

HIMI N: Analysis of Autonomic Nervous Reactions Accompanying Nausea Induced by Visual Stimulation 229-241

In this study, the autonomic nervous reactions accompanying nausea induced by visual stimulation were analyzed quantitatively in humans.

Nineteen healthy subjects who were sitting, and who were both physically rested and relaxed, were exposed to a six-minute oscillating movie as visual stimulation. Before, during and after watching the movie, gastric myoelectric activities (EGG), heart rate (ECG), respiration frequency, perspiration volume from the surface of the right palm and forehead, and peripheral blood flow in a forefinger were measured in each subject. These items were analyzed as an index of autonomic nervous activities. The examination period was divided into four phases, i.e., phase 1: control, phase 2: the first half of watching the movie, phase 3: the latter half of watching the movie and phase 4: the five minute period after watching the movie.

The scores for 13 items of subjective symptoms, which the subjects were questioned about before and after watching the movie, showed that the visual stimulation sufficiently evoked nausea. Analysis of the EGGs showed that the amplitude of gastric myoelectric activities were augmented in phase 3 as compared to those in phase 1 ($P<0.05$). However, distribution of amplitude of bradygastria, normalgastria and tachygastria did not change significantly among the phases. The heart rate decreased in phase 2 ($P<0.05$), but this decrease was temporary and soon returned to the control level. The respiration frequency increased during the phases 2 and 3 ($P<0.05$). The perspiration volume from the palm showed no change during the examination but that from the forehead increased during watching of the movie ($P<0.05$). Peripheral blood flow temporarily decreased in phase 2 ($P<0.05$), but returned to the control level in the following phases. In 6 fasting subjects, augmentation of EGG amplitude in phase 2 was smaller than that in the other 13 postprandial subjects. The subjective nausea symptoms score in the fasting subjects was lower than that in the postprandial subjects ($P<0.05$).

The expressions of these autonomic nervous reactions were presumed to be the preparations for vomiting, and the results of unconscious activities to prevent the transition to vomiting from nausea.

In conclusion, nausea is attended by fast and temporary parasympathetic nervous activity and the mixture of sympathetic and parasympathetic nervous activities in the latter phases.

[Introduction] Intrarectal administration of indomethacin induces longitudinal ulcers of the small intestine in rats similar to those in Crohn's disease. A recent study reported that lipopolysaccharide from intestinal flora played a central role in this experimental enteropathy.

[Aims & Methods] The aim of this study was to investigate the role of macrophages in indomethacin-induced enteropathy. In the first experiment, male Wistar rats were intraperitoneally given liposomes containing 50, 200 or 400 mg/kg of dichloromethylene-bisphosphonate (Cl₂MBP), which is known to injure macrophages. Four days after the Cl₂MBP-liposome administration, the number of macrophages in the small intestine was evaluated by the immunohistochemical method. In the second experiment, the rats administered 400 mg/kg of Cl₂MBP-liposomes were intrarectally given 24 mg/kg of indomethacin. In the third experiment, the conventional Wistar rats were intraperitoneally given anti-cytokine neutralizing antibodies against tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and interleukin-1 β (IL-1 β) before indomethacin administration. In the fourth experiment, after administration of Cl₂MBP-liposomes, the macrophage-depleted rats were given recombinant rat TNF- α , IL-6 and IL-1 β before indomethacin administration. In all experiments except the first one, small intestinal damage was macroscopically and histologically assessed 24 hours after indomethacin administration.

[Results] In all the rats administered Cl₂MBP-liposomes, depletion of macrophages in the small intestine was observed. Indomethacin-induced small intestinal damage in these macrophage-depleted rats strikingly decreased to 19.6%. Administration of anti-TNF- α , IL-6 and IL-1 β neutralizing antibodies significantly ameliorated indomethacin enteropathy in a dose-dependent fashion. Inhibition of enteropathy by a combination of the three antibodies reached up to 87.5%, which was equal to that in the macrophage-depleted rats. Additional administration of recombinant rat proinflammatory cytokines restored indomethacin enteropathy in the macrophage-depleted rats.

[Conclusions] The results indicated that macrophages play an important role in indomethacin enteropathy in rats via the production of proinflammatory cytokines.

[Background] The effects of chemopreventive agents on carcinogenesis were examined using a hamster model (cholecystoduodenostomy with dissection of the extrahepatic bile duct at the distal end of the common duct [CDDB] model) initiated with *N*-Nitrosobis (2-oxopropyl) amine (BOP).

It is recognized that the CDDB model replicates pancreaticobiliary maljunction in man.

[Material and method] Seven-week old Syrian golden hamsters were operated on for the CDDB model.

Four weeks after CDDB, all the animals were subcutaneously injected with BOP (10 mg/kg) weekly for six weeks.

The animals were divided into six groups; group 1 received drinking water throughout the experimental period, group 2 received cimetidine throughout the experimental period, group 3 received FOY-305 throughout the experimental period, group 4 received ranitidine throughout the experimental period, group 5 received etodolac throughout the experimental period, and group 6 received MGN-3 throughout the experimental period.

[Results] The mean number of carcinomas and total lesions in the pancreas, atypical hyperplasia lesions in the extrahepatic bile duct, atypical hyperplasia and carcinoma lesions in the intrahepatic bile duct, and atypical hyperplasia and total lesions in the gallbladder in the etodolac group were significantly less than those in the no therapy group.

The mean number of hyperplasia and total lesions in the pancreas, atypical hyperplasia and total lesions in the extrahepatic bile duct, and total lesions in the gallbladder in the cimetidine group were significantly less than those in the no therapy group.

The mean number of hyperplasia lesions in the pancreas in the ranitidine group was significantly less than that in the no therapy group, but no difference in other lesions was observed.

The mean number of hyperplasia and total lesions in the pancreas, atypical hyperplasia and total lesions in the extrahepatic bile duct, atypical hyperplasia lesions in the intrahepatic bile duct, and atypical hyperplasia and total lesions in the gallbladder in the FOY-305 group was significantly less than those in no therapy group.

The mean number of hyperplasia lesions in the gallbladder in the MGN-3 group was significantly less than that in the no therapy group. There was not a difference in the mean number of total lesions in the intrahepatic bile duct, but the mean number of hyperplasia lesions in the MGN-3 group was significantly higher than that in the no therapy group.

[Discussion and conclusion] These results suggest that etodolac, which has the inhibitory effects of a cyclooxygenase-2, has chemopreventive potential in the CDDB model.

Cimetidine and ranitidine are histamine type-2 receptor antagonists. The main chemopreventive effect of cimetidine might be its inhibitory effects on E-setectoin. It does not influence the quantity of reflux of duodenal contents into the biliary tract.

The serine protease inhibitor FOY-305 inhibited lesion development. This is probably because this CDDB model affects the activity of the pancreatic enzyme.

Etodolac, cimetidine and FOY-305 can be administered orally and no side effects were seen.

These results suggest that these agents escapes from MGN-3 have a chemopreventive potential in the CDDB model.

Although correlation between variations in the inspiratory to expiratory ratio (I:E ratio) and intracranial pressure (ICP) has not been clarified, the study of Mihira showed that IRV (at I:E ratios of 1.7:1, 2.3:1, and 4:1) does not influence ICP in dogs with normal or elevated ICP. In order to estimate the influence of lowered lung compliance on ICP during IRV, an additional study was designed to observe the effects of the I:E ratio=1:2 to 4:1 on ICP in 10 dogs with pulmonary edema induced by Oleic acid. Following baseline measurement of control ventilation (I:E ratio=1:2), lung edema was induced by venous injection of Oleic acid (0.05 mL/kg). After verifying the reduction of lung compliance, four different I:E ratios were applied in the order of I:E=1:2, 1.7:1, 2.3:1, and 4:1. Throughout the period of these measurements, PaCO₂ constantly maintained normocapnia and arterial blood pressure was kept within normal range.

Intracranial hemodynamics (ICP, cerebral perfusion pressure), lung mechanics (mean airway pressure (mAWP), peak inspiratory pressure (PIP), lung compliance), systemic hemodynamics (mean arterial pressure, mean pulmonary artery pressure, central venous pressure, cardiac output), and blood gases were measured at 30 min under every I:E ratio ventilatory mode.

In these dogs with pulmonary edema, mAWP significantly increased during IRV in comparison with that during control ventilation ($p<0.05$), but there was no significant difference in PIP between control ventilation and IRV. ICP remained unchanged during IRV (12.5 ± 4.2 , 10.0 ± 2.9 , 11.1 ± 2.2 , 11.3 ± 2.7 at I:E=1:2, 1.7:1, 2.3:1 and 4:1, respectively).

This study suggested that IRV (at I:E ratios of 1.7:1, 2.3:1 and 4:1), which can minimize ventilator-induced lung injury, has no influence on ICP. Therefore, IRV may be one beneficial option as ventilation strategy for acute respiratory distress syndrome with intracranial hypertension.

TAKEO T, MAJIMA T and TSUNODA T: Carcinogenesis and Change in the Biliary Epithelium in a Hamster CDDB Model without Carcinogen 279-286

It is well known that pancreaticobiliary maljunction (PBM) in the pancreatobiliary system promotes development of biliary carcinoma in man.

The reflux of pancreatic juice into the biliary tract is considered to be one factor promoting biliary carcinoma.

Therefore, we carried out a cholecystoduodenostomy with dissection of the extrahepatic bile duct at the distal end of the common duct (CDDB) in hamsters in such a way that pancreatic juice and duodenal contents would enter the biliary tract.

After with CDDB, all the animals were fed a basal diet and provided drinking water ad libitum without the use of a carcinogen until they were sacrificed at 6 months or 12 months.

In the six-month group, hyperplasia of the epithelium in the gallbladder was observed in 100%. Severe dysplasia of the epithelium in the gallbladder was noted in one out of six hamsters.

The cell kinetics of the gallbladder epithelium were examined using the PCNA-labeling index (PCNA LI). A high PCNA LI in the epithelium of the gallbladder was demonstrated in hamsters that had undergone CDDB but not in those who had not.

Although inflammatory cells permeated the epithelium of the extrahepatic bile duct, no hyperplasia was observed.

No pathological findings were made in the liver or pancreas.

In the 12 month group, hyperplasia of the epithelium of the gallbladder was observed in 100% and of the extrahepatic bile duct in 50%. Extrahepatic bile duct carcinoma was found in 1 out of 14 hamsters. K-ras gene mutation was not detected.

In conclusion, the CDDB procedure itself greatly accelerated cell turn-over of the epithelium in the extrahepatic biliary system.

We could observe extrahepatic biliary carcinogenesis in the model without a carcinogen.

This model allows for observation of the process from hyperplasia to carcinoma without the use of a carcinogen, and is a useful model for investigating and clarifying the mechanism of carcinogenesis in the extrahepatic biliary system.

HIRAI S: A Morphological Study of TUNEL Positive Dying Cells in the Developing Inner Ear of Mouse Embryos -CDDP-induced Change- 287-296

In the recent studies of cell death, dying cells judged by the TdT-mediated dUTP nick end-labeling (TUNEL) method have been classified into "apoptotic" and "non-apoptotic" cells. In this study, 12-day-old mouse embryos were used. The percentage of "apoptotic" and "non-apoptotic" cells among total dying cells in inner ear were calculated, and the effects on inner ear's cell death of cis-diammine-dichloroplatinum (CDDP) were examined. Five inner ears from normal embryonic mice (Control group) and five inner ears from CDDP treated embryonic mice (CDDP group) were used. TUNEL positive dying cells occurring in apoptotic cell death (ACD) and non-apoptotic cell death (NACD) were classified by light microscopy, and the numbers in ACD and NACD in the whole inner ear were counted. About 90% of the inner ear dying cells of the Control group were ACD and about 10% were NACD. About 70% of the inner ear dying cells in the CDDP group were ACD and about 30% were NACD. It was suggested that ACD essential to development of inner ear, and increased NACD might be defensive phenomenon against CDDP toxicity.

Stercoral colonic perforation is a relatively rare entity. This paper presents such a case in a 66-year-old woman.

The patient was visited the hospital because of abdominal pain. Her abdomen was board-like, there was severe tenderness in the left lower quadrant, and bowel sounds were hypoactive. The abdominal x-ray film showed free air beneath the bilateral diaphragm.

Lower gastrointestinal perforation and generalized peritonitis were diagnosed and an emergency operation performed. At laparotomy, the intestine from the descending colon to the rectum was filled with hard stool. A perforation was present in the sigmoid colon and, in the vicinity of the perforation, the stool mass had fallen away from the inside of the intestine. A Hartmann procedure was employed. On the resected material, the perforation was oval in shape. From operative and histopathological findings, a definite diagnosis of stercoral colonic perforation was made. The postoperative course was uneventful. Twelve months after the operation, closure of an artificial anus and an anastomosis between the descending colon and the rectum were performed.