cis-Diamminedichloroplatinum(II) (cisplatin or cis-DDP) is one of the most widely used cytotoxic anticancer drugs. The therapeutic effect is believed to arise from consequence of cisplat in binding to DNA. However, its clinincal efficacy is often limited due to the induction of secondary resistance. Classical anti-cancer drug resistance mechanism is frequently associated with overexpression of P-glycoprotein, a member of the ATP binding cassette family of transmembrane transport proteins capable of expelling certain cytotoxic drugs and maintaining their non-lethal intracellular level. Recently the finding that acquired multidrug resistance occurs in the absence of ATP binding cassette family protein overexpression has provided support for the existence of other mechanisms. We established cisplatin-resistant cell lines to study mechanisms of cisplatin resistance. Acquired resistant cells were obtained by growing K562 cells in stepwise increasing concentrations of cisplatin to produce resistant cell lines (K562/CDDP). The resistant cells represent resistant factor of 4.87. No differences were noted on drug accumulation between cisplatin resistant and sensitive cells. In addition, the levels of cisplatin bound to DNA in K562/CDDP decreased more rapidly than sensitive cells, suggesting that increased DNA repair capacity plays a partial role in the acquired resistance. Additionally, K562/CDDP cells were more resistant to apoptosis. DNA fragmentation and Western blot analysis showed that K562/CDDP cells had significantly more resistant to proteolytic activation of caspase-3 with higher levels of the anti-apoptotic protein Bcl-2. These results suggest that blocking of apoptosis through the suppression caspase-3 activation in K562 cells may be responsible for cisplatin resistance.

[PA1-4] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Comparison of antitumor activity between oxaliplatin and cisplatin given alone and in combination with 5-fluorouracil in human gastric cancer cells with different mismatch repair enzyme status.

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Oxaliplatin (LOHP) approved for metastatic colorectal cancers showed activity against various tumors including cisplatin (CDDP)-resistant tumors. Although its activity against gastric cancer has been suggested, no preclinical data are available to support its clinical application. We evaluated antitumor activity of LOHP alone and in combination with 5-FU and then compared with that of CDDP in five human gastric cancer cell lines *in vitro*. LOHP showed cytotoxicity similar to CDDP as determined by XTT assay with IC_{50} ranging from 1.58 to 17.0㎍/㎖. Deficiency of mismatch repair (MMR) enzyme causes resistance to many cytotoxic drugs including CDDP and 5-FU. SNU-1 cells are hMLH1-deficient due to a non-sense mutation resulting in protein truncation. However, no significant resistance to CDDP was observed in SNU-1 when compared with MKN-45 cells expressing hMLH1 abundantly. When combined with 5-FU, synergistic interaction of both LOHP and CDDP was dependent on cell line, dose ratio, and fraction affected. In MKN-45, both LOHP+5-FU and CDDP+5-FU showed similar synergistic interaction profiles. In MMR deficient-SNU-1, however, the synergism of LOHP+5-FU was greater than that of CDDP+5-FU. In summary, LOHP alone was as active as CDDP against human gastric cancer cells and its synergistic interaction with 5-FU was superior to that of CDDP. The present study indicates that LOHP may be a promising agent not only as monotherapy but also in combination with 5-FU against human gastric cancers.

[PA1-5] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Mechanism of Epibatidine-Induced Catecholamine Secretion in the Perfused Rat Adrenal Gland

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The present study was attemted to invesigate the characteristics of epibatidine on secretion of catecholamine (CA) in the isolated perfused rat adrenal gland and to establish the mechanisim of action. Epibatidine (3 ηM) injected into an adrenal vein produced a great response of in CA secretion from the perfused rat adrenal gland. However, upon the repeated injection of epibatidine (3 ηM) at 15 min intervals, Ca secretion was rapidly decreased after 2nd injection of epibatidine. However, there was no difference between CA secretory responses of both 1st and 2nd periods by the successive administration of epibatidine at 120 min-intervals. Tachyphylaxis to releasing effects of CA evoked by epibatidine was observed by the repeated administration. Therefore, in all subsequent experiments, epibatidine was not administered successively more than 120 min-intervals. The epibatidine-induced CA secretion was markedly inhibited by the pretreatment with atropine,chlorisondamine, pirenzepine, nicardipine, TMB-8, and perfusion of Ca2+-free krebs solution containing EGTA, while was not affected by diphenhydramine. Moreover, the CA secretion evoked by ACh for 1st period(0-4min)was potentiated by the simultaneous perfusion of epibatidine (1.5 ηM), but followed by great reduction immediately after 2nd period. The CA release evoked by high potassium(5.6 ηM) for 1st period (0-4 min) was also enhanced by the simultaneous perfusion of epibatidine, but those immediately after 2nd period were not affects. Taken together, these experimental data suggest that epibatidine causes catecholamine secretion in a calcium dependent fashion from the perfused rat adrenal gland through activation of neuronal cholinergic (nicotine and muscarinic) receptors location in adrenomedullary chromaffin cells. It also seems that epibatidine-evoked catecholamine release is not relevant to activation of cholinergic histaminergic receptors.

[PA1-6] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Evaluation of COX-2 expression in human gastric tumors and COX-2 suppression by aspirin and SC-236 in human gastric cancer cells in vitro.

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Over-expression of cyclooxygenase (COX)-2 has been observed in various tumors and specific COX-2 inhibitors are being tested in clinical trials for colon cancer prevention. In this study, COX-2 expression in gastric tumors and the effect of non-specific (aspirin) and specific (SC-236) COX-2 inhibitors in human gastric cancer cell lines in vitro were studied. COX-2 protein was expressed in ~80% and ~20% of glandular epithelial (GE) cells in tumor tissue (T) and adenomatous polyp, respectively, and mainly localized in the luminal side. No expression was seen in atrophic gastritis. Infiltrated inflammatory cells showed over-expression of COX-2 protein. COX-1 protein expression was negligible in all tissues. COX-2 mRNA level by RT-PCR was higher in T than the adjacent normal tissue. The basal levels of COX-2 mRNA and protein showed different rank orders among four human gastric cancer cell lines, among which SNU-216 showed significant level of both mRNA and protein and was selected for in vitro exp. The suppression of COX-2 mRNA was shown after 24 hr and 48hr at 10 mM and 5mM of aspirin, respectively. Compared to COX-2, COX-1 protein was expressed at a lower level and suppressed by lower conc of aspirin (1mM vs 20 mM) after 48hr exposure. PGE2 production decreased to 50% after 24hr exposure at 20mM of aspirin as determined by EIA. COX-2 protein expression was suppressed after exposure to 1 mM of SC-236 for 48hr. The cytotoxic $IC_{50,72hr}$ was 14.9 mM as measured by XTT and at this conc, apoptosis was induced after 12hr shown by DAPI staining. In summary, over-expression of COX-2 mRNA and protein was observed in pt tumors and cancer cell lines, and SC-236 showed potent cytotoxicity via apoptosis and effectively suppressed COX-2 protein expression. These data indicate that (1) COX-2 over-expression may contribute to carcinogenesis of gastric cancer and (2) studies on the detailed molecular mechanisms of this selective COX-2 inhibitor are needed.