STRUCTURE-ACTIVITY RELATION OF SULFONYLUREA COMPOUNDS (SUC) ON NaCl-TRANSPORT IN ISOLATED PERFUSED RABBIT CORTICAL THICK ASCENDING LIMBS OF HENLE'S LOOP (cTAL)

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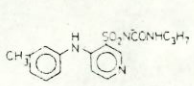
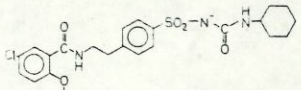
Antidiabetic SUCs inhibit ATP-dependent K^+-channels in pancreatic ß-cells; diuretic SUCs inhibit the $Na^+2Cl^-K^+$-cotransporter and Cl^--channels in the cTAL. This study examines the structure-activity relation of SUCs on equivalent short circuit current (I_{SC}) in cTAL segments. Diuretic SUCs were derivatives of torasemide (TOR), with the meta-toluol- (R_1) and the iso-propyl-group (R_2) replaced by cyclo-alkyl residues (6-8). Half maximal inhibition of I_{SC} after luminal ($IC_{50,l}$, µmol/l) and after basolateral addition ($IC_{50,bl}$), and lipid solubility as log of octanol/water-distribution (P) were determined.



torasemide



glibenclamide

R_1/R_2	TOR	6/6	6/7	6/8	7/6	8/6	8/7	8/8
$IC_{50,bl}$	37	>100	>100	85	>100	80	20	70
$IC_{50,l}$	.24	30	9.6	14	3.5	.40	2.0	.10
P	.45	1.3	1.7	2.1	1.7	2.1	2.4	2.7

The introduction of cyclo-alkyl residues increases lipid solubility and preserves the affinity to the $Na^+2Cl^-K^+$-cotransporter (e.g. 8/8). Antidiabetic SUCs (glibenclamide, glipizide, gliquidone, glibornuride, glisoxepide, tolbutamide) had no effect from the lumen and basolateral side except for glibenclamide which inhibited I_{SC} with an $IC_{50,bl}$ of 80 µmol/l. We conclude that antidiabetic SUCs do not inhibit the luminal cotransporter and K^+-channel nor the basolateral Cl^--channel in cTAL. Supported by DFG Gr 480/9

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