Viewpoint: untoward effects of beta-adrenoceptor agonists in asthma

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ABSTRACT: Beta-adrenoceptor agonists are potent and selective relaxants of airway smooth muscle. They produce symptomatic bronchodilatory effects and are the most widely used therapy in asthma. In patients with asthma, they usually exert a reduction of airway resistance, but there have been several reports of episodes of increased airway obstruction, arterial hypoxaemia and even death associated with such therapy. "Anomalous or paradoxical bronchospasm" are appropriate terminologies to describe this unexpected phenomenon. Five mechanisms have been proposed to account for anomalous responses to these substances: 1) reactive myogenic tone; 2) metabolic products with spasmogenic activity; 3) adrenoceptor tachyphylaxis; 4) increased inflammatory burden; and 5) induction of airway hyperreactivity. Following a review of the relative merits of each proposal, it is concluded that increased inflammatory burden and induction of airway hyperreactivity, alone or in combination, provide the most plausible explanation for paradoxical bronchospasm.

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Bronchodilatory actions of beta-adrenoceptor agonists

Beta-adrenoceptor agonists relax isolated airway smooth muscle, whether tone has developed spontaneously or as a result of addition of spasmogens, e.g. histamine or methacholine, to the tissue bath. Relaxation of human tracheal or bronchial muscle is achieved when concentrations of (±)isoprenaline exceed $10^{-9}$ M [1-3].

The capacity of beta-adrenoceptor agonists to relax airway smooth muscle has been accounted for by a model, in which interaction between the agonist and beta-adrenoceptors at the surface of airway smooth muscle induces adenylate cyclase activation and generation of 3', 5' cyclic adenosine monophosphate (cAMP) with consequent dephosphorylation of protein kinase and reduced activation of myosin light chain kinase. Activation of adenylate cyclase as a mechanism whereby cells respond to adrenoceptor agonists is extensively supported by biochemical studies on a range of cell types [4]. However, elevation of cAMP within airway smooth muscle only becomes evident at drug concentrations considerably in excess of those needed to achieve maximal relaxation in vitro [5]. Thus, the bronchodilator effect of beta-adrenoceptor agonists is difficult to explain, other than by proposing that adenylate cyclase activation is restricted to certain sub-components, and that the marginal increase in cAMP, associated with relaxation of smooth muscle, may reflect the low incidence of receptor occupancy needed to achieve physiological or pharmacological response in this tissue.

Paradoxical bronchospasm

Airway smooth muscle consistently relaxes when beta-adrenoceptor agonists are added to the fluid bathing in vitro preparations. Inhaled or injected beta-adrenoceptor agonists regularly induce a reduction of airway obstruction in man or in animals subjected to bronchoconstrictor stimuli. These observations implied that beta-adrenoceptor agonists could cause relaxation of airway smooth muscle in asthma, which clinical investigation proved to be correct. Nonetheless, there have been intermittent reports of a worsening of asthma with increased airflow obstruction following administration of beta-adrenoceptor agonists, whether by oral [6], intravenous [7, 8] or inhaled [9-13] routes. Such effects have a very low incidence or, if widespread, are nullified by bronchodilator effects in most individuals.

"Anomalous bronchospasm" and "paradoxical bronchospasm" are terminologies which seem appropriate in that an unexpected and unexplained phenomenon is indicated. Terms such as "rebound bronchospasm" and "tachyphylaxis" should be avoided, because they imply specific mechanisms, which may not indicate why the phenomenon is manifest so infrequently, and may be difficult to substantiate.
Proposed mechanisms for paradoxical bronchospasm

Five proposals have been considered to explain "paradoxical bronchospasm" secondary to administration of drugs that are categorized as beta-adrenoceptor agonists: 1) reactive myogenic tone; 2) metabolic products with spasmogenetic activity; 3) beta-adrenoceptor tachyphylaxis; 4) increased inflammatory burden; 5) induction of airway hyperreactivity.

1) Reactive myogenic tone

It has been suggested that adverse effects of beta-adrenoceptor agonists on the airways is due to "rebound bronchospasm" [7, 14]. This term implies that bronchodilator responses to beta-adrenoceptor agonists can induce a subsequent bronchoconstrictor event. Presumably this concept has its origin in the myogenic constrictor responses that can be elicited by physical dilatation of blood vessels [15]. Although reactive spasm in response to abrupt stretching is documented for vascular smooth muscle, there is no evidence for such a phenomenon in airway smooth muscle. Clinically, reactive bronchospasm has not been reported after physical dilatation of locally constricted tracheal and bronchial areas in children, or after bronchoalveolar lavage in asthmatics of any age. Segments of bronchial or tracheal muscle can develop tone in vitro and such myogenic tone is lost on addition of beta-adrenoceptor agonists or other relaxants. Following removal of the relaxant by washing, the preparation recovers tone without exceeding earlier developed tension. Similar changes can be observed in lung segments perfused via the airway lumen (Chapman et al unpublished observations). In anaesthetized animals, after airway obstruction has been induced by intravenous infusion of spasminogens, spasmylytic agents such as xanthisne cause an abrupt reduction of airflow obstruction which resolves progressively, returning to the original level of obstruction. Thus, the concept of rebound bronchospasm has no experimental counterpart in vivo or in vitro.

2) Metabolic products

When beta-adrenoceptor agonists are administered in man they are eliminated by metabolic processes, which raises the possibility that specific metabolites might act as constrictor agents. For instance, (±)isoprenaline is metabolized in part by catechol-o-methyl transferase (COMT) to a 3-methoxy derivative, which has weak beta-adrenoceptor antagonist activity [16]. Although this metabolite will always attenuate the effect of (±)isoprenaline, the amount required to achieve blockade of beta-adrenoeceptors considerably exceeds concentrations found in clinical circumstances [17]. Furthermore, whilst such events might be proposed to account for anomalous responses to isoprenaline, this type of explanation cannot extend to drugs with alternative metabolic pathways and different metabolic products.

3) Beta-adrenoceptor tachyphylaxis

After exposure to an agonist (usually in considerable excess), certain tissues show diminished response to that agonist. Classically, this reduced responsivity has been termed tachyphylaxis. The loss of sensitivity may be accompanied by a reduced incidence of receptors at the cell surface, a process that has led to introduction of the term "down-regulation". In asthma patients, changed responsivity to beta-adrenoceptor agonists at extra-pulmonary sites (e.g. eye and peripheral blood) can be detected [18, 19] and such phenomena have been offered as evidence favouring impaired beta-adrenoceptor responsivity in all tissues as a determinant of asthma pathology. Consequently, it has been widely presumed that asthmatic airway smooth muscle becomes desensitized to beta-adrenoceptor agonists, even though prospective clinical studies in asthma fail to detect such a phenomenon [20, 21]. Animal studies indicate that tachyphylaxis in airway smooth muscle to beta-adrenoceptor agonists occurs only when large doses are applied over long periods (e.g. 75 mg·kg⁻¹ per day subcutaneously for three days in rats) [22]. It follows that loss of responsivity to beta-adrenoceptor agonists is an improbable outcome of sympathomimetic therapy in asthma, so that some other explanation must be sought for diminished responses when these occur. Note that even if tachyphylaxis to beta-adrenoceptor agonists did occur in asthmatic airways, it would not provide an adequate explanation for paradoxical bronchospasm; the consequence of reduced responsivity is merely a reduced bronchodilator response, not a bronchoconstrictor response.

4) Increased inflammatory burden

The airways of asthmatic patients are characterized by persistent inflammation with impaired mucociliary clearance and are subject to persistent constrictor stimuli; hence, inhaled particles encounter turbulent airflow in major bronchi and impact largely in the central airways [23]. The relaxant effect of beta-adrenoceptor agonist drugs reduces obstruction within major airways and so improves subsequent or concomitant delivery of aerosols into more peripheral airways (fig. 1). Thus, it has been recommended that administration of inhaled therapy be regularly spaced [24], and that beta-adrenoceptor agonists be used prior to the inhalation of other drugs to decrease their side-effects [25].

It follows that bronchodilator therapy will increase the deposition within the airways, not only of other therapeutic agents, but also of noxious particles such as pollens, animal danders and endotoxins, especially as small doses of beta-adrenoceptor agonists fully inhibit acute (i.e. early) allergic bronchospasm [26], which might otherwise restrict ingress of such inflammatory burden. The consequences of increased allergen deposition in the airways would only be detected when bronchodilator responses have waned. Accordingly, it has been reported that there is an increase in the incidence and intensity of
late-onset reactions following administration of a beta-adrenoceptor agonist prior to allergen challenge [27]. Guinea-pig lungs are highly sensitive to airway spasmogens, hence this phenomenon can be readily demonstrated in sensitized guinea-pigs. In such animals, a prominent intrapulmonary eosinophilia can be revealed in response to allergen inhalation. This effect can be inhibited by all classes of anti-asthma drugs [28], with the notable exception of the beta-adrenoceptor agonist, salbutamol, (fig. 2) which invariably kills such animals unless the dose is substantially reduced.

It is frequently stated that beta-adrenoceptor agonists do not inhibit or diminish late-onset reactions to allergen, but this opinion may prove to be invalid. Beneficial effects of the drug may be obscured either by decreased delivery of beta-adrenoceptor agonist during the (late) periods of airway obstruction, or by an increased delivery of allergen after the (early) bronchoconstrictor response has been reversed by a beta-adrenoceptor agonist. The effect of beta-adrenoceptor agonist remains uncertain, but could be resolved by administration of constant doses of allergen in the presence and absence of intravenous administration of beta-adrenoceptor agonists. Since both the bronchodilator effect of the beta-adrenoceptor agonist, and the bronchoconstrictor effect and airway obstruction due to allergen, can enhance or restrict drug delivery by inhalation, it is not possible to control or realistically estimate drug delivery by this route.

Furthermore, ventilatory indices cannot be used to anticipate aerosol deposition (fig. 1).

5) Induction of airway hyperreactivity

The possibility that beta-adrenoceptor agonists might induce airway hyperreactivity should have been considered at the time of the asthma death epidemic, for it had already been demonstrated that systemic treatment with (±)isoprenaline caused an increased sensitivity of guinea-pigs to the noxious effect of inhaled histamine [29, 30]. Recently, investigation of the effects of platelet activating factor (PAF) on guinea-pig airways revealed that (±)isoprenaline intensified PAF-induced airway hyperreactivity [31]. Further investigation has led to the recognition that (±)isoprenaline per se induces airway hyperreactivity by a process that cannot be accounted for by an action on beta-adrenoceptors [32]; thus, increased airway reactivity is accompanied by little or no loss of beta-adrenoceptor responsivity in airways; furthermore, development of airway hyperreactivity is not inhibited by selective antagonists of beta-adrenoceptors [33] and is demonstrated equally by both (+) and (-) isomers of isoprenaline [32]. This latter observation is in contrast to the bronchodilatory effect of beta-adrenoceptor occupancy, since (+) isoprenaline has a thousand times less bronchodilator activity than the (-) isomer. The effect of
Fig. 2. – Deaths and intrapulmonary eosinophilia related to salbutamol in allergen-sensitized guinea-pigs. Following sensitization of guinea-pig lungs by repeated intra-peritoneal injections of ovalbumin, inhalation of allergen produced a prominent intrapulmonary eosinophilia when studied at 24 h. This effect could be inhibited by pre-treatment with 5 day subcutaneous infusions of dexamethasone (1.0 mg·kg⁻¹ per day), aminophylline (10 mg·kg⁻¹ per day) and ketotifen (1.0 mg·kg⁻¹ per day), (p<0.05). However, when the beta-adrenoceptor agonist, salbutamol, was similarly administered in the usual doses of 1.0 mg·kg⁻¹ per day) the sensitized animals died immediately after challenge (10 deaths in 10 animals), and no record of pulmonary eosinophilia could be made. When the salbutamol dose was reduced to one-tenth (0.1 mg·kg⁻¹ per day), there were less <0.01) rather than inhibited. The brackets after the drug names show the number of animals studied in each group.

(±)isoprenaline on airway hyperreactivity is only evident when the vagus is intact, and may be dependent on the activity of peptidergic neurotransmitters since it is not influenced by atropine (Morley and Sanjar, unpublished observations).

The development of increased bronchial hyperreactivity in both paediatric and adult patients with asthma, after several weeks of therapy with beta-adrenoceptor agonists, has been documented in the recent clinical literature [14, 34, 35].

Discussion

The problem of paradoxical responses during beta-adrenoceptor agonist therapy of asthma has been evident for almost fifty years. This adverse effect has been infrequently reported [6-13], leading to the presumption that it is rare. This may be valid, but the alternative possibility that adverse effects are usually obscured by the symptomatic efficacy of bronchodilator therapy, is worth consideration.

Of the mechanisms considered to account for paradoxical bronchospasm, increased inflammatory burden and induction of hyperreactivity as a direct response to exposure to the drug seem the most probable explanations. In either circumstance, the occurrence of such a phenomenon can be expected to remain undetected in a substantial proportion of patients.

Alternative proposals appear implausible. Rebound bronchospasm is a concept that is not supported by laboratory evidence and does not extend to other bronchodilators such as theophylline. Metabolic events could contribute to such an effect but such an explanation would only account for effects of specific drugs, such as isoprenaline.

Tachyphylaxis is also an inadequate explanation, since the property of decreased beta-adrenoceptor responsivity is difficult to demonstrate in airway smooth muscle and, even if present, it would only contribute to reduced bronchodilator response, not to airway obstruction.

Since evidence already exists that an increased incidence of late-onset reactions to allergen follows pretreatment with beta-agonists [27], and since avoidance of an increased load of environmental allergens is held to be of clinical benefit [36, 37] and universally prescribed, the occurrence of an increased allergic or inflammatory burden secondary to a bronchodilator response must be a common effect since patients use beta-agonist therapy for relief of symptoms when exposed to asthmogenic
stimuli such as dusts and allergens. Whilst obvious, such effects would easily be overlooked in patients using symptomatic bronchodilator therapy because such drugs produce protracted bronchodilator effects; consequently, a substantial proportion of patients can have progressive pathology that remains undetected, or will exhibit a worsening clinical condition that is attributed to disease intensification per se. Hitherto, these possibilities have generally been disregarded, partly because resolution of this issue would require clinical trials of prophylactic anti-asthma drugs in which beta-adrenoceptor agonist use is restricted. Nonetheless, further investigation of these aspects of beta-adrenoceptor agonist therapy is warranted.

![Diagram showing incremental increase in Rl](image)

Fig. 3. - Increased airway resistance (Rl) resulting from sequential intravenous injections of histamine (1.0, 1.8 and 3.2 μg·kg⁻¹) in guinea-pigs. In the right panel are the responses to histamine for three guinea-pigs that have received a sustained subcutaneous infusion of salbutamol (100 μg·kg⁻¹ per h) over four days. The responses are markedly enhanced at all three histamine concentrations by comparison with those in five sham-treated animals (left panel), which have a histamine sensitivity indistinguishable from that of untreated animals. □: histamine 1.8 μg·kg⁻¹ i.v.; □: histamine 1.0 μg·kg⁻¹ i.v.; □: histamine 0.56 μg·kg⁻¹ i.v.; □: histamine 0.06 μg·kg⁻¹ i.v.

Alternatively, or additionally, induction of airway hyperreactivity may arise as a direct consequence of exposure to beta-adrenoceptor agonists. Whether this phenomenon is revealed in certain individuals because of an inherent idiosyncrasy, or as a result of prior exposure to allergens or other sensitizing agents, has yet to be resolved. However, idiosyncratic sensitivity should not be considered unlikely, as this pattern has been reported both during study of asthmatics [38, 39] and after accidental administration of beta-adrenoceptor antagonists [40], which cause a form of hyperreactivity in laboratory animals that is similar to that produced by (+)-isoprenaline [41]. Since the capacity of (+)-isoprenaline to induce airway hyperreactivity is independent of beta-adrenoceptor occupancy, it follows that drug applications at higher frequency during circumstances of increased asthma symptoms and reduced responsivity to bronchodilator effects of beta-agonist may unwittingly enhance airway hyperreactivity. This phenomenon can be readily illustrated in the guinea-pig, where sustained administration of salbutamol in high doses will cause a reduced responsivity to beta-adrenoceptor agonists and, at the same time, an increased responsivity to airway spasmogens (fig. 3). It is important to ascertain in humans if the hyperreactivity associated with the use of beta-adrenoceptor agonists is also independent of adrenoceptor occupancy in asthma patients.

**Conclusion**

There is now sufficient evidence to indicate that adverse effects of beta-adrenoceptor agonists in patients with asthma may intensify disease. The purpose of this review is to direct the attention of clinical investigators to this issue, so that the origin of adverse responses may be resolved on the basis of studies in clinical asthma, rather than in laboratory models in experimental animals.

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**References**


RÉSUMÉ: Les agonistes des béta-adrénergiques ont une action relaxante puissante et sélective sur le muscle lisse des voies aériennes. De la sorte, ils entraînent des effets bronchodilatatateurs perceptibles et sont les plus largement utilisés dans le traitement de l'asthme. Chez les patients atteints d'asthme, ces produits entraînent habituellement une réduction de la résistance des voies aériennes; toutefois, des épisodes d'accroissement de l'obstruction des voies aériennes, de l'hypoxémie artérielle et même des décès, ont été mis en relation avec ce type de traitement dans une série de rapports des 50 dernières années. Une broncho spasme anormal ou paradoxal est une dénomination appropriée pour la description de ce phénomène inattendu. Ceux mécanismes ont été proposés pour expliquer les réponses anormales à ces médicaments: 1) tonus myogène réactif; 2) produits métaboliques à activité spasmylaxie; 3) souches lymphocytaires des adréno-récepteurs; 4) accentuation de la charge inflammatoire; 5) induction d'une hyperactivité des voies aériennes. Après une revue des mérites relatifs de chacune des hypothèses, l'on peut conclure qu'une charge inflammatoire accrue et l'induction d'une hyperactivité des voies aériennes, seules ou en association, fournissent l'explication la plus plausible du bronchospasme paradoxal.