The β2 receptor and airway hyper-responsiveness: are sensory nerves involved?

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The use of β2 agonists for the control of symptoms is central to the treatment of patients with asthma. However, there is controversy surrounding the regular use of this drug class as numerous studies have demonstrated a variety of changes that can be considered unwanted attributes, particularly when these drugs are used regularly as monotherapy. These include increased bronchial hyper-responsiveness (BHR) to inhaled contractile agents and an increase in the allergen-induced early and late asthmatic response following regular treatment with short-acting β2 agonists (SABAs). Furthermore, a number of studies have suggested that regular treatment with inhaled SABAs and long-acting β2 agonists (LABAs) by inhalation leads to a loss of bronchoprotection and with salmeterol treatment an excess mortality in patients receiving the combination therapy. The levels of brain-derived neurotrophic factor (BDNF) were elevated in both serum and platelets obtained from patients receiving monotherapy with salmeterol, and the changes in BDNF levels correlated with the changes in PC20, although the levels of BDNF decreased significantly and there was no such correlation with changes in PC20 in the patients receiving the combination therapy. The changes in PC20 following monotherapy with inhaled salmeterol did not show a correlation with known β2 receptor polymorphisms. A number of other investigators have suggested a role for BDNF in BHR as this is a mediator that is increased in subjects with asthma, both in the lung and in platelets, and which at least in animal models can induce BHR associated with changes in neuronal activity. In patients with asthma, the systemic levels of BDNF are also elevated, whilst they correlate with BHR. Increases in BDNF levels in the lung following allergen challenge of patients with asthma can be reduced by glucocorticosteroids. Airway sensory nerves have also been implicated in the pathogenesis of BHR induced by a number of stimuli, including treatment with regular β2 agonists, and it is of particular interest that platelet activation has also been observed to play a central role in allergen-induced BHR experimentally, supporting the observations of Virchow and colleagues in the present study. Interestingly, salmeterol enhanced the secretion of BDNF from tumour necrosis factor α (TNFα)-stimulated human peripheral blood mononuclear cells, whilst BDNF secretion was inhibited by fluticasone. Clearly it would be of interest to see if salmeterol also caused an increase in BDNF secretion from platelets, thus allowing a clearer link between platelet activation, BDNF and the exacerbation of BHR observed following monotherapy with regular inhaled salmeterol. Whilst the acute benefits of β2 agonist therapy are well accepted, the worsening of asthma control with chronic β2 agonist treatment is not as well accepted, with a recent study reinforcing the safety of regular β2 agonists use. Nonetheless, a number of mechanisms have been put forward to explain worsening asthma control with regular β2 agonist treatment, including increased antigen burden, increased BHR induced by the (+) enantiomer and loss of bronchoprotection. Recently, the role of β2 receptors in asthma has become more complicated with the recognition that β-blockers, which have traditionally been contraindicated in the treatment of patients with...
Mechanisms of adverse effects of β-agonists in asthma

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Short-acting β-agonist (SABA) drugs have been mainstays of asthma therapy for many decades and are recommended treatment at all levels of asthma severity, as they provide prompt relief of asthma symptoms through smooth muscle relaxation and, thereby, bronchodilatation. At all levels of asthma severity more severe than mild intermittent, SBAs are recommended to be taken as required for relief of symptoms in conjunction with inhaled corticosteroids (ICSs) taken as regular maintenance treatment. However, in mild asthma SBAs are recommended as monotherapy without co-concomitant ICS therapy, and in both mild and more severe asthma, greatly increased SABA use at times of asthma exacerbation is almost universal. Here we discuss the safety of inhaled β-agonist monotherapy in asthma and argue against the continued use of β-agonist monotherapy (both short and long-acting) in the absence of concomitant ICS therapy in a combination inhaler.

Several epidemiological studies link overuse of SABA therapies at times of asthma exacerbation with increased risk of hospitalisation or mortality.1,2 The mechanisms underlying this increased risk have not been clearly determined, but are most likely to involve complex mechanisms including delays in seeking medical care, potential cardiac (tachycardia) and metabolic (hypokalaemia) adverse effects as well as possible effects on underlying asthma severity. Although fenoterol, the SABA linked with the epidemic of asthma mortality in the early 1980s in New Zealand3 and some other countries,4 has greater cardiac effects than other SBAs, the reduction in hospitalisations due to asthma exacerbations (along with a reduction in asthma mortality) following the withdrawal of high dose fenoterol in New Zealand in 1990 suggested that the reduction in asthma mortality was not wholly due to reduction in cardiac/ metabolic side effects, but probably also due to an effect on disease severity (because if the reduction in mortality were due to reduction in cardiac side effects, the rate of hospitalisations due to asthma exacerbations should have remained unchanged).5