Purinergic regulation of epithelial Na^+ channels

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The epithelial Na^+ channels (ENaC) expressed in Na^+-absorbing tissues, such as the kidney collecting duct, distal colon and the respiratory epithelium, play an important role in Na^+ and fluid homeostasis, controlling blood pressure and regulating the level of alveolar fluid. Aberrations of ENaC function may lead to hypertension, hypotension, pulmonary edema and reduction of mucociliary clearance of the airways. The epithelia lining the lung, kidney and gut release nucleotides in response to physiological stimuli, activating P2Y purinergic receptors in either an autocrine or paracrine manner to regulate an array of physiological mechanisms, including ion transport by these tissues. In the aldosterone-sensitive segment of the kidney, activation of purinergic receptors at the apical or basolateral membranes significantly inhibits amiloride-sensitive Na^+ absorption mediated by the epithelial Na^+ channels (Vallon, 2008). Similarly, inhibition of ENaC during purinergic receptor activation has been reported in epithelia lining the lung and gut (Kunzelmann *et al.,* 2001; Matos *et al.,* 2007). The absence of any negative effect of nucleotides on the activity of ENaC in $P2Y_2$ knock-out mice (Matos *et al.,* 2007) suggests that $P2Y_2$ receptors may be responsible for purinergic regulation of ENaC. In the past decade, the $P2Y_2$ receptor-activated signaling mechanisms that regulate activity of ENaC have been extensively investigated. It has been reported that nucleotides may mediate their effect on ENaC via pertussis toxin-sensitive G-proteins (Kunzelmann *et al.,* 2002). Our recent studies, which used gene interference and gene expression techniques, suggest that free $G\beta\gamma$-dimers, released from pertussis-sensitive G-proteins during $P2Y_2$ receptor activation, may mediate the purinergic regulation of ENaC activity. The signaling mechanism involved requires activity of PLCβ4, but appears to be independent of the traditional signaling effector molecules downstream of PLC, such as $[Ca^{2+}]_i$, PKC or MAP kinase. We conclude that depletion of membrane phophatydylinositol 4,5-biphosphate (PIP_2), induced by activity of PLC activated during $P2Y_2$ receptor stimulation, may play an important role in mediating downregulation of ENaC activity during $P2Y_2$ receptor activation.

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