Katz B & Thesleff S. A study of the 'desensitization' produced by acetylcholine at the motor end-plate. *J. Physiol.—London* 138:63-80, 1957.
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Ionophoretic microapplication was used to study the desensitization of the cholinergic receptor produced by depolarizing drugs at the frog motor end-plate. The variations and time course of the desensitizing process were examined with different doses of the agonists acetylcholine, carbachol, and succinylcholine. To explain the kinetics of the process, a four-stage scheme was proposed in which the receptor molecule in the presence of an agonist changes from an "effective" to a "refractory" state. [The *SCI*® indicates that this paper has been cited in more than 950 publications, making it the most-cited paper from this journal.]

Desensitization and Depolarizing Drugs

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In my PhD thesis (1952), I described the pharmacology and clinical use of succinylcholine as a short-acting muscle relaxant. The next step in my research was to try to learn the exact mode of action of succinylcholine at the neuromuscular junction.

At that time, W.D.M. Paton and E.J. Zaimis[1] had shown that decamethonium, a structurally related compound, depolarized the postsynaptic end-plate and blocked transmission by what they called a depolarization block. To make similar experiments I went to Anders Lundberg at the Caroline Institute in Stockholm. We studied the ganglionic block produced by the cholinergic agonist nicotine and observed to our surprise that the block did not correlate with depolarization but persisted following repolarization of the cell.[2] Later, I found that cholinergic agonists like acetylcholine, nicotine, decamethonium, and succinylcholine had a similar dual action at the postsynaptic muscle end-plate, the initial depolarization being followed by repolarization and a phase of insensitivity or desensitization of the receptor to further application of the agonist.[3] Similar results were reported by P. Fatt[4] and J. del Castillo and B. Katz.[5] In 1956, I got the opportunity to go to the Department of Biophysics at University College London and to work with Katz.

Del Castillo and Katz[6] had developed an ionophoretic micromethod for the application of drugs to the motor end-plate, enabling the study of the kinetics of drug-receptor interactions. By this technique, we could examine the time-course of depolarization and the onset and recovery of receptor desensitization at the frog neuromuscular junction. Our results prompted us to suggest a four-step model in which the receptor molecule in the presence of an agonist changes from an "effective" to a refractory or desensitized state from which recovery occurs by a process that is delayed by the presence of the agonist.

For me, as a young scientist, these studies under Katz's guidance proved immensely stimulating and led me to devote the rest of my scientific career to the study of various aspects of neuromuscular transmission.

Desensitization of the nicotinic cholinergic receptor has been studied subsequently by a number of rapid kinetic techniques in various laboratories, and our four-stage general model is consistent with a majority of the experimental observations. Operationally, one can define desensitization of the receptor as inactivation of its ion channel in the presence of an agonist. The detailed molecular mechanism underlying desensitization, however, is not known.[7]

The reason that this paper has become a *Citation Classic* is that desensitization has been shown to be present at most, if not at all, ligand-gated ion channels. It has been suggested that desensitization plays a role in the operation of various neuronal networks associated with memory and learning. Obviously, desensitization is of major importance for the understanding of the mode of action of receptor agonists, like succinylcholine and decamethonium.

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