Drug–Receptor Interactions: It is a Numbers Game

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Any typical neurological drug (molecular weight <400 g/mol) administered in a standard 10–100 mg dose delivers approximately 10^{20} individual drug molecules into the human body. An average adult body is composed of 7×10^{27} molecules housed within its 37 trillion individual cells, each containing 10^{12} molecules, and existing within an extracellular fluid milieu containing 10^{25} molecules/litre (and this number does not include the 38 trillion microbial cells that make up everyone's individual microbiome – the microbes outnumber our own cells by a 10/1 ratio). Each drug molecule thus has a one-in-ten-million chance

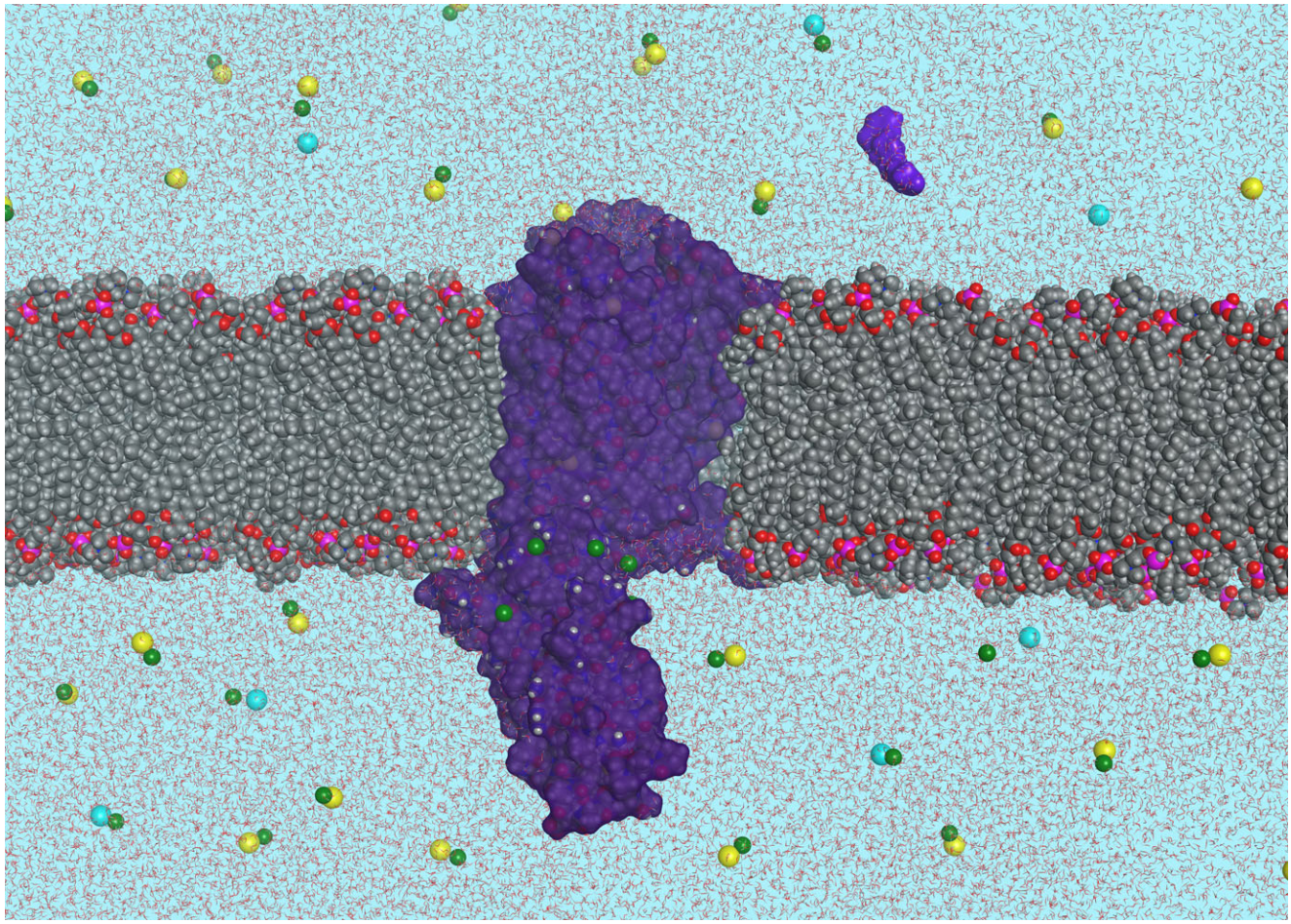

Figure 1: *Treatment of Acute Agitation: Frozen-in-time snapshot during a molecular dynamics simulation of a ziprasidone molecule [purple] approaching its 5HT2A receptor [purple] protein embedded within a neuronal membrane segment [gray with red phosphate heads] and surrounded by a dense water matrix [fine red angular lines] containing ions (Na^+[yellow], K^+[blue], Cl^-[green]).*

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that any molecule it bumps into during its gums-to-brain pharmacokinetic journey will ultimately be its receptor – a process requiring 33,000 intermolecular bumps per second if the drug is to find its receptor and work within five minutes, or 2,800 intermolecular bumps per second if the drug is to work within one hour. And even when the drug collides with its target receptor, there are no guarantees that it is anywhere near its actual receptor. A standard sized protein (300–400 amino acid sequence) has a surface area of approximately 630,000 $Å^2$; a typical drug receptor site has a surface area of 90–100 $Å^2$ – thus, the receptor only occupies about 1/7,000 of the protein's surface.[1,2] Accordingly, when the drug finally does reach its target receptor, usually a protein, it may have to randomly bump along the surface, sustaining thousands of more collisions before it "falls" into its receptor. Finally, if the receptor is within brain (comprising 86 billion neurons, 90 billion glial cells, 125 trillion cortical synapses, and 8.3×10^{25} water molecules), it must first traverse the blood-brain barrier by either passive diffusion or active transport – yet another hurdle (see Figure 1).

These numbers represent a major challenge when trying to discover drugs, a challenge which is particularly prevalent during the pursuit of neurological drugs.[3] Although estimates vary, in theory, there could be approximately 10^{200} possible different "small" organic molecules in the universe; of these, "only" about 10^{60} have the properties and characteristics that render them drug-like (every drug is a molecule, but every molecule is not a drug).[4,5] However, because of the blood-brain barrier and other challenges when delivering drugs to brain, a conservative estimate suggests that in theory there may be only 6×10^{15} small molecules which have what it takes not just to be drug-like, but neuroactive drug-like.[6] Recently, the Chemical Abstracts Service Registry, the world's largest database of unique chemical substances, marked the creation of humankind's 250 millionth unique new chemical entities (it was a novel oligonucleotide). In the history of humanity, we have only physically created 2.5×10^8 molecules, a truly insignificant number when one considers that 10^{200} organic molecules exist in theory; currently, chemists are creating a new chemical substance about once every 2.5 min.[7] Clearly, when it comes to exploring neuroactive chemical space, we are still in our infancy – on the other hand, the future is almost boundless.

Conflict of Interest

No conflict of interest to declare.

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