FORUM MINIREVIEW

The Non-neuronal Cholinergic System

Preface

Koichiro Kawashima^{1,*} and Yasuyuki Nomura²

¹*Department of Pharmacology, Kyoritsu College of Pharmacy, Tokyo 105-8512, Japan*

²*Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan*

Although acetylcholine (ACh) is well known as a neurotransmitter of the cholinergic nervous systems of the animal kingdom, ACh and/or choline acetyltransferase (ChAT) — an ACh synthesizing enzyme — have also been identified in bacteria, fungi and plants. Moreover, ACh has been found in a variety of non-neuronal tissues or organs, where the expression of both muscarinic and nicotinic ACh receptors suggests the ubiquitous expression of the non-neuronal cholinergic system involved in the regulation of cell functions. The most significant advances within the field were discussed in “The Symposium on Non-neuronal Cholinergic Systems,” held for the first time at the 73rd Annual Meeting of The Japanese Pharmacological Society (March 24, 2000; Yokohama).

The biological role of non-neuronal ACh in plants and humans was reviewed by Ignaz Wessler (University of Mainz, Mainz, Germany). This classical neurotransmitter is an extremely old molecule on the evolutionary scale, being present in both procaryotic and eucaryotic cells, including human non-neuronal cells. Investigation of the effects of cholinergic agonists and antagonists has revealed some of the biological functions of the non-neuronal cholinergic system. In plants, ACh is involved in the regulation of water homeostasis and photosynthesis; in humans, non-neuronal cholinergic systems participate in the regulation of such elementary cell functions as proliferation, differentiation, cellular motility, cell-cell interactions and secretion, as well as in the transport of water and nutrients.

Takeshi Fujii (Kyoritsu College of Pharmacy, Tokyo) reviewed **an independent non-neuronal cholinergic system in lymphocytes**. The synthesis of ACh was confirmed in human leukemic T-cell lines based on the presence of ACh itself, ChAT protein and on the expression of its mRNA. Stimulation of human leukemic T-cell lines and mononuclear leukocytes enhances both the synthesis and the release of ACh, which is indicative of the activation of the lymphoid cholinergic system during immune responses. Several muscarinic ACh receptor subtypes (M₁ – M₅) are expressed in lymphocytes, and neuronal type nicotinic

receptor subunits have also been detected. Stimulation of lymphocytes with ACh or muscarinic receptor agonists elicits oscillations in the intracellular Ca²⁺ concentration and upregulation of c-fos gene expression.

The role of muscarinic ACh receptors in interleukin-2 (IL-2) formation by lymphocytes was described by Yasunobu Okuma (Hokkaido University, Sapporo). Oxotremorine-M, an M₁/M₃ agonist, enhances IL-2 production in human peripheral blood lymphocytes and in Jurkat cells, a human leukemic T-cell line expressing the M₁ and M₂ muscarinic receptor subtypes. The effect in Jurkat cells appears to be mediated by M₁ receptors via AP-1, MAP kinase and c-Jun N-terminal kinase dependent pathways.

Non-neuronal neurotransmitters including ACh in amniotic epithelial cells (AECs) were described by Norio Sakuragawa (National Institute of Neuroscience, Tokyo). ChAT activity, as well as expression of ChAT protein and mRNA, has all been detected in AECs. ACh is present in both the amniotic fluid and in the AECs themselves, although the physiological role of amniotic ACh remains unclear.

The non-neuronal cholinergic system in the endothelium was reviewed by Charles J. Kirkpatrick (University of Mainz, Mainz, Germany). Positive ChAT immunoreactivity and ChAT activity were found in human endothelial cell (EC) samples, obtained from umbilical cord, angiosarcoma and human skin blood vessels. Immunocytochemical studies indicated the expression of the vesicular ACh transporter (VACHT) system in EC. Now that the existence of essential elements of the cholinergic system (ChAT, VACHT, ACh) in human EC has been demonstrated, the biological function of endothelial ACh is the focus of research.

Concluding remarks. Accumulating evidence clearly shows the presence of non-neuronal cholinergic systems in epithelial, endothelial, mesothelial and circulating cells. The key question now is: What is the physiological significance of the non-neuronal cholinergic system? Addressing this question should contribute to a better understanding of the pathophysiology of a variety of diseases and to the development of drugs with novel mechanisms of action.

*Corresponding author. FAX: +81-3-5400-2698

E-mail: kawashima-ki@kyoritsu-ph.ac.jp