CONF-921180-- BNL--48510

DE93 007283

Drug Pharmacokinetics and Pharmacodynamics: Technological Considerations

Joanna S. Fowler, Nora D. Volkow and Alfred P. Wolf, Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973

PET was developed as a scientific tool for examining biochemical transformations in living systems, in particular the human body. Over the past 15 years the application of PET as a scientific tool applied to problems in the neurosciences has undergone remarkable growth due in major part to its ability to non-invasively track the regional distribution and kinetics of labeled compounds in the human brain and to measure changes brought about by disease and by cognitive or somatosensory or drug challenge. Additionally, the use of PET to examine drug pharmacokinetics and pharmacodynamics and the relationship of these properties to the behavioral, therapeutic and toxic properties of drugs and substances of abuse is emerging as a powerful new scientific tool. PET provides a new perspective on drug research by virtue of its ability to directly assess both pharmacokinetic and pharmacodynamic events as is shown in the figure.

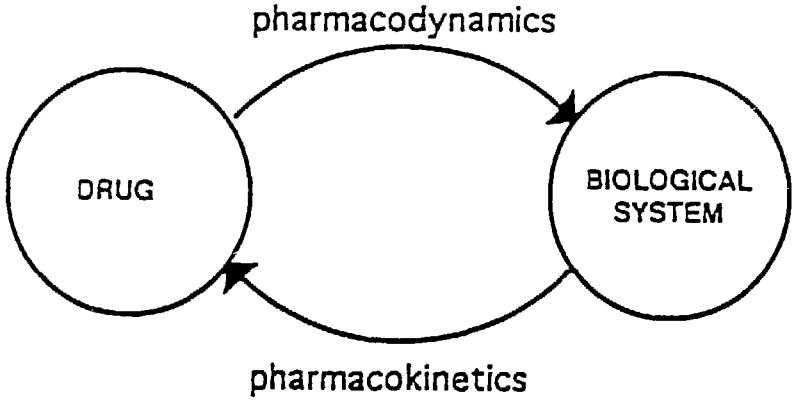

Figure 1. Scheme showing the interactions between a drug and a biological system through pharmacodynamic and pharmacokinetic events. Adapted from B. Testa, TIPS 8: 381, 1987.

The pharmacokinetic properties of a drug, which comprises all of the biological processes which determine the fraction of the drug available, can be measured using the labeled drug itself. For example, the labeled drug can be used to measure the absolute uptake, regional distribution and kinetics of a drug at its site of action in the body. Additionally the labeled drug and whole body PET can be used to determine the target organs for the drug and its labeled metabolites and thus provide information on potential toxic effects as well as tissue half lives. On the other hand, different labeled tracers can be used to assess drug pharmacodynamics which include the biological processes involved in the drug's effects. For example, with appropriate radiotracers, the effects of a drug on metabolism, neurotransmitter activity, blood flow, enzyme activity or other processes can be probed. These parameters can be

assessed directly in the human body both in normal controls and in patients and serial studies can be done where a subject serves as his own control. Moreover, multiple tracers can be used so that different parameters can be assessed in the same subject. An important point is that PET can be used to assess the behavior of a drug at its site of action directly in human subjects. This is relevant both because drug pharmacokinetics and pharmacodynamics may vary across animal species. It also enables the assessment of drug behavior in diseases where there are no animal models. This information places PET in a unique position to contribute significantly to the process of understanding the molecular mechanisms underlying drug action while at the same time addressing some very practical questions such as determining effective drug doses for clinical trials for new drugs, determining the duration of drug action and examining potential drug interactions.

The expansion of the use of PET to examine pharmacokinetic and pharmacodynamic properties of drugs is critically dependent on the following factors:

(1) Basic research in radiotracer chemistry to expand the range of labeled drugs and tracers available for research in the neurosciences. The development of tracers for examining different aspects of monoaminergic systems is of special importance in view of the need for quantitating the efficacy of drugs for treating neurodegenerative diseases and ischemia.

(2) A critical application of mechanistic biochemistry and pharmacology and the principles of tracer kinetics to evaluate new tracers with special attention to their sensitivity to clinically relevant changes in different biological parameters.

(3) The application of multitracer protocols and drug challenge strategies to examine changes in neurotransmitter properties resulting from drugs or from disease and the relationship of these changes to functional activity.

(4) The expansion and facilitation of the use of PET by the pharmaceutical industry for the development of new drugs, for choosing appropriate protocols for clinical trials, and for assessing efficacy in order to expediate the introduction of improved drugs into the practice of health care.

Supported by DOE/OHER, NINDS and NIDA.

(1) Fowler J. S., Wolf A. P. and Volkow N. D. New Directions in Positron Emsission Tomography. Part II. Annual Reports in Medicinal Chemistry, Vol 25: 261=269, 1990.