Anaphylactoid Properties of LHRH Analogs

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INTRODUCTION

The isolation and structural elucidation of LHRH by Schally [1] and Guillemin [2] in 1971 led to the synthesis of analogs which have been proposed for use in a variety of clinical disorders such as endometriosis, precocious puberty and prostatic carcinoma. These analogs have included both agonists, many of which are currently being studied clinically, and more recently, competitive antagonists. The first LHRH antagonists which were synthesized in 1972 [3] were not very potent, but did support the feasibility of synthesizing competitive antagonists. This led to research in many laboratories to improve the potency of antagonists. As reviewed by Karten [4], a large number of chemical modifications of LHRH have been attempted. Substitutions at positions 2, 3 and 6 have been among the most effective, although the structure-activity relationships in this work appear to be very complex. One series of analogs with an arginine substituted at position 6 appears to be most potent [5,6]. One of these, [N-Ac-D-Nal(2), D-pF-Phe2, D-Trp3, D-Arg6]LHRH has been proposed for clinical studies.

During drug toxicity studies with this peptide, Schmidt, et al. [7] observed vascular permeability changes in rodents treated with the compound. Studies in our laboratories to further characterize these changes led us to conclude that these changes were identical to cutaneous anaphylaxis reactions possibly as a result of a direct action of the drug on mast cell mediator release. A program in our laboratory [8,9] screening a full series of LHRH antagonists demonstrated that the potencies of these peptides, in assays measuring LHRH antagonist activity, do not correlate with their ability to cause cutaneous anaphylaxis. These data suggested that the LHRH inhibiting and anaphylactoid activities were not linked, and a potent LHRH antagonist with a minimal potential to cause an allergic reaction could be identified. Before describing the data of these peptides on histamine release, we will briefly outline some of the pertinent biochemical events that occur during mast cell/basophil secretion.
MAST CELL/BASOPHIL MEDIATORS

Mast cells and basophils secrete substances that mediate immediate-type hypersensitivity reactions when an appropriate stimulus binds to cell surface IgE receptors and subsequently cross-link these receptors. These mediators can be either pre-formed or stored in secretory granules or are newly generated. In human mast cells the pre-formed mediators include histamine, heparin, and tryptase along with acid hydrolases, oxidative enzymes, and chemotactic substances, whereas the newly formed mediators include arachidonate-derived substances such as the slow-reacting substances (SRSs) and prostaglandin D₂ (PGD₂), in addition to platelet activating factor (PAF). Because mast cells occupy strategic positions in and around venules and in connective tissues of cutaneous, mucosal, and serosal surfaces, the mediators exert their activity at these locations.

Activation of Mediator Secretion. Multiple mechanisms cause degranulation and mediator release from mast cells and basophils (Fig. 1). Cross-linkage by specific antigen of IgE that is bound to mast cell and basophil plasma membranes via receptors specific for the Fc region of IgE is the mechanism most relevant to human disease, such as asthma and allergic rhinitis.

![Diagram of the mast cell](image-url)

FIGURE 1 The mast cell