TRANSIENT RECEPTOR POTENTIAL VANILLOID 1, SUBSTANCE P & REACTIVE OXYGEN SPECIES MEDIATE ETHANOL-INDUCED GASTRIC INJURY

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Introduction. The gastrointestinal tract is innervated by capsaicin-sensitive neurons containing a variety of peptides such as the neurokinin substance P (SP). SP, activating the neurokinin receptor type 1 (NK_1R), evokes the release of reactive oxygen species (ROS) in rat peritoneal mast cells, releasing mediators that are known to induce cellular stress in a number of organs. Although NK_1R antagonists prevent ethanol (EtOH)-induced gastric lesions, the mechanisms by which EtOH releases SP and SP damages the mucosa are still unknown. We hypothesized that EtOH activates transient receptor potential vanilloid 1 (TRPV1) on sensory nerves to release SP, which then stimulates epithelial NK_1R to generate damaging ROS. ***Methods.*** SP release was assayed in slices of the oxyntic region of the mouse stomach by enzyme-immunoassays. To determine the area of EtOH-induced gastric hemorrhagic lesions, the stomach was opened, photographed, and gross gastric injury was assessed by computerized planimetry. ROS-production was analysed in the mouse and rat oxyntic mucosa by confocal laser scanning microscopy using the indicator of peroxynitrite formation, dichlorofluorescein-diacetate. At last, localization of NK_1 and SP in oxyntic mucosa of rat and mouse stomach was performed by immunofluorescence. ***Results.*** EtOH (3%)-induced SP release from slices of mouse stomach (5.1 ± 0.7 fmol/g/20 min, n=8) was significantly prevented by sensory nerve desensitisation (83% of inhibition, n=10) and TRPV1 antagonism (capsazepine, 10 μM, 91% of inhibition, n=10). Orally administered EtOH (60 and 90%, 14 ml/kg) caused hemorrhagic gastric lesions that were significantly prevented by TRPV1 and NK_1R antagonism or deletion, and by the pre-treatment with three different ROS scavengers (N-acetylcysteine, ascorbic acid and lipolic acid). Again, capsaicin and exogenous SP stimulated generation of ROS by superficial gastric epithelial cells expressing NK_1R by a NK_1R-dependent mechanism. Co-administration of innocuous doses of EtOH (30%) and SP (1 μmol/kg i.v.) caused lesions by a TRPV1-independent but NK_1-dependent process. ***Conclusions.*** Here we show that EtOH activates TRPV1 on sensory nerve endings in the gastric mucosa to stimulate release of SP. EtOH causes hemorrhagic lesions of the superficial gastric mucosa at sites of NK_1R expression and ROS generation by a TRPV1- and NK_1R-dependent mechanism. This mechanism is identical in mice and rats, and may be conserved amongst species. Thus, antagonism of TRPV1 and the NK_1R may protect against the damaging effects of EtOH on the gastric mucosa, and possibly other epithelial tissues.