NEUROSCIENCE

Perceptions of a Receptor

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I like history. Nothing gives one a better feel for a subject than knowing how it developed. *Nicotinic Acetylcholine Receptors* concentrates on the French contribution to knowledge about these neurotransmitter receptors, and it's a good (if, at times, idiosyncratic) read.

The nicotinic acetylcholine receptors are often referred to as the most investigated and best understood type of ligand-gated ion channel. That is probably true of the type that occurs in electric eels and rays, and the very similar receptor that mediates neuromuscular transmission in vertebrates, but the sorts of nicotinic receptor that occur in the central nervous system are much less well understood.

I can remember well the April 1972 meeting at which, with a flourish, Jean-Pierre Changeux produced from his pocket a tube with a thin blue band and proclaimed, "We have the receptor." Beginning in the early 20th century, most people had supposed that a receptor must be something like an enzyme, and here at last was the proof. After that, progress was fast. Soon cloning (largely in Japan) determined the primary sequence of the receptor subunits, and the invention of the patch clamp method led to much better functional studies of the receptor. Collaborative work (at first, largely between German and Japanese researchers) revealed the nature of the adult and embryonic forms of the receptor and the location of the ion channel within it.

Nicotinic Acetylcholine Receptors
From Molecular Biology to Cognition

by Jean-Pierre Changeux and Stuart J. Edelstein

Odile Jacob, New York. 296 pp. $99. ISBN 9780976890805.

This book covers everything about the nicotinic receptors from purification, function, and structure through to speculations about the role of the neuronal type of nicotinic receptors that are found in the brain. Many parts are good, but Changeux (Institut Pasteur) and Stuart Edelstein (University of Geneva), like all of us, are perhaps victims of their own backgrounds. They deal much more authoritatively with the biochemical and structural aspects of the receptors than the functional aspects.

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Throughout the book, the authors contrast two types of models for receptor activation by agonists: allosteric models ("good") and sequential models (as used by electrophysiologists, "bad"). In my view, this distinction is totally spurious. The authors never really define "sequential," but usually it seems to mean that the unliganded open state is omitted from a postulated mechanism. When that is done, it is done for practical reasons. The authors are speaking theoretically, but when working with experimental results, one can't fit parameters about which the data contain no information. It is obvious that unliganded open channels must exist: in principle, from Boltzmann's law; in practice, from mutant receptors that open in the absence of agonist at a rate fast enough to measure. Any apparent difference in approach is a difference between those who have data and those who haven't.

Such misapprehensions give rise to some surprising assertions. For example, "these [single channel] studies do not give the exact relationship between binding events and channel opening events. The [Monod-Wyman-Changeux] formalism, on the other hand, makes specific experimental predictions for these relationships." In fact, all postulated mechanisms make such predictions.

Or, "In conclusion, experimental data—particularly the data concerning pleiotropic pathological mutations in the nicotinic receptor …—that are readily accounted for by the allosteric schema cannot be satisfactorily represented by the sequential schema." (Here, "pleiotropic" means that when you mess with the structure of a protein it can have complicated and unpredictable effects.) This is simply untrue. The authors present two pages devoted to simulations (based on numbers from the literature) that purport to show that the effect of a mutation is mediated by changing the equilibrium constant L_0 for the conformation change (shut to open) of the unliganded receptor. The simulations bear a qualitative resemblance to observations made by Ohno *et al.* (*1*), but they do not fit them. Nevertheless, the authors conclude that their postulated mechanism is correct. Although, the idea that mutations change L_0 is attractive, the evidence is not strong. Perhaps the best evidence comes from some very thorough work by Auerbach's lab (*2*), but that work is not cited. Even more surprising, in discussing transduction of the signal from the binding site to the channel gate, the authors ignore the whole body of work by Auerbach and Grosman (*3*) on phi-analysis as well as related work on the flip mechanism (*4*).

A lack of precision also appears in the discussion of "allosteric diseases." Since around 1980, it has been appreciated that the physiological event triggered by the agonist is a short burst of channel openings, the duration of which controls the decay rate of the synaptic current. Mutations can slow this decay either by making the individual openings longer or by producing more (re-)openings without changing the length of each. The latter occurs when the mutation slows the dissociation of agonist. Several mutations of this sort have been described, the classical one being αG153S. Sine *et al.* noted that "its prolonged activation episodes arise primarily from a decreased rate of dissociation of [acetylcholine], allowing repetitive opening during [acetylcholine] occupancy" (*5*). Yet the book incorrectly states that the effect is to produce "longer openings," thus ignoring the last 25 years of developments in the understanding of synaptic currents.

The word allosteric seems to appear on almost every page, although in most cases it could be omitted without changing the meaning. I have never found the word very useful, if only because it is used in so many different senses (*6*). To the list we can now add "allosteric diseases."

The authors give an informative account of their behavioral studies with knockout mice, but, for me, it is rather spoiled by a hyperbolic style: "In conclusion, from the cognitive perspective, these findings clearly illustrate the involvement of nicotinic receptors in regulating the transition between states of consciousness." And if you don't quite follow that, you are referred to a network diagram that strikes me as little more than fantasy. The fact is that cholinesterase inhibitors do little or no good for Alzheimer's disease (*7*), never mind regulating consciousness.

The account Changeux and Edelstein provide in *Nicotinic Acetylcholine Receptors* is very good in parts. Nonetheless, as an overall view of the current state of our understanding, it is not only incomplete but sometimes positively misleading.

References

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