

This Week's Citation Classic™

Krnjević K. Chemical nature of synaptic transmission in vertebrates. *Physiol. Rev.* 54:418-540, 1974.

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A comprehensive survey is presented of mechanisms of synaptic transmission in both the peripheral and central nervous system, with particular emphasis on the identity of various excitatory and inhibitory chemical transmitters, and their specific modes of action. [The SCJ® indicates that this paper has been cited in over 910 publications since 1974.]

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"The idea that nerve cells might communicate with each other by releasing specific chemicals with excitatory or inhibitory properties can be traced back to the late nineteenth century. But it began to be taken really seriously only about 50 years ago, when Dale¹ and his colleagues, in England, first obtained strong evidence that acetylcholine was the transmitter of excitation at nerve-muscle and ganglionic junctions. Like all new concepts, it met with a great deal of resistance. Most of the opposition came from electrophysiologists who were quite happy—indeed much preferred—to think of the nervous system (especially the brain) in terms of purely electrical signals. They did not want to have to be bothered with chemistry and drugs—what was often referred to as 'soup physiology.'

"At the beginning of the 1950s, however, Eccles,² who had been one of the most prominent opponents, became an

equally vocal advocate of chemical transmission at central synapses. His experiments on the spinal cord started a new search for possible transmitter substances. By more precise electrophysiological techniques, it became possible to release minute amounts of various substances from microelectrodes inserted into the brain and spinal cord and thus examine their effects on individual nerve cells. Numerous such 'iontophoretic' studies revealed widespread powerful and rapid (and therefore transmitter-like) actions of some well-known naturally occurring amino acids (glutamate, aspartate, gamma-aminobutyric, and glycine). These findings came as a great surprise. It had been expected that peripheral transmitters, such as acetylcholine and noradrenaline, would have a prominent role in the central nervous system (CNS). Amino acids, with well-identified roles in cellular metabolism, protein synthesis, etc.—and found abundantly throughout the brain—did not fit then current notions about transmitters. By the end of the 1960s, however, in the absence of any serious alternative, the amino acids were generally becoming accepted as the most widespread rapidly acting excitatory and inhibitory transmitters in the CNS.

"The invitation to write a review on this topic—in which I had been much involved for some years—thus came at an opportune time. What success the review has had I would ascribe to its convenient summarizing of an already vast literature (it achieved some notoriety by listing over 1,200 references); as well as to the fact that the field had reached a certain level of maturity—the status of a 'normal science.' This was before the neuropeptides burst upon the scene, initiating another revolution—but this is another story (cf. D.T. Krieger³)."

1. Dale H H. Acetylcholine as a chemical transmitter of the effects of nerve impulses. *J. Mt. Sinai Hosp.* 4:401-29, 1938.
2. Eccles J C. *The neurophysiological basis of mind.* Oxford: Clarendon Press, 1953. 314 p.
3. Krieger D T. Brain peptides—what, where, and why. *Science* 222:975-85, 1983.