LETTERS TO THE EDITOR

Inhibition of T cell proliferation by human alveolar macrophages

The demonstration by Upham et al. that human alveolar macrophages selectively inhibit proliferation of T cells by secretion of unidentified effector molecules raises the question as to whether pathological processes in the lung characterised by extensive macrophage recruitment or activation can have a systemic effect on T cell development. It has been shown in several studies that patients with pulmonary tuberculosis who are not infected by HIV often show a lymphopenia principally affecting the CD4+ T cells. It appears to be a transient phenomenon as the CD4+ count reverts to normal after successful therapy. A similar transient lymphopenia has also been observed after antigenic bronchial provocation in asthmatic subjects.

It would be of great interest to determine whether this systemic phenomenon is due to the same mechanism as the one described by Upham et al., whether it accounts (at least in part) for the so-called "idiopathic CD4+ T lymphopenia syndrome," and whether it affects the balance between Th1 and Th2 cells which may be critical to the pathogenesis of both asthma and tuberculosis.

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Adenosine and adenosine antagonist in asthma

I read with interest the excellent update on adenosine by Polosa and Holgate. An important use of this challenge agent is demonstrated and adenosine antagonism as a potential treatment for asthma is revisited. However, the role of adenosine as a mediator of asthma is somewhat inconsistent with several functional observations. Besides the fact that adenosine has dual effects in many systems, data are available particularly involving the pharmacology of enprofylline (3-methyl xanthine)—which suggests that the therapeutic efficacy of theophylline (1,3-dimethyl xanthine) in asthma may not reflect adenosine antagonism. This latter aspect is significant because theophylline, at therapeutics concentrations, effectively antagonises adenosine (at receptors and functionally in vivo).

Qualitatively different from theophylline, enprofylline does not antagonise the physiological/pathophysiological actions of adenosine yet enprofylline and theophylline share several pharmacological actions including cardiac stimulation, microvascular anti-exudative activity, and a range of smooth muscle relaxant effects although enprofylline is consistently about three times more potent than theophylline. Equally, enprofylline is about three times more potent than theophylline in asthma as a bronchodilator, as an inhibitor of histamine-induced bronchoconstriction, as an inhibitor of mast cell release, and gastric secretory effects. This distinct human pharmacology is evidence for the clinically effective adenosine antagonist of theophylline and indicates that enprofylline tonically suppresses volume and acidity of gastric secretion, natriuresis, gastric acid secretion, etc. One might therefore conclude that adenosine antagonism should probably be avoided in asthma therapy because it may be associated with less desirable excitatory extrapulmonary effects.

Antagonism of A1 adenosine receptors by enprofylline may explain the "adenosine hypothesis." By inferring this, Polosa and Holgate lend greater weight to observations that disagree with the anti-asthma potency ratio between enprofylline and theophylline that may require 300 µM drug concentrations for effective function (inhibition of mast cell release) than, for instance, to the work by Clarke et al. which showed that theophylline, but not enprofylline, protects against adenosine induced obstruction in asthma (see also references 18 and 21 in the review by Polosa and Holgate).

If the clinical efficacy of the xanthines in asthma cannot be explained by adenosine antagonism, phosphodiesterase inhibition may offer an alternative explanation but, unfortunately, there are also doubts about this—hence the widely promoted non-xanthine phosphodiesterase IV inhibitors cannot rely on theophylline for any predictable clinical efficacy. Perhaps both adenosine antagonism and phosphodiesterase inhibition are examples of how theoretically attractive mechanisms may prevent unbiased exploration of truly important in vivo modes of action of anti-asthma drugs.

Incidentally, enprofylline was discovered by unexpected observations in complex biosystems. Such exploratory in vivo work, if allowed, will continue to be a source of novel drugs; when successful, one should not be surprised to learn that the discovered class of drug was not predicted by reductionist research paradigms. The new efficacious compounds may thus unravel novel mechanisms—for example, omeprazole and the acid pump—or, as with the experimental drug enprofylline, the new properties will seriously question the therapeutic relevance of a widely held mechanism.

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References


3 Reynolds HY. Lung inflammation: normal host defense or a complication of some diseases. Immunology 1984; 52:786–95.

4 Lin CY, Pabst R, Binns RM, Licence ST, et al. Regulation of T cell development and whether it affects on the overall recirculation of this process during inflammatory diseases characterized by enhanced lung macrophage recruitment/activity may result in significant effects on the overall recirculating T cell compartment is thus worthy of more detailed investigation.


AUTHORS’ REPLY

We read with interest the letter from Professor Persson but we remain somewhat confused about the point or points he raises. The review we wrote was intended to draw attention to adenosine bronchial pronociceptive effects. It did not argue that adverse effects of xanthines operating through this receptor could be avoided.1

It was also stated that, because enprofylline did not have pharmacological and therapeutic actions, it was unlikely that adenosine antagonism could be involved. As pointed out in our review, it is now known that there exist two types of adenosine A2 receptor designated A2a and A2b.4 While enprofylline has little or no effect against A2a receptors, it is a selective, albeit weak, antagonist at the A2b receptor—the adenosine receptor subtype found both on canine and human mast cells. Thus, if adenosine is released in pharmacologically active concentrations in asthmatic airways, for which there is good evidence, then enhancement of mast cell mediator release via A2b receptors is a probable scenario. As a consequence, enprofylline could have produced at least some of its therapeutic effect in asthma by inhibiting A2b receptor mediated mast cell releasability. This may or may not have implications for the clinical efficacy of enprofylline, which is only a weak A2a antagonist, but the A2b receptor does present a potential new therapeutic target for asthma against which new drugs might be developed.5

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