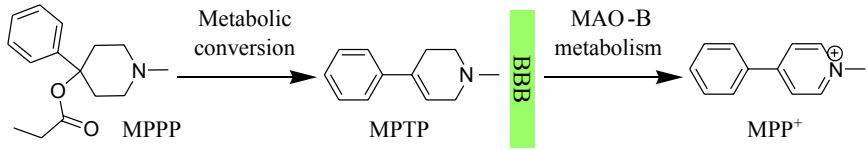

FIGURE 6.19 Desmethylprodine (MPPP) is an opioid analgesic that is no longer marketed due to the formation of the metabolites MPTP and MPP^+. MPTP enters the brain, where it is converted to MPP^+ by the enzyme MAO-B. MPP^+ cannot exit the brain and kill dopamine-producing cells in the brain leading to the rapid development of Parkinson's disease symptoms including paralysis. MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+, 1-methyl-4-phenylpyridinium; MAO-B, monoamine oxidase B; BBB, blood–brain barrier.

generates dopamine enabling movement), and kills these cells. The death of these cells causes rapid development of Parkinson's disease symptoms and paralysis. In this case, the combination of metabolism and compound distribution leads to terrible outcome that would not occur in the absence of MPPP's ability to distribute into the brain.[27]

As was the case with absorption, issues of permeability can play a major role in determining the extent of distribution of a compound, but there are other factors that can have an impact on this process. Plasma protein binding and transporter proteins also play a significant role in determining the relative concentration of potential drug compounds in various areas of the body. Each of these factors warrants consideration in designing and evaluating potential new therapeutic entities.

Permeability

When a compound is delivered orally, the first biological barrier that it encounters is the lining of the gastrointestinal tract, but this is not the only barrier a compound may be required to cross in order for it to influence a biological system. If the targeted macromolecule is inside a particular cell type such as a cardiac myocyte, an islet cell of the pancreas, or an astrocyte within the brain, then the passage through an additional biological membrane will be required. In order to reach many of these targets, compounds must exit the systemic circulation and then enter the targeted cells. As such, the ability of a given compound to distribute into the proper tissues and cell types will be controlled in part by the compound's permeability through the various biological barriers between bloodstream and the target of interest. A compound that can achieve passage into the systemic circulation via absorption or one that is delivered via a method that bypasses oral absorption (e.g., intravenous injection or similar methods), but cannot distribute to the intended target of interest will have limited utility as a therapeutic agent due to poor target engagement.