binding site. In contrast, HSA can interact with acid, basic, and neutral compounds in a large number of primary and secondary binding sites. A single molecule of HSA can, for example, bind to at least 10 molecules of imipramine.[41]

The importance of plasma protein binding of drugs is expressed in the "free drug hypothesis"[42] which states that plasma protein bound compounds are incapable of passive diffusion and paracellular transport. Only "free" compounds, those that are not bound to plasma proteins, can cross biological barriers and gain access to tissues and organs outside of the bloodstream (Figure 6.22). In other words, plasma protein binding

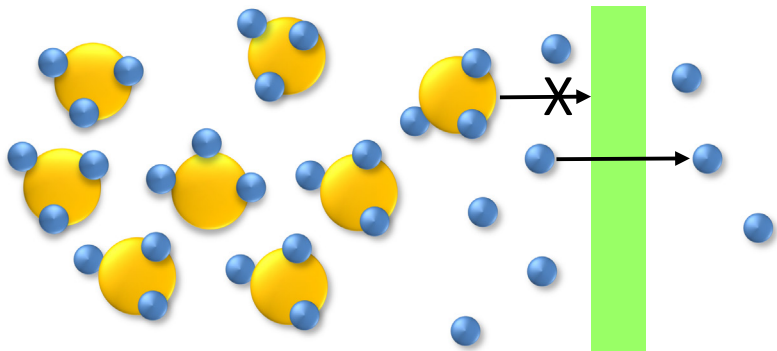

FIGURE 6.22 According to the "free drug hypothesis" compounds (blue) that are bound to plasma protein (yellow) are incapable of crossing a cellular membrane (green).

can have a direct impact on compound distribution. The level of impact will depend on both the extent of binding, often expressed as a percent of compound bound at equilibrium, and the association/disassociation rate. Compounds that are highly protein bound and have a very slow disassociation rate, for example, may be restricted to the bloodstream, as very little of the free drug is available. This can restrict entry of compounds into target tissues, the impact of which can be either positive or negative depending on the perspective. Brain penetration, for example, may be limited, which would be bad for compounds designed to modulate CNS targets, but good for compounds with potential CNS side effects. Liver metabolism and excretion by the kidneys may also be decreased in these situations, leading to improvements in pharmacokinetic properties. On the other hand, compounds that are highly protein bound and have a slow on/off rate are also less available to interact with their intended target, so their therapeutic impact may be less than anticipated. Compounds that possess these properties are "restricted" by plasma protein binding effects.