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The Physiological Meaning of Rapid Responses to Steroid Hormones in Epithelia

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Over the past decade the number of reports dealing with cell signalling aspects of fast actions of steroid hormones has multiplied without an accompanying validation of their physiological meaning. The reasons for this mismatch between signal transduction and a physiological role are in the main due to difficulties in identification of the 'non-genomic' hormone receptor and the apparent lack of rapid effects on trans-epithelial ion transport. In vascular tissue, the rapid responses to aldosterone may be important in the acute control of blood pressure (1). However, in epithelial target tissues, the rapid non-genomic effects of aldosterone and oestrogen have been difficult to reconcile with the known 'classical' latent genomic effects of these hormones on salt and fluid retention. In human and rat distal colon, both these hormones cause rapid activation of Na/H exchange at the basolateral cell membrane which is dependent on protein kinase C and Ca^{2+} signal transduction (2-5). Aldosterone and oestradiol differ in their protein kinase signal transduction. Oestradiol stimulates PKA by first activating PKCδ and adenylate cyclase and cAMP. In contrast, aldosterone has no effect on cAMP or PKA activity. The effects of aldosterone and oestradiol on PKC are isoform-specific. Aldosterone activates PKCα only, whereas oestradiol stimulates both PKCα and PKCδ (6). The stimulation of PKC and the Na/H exchanger are required for the effects of these hormones on basolateral K^+ channels. Both aldosterone and 17-beta-oestradiol, at physiological concentrations (0.1-1 nM), activate within 5 min, a class of ATP-sensitive- K^+ channels and inhibit a class of calcium-dependent K^+ channels in human distal colon. The K-ATP channel is required for K^+ recycling in surface cells and maintains the electrical driving force for amiloride-sensitive sodium absorption. The K-Ca channels are involved in charge balance for chloride secretion in crypt cells (7). Thus it would appear that the rapid response to these steroid hormones in pluripotential epithelia is to enhance the capacity for absorption while down-regulating the potential for secretion. In support of this hypothesis, we have recently shown that oestradiol inhibits both forskolin and carbachol-stimulated secretion in rat distal colon (8).

Some of the classical models for studying genomic effects of aldosterone in epithelia are the amphibian skin and urinary bladder. A rapid non-genomic effect of aldosterone to activate basolateral K-ATP channels has been demonstrated in the sodium-absorptive cells of frog skin (9). These effects occur within 5 min, yet the stimulation of trans-epithelial sodium absorption does not occur until 1-2 hr post hormone. This paradox is understood when we consider that the membrane potential is already close to the equilibrium potential for K^+. Therefore activation of basolateral K-ATP channels will not greatly influence the electrical driving force for Na^+ absorption but will increase the basolateral membrane conductance. This will serve as a 'physiological voltage-clamp' which will counteract membrane depolarization produced by Na^+ entry into the cell during the genomic phase of enhanced sodium absorption. The physiological role, therefore, of a rapid and maintained response to aldosterone may be to preserve the driving force for chronic Na^+ absorption.

Frog skin has also been used as a model to study electrogenic proton secretion which is also a characteristic function of renal intercalated cells. Aldosterone rapidly activates hydrogen flux out of mitochondria-rich cells by causing fusion of vesicles containing proton-ATPase pumps with the apical membrane (10). Since sodium absorption and proton secretion are indirectly electrically coupled under physiological conditions, the rapid effects of aldosterone to stimulate H^+ pumping will also cause a rapid increase in transepithelial Na^+ absorption. Practically all transport studies in tight epithelia are done under non-physiological conditions (high luminal Na^+ concentration and short-circuit current conditions), when H^+ and Na^+ fluxes are uncoupled. It is most likely, therefore, we have missed for over the past thirty years, a physiological fast effect of aldosterone on transepithelial Na^+ uptake. Clearly, the reconciliation of rapid effects of

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steroid hormones on cell signaling with a physiological role requires an integrative approach where both the measurement of the cytosolic transduction processes and the ion transporter effects are determined simultaneously in whole tissue and under physiological conditions.

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