ADENOSINE AND ITS ROLE IN ASTHMA

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ABSTRACT

Endogenous adenosine formed from ADP and AMP by the action of ATPase and 5'-nucleotidase is known to cause bronchoconstriction and asthma in humans. It has been suggested that this action of adenosine is due to its binding to specific purino receptors in the mast cells in the lungs and consequent release of mediators which elicit bronchoconstriction and asthma. The release of these mediators leading to asthma was also believed to be due to vagal stimulation by adenosine. Though the role of adenosine in causing bronchoconstriction leading to asthma is well confirmed the actual mode of action and details of the mechanisms involved in the clinical manifestation of asthma remain unclear.

KEY WORDS : Adenosine, Asthma, Bronchoconstriction, Allergy, Mast Cells.

INTRODUCTION

Studies on the uptake of polyamines by isolated perfused rabbit (1) and rat (2) lungs indicated significant uptake of these compounds by the lungs. However, repeating these experiments with adenosine alone failed due to formation of edematous lungs with significant water uptake and weight gain (unpublished). Studies with adenosine indicated that this macromolecule is a modulator of human allergic reaction leading to asthma (3). Adenosine is a naturally occurring purine nucleoside, the major source of which is adenosine 5-monophosphate (AMP). Under conditions of high energy demand adenosine triphosphate (ATP) is broken down by an ATPase to AMP which is then cleared by 5'-nucleotidase to yield adenosine (4). That this released adenosine would act as an initiator of asthma was first suggested by Marquardt et. al. (5) who demonstrated that this nucleoside by some mechanism stimulated the secretion of histamine leading to allergic asthma.

Further work done in this field has shown that adenosine induced bronchoconstriction is rapid in onset reaching a maximum in 3 to 5 min with slow recovery thereafter (6). However, the related purine nucleoside guanosine (6) and deaminated adenosine metabolite inosine (3) were unable to provoke

bronchoconstriction when inhaled by asthmatic subjects over a concentration range similar to that used for adenosine suggesting that the ability of this compound to cause bronchoconstriction is a specific biological activity. Further AMP and adenosine diphosphate (ADP) on a molar basis have been shown to be bronchoconstrictor agents equally as potent as adenosine (3). However, in the last few years a number of workers have indicated a direct role for AMP in causing bronchoconstriction and a lot of chemicals have been shown to suppress AMP induced asthma (7-12).

ADENOSINE RELEASE AND ASTHMA

It is now well established that the role of adenosine in the pathogenesis of asthma is due to its release *in vivo* following provocation of the airways (13). This conclusion is based on the observation of the release of adenosine in animal lungs during hypoxia (14) or following antigen challenge (15). Even in human asthmatic subjects the release of adenosine has been reported (13) consequent to methacholine or certain other allergen challenge leading to bronchoconstriction. Further it has also been shown that asthmatic children also manifest an increase in adenosine and AMP in the lungs consequent to bronchial provocation by methacholine

and exercise (16).

Further, proof of the release of adenosine an endogenous mediator in asthma was the significant increase of this nucleoside in plasma after methacholine induced bronchoconstriction (3). It is possible that adenosine release in association with asthma is a non specific phenomenon consequent to hypoxia resulting from regional ventilation perfusion inequalities (17). Nevertheless, with regard to certain organs, there are reports which suggest beneficial signaling response of adenosine on release which occurs during oxygen demand in the heart (18). Positive adaptive responses with adenosine have been reported (18) in brain, skeletal muscle, adipose tissue, intestine and kidney. However, the negative response of adenosine in lungs of humans leading to asthma remains controversial and unclear (6, 19).

RECEPTOR MEDIATED ADENOSINE INDUCED ASTHMA

Evidence that the bronchoconstrictor response to adenosine is mediated by its interaction with specific cell surface receptor is based on the observation that closely related nucleotides do not reproduce this response seen with adenosine as explained earlier. Secondly, theophylline administered orally or by inhalation to atopic asthmatic subjects led to significant protection against adenosine induced bronchoconstriction but did not show a similar effect against histamine induced asthma (20). Another line of evidence to support the concept of adenosine induced asthma consequent to its attachment to specific receptors comes from work done using dipyridamole which inhibits the facilitated uptake of adenosine. Dipyridamole caused only a small enhancement of bronchoconstriction by the nucleoside but showed no response to the effect on the airways by histamine (21). Further, confirmation of the action of adenosine to cause bronchoconstriction may be mediated by its binding to airway receptors is supported by the identification of specific receptors subtypes in the lungs of both animals and humans which bind to adenosine leading to asthma (22). Recent research has firmly established the existence of specific adenosine

receptors identified as A1, A2b and A3 and their characteristics have been studied (23-25). Further efforts are on to target these receptors with certain drugs to suppress the adenosine binding to them which would prevent asthma in which some success has been reported (26, 27) using experimental models.

MAST CELLS IN ADENOSINE ACTION

It has been suggested that the action of adenosine on air way mast cells leads to bronchoconstrictor effect in asthmatics (28, 29). Support for the involvement of air way mast cells in adenosine induced asthma is derived by the observation that sodium chromoglycate a drug with mast cell stabilizing properties protects against bronchoconstriction induced by adenosine but not by histamine (30). Similar but more potent activity is seen by another drug nedochromil sodium (31). Further studies indicated that the aforesaid drugs as well as few others like enprofylline and theophylline functioned by acting as antagonist to specific receptors in human mast cells (32, 33) which otherwise is capable of binding to adenosine resulting in bronchoconstriction (34).

The role of mast cells in the bronchoconstriction effect of adenosine through mediator release was supported by the observation that allergic non-asthmatics are more sensitive to the nucleoside than non- allergic subjects (13). Further, it was observed that histamine receptor antagonist terfenadine had an inhibitory effect on adenosine induced bronchoconstriction. This drug had no other pharmacological activity as demonstrated by lack of suppression of bronchoconstrictor response to inhaled methacholine (35). It is now believed that endogenous adenosine is primarily responsible in provoking bronchoconstriction (36) by preferentially stimulating purino receptors to enhance mediator release from human lung mast cells and basophils (13). Various types of mast cell derived mediators like Prostaglandin D₂, histamine and tryptase have been suggested to lead to bronchoconstriction (37, 38). Hence, though mast cell involvement in adenosine induced asthma is confirmed the exact mechanism of action remains controversial.

NEUROLOGICAL INVOLVEMENT IN ADENOSINE INDUCED ASTHMA

Although it is well documented that the adenosine induced bronchoconstriction is mainly due to mast cell mediator release, vagal reflexes have also been implicated. Studies using specific muscarinic receptor antagonist ipratropium bromide showed an increased requirement of adenosine to cause asthma after prior exposure to the bromide derivative suggesting a vagal reflex (39). Further confirmation for possible vagal reflex in bronchospastic response can be seen from the work of Okayama et.al. (40), who demonstrated an inhibitory effect on adenosine induced bronchoconstriction in asthmatic subjects who inhaled atropine and lignocaine. The neurological involvement in adenosine induced asthma was explained on the basis of hydrolysis of ATP in nerve endings to yield adenosine by ATPase and 5' nucleotidase action which

can then serve as presynaptic regulator (41). It was also suggested that adenosine could also be generated by post-synaptic cells by a similar mechanism (41). Consequently, it was indicated that this adenosine formed could lead to a simultaneous release of neurotransmitters and preformed proinflammatory mediators causing bronchoconstriction.

Conclusion

Screening of a lot of work published in scientific literature, over the years, indicates a significant variation in proposed mechanisms such as involvement of prostaglandins (42), phosphodiesterase modulation (43), potentiation of adenylyl cyclase action (44), role of heparin (45), and specific lipoxygenase effect (46) to explain the role of adenosine in asthma. There is a lot of potential for further work on adenosine and its role in asthma.

REFERENCES

1. Rao, S.B. and Mehendale, H.M. (1987) Uptake and disposition of putrescine, spermidine and spermine by rabbit lungs. *Drug Metab. Dispos.* 15, 189-194.
2. Rao, S.B. and Mehendale, H.M. (1988) Passive sequestration of putrescine spermidine and spermine by rat lungs. *Biochem. Biophys. Acta.* 966, 22-30.
3. Phillips, G.D. and Holgate, S.T. (1988) The mechanism of adenosine - induced bronchoconstriction in asthma *ISI Atlas of Sci. Pharmacol.* 28- 32.
4. Fain, J.N. and Malbon, C.C. (1979) Regulation of adenylyl cyclase by adenosine *Mol. Cell. Biochem.* 25, 143 - 169
5. Marquardt, D.L., Parker, C.E. and Sullivan, T.J. (1978) Potentiation of mast cell mediator release by adenosine *J. Immunol.* 120, 871 - 878
6. Cushley, M.K, Tattersfield, A.E. and Holgate, S.T. (1983) Inhaled adenosine and guanosine on airway resistance in normal and asthmatic subjects. *Brit. J. Clin. Pharmacol.* 15, 161-165
7. Fowler, S.J., Dempsey, O.J., Sims, E.J. and Lipworth, B.J. (2000) Screening for bronchial hyperresponsiveness using methacholine and AMP. Relationship to asthma severity and beta (2) receptor genotype. *Amer. J. Resp. Crit. Care.* 162, 1318-1322.
8. Avital, A., Godfrey, S. and Springer, C. (2000) Exercise, methacholine and AMP challenges in children with asthma: relation to severity of the disease. *Pediatr. Pulmonol.* 30, 207-214.
9. Jokic, R., Swystun, V.A., Davis B.E. and Cockcroft, D.W. (2001) Regular inhaled salbutamol: effect on airway responsiveness to methacholine and AMP and tolerance to bronchoprotection. *Chest* 119, 370-375.
10. Holgate, S.T., Arshad, H., Stryczak, P. and Harrison J.E. (2000) Mometasone furoate antagonizes AMP induced bronchoconstriction in patients with mild asthma. *J. Allergy Clin. Immunol.* 105, 906-911.

11. Rutgers, S.R., Koeter, G.H., Vander Mark, T.W. and Postma, D.S. (1999) Protective effect of oral terfenadine and not inhaled ipratropium on AMP induced bronchoconstriction in patients with COPD. *Clin. Exp. Allergy* 29, 1287-1292.
12. Nightingale, J.A., Rogers, D.F. and Barnes, P. J. (1999) Differential effect of formoterol on AMP and histamine reactivity in asthma. *Amer. J. Resp. Crit. Care Med.* 159, 1786-1790.
13. Church, M.K. and Holgate, S.T. (1986) Adenosine and asthma *Trends in Pharmacol. Sci.* 7, 49-50
14. Mentzer, R.M., Rubio, R. and Berne, R.M. (1975) Release of adenosine from hypoxic canine lung tissue and its possible role in the pulmonary circulation. *Amer. J. Physiol.* 229, 1625 - 1631.
15. Ng, W.H., Polosa, R. and Church, M.K. (1990) Adenosine bronchoconstriction in asthma: investigation into its possible mechanism of action. *Brit. J. Clin. Pharmacol.* 30, 898 - 905
16. Avital, A., Springer, C., Bar - Yishay, E. and Godfrey, S. (1995) Adenosine, methacholine and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. *Thorax* 50, 511- 516
17. Mann, J.S., Holgate, S.T., Renwick, A.G. and Cushley, M.J. (1986) Airway effects of purine nucleosides and nucleotides and release with bronchial provocation in asthma. *J. Appl. Physiol.* 61, 1667- 1676
18. Berne, R.M. (1985) In *Purines: Pharmacol. and Physiological roles* Ed. Stone, T.W. Mac Millan, London. p. 125- 130
19. Phillips, G.D., Refferty, P., Beasley, C.R.W. and Holgate S.T. (1987) The effect of oral terfenadine on the bronchoconstrictor response to inhaled histamine and AMP in non- atopic asthma. *Thorax* 42, 939 - 945.
20. Cushley, M.J., Tattersfield, A.E. and Holgate, S.T. (1984) Adenosine induced bronchoconstriction in asthma: antagonism by inhaled theophylline. *Amer. Rev. Respir. Dis.* 129, 380- 384.
21. Cushley, M.J., Tallant, N. and Holgate, S.T. (1986) The effect of single dose intravenous dipyridamole on histamine and adenosine induced bronchoconstriction in normal and asthmatic subjects. *Eur. J. Respir. Dis.* 86, 185 - 192.
22. Pauwels, R.A. and Joos, G.F. (1995) Characterization of the adenosine receptors in the airways. *Arch. Int. Pharmacodyn. Therp.* 329, 151- 160.
23. Feoktistov, I. and Biaggioni, I. (1997) Adenosine A2b receptor. *Pharmacol. Rev.* 49, 381-402.
24. Linden, J., Auchampach, J.A., Jin, X. and Figler, R.A. (1998). The structure and function of A1 and A2b receptors. *Life Sci.* 62, 1519-1524.
25. Jacobson, K.A. (1998) Adenosine A3 receptors: novel ligands and paradoxical effects. *Trends Pharmacol. Sci.* 19, 184-191.
26. Fozard, J.R. and Hannon, J.P. (1999) Adenosine receptor ligands : potential as therapeutic agents in asthma and COPD. *Pulm. Pharmacol. Ther.* 12, 111-114.
27. Feoktistov, I., Polosa, R., Holgate, S.T. and Biaggioni, I. (1998) Adenosine A2b receptors: a novel therapeutic target in asthma. *Trends Pharmacol. Sci.* 19, 148-153.
28. Polosa, R., Crimi, N., Vancheri, C., Holgate, S.T. Church, M.K. and Mistretta, A. (1995) Release of Mast cell derived mediators after endobronchial adenosine challenge in asthma. *Amer. J. Respir. Crit. Care Med.* 151, 624- 629.
29. Forsythe, P. and Ennis, M. (1999) Adenosine, mast cell and asthma. *Inflamm. Res.* 48, 301-307.

30. Cushley, M.J., and Holgate, S.T. (1985) Adenosine induced bronchoconstriction in asthma: Role of mast cell mediator release. *J. Allergy Clin. Immunol.* 75, 272 - 278.
31. Howarth, P.H., Durham, S.R., Lee, T.H., Kay, A.B. and Holgate, S.T. (1985) Influence of albuterol, cromolyn sodium and ipratropium bromide on the airway and circulating mediator responses to antigen bronchial provocation in asthma. *Amer. Rev. Respir. Dis.* 132, 986 - 992.
32. Feoktistov, I. and Biaggioni, I. (1995) Adenosine A2b receptors evoke interleukin- 8 secretion in human mast cells: An enprofylline sensitive mechanism with implications for asthma. *J. Clin. Invest.* 96, 1979 - 1986.
33. Coward, W.R., Sagara, H. and Church, M.K. (1998) Asthma, adenosine, mast cells and theophylline. *Clin. Exp. Allergy.* 28, 42-46.
34. Marquardt, D.L. (1998) Mast cell adenosine receptor characteristics and signalling. *Adv. Exp. Med. Biol.* 431, 79-82.
35. O'Connor, B.J., Fuller, R.W. and Barnes, P.J. (1994) Nonbronchodilator effects of inhaled beta2 agonists: Greater protection against AMP than methacholine induced bronchoconstriction in asthma. *Amer. J. Respir. Crit. Care Med.* 150, 381 - 387.
36. Driver, A.G., Kukoly, C.A., Ali, S. and Mustafa, S.J. (1993) Adenosine in bronchoalveolar lavage fluid in asthma. *Amer. Rev. Respir. Dis.* 148, 91 -97.
37. Polosa, R., Nig. W.H., Crimi, N., Vancheri, C., Holgate, S.T. Church, M.K. and Mistretta, A. (1995) Release of mast cell derived mediators after endobronchial adenosine challenge in asthma. *Amer. J. Respir. Crit. Care Med.* 151, 624- 629.
38. Forsythe, P., McGarvey, L.P., Heaney, L.G., MacMohan, J. and Ennis, M. (1999) Adenosine induces histamine release from human bronchoalveolar lavage mast cells. *Clin. Sci.* 96, 349-355.
39. Crimi, N., Palermo, F., Oliver, R., Polosa, R., Settineri, I and Mistretta, A. (1992) Protective effects of inhaled ipratropium bromide on bronchoconstriction induced by adenosine and methacholine in asthma. *Eur. Respir. J.* 5, 560- 565
40. Okayama, M., Ma, T.Y. and Mataoka, I. (1986) Role of vagal nerve activity on adenosine induced bronchoconstriction in asthma. *Amer. Rev. Respir. Dis.* 133, 93 -97.
41. Pauwels, R. (1987) The role of adenosine in bronchial asthma. *Bull. Eur. Physiopathol. Respir.* 23, 203 - 208.
42. Wang, M., Wisniewski, A., Pavord, I., Knox, A. and Tattersfield, A. (1996) Comparison of three inhaled non-steroidal anti-inflammatory drugs on the airways response to sodium metabisulphite and AMP challenge in asthma. *Thorax*, 51, 799- 804.
43. Barnes, P.J. (1995) Cyclic nucleotides and phosphodiesterases and airway function *Eur. Respir. J.* 8, 457 - 462.
44. Mundell, S.J., Olah, M.E., Panettieri, R.A., Benovic, J.L. and Penn, R.B. (2001) Regulation of G protein-coupled receptor-adenyl cyclase responsiveness in human air way smooth muscle by exogenous and autocrine adenosine. *Amer. J. Resp. Cell. Mol. Biol.* 24, 155-163.
45. Ceyhan, B.B. and Celikel, T. (1997) Effect of inhaled heparin on adenosine induced bronchial hyperreactivity. *Int. J. Clin. Pharmacol. Ther.* 35, 208-213.
46. VanSchoor, J., Joos, G.F., Kips, J.C., Drajesk, J.F., Carpenter, P.J. and Pauwels, R.A. (1997) The effect of ABT-761 a novel 5-lipoxygenase inhibitor on exercise and adenosine induced bronchoconstriction in asthmatic subjects. *Amer. J. Resp. Crit. Care Med.* 155, 875-880.