EDITORIAL

Histopharmacology

Histopharmacology—research in histochemistry related to pharmacology and research in pharmacology related to histochemistry—exists, but is not applied, much to the detriment of histochemical pursuits in drug research. Histopharmacology should be an integral part of drug development.

Histochemical approaches are required for drug target identification and characterization (Stumpf 2003,2007a). However, few pharmaceutical companies realize the significance of histochemical information for understanding drug actions. As a result, laboratories for histopharmacology that could provide needed experience and data are practically non-existent. The marginalization of histochemistry in drug research and development deserves attention.

The subject of histopharmacology is interdisciplinary. Perhaps this is one reason why it is absent in curricula of pharmacology and pharmacy. Or perhaps it is simply too remote from the contemporary focus on molecular biochemistry and expedient in vitro procedures, which bypass details on cell and tissue composition. Considering microscopic target identification as non-expedient, thus omitting needed information, contributes to costly failures in the drug industry (Stumpf 2007a).

In journals of histochemistry, numerous articles relate to drug mechanisms of action. However, connections to pharmacology are not always apparent, and pharmacologists have taken little notice, even considering the availability of Internet searches. Efforts can be made to increase awareness of the utility of histochemistry.

Histochemistry has much to offer to pharmacology, for both basic and applied research. This would include, for instance, high-resolution imaging with labeled drugs, as in autoradiography (Stumpf 2003), antibodies to receptors and cellular products, as in immunocytochemistry (Stumpf 2003), and nanoparticles (Debbage and Jaschke 2008). The track record is there. Identification and characterization of target tissues through receptor microscopic autoradiography, combined with immunocytochemistry, pioneered progress in understanding the actions of vitamin D that was seminal for follow-up studies and new therapies. These histochemical discoveries finally displaced the incontrovertible calcium dogma with a new, expanded concept of the main role of vitamin D. Histochemical data, contradicting those from biochemical assays, preceded recent developments by more than 20 years and pointed conclusively to vitamin D as a regulator of vital functions that involve select cell proliferation and differentiation and endocrine secretion. Multiple unexpected target cell populations have been discovered and defined in skin, brain, and pituitary, and in endocrine, reproductive, cardiovascular, digestive, and other systems (Stumpf 1995,2007b).

Another example is the blood–brain barrier. Pharmacologists tend to consider the brain a unit, with a capillary endothelium of tight junctions and a lack of fenestration. If no drug has been detected in chunks of homogenized brain, and nothing is detectable with one of the common scanning-imaging procedures, confirmed by equally expedient whole-body autoradiography with 20–40-μm-thick sections, it is concluded that no drug has entered the brain. But histological and functional evidence may provide different data and predictions. Brain, like other organs, even more so, is not uniform. Ventricular ependyma may allow bypassing a capillary barrier at its own regional rate. And there is no blood–brain barrier in areas of the vascular organ of the lamina terminalis, the subfornical organ, the hypothalamic median eminence, the pineal recess organ, and the area postrema. Thus, again, without sensitive and high-resolution histochemical approaches, results from in vitro models and extrapolations based on data without histopharmacology input can be flawed.
There are numerous other contributions of histochemistry that could be cited (e.g., Jacobowitz et al. 2004).

The question arises: Should we profile the area of histopharmacology as a specific category of histochemistry, with journal issues focusing on this topic and related symposia in association with pharmacologists and pharmacists? Likewise, should histopharmacology become an acknowledged part of pharmacology, recognized in the pursuit of research, conferences, and curricula?

Promoting and visualizing research in histochemistry related to drugs would fill a gap in drug development by increasing attention to cellular and tissue organization. Directed histopharmacological efforts could complement current absorption, distribution, metabolism, excretion procedures, whose results reflect the limited resolution and related pitfalls caused by common use of homogenized organ samples, low-resolution imaging, and extrapolations from blood bioavailability without identification and characterization of in vivo targets. Histopharmacology offers precise methods that can inform about essential details that are difficult or impossible to obtain otherwise. It can provide basic, indispensable information for systems pharmacology, for fingerprinting of analogs, for understanding mechanisms of action, and for guiding developments of drugs.

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Literature Cited