8.3 IN VIVO IMAGING WITH PET: CONCEPTS AND METHODS

In PET, a ligand is labeled with an unstable, radioactive isotope which emits a detectable amount of radiation. When this radioactive ligand is injected into a living being, the distribution of that ligand can be followed via the detection of the radiation in a noninvasive way. If the radioligand binds selectively to a biological target, the interaction of the radioligand with its target, for example, a receptor, can be visualized. The primary information that can be gained from such experiments is the biodistribution of the radioligand–target complex in a timely fashion (dynamic PET data). However, secondary biochemical parameters such as in vivo binding affinities or reaction rates can be quantified via simple kinetic modeling models of the dynamic PET data.

In general, there are two ways to utilize molecular imaging in the drug discovery and development process: Either a PET ligand (often referred to as a tracer) can be used to investigate a specific target directly, such as a receptor or enzyme (direct approach) or a tracer can be used to determine secondary effects like the proliferation rate of a tumor before and after treatment (functional response studies).

8.3.1 Direct Approach

The direct approach often employs competition studies where the binding of a PET ligand is challenged with a novel drug (blocking studies). This can be done with another ligand (normal block) or the unlabeled version of the PET ligand (self-block). The outcome of such an intervention study provides information about the in vivo selectivity of the drug, but can also be used to study a drug's receptor occupancy. This is helpful to determine the maximum and optimal clinical dose. The receptor occupancy can be determined from the relative changes in the binding potential with increasing doses of the prospective drug molecule. Thus, the direct approach can be used to study the ability of a specific drug to engage a particular receptor or transporter in vivo. Pharmacokinetic and pharmacodynamic parameters of the potential new drug molecules can also be evaluated.

8.3.2 Functional Response Studies

This approach relies on a test–retest PET study of the same subject before and after treatment. The PET tracer is not necessarily targeting the same enzyme or receptor as the compound used in the investigation. Usually, established PET ligands like [^{18}F]2-fluoro-2-deoxy-*d*-glucose (FDG) are used to determine a functional response.

8.4 POSITRON EMISSION TOMOGRAPHY (PET)

8.4.1 Basic Principles

The basic imaging principle in PET makes use of the unique decay characteristics of positron emitting radionuclides: a neutron-deficient isotope converts a proton into a neutron with subsequent emission of a positron (β^+ particle). Once emitted, this positron travels up to a few millimeters until it encounters an electron—typically from an adjacent water molecule. Upon contact, a positron and an electron merge into a positronium which annihilates almost instantaneously into γ-photons moving in opposite directions. The coincident detection of several of these photon pairs in dedicated scanners form the basis of PET imaging, since computational reconstruction along straight lines between detector pairs allows the determination of the photon's source of origin in a three-dimensional space (Figure 8.2).

An example of how a PET image may look like is shown in Figure 8.3, which displays a PET image of phosphodiesterase 10A, a drug target for several neurological diseases in the CNS.