DRUG LOCALIZATION IN TISSUES AND CELLS

RECEPTOR MICROSCOPIC AUTORADIOGRAPHY - METHOD MANUAL

A Basis for Tissue and Cellular Pharmacokinetics,
Drug Targeting, Delivery, and Prediction

By

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Preface

Corpora non agunt nisi in loco

Knowledge about in vivo sites of receptor association and deposition is necessary for the understanding of mechanisms of action of drugs and any bioactive compounds. Detection and characterization of specific targets require methods with high sensitivity and high resolution. Radioassays with excised organs or pieces of tissue and whole body autoradiography – commonly used in pharmacokinetic studies – inform about high capacity-low specificity sites, but rarely about receptor-related high specificity low capacity sites. Information is lacking about in vivo binding to receptors, related half life, and hierarchy of affinities to receptors in different target cell populations. Such in vivo information is, however, essential. It cannot be derived from measurements of compound levels in whole organs or pieces of organs, blood and other body fluids, whose concentrations and kinetics may be quite different from those at receptor sites. Also, results from in vitro experiments, while helpful, differ and cannot substitute for in vivo information.

Receptor micro autoradiography is an indispensable basis for tissue and cellular pharmacokinetics. It combines qualitative and quantitative information on morphology and labeled-compound deposition and specific binding. It provides cellular-subcellular resolution in the direct context of organ and tissue structures, being at once detailed and integrative. Its high predictive value and advantages for drug targeting have been documented.

By contrast, various autoradiographic techniques recommended in the literature and common in practice are not suitable for the localization of diffusable compounds. Most of these techniques lack not only resolution, but also rigorous testing against translocation and loss. Data derived from such procedures often are unspecific and may even yield artifacts that can be mistaken as results.

The method outlined here has been carefully designed and tested. Loss and translocation of radiolabeled compounds are avoided and tissue structure is preserved. It has a long track record of success.

This Manual is based on several decades of experience. It provides detailed instructions. If followed, important new information that is otherwise difficult or impossible to obtain will be gained.

This book is, however, not only a method manual. It is also a personal account of a dogged pursuit that brought success through the systematic use of the newly developed techniques, often with unexpected and startling results that led to new understandings and concepts.