Pharmacological Seminar in Shinshu University Graduate School of Medicine:

Title: Molecular mechanisms underlying regulation of biological system by ion channels

Date: 17:00 - 18:15, March 18, 2019

Place: Asahi Life Science Research Building 9F Room D

Organizer and Chair: Prof. Mitsuhiko Yamada, M.D. Ph.D., Department of Molecular Pharmacology, Shinshu University School of Medicine, Matsumoto 390-8621 Japan

Remarks: Attending this seminar will be counted as credits of Master course students.

Contact: Prof. Mitsuhiko Yamada, Department of Molecular Pharmacology

Abstract

1. 17:00-17:35

The role of calcium in catecholaminergic automatic activity in cardiac muscle of the pulmonary vein of the rat

Ian Findlay, Ph.D.

Pharmacology Laboratory, Faculty of Pharmacy, University of Tours, France.

Abstract: Work in our laboratory is centered upon the physiology of cardiac muscle which extends into the pulmonary veins because this is a source of ectopic activity triggering paroxystic atrial fibrillation in man.

We previously reported (Doisne et al., 2009, AJP Heart 297, H102-H108) that the nonselective sympathetic agonist Noradrenalin induced automatic electrical activity in the pulmonary vein of the rat. This automatic activity consists primarily of repetitive bursts of slow action potentials. It requires the simultaneous activation of α_1- and β_1-adrenergic receptors.

Here I will describe a series of experiments where we have investigated the roles of extracellular Ca^{2+}, trans-membrane Ca^{2+} flux and intracellular Ca^{2+} cycling in this phenomenon. The results cannot be explained by any known model of automatic activity in mammalian cardiac muscle.

2. 17:35-17:55

Quantitative analyses of an atypical motion in cochlear sensory epithelium

Takeru Ota[1], Fumiaki Nin[1], Samuel Choi[2,3], Hiroshi Hibino[1,2]

[1]Department of Molecular Physiology, Niigata University School of Medicine, Niigata 951-8510, Japan; [2]AMED-CREST, AMED, Niigata 951-8510, Japan; [3]Department of Electrical and Electronics Engineering, Niigata University, Niigata 951-8510, Japan

Abstract: Mammalian hearing is achieved by electrical stimulation of the auditory nerve. The electrical signals are produced by the cochlea of the inner ear. This process is triggered by sound-evoked nanoscale vibrations in the sensory epithelium inside the organ. The epithelium contains outer hair cells that have mechanosensory hair bundles at the apical surface. The deflection of the bundles enters cation through ion channels. The epithelial vibrations are modulated by cation-induced elastic motions in the cell bodies. How the vibrations are regulated in vivo has not yet been fully elucidated. Here we develop an advanced laser interferometry that precisely detects the vibrations. When a live guinea pig was exposed to acoustic stimuli, the interferometer quantitatively recorded the vibration amplitude of the sensory epithelium as described elsewhere. Additionally,

an upward baseline shift of several nanometers was also detected. This motion was negligible when the animal was dead or under pharmacological perturbation of cell body motions. A theoretical approach further suggested that the shift protects the epithelium from injury induced by strong stimuli.

3. 17:55-18:15

Factors inducing final cardiomyocyte maturation in mice

Hiroyuki Kawagishi, Tsutomu Nakada and Mitsuhiko Yamada

Department of Molecular Pharmacology, Shinshu University School of Medicine

Abstract: Murine cardiomyocytes are still immature at birth. Within one month, they are rapidly maturated through physiological hypertrophy, enrichment of sarcoplasmic reticulum and formation of t-tubules bearing abundant L-type Ca^{2+} channels. This channel is involved in the Ca^{2+}-induced Ca^{2+} release that causes maturated excitation-contraction (EC) and forceful ventricular contraction. Although these phenotypic changings are discerned, it is unclear which factors are responsible for final cardiomyocytes maturation. In mammalian heart, the concentration of several cytokines, growth factors and hormones are known to change after birth. To assess the effect of these factors in the final cardiomyocyte maturation, we administered several inhibitors/antagonists into mice from postnatal day 1 (P1) to P20 or P30. Then, electrocardiogram and echocardiogram were performed to evaluate the cardiac function. We found that although electrocardiogram was unchanged, the left ventricular fractional shortening was significantly lower in mice treated with nintedanib, an inhibitor of FGF, PDGF, and VEGF receptors, or SC144, a glycoprotein130 antagonist than with vehicle. Analysis of intracellular Ca^{2+} transients of isolated ventricular cardiomyocyte revealed a significantly smaller peak of twitch Ca^{2+} transients in cardiomyocytes of nintedanib- or SC144-treated mice compared with control, indicating that these inhibitors impaired the final maturation of EC coupling. Taken together, it was suggested that the signaling pathways mediated by FGF/VEGF/PDGF receptors or glycoprotein130 play essential roles in the final cardiomyocyte maturation after birth.