A new mechanism for respiratory syncytial virus-induced $\beta_2$-adrenergic receptor insensitivity

Christine Clerici

Institut National de la Santé et de la Recherche Médicale, U773, CRB3; Université Denis Diderot-Paris 7, AP-HP, Hôpital Bichat-Claude Bernard, Service de Physiologie, Paris, France

Respiratory syncytial virus (RSV) is the most common infectious cause of wheezing in infants and children and is a frequent initiator of acute asthma exacerbations (13). The mechanism by which RSV results in airway obstruction is not completely understood but includes an increase in airway smooth muscle constriction and the presence of airway edema with mucus secretion and of luminal collections of desquamated airway epithelial and inflammatory cells (14). Airway epithelial cell involvement has a central role in the pathophysiology of RSV infection and directly participates in the airway obstruction through several pathways. RSV replicated in the nasopharyngeal epithelium and spread to the lower respiratory tract via epithelial cell-to-cell transfer along intracytoplasmic bridges leads to sloughing and necrosis of the epithelial surface and mucus plugging of the airway. In addition, epithelial cells infected by RSV secrete a large panel of chemokines, among them CC (RANTES, MCP-1, MIP-1$\alpha$, and MIP-1$\beta$) and CXC chemokines (IL-8, CXCL8) that are directly involved in the recruitment of immune and inflammatory cells, which in turn induce increased vascular permeability with airway edema and may favor, through a paracrine pathway, constriction of smooth muscle cells (16). Finally, a recent study shows in RSV-infected mice a decrease of Na transport across distal airway epithelium with reduced alveolar fluid clearance (AFC) (5) favoring alveolar edema, which could participate in distal airway obstruction.

$\beta_2$-adrenergic receptors ($\beta_2$-AR) are distributed along airway epithelial cells, and their number rises with increasing airway generation, with the greatest amount in the distal airways and in the alveoli. More than 90% of all human lung $\beta_2$-AR are localized in the alveoli where the $\beta_2$ predominate both in alveolar type 1 and type 2 cells (3). $\beta_2$-AR mediated differential and important effects that may limit the consequences of RSV infection both in airway epithelial and smooth muscle cells. Previous reports have shown that, in infected airway epithelial cells, $\beta_2$-agonists reduce inflammatory cytokine production (11). Moreover, it has been largely demonstrated that $\beta_2$-agonists accelerate AFC in injured lung via an increase of alveolar active Na transport (7, 10). Although a potential benefit of $\beta_2$-agonist medication on RSV infection-induced airway obstruction may be expected, the results of clinical studies have not been conclusive (15). Meta-analyses have shown little or no overall benefit in children with RSV infection, leading the American Academy of Pediatrics to recommend that bronchodilators should not have been used routinely in the management of bronchiolitis. Until now, the mechanisms of insensitivity to $\beta_2$-agonists in RSV infection have not been elucidated. The report of Davis and colleagues (6), in this issue, suggests that $\beta_2$-AR insensitivity to agonists is related to $\beta_2$-AR desensitization as a consequence of G protein-coupled receptor kinase (GRK) 2-mediated uncoupling of $\beta_2$-AR from adenylyl cyclase.

The $\beta_2$-AR is a member of the very large 7-transmembrane receptor superfamily of G protein-coupled receptors. $\beta_2$-AR exist in an equilibrium between at least two structural conformations, inactive and active, based on their ability to associate with the stimulatory heterotrimeric guanosine triphosphate binding protein $G_s$ (9). At rest, a small fraction of the $\beta_2$-AR population is in an active signaling state that accounts for basal cAMP production. During agonist stimulation, the receptor is moved from an inactive to active state, dissociates G protein trimer into a $G_s$-subunit and a $\beta\gamma$-dimer. $G_s$ binds to and activates adenylyl cyclase, causing increased cAMP, which in turn activates PKA and probably PKG. Shortly after activation by agonists, the $\beta_2$-AR signaling is attenuated by protein receptor kinases, GRKs, PKA, and PKC, acting on specific serine and threonines in the intracellular receptor domains. The receptor phosphorylation reduces its interaction with $G_s\alpha$ and diminishes its affinity to the ligand. GRK2 phosphorylation of the $\beta_2$-AR facilitates binding of the receptor to $\beta$-arrestins, which promotes receptor internalization and degradation or recycling (1). Also, the $\beta\gamma$-dimer dissociated from $G_s\alpha$ is not silent and may couple to inflammatory kinases such as mitogen-activated protein kinase and may coactivate AKT. There is also direct evidence that $\beta_2$-receptors may couple to other G proteins, triggering entirely different transduction pathways. The most important known example is $G_i\alpha$ coupling to PKC, a pathway usually associated with transduction of inflammatory mediator receptors (2).

In this work, Davis et al. (6) used an vivo functional model to analyze the $\beta_2$-agonist sensitivity during RSV infection. The same group has previously showed that RSV-infected mice have reduced AFC due to decreased active Na transport in distal airway epithelium (4, 5). In the present study, they demonstrated a loss of sensitivity of AFC to $\beta_2$-agonists in RSV-infected mice compared with control. Their data support the contention that RSV-induced $\beta_2$-AR desensitization resulted from receptor uncoupling due to phosphorylation by GRK2. This desensitization occurred without internalization or degradation of the $\beta_2$-AR and was associated with increased membrane $\beta_2$-AR density. This desensitization was agonist independent and could not be explained by chronic elevation of endogenous catecholamines. In this model, GRK2 was directly activated by PKC$\xi$, which is known to be a target of RSV infection. Davis et al. also demonstrated that RSV infection-induced PKC$\xi$ activation results from ligation of the chemokine CXCR8, released in response to RSV infection, on the CXCR1/2 protein-coupled receptors. This work by Davis
et al. is the first report demonstrating a loss of sensitivity to β2-agonists by respiratory epithelium following viral infection, and the step-by-step analysis of β2-AR desensitization represents an important advance in the understanding of β2-AR insensitivity. In contrast to that which is usually observed during agonist stimulation, the desensitization of β2-AR during RSV infection was not associated with internalization and degradation of the receptor. In line with this result, a recent work done in HEK cells suggests that internalization and endosomal trafficking are not necessary for the resensitization of β2-agonist receptors since the dephosphorylation can occur at the plasma membrane through factors that are either expressed constitutively at the plasma membrane or recruited during receptor activation (8). Finally, this study indicates that β2-AR desensitization occurred through an agonist-independent pathway and demonstrates for the first time that the chemokine CXCR8 has a major role in β2-AR insensitivity.

This study points out the central role of the airway epithelium in RSV infection, particularly through the secretion of chemokines, which both initiates pulmonary inflammation by mediating immune cell chemotaxis but also led to insensitivity of β2-AR, and therefore limits the beneficial effect of β2-agonists. Although there are undoubtedly differences between the murine model of RSV infection and the human disease, including β2-AR polymorphisms in humans (12), improved control of RSV-induced chemokine production represents an important therapeutic goal both by reducing inflammation and by restoring β2-AR sensitivity.

REFERENCES