The effect of cholesterol on TRPV1 function in control and streptozotocin-induced diabetic rat urinary bladder

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The TRPV1 ion channel is localised on sensory nerve endings and is activated by heat, acid and by lipid ligands including capsaicin. The TRPV1 channel may be associated with lipid rafts to facilitate interaction with specific lipid metabolites that activate the receptor. Liu et al. (2006) showed that the depletion of cholesterol from primary cultures of sensory neurons with methyl-β-cyclodextrin reduced capsaicin-activated currents.

In streptozotocin (STZ) treated rats, capsaicin evoked contractions in bladder are reduced compared to controls (Pinna et al., 1994). We have examined the effects of cholesterol depletion with methyl-β-cyclodextrin on capsaicin responses in bladder from control and STZ treated rats to see if modulation of cholesterol levels might explain the changes in response.

In the present study, it was found that adding cholesterol as cholesterol-PEG (5 mg/ml), or methyl-β-cyclodextrin (0.005 mg/ml) did not have any effect on the responses of control and diabetic rat bladder strips to carbachol or to the TRPA1 agonist allyl isothiocyanate. Methyl-β-cyclodextrin (0.005 mg/ml) enhanced the maximal contractile responses to TRPV1 agonist capsaicin in control and diabetic rat bladder strips. Cholesterol-PEG (pure cholesterol) (5 mg/ml) significantly lowered the maximal contractile responses to TRPV1 agonist capsaicin of rat bladder strips in both control from 25.31 ± 3.57 to 8.71 ± 3.38 g/g and STZ treated strips from 9.06 ± 1.69 to 4.03 ± 0.49 g/g (n=6) (p<0.05). α-cyclodextrin and β-cyclodextrin are not thought to sequester cholesterol (Vial and Evans, 2005) and so these two compounds were used as negative controls. Surprisingly, α-cyclodextrin (10⁻⁵ M) and β-cyclodextrin (10⁻⁵ M) at the same concentrations enhanced the contractile responses to TRPV1 agonist capsaicin in the control and diabetic rat bladder strips, an effect similar to that of methyl-β-cyclodextrin. These effects of cyclodextrin are specific to capsaicin activated contractions and not seen with TRPA1 activation, suggesting that the effects are not mediated downstream of channel activation. The results show that all three cyclodextrin molecules produce the same effect on the response to TRPV1 agonist capsaicin in rat bladder possibly by changing the local membrane environment of the TRPV1 channel.