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Of mice and men—the curious tale of β blockers in asthma

Stimulation of airway β 2-adrenoceptors (β 2ADR) by shortacting or longacting β agonists (LABA) via the classic (canonical) G protein cyclic adenosine monophosphate (Gs-cAMP) signalling pathway results in bronchodilation and relief of asthma symptoms. However, β 2-agonists can also activate non-canonical (Gs-cAMP independent) β -arrestin mediated proinflammatory signalling pathways via extracellular signal regulated kinases (ERK1/2).¹ In knockout mice, β -arrestin-2 regulates the development of allergic asthma.² Chronic exposure to LABA causes adaptive downregulation and uncoupling of β 2ADR with associated subsensitivity of response and in some cases worse asthma control.³ In the antigen-driven mouse model, depletion of adrenaline, the natural ligand for the β 2ADR, prevented the development of asthma.⁴ Replacement of β 2ADR signalling by administration of the LABA formoterol restored the asthma phenotype, showing that agonist induced activation of β 2ADR results in the development of asthma.⁴ This finding suggests paradoxically that use of an inverse agonist might be a better strategy in asthma management than use of a β 2ADR agonist. An inverse agonist is one which stabilises the inactive receptor conformation and blocks its constitutive activity by switching off β 2ADR signalling.

β antagonists are contra-indicated in patients with asthma, even patients using β 1 selective drugs, because of the effects of dose related β 2ADR blockade, which promotes cholinergic transmission and bronchoconstriction, especially upon first dose exposure. Therefore to ever consider use of a non-selective β blocker such as nadolol as anti-asthma treatment would seem counterintuitive.

Some researchers have proposed that switching off β 2ADR (thereby lowering cAMP) with an inverse

β 2 agonist such as nadolol might paradoxically result in an improvement in airway hyper-responsiveness and associated control.⁵ This idea was supported by data from knockout mice devoid of β 2ADR who, when exposed to antigen, did not develop airway hyper-responsiveness or other cardinal inflammatory features of the asthma phenotype, while the same effect also occurred with nadolol treatment in wild type mice expressing β 2ADR.⁶ Moreover, nadolol confers complimentary corticosteroid sparing anti-inflammatory activity in the mouse model.⁷

The beneficial effect of β blockers in adrenaline depleted mice was subsequently suggested to be ligand specific, since exposure to propranolol but not nadolol resulted in the development of the asthma phenotype, whereas in wild type mice, nadolol but not propranolol prevented the occurrence of asthma.⁸ Thus nadolol reduces cAMP as a canonical inverse agonist and is a non-canonical neutral antagonist on ERK1/2,¹ resulting in an overall anti-asthmatic profile. Propranolol acts as a so-called biased ligand, stimulating ERK1/2 as a non-canonical partial agonist while reducing cAMP as a canonical inverse agonist, resulting in a net null or pro-asthmatic profile (figure).^{1,8}

Studies in people with asthma have revealed conflicting results with oral non-selective β blockers. Two open-label studies with nadolol (10–40 mg/day) in inhaled corticosteroid naive intermittent asthma reported improvements in methacholine airway hyper-responsiveness.^{9,10} Under the same reasoning that a LABA would never be given without an inhaled corticosteroid, nadolol should not be given as a monotherapy (ie, without an inhaled corticosteroid) either. By contrast, two placebo controlled trials of propranolol (20–80 mg/day) in

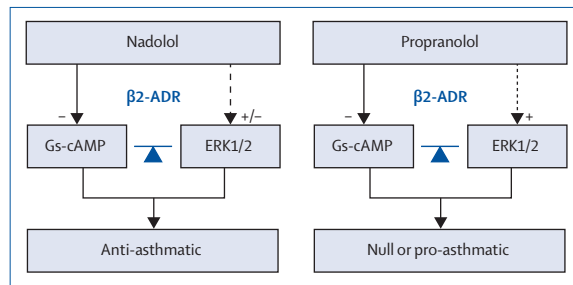


Figure: Effects of β -blockers on canonical (Gs-cAMP) and non-canonical signalling (ERK1/2)

Nadolol acts as an inverse agonist (solid arrow) reducing cAMP and a neutral antagonist (dashed arrow) on ERK1/2. Propranolol acts as an inverse agonist (solid arrow) to reduce cAMP and as a partial agonist (dotted arrow) to stimulate ERK1/2. Signs indicate stimulatory [+], inhibitory [-], or neutral [+/-] effects on signalling. Gs-cAMP=G protein cyclic adenosine monophosphate. ERK1/2=extracellular signal regulated kinases. β 2ADR= β 2-adrenoceptors.

patients with persistent asthma that were being given concomitant inhaled corticosteroids reported no improvement in methacholine or histamine airway hyper-responsiveness or in other inflammatory markers.^{11,12} Furthermore, the salutary effect of an increased inhaled corticosteroid dose suggested that propranolol potentially had further room for improvement and no corticosteroid sparing activity occurred.¹² The concomitant inhaled corticosteroid might have either nullified the effect of propranolol through β 2ADR up-regulation, or perhaps counteracted a putative proinflammatory action of propranolol.

Both of these studies^{11,12} reported a non-significant 2–4% decrease in prechallenge forced expiratory volume in 1 s (FEV₁) after propranolol versus placebo; additionally, reliever use, asthma control, and quality of life were not significantly affected in both studies. The effect of sequential nebulised salbutamol and ipratropium after challenge showed a significant 5% attenuation in FEV₁ between propranolol and placebo, although full recovery back to baseline occurred by 30 min. Hence, it might be possible to overcome the competitive antagonism due to propranolol with a higher dose of β 2 agonist. During initial propranolol dose titration, concomitant tiotropium prevented bronchoconstriction because of increased cholinergic transmission.¹³ Post-hoc analysis showed that propranolol induced bronchoconstriction was greater in patients who expressed the arginine-16 β 2ADR polymorphism than those who did not.¹⁴

A placebo controlled trial (ClinicalTrials.gov, number NCT01804218) assessing oral nadolol as monotherapy in mild inhaled corticosteroid naive asthma will complete in 2016. Under the assumption that nadolol is shown to attenuate methacholine airway hyper-responsiveness, it would also need to have anti-inflammatory activity similar to a low dose inhaled corticosteroid. An inhaled formulation of nadolol in development (Invion Ltd, Brisbane, Australia) might offer a superior therapeutic ratio than oral nadolol as a result of a higher lung concentration along with lower systemic exposure because of its hydrophilicity.

If switching off β 2ADR with an inverse agonist were shown to confer improvements in persistent asthma, this finding would surely challenge present dogma and guidelines regarding continuous β 2ADR stimulation with LABA. Cardiologists have already adopted the approach of moving treatment of heart failure from β agonists to their antagonists. Perhaps, in turn, pulmonologists now need to start thinking along similar lines for the treatment of asthma.

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Treatment of cystic fibrosis in low-income countries



The duration and quality of life of patients with cystic fibrosis in developed countries has been substantially improved in the past two decades. By contrast, individuals with cystic fibrosis who live in low-income settings without the resources necessary to optimise cystic fibrosis care tend to have a worse clinical outcome than those from more affluent areas, including later age at diagnosis, worse nutritional status, and worse lung function. Present cystic fibrosis care guidelines, generally designed to be used in developed countries, include treatments not available in resource-poor settings. Does the high-cost and intensity of such treatments preclude residents of developing countries from benefitting from enhanced cystic fibrosis care?

On the basis of our experience caring for Palestinian patients living in the West Bank and Gaza, and our involvement in projects in countries with limited resources in South America and eastern Europe, we believe that treatment strategies for cystic fibrosis¹ can be adapted to improve longevity and quality of life for patients living in resource-poor countries. These improvements are based on early diagnosis, treatment at specialised cystic fibrosis centres, affordable nutritional optimisation, airway clearance treatments, infection control, and lower-cost drug delivery systems. The emphasis in low-income settings should be on adherence and compliance.

Early diagnosis and intervention can have substantial long-term benefits for patients with cystic fibrosis. Educational programmes aimed at increasing awareness in the medical community and the general public will help early diagnosis. Once diagnosed, patients should be referred to a cystic fibrosis centre. In view of restricted resources, minimum staffing of a cystic fibrosis centre should include a physician, nurse, dietitian, and physiotherapist with expertise in cystic fibrosis.^{2,3}

Nutritional status is a key prognostic factor in cystic fibrosis and in developing countries since many

residents, especially children, have poorly balanced diets and are malnourished. The malabsorption associated with cystic fibrosis will exacerbate dietary deficits; the initiation of pancreatic enzyme replacement therapy and the consumption of fat-soluble vitamins immediately after diagnosis is therefore essential. The cystic fibrosis dietitian should counsel families on how to maintain a high calorie, high fat diet (120–160% of the normal recommended daily calorie allowance, with 35–40% of the calories coming from fat) based on local natural dietary products at relatively low cost. When fat-soluble preparations of vitamins A, D, and E are not available, foods rich in these vitamins can be consumed instead. Adequate hydration and salt supplementation, especially in warm climates, is crucial.

Airway clearance is the keystone to enhance mucociliary clearance⁴ and needs to be emphasised in developing countries where medical resources are inadequate and prolonged hospital admission might not be a viable option. At the time of diagnosis, instructions on how to do manual physiotherapy should be given to parents or other family members and started even in patients who are asymptomatic. Inexpensive mechanical airway clearance devices that were specifically developed for cystic fibrosis—including oscillating positive expiratory pressure devices—can be purchased and shipped to the patients' homes. Hypertonic saline is inexpensive and easily prepared (by adding 7 g of sodium chloride granules to 100 mL of boiled water) and can be used as a first-line inhalation treatment. In our experience, we have noted that dornase alfa (pulmozyme, Genentech, San Francisco, USA), an important but expensive airway clearance drug, is available in some developing countries but not others, so hypertonic saline might be the only available treatment.

