True Cell Simulations Inc.
cell blog
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14. Chance and Necessity in Cellular Signal Transduction

J. Monod (Nobel Prize in Physiology or Medicine, 1965) published "Chance and Necessity" in 1971. In this book, he discussed a wide range of topics, including evolution, ontogeny, the immune system, genes, proteins, and the brain, drawing on his perspective on chance and necessity. In this blog, I discuss chance and necessity in cellular signal transduction.

I saw it! : We can detect very weak light. How weak is it? There are old (Hecht, S., et al., J. Opt. Soc. Am. 1942) and new reports (Tinsley, J.N., et al., Nature Comm., 2016). In the old report, a wisely combined approach of theory and experiment was employed. In the new report, a modern setup was deployed. Both reached the same conclusion that humans can recognize a single photon (unbelievably weak!).

How can we detect a single photon? By investigating a photoreceptor cell rod anatomically, we find a structure called the disk[*1]. There are 2,000 stacked disks in a frog rod, and protein rhodopsins, which detect photons, are densely packed in the disk membrane (10^9 /rod). The detection of a photon by a single rhodopsin is the first step of our vision. The photon-rhodopsin interaction, however, is stochastic. Photoisomerization of a rhodopsin by a photon may or may not occur. This problem is solved by the stacked disks with densely packed rhodopsins as shown above. This structure enables a single photon to interact with any of the rhodopsins in a rod, leading to a deterministic biochemical process by amplifying the photon detection event through multiple amplifying steps. The amplified signal finally closes ion channels on a rod cell membrane, which is then transmitted to the brain. Thus, photoreceptor cells convert a chance event (stochastic event) of photon detection to a necessity result (deterministic result) of ion channel closure, leading to a whole-cell response. Rods possess mechanisms that convert a chance event into a necessity result.

*1 There are rod and cone photoreceptor cells in the retina. Rods possess high sensitivity, but with monochromatic vision. In contrast, the light sensitivity of cones is lower, but they offer color vision.

Biochemical reactions: A mechanism converting a chance event to a necessity result is not specific to photoreceptor cells. Binding of ligands to receptor proteins is required to transmit a chemical signal from the outside to the inside. How sure is this event going to happen? This depends on the concentration of ligand, its duration, and the density of receptor proteins on a cell surface. Here, we figure out its necessity by calculating intermolecular distances of insulin-insulin receptor and glutamic acid-glutamic acid receptor (AMPA receptor) in the brain.

Surface density of insulin receptor was assumed to be 10^5 molec/cell, which has been reported to be 10^2-2×10^5 molec/cell with its maximum in hepatocytes. If insulin receptors are distributed on a spherical cell surface of 20 μm in diameter, we obtain an average intermolecular distance of 127 nm. If the plasma insulin concentration is 0.776 nmol/L (Sunagawa, M., et al., 2004), we obtain an average intermolecular distance of 1.6 μm. The average intermolecular distance of AMPA receptors of 47.6 nm was obtained from its surface density of 560 molec./μm^2 at synaptic head, and that of glutamic acid at synaptic cleft, 7.35 nm, was obtained from its concentration in the synaptic cleft of 1 mmol/L. Thus, the obtained intermolecular distances and crowdedness are schematically shown in Fig.1.

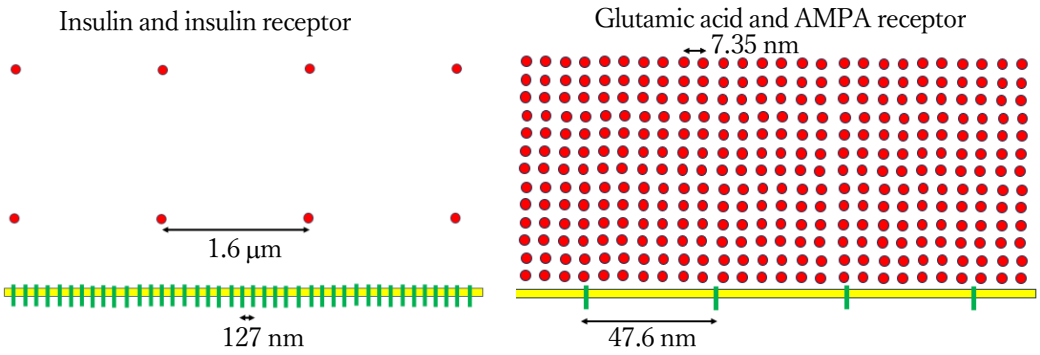

Fig.1 Average intermolecular distances of ligands (red circles) and receptors (short green bars) for insulin-insulin receptors (left) and glutamic acid-AMPA receptors (right). Yellow horizontal bars are cell membranes. Ligands are placed on a grid for simplicity. Note that this is a schematic figure, because 2D membrane and 3D extracellular space are reduced to 1D and 2D, respectively.

By comparing Fig.1 left and right, it is postulated that the rate of insulin binding to its receptor is low (chance event), while that for glutamic acid is high (necessity event), because average intermolecular distances of ligand and receptor for glutamic acid and AMPA receptor are <1/200 and 1/2, respectively, compared to those for insulin and its receptor. Thus, the interaction between insulin and insulin receptor is postulated to initiate a chain of biochemical reactions converting a chance event to a necessity result after insulin binds to its receptor, as in rods. Another possibility is that insulin-binding may occur without initiating the conversion process from a chance event to a necessity result, if there is no need for a quick response. On the contrary, in glutamic acid-AMPAR case, such conversion will not be initiated, because glutamic acid binding to an AMPA receptor occurs almost deterministically with a quicker process.

Cells are living in a world of chance. Cells cannot predict which ligand is coming at what time with what abundance. This is comparable to humans several decades ago, when we could not predict when and where an asteroid would make an impact on the Earth. On the other hand, synaptic transmission by glutamic acid and AMPA receptors, shown in Fig.1 right, seems to be governed by deterministic mechanisms. The same will also be true in glucose transport by glucose transporters and autonomous circadian rhythm generation by a single cell (both not shown here). These all seem to be governed by deterministic mechanisms leading to necessity results. Therefore, we may conclude that cells reside in a mixed environment of chance and necessity, and they possess mixed molecular mechanisms that can manage both chance and necessity events. If this view is correct, what is the difference between these two mechanisms? Is there any difference?