Inhaled Adrenergic Bronchodilators: Historical Development and Clinical Application

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Introduction

Beta (β) agonist bronchodilators represent the largest single drug group among the various classes of inhaled therapeutic aerosol drugs. They also represent one of the most interesting examples of drug class development, illustrating the gradual unfolding of receptor theory concomitant with synthesis of improved drug molecules.

Historical Perspective

Ephedrine, a sympathomimetic agent contained in the plant Ephedra vulgaris, was known to the Chinese as early as 3000 BC and was used to make the drug ma huang for the treatment of asthma.[1] In the late 1800s, adrenal extracts began to be investigated and used for their vasoconstricting properties in the treatment of rhinitis and conjunctivitis, as well as asthma.[2,3] In 1899, epinephrine received its name from Abel and was soon isolated and synthesized independently by Stolz and Dakin.[4] The term "adrenaline" may have been first coined by Wilson in 1901 to refer to epinephrine.[5] In 1903, epinephrine was used by both the oral and subcutaneous routes to treat asthmatics, with subcutaneous delivery found to be more effective than oral.[6] Asthma was initially thought to be caused by vasodilation, and the efficacy of epinephrine was explained by its vasoconstricting property. It was for this reason that cocaine, a potent vasoconstrictor, had been used beginning around 1800 in asthma and rhinitis. However, in 1907 Kahn demonstrated the bronchodilator effect of epinephrine.[7] Following this, both the vasoconstrictive and bronchodilator effects of epinephrine were thought to be the basis for its beneficial effect in asthma. Barger and Dale reported the use of epinephrine as an aerosol in 1910.[8] Not until 30 years later did isoproterenol appear for bronchodilator use, and isoetharine, synthesized as early as 1936, was first reported in treating asthma in 1951.[9]

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Today, epinephrine is still available for use as a bronchodilator aerosol. Of a total of 10 drugs in the adrenergic bronchodilator group currently available as orally inhaled aerosols in the United States, nine are derivatives of epinephrine. The development of adrenergic agents has proceeded apace, with continuously improving knowledge of the receptors stimulated by these drugs. In particular, the β adrenergic receptor is now fully identified and its function clarified in detail.

Differentiation of Adrenergic Receptors

Originally, identification of adrenergic receptors was inferred indirectly from the different effects of individual adrenergic drugs. Although such drugs as epinephrine, isoproterenol, and phenylephrine were all sympathomimetic, different physiologic effects were observed among these agents. In 1948, Raymond Ahlquist published his classic paper proposing that there were two distinct adrenergic receptors, α and β.[10] The α receptor was associated with excitatory functions, with the exception of the intestine, where an inhibitory effect was observed. The β receptor was associated with inhibition, with the exception of the myocardium, where an excitatory effect was observed. This concept of two fundamental types of receptors mediating the effects of the sympathetic nervous system contrasted with the previously espoused view of Cannon and Rosenbleuth of two excitatory and inhibitory substances, sympathin E and sympathin I, as adrenergic mediators.[10]

Subsequently, Lands et al further subdivided the β receptor into two subtypes, denoted as β-1 and β-2.[11] β-1 receptors increase cardiac rate and force, relax intestinal smooth muscle, and account for the excitatory effects seen with drugs such as isoproterenol. β-2 receptors mediate the relaxation of bronchial, uterine, and vascular smooth muscle. The location of β-2 receptors within the airway, combined with localized targeted delivery of inhaled β-2 agonists to the airway, provides an optimal method of bronchodilation in reversible air flow obstruction.

The human β receptor has been cloned and studied; it consists of 413 amino acids, and is a member of the 7-transmembrane family of receptors.[12] β receptors have now been subdivided into three groups: β-1, β-2, and β-3, which are identified predominantly in cardiac, airway smooth muscle, and adipose tissue, respectively.[13] The β receptor polypeptide has an extracellular terminus, loops 7 times through the cell membrane lipid bilayer, and has an intracellular terminal carboxyl group, as illustrated in Figure 1.[14]

Viewed three-dimensionally, the membrane-spanning loops of the β receptor form a cylindrical or barrel-shaped structure. β agonists bind inside of the barrel, about 30–40% of the way into the bilayer, to the third, fifth, and possibly sixth transmembrane loops. The β receptor acts through a guanine nucleotide-binding protein, or G protein, which links the receptor functionally with the effector enzyme, adenylyl cyclase. Adenylyl cyclase in turn produces cyclic adenosine monophosphate, which is the "second messenger" considered to be responsible for the activity of β agonists, such as bronchodilation.

Development of β Agonist Bronchodilators

The prototypical drug in the adrenergic bronchodilator group is epinephrine, a naturally-occurring, endogenous sympathetic neurotransmitter. Adrenergic bronchodilators, and the later agents, which were β-2-specific agonists, represent modifications of the chemical compound, β phenylethylamine, illustrated in Figure 2.

The aromatic portion consists of the benzene (or phenyl) ring together with the aliphatic ethylamine side chain. The terminal amine and the benzene ring are connected by an α and β carbon, which should not be confused with the α and β receptors of the sympathetic nervous system.

β Agonists as Stereoisomers

Molecular compounds with carbon atoms that are bonded to 4 different atoms or groups can have two distinct spatial arrangements that give them an asymmetry, or chirality. An example is given by the β carbon on the ethylamine side chain of the adrenergic drug molecules. Rotation about this chiral, or asymmetric center, produces two nonsuperimposable mirror images, termed enantiomers, or simply isomers, as shown in Figure 3 for β-phenylethylamine with an OH group on the β carbon.

Enantiomers have similar physical and chemical properties (melting points, boiling points, solubility, chemical reactivity).[15] However, they do not have the same receptor specificity and therefore do not have the same physiologic effects. The two mirror images of the β OH phenylethylamine analogues rotate light in opposite directions, leading to their designation as dextrorotatory (D) or levorotatory (L). Based on absolute spatial configuration, these isomers are referred to as R- (levo-) or S- (dextro-), respectively. The R- (levo-) form of epinephrine is active on the β receptor and produces bronchodilation. β agonists have been produced synthetically as racemic mixtures (ie, a 50:50, equimolar mix of the R- and S-isomers). Natural epinephrine, such as that obtained from bovine extract, occurs as the R- (levo-) isomer only, whereas the inhaled aerosol formulation is the racemic mixture. A newly released (March 1999) drug, levalbuterol, is the single R-isomer form of racemic albuterol.

Specific Adrenergic Bronchodilators

The development of drugs in the β agonist bronchodilator group has followed from modifications to the original
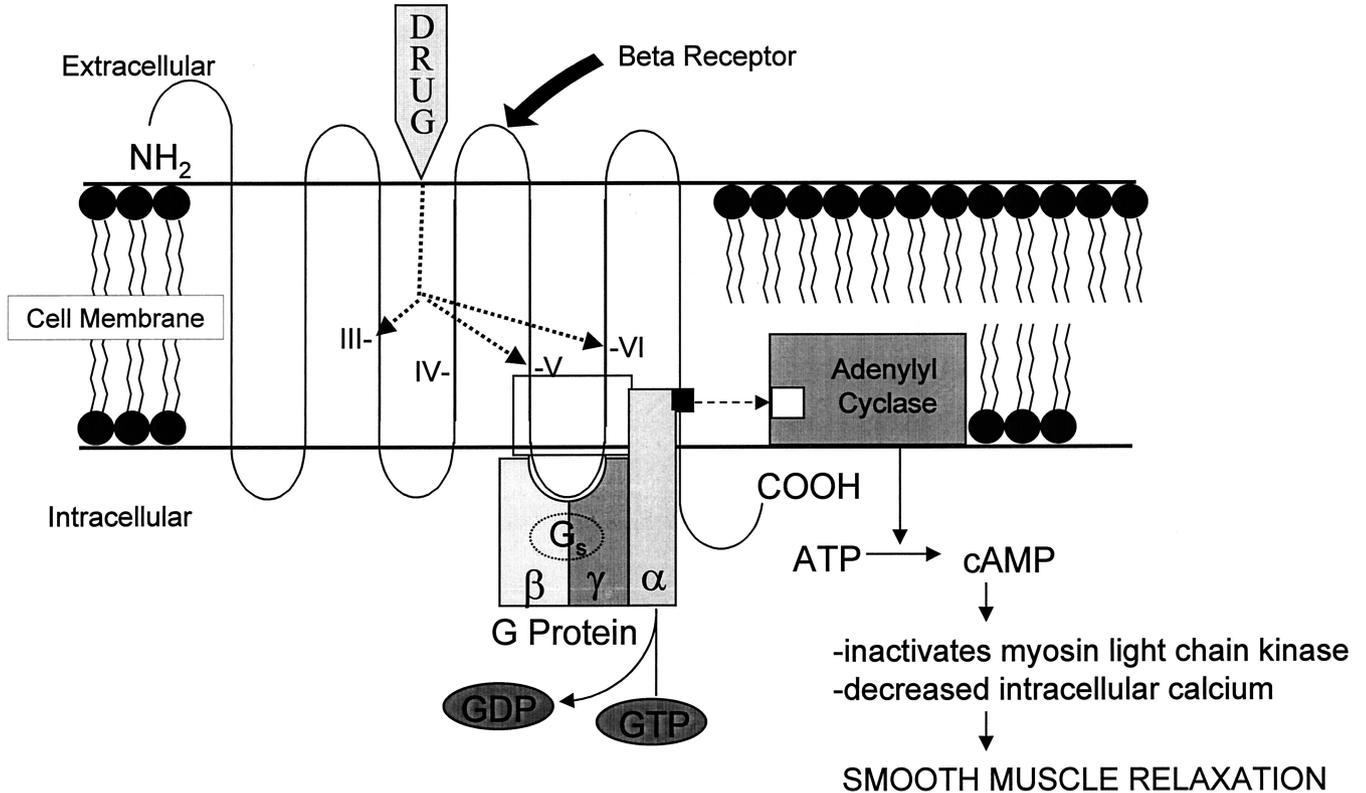
Fig. 1. A simplified two-dimensional view of the β receptor, which is a polypeptide traversing the cell lipid membrane 7 times, with an extracellular and an intracellular terminus, and which is linked to a guanine-binding protein on the intracellular face. GDP = guanosine 5'-diphosphate. GTP = guanosine 5'-triphosphate. ATP = adenosine 5'-triphosphate. cAMP = cyclic adenosine monophosphate.
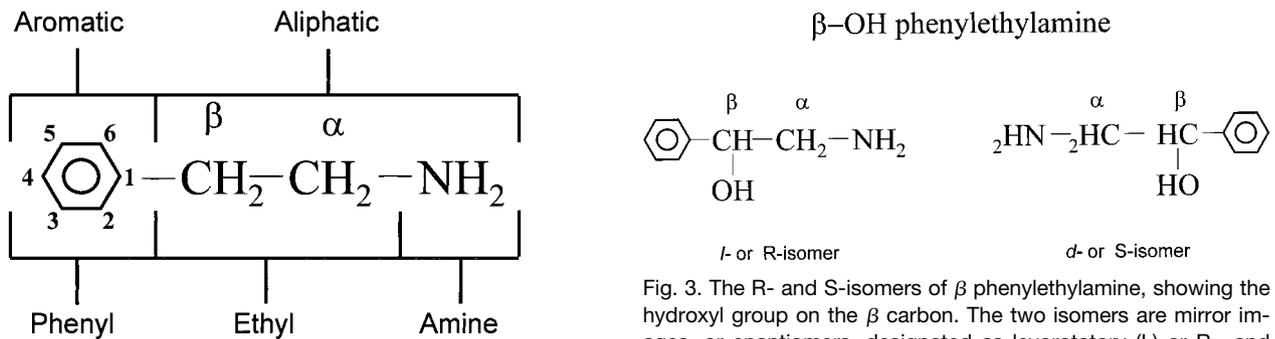
β– phenylethylamine

Fig. 2. The parent compound of the adrenergic bronchodilator drugs, β phenylethylamine. (Modified from Reference 3, with permission.)

β–OH phenylethylamine

Fig. 3. The R- and S-isomers of β phenylethylamine, showing the hydroxyl group on the β carbon. The two isomers are mirror images, or enantiomers, designated as levorotatory (L) or R-, and dextrorotatory (D) or S-. (From Reference 3, with permission.)

chemical structure of epinephrine, with changes in both the catechol nucleus and the amine side chain, as seen in Figure 4. Specificity for the β-2 receptor was explained by the "keyhole" theory of β adrenergic receptors, which stated that the larger the moiety attached to the nitrogen end of the catecholamine, the greater the β-2 specificity.[9,16] In general, longer duration of action was obtained by modifying the catechol ring, and greater β-2 specificity was seen with enlargement of the moiety attached to the amine group. More recent modifications of the length of the ethylamine side chain led to long-acting compounds such as salmeterol. The most recent development has been isolation of the single isomer molecule to replace the racemic mixture, as illustrated by levalbuterol. Table 1 lists the adrenergic bronchodilator group used as orally inhaled agents, and includes the older drugs, isoproterenol and isoetharine, for completeness and comparison.
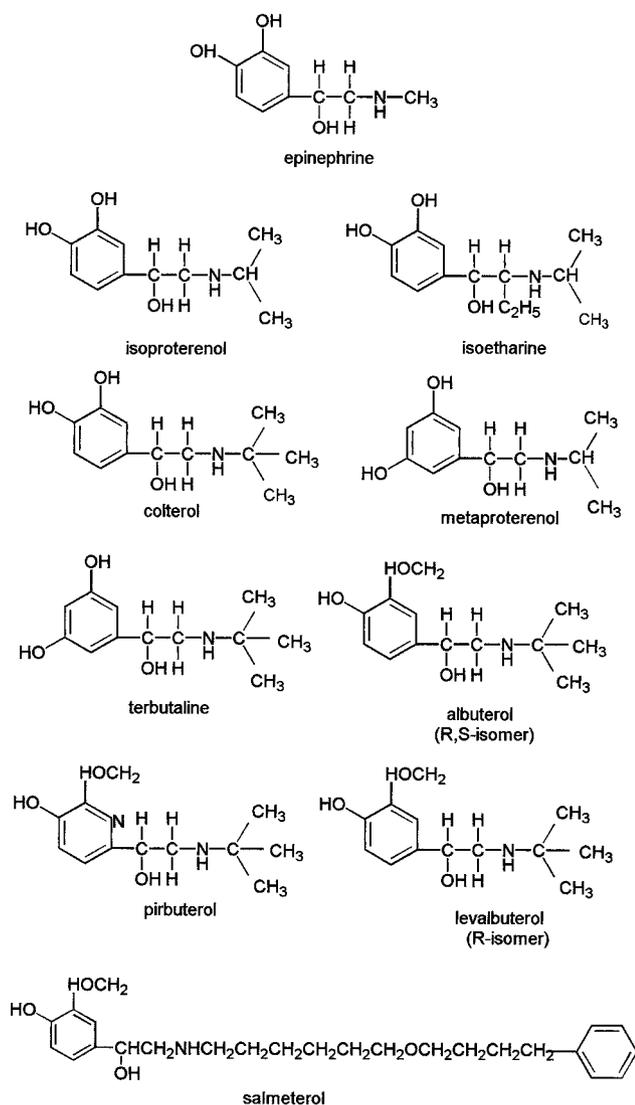
Fig. 4. Structures of epinephrine and other adrenergic bronchodilators available as orally inhaled aerosol formulations. With the exception of natural epinephrine and levalbuterol, all formulations are racemic mixtures and are shown in the same orientation for clarity. The isomers of racemic albuterol and levalbuterol are labeled to indicate the difference in these two drugs.

Epinephrine (adrenaline). Epinephrine is referred to as a catecholamine, since the benzene ring with its hydroxyl attachments forms a catechol nucleus, to which is attached the amine side chain. A catecholamine such as epinephrine, isoproterenol, or isoetharine is rapidly metabolized by the enzyme, catechol-O-methyl-transferase, or COMT. The enzyme methylates the carbon-3 hydroxyl attachment on the catechol nucleus, thereby inactivating the drug. Epinephrine stimulates both α and β adrenergic receptors. It has the smallest moiety attached to the terminal nitrogen of all the inhaled adrenergic bronchodilators, resulting in no β-2 specificity. Because of its lack of receptor specificity, there is a high prevalence of adverse effects, such as

tachycardia, elevated blood pressure, tremor, headache, and insomnia, in addition to the desired therapeutic effect of bronchodilation. The bronchodilatory effect of epinephrine is very rapid in onset, but also quite short, approximately one hour of duration, since the drug is metabolized by COMT and monoamine oxidase.

As previously stated, the inhaled formulation of epinephrine is the racemic mixture of the naturally-occurring R-isomer. Since only the R-isomer is active on the adrenergic receptors, a 1:100 strength formulation of the natural, single-isomer form is used for inhalation, whereas the racemic mixture is a 2.25% strength solution. Since epinephrine is active on α adrenergic receptors as well as β receptors, it is often used as a topical vasoconstrictor in treating stridor and croup, and during endoscopy to control bleeding.[3,17]

Isoproterenol (isoprenaline). Isoproterenol has an isopropyl group attached to the terminal nitrogen, giving it a larger group at this site and, in keeping with the keyhole theory of β-2 specificity, shifts its activity from α to largely β stimulation. Since the catechol nucleus remains the same as epinephrine, the drug is still vulnerable to inactivation by COMT, giving it a very short duration, approximately 1.5–2 hours. Since isoproterenol is a potent but nonspecific β agonist, activating both β-1 and β-2 receptors, tachycardia is a common adverse effect, even when administered via inhalation. Isoproterenol lacks the pressor effects of epinephrine and can cause vasodilation in sufficient parenteral doses. A combination of isoproterenol 0.25% and cyclopentamine 0.5% (an α receptor agonist) was marketed in the 1970s as Aerolone, in a dose of 0.5 mL for nebulizer treatment. The combined α and β effects with the compound were thought to produce bronchodilation with vasoconstriction (decongestion) in the airway, similar to the broader effects seen with epinephrine.[18]

Isoetharine. Isoetharine has an ethyl group attached to the α carbon atom of the amine side chain, in addition to the isopropyl group at the terminal nitrogen seen with isoproterenol. This further increase in side chain bulk made isoetharine the first β-2-specific inhaled aerosol bronchodilator, which was available in a metered-dose form (Bronkometer) and a 1% nebulizer solution (Bronkosol). Although its bronchodilator activity is less than isoproterenol, the minimal cardiac adverse effects made it a more attractive β agonist for many clinicians in the 1970s in the United States.[9] Since it is also a catecholamine, the duration of action was limited to approximately 1.5–2 hours. An original formulation of isoetharine (Bronkosol) contained phenylephrine, a pure α agonist as well as thenyldiamine, an antihistamine. Both phenylephrine and thenyldiamine were subsequently deleted from the formulation.

Table 1. Inhaled Adrenergic Bronchodilator Agents Currently Available in the United States

Drug	Brand Name	Receptor Preference	Adult Dosage	Time Course (onset, peak, duration)
epinephrine	Adrenalin	(α, β)	SVN: 1% solution, 0.25–0.5 mL (2.5–5.0 mg), qid MDI: 0.2 mg/puff, 2 puffs, as ordered or needed	3–5 min 5–20 min 1–3 h
racemic epinephrine	microNefrin	(α, β)	SVN: 2.25% solution, 0.25–0.5 mL (5.63–11.25 mg), qid	3–5 min 5–20 min 0.5–2 h
isoproterenol	Isuprel	(β)	SVN: 0.5% solution, 0.25–0.5 mL (1.25–2.5 mg), qid MDI: 131 μg/puff, 2 puffs, qid	2–5 min 5–30 min 0.5–2 h
isoetharine	Bronkosol	(β-2)	SVN: 1% solution, 0.25–0.5 mL (2.5–5.0 mg), qid MDI: 340 μg/puff, 1–2 puffs, qid	1–6 min 15–60 min 1–3 h
terbutaline	Brethine	(β-2)	MDI: 200 μg/puff, 2 puffs, q 4–6 h	5–30 min 30–60 min 3–6 h
metaproterenol	Alupent	(β-2)	SVN: 5% solution, 0.3 mL (15 mg), tid, qid MDI: 650 μg/puff, 2–3 puffs, tid, qid	1–5 min 60 min 2–6 h
albuterol	Proventil Proventil HFA Ventolin	(β-2)	SVN: 0.5% solution, 0.5 mL (2.5 mg), tid, qid MDI: 90 μg/puff, 2 puffs, tid, qid DPI: 200 μg capsule, 1 capsule, q 4–6 h	15 min 30–60 min 5–8 h
bitolterol	Tornalate	(β-2)	SVN: 0.2% solution, 1.25 mL (2.5 mg), bid-qid MDI: 370 μg/puff, 2 puffs, q 8 h	3–4 min 30–60 min 5–8 h
pirbuterol	Maxair	(β-2)	MDI: 200 μg/puff, 2 puffs, q 4–6 h	5 min 30 min 5 h
salmeterol	Serevent	(β-2)	MDI: 21 μg/puff, 2 puffs, bid DPI: 50 μg/blister, 1 inhalation bid	20 min 3–5 h 12 h
levalbuterol	Xopenex	(β-2)	SVN: 0.63 mg, q 6–8 h or 1.25 mg, tid	15 min 30–60 min 5–8 h

SVN = small-volume nebulizer. MDI = metered-dose inhaler. DPI = dry powder inhaler.

Bitolterol. Although bitolterol was not the next inhaled β agonist to become available after isoetharine in the United States, it can be considered with the other catecholamines such as epinephrine, isoproterenol, and isoetharine. Bitolterol to date has been the only prodrug approved for use as an inhaled bronchodilator in the United States. The prodrug form, bitolterol, possesses two toluate ester groups on the benzene ring at the carbon 3 and 4 positions. Esterase enzymes present in the lung hydrolyze bitolterol to the active catecholamine form, colterol. The hydrolysis proceeds gradually, giving bitolterol a longer duration of action, possibly 5–8 hours, and the bulky side chain confers β-2 specificity. Although interesting from a pharmacological perspective, bitolterol was not widely accepted for clinical use.

Metaproterenol (orciprenaline). Metaproterenol introduced a new generation of β agonists by modifying the catechol ring structure to produce a resorcinol. The hydroxyl groups were shifted from the carbon 3 and 4 positions to the "meta" position of carbons 3 and 5. This prevented degradation by COMT, allowing longer duration of action, 4–6 hours. Except for the change in the catechol attachments, metaproterenol is the same as isoproterenol, and has substantial cardiac adverse effects, compared to subsequent β-2-specific agonists.

Terbutaline. Terbutaline became available for parenteral (subcutaneous) use in the 1970s, and later was released in a metered-dose inhaler (MDI) formulation. Terbutaline possesses a tertiary butyl group on the terminal nitrogen of the side chain, giving it greater β-2 specificity than isoetharine or metaproterenol. The drug has the same 3,5 meta-dihydroxy groups as metaproterenol, making it a member of the resorcinol group and thereby increasing its duration of action to 4–6 hours. Because the MDI formulation was not available originally, and terbutaline was considered by many clinicians to be superior to metaproterenol, the injectable ampule solution of 1 mg/mL was often used as a nebulizer solution. Dosing was largely empirical and, based on personal knowledge, could range from 0.5 mg to as much as 9 or 10 mg in a nebulizer treatment.

Albuterol (Salbutamol). Albuterol is identical chemically to terbutaline, with the exception of a methanol attachment at the carbon 3 position of the benzene ring, making it a saligenin. The drug possesses β-2 specificity as well as an approximately 6-hour duration of action because of its protected ring structure and bulky side chain. Albuterol is available in multiple dosing forms, including a nebulizer solution, an MDI, a dry powder inhaler, and oral tablets. An extended release oral tablet formulation is also available. Because of its versatile formulations, good bronchodilating action, and minimal adverse effects, albuterol became the most commonly prescribed bronchodilator in reactive airways disease in the United States during the 1980s and 1990s.

Pirbuterol. Pirbuterol is structurally identical to albuterol, with one exception: a nitrogen atom is inserted in place of the second carbon atom on the benzene ring, forming a pyridine nucleus. Pirbuterol is also β-2 specific and has an approximately 5-hour duration of bronchodilating action. This drug has been available in the United States in either a pressurized MDI or a breath-actuated MDI (Autohaler) to minimize hand-breath coordination problems.[19]

Salmeterol. Although a sustained-release formulation of albuterol intended to provide extended bronchodilation for up to 12 hours had been previously released, salmeterol, approved in 1994, represents the first true long-acting β agonist bronchodilator in the inhaled aerosol group. Salmeterol xinafoate is the 1-hydroxy-2-naphthoic salt of salmeterol base, with 36.25 μg of the salt equivalent to 25 μg of the base. The drug is a modification of albuterol, with a long lipophilic N-substituted side chain. The long side chain increases the lipophilicity of salmeterol and binds to an area of the β receptor within the lipid membrane referred to as an exosite. With the lipophilic tail anchored, the active phenyl ethanolamine "head" alternately engages and disengages from the active receptor site, thus providing ongoing stimulation of the receptor and giving a 12-hour duration of action. The drug is ultimately metabolized by hydroxylation, with elimination in the feces.[20,21]

Levalbuterol. In March of 1999 the single R-isomer form of racemic albuterol, levalbuterol, was approved for general clinical use in the United States as Xopenex, in a 0.63 mg and 1.25 mg unit dose for nebulization. With the exception of natural epinephrine, which is the R- (L) isomer, levalbuterol is the only single-isomer β agonist available at this time. The 0.63 mg dose is comparable to the 2.5 mg racemic albuterol dose in onset and duration, and the 1.25 mg dose has shown a higher peak effect on flow, with an 8-hour duration in a study by Nelson et al.[22]

Adverse Effects With β Agonists

General Adverse Effects

The development of the β agonist drug class has been toward increasing receptor selectivity with minimal adverse effects. Table 2 lists adverse effects that can be seen with β agonists and that are dose-dependent. With newer β-2-selective agents, the most common adverse effect in standard doses is tremor, with shakiness, irritability, insomnia, and headache also reported. These effects are typical adrenaline-mediated responses seen with sympathetic nervous system activation. Older catecholamine agents that lacked β-2 specificity increased cardiac output and oxygen consumption. The β-2-selective agents can also stimulate tachycardia in sufficient doses, but agents such as terbutaline or albuterol can improve cardiac performance with reduced afterload through peripheral vasodilation.[23] Clinically important hyperglycemia and hypokalemia are not commonly seen in standard doses, but can become important in a dose-dependent fashion with high doses or continual nebulization.[24,25] A drop in arterial partial pressure of oxygen is possible, with mismatched ventilation/perfusion during reversal of bronchoconstriction, but has not been found to be clinically important, and is transient. This

Table 2. Possible Adverse Effects of Beta Agonists

Tremor
Palpitations, tachycardia
Increased blood pressure
Headache
Insomnia
Nervousness
Dizziness
Nausea
Tolerance
Decrease in P_{aO_2}
Hypokalemia
Hyperglycemia
FREON-induced bronchospasm (MDIs only)

P_{aO_2} = arterial partial pressure of oxygen.
MDI = metered-dose inhaler.

was noted with isoproterenol in asthma patients, but the decrease in arterial partial pressure of oxygen was ≤ 15 mm Hg, and reversed within 15–20 minutes.[25]

Tolerance to β Agonists

Of more concern is the tachyphylaxis and tolerance that may occur with exposure to β agonists. The development of tolerance to β agonist bronchodilators is a complex phenomenon. The terms tachyphylaxis and tolerance actually describe a multiple-stage process of changes in the β receptor with agonist exposure.

Initial exposure to a β agonist produces a rapid desensitization of the β-2 receptor through a process of uncoupling of the receptor from the enzyme effector system.[13,14] This is a transient process and is quickly reversed with removal of the agonist, to allow further receptor stimulation. With more prolonged exposure to a β agonist, there is some loss of cell surface receptors through a process described as internalization or sequestration.[13] This internalization may be part of the sequence of resensitization of the receptor through dephosphorylation. Internalization may require hours for reversal. With hours of agonist exposure there is a net loss of cellular receptors, termed down-regulation. This is denoted as long-term desensitization.[14] These desensitization processes regulate a certain refractory state of the β receptor itself. In addition, β agonists can negatively modulate β-2 receptor gene expression, leading to longer-term down-regulation and loss of β receptors. Hayes et al reported a 22% decrease in β receptor density in the lung, measured via positron emission tomography scanning, with albuterol 4 mg orally bid and 200 μg inhaled qid over two weeks, with a reduction in bronchodilator response.[26]

These processes result clinically in (1) some decline in bronchodilator response following continual maintenance treatment with a β agonist, (2) decline in adverse effects such as tachycardia and muscle tremor, and (3) loss of bronchoprotection against airway challenge.

Corticosteroids can increase β-2 receptor gene transcription, leading to up-regulation of the receptors.[14] This effect further supports the use of corticosteroids in asthma, both for preserving β receptor density and for their anti-inflammatory effects.

The "Asthma Paradox"

Despite improvements in receptor-specific β agonist bronchodilators, there have been troubling associations between increased deaths from asthma and the use of these agents, a situation that has been termed the "asthma paradox."[27]

Asthma Mortality. In the 1960s, there was a reported increase in deaths among asthma patients in Great Britain, where a high-dose formulation of isoproterenol (known as isoprenaline-forte) with 400 μg per puff was used.[28,29] The asthma death rate returned to previous levels following removal of the product from the market.[30] Data from New Zealand in the 1980s showed another increase in asthma mortality and suggested an association with inhaled fenoterol (200 μg/puff), a potent β agonist.[31] Interpretation of the New Zealand data has been questioned by others, who found no correlation between asthma mortality in that country and use of the inhaled β agonists, fenoterol, and albuterol.[32] It has been noted that asthma mortality subsequently declined in New Zealand, despite increasing sales of all β agonists, including fenoterol.[33] In 1992, Spitzer et al published results from a Canadian case-control study that found an association between asthma mortality and the use of β agonist bronchodilators.[34] The use of two or more canisters per month of fenoterol or albuterol was associated with an increased risk of death. Obviously, the question becomes: is increased use of a β agonist a marker of asthma severity, or causal in nature? A correlational study can only indicate an association, not causality.

Asthma Morbidity. It has been suggested that not only mortality but asthma morbidity may be negatively affected by β agonist use. A study by Sears et al published in 1990 concluded that intermittent use of a β agonist (fenoterol) gave better asthma control than regular treatment, based on results with 64 mildly-to-moderately asthmatic subjects.[35] Control was evaluated using morning and evening peak flows, symptom diaries, use of rescue β agonist, and need for oral prednisone. In 17 subjects asthma was better controlled with regular inhaled bronchodilator, whereas in 40 subjects control was superior with as-needed bronchodilator use. Seven subjects showed no difference between the two treatment regimens. Mean values and magnitude

of change in the measures used were not reported originally, only the percentage of patients showing a change, and this has been pointed out as a limitation of the report.[30] A subsequent report provided lung function data from the study of Sears et al, showing an approximately 5% difference in forced expiratory volume in the first second between regular use and rescue use of inhaled fenoterol.[36]

Loss of Bronchoprotection. There have also been data to indicate that there is a heightened sensitivity to bronchoconstricting stimuli with β agonist use, although bronchodilator effects remain. The loss of bronchoprotection has raised concerns that β agonists may actually "sensitize" asthmatics to inflammatory stimuli. O'Connor et al examined the protective effect of a single 500 μg inhalation of terbutaline with adenosine monophosphate and methacholine challenge, before and after 7 days of treatment with 500 μg of terbutaline qid. There was a significant decline in the PC_{20} (provocational concentration [ie, dose] producing a 20% decrease in forced expiratory volume in the first second) for both adenosine monophosphate and methacholine after 7 days of treatment.[37] Cockcroft et al found a greater loss of protection against allergen than against methacholine in mildly asthmatic subjects treated for 14 days with albuterol 200 μg qid.[38] The implication of these effects is that, with regular β agonist treatment, asthmatics may show a bronchodilator response that masks increased sensitivity to airway allergens.

Is the S-isomer Inactive?

It has been accepted in the past that only one of the stereoisomers of epinephrine analogues is physiologically active. Recent in vitro and clinical data[39–43] suggest that the S-isomer form of albuterol may have effects that can antagonize the desired bronchodilating action of the R-isomer. Table 3 summarizes the physiologic effects of the S-isomer of albuterol. Templeton et al found that (S)-salbutamol ([S]-albuterol) enhanced the contractile response of isolated human bronchial tissue to stimuli by histamine and leukotriene C_4.[39]

Mitra et al showed that S-albuterol increases intracellular free calcium in bovine tracheal smooth muscle cells.[40] In contrast, R-albuterol decreased calcium concentrations in the same study. More interesting was the finding that the increase in calcium from S-albuterol was blocked by atropine, implying that the S-isomer attaches to muscarinic receptors and not β receptors. Work by Volcheck et al found that the S-isomer of albuterol significantly enhanced superoxide production by eosinophils in response to interleukin 5 stimulus in vitro, whereas racemic mixtures containing both the R- and S-isomers inhibited such production.[41] Superoxide production is a marker of inflammatory activity, and this finding implies that the S-isomer of al-

Table 3. Summary of the Physiological Effects of (S)-Albuterol

Effect	Reference
Increases intracellular calcium concentration	Mitra, 1993[40]
Binds to muscarinic receptors	Mitra, 1993[40]
Enhances experimental airway responsiveness	Johansson, 1996[43]
Increases contractile response of bronchial tissue to histamine or leukotriene C_4 (LTC_4)	Templeton, 1998[39]
Enhances eosinophil superoxide production with interleukin-5 stimulation	Volcheck, 1998[41]
Slower metabolism than R-albuterol, with accumulating plasma levels*	Boulton, 1997[42]

*Finding may vary with metered-dose inhaler or metered-dose inhaler with holding chamber aerosol administration.[44]

buterol has a pro-inflammatory effect. A difference in the rate of metabolism of the two isomeric forms of albuterol has also been found. Boulton et al found higher plasma levels of the S-isomer than the R-isomer with oral dosing of racemic albuterol in 12 healthy males.[42] The accumulation of the S-isomer could further contribute to possible pro-inflammatory effects with the administration of a racemic mixture of albuterol. Dhand et al recently reported lower plasma levels of (S)-albuterol than (R)-albuterol when racemic albuterol was administered via MDI or MDI with holding chamber.[44] They attributed this interesting finding to a preferential retention of the S-isomer in the lung when inhaled. This result contrasts with plasma levels of (R)- and (S)-albuterol when given via nebulization or dry powder inhaler.[45,46]

β Agonists and the National Asthma Education and Prevention Program Guidelines

Discussion of a possible relationship between β agonists and asthma should occur in the context of the recently revised National Asthma Education and Prevention Program guidelines for asthma treatment and prevention. Both the 1991 and the 1997 document clearly differentiate β agonists (with the exception of salmeterol) as "relievers" and not "controllers."[47] This distinction aligns with the increased emphasis on asthma as a disease of chronic airway inflammation. Treatment of bronchospasm with a β agonist addresses symptoms and effects of the inflammation, but not the underlying inflammation process itself. Such a view of asthma would predict that rescue treatment will ultimately be unsatisfactory as primary or sole therapy. This shift in understanding of the pathophysiology of asthma changes our understanding of the use of β agonists in managing asthma. Anti-inflammatory agents become

the drug of choice to manage persistent asthma. This may reduce the association seen between β agonists and asthma mortality.

The exact effect of β agonists in asthma remains a subject of debate. Several hypotheses can be advanced to explain the apparent worsening of asthma with use of β agonists:

• β agonists cause increased sensitivity to allergenic and irritant stimuli in asthmatics, possibly through down-regulation of β receptors in the airway.

• β agonists may be used by practitioners to manage asthma with inadequate or no anti-inflammatory therapy.

• Self-reliance on rescue β agonist therapy when confronted with worsening airway obstruction is substituted for professional medical treatment, with potentially lethal delays in seeking treatment.

• Accumulation of the S-isomer of racemic β agonist mixtures exerts deleterious or pro-inflammatory effects in the airway.

• There is increased airway irritation (as well as increasing asthma prevalence) with increased environmental pollutants and with lifestyle changes that cause increased allergen exposure.

Ultimately, the changes seen in the prevalence of asthma may reflect multiple factors and the interaction of these factors rather than a single cause.

Summary

The adrenergic bronchodilators that have been developed for oral inhalation represent successive refinement in terms of receptor specificity and duration of action. β agonist bronchodilators have durations of 4–6 hours, or, in the case of salmeterol, of up to 12 hours, offering convenient dosing. Inhalation of the aerosol formulations targets the lung directly. The release of levalbuterol now provides an agent with a single isomer active on β-2 receptors. The currently available agents offer clinicians and patients with reversible obstructive lung disease a choice of sophisticated drugs for airway smooth muscle relaxation. Although improvements in the drugs have reduced adverse effects and β agonists are considered safe, concerns persist about the effect of β agonists in asthma. An improved understanding of asthma pathophysiology may lead to more appropriate use of β agonists in asthma.

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