Mechanisms of Action of Hormones and Drugs on NaCl Transport across Renal Tubules (Effects of prostaglandin E_2 on the CNT and CCD)

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1. Effects of prostaglandin E_2 (PGE_2) on ion transport were examined by observing the transmural (V_T) and basolateral membrane voltage (V_B) in the in vitro perfused rabbit connecting tubule (CNT) and the cortical collecting duct (CCD).
2. Addition of 1 μM PGE_2 to the bath induced a biphasic response of transmural voltage (V_T), with initial negative V_T deflection followed by positive deflection in the CNT, but monophasic negative deflection in the CCD. Because PGE_2 had no effect on the basolateral membrane voltage (V_B), PGE_2 mainly causes changes in the apical membrane voltage.
3. Elimination of Na^+ from the lumen abolished the PGE_2-induced V_T response in the CNT. In the presence of 10 μM luminal amiloride, PGE_2 only caused initial negative deflection without causing later positive deflection. The positive V_T deflection induced by PGE_2 in the CCD was also blocked by luminal amiloride.
4. Addition of ouabain (0.1 mM) to the bath completely abolished the PGE_2-induced V_T changes in the CNT, indicating that intact Na^+-K^+ pump is prerequisite for the V_T response to PGE_2.
5. Addition of 2 mM Ba^{2+} to the lumen did not affect biphasic V_T response to PGE_2, indicting that Ba^{2+} sensitive K^+ conductance is not involved.
6. Basolateral addition of 0.1 mM 8-(p-chlorophenylthio)-cAMP inhibited only the negative V_T deflection induced by PGE_2.
7. The positive V_T deflection was blocked by basolateral addition of 50 μM 8-(N,N-dimethylamino) octyl-3,4,5-trimethoxy-benzoate hydrochloride (TMB-8), an inhibitor of intracellular Ca^{2+} release. But elimination of luminal Ca^{2+} did not affect the biphasic response to PGE_2.
8. These findings suggest that the initial negative V_T deflection is caused by an increase in Na^+ influx across the luminal membrane through an amiloride-insensitive Na^+ conductive pathway, whereas the later positive deflection is caused by the inhibition of Na^+ influx through the amiloride-sensitive Na^+ conductive pathway. The cAMP messenger system may be responsible for the initial negative deflection, whereas an increased intercellular Ca^{2+} released from the store is necessary for the later positive deflection caused by PGE_2. The response in the CCD is comparable to the later response in the CNT.