Dept of Pharmacology, College of Pharmacy, Chung Ang University

It has been shown that SNP or SIN-1-induced decrease of the tone in cat LES is mediated via a NO/cGMP-dependent contraction. This study was performed using organ bath to define the participation of NO/cGMP signaling pathway on the relaxation in presence of contractile agent (carbachol). It was investigated the effect of soluble guanylate cyclase inhibitors, LY-83583 and 1H-[1,2,4]oxadiazolo[4,3-α]quinoxalin-1-one (ODQ), on sodium nitroprusside (SNP), 3-morpholino-sydnomine (SIN-1), or forskolin-induced muscle relaxation. SNP caused dose-dependent relaxation of the contraction induced by carbachol. Preincubation with NO synthase inhibitor N^{ω}-nitro-L-arginine (L-NNA) and LY-83583 had no influence on the relaxations induced by SNP. In contrast, the relaxation to SNP was blocked by ODQ. SIN-1 produced dose-dependent relaxation which was attenuated by L-NNA or ODQ, but not by LY-83583. Forskolin (0.1~10 mM) produced dose-dependent relaxation which was not inhibited by ODQ. These results suggest that SNP, or SIN-1-induced muscle relaxation in the presence of conteactile agent using cat LES is mediated by a cGMP/NO-dependent mechanism, which is similar to the relaxation to the resting tone

[PA1-35] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

Effects of Ras farnesyltransferase inhibitor, SCH66336, on insulin actions in insulin-sensitive HIRc-B fibroblasts

Yi SJ°, Choi JE, Park SN, Ha JB, Pai JK # and Jhun BH

Laboratory of Cell Biology, Dept of Pharmacy, Pusan National University, Pusan, Korea and #Department of Tumor Biology, Schering-Plough Research Institute, New Jersey, USA

Ras has been shown to be a key regulator in the mitogenic signal transduction pathways of insulin. SCH66336, an orally bioavailable nonpeptide tricyclic farnesyltransferase inhibitor of Ras, is currently under clinical trials in cancer patients. In the present studies, we examined the effects of SCH66336 on the insulin signaling pathways in HIRc-B cells, Rat 1 fibroblast overexpressing human insulin receptors. The DNA synthesis, c-Jun expression and membrane ruffling induced by insulin were blocked by microinjection of GST-fusion dominant negative Ras, GST-RasN17, confirming that Ras protein is involved in the insulin mitogenic siganling pathways. The prenylation of an isoform of endogenous Ras in HIRc-B cells was inhibited by SCH66336 in dose-dependent manner. SCH66336 caused partial dose-dependent inhibition of DNA synthesis induced by insulin, while it did not affect cell viability, c-Jun expression, and membrane ruffling induced by insulin. These results indicate that 1) SCH66336 partly blocked insulin actions leading to mitogenesis of insulin and 2) isoform of Ras, probably K/N-Ras, which is unaffected by SCH66336, may be involved in insulin signaling pathways.

[PA1-36] [04/21/2000 (Fri) 10:30 - 11:30 / [1st Fl, Bldg 3]]

The involvement of Kupffer cells in ischemia/reperfusion-induced hepatic injury

Lee YG°, Lee SH, Lee SM

College of Pharmacy, Sungkyunkwan University

Temporary interruption of hepatic blood flow is often required in the management of acute hepatic trauma and is obligatory during liver transplantation. Although growing evidences have been shown that Kupffer cells are involved in hepatic ischemic injury the mechanism of this injury still unclear. Therefore, these studies were designed to evaluate the role of Kupffer cells in hepatic ischemia/reperfusion in isolated perfused rat liver. Kupffer cells were destroyed selectively with gadolinium chloride treatment (GdCl3, 10mg/Kg) 2days prior to operation. Isolated rat livers from fasted 18 hours were preserved in UW (University of Wisconsin solution) at 4℃ for 24 hours after