Chapter 9

Cholinergic Receptors in Human Brain Arteries and Microvessels

Alterations in Alzheimer’s Disease

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Introduction

Cholinergic mechanisms have long been known to be implicated in the regulation of cerebral blood flow (CBF). The parasympathetic control of brain superficial vessels and the intracerebral cholinergic regulation of cerebral cortex microvasculature are well described. In vivo administration of acetylcholine (ACh) or cholinomimetics, as well as stimulation of specific neuronal structures, result in CBF increase sensitive to muscarinic and/or nicotinic blockade. In vitro administration of ACh to human isolated brain arteries results almost exclusively in an endothelium-dependent relaxation. This prominent dilatory effect contrasts with the dual vasomotor response (dilatation followed by constriction at higher doses of ACh) observed in such species as the dog and cat. At the level of the intraparenchymal microvessels, ACh induces vasodilatation and could mediate functions such as the fine tuning of local CBF and possibly blood–brain barrier permeability. Recent evidence indicates that ACh is

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not a direct smooth muscle vasodilatory agent, but rather interacts with specific cholinergic receptors strategically located on nerve terminals and/or endothelial cells to modulate the synthesis and release of a relaxing factor, corresponding to nitric oxide (NO).\textsuperscript{12-15} ACh has also been implicated in the release of other vasoactive neurotransmitters.\textsuperscript{9,16,17} However, a direct effect on the cerebrovascular smooth muscle cannot be totally excluded, at least in species in which cerebral blood vessels constrict in response to ACh.\textsuperscript{12}

In most cerebrovascular cholinergic-related functions, muscarinic receptors have been implicated, although nicotinic receptors also seem to be involved.\textsuperscript{4,6,14} Muscarinic receptors are highly heterogeneous, and five different receptor genes have recently been cloned (m\textsubscript{1}–m\textsubscript{5}) (for review, see ref. 18). A pharmacological profile has been described for the five cloned receptors,\textsuperscript{19,20} but unequivocal identification can only be achieved by the use of molecular biology techniques wherein the expression of a given receptor can be assessed. Using pharmacological approaches, multiple muscarinic receptor subtypes have been identified at the cerebrovascular level,\textsuperscript{21,22} but little is known in the human, although such information is essential for our understanding of cholinergic regulation of CBF at both the extra- and intracerebral level. Moreover, perfusion of the cerebral cortex is governed by the combined action of pial and the intracortical vessels, which are under the influence of cholinergic parasympathetic\textsuperscript{23,24} and intracerebral nerves,\textsuperscript{1-3} respectively. In view of the known dysfunction of the intracerebral (mainly basal forebrain) cholinergic system in Alzheimer’s disease\textsuperscript{25} (AD) and of the most likely alterations of peripheral cholinergic nervous systems in this pathology (see Cholinergic Pial Vessel Functions in Alzheimer’s Disease), it is possible that the parasympathetic control of cerebral blood vessels is affected in AD.

In the present study of human brain vessels and microvessels, we report on the pharmacological and molecular identification of cerebrovascular muscarinic receptor subtypes. In addition, parasympathetic cholinergic neuronal and receptor functions were assessed in pial vessels from histopathologically confirmed cases of Alzheimer’s disease and compared to age-matched nondemented subjects. Parts of these results have been published\textsuperscript{22} or have appeared as abstract presentations.\textsuperscript{26,27}