

Selective iNOS inhibition enhances spontaneous gallbladder motility

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Gallbladder inflammation is a common disease. Inducible nitric oxide synthase (iNOS) plays a major role in several inflammatory diseases, and selective inhibitors of iNOS activity are being developed as therapeutic agents. iNOS is continually expressed in the gastrointestinal tract of several species, however its expression in normal possum gallbladder has not been reported. Aim: Determine the effect of iNOS inhibition on normal gallbladder motility. Methods: A new highly selective iNOS inhibitor AR-C102222AA (AR-C) was used. The actions of AR-C were evaluated on possum gallbladder, in-vivo (thiopentone IV infusion; 1% at 0.8ml/h) and in-vitro muscle strip experiments. A selective neuronal nitric oxide synthase (nNOS) inhibitor S-Methyl-L-thiocitrulline (SMTC) was used to confirm the observed responses were not due to interactions with nNOS. In preliminary studies, PCR of mRNA extracted from possum gallbladder was performed using possum iNOS primers. Results: In-vivo, AR-C (30 µmol/kg IV) increased gallbladder contraction frequency ($P < 0.05$; $n = 8$), and SMTC (1-500 µg IV) had no effect ($P > 0.05$; $n = 5$). In-vitro, AR-C (0.1-1000 µM) produced a concentration-dependent increase in spontaneous gallbladder contractile activity and tone ($P < 0.05$ for each; $n = 6$ animals). The maximum effect was approximately a 2-fold increase in activity and 2.5 fold increase in tone. Preliminary investigations found pre-treatment of the gallbladder muscle strips with the neurotoxin tetrodotoxin (1 µM) did not prevent the AR-C induced increase in activity ($n = 3$). SMTC administration did not influence the spontaneous activity of gallbladder strips ($P > 0.05$; $n = 5-6$). Preliminary gene expression analysis revealed the presence of iNOS mRNA in normal gallbladder. Conclusions: These data suggest that iNOS is continually expressed in the gallbladder and may release low levels of nitric oxide, which may modulate spontaneous gallbladder motor activity.

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