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Adenylate Cyclase Activity in Mononuclear Leucocytes from Patients with Atopic Dermatitis

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The underlying abnormality that leads to the atopic diathesis is unknown. However, an attractive idea is the concept of a genetically inherited biochemical abnormality that promotes exaggerated immunological and pharmacological responses to environmental stimuli.

The cyclic nucleotide system acts as a secondary intracellular messenger for the action of numerous cell stimuli and appears to be an important regulatory mechanism of many cellular functions.

Szentivanyi's proposal (16, 17) that an abnormality of this system would be a good candidate for the constitutional basis of atopic disease has led to intensive investigation of the cyclic nucleotide system in atopic dermatitis.

His original concept was that blockade of B receptors caused diminished cyclic AMP production by adenylate cyclase. In general cyclic AMP fulfils an inhibitory action on cellular function and loss of this inhibition could cause the pharmacological and immunological imbalance seen in atopic diseases.

Subsequent to Szentivanyi's hypothesis several investigators demonstrated diminished cyclic AMP responses to B agonists in atopic disorders (11, 10). However, later studies indicated that the defect was not limited to the B receptor because atopic mononuclear leucocytes also show diminished cyclic AMP responses to histamine and prostaglandin E (12, 1, 14). All of these hormones act via a complex membrane enzyme called adenylate cyclase (8). The cell surface receptors activate stimulatory or inhibitory subunits influencing the rate of production of cyclic AMP by the catalytic unit. A defect of the adenylate cyclase enzyme below the receptors could account for the diminished cyclic AMP responses seen with B agonists in atopic dermatitis.

The activity of adenylate cyclase can be measured directly on cell homogenates or membrane preparations by a radioenzyme assay described by Saloman (13) and the use of Forskolin (15) a catalytic unit stimulator allows the function of the catalytic unit to be measured.

Using these probes of adenylate cyclase activity Guerin, Chan and Hanifin reported increased mononuclear leucocyte adenylate cyclase catalytic unit activity in atopic dermatitis (4). They did not find any differences in basal unstimulated or isoprenaline stimulated adenylate cyclase activity between atopic dermatitis and normals.

Adenylate cyclase activity varies between different leucocyte populations (2). Although most mononuclear leucocyte preparations are predominantly lymphocytes they also contain approximately 20–30% monocytes. Consequently the study of the enzyme activity of pure leukocyte preparations becomes important.

We purified mononuclear leukocytes (MNL) from eight normal and nine atopic dermatitis patients into monocyte rich (MR 64% pure) and lymphocyte rich (LR 94%) subsets on Percoll gradients. No differences in the constitution of the subsets was seen between atopics and normals.

Adenylate cyclase activity was measured on homogenate preparations of the leucocyte

Table I. *Adenylate cyclase activity of mononuclear leucocytes, lymphocyte enriched and monocyte enriched preparations from atopic dermatitis (AD) and normals*
pMol/min/10 cells ±SEM

	(*n*)	MNL	MR	LR
AD	(9)	7.3±1.5	9.0±2.3	1.4±0.5
Normal	(8)	7.6±2.6	5.9±1.6	2.3±0.7

subsets using the method of Saloman (13) in the presence of a phosphodiesterase inhibitor. The results are shown in Table I. Monocytes showed higher adenylate cyclase activity than lymphocytes in both atopic and normal preparations. No differences were seen between atopic and normal MNL or LR preparations. The slight increase of atopic MR adenylate cyclase activity over normals did not reach statistical significance.

Forskolin (10—5M) cause a significant ten-fold rise in adenylate cyclase activity over basal levels but no significant differences were seen between atopics and normals. This differs from earlier results but may be because the earlier studies were performed on purified membrane samples (4). Normal adenylate cyclase activity has also been demonstrated in atopic skin, although assay techniques were quite different (9).

In contrast to the normal adenylate cyclase activity of atopic mononuclear leucocytes, cyclic AMP catabolism would appear to be increased. Cyclic AMP phosphodiesterase activity is markedly elevated in mononuclear leukocytes from atopic dermatitis and kinetic studies suggested the increased activity may be found in the monocyte (3).

Further studies on highly purified monocyte preparations confirm this finding. We demonstrated significantly elevated phosphodiesterase activity in monocytes purified from the peripheral circulation of atopic dermatitis patients (7).

In summary recent investigation implicates elevated phosphodiesterase activity in the presence of normal adenylate cyclase activity as the explanation for B adrenergic hyporesponsiveness.

This abnormality is certainly present in the atopic monocyte and would explain the recent finding of impaired monocyte function associated with abnormal cyclic AMP responses to agonist stimulation (6). The abnormal cyclic nucleotide control of monocyte function resulting from this underlying enzyme imbalance may lead to sequelae such as faulty antigen presentation, and altered monocyte lymphocyte interaction leading to many of the immunological abnormalities found in atopic dermatitis (5).

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