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Direct evidence for the exclusion of desensitization to capsaicin during two weeks treatment in human healthy subjects

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Backgrounds: Indomethacin (IND) produces gastric mucosal damage in human healthy subjects, producing an increase of gastric microbleeding (Moron *et al.*, 2003). It was also proved that the application of capsaicin is able to prevent IND-induced gastric mucosal bleeding (Mózsik *et al.*, 2003). IND acts *via* the inhibition of COX-l and COX-2 (0.30; Johns, 1999). Many researches suggest the existence of the desensibilisation of polymodal afferent nerves to capsaicin during the lifespan, producing different gastrointestinal disorders.

Aims: (i) To study the effectivity of capsaicin on the IND-induced gastric mucosal damage in human healthy subjects before and after a chronic (2 weeks) capsaicin treatment; (ii) to compare the extents of IND-induced gastric microbleedings without and with administration of capsaicin (200 and 400 μg) intragastrically before chronic administration of capsaicin (3 $\times$ 400 μg, i.g.) and (iii) to prove or to exclude the presence of desensitation of polymodal afferent nerves to capsaicin in human healthy subjects during the chronic, two weeks (3 $\times$ 400 μg, i.g.) capsaicin treatment.

Materials and methods: The observations were carried out in 14 human healthy subjects (aged 40 $\pm$ 10 years). They had no complaints, and had negative physical status and well as laboratory parameters. The extent of IND (3 $\times$ 25 mg/day)-induced gastric mucosal microbleedings (without and with application of capsaicin in doses of 200 and 400 μg, i.g.) was measured by the measurement of gastric microbleeding using the method of Hunt *et al.* (1979). The results were repeated on the same human healthy subjects after the two weeks treatment with capsaicin (3 $\times$ 400 μg ig), when the extent of IND-induced gastric mucosal bleeding (without and with application of 200 and 400 μg given orally) was calculated. The extent of the gastrointestinal bleeding was expressed in ml/day (as means $\pm$ S.E.M.; $n = 14$). The observations were carried out according to good clinical practice (GCP). The human healthy subjects were randomized to the entry of the observations, however all human subjects received the same schematic treatment and went over the all observations. Ethical Permission was obtained from the Regional Ethical Committee of Pécs University, Pécs, Hungary (April, 1997).

Results: (i) IND produced the same extent of gastric microbleeding before and after the 2 weeks of capsaicin treatment (without acute administration of capsaicin 400 μg i.g. ED_{50} = 400 μg of capsaicin on the inhibition of gastric acid secretion);

(ii) the acutely applied capsaicin (given intragastrically in different doses) dose-dependently prevented the IND-induced gastric microbleedings; (iii) the extent of the IND-induced gastric microbleedings and the dose-dependent preventive effects of capsaicin were the same before and after 2 weeks of capsaicin (3×400 μg/day orally) treatment.

Conclusions: Because the extent of IND-induced gastric microbleedings and the capsaicin preventive effect (in a dose-dependent manner) was found the same extent before and after the 2 weeks of capsaicin treatment, we exclude the development of desensibilisation of polymodal afferent nerves to capsaicin. The statement of the 'decreased sensibilisation of capsaicin-sensitive afferent nerves' has to be reconsidered in the evaluation of the polymodal capsaicin-sensitive role for evaluation of their possible ethiological role in the development of different gastrointestinal disorders.

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