This Week's Citation Classic®

Krnjevic' K & Phillis J W. Iontophoretic studies of neurones in the mammalian cerebral cortex. *J. Physiol.* 165:274-304, 1963. [Agricultural Research Council Institute of Animal Physiology, Babraham, Cambridge, England]

Numerous possible excitatory and inhibitory agents were tested on over 4,000 neurons. Because of their great potency, and the rapid time course and wide distribution of their actions, the endogenous amino acids glutamate and g-aminobutyric acid were proposed as strong candidates for the role of excitatory and inhibitory synaptic transmitter, respectively. [The *SCI*® indicates that this paper has been cited in more than 550 papers.]

Amino-Acid Transmitters

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Younger neuroscientists may find it hard to believe that 30 years ago no one even suspected that glutamate might have any kind of function as a synaptic transmitter. Its ubiquitous presence—at a high concentration in just about all cells—was readily explained by its importance for cell biochemistry: as a major constituent of proteins, through its close relation to the Krebs cycle, etc. It just did not feel right as a potential transmitter substance.

A significant negative feature (as I suggested in 1965[1]) was the lack of any actions on the smooth muscle preparations that had been so fruitful for studies of peripheral transmitters. So our proposal that glutamate was the excitatory transmitter in the cortex met with little response. This idea was accepted only very gradually[2]—in good part because no useful antagonists could be identified until it was realized that there are several kinds of glutamate receptors.[3] At present, of course, there seem to be very few exceptions (e.g., Renshaw cells) to the general rule that fast excitatory synaptic transmission is mediated by glutamate and/or apartate (or perhaps one of the closely related sulphonic acids).[4,5]

For g-aminobutyric acid **(GABA),** the situation was somewhat different. There had been sound reasons for viewing **GABA** as an inhibitory transmitter,[6] but by the early 1960s, they had been unwisely discounted. Our proposal was received, at first, with a good deal of skepticism. But, by the end of the decade, **GABA** was becoming widely recognized as the main inhibitory in the cortex, and indeed throughout most of the brain.

Looking back, it is undoubtedly gratifying that present views about the main transmitters at central synapses are pretty much what we proposed 25 years ago. We were fortunate in that we started with few preconceived ideas about transmitter agents in the cortex. John W. Phillis (who had just obtained his PhD, working in David Curtis's laboratory in Canberra) and myself both had experience of the iontophoretic technique. Our knowledge of the central nervous system, however, was essentially limited to the spinal cord. We therefore ventured into the cortex with very ignorant, but therefore open minds.

The experiments were done at the ARC Institute at Babraham, England, which, under the aegis of John Gaddum, was becoming a major center of brain research. It is interesting to reflect, however, that much of the pioneering work that identified the main central transmitters was done by ex-colleagues or students of John Eccles, who for so long had been one of the most outspoken opponents of the chemical theory of synaptic transmission!

1. **Krnjevic'** K. Transmitters in the cerebral cortex. *Proceedings of the 23rd International Congress of Physiological Sciences.* 1965. Tokyo. Amsterdam. The Netherlands: Excerpta Medica Foundation. 1965. p. 435-43.
2.----------. (Iversen L L & Goodman E, eds.) *Amino acid transmitters: 30 years progress in research.* Oxford. England: Oxford Science Publications, 1986. p. 3-15.
3. **Watkins J C & Olverman H J.** Agonists and antagonists for excitatory amino acid receptors. *Trends Neurosci.* 10:265-72, 1987. (Cited 250 times.)
4. **Mayer M L & Westbrook** G **L.** The physiology of excitatory amino acids in the vertebrate central nervous system. *Prog. Neurobiol.* 28:197-276. 1987. (Cited 415 times.)
5. **Dtngledine R, Boland L M. Chamberlin N L. Kawasaki K, Kleckner** N W, Traynellis S F & Verdoorn T A. Amino acid receptors and uptake systems in the mammalian central nervous system. *Crit. Rev. Neurobiol.* 4:1-96. 1988.
6. **Elliot A** C & **Jasper H H.** Gamma-aminobutyric acid. *Physiol. Rev.* 39:383-406. 1959.
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