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ORIGINAL ARTICLE

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Cellular and substrate adhesion molecules (integrins) and their ligands in cerebral amyloid plaques in Alzheimer's disease

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Abstract Integrins belonging to different subfamilies can be identified immunohistochemically in cerebral amyloid plaques. Monoclonal antibodies against the VLA family β1-integrins show staining of the corona of classical amyloid plaques for β1, α3 and α6. Immunostaining reveal also the presence of collagen and laminin in the corona. Activated microglial cells in classical plaques strongly express receptors belonging to the LeuCAM family (β2 integrins). The ligands ICAM and activated complement C3 are found in both amorphous and classical plaques. Vitronectin receptor (αv) is found in glial cells in classical plaques but its ligand vitronectin is seen in both amorphous and classical plaques. The data presented here demonstrate the presence of different cellular and substrate adhesive molecules (intregrins) and their ligands in classical plaques. The findings suggest that amyloid plaques show signs of regeneration and tissue remodelling.

Key words Adhesion molecules · Integrins · Laminin
Amyloid plaques · Alzheimer's disease

Introduction

Cerebral amyloid deposits are a prominent feature of the pathological process in Alzheimer's disease. The amyloid fibrils consist of aggregates of a 4 kDa cleavage product, termed β/A4 of β-amyloid protein, derived from a larger membrane spanning molecule, the amyloid precursor protein (APP) (Glenner and Wong 1984; Masters et al. 1985; Selkoe et al. 1986; Kang et al. 1987). There is strong evidence that changes in APP metabolism result in β/A4 amyloid deposition; a crucial event in the pathogenesis of Alzheimer's disease (Selkoe 1991). Though the precise functions of APP are unclear, a role in neurogenesis or axon and dendrite sprouting, or more generally in tissue regeneration, has been suggested (Müller-Hill and Beyreuther 1989) in conjunction with the finding that pathological axon and/or dendrite sprouting may occur in Alzheimer's disease (Geddes et al. 1985).

Several types of cerebral β/A4 plaques have been described. The classical amyloid plaque has a β/A4-positive congophilic core surrounded by a corona of dystrophic neurites and glial cells. The amorphous or diffuse, non-congophilic plaques show no neuritic and glial change (Tagliavini et al. 1988; Yamaguchi et al. 1988; Rozemuller et al. 1989b) and probably represents an early stage in plaque formation (Ikeda et al. 1989; Rozemuller et al. 1989b). Using immunohistochemical techniques, the serine protease inhibitors α1-antichymotrypsin (Abraham et al. 1988) and serum amyloid P component (Coria et al. 1988) as well as several complement factors (Eikelenboom and Stam 1982; Ishii and Haga 1984) are found in both amorphous and classical plaques (Rozemuller et al. 1989b). Complement proteins and α1-antichymotrypsin are not bound as native proteins to amyloid plaque structures but are found in activated forms (Eikelenboom et al. 1989, 1992; McGeer et al. 1989; Rozemuller et al. 1991; Rogers et al. 1992). The presence of activated proteases and protease inhibitors is interesting as there is a delicate balance between proteases and protease inhibitors that modulates neurite elongation and regeneration (Monard 1988). Activated proteases can degrade extracellular matrix components and they have an important role in sustaining both cell migration and growth cone movement. Cell migration and sprouting are also mediated by cell adhesion and laminin and collagen IV have been identified in senile plaques (Perlmutter et al. 1991; Murtomaki et al. 1992) but there are contradictory data on the presence of fibronectin in plaques (Koike et al. 1988; Howard and Pilkington 1990). Cell adhesion to extracellular matrices is mediated by integrins (Hynes 1987; Ruoslahti and Piersbacher 1987; Hemler 1990; Springer 1990). There are three subfamilies each defined

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Table 1 Integrin family of cell-cell and cell-matrix receptors and their ligands

Subunits	CD notation	Names	Ligands
$\alpha_1 \beta_1$	CD-/CD29	VLA-1	Laminin, collagen
$\alpha_2 \beta_1$	CD49b/CD29	VLA-2	Laminin, collagen
$\alpha_3 \beta_1$	CD-/CD29	VLA-3	Fibronectin, laminin, Collagen, epiligrin
$\alpha_4 \beta_1$	CD49d/CD29	VLA-4	Fibronectin, VCAM-1
$\alpha_5 \beta_1$	CD-/CD29	VLA-5	Fibronectin
$\alpha_6 \beta_1$	CD49f/CD29	VLA-6	Laminin
$\alpha_L \beta_2$	CD11a/CD18	LFA-1	ICAM-1,2,3
$\alpha_m \beta_2$	CD11b/CD18	Mac-1, CR3	C3bi
$\alpha_x \beta_2$	CD11c/CD18	p150/95	?
$\alpha_v \beta_3$	CD51/CD61	VNR	Vitronectin, fibrinogen, van Willebrand factor, Thrombospondin
$\alpha_{IIb} \beta_3$	CD41/CD61	gp IIb/IIIa	Fibrinogen, fibronectin van Willebrand factor

by a common β subunit which shares multiple distinct a subunits (see Table 1). The VLA protein family shares a common β1 subunit and consist of extracellular matrix receptors with binding specificity for collagen, fibronectin and laminin. The LeuCAM family is involved in leucocyte cell adhesion and shares a common β2 subunit. The cytoadhesion family shares a common β3 subunit and its members bind to extracellular matrix and plasma proteins. The complexity of the integrin family has recently been emphasised by the discovery of novel β-subunits that can also associate with the α4, α6 and αv subunits. The αv subunit appears to be particularly versatile as it combines with five different β subunits (Springer 1990; Ruoslahti 1991).

In an earlier study we demonstrated that microglial cells in classical plaques express integrins of the β2 subfamily (Rozemuller et al. 1989a). In this study we have investigated the presence of integrins belonging to the different β subfamilies and their ligands immunohistochemically in amorphous and classical plaques.

Materials and methods

Brain tissue was obtained from 6 patients (aged 49–82 years) with clinical and pathological diagnosis of Alzheimer's dementia. Small pieces of parietal and temporal cortex were frozen in liquid nitrogen 5 h after death for immunohistochemical studies. The pathological diagnosis was based on histological staining (haematoxylin and eosin, Congo red, Bodian, Kluever-Barrera) performed on prolonged formalin-fixed, paraffin-embedded tissue (10% formalin for 4–5 weeks).

For immunohistochemical staining on frozen tissue, 8 µm thick cryostat sections were mounted on poly-L-lysine coated glass slides, air-dried and fixed in acetone for 10 min before use. The primary antibodies used in this study are listed in Table 2, together with their sources. All antibodies were appropriately diluted in phosphate-buffered saline (PBS), pH 7.4, containing 1% bovine serum albumin. Incubation with the primary antibodies was performed overnight at 4° C and followed by repeated washes in PBS. Peroxidase activity was visualised using 3,3 diamino-benzidine (DAB) (5 mg DAB in 10 mg PBS, pH 7.4, containing 0.02% hydrogen peroxide, for 3–5 min). Sections were counterstained with Congo red (Puchter et al. 1962) to visualize the amyloid. After Congo red staining, sections were dehydrated and mounted in malinol. The indirect peroxidase conjugate technique was used to demonstrate specific mouse or rat monoclonal antibodies and the peroxidase-anti-peroxidase (PAP) technique for rabbit polyclonal antibodies. The indirect peroxidase conjugate technique was as follows: acetone-fixed cryostat sections were washed in PBS and incubated overnight with the primary antibodies and in the second step with peroxidase-labelled rabbit anti-mouse antisera (Dako, Denmark) or rabbit anti-rat-antisera (Dako) for 30 min. Peroxidase was revealed by the DAB method. In the PAP technique, acetone-fixed cryostat sections were pre-incubated with normal swine serum and incubated with the primary rabbit antisera overnight. After a second pre-incubation with normal swine serum, sections were incubated with swine anti-rabbit immunoglobulins (Dako) for 30 min. In the third step sections were incubated with rabbit PAP complex, (Dako) for 30 min. Peroxidase activity was revealed by the DAB method.

Double staining for β/A4 and complement C3 and for β/A4 and vitronectin was performed by incubating overnight simultaneously with anti-A4 rabbit polyclonal antibodies and monoclonal antibodies for complement C3d or vitronectin, followed in the second step by an incubation with alkaline-phosphatase-labelled goat-anti-rabbit (Tago, Burlingame, Calif., USA) and biotinylated horse anti-mouse antibodies (Vector, Burlingame, Calif., USA). In the third step sections were incubated with peroxidase-labeled avidin-biotin-complex (Vector elite kit). Alkaline phosphatase activity was visualised using naphtol AS-MX phosphate as substrate and fast blue BB as coupling agent. Secondary antisera and reagents were tested for lack of cross-reactivity and nonspecific staining. Specificity of the polyclonal fibronectin antiserum was confirmed by absorption with purified fibronectin.

Antiserum against fibronectin was incubated overnight at 4° C with several dilutions of fibronectin (Dako) ranging from 5 µg to 100 µg and centrifugated at 10000 g. The supernatant was used as primary antibody.

Results

Antisera against β/A4 showed two basic types of plaques: amorphous non-congophilic plaques and classical plaque with β/A4 positive congophilic deposits (see Rozemuller et al. 1989b). The amorphous plaques were present in all cortical layers and outnumbered the classical plaques. Immunohistochemical findings on amorphous and classical plaques for the integrin family and their ligands are summarized in Table 3. The types of plaques were identified by counterstaining with Congo-red, double immunostaining with antisera against β/A4 or by study of adjacent sections immunostained for β/A4.

Monoclonal antibodies against the VLA family demonstrated, except for staining of blood vessels, a punctate immunostaining of the corona of classical plaques for β1 (Fig. 1), α3 (Fig. 2) and α6 (Fig. 3). The congophilic core of the classical plaques did not show immunostaining. In some cases amorphous plaques also showed a weak diffuse immunostaining for β1 (Fig. 4). No immunostaining of plaques was seen with the monoclonals against α4 and α5. With antisera against collagen IV and laminin punctate immunostaining was found associated with congophilic plaques. In typical classical plaques immunolabelling for collagen IV (Fig. 5) and laminin (Fig. 6) was clearly seen small as ring-like structures in the corona. Monoclonal antibodies against three different epi-

Table 2 Sources immunoenzymatic technique and selected references of monoclonals and antibodies

Antigen	Antibody	Source	References
β/A4 protein	rabbit polyclonal	gift Masters	Masters et al. (1985)
Common b1 (CD29)	K 20 (mouse)		Amiot et al. (1988)
VLA-2 (CD49b)	10 G 11 (mouse)	gift van dem Borne	Giltay et al. (1989)
VLA-3	J 143 (mouse)	gift Klein	Kantor et al. (1987)
VLA-4 (CD49d)	HP 2/1 (mouse)	gift Sanchez-Madrid	Sanchez-Madrid et al. (1986)
VLA-5	SAM-1 (mouse)	gift Figdor	Keizer et al. (1987)
VLA-6 (CD49f)	GoH3 (rat)	gift Sonnenberg	Sonnenberg et al. (1988)
Common b2 (CD18)	LFA-1b (mouse)	gift Miedema	Miedema et al. (1984)
LFA-1α (CD11a)	SPV-L7 (mouse)	gift Miedema	Keizer et al. (1985)
CR3α (CD11b)	Bear-1 (mouse)	gift Miedema	Keizer et al. (1985)
p150/95 (CD11c)	Leu M5 (mouse)	Becton & Dickinson	Schwarting et al. (1985)
Common β3 (CD61)	C17 (mouse)	gift von dem Borne	Tetteroo et al. (1983)
VNR (CD51)	NKIm9 (mouse)	gift Figdor	
Collagen IV	rabbit polyclonal	DAKOPATTS	
Laminin	rabbit polyclonal	DAKOPATTS	
Fibronectin	rabbit polyclonal	DAKOPATTS	
– gelatin bind. fr.	4B2 (mouse)	Boehringer	
– heparin bind. fr.	3E1 (mouse)	Boehringer	
– cell attach. bind. fr.	3E3 (mouse)	Boehringer	
VCAM-1	4B9 (mouse)	gift Pals	Schwartz et al. (1990)
ICAM-1	RR-1/1 (mouse)	gift Pals	Dustin et al. (1986)
C3c (neo-epitope)	AC3–9 (mouse)	gift Hack	Hack et al. (1988)
C3d (neo-epitope)	AC3–15 (mouse)	gift Hack	Hack et al. (1988)
Vitronectin	mouse menoclonal	Chemicon	
gp IIb/IIIa.	Y2/51(GpIIIa. (mouse)	gift Mason	
Fibrinogen	rabbit polyclonals	DAKOPATTS	

Table 3 Immunohistochemical findings of integrins and their ligands in amorphous and classical plaques

Receptor	Amorphous plaques	Classical plaques	Ligands	Amorphous plaques	Classical plaques
β_1 CD29	(–)	+			
α_2 CD49b	–	–			
α_3 CD-	–	+	Collagen IV	–	+
α_4 CD49d	–	–	VCAM-1	–	–
α_5 CD-	–	–	Fibronectin	–	–
α_6 CD49f	–	+	Laminin	–	+
β_2 CD18	–	+			
α_l CD11a	–	+	ICAM-1	+	+
α_m CD11b	–	+	iC3bi	+	+
α_x CD11c	–	+			
β_3 CD61	–	(–)			
α_v CD51	–	+	Vitronectin	+	+
			gp 11b/111a	–	–

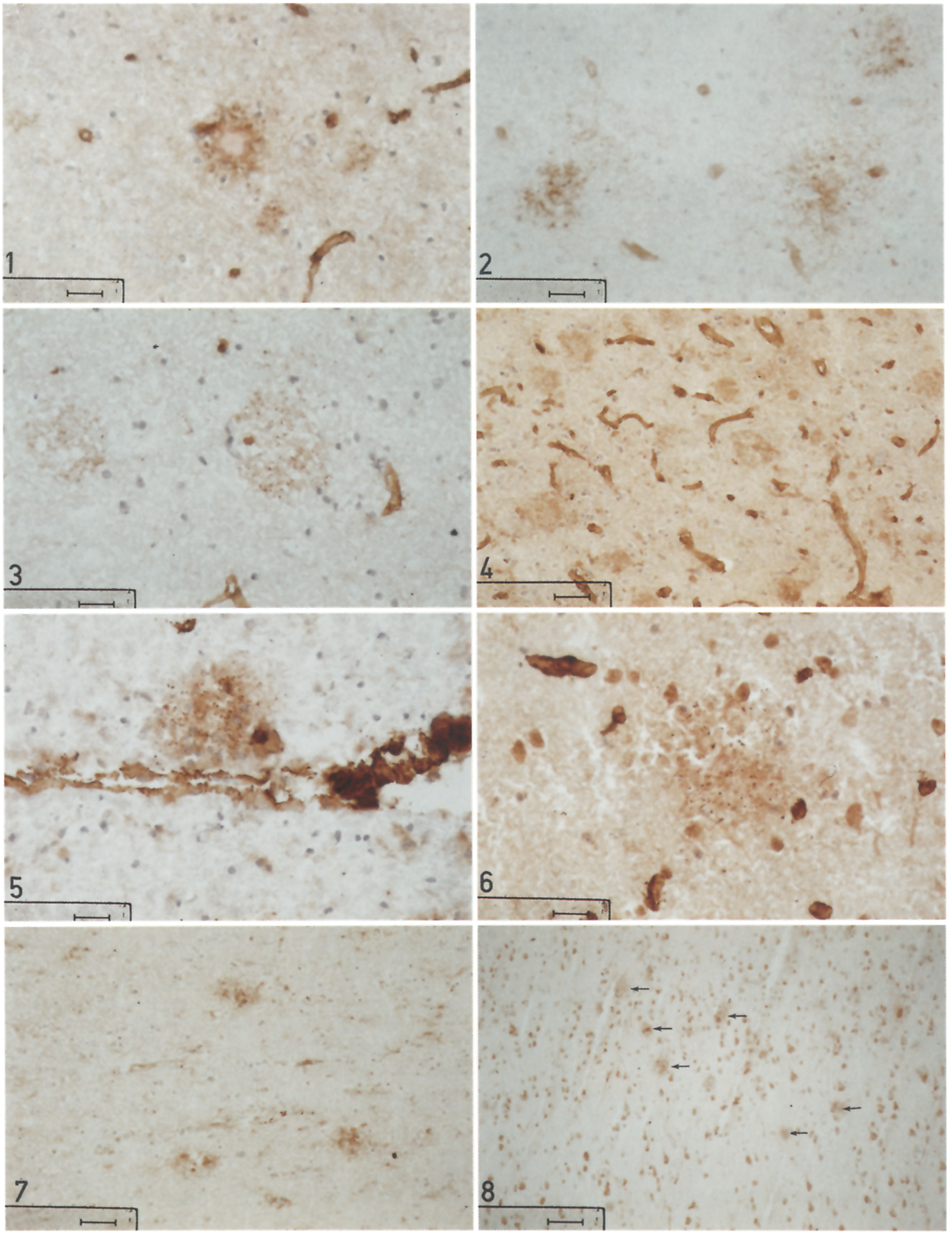
topes of fibronectin did not visualize plaques in contrast to a rabbit antiserum against fibronectin (Dako) which stained both amorphous and classical plaques. However, this immunostaining could not be absorbed with fibronectin.

With both monoclonals against β2 chain and with monoclonals against the different α chains (CD11c, CD11b, CD11c) immunolabelled clusters of small glial fibres were seen in the neuropil. These clusters were associated with congophilic classical plaques but not with the non-congophilic amorphous plaques. Immunostaining for ICAM-1 demonstrated immunostaining of amorphous plaques and the corona of classical plaques. Endothelial cells of blood-vessels showed a weak immunolabelling for ICAM-1. Nearly all amorphous and classical plaques showed strong immunolabelling for complement protein C3 fragments except some small amorphous plaques with a diameter of less than 20 μm.

Monoclonal antibodies against αv showed immunolabelling of glial cells around the amyloid core in classical plaques (Fig. 7). The pattern of immunostaining for β3 was similar but weaker and a number of classical plaques did not show immunolabelling. Amorphous and classical plaques were immunolabelled for vitronectin (Fig. 8). No immunostaining of plaques was found for gp IIb/IIIa and fibrinogen.

Discussion

Earlier investigators of Alzheimer's disease have noted that the brain is not simply undergoing degeneration but shows signs of regeneration and sprouting in and outside the amyloid plaques (Fischer 1907; Bouman 1934). Regulation and tissue degradation and remodelling involves a complex network including proteases, cytokines, growth factors, protease inhibitors, integrins and adhesion molecules (Masure and Opdenakker 1989). The presence of different integrins and their ligands in plaques is shown here. A punctate immunolabelling was found in the corona of classical plaques for VLA-3, VLA-6, collagen IV and laminin. The ring-like, punctate staining pattern in the corona seems to outline dystrophic neurites. The appearance of laminin and its receptor VLA-6 in the neuropil of adult brain is remarkable because laminin is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not expressed in the fully developed brain. Laminin is a neurite outgrowth-promoting factor and appears only transiently during embryogenesis in the brain (Sanes 1989). The presence of laminin in the corona of classical plaques agrees with the suggestion that neurites in amyloid plaques may show an aberrant regeneration response (Geddes et al. 1985). Recently, interactions between APP and laminin (Narindrasorassak et al. 1992) and APP and collagen IV (Breen et al. 1992) have been described in in-vitro studies. With respect to cerebral β/A4 deposits, APP is found immunohistochemically in the corona of classical plaques but not in the amorphous plaques (Sjohi et al. 1990; Joachim et al. 1991; Rozemuller et al. 1993). The present findings show that APP-laminin and APP-collagen IV interactions are not only an in-vitro phenomena. There are contrasting data on the presence of fibronectin in amyloid plaques; Koike et al. (1988) reported no immunostaining but Howard and Pilkington (1990) found immunoreactivity. We found immunostaining of plaques with a commercial rabbit antiserum (also used in the study of Howard and Pilkington) but this staining was not absorbed out with fibronectin. Three different antibodies against fibronectin did not immunostain plaques. So we did not detect immunoreactivity for fibronectin or fibronectin receptor VLA-5 in amorphous and classical plaques. Although fibronectin has been shown to interact with C1q (Pearlstein et al. 1982) and amyloid P component (Rostagno et al. 1986), both β/A_4 associated proteins, our results do not indicate the involvement of fibronectin in the pathogenetic mechanism of cerebral amyloid deposition.

VCAM, the ligand for VLA4 expressed on lymphocytes, and ICAM, the ligand for LFA-1, are molecules induced by inflammatory mediators and are involved in adhesion and migration of leucocytes. In classical plaques microglial cells strongly express LFA-1 (CD11a) and the corona shows immunostaining for ICAM-1 (Rozemuller et al. 1989a; Akiyama et al. 1990). Immunohistochemical data showing that classical plaques are characterized by complement activation and the presence of activated microglial cells expressing certain monocyte/macrophage markers are highly suggestive of an inflammatory response (Eikelenboom and Stam 1982; Ishii and Haga 1984; Rogers et al. 1988; McGeer et al. 1989; Rozemuller et al. 1989a). ICAM-1 was found within plaques and on vascular endothelium (Rozemuller et al. 1989a; Eikelenboom et al. 1991; Frohman et al. 1991). In normal brain tissue ICAM-1 immunoreactivity is principally restricted to vascular endothelium (Frohman et al. 1991). In the present study we did not detect immunohistochemically VCAM-1 on the vascular endothelium in cerebral tissue in many plaques. This agrees with the view that classical plaques are the site of a locally induced chronic inflammatory response without influx of leucocytes from blood into the neuropil (Eikelenboom et al. 1991; Rozemuller et al. 1992).

Immunoreactivity for vitronectin has been found in senile plaques (Akiyama and McGeer 1991). In the present study we demonstrated immunostaining for vitronectin in both amorphous and classical plaques. Recently thrombospondin was identified immunohistochemically in senile plaques (Bueé et al. 1992). Both vitronectin and thrombospondin are ligands for the vitronectin receptor (αvβ3). Immunostaining for the a subunit of vitronectin receptor (αv) show labelling of glial cells in classical plaques. The immunolabelling for the β3 chain was much weaker or absent in plaques. These findings are in agreement with the observations of Akiyama et al. (1990) and indicate that the a subunit of vitronectin receptor is perhaps associated with a β subunit different from β3.

We have found that the different integrins are mainly seen in the corona of classical plaques. In the corona the dystrophic neurites are outlined by collagen, laminin, VLA3 ($\alpha_3\ \beta_1$) and VLA6 ($\alpha_6\ \beta_1$) and activated microglial cells express integrins of the β_2 subfamily. The expression of cellular and matrix adhesion molecules is regulated by transforming growth factor β (TGFβ) (Heino et al. 1989; Ignotz et al. 1989). TGFβ is present in plaques and its concentration appears to be increased in the surrounding cells (van der Wal et al. 1993). In vitro TGFβ binds to derivates of APP (Bodmer et al. 1990). It has been suggested that APP is found in the corona of classical plaques immunohistochemically but not in amorphous plaques. Thus, the increased expression of APP, upregulation of integrins and the expression of substrate adhesion molecules in the corona of classical plaques may be closely associated events in the formation of classical plaques. This interpretation is in accord with the view that APP plays an essential role in the cell-cell and cell-matrix interactions and supports the suggestion that classical plaques do not simply reflect degeneration but are partly due to an aberrant regeneration response.

Fig. 1 Punctate immunolabelling for β_1 in the corona of a classical plaque. *Bar* is 20 mm

Fig. 2 Immunolabelling of three plaques for VLA-3. *Bar* is 20 mm

Fig. 3 Immunolabelling of two plaques for VLA-6. *Bar* is 20 mm

Fig. 4 Numerous amorphous plaques show a weak immunostaining for β_1. *Bar* is 40 mm

Fig. 5 Punctate immunolabelling of a classical plaque for collagen IV. *Bar* is 20 mm

Fig. 6 Punctate immunolabelling of a plaque for laminin. *Bar* is 20 mm

Fig. 7 Immunostaining for the vitronectin receptor (α_v) shows labelling of glial cells in the corona of classical plaques. *Bar* is 20 mm

Fig. 8 Immunoreactivity for vitronectin in plaques (*arrows*) and neuronal cells. *Bar* is 40 mm

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