DIURETIC EFFECTS ON NaCl TRANSPORT BY THE FLOUNDER URINARY BLADDER (PSEUDOPLEURONECTES AMERICANUS)

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Previous results have demonstrated that the urinary bladder, Pseudopleuronectes americanus, contains a NaCl cotransport system which is relatively insensitive to the loop diuretics, furosemide and bumetanide, while being sensitive to hydrochlorothiazide and metolazone. The present experiments were conducted to examine the following questions: a) What is the dose response curve to hydrochlorothiazide? b) Is there evidence for interaction of the thiazide diuretics with a Cl binding site? c) What are the relative effects of other thiazide type diuretics and do the structure activity principles derive from whole animal experiments apply to the in vitro bladder experiments? And, d) is there evidence for cross-reactivity with known blockers of Cl channels?

The results demonstrated that hydrochlorothiazide had an IC_{50} of approximately 10 μM from the mucosal solution. Lowering mucosal Cl concentration shifted the dose response curve to the left consistent with the idea that thiazides interacted with a Cl binding site. The figure shows the structure of hydrochlorothiazide. In keeping with the commonly accepted structure-activity relationships deduced from whole animal clearance studies the results of the experiments support the following generally held principles: 1) that the sulfamoyl group on position 7 is necessary for diuretic effect, 2) substitution of nonpolar groups at position 3 enhance the diuretic potency, and 3) substitution of polar groups at position 3 reduce the diuretic potency. In addition, metolazone, tizolemide and indapamide all demonstrated approximately similar potencies to hydrochlorothiazide indicating that these agents probably also have their diuretic effects at the same site as hydrochlorothiazide.

Two other families of Cl transport inhibitors were tested. Compounds of the [aryloxy]acetic acid family showed that ethacrynic acid had low or no potency where as indacrinone and structurally related compounds exhibited good potency from the mucosal solution. Compounds of the anthranilic acid family that have been shown to be inhibitors of Cl channels also demonstrated similar potency to hydrochlorothiazide from the mucosal surface. Diphenylamine carboxylate, the most potent inhibitor of this class, did not inhibit Cl transport when applied from the serosal surface.

In conclusion, these experiments demonstrate some differences between expected potency of the thiazide-type diuretics from in vivo clearance studies. In addition, they demonstrate that inhibitors of other types of Cl transport (i.e. Cl channels) can also be inhibitors of NaCl cotransport.

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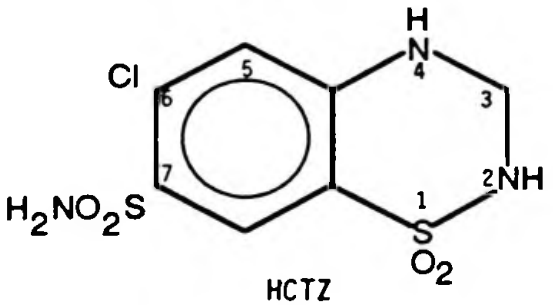

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