THE EFFECTS OF BAY K 8644 IN VOLTAGE CLAMP STUDIES: INDICATIONS FOR A COMMON MOLECULAR MODE OF ACTION OF Ca-AGONIST AND Ca-ANTAGONIST DI-HYDROPYRIDINES. M. Bechem, M. Schramm. Institute of Pharmacology, Bayer AG, D 5600 Wuppertal 1, FRG.

We have investigated the effects of the Ca-agonist dihydropyridine (DHP) BAY K 8644 on whole cell Ca-currents (ICa) in isolated, cultured atrial myocytes. Peak ICa during various clamp potentials was strongly increased at 0.03 µM BAY K 8644, while it was decreased at 3 µM at membrane potentials more positive than -20mV. At this high concentration an enhanced ICa could only be observed at more negative clamp potentials. Analysis of the IV-curves shows that the increase in ICa is caused by a dose-dependent shift of the single channel open probability curve to negative potentials,while the decrease results from a reduced number of available Ca-channels at high concentrations.Analyses of the ICa-activation and deactivation kinetics show that the voltage dependent mean closed times are unaffected, while the mean open times are prolonged concentration-independently.From these results a model has been derived explaining the drug effects by its binding kinetics only to the open state, resulting in an increase both of ICa as well as of Ca-channel inactivation. In addition, the same model is able to explain the effects of Ca-antagonist DHPs by a prevailing inactivation.

MYOCARDIAL STRESS WITH CATECHOLAMINE ADMINISTRATION AND CORONARY BLOOD FLOW. R.M. Berne, J.M. Gidday, H.E. Hill and R. Rubio. Department of Physiology, University of Virginia School of Medicine, Charlottesville, VA 22908 U.S.A.

It is well known that an increase in the rate of cardiac metabolism is accompanied by a parallel increase in coronary blood flow, and adenosine (ADO) is thought to be a primary mediator of this relationship. Indirect estimates of interstitial fluid (ISF) ADO levels by measurement of arterial and venous blood, lymph, tissue or pericardial infusate concentrations are all suspect because of cellular uptake (especially endothelial and blood cells) and protein binding of ADO, as well as unknown rates of equilibration between tissue compartments. With use of a covered fluid-tight chamber ($2cm^2$) containing 200 µl (1mm deep) of Krebs-Henseleit solution placed on the left ventricular wall of the open chest dog, estimates of ISF ADO were obtained. Equilibration between tissue and chamber concentrations were reached in 2-4 min at a value of 0.1 to 0.15 µM. With dobutamine administration (10 µg/kg/min i.v.) dP/dt increased 2-fold and the ADO concentration of the chamber fluid also increased 2-fold. Recovery values were not significantly different from controls. With norepinephrine administration (0.1 µg/kg/min i.v.) increments in coronary blood flow increased 170% and the ADO concentration of chamber fluid increased 176%. However, the percent changes showed variation from dog to dog. These findings support a role for adenosine in mediating changes in CBF in catecholamine-induced myocardial stress. Supported by HL-10384.

EFFECTS OF A23187 ON THE TRANSMEMBRANE ELECTRICAL ACTIVITY OF PACEMAKER CELLS OF RABBIT S.A.NODE. A.Bhatnagar, O.Tripathi. Pharmacology Division,Central Drug Research Institute, Lucknow, India.

The $Ca^{2+}$ ionophore, A23187,facilitates cellular $Ca^{2+}$ transport including the myocardium and exerts chronotropic effects on atria. This suggests its effects on the pacemaker cells (PC),where $Ca^{2+}$ influx is crucial for impulse generation. The mechanism of action of A23187 was analysed by studying its effects on action potential(AP) of PC in rabbit SA node (Tyrode: $Ca^{2+}$ 1.8 mM, pH 7.4,37°C; AP recorded by glass microelectrodes). A23187 ($5x10^{-8}$ - $5x10^{-6}$M) applied for 5-15 min caused a reduction in cycle length (CL,50%), AP amplitude and maximum diastolic potential (MDP)(5-15 mV). AP duration at -40 mV and rate of diastolic depolarisation(DD, $V^4_{max}$)were increased by 75% & 100% respectively but the upstroke velocity ($V^o_{max}$) remained unaltered. Maximal effects were produced by the first application of its effective dose. The 'effective'I-V curves for repolarisation phase show an increase in total current flow during this phase; similar curves for DD indicated an even greater increase in the current,particularly during the later part of this phase. These effects on membrane currents were seen at $\leq 1x10^{-6}$M,the concentrations $\geq 5x10^{-6}$M greatly reducing them. It is concluded that A23187 did not increase $Ca^{2+}$ channel activity in PC. Its positive chronotropic effect is mainly due to increased rate of DD; a contribution of changes in other currents to it cannot be ruled out.