

Accepted Manuscript

The beta adrenergic theory of bronchial asthma: 50 years later

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PII: S0091-6749(19)30946-7

DOI: <https://doi.org/10.1016/j.jaci.2019.07.010>

Reference: YMAI 14094

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 25 March 2019

Revised Date: 25 June 2019

Accepted Date: 12 July 2019

Please cite this article as: Camoretti-Mercado B, Lockey RF, The beta adrenergic theory of bronchial asthma: 50 years later, *Journal of Allergy and Clinical Immunology* (2019), doi: <https://doi.org/10.1016/j.jaci.2019.07.010>.

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Keywords: airway smooth muscle, allergy, asthma, beta receptor, bitter taste receptor

Disclosure of potential conflict of interest: none

Funding sources: Joy McCann Culverhouse Endowment

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21 Andor Szentivanyi, MD published his proposed “The Beta-Adrenergic Theory of Atopic
22 Abnormality in Bronchial Asthma” in 1968¹. He opens his editorial by quoting Francis M.
23 Rackemann, who in 1931 wrote, “The situation is somewhat analogous to that of a loaded gun.
24 A good deal of knowledge is being obtained about the great variety of triggers (extrinsic and
25 intrinsic causes) which fire the charge; but why is the gun loaded? And what constitutes this
26 load?”¹. Dr. Szentivanyi continues, “However, ... immunologic concepts cannot easily account
27 for some of the significant facts surrounding this disease”, leading to his proposed theory.

28
29 Richard F. Lockey, MD, senior author, was a fellow in training in allergy and immunology at the
30 University of Michigan in 1968 and remembers the impact this article had on the specialty. At that
31 time, a beta agonist, nebulized isoproterenol, was the standard of care for acute asthma, but it
32 was recognized as being potentially dangerous especially when overutilized. Actually, undesired
33 actions of isoprenaline on various organs due to its non-selectivity were considered at the root of
34 the increased mortality of young asthmatics using the drug in the 1960s in U.K., New Zealand,
35 Ireland, Australia and Norway, where a five-times stronger preparation was marketed. Countries
36 that did not experience this increase in asthma deaths had similar or higher drug utilization but a
37 lower drug concentration. A case-control study performed in the early 1980s also in New Zealand
38 found that repeated inhaled fenoterol increased the risk of death in patients with asthma even
39 after adjustment for disease severity and other asthma drugs used.

40
41 Beta receptor research became very popular for the next decades following Szentivanyi's
42 proposal. However, with the discovery of other pathophysiologic mechanisms of asthma, such as
43 allergic inflammation, genetic influences affecting lung epithelial cell function, and airway
44 remodeling, the beta receptor theory of asthma took a less prominent role in asthma research.
45 Today, the beta receptor has gained renewed importance in the understanding and management
46 of asthma with a better appreciation of the biology and pharmacology of the β 2-adrenergic

receptor (AR), the role of the airway smooth muscle (ASM), and the elucidation of novel pathways leading to bronchodilation. With more selective agonists, short-acting beta agonists (SABA) remain the mainstay to treat acute asthma whereas long-acting beta agonists (LABA), combined with inhaled corticosteroids (ICS), have synergistic beneficial effects.

Update on beta adrenergic receptor biology

According to Szentivanyi, "... abnormality in asthma lies in the reduced functioning ... of the beta adrenergic system ...", whose imbalance was mainly due to the receptor, a proposed enzyme with a decreased synthesis, partial dysfunction, or abnormal binding to catecholamines. Two adrenergic receptors, α and β , were thought to exist, with the β receptor considered to be the so-called adenyl cyclase enzyme, perhaps a lipoprotein part of an organelle associated with the cell membrane. In this model, 3',5'-cyclic adenosine monophosphate (cAMP) was synthesized from the catecholamine-adenylate cyclase interaction, destroyed by a phosphodiesterase (PDE), was a mediator of catecholamine action, and the link with the mechanical effects on muscle.

What is the current understanding of β 2-AR function? Present knowledge of the β 2-AR signaling pathway is built largely on progress associated with molecular biology and x-ray crystallography. The β 2-AR is a seven-transmembrane G-protein coupled receptor (GPCR) that activates the stimulatory G-protein (Gs) to activate adenylate cyclase (AC) and increase cAMP (Fig. 1). Elevated cAMP activates multiple targets in many cells including protein kinase A (PKA), exchange proteins activated by cAMP (Epac), and cyclic nucleotide gated (CNG) channels. However, the predominant functional target of cAMP in ASM appears to be PKA which relaxes ASM through various mechanisms including the reduction of intracellular calcium. Activated PKA induces both inactivation of myosin light-chain kinase and activation of myosin light chain phosphatase, promoting SM relaxation. Because of Ca^{2+} efflux, Ca^{2+} -activated potassium channels open causing hyperpolarization and further inhibition of ASM contraction.

The increased tolerance to epinephrine postulated by Dr. Szentivanyi is explained by the exquisite regulation of β 2-ARs. Inhalation of SABAs reduces asthma attacks but their chronic use leads to tachyphylaxis and compromised therapeutic effect. This phenomenon stems from receptor desensitization and downregulation via sorting to the lysosomes and degradation by proteases. Mechanistically, prolonged agonist stimulation induces β 2-AR phosphorylation by G protein coupled receptor kinases (GRK) resulting in interference of receptor coupling to Gs, AC desensitization, and receptor binding to the adaptor β -arrestin with subsequent receptor sequestration (Fig. 1). cAMP promotes β 2-AR downregulation through receptor phosphorylation by PKA and reduction of β 2-AR mRNA levels. Moreover, formoterol, a LABA, induces PDE4 mRNA upregulation in ASM and lowers cAMP abundance. Structure-function studies indicate that β 2-ARs that are unable to couple Gs could be sequestered normally but their downregulation by agonist requires coupling.

Despite the demonstration of the benefits of β -agonists in short-term trials, chronically treated asthmatics with SABA sometimes experience, paradoxically, increased bronchoconstriction. Salmeterol and formoterol are the most commonly utilized LABAs. Reports of asthma exacerbations and death in a very small percentage (<1%) of asthmatics prompted the U.S. FDA in 2010 to require a black box warning on all LABA-containing products. The FDA announced the need to conduct clinical trials comparing the addition of LABAs to ICS versus ICS alone. These studies recruited over 46,000 subjects and showed that the risk of serious asthma-related events and deaths and the number of hospitalizations were not greater with ICS/LABAs than ICS alone and that the combination was also effective and beneficial as well^{2,3,4}. Therefore, the FDA removed the warning on LABA combined with a glucocorticoid in asthma medications in 2018, but it remains in all single-ingredient LABA medications. Thus, LABAs should not be used as

monotherapy to treat asthma but only in combination with a corticosteroid, the latter of which treats the underlying inflammation of the airways.

Adverse effects of β -agonists were more pronounced when high intrinsic efficacy agonists were utilized and could be correlated with certain β 2-AR genotypes, rare variants, and disease severity. Over 50 single nucleotide polymorphisms (SNPs) within the β 2-AR gene (*ADRB2*) have been identified. Some variants have functional effects and Arg16Gly is one of the most common SNPs studied. Asthmatics with the Gly/Gly genotype exhibit an increase in morning-peak expiratory flow rate (M-PEFR) with regularly scheduled albuterol versus placebo. In contrast, patients with the Arg/Arg genotype show an increase in M-PEFR with placebo and no significant change with albuterol. Moreover, asthmatics with the Arg/Arg versus Gly/Gly genotype improved their M-PEFR during the run-in period when all subjects only received placebo⁵. All patients had access to ipratropium bromide as a primary rescue medication throughout the entire trial. This protocol diverged from other studies that used as-needed β -agonists as a rescue medication. It unmasked an improvement in airway obstruction in Arg/Arg patients with withdrawal of as-needed albuterol. Whether this effect is related to enhanced sensitivity to ipratropium bromide action in this population is unknown.

Race and ethnicity are risk factors for asthma in African Americans (AA) and Puerto Ricans (PR), who exhibit higher morbidity and mortality rates than non-Latino Whites (NLW) of European ancestry. Ortega et al.⁶ identified six rare *ADRB2* variants in AA, PR, and NLW subpopulations not associated with asthma susceptibility. However, they found an increased likelihood of asthma exacerbation-driven hospitalizations when using LABA both in NLW who have the ¹⁶⁴Ile variant and in AA harboring the 25 bp promoter insertion. This finding suggests that rare *ADRB2* variants versus common SNPs such as Gly16Arg might contribute to life-threatening asthma events.

Variability of β -agonist response that is not satisfactorily explained by differences in the coding or regulatory 5'-untranslated region (UTR) of *ADRB2* could involve the 3'-UTR that contains a poly-C tract with 11, 12, or 13 Cs. Cells transfected with *ADRB2*(Arg16)-C11 but not *ADRB2*(Arg16)-C12 exhibit a low-response phenotype due to a decreased baseline receptor expression and increased receptor downregulation.

The role of the airway smooth muscle

Dr. Szentivanyi's postulate takes into consideration that smooth muscle spasm is one of the principal components of bronchial obstruction. Whether the ASM of asthmatics and non-asthmatics are intrinsically different is not yet fully established, partially due to the scarcity of adequate human specimens for experimentation. Ex vivo studies of fatal asthma show increased muscle response to bronchoconstrictors and reduced relaxation to isoproterenol compared to controls⁷. Moreover, proliferation of ASM single cells growing in culture is elevated in patients with asthma¹⁹. Recent studies report that the mechanical properties of ASM from asthmatics and non-asthmatics seem to be equivalent except for increased passive stiffness and less attenuation in force after stretch in asthmatic tissue⁸; this is consistent with less airway dilation induced by deep inspiration observed in asthmatics. Ijpma et al.⁹ reported that contractility of tracheal and bronchial SM is not increased in asthma, although the responsiveness of intrapulmonary airways was not examined. It is important to note that the effect of desensitization or aggravated response because of prolonged agonist exposure is not addressed in most studies.

Dr. Szentivanyi's model also states that the principal tenets of "...the beta adrenergic theory regards asthma not as an 'immunological' disease but as a unique pattern of bronchial hyperreactivity to a broad spectrum of immunological, psychic, infectious, chemical, and physical

stimuli.” Today, we know that the pathophysiology of asthma is multifactorial, consisting of various phenotypes and endotypes, and that medications which stimulate the beta receptor on the ASM are efficient bronchodilators to treat this disease regardless of the triggering factors and accompanying co-morbidities.

New direct bronchodilators

β -agonists are the only bronchodilators that directly effect ASM function. Importantly, agonists of bitter taste receptors (TAS2R), a family of GPCRs present in the lung, represent a potential new class of medications that could effectively dilate ASM when stimulated with bronchoconstrictors such as histamine, methacholine, or bradykinin¹⁰. Attractive characteristics of TAS2R agonists include their direct effect on ASM through the utilization of a mechanism distinct from the β 2-AR, preserved functionality in asthmatic ASM and in the presence of inflammation, and a small degree of tachyphylaxis. GPCRs are localized at the cell membrane, accessible to the environment, and constitute the targets of about 35% of approved drugs. Future studies will establish whether novel TAS2R agonists could be added to current or new β 2-agonists to treat asthma.

The β 2-receptor and its signaling pathway remain sentinel to the pathogenesis and treatment of asthma. This system has been forgotten to some extent because of the emphasis on inflammation as the prominent etiology of asthma. Asthma is a heterogeneous disease with multiple abnormalities including those of the β 2-AR. Additional research is needed to further elucidate the importance of this receptor and the pathways involved in asthma management.

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Figure legend

FIG. 1 Bronchodilation through activation of β 2-AR. Upon β -agonist binding, the α_s subunit of the small G-protein Gs is activated and stimulates adenylate cyclase (AC) and protein kinase A (PKA) via cAMP. Active PKA phosphorylates several proteins (MYPT, MLCK, IP3R), resulting in myosin light chain phosphatase (MYPT) activation, inhibition of myosin light chain kinase (MLCK), and modulation of inositol 1,4,5-trisphosphate receptor (IP3R) to limit Ca^{2+} mobilization. These events oppose muscle contraction. cAMP also binds to exchange proteins activated by cAMP (Epac) to induce relaxation, to phosphodiesterases (PDEs) that hydrolyze cAMP, and to cyclic nucleotide-gated (CNG) channels (not shown). Negative regulation (dotted arrows) involves phosphorylation of AC and β 2-AR by PKA. Modified β 2-ARs become uncoupled, desensitized, and competent for internalization. GPCR kinases (GRKs) phosphorylate ligand-occupied β 2-AR. β -arrestin binds the phosphorylated receptor, blocks receptor interaction with Gs, initiates receptor internalization, and directs internalized β 2-ARs to lysosomes for degradation. A fraction of the receptors recycles to the cell membrane. Cell membrane is not depicted. GDP, guanosine diphosphate; GTP, guanosine triphosphate; P, phosphate group.

