchyma, relatively little is known about the MHC bearing cells in the ventricular system apart from the observations of Matyszak et al. (1992) and Perry et al. (1993) who described the presence of numerous class II (Ia) positive cells, primarily stromal macrophages, in the choroid plexus of normal adult rats and mice. Sasaki & Nakazato (1992) also described expression of MHC II antigen in vascular cells and macrophage-like cells in choroid plexus stroma in normal human brain.

The present study demonstrated a considerable expression of MHC encoded antigens (class I and II) on epiplexus cells in adult rats. This leads us to propose a possible immunoregulatory role for them in the ventricular system. The expression of MHC molecules is essential in the process of antigen recognition by cytotoxic and helper T cells. It is known that class I MHC antigen serves as the restriction element for T cytotoxic/suppressor lymphocytes while class II MHC antigens are required for the presentation of foreign antigens to T helper/inducer lymphocytes (Weinstein et al. 1990). It is therefore possible that the presence of class I and II MHC antigens on epiplexus cells in adult rats may facilitate their interaction with cytotoxic/suppressor and helper/inducer T lymphocytes. Bigner (1992) reported that normal CSF contains some lymphocytes and, in infections, CSF is usually nonspecific with a predominance of lymphocytes. In this connection, it is conceivable that epiplexus cells in CSF could partake in the important role in self-recognition and antigen presentation.

In the present study, class I MHC antigen was demonstrable in an appreciable number of epiplexus cells in postnatal rat brains but the expression of class II MHC antigen was very low. It would seem therefore that epiplexus cells are not actively engaged in antigen presentation in normal postnatal brain. The increase in the number of epiplexus cells labelled with OX-6 in adult rats is indicative of an upregulation of class II MHC antigen with age. The present findings, when taken into consideration with those of our previous study (Kaur & Ling, 1992) which showed that the class II MHC antigen on microglia appeared to be downregulated with age, confirm the work of Perry et al. (1993) who stated that in the choroid plexus there is a population of macrophages that show an upregulated phenotype when compared with microglia. The different immunophenotypic features between intraventricular macrophages and microglia

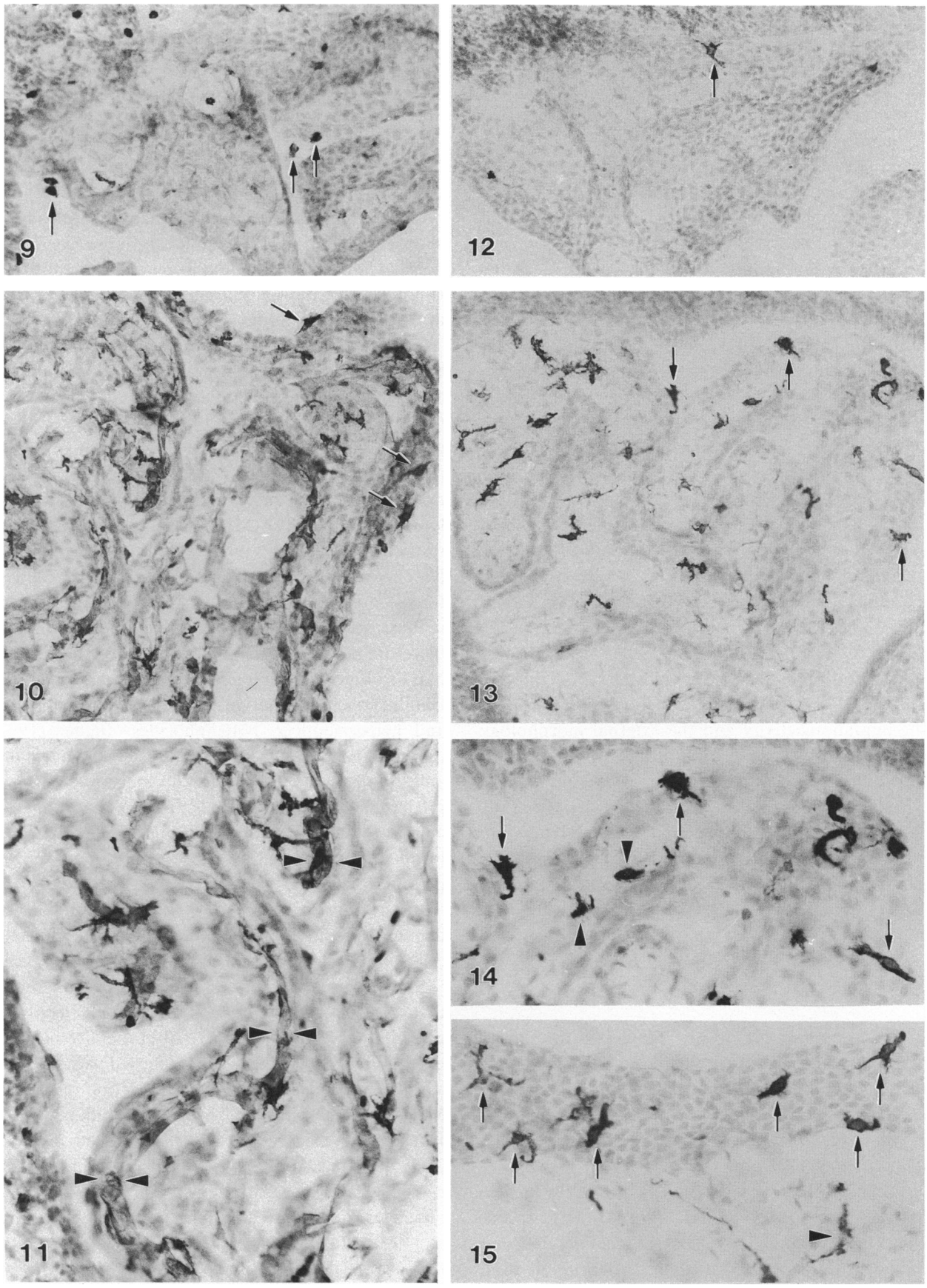


Fig. 9. A 7-d-old rat (serving as control as in Fig. 10) killed after 6 d of successive i.p. injections of sterile distilled water. OX-18 positive epiplexus cells (arrows) are distributed over the choroid epithelium.

may be related to their different local environments, e.g. the upregulation of class II MHC antigen in epiplexus cells in adult rats may have resulted from the induction of foreign antigens that might have gained access into CSF in the course of development.

The present immunohistochemical study showed that epiplexus cells in rats of different ages exhibited LCA marked by OX-1. LCA is localised on leucocytes, including monocytes and macrophages (Sunderland et al. 1979). Our finding therefore supports the proposed monocytic origin of the cells (Sturrock, 1978; Ling, 1979, 1981, 1983; Maxwell & McGadey, 1988; Maxwell et al. 1992; Lu et al. 1993*a*, *b*). The significance of the vigorous expression of LCA in epiplexus cells is only speculative. It is possible that monocytes retain their surface antigens after their entry into the ventricles to become the epiplexus cells. The monocytic origin of epiplexus cells is further evidenced by their expression of CR3 receptors as detected by OX-42. The presence of these receptors on epiplexus cells could be related to their possible role in endocytosis.

The most remarkable finding in the present study is the induction and upregulation of class II MHC antigen expression on epiplexus cells in postnatal rats after 6 successive injections of IFN-γ which is known to be a highly potent inducer of MHC antigens, especially class II, for brain microglia both in vitro (Sasaki et al. 1989; De Groot et al. 1991) and in vivo (Steiniger & van der Meide, 1988; Vass & Lassmann, 1990). The expression of class I MHC antigen on epiplexus cells was also upregulated by IFN-γ injections. Our results suggest that epiplexus cells responded to the administered IFN-γ and as a result a high level of MHC antigens was raised in these cells. The induction of class I MHC antigen expression on the endothelium of blood vessels in the stroma of the choroid plexus confirms the work of Male & Pryce (1988) who reported an enhanced class I MHC antigen expression on brain endothelium after IFN-γ stimulation.

While it is unequivocal from this study that the epiplexus cells in postnatal rat brains are responsive to IFN-γ. The route of entry of IFN-γ into the CSF, however, remains speculative. Our previous studies (Lu et al. 1993*a*, *b*) showed that rhodamine isothiocyanate or horseradish peroxidase when introduced intraperitoneally subsequently passed through the blood-CSF barrier to be taken up by the epiplexus cells. It seems justifiable, therefore, to assume that IFN-γ when injected i.p. could also cross the blood–CSF barrier to gain access into the same site where the epiplexus cells would be exposed to it.

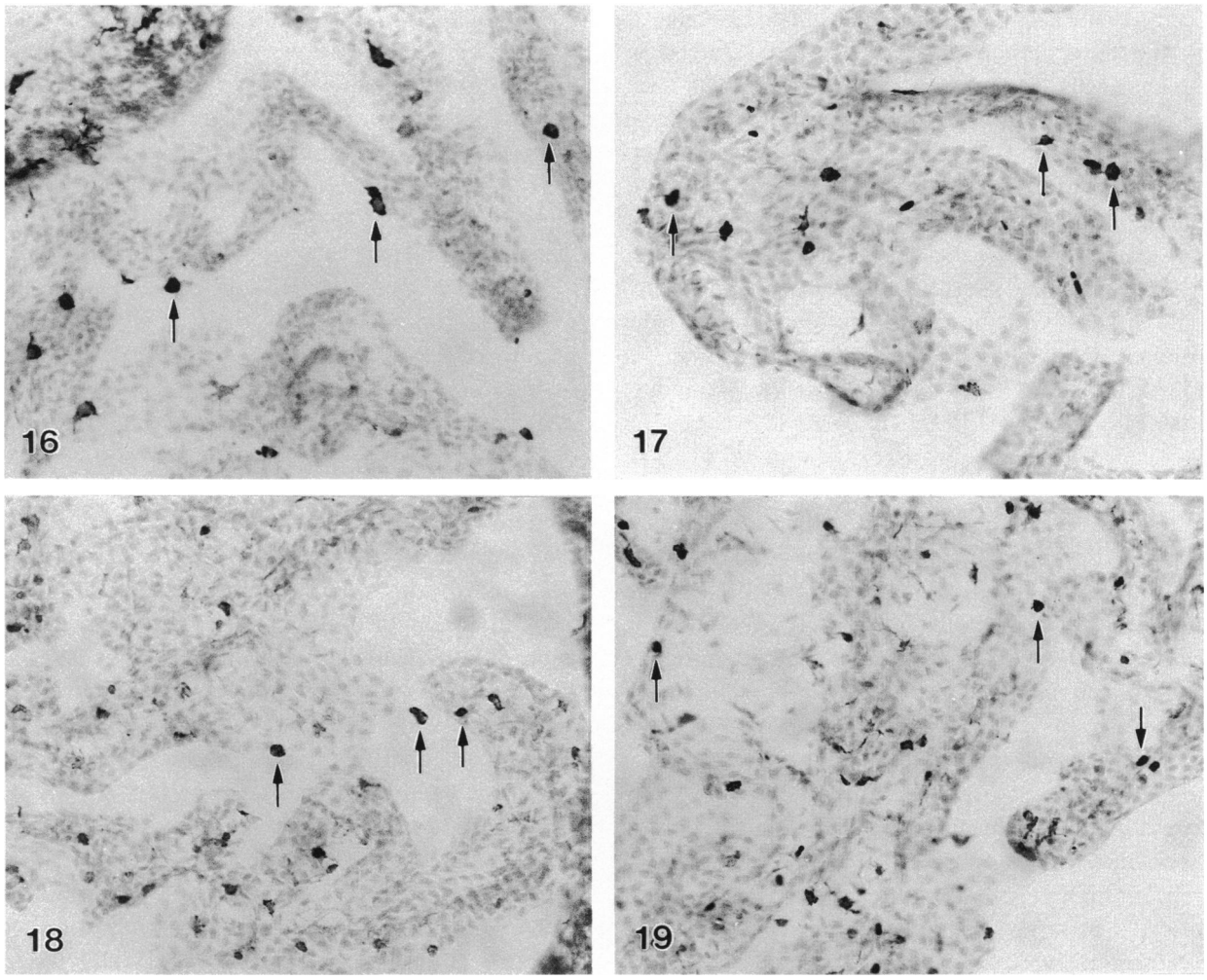
It has been speculated that the expression of MHC antigen is related to the amount of IFN-γ and the number of IFN-γ receptors present on cells (Sasaki & Nakazato, 1992). The present study showed that systematically administered IFN-γ enhanced both class I and II MHC antigen expression on epiplexus cells. However, to achieve this, it was necessary for the lymphokine to be given by successive i.p. injections over a prolonged period (i.e. 6 d). Thus the frequency of administration of IFN-γ and the survival interval allowed are important factors in the induction of the expression of MHC antigens on epiplexus cells. Class MHC II antigen expression was not elicited after single injection. This could have been due to a rapid elimination of IFN-γ as was described by other authors (Steiniger & van der Meide, 1988). The present study also showed that the immunostaining of epiplexus cells with OX-1 and OX-42 was not altered by IFN-γ injections. This confirms the finding of Vass & Lassmann (1990) who found that after intrathecal injection of IFN-γ, the expression of MHC antigens on brain cells was enhanced but the expression of CR3 on these cells was not affected.

An interesting finding of this study was that after IFN-γ application into postnatal rats, not only were the numbers of the OX-6 and OX-18 increased, but their external morphology was altered. The majority of the OX-6 and OX-18 positive cells transformed into elongated or ramified cells bearing a variable number of long branching processes. The number and external morphology of cells immunolabelled by OX-42 and OX-1, however, remained relatively unchanged, most being round with some bearing short stout processes. These results appear to suggest that there may be 2 or more subtypes of epiplexus cells. In other words, some epiplexus cells are endowed with MHC antigens while others exhibit CR3 and LCA antigens. Their het-

Figs 10, 11. A 7-d-old rat killed after 6 d of successive i.p. injections of IFN-γ. Epiplexus cells (arrows) strongly immunoreactive with OX-18 appeared to have increased when compared with those of the control rats (Fig. 9). The stained cells become elongated or ramified, bearing long processes. Note that the blood vessels of the choroid plexus are also stained (Fig. 11, arrowheads).

Fig. 12. Immunostaining with OX-6 in the choroid plexus in the lateral ventricle of a 7-d-old rat (serving as control as in Fig. 13) killed after 6 d of successive i.p. injections of sterile distilled water. Very few epiplexus cells (arrow) are stained.

Figs 13, 14, 15. Choroid plexus in the lateral ventricle of 7-d-old rats killed after 6 d of successive i.p. injections of IFN-γ. A large number of epiplexus cells (arrows) and stroma macrophages (arrowheads) are strongly reactive with OX-6. The epiplexus cells are elongated and extremely ramified bearing long processes best illustrated when the section is cut tangentially through the epithelium (Fig. 15).



Figs 16, 17. Choroid plexus in the lateral ventricle of 7-d-old rats killed after 6 d of successive i.p. injections of sterile distilled water (Fig. 16) and IFN-γ (Fig. 17). The OX-42 immunoreactivity and number of epiplexus cells (arrows) of rats in both groups are comparable.

Figs 18, 19. Epiplexus cells immunostained with OX-1 in 7-d-old rats killed after 6 d of successive i.p. injections of sterile distilled water (Fig. 18) and IFN-γ (Fig. 19). The immunoreactivity and number of epiplexus cells (arrows) in both groups of rats are comparable.

erogeneity would account for their differential response to IFN-γ. Cells encoded with MHC antigens were clearly responsive to IFN-γ to become elongated or ramified cells bearing long processes. The significance of their morphological transformation remains uncertain. It is conceivable that with elongation and extensive ramification, the surface area of the cell would be increased considerably, resulting in a wider spread of the surface antigens (e.g. class II MHC antigen) probably facilitating their interaction with T lymphocytes in a possible immunological process in the ventricular system.

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