8.4.3 Nonspecific and Unspecific Binding

In general, a ligand's nonspecific binding is a crucial factor in PET ligand development since it has a great impact on the contrast in the final PET images. Nonspecific binding should not be confused with unspecific binding. Nonspecific binding refers to the compound's propensity to bind to membranes, proteins, lipids, or other cell components without a specific and selective target in a nondisplaceable way, whereas unspecific binding refers to interactions with other well defined targets (e.g., receptors or enzymes). If a given region of interest that contains the targeted receptor or transporter is saturated with uniformly distributed radioligand, it is not possible to detect minute changes in the binding to the target. In fact, nonspecific binding is one of the main reasons why ligands with a promising in vitro profile fail to be successful PET ligands in vivo.

Nonspecific binding is usually evaluated in a blocking experiment. Here, the binding of the radioligand is challenged with a pharmacological dose of a compound that is known to reach and interact with the target. If it is not possible to displace the binding of the radioligand, further development is usually discontinued. Nonspecific binding is often correlated with the lipophilicity of the ligand and the octanol/water distribution coefficient at physiological pH (log $D_{7.4}$) can be used as a rough indicator. For PET ligands used in neuroimaging, a log $D_{7.4}$ in the range of 2–3 is considered to be optimal, but there are several successful PET ligands that do not meet that criteria and many radioligands within this range still show high nonspecific binding.

8.4.4 In Vivo Selectivity and B_{max}

Even if a PET ligand is not completely selective toward a given target, it may still be effective as a PET ligand as the relative receptor density (B_{max}) of the target in different regions is an important parameter to consider. The B_{max} value is a measure of how many receptors are present in a given region. Low selectivity of a compound toward a certain receptor may be compensated by a high B_{max} value of the desired target in a particular region. Thus, the observed PET images are a function of the relative affinity of the ligand toward a target and the B_{max} value of that target in a specific region. Usually, PET ligands should be at least 10-fold selective when the relative selectivity and receptor density are taken into consideration.

8.4.5 Tracer Principle

In PET studies using the direct approach, a ligand interacts with the target in question, but it is important to keep in mind that the radioligand is given in very small doses—usually <5 μg for human applications. Thus, the ligand will not be able to influence any physiological process—i.e., to evoke a pharmacological response via the activation of a receptor or inhibition of an enzyme, as the injected dose is typically ~1000-fold lower than the pharmacological dose. This means that it is possible to investigate the function of drug targets, like a transporter in a cell membrane, without disturbing the function of that transporter, since PET is sufficiently sensitive to detect trace amounts of a labeled compound. This concept is often referred to as "the tracer principle." In order to make this possible, it is important that the radioligand is produced with a high specific activity (A_s), which is determined as the ratio between labeled and unlabeled ligand.

8.4.6 Dosimetry

A test subject involved in a PET experiment is exposed to potentially harmful ionizing radiation. Dosimetry relates to the quantification and risk assessment of that exposure. The radiation burden for a PET scan depends on the amount of injected radioactivity, the radionuclide itself and the tissue in which the radioactivity is released. One should strive to keep the exposure to an absolute minimum. The dosage is measured in Sievert [Sv]. [^{18}F]FDG is the most frequently