

***Helicobacter pylori* associated effects on inflammatory radical formation and angiotensin II receptors in the stomach**

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssal 1, Drottning Silvias barn- och ungdomssjukhus, Göteborg, fredagen den 9 november 2007 kl. 13.00

av

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Legitimerad läkare

Fakultetsopponent:

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Avhandlingen baseras på följande arbeten:

I. Elfvin A, Bölin I, Von Bothmer C, Stolte M, Watanabe H, Fändriks L, Vieth M. *Helicobacter pylori* induces gastritis and intestinal metaplasia but no gastric adenocarcinoma in Mongolian gerbils. Scand J Gastroenterol. 2005;40(11):1313-20.

II. Elfvin A, Bölin I, Lönroth H, Fändriks L. Gastric expression of inducible nitric oxide synthase and myeloperoxidase in relation to nitrotyrosine in *Helicobacter pylori*-infected Mongolian gerbils. Scand J Gastroenterol. 2006;41(9):1013-8

III. Elfvin A, Edebo A, Bölin I, Fändriks L Quantitative measurement of nitric oxide and hydrogen peroxide in *Helicobacter pylori* infected Mongolian gerbils *in vivo*. Scand J Gastroenterol. 2007; 42(25):1-7

IV. Elfvin A, Edebo A, Hallersund P, Casselbrant A, Fändriks L. Gastric expression of NADPH oxidase, inducible nitric oxide synthase and myeloperoxidase in relation to nitrotyrosine in *Helicobacter pylori*-infected humans. In manuscript

V. Hallersund P, Ewert S, Casselbrant A, Helander H F, Edebo A, Fändriks L, Elfvin A. Angiotensin II receptor expression and location in normal and *Helicobacter pylori*-infected stomach of the Mongolian gerbil. Submitted

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ABSTRACT

Helicobacter pylori infection of the stomach always results in mucosal inflammation and a marked systemic immune response. Despite the profound host defence reactions the bacterium avoids elimination and persists in the mucosa. This results in chronic inflammation and an increased risk for peptic ulcers and adenocarcinoma. Still a majority of infected individuals never develop any symptomatic disease. Previous results from our laboratory indicate that *H. pylori* reduces the power of host defence by restricting gastric NO production by pathogen-derived competitive iNOS inhibitors. It was considered of interest to further investigate not only the *H. pylori* associated inhibition of nitro-radical formation, but also interactions with the oxy-radical formation in gastric carcinogenesis. Furthermore, because the renin angiotensin system (RAS) recently was ascribed immunomodulatory actions, it was considered of interest to also explore if *H. pylori* influences the presence and location of this regulatory system in the gastric mucosa. The *H. pylori* infected Mongolian gerbil was used as the experimental model and was followed up to 18 months after infection. A first aim of this thesis was to by use of histopathology validate the model's suitability for studies of *H. pylori* (strains SS1 and TN2GF4) induced gastric mucosal pathology. The results indicate that the *H. pylori* infected Mongolian gerbil cannot be confirmed as being a cancer model, but it is suitable for studies of acute and chronic mucosal inflammation. The Mongolian gerbil model was then used to elucidate *H. pylori* strain dependency on the expression of the oxy- and nitro-radical forming enzymes, and to investigate whether *H. pylori* infection results in inhibition of either or both of the nitro- and oxy-radical formation. Western blotting was used to assess iNOS and MPO expressions as representatives for nitro- and oxy radicalforming pathways, respectively. Radical formation was assessed as presence of nitrotyrosine or by use of NO or H₂O₂ sensitive microelectrodes. The results confirm that *H. pylori* infection in Mongolian gerbils despite an up-regulation of nitro- and oxy-radical forming enzymes results in inhibition of radical formation. Response patterns differed over time in relation to the *H. pylori* strain under study. The results were confirmed in human gastric specimens using similar western blot assessing expression of nitro- and oxy-radical forming enzymes as well as nitrotyrosine. Finally, gene transcripts and immunoreactivity to the angiotensin II receptors AT1R and AT2R were found present in the antral wall of the Mongolian gerbil. The investigation indicated a possible *H. pylori* strain dependent influence on the AT1R expression.

The present studies on experimentally infected Mongolian gerbils and asymptomatic human tissues support strongly that *H. pylori* avoids to be eliminated from the gastric mucosa by interfering with the nitro- and oxy-radical formation. In addition the investigations also suggest the presence of a *H. pylori* strain dependent influence on the AT1R expression constituting a novel immunomodulatory principle.

Key words: *Helicobacter pylori*, Mongolian gerbil, gastric adenocarcinoma, nitro-radical, iNOS, nitric oxide, nitrotyrosine, oxy-radical, myeloperoxidase, angiotensin II, AT1R, AT2R,