Fatima Yusuf[1], Andrew P. Prayle[2], Michael P. Yanney[1]

michael.yanney@nhs.net

www.linkedin.com/in/michael-yanney-3a9a8247

Editorial

# $\beta_2$-agonists do not work in children under 2 years of age: myth or maxim?

## Introduction

The question of whether infants <2 years of age have functional pulmonary β-adrenoceptors has caused confusion since the discovery and use of commercially available salbutamol in 1969 [1]. For many of us, the "received wisdom" taught in clinic and on the wards is that infants with bronchiolitis do not respond to salbutamol because they do not have $\beta_2$-adrenoceptors. However, is this really the case? In this article, we have tried to weigh the evidence that has been available in the last 50 years in order to reach a logical conclusion.

Unfortunately, the terminology used within the literature for pre-school and infant wheezing disorders is confusing. In the USA and some European countries, the diagnosis of bronchiolitis may include children ≤2 years of age with an acute wheezing illness who have a history of recurrent bouts of wheezing; this differs from the commonly accepted UK definition.

For the purposes of this paper, whilst acknowledging that not all will agree with the following classification, we recognise that different pathophysiological processes can lead to acute episodic wheeze in infancy: inflammation and mucus plugging obstructing airways, mucosal wall oedema and bronchospasm [2].

In our view, bronchiolitis is a clinical diagnosis, beginning with an upper respiratory tract infection followed by signs of respiratory distress, a harsh cough, bilateral crackles, air trapping and wheeze, and is caused by infection and inflammation of the bronchioles. In contrast, children over 1 year to 18 months who have wheeze are more likely to have acute bronchospasm. We recognise several subtypes of this episodic pre-school wheeze, including viral-induced wheeze, multi-trigger wheeze and post bronchiolitis wheeze. Clearly, infants with bronchospasm are more likely to respond to bronchodilators.

## What are β-adrenoceptors?

The β-adrenoceptor is a cell membrane-spanning receptor, with at least three subtypes. $\beta_1$-adrenoceptors are largely cardiac, whereas $\beta_2$ receptors are found in the lungs, liver, vascular tissue and uterine muscles. Within the lung, $\beta_2$-adrenoceptors are largely located on airway smooth muscle, but are also located on type II pneumocytes, epithelial and endothelial cells, and mast cells. $\beta_2$-adrenoceptors mediate their action through G protein-coupled adenylate cyclase activation, increased cAMP and the inhibition of calcium release from intracellular stores, ultimately leading to smooth muscle relaxation and bronchodilation (figure 1). However, nothing is so straightforward in biology, and there are other mechanisms at play that also mediate the effects of $\beta_2$-agonists. Salbutamol, the archetypal respiratory $\beta_2$-agonist, also acts on cardiac $\beta_1$-adrenoceptors, and therefore also induces tachycardia.

**Cite as**: Yusuf F, Prayle AP, Yanney MP. $\beta_2$-agonists do not work in children under 2 years of age: myth or maxim? *Breathe* 2019; 15: 273–276.

@ERSpublications
**Wheezy infants do not respond to bronchodilators despite evidence of functioning β-adrenoceptors. This is because the predominant aetiology, bronchiolitis, is characterised by small airway oedema and increased mucus, for which $\beta_2$-agonists are ineffective.** http://bit.ly/2Ws9ffh

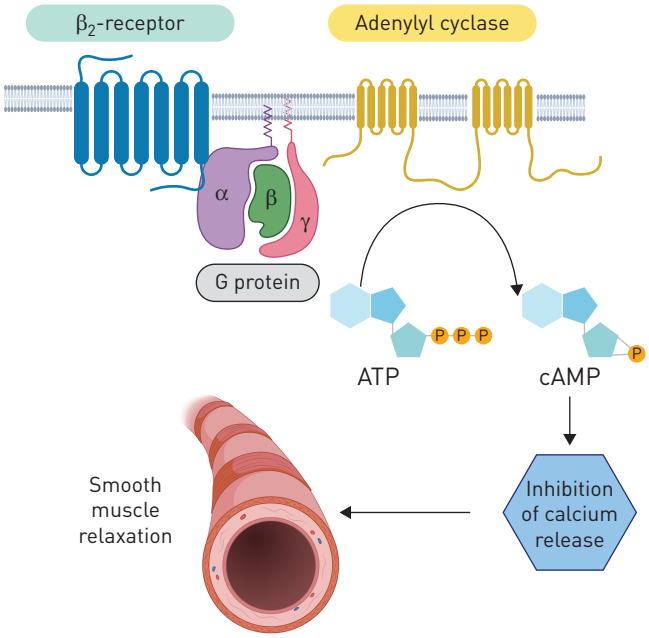


**Figure 1** *Simplified diagram to illustrate the mechanism of action of the $\beta_2$-receptor. The G protein-coupled receptor is activated by agonist binding, leading to conversion of ATP to cAMP by adenylyl cyclase, and downstream inhibition of intracellular calcium release, and subsequent bronchial smooth muscle relaxation. Figure created using BioRender.com*

## Do infants with bronchiolitis respond to bronchodilators?

We know from our daily practice, and from the literature, that infants <12 months of age with wheeze predominantly have bronchiolitis, and do not respond clinically to salbutamol. Measurement of airflow resistance in young children is challenging, and therefore there are few reports in the literature, but they support the notion that bronchodilators have little impact upon bronchial airflow in acute wheeze in younger infants and babies. A selection of lung laboratory studies are presented in table 1, which all show the minimal impact of salbutamol and other bronchodilators on lung function parameters in the context of acute bronchiolitis.

Indeed, subsequent to these studies from the last century, a number of larger randomised trials have assessed bronchodilators, and were summarised in a network meta-analysis [9]. That review concluded that salbutamol is ineffective in bronchiolitis. The authors of the review did suggest that adrenaline may be beneficial in reducing admissions on day 1, and potentially in reducing admissions 1 week after initial presentation when given in combination with dexamethasone, but both of these conclusions were from single studies. A subsequent meta-analysis investigating bronchodilators in combination with steroids found five trials incorporating 1157 patients and failed to demonstrate any benefit of the adrenaline–dexamethasone combination treatment strategy in infants with bronchiolitis [10].

The current *Cochrane Review* summarises data from 1992 infants, and found that there was no impact on saturation, duration of hospitalisation or the clinical score of inpatients [11].

Therefore, both physiological studies and clinical trials support the notion that salbutamol and other bronchodilators have no impact on wheeze in bronchiolitis. From this, it has erroneously been concluded that there are no β-adrenoceptors in the infant lung.

## Why does salbutamol have a limited effect in bronchiolitis? Lessons from the histology

Acute respiratory viral infection in infants leads to bronchiolitis of the medium and small bronchioles [12]. In *post mortem* specimens of respiratory syncytial virus bronchiolitis (where the infants did not die from bronchiolitis), mucosal oedema and inflammatory debris cause airway obstruction, and there is associated lymphoid hyperplasia, which also impacts on bronchiolar calibre. The obstruction demonstrated on histology is therefore at the level of the bronchioles, and the nature of the obstruction is oedema and mucous plugging, with additional extrinsic compression. Administering a bronchodilator will have little impact upon any of these mechanisms of airway obstruction, and therefore it is unsurprising that bronchodilators have minimal effect in bronchiolitis.

## Infants do have functioning $\beta_2$-adrenoceptors

It is a myth that there are no $\beta_2$-adrenoceptors in the developing lung. In fact, radio-pharmacological studies have demonstrated pharmacologically functional adrenoceptors in mammals on day one of life [13]. $\beta_2$-adrenoceptors are clearly found in bronchial smooth muscle, in addition to pulmonary vasculature and type II alveolar cells.

Furthermore, a series of physiological experiments in the 1980s demonstrated that β-adrenoceptors were functional and important in maintaining bronchial airway tone. In a group of 10 infants, lung function performed before and after nebulisation of water showed an increase in the mean airway resistance (indicating bronchoconstriction) over a period of 5 min post nebulisation [14]. After return to baseline and administration of salbutamol, further administration of water had no impact upon airways resistance or specific conductance, indicating that salbutamol prevented bronchoconstriction.

To further demonstrate that salbutamol is a bronchodilator in infancy, Henderson *et al.* [15] administered histamine to 40 infants, and randomly

**Table 1** *Selected laboratory studies on bronchodilators in bronchiolitis*

| First author [ref.] | Population | Methodology | Intervention | Finding |
|---|---|---|---|---|
| **Radford [3]** | 10 infants aged 8–43 weeks with "wheezy bronchitis" and 16 controls | Whole body plethysmography used to measure airway resistance and thoracic gas volume | 10 mL of 0.5% salbutamol solution | Thoracic gas volume and airway resistance were higher in cases compared with controls<br>No change in thoracic gas volume or airway reflexes |
| **Rutter [4]** | 16 infants aged 3 months to 3 years | Respiratory resistance was measured with forced oscillation technique | Salbutamol 1 mL of 0.25% solution | No change in expiratory resistance after administration of salbutamol |
| **Lenney [5]** | 21 babies aged 2–17 months with acute wheeze | Respiratory resistance measured with forced oscillation technique | 2 mL of 0.25% phenylephrine or 2 mL 0.4% adrenaline hydrochloride | No change in respiratory resistance |
| **Tal [6]** | 32 infants aged 0–12 months with acute wheeze | A clinical scoring system | 2×2 factorial design testing both salbutamol and dexamethasone | No effect of salbutamol alone<br>Potentially some effect of combined salbutamol and dexamethasone |
| **Stokes [7]** | 25 infants aged 5–48 weeks | Calculated total work of breathing using an inflatable jacket to measure tidal volume and oesophageal pressure manometry | 5 mg salbutamol was nebulised | Work of breathing increased by mean 21% after administration of salbutamol |
| **Hughes [8]** | 17 infants with respiratory syncytial virus bronchiolitis aged 8–50 weeks | Infant pulmonary function measurements (external compression for forced expiratory flow–volume measurement) | Nebulised salbutamol 0.2 or 0.3 mL of 0.5% salbutamol depending upon weight | No change in most pulmonary function parameters<br>Fall in the maximum flow at functional residual capacity following salbutamol |

allocated infants to receive either salbutamol or saline. They found that salbutamol induced a more rapid recovery of maximal flow rates, in contrast with saline controls. These studies therefore demonstrate that $\beta_2$-adrenoceptors are functional in the infant lung.

## Conclusion

We argue that infants <1 year of age have functional $\beta_2$-adrenoceptors within the lung. The reason for the lack of improvement with β-agonists in wheeze associated with acute bronchiolitis, is that bronchiolitic wheeze is caused by mucous obstruction and airway oedema at the level of the bronchioles, rather than due to muscular constriction (bronchospasm) at the level of the bronchi. It is therefore unsurprising that wheeze in bronchiolitis does not resolve with β-agonists such as salbutamol, as the mechanism of wheeze is different. It is for this reason, rather than a mythical lack of receptors, that salbutamol has no role in the treatment of bronchiolitis.

**Affiliations**

**Fatima Yusuf[1], Andrew P. Prayle[2], Michael P. Yanney[1]**

[1]Sherwood Forest Hospitals Foundation Trust, Sutton-in-Ashfield, UK. [2]Division of Child Health, Obstetrics & Gynaecology, Nottingham University Hospitals, Queens Medical Centre, Nottingham, UK.

**Conflict of interest**

F. Yusuf has nothing to disclose. A.P. Prayle reports non-financial support from Cambridge Research Innovations LTD (provision of N-Tidal C devices free of charge to investigate pre-school and school age wheezing disorders), outside the submitted work. This work is investigating novel physiological measures, including investigating bronchodilators in children. M.P. Yanney has nothing to disclose.

## References


1. Cullum VA, Farmer JB, Jack D, *et al.* Salbutamol: a new, selective beta-adrenoceptive receptor stimulant. *Br J Pharmacol* 1969; 35: 141–151.
2. Bush A, Nagakumar P. Preschool wheezing phenotypes. *EMJ* 2016; 1: 93–101.
3. Radford M. Effect of salbutamol in infants with wheezy bronchitis. *Arch Dis Child* 1975; 50: 535–538.
4. Rutter N, Milner AD, Hiller EJ. Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. *Arch Dis Child* 1975; 50: 719–722.
5. Lenney W, Milner AD. Alpha and beta adrenergic stimulants in bronchiolitis and wheezy bronchitis in children under 18 months of age. *Arch Dis Child* 1978; 53: 707–709.
6. Tal A, Bavilski C, Yohai D, *et al.* Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983; 71: 13–18.
7. Stokes GM, Milner AD, Hodges IG, *et al.* Nebulised therapy in acute severe bronchiolitis in infancy. *Arch Dis Child* 1983; 58: 279–282.
8. Hughes DM, Lesouef PN, Landau LI. Effect of salbutamol on respiratory mechanics in bronchiolitis. *Pediatr Res* 1987; 22: 83–86.
9. Hartling L, Fernandes RM, Bialy L, *et al.* Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. *BMJ* 2011; 342: d1714.
10. Kua KP, Lee SWH. Systematic review and meta-analysis of the efficacy and safety of combined epinephrine and corticosteroid therapy for acute bronchiolitis in infants. *Front Pharmacol* 2017; 8: 396.
11. Gadomski A, Scribani M. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev* 2014; 6: CD001266.
12. Johnson JE, Gonzales RA, Olson SJ, *et al.* The histopathology of fatal untreated human respiratory syncytial virus infection. *Mod Pathol* 2007; 20: 108–119.
13. Schell DN, Durham D, Murphree SS, *et al.* Ontogeny of beta-adrenergic receptors in pulmonary arterial smooth muscle, bronchial smooth muscle, and alveolar lining cells in the rat. *Am J Respir Cell Mol Biol* 1992; 7: 317–324.
14. O'Callaghan C, Milner AD, Swarbrick A. Nebulised salbutamol does have a protective effect on airways in children under 1 year old. *Arch Dis Child* 1988; 63: 479–483.
15. Henderson AJ, Young S, Stick SM, *et al.* Effect of salbutamol on histamine induced bronchoconstriction in healthy infants. *Thorax* 1993; 48: 317–323.