Receptors, Hummingbirds, and Refrigerators

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Over the past 10 years the formal distinction between endocrinology and neuroscience has inexorably been breaking down. This is entirely appropriate, given that the nervous system and hormones are the two principal communication systems within the body. However, despite recently discovered parallels, there are important and very basic differences. Given the similarities in terms of signals, not surprisingly the outstanding differences between the two systems are in the receptors to which signals bind.

Nerves are like a telephone network: discrete anatomic pathways along which pass electrical messages. The chemical signals and their receptors are at synapses and neuroeffector junctions. Hormones, in contrast, are like radio: the message is spilled out indiscriminately into the bloodstream. With certain exceptions (blood-brain barrier, blood-testis barrier) the signal is dispersed over extracellular fluid, body water). Any cell can hear an endocrine signal as long as it has an appropriate receptor, just as a radio broadcast can be picked up anywhere with an appropriate receiver.

The second way in which the nervous system and the endocrine system differ is in terms of time. At the neuromuscular junction, for example, the acetylcholine receptor needs to bind and release acetylcholine in milliseconds. The whole process of signal generation, receptor occupancy, and signal dissipation by diffusion/reuptake/metabolism needs to be able to be repeated many times a second: think of the pianist's fingers in the Minute Waltz.

In contrast, the time constants of the endocrine system are determined by space constraints. At the onset, circulation time in humans is ~45 s; if a message is delivered via the bloodstream, there is thus an inevitable lag period of ~1 min. Experimentally, endocrine time is minutes, hours, days, or even months.

These differences in the time and space dimensions of the two major extracellular communication systems in the body entail major differences in the receptors in the two systems. Experimentally, hormone receptors have high affinity (K_d 10^-8 to 10^-11 M); those for neurotransmitters have much lower affinity (K_d 10^-4 to 10^-7 M). Why is this so?

"Why" is an unfashionable—potentially teleological—word to preface a question in biology. In an attempt to justify asking why, we should consider the basic equation describing the interaction of a signal (S) and a receptor (R).

First, if there is the possibility of a reversible interaction, we can write

\[ S + R \rightleftharpoons S \cdot R \quad (1) \]

on the assumption that one molecule of signal binds to one molecule of receptor.

Second, mass action can be invoked, so that, not altogether surprisingly, we can write

\[ [S] \cdot [R] = \frac{k_1}{k_{-1}} [S \cdot R] \quad (2) \]

where the square brackets denote, as is customary, the molar concentrations of the reactants, and \( k_1 \) and \( k_{-1} \) denote the rate constants of the forward and backward reactions, respectively. The rate at which the reaction goes forward is a function of the concentration of each reactant ([S], [R]) and of \( k_1 \), the rate at which it goes backward is a function of the concentration of product ([S \cdot R]) and of \( k_{-1} \).

That said, at equilibrium the rates of forward and backward reactions are equal; thus we can write

\[ k_1 [S] [R] = k_{-1} [S \cdot R] \quad (3) \]

With a minimum of algebra, this can be rewritten

\[ k_{-1}/k_1 = \frac{[S] [R]}{[S \cdot R]} \quad (3a) \]

The quotient \( k_{-1}/k_1 \) (the dissociation rate constant divided by the association rate constant) is termed the equilibrium dissociation constant and is usually designated K_d.

K_d provides a numerical value for the affinity of binding. If half of the receptors in a system are occupied, the other half are empty, under these circumstances [R] = [S \cdot R]. If this is the case these terms can be cancelled in Eq. 3a, and K_d = [S]. In words, the K_d is the free concentration (not the total) of signal required to half saturate the receptors. Its dimensions are molar, and obviously, the less signal needed to half saturate the receptors, the higher the affinity of the binding interaction.

Now back to hormones and neurotransmitters. The K_d of binding is a function of both \( k_1 \) and \( k_{-1} \), as shown in Eq. 3a, so that theoretically both contribute equally to the final K_d value. In practice, the range of association rate constants determined experimentally is relatively narrow, reflecting ineluctables such as diffusion constants and unstirred layers. Given the relative equivalence of on rates, the major determinant of affinity is the off rate.

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Now a neurotransmitter receptor has to have a fast on rate and a slow off rate; this combination is reflected in a relatively low affinity. If the affinity is low (for example, if \( K_d = 10^{-5} \) M), then the system needs very rapid, very high local concentrations of signal and very rapid, very efficient mechanisms to clear signal. At the neuromuscular junction, for example, this is achieved by confining signal to a very small volume: think of the 60-Å gap between the apposed cell membranes.

For reasons that are only slightly less obvious, a hormone receptor has to have a fast on rate and a slow off rate: this combination is reflected in relatively high affinity. If the affinity is high (for example, if \( K_d = 10^{-9} \) M), then the system can operate with very low local concentrations of signal, consistent with the hormone being diluted in relatively enormous volumes.

In this way, then, the two major communication systems in the body differ fundamentally. The endocrine system has sacrificed time to be able to get its messages everywhere; the nervous system has sacrificed space to be able to get its messages to selected locations very rapidly. This rather grandiose notion is in fact reflected in the receptors in the two systems. For neurotransmitters, signal-receptor interaction is fast, but signal is confined; for hormones, signal is dispersed, but the signal-receptor interaction is much longer lived.

Two hypothetical examples may serve to illustrate this fundamental difference. If acetylcholine had for its receptors at the neuromuscular junction the same affinity as progesterone has for progesterone receptors, a hummingbird, beloved of National Geographic photographers, with wings still blurred at 1/1,000 s exposure, would be able to beat its wings twice a minute.

Conversely, if progesterone had an affinity equivalent to that of acetylcholine for its receptors, a pregnant woman would need to make her own weight in progesterone each month of pregnancy to keep plasma levels high enough to occupy the receptors equivalently. Even with 100% efficiency of conversion, this would require an additional 25,000 kilocalories per day, and unless the placenta became a great deal smarter, it would need to be the size of a 14-cubic-foot refrigerator.

For neither the hummingbird nor the pregnant woman can these scenarios be construed as providing a selective advantage. Therefore, it seems clear that we have evolved communication systems that may use the same signals but very different receptors, and that the properties of these receptors reflect the different space and time constraints within each of the two signaling systems.

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**Jan Evangelista Purkyně (Purkinje) 1787–1869**

E. Trávníčková and S. Trojan

December 1987 will be the bicentennial anniversary of the birth of a famous Czech natural scientist and physician, Jan Evangelista Purkyně. His name is often better known as Purkinje, a spelling that he himself adopted so that German speakers would pronounce it correctly.

Purkyně was a universal genius. He was not only a unique and inquisitive scientist, a gifted teacher, and a talented organizer, he was also a poet, a musician, an editor and contributor to many journals, a writer of popular scientific treatises, the founding member of scientific societies and organizations, and a socially active citizen. Besides this, Purkyně was an enthusiastic patriot who related his scientific achievements to the restoration and reanimation of the Czech nation.

**Childhood and early education**

Purkyně was born on 18 December 1787 at Libochovice, a small town in central Bohemia. At that time, Bohemia had been under Hapsburg rule for a period of almost 200 years during which the Czechs were subjected to national and social oppression. This state of affairs lasted until the end of the First World War, when an independent Czechoslovakian state was founded.

The region where Purkyně was born is famous for its fruit and vegetable farms. His father was an overseer at the country seat of Count Dietrichstein and lived at the Libochovice Castle. This was a happy period for Jan, but it did not last for long. His father died before he was 6 years old, and his mother had to take care of him and his younger brother while the family's financial situation deteriorated.

At an early age, Jan expressed an interest in education and also in painting. Besides his obligatory school attendance, he learned Latin and Greek and became acquainted with astronomy.

At that time, all education was in the hands of the Church, and an impecunious student could obtain bed and lodging in a monastery. Therefore Jan's mother arranged his schooling in an institution belonging to the Order of Piarists. He decided that the best way to become a teacher and scientist was to enter the Piarist Order. He became a novice and taught in the monastery school while he continued his own studies. He enjoyed poetry, which he subsequently both translated and wrote.