S 12-4

CARDIAC K^+ CHANNELS

Yoshihisa Kurachi

Division of Molecular and Cellular Pharmacology, Department of Pharmacology, Graduate School of Medicine, Osaka University, Osaka, Japan

Various cardiac K channels are targets for a number of drugs. Among them, especially, HERG channel (I_{KR}) is important for elucidating the mechanism for drug-induction of lethal cardiac arrhythmia. We have examined various HERG channel blockers and found that there are a number of divergent actions of drugs on the channel. (1) Some of the drugs not only block HERG but stimulate it, which is called "facilitation". Facilitation is mediated by the drug interaction with a site of HERG channel pore distinct form the binding site for block. (2) There are a variety of voltage-dependent dynamics in drug-block of HERG. Both are important for the phenotypes in the action potential properties of the drugs. We will discuss the future possibility for prediction of the effects of HERG-channel blocking drugs on cardiac action potentials from the structure of the chemical compounds. This may be useful for the safer usage of drugs and facilitation of drug-development.

S 13-1

MODULATION BY BRAIN NATRIURETIC PEPTIDE OF GABA RECEPTORS ON RAT RETINAL ON-TYPE BIPOLAR CELLS

Xiong-Li Yang, Li-Hui Cao and Yong-Chun Yu

Institute of Neurobiology

Natriuretic peptides (NPs) may work as neuromodulators through their associated receptors (NPRs). By immunocytochemistry we showed that NPR-A and NPR-B were abundantly expressed on both ON type and OFF type bipolar cells (BCs) in rat retina, including the dendrites, somata, and axon terminals. Whole cell recordings made from isolated ON type BCs further showed that BNP suppressed $GABA_A$ receptor-, but not $GABA_C$ receptor-, mediated currents of the BCs, which was blocked by the NPR-A antagonist anantin. The NPR-C agonist c-ANF did not suppress $GABA_A$ currents. The BNP effect on $GABA_A$ currents was abolished pre-incubation with the pGC-A/B antagonist HS-142-1, but mimicked by application of 8Br-cGMP. These results suggest that elevated levels of intracellular cGMP due to activation of NPR-A may mediate the BNP effect. Internal infusion of the PKG inhibitor KT5823 largely blocked the BNP-induced reduction of $GABA_A$ currents. Moreover, calcium imaging showed that BNP caused a significant elevation of intracellular calcium that could be due to increased calcium release from intracellular stores by PKG. The BNP effect was blocked by the ryanodine receptor modulators caffeine, ryanodine and ruthenium red, but not by the IP3 receptor antagonists heparin and xestospongins-C. Furthermore, the BNP effect was abolished following application of the blocker of endoplasmic reticulum Ca^{2+}-ATPase thapsigargin and greatly reduced by the calmodulin inhibitors W-7 and calmidazolium. We therefore conclude that the increased calcium release from ryanodine sensitive calcium stores by BNP may be responsible for the BNP-caused $GABA_A$ response suppression in ON type BCs through stimulating calmodulin. We further showed in both retinal slice and isolated cell preparations that such modulation of $GABA_A$ currents by BNP was observed only when GABA was focally applied to the axon terminal, but not the soma/dendrites of these cells. Consistent with this result, BNP induced a prominent increase in $[Ca^{2+}]_i$ at the axon terminal, which was blocked by anantin, but much less at soma/dendrites. It seems likely that BNP-induced modulation of $GABA_A$ currents in ON type BCs is spatially dependent.

Key Words: brain natriuretic peptide, GABA receptor, intracellular calcium, bipolar cell