The Role of the Membrane in Neurotransmitter Interactions with Their Receptors

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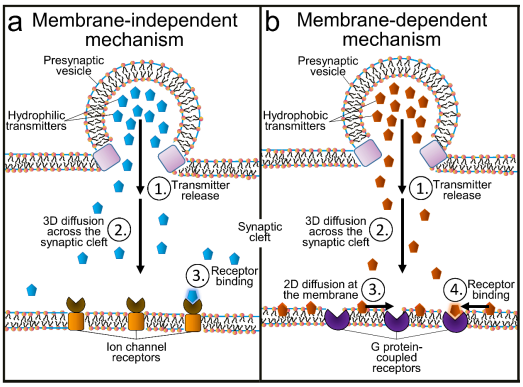
The interactions between neurotransmitters, their receptors, and cell membrane are not fully understood, although there is a growing awareness of the role of the membrane phospholipid composition in several neuropathologies, such as depression, schizophrenia, and Alzheimer's disease. Moreover, differences in the membrane composition are known to affect the functions of the receptors on the membrane and the interactions between neurotransmitters and membrane [1,2].

Traditionally, the neurotransmission is described as a process in which the neurotransmitters are released from presynaptic vesicle and neurotransmitters diffuse over the synaptic cleft towards the postsynaptic membrane. The process ends when the neurotransmitters are binding to their receptors and the postsynaptic neuron is activated. However, there are many macromolecules in the synaptic cleft, which can interact the neurotransmitters water-soluble domains in a non-specific way. These non-specific interactions might cause changes in the binding process.

In our recent study [3], we were able to categorize neurotransmitters in two groups based on the varying degrees of reversible membrane attachment. Membrane-binding neurotransmitters, such as dopamine, adenosine, and epinephrine, are binding to G-protein coupled receptors that have their binding pocket close to lipid bilayer. On the other hand, the membrane-nonbinding neurotransmitters, such as acetylcholine, glutamate, and glycine, are targeting ligand-gated ion channels whose binding pockets are located far from the membrane surface. After these observations, we postulated that there is a membrane-mediated mechanism for neurotransmission entry. In this mechanism, certain neurotransmitters first bind to the membrane and then laterally diffuse to the receptor's binding site.

To this end, we used atomistic molecular dynamic simulations, free energy calculations, and accelerated molecular dynamics simulations to confirm the most probable pathway of dopamine and adenosine entry in their receptors. Our study suggests the entry to take place via the membrane-water interface.



[1] Wang, Chunhua, et al. *J Phys Chem B,* **2010**, 196-203.
[2] Orłowski, Adam, et al. *J Neurochem,* **2012,** 681-690.
[3] P. A. Postila, I. Vattulainen, T. Róg, *Sci. Rep*, **2016**, *6, 19345*.