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Thymomimetic drugs: A New Advances in Immunotherapy

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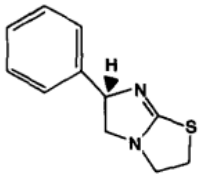
Thymomimetic drugs are named for their ability to mimic the action of the thymus in the maturation and functional alteration of prothymocytes and mature thymusdependent (T) cells. Hormones secreted by the thymus perform these functions, thus the thymomimetic drugs reproduce the action of thymic hormones. There are two classes of compounds which act in this manner: (1) those which induce thymic hormones or a thymic hormone-like substance, e. g., levamisole and (2) those which simulate the action of thymic hormones, e. g., isoprinosine. Both classes of drugs have been demonstrated to have some utility in restoring defective cellular immune response in experimental animals and in clinical trials.

The use of the term thymomimetic is not synonymous with mimicking the action of thymic hormones but rather the action of the thymus. The influence of products other than thymic hormones, like interleukins, which may induce maturation of immature thymus cells implies that the process of T cell maturation involves at least two different regulatory steps (i. e., administration of both thymic hormones and interleukins). In fact, this multi-step maturation process may involve IL-2 at a time prior to thymic hormone action. The concept that thymic hormones are needed before the interleukins is changing.

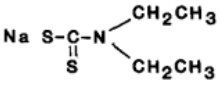
Upon exiting the thymic cortex, the thymocytes move out to the periphery either directly or by way of the thymic medulla. There is evidence that both routes are utilized. This mature T cell enters the circulation and, to an extent, takes up residence in T cell-dependent areas of lymph nodes, spleen, Peyers patches, etc. In the periphery the T cell maintains sensitivity to thymic hormones which then modulate receptor display and functions including; proliferation, cytotoxicity, lymphokine production, and helper or suppressor activity. Two assays are commonly used to assess sensitivity of the post-thymic T cell to hormones. One, the Bach assay [3] utilizes a subset of murine T cells (perhaps the post-thymic precursor described by Stutman) whose display of receptors for sheep erythrocytes (SRBC) is inhibited by azathioprine. In the presence of azathioprine, the appropriate inducer, in this case thymic hormones, e.g.,

thymulin, will restore the display of SRBC receptors within 1 hour. The Wybran and Fudenberg assay [2] assesses the ability of circulating human T cells to form "active" rosettes with SRBC within 1 hour. Even in the presence of a thymus and circulating thymic hormones this response can be augmented by the appropriate inducer, such as a thymic hormone. When there is a thymus deficiency, depressed active rosetting is observed.

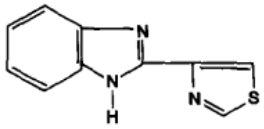
Thymic hormone(s) exert an influence on receptor induction in prothymocytes and on a subset of mature T cells which is linked to the cyclic AMP system. Their influences in the modulation of receptor display and function(s) of mature T cells is linked to the cyclic GMP system. Within this context, it has been experimentally shown that the actions of thymic hormones can be mimicked at one or the other level by a variety of drugs and biologic agents which impinge on the appropriate cyclic nucleotide system. The mechanisms are, however, contrasting and agents which induce T cell differentiation via cyclic AMP generally inhibit mature T cell functions, and those which promote T cell active rosettes and function via cyclic GMP are inactive in the differentiation assays. Because these cyclic nucleotide activating agents can only mimic one part but no other parts of thymic hormone action, they cannot be considered as thymomimetic. However, their use at the appropriate time with regard to T cell maturation or function, may effectively reproduce thymic hormone action in vivo. Fortunately, thymomimetic drugs are available which will faithfully reproduce the actions of thymic hormones; whether cyclic nucleotide mechanisms are involved in the various actions of these drugs is still unclear. In general, the drugs which induce T cell differentiation in the Komuro-Boyse assay and increase receptor display of mature T cells in the Wybran and Fudenberg assay, or which induce in vivo factors which are active in both assays, would most reliably be considered thymomimetic.



LEVAMISOLE
L-2,3,5,6 TETRAHYDRO-6-PHENYL-
IMIDAZOLE (2,1-b) THIAZOLE HYDROCHLORIDE



DTC-DIETHYLDITHIOCARBAMATE



THIABENDAZOLE

The Bach assay has not been used extensively to test the actions of thymomimetic drugs. Only levamisole has been shown to be directly active in this assay [4]. It is notable that the Bach assay employs 6-

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mercaptopurine (azathioprine) as the inhibitor of rosetting and it will be of interest to determine if the 9-substituted purines are competitive agonists for a receptor acted on by this inhibitor. One striking observation [5], which apparently has not been pursued, is that a single dose of cyclomunine (a cyclosporin A-like compound with immunostimulating properties in vivo at low doses) increases serum thymulin levels for up to 240 days as measured by activity in the Bach assay. Stimulation of thymic epithelial cells by cyclomunine has been postulated as the mechanism of action (Pompidou, personal communication).

Therapeutic Potential of Thymomimetic Drugs -

Levamisole and isoprinosine both have limitations regarding their therapeutic usefulness. They are relatively mild in their action. Levamisole treatment often takes weeks to months to achieve effects. In addition, animals and humans who do not respond to levamisole therapy have been demonstrated in virtually all experiments, although there is no immunopharmacologic explanation for this. Its side effects (particularly agranulocytosis) are significant. Apparently, some of the other sulfurcontaining compounds are less toxic and may be more potent and, therefore, offer significant potential for improving the limited immunotherapeutic efficacy of levamisole. Isoprinosine is non-toxic generally, must be administered in relatively high doses, but is more consistent in its action than levamisole.

The thymic hormones singly and collectively have demonstrated action in primary immunodeficiencies, particularly the DiGeorge syndrome and severe combined immunodeficiency. Several reports indicate activity in human cancer. Levamisole, isoprinosine, and the various thymic hormones have received diverse clinical emphasis, including infections, [6]. If one accepts, as their immunopharmacologies indicate, that their modes of action are similar, then the clinical activities demonstrated for one carry implications for the others. To carry this argument one step further, we suggest that it would be useful to examine the thymomimetic drugs and thymic hormones for therapeutic activity in the following clinical situations:

l) Cancer- to increase the period of remission following cytoreductive therapy, to decrease the number of metastases in other tumors, or to decrease the incidence and severity of infection following immunosuppressive cytoreductive therapy.

2) Infection-to decrease the duration and severity of infection with a variety of pathogens, especially viruses for which antimicrobials are not available.

3) Autoimmunity-to decrease autoimmune phenomena and to restore cellmediated immune response.

4) Aging-to improve impaired cellular immune responsiveness and decrease the incidence of sequelae like cancer, infections, and autoimmunity.

5) Acquired immunodeficiency including AIDS-to partially restore cellular immunity when a reserve of T cell numbers and function exist.

In general, there is little expectation for this form of therapy in late-stage active progressive cancer or AIDS. In these circumstances, alternative, complex strategies, using combined immunotherapeutic modalities have been advocated by us [6,7]. In these circumstances the use of synergistic combinations of agents would appear to offer the greatest hope. It seems likely that combinations of thymic hormones and/or thymomimetic drugs with interleukin 2 or other lymphokines like alpha interferon should prove worthwhile. In conclusion, drugs with thymomimetic activity exist and have been demonstrated to have immunopharmacologic and clinical efficacy.

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