likely to be involved in the relief of migraine pain. Such finding can be used to direct the future development of more effective drugs.

8.8.3 Drug Pharmacokinetic Characterization

Labeled versions of drug molecules can be very useful when evaluating their pharmacokinetic profile. But as mentioned earlier, an effective drug does not necessarily make a good PET ligand. Nonspecific binding, irreversible/slow binding kinetics, or a receptor-rich profile may compromise the success of such investigations. Nevertheless, if possible, such investigations may provide very valuable information and PET has been used to profile [^{18}F]tamoxifen—an estrogen receptor antagonist and [^{11}C]vortioxetine—an atypical antidepressant.

Parameters such as BBB passage, metabolism, biodistribution, and reversibility of target binding of a drug can be investigated and quantified using the isotopically labeled drug. An illustrative example is the preclinical evaluation of two different neurokinin 1 (NK1) receptor antagonists, GR203040 and GR205171. Both displayed a promising in vitro profile to treat migraine, emesis, and pain. ^{11}C-labeling and subsequent nonhuman primate PET evaluation studies of both compounds revealed that [^{11}C]GR205171 showed superior in vivo binding characteristics (for example, higher brain uptake and target binding, lower nonspecific and unspecific binding) than [^{11}C]GR203040. Based on those results, GR205171 was selected for further investigations and eventually evaluated in clinical trials.

8.8.4 Finding the Right In Vivo Dose

Incorrect dosage of potential drug candidates in clinical trials is one of the major reasons why compounds fail in the development process. Thus, it is very important to be able to determine target occupancy levels of the drug molecules at different doses and correlate these data with the in vivo potency. The ideal dose of a drug is one that is high enough to have the desired effect, but not so high that possible side-effects begin to appear. Identification of the appropriate dose range in vivo is perhaps the most important application of PET in the drug discovery process.

One such example is from the dopaminergic receptor system, see Figure 8.9. PET studies with [^{11}C]raclopride and [^{18}F]desmethoxyfallypride have defined a narrow and optimal therapeutic window of 65%–78% D_2 receptor blockade using D_2 antagonists. Most antipsychotics show optimal clinical efficacy within this therapeutic window with minimal side effects. Increasing striatal D_2

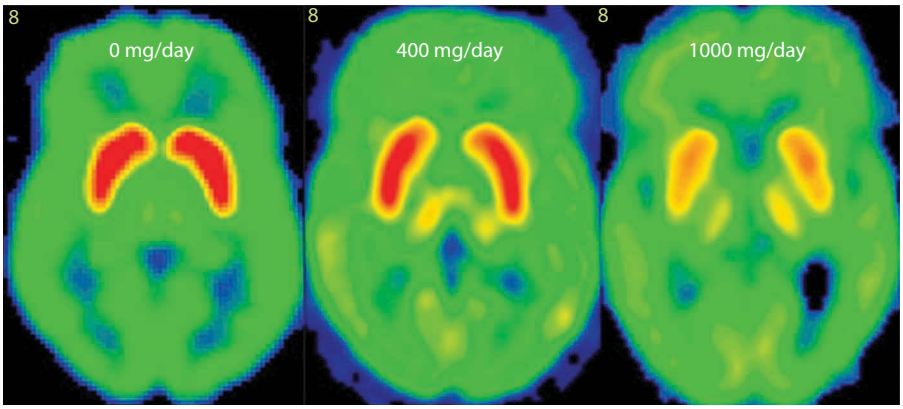

FIGURE 8.9 Increasing receptor occupancy at increasing doses of amisulpride (an atypical antipsychotic) manifests itself by decreasing [^{18}F]desmethoxyfallypride binding to $D_{2/3}$ receptors in striatum. (Reprinted with permission from Piel, M., Vernaleken, I., and Rösch, F., Positron emission tomography in CNS drug discovery and drug monitoring, *J. Med. Chem*., 57, 9232–9258. Copyright 2014 American Chemical Society.)