REPORT ON THE 5TH INTERNATIONAL MEETING OF THE INFLAMMATION RESEARCH ASSOCIATION

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This meeting of the Inflammation Research Association (IRA) coincided with the 20th anniversary of its founding by a group of industrial pharmacologists in the USA. While still based in that country the occurrence of international meetings of the IRA at 2-year intervals in more recent years has given the opportunity for industrial and academic scientists of all disciplines from other countries to contribute to these meetings, which have proved to be of high quality.

The theme of this 5-day meeting was "Progress in Inflammation Research and Therapy" and the main topics covered were (a) leukocyte biology, (b) cytokines, (c) proteinases and tissue destruction, and (d) clinical aspects of therapy. A miscellany of other interesting topics was covered in the poster and workshop sessions.

Leukocyte Biology

With current interest so high in leukocyte biology it was most appropriate that the opening Plenary Lecture was given by Dr Ralph Snyderman, Professor of Medicine at Duke University, on 'Molecular Mechansims of Leukocyte Activation by Chemoattractants'. In a lucid review he covered the central role of the activation of the various G-proteins and the phosphoinositoside pathway during the biphasic responses characterizing membrane activation during the presumptive early events in chemotaxis, superoxide production and lysosomal enzyme release. This culminated in presentation of evidence for the role of an alternate pathway of phosphatidyl choline hydrolysis mediated by phospholipase D in the second, or sustained, response to chemoattractant stimuli, which, like the conventional pathway, also involves calcium influx.

The nature was discussed of the receptor for the peptide, f-Met-Leu-Phe (FMLP), recently cloned and expressed by Dr Snyderman's group and some others. The characteristics of this receptor resemble many others for hormones involved in G-protein activation in having 7 membrane-spanning domains of rather similar appearance, yet having small and obviously important subtleties that presumably underly their specificity. Thus the FMLP receptor appears, by comparison with the β-adrenergic receptor, to have a shorter third loop and and also a shorter tail...
projecting into the intracellular region. Sites of phosphorylation on these proteins also differ. What role these structural properties have in the interactions with G-proteins and the apparently later activation of arachidonic acid release following these earlier events as he described still has yet to be resolved. Dr Snyderman suggested that the various events characterizing activation of respective chemoattractant receptors, the various \( \alpha \)-subunits of G-proteins, and membrane lipid hydrolysis products might well be a useful focus for pharmacological intervention in the years to come; a point not lost on this particular audience.

The structural properties of the receptors for the formyl peptide, \( N \)-formyl-methionyl-leucyl-phenylalanine (FMLP), and the complement C5a component were discussed by Skar (University of New Mexico and Los Alamos National Fluorocytometry Facility, Albuquerque, New Mexico) and Mollison (Abbott Laboratories, Abbott Park, Illinois) respectively. With fluorescent probes developed in collaboration with workers at Ciba-Geigy, i.e. FITC-peptides incorporating the FMLP molecule and higher or lower chain lengths, or fluorescein-labelled antibodies and examining neutrophils so treated by flow cytometry. In some studies by fluorescence polarization it has been possible to snap-shot the assembly of the ligand-receptor complexes. Addition of a guanine nucleotide converts the receptor from a high affinity to a low affinity form; such studies were visualized in digitonin permeabilized cells. With binding of peptides of various lengths measured by fluorescence polarization it was found that hexapeptides, or larger molecules exhibited quenching, and smaller peptides, including FMLP, were not, indicating the latter fit into a site pocket whereas the former project out of the site.

Overall some 7 different sites scattered throughout the C5a molecules were identified as participating in the binding to its receptors, using site-directed mutants assayed by the microdroplet chemokinesis technique. Principal features of this included: (a) the C-terminal region though conformationally independent and not essential for agonist activity does add to the potency of C5a, and (b) there is a disulphide region in which those amino acids at positions 29, 33, 40, 68 and 72 appear important for binding, with a long-distance effect noted by amino acids at positions 13-20.

Adhesion-promoting receptors on phagocytes were considered by Wright (Rockefeller University, New York). In particular, the cooperation of the CR3 and LFA-1 on neutrophils to their binding to endothelial ILAM-1 molecules during adhesion prior to diapedesis. The range of such receptor molecules, CD-18 integrins, found on leukocytes is considerable (of which many have synonymous, if not confusing, names), and no doubt afford possibilities for selective probing of the processes of recruitment, adhesion and movement of these cells. The physiological importance of the CD3 receptors was illustrated by their lack in certain patients from Quebec (Canada) with an inherited deficiency thereof; the consequence of this is that the patients are extremely susceptible to infections. Also, a monoclonal antibody to CD3 (IB4) was shown to protect against a microbial meningitis induced in rabbits. Several posters showed the role of CD-18 molecules on the neutrophil-mediated endotoxin shock and Shwartzman reaction of the skin in rabbits and antigen-induced airway hyper-responsiveness in guinea pigs (Argenbright and Barton, Weldon et al., and Noonan et al., respectively, Boehringer Ingelheim, Ridgefield, Connecticut: see Figures 1a and b), the phorbol ester-induced neutrophil accumulation and plasma extravasation in rabbit lungs (Meurer et al., Merck, Sharp & Dohme, Rahway, New