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NEUROTROPHIC PROPERTIES OF LEPTOMENINGES

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The leptomeninges, consisted of pia mater and arachnoid, cover the surface of brain parenchyma. Leptomeningeal cells produce a number of biologically active proteins, including prostaglandin-D synthase, cyclooxygenase-1, -2, insulin-like growth factor-II, insulin-like growth factor-binding proten-2, andapolipoproteinE, released into the cerebrospinal fluid. The involvement of leptomeninges in neurotrophic, scavenging, and transport activities as well as inflammatory responses, associated with the brain, is reviewed. ***Biomed Rev 1999; 10: 31-36.***

INTRODUCTION

The leptomeninges are a connective tissue compartment composed of pia mater and arachnoid. The adventitial leptomeninges surrounding the cerebral vessels are built up of collagen fiber bundles.Thepiamater covering the brain parenchyma has wide intercellular spaces with sparse and fine fiber bundles. This compartment is composed of a delicate but continuous layer of cells joined by desmosomes and nexuses. The trabecu-lar leptomeninges, linking arachnoid and pia mater, are in the subarachnoid space filled with cerebrospinal fluid (CSF). Generally, the border between the outer arachnoid layer and the neurothelium is the CSF-blood barrier. Both pia mater and arachnoid develop from a mesenchymal meninges primitiva on the telencephalic surface, and display a common cytologic characteristics. Accumulating physiological evidence supports the assumption that leptomeningeal cells are not merely brain-covering cells. For example, fetal brain neurons transplanted into the meningeal or subarachnoid space survive for a long time and keep on functioning (1). When fetal rat leptomeningeal tissue is transplanted onto the median emi-nence of the hypophysectomized rat, many regenerating nerve fibers penetrate into the transplanted tissue (2). Moreover, 6-hydroxydopamine treatment of the brain surface causes degeneration of leptomeningeal cells which results in an abnormal development of Cajal-Retzius cells (3). These physiological findings indicate that leptomeninges secrete some biologically active substances that play an important roles in the regulation of brain functions.

PROTEINS PRODUCED BY LEPTOMENINGES

By immunocytochemistry and *in situ* hybridization methods, many biologically important proteins are found in leptomeninges. These include transforming growth factor-beta 1 (TGF-p1) (4), prostaglandin-D synthase (beta-trace protein) (5), and parathyroid hormone-related protein (PTHRP) (6). Likewise, insulin-line growth factor-II (IGF-II) and mRNA for IGF binding protein-2 (IGFBP-2) and IGFBP-4 are localized in leptomeninges (7-10). Transferrin and transthyretin mRNA are also located in this structure (11). Likewise, human laminin M chain (merosin) and fubulin, an extracellular matrix protein, are expressed in

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leptomeninges(12,13). Leptomeninges from the normal, aged, and Alzheimer's disease (AD) brains contain high levels of p-amyloid protein and p-amyloid precursor protein (14-16). In addition, several other proteins have been identified in medium conditioned with cultured leptomeningeal cells (17,18). These include prostaglandin-D synthase, IGFBP-2,-4, apolipoprotein E (apoE), beta2-microglobulin (P 2-M), cystatin C, IGF-II, des-1 -IGF-II, secreted protein acidic and rich in cysteine, transferrin, ly sozyme C, peptidyl-prolyl *cis-tmns* isomerase (cyclophilin C), ubiquitin, extracellular superoxide dismutase, and collagen a-1 (III). Figure 1 presents a schematic view of leptomeninges and CSF, including a selected list of leptomeninges-derived molecules.

LEPTOMENINGES: A MEUROTROPHIC SURFACE

Most of the leptomeningeal cell-derived proteins are CSF components. Prostaglandin-D-synthase and cystatin C are known to be beta-trace protein and gamma-trace protein, respectively, in CSF (19,20). IGF-E, the major IGF in the brain, is present as a complex with IGFBP-2 in CSF (21,22). ApoE and transferrin are also essential components of CSF (23). IGF-II is one of the majorneurotrophic factors in the brain. In addition,p2-M seems to have a neurotrophic potential, mediated by p2-M-induced collagenase synthesis (24) and stimulation of DNA and protein synthesis (25). Further, a diffusible substance secreted by leptomeningeal cells is a key chemotactic factor stimulating and directing the migration of cerebellar external granular cells (26).

It is therefore likely that leptomeninges exert trophic action on neuronal and glial cells through the release of neurotrophic factors into CSF. Accordingly, fibroblast growth factors enhance nerve growth factor (NGF) secretion by fibroblasts derived from leptomeninges but not by microglia (27). In addition, chronic intraventricular infusion of recombinant human NGF results in axonal sprouting and glial cell hyperplasia in the leptomeninges (28). Furthermore, NGF-gamma, a serine pro-teas of the kallikrein family, is a potent IGFBP-3 protease (29). These data suggest that NGF may be involved in the growth of cells no only by binding to its receptors but is capable of cleaving IGFBP and thus enhancing IGF action. This synergis-tic action of NGF and IGF may be involved in cell growth and repair in the brain. Further, as indicated above, laminin is expressed in meningeal tissue (12), and this matrix protein may synergistically with NGF promote neuronal survival (30).

CARRIER PROTEINS

Several protein molecules capable to bind biologically important substances are produced by the leptomeninges. They include prostaglandin-D-synthase, IGFBP-2, IGFBP-4, apoE, transferrin, and transthyretin, a carrier of thyroid hormone. Prostaglandin-D synthase is a retinoid-binding protein (31). Retinoic acid synthesis by leptomeninges is comparable to rates found in liver (32), and cellular retinol-binding protein type-I is found in both leptomeninges and choroid plexus as well as the wall of cerebral blood vessels (33). This binding protein may transport retinol across the blood-CSF barrier, and hence the leptomeninges play an important role in the regulation of metabolism and/or transport of vitamin A in the brain. Further, apoE, a known risk factor for AD, and cholesterol carrier, has a high affinity for P-amyloid protein (34-36). The leptomeninges from both aged and AD's brains contain very high levels of P-amyloid protein. Although the origin of such p-amyloid protein in the leptomeninges is suspected to be vascular muscle cells, we could not exclude the possibility that the insoluble p-amyloid protein is also derived from leptomeningeal cells themselves. Since the amount of soluble P-amyloid protein in the leptomeninges is comparable to that in the blood vessel wall (16), leptomeninges seem to be a large reservoir of this protein in aged and AD brains. In fact, human leptomeningeal cells implanted into the rat brain have been shown to produce a large amount of human P-amyloid protein as well as p-amyloid precursor protein (36). In canine leptomeningeal organ cultures, exo-genously added P-amyloid protein is focally deposited in the vessel walls (37). Therefore, the disturbance of apoE and amyloid protein metabolism in the leptomeninges may cause the deposition of P-amyloid protein in the aged and AD brain. It is also noteworthy that the abnormality of apo E, cystatin C, and transthyretin results in the amyloid deposits (11-38). Hence, one of the main roles of leptomeninges seems to be that of carrier of substances through the blood-CSF barrier.

SCAVENGER PROTEINS

The precise roles of most protein factors produced by leptomeninges are not completely understood. For instance, transferrin is an essential carrier of iron ion (39), but few data suggest its role in the process of neuronal degeneration. Accordingly, the distribution patterns of transferrin, apoE, cystatin C, p2-M, and apoE in the neurons fated to die after hypophysectomy or ischemia have been studied (40-42). The accumulation of these proteins in the injured neurons suggests the involvement of such carrier proteins in the process of neuronal degeneration. Cystatin C is a potent inhibitor of cysteine proteases, such as cathepsins. Cathepsins in neurons are activated during the early stages of ischemia (43), suggesting a possibility that cystatin C may form a complex with such proteases derived from injured neurons. As indicated above, apoE binds cholesterol released from injured neurons. The cholesterol, combined with apoE, may be reutilized by regenerating neurons through a receptor-mediated uptake. Soluble P2-M not accumulate in the atrophied CA1 neurons after ischemia, but intensive accumulation of this protein appears in the vasopressin-positive neurons after hypophysectomy (40). Although injured CA1 neurons never regenerate after

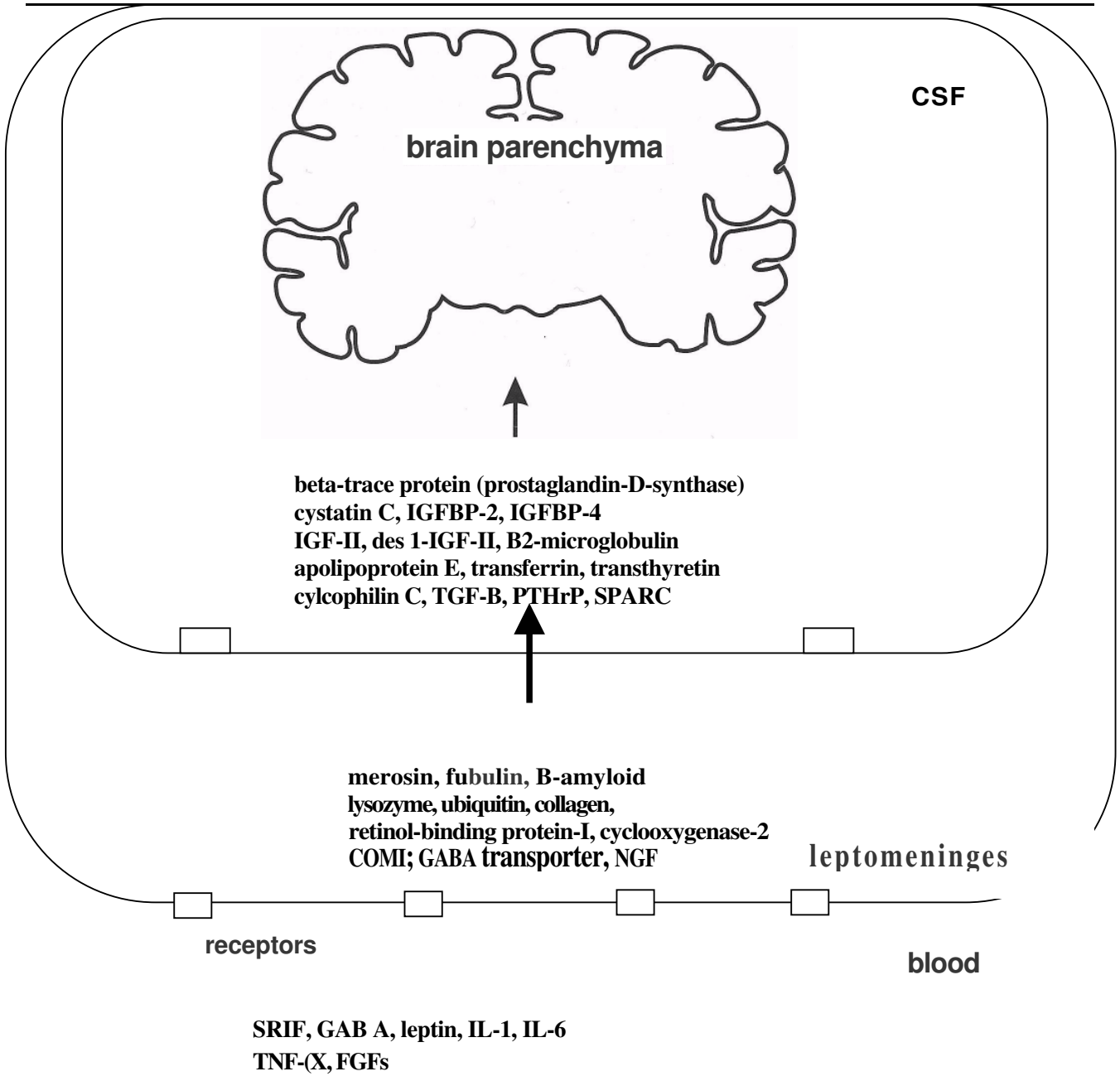

Figure 1. A schematic drawing ofleptomeningeal and cerebrospinal fluid (CSF) compartment. A selected list of leptomeninges-derived molecules is also presented (the abbreviations are indicated in the text).

ischemia, parts of vasopressin neurons can regenerate their fibers after hypophysectomy. It is likely therefore that p2-M accumulated in the injured cell bodies is involved in the neuronal regeneration. Probably, CSF (32-M may act as a neurotrophic factor. Altogether, these findings may support the hypothesis that leptomeninges take part in scavenging the waste materials, especially at the border between brain and blood. This appears to be beneficial for the maintenance of brain neurons.

INFLAMMATION

The role of prostaglandin-D synthase, the basic product of cultured leptomeningeal cells, is unclear. This glycoprotein catalyzes the isomerization of prostaglandin H2 to prostaglandin D2, which has several central actions, including sleep induction. Intravenous or intraventricular injection of selenium compounds, an inhibitor of this enzyme, inhibits sleep in rats. Since there is no difference between day and night level and activity of prostaglandin-D synthase in rat CSF (44), it is unlikely that this enzyme directly regulates sleep behavior under normal condition. One possibility is that prostaglandin-D-synthase is involved in the sleep induced during pathological conditions, such as inflammation. Specifically, leptomeninges contain various immune cells, including mast cells, macrophages, and lymphocytes (45,46), known to secrete NGF, a neurotrophin implicated in large number of inraiune-inflammatory events (this volume of *Biomedical Reviews).* Further, cyclooxygenase-1 (COX-1) and COX-2 are induced in vascular and peri vascular cells in the leptomeninges after inflammatory stimuli, such as lipopolysaccharide and cytokines, particularly, interleukin-lbeta (IL-113) (47,48). Such an expression of COX, leading to an increased prostaglandin levels, could be involved in brain inflammatory responses. It would be interesting as to whether the expression of CSF prostaglandin-D synthase could also be altered in response to inflammatory stimuli. Since IGF and IGFBP are implicated in inflammation and cell growth, one may try to examine whether IGFBP proteases (29,49) are expressed in the leptomeninges.

RECEPTORS

Various factors including neurotransmitters, growth factors, and cytokines affect the function and growth of leptomeningeal cells. For example, SMS 201-995, a somatostatin agonist, has an effect on [3H]-thymidine incorporation by meningeal cells (50). In addition, catecholamine-O-methyl transferase is known to be distributed in leptomeninges, and 6-hydroxydopamine treatment causes leptomeningeal degeneration, resulted in the disorganization of Cajor Retzius cell (3). These findings suggest that leptomeningeal cells can receive information from both the central and peripheral neurons. However, the innervation of the leptomeninges (except adventitial) is not intense (51). One explanation is that the leptomeninges receive the information through CSF. For example, gamma-aminobutyric acid (GAB A) transporter mRNA are distributed in the leptomeninges (52). Such transporters may help to regulate the amount of GAB A available to proliferating and migrating neurons at the subpial surface, at least during perinatal development. Intriguingly, it was reported that binding sites of leptin, a cytokine secreted not only by adipose tissue, are found in both leptomeninges and choroid plexus (53,54). Whether leptin may be involved in inflammatory processes in the leptomeninges, remains to be evaluated. Accordingly, IL-1 receptors are detected at high density in the leptomeninges (55). And injection of IL-1 into the brain parenchyma increases serum permeability in the leptomeninges, but not in the blood-brain barrier at the injection site
(56). Furthermore, injection of IL-6 into the lateral ventricle increases the expression *ofc-fos* mRNA in leptomeningeal cells (57).

CONCLUSION

The leptomeninges are source of and target for a number of biologically active molecules which play important roles in neurotrophic, scavenging, and transport activities as well as inflammatory processes in the brain.

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