

Editorial

β_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 β_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. β_1 -adrenoceptors are largely cardiac, whereas β_2 receptors are found in the lungs, liver, vascular tissue and uterine muscles. Within the lung, β_2 -adrenoceptors are largely located on airway smooth muscle, but are also located on type II pneumocytes, epithelial and endothelial cells, and mast cells. β_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 β_2 -agonists. Salbutamol, the archetypal respiratory β_2 -agonist, also acts on cardiac β_1 -adrenoceptors, and therefore also induces tachycardia.

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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 β_2 -agonists are ineffective. <http://bit.ly/2Ws9ffh>



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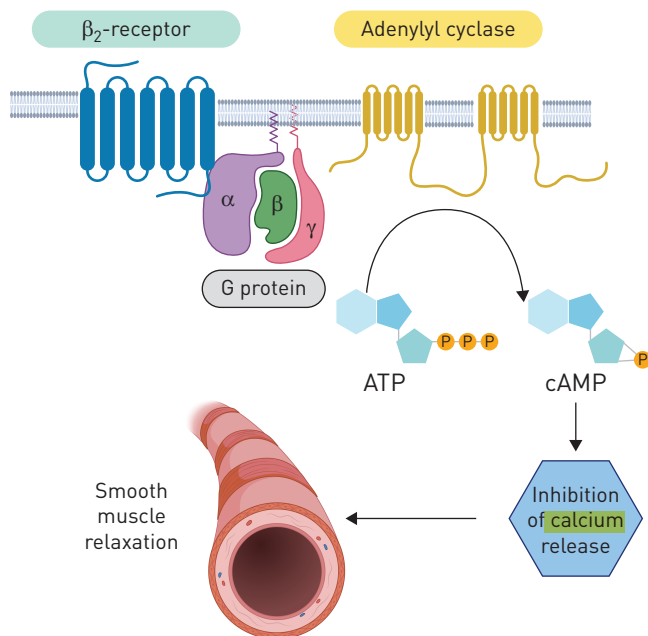


Figure 1 Simplified diagram to illustrate the mechanism of action of the β_2 -receptor. The G protein-coupled receptor is activated by agonist binding, leading to conversion of ATP to cAMP by adenylyl cyclase, and downstream inhibition of intracellular calcium release, and subsequent bronchial smooth 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 β_2 -adrenoceptors

It is a myth that there are no β_2 -adrenoceptors in the developing lung. In fact, radio-pharmacological studies have demonstrated pharmacologically functional adrenoceptors in mammals on day one of life [13]. β_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 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 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 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 β_2 -adrenoceptors are functional in the infant lung.

Conclusion

We argue that infants <1 year of age have functional β_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.

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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.

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