CC/NUMBER 46
® NOVEMBER 12, 1990

This Week's Citation Classic

Robbins J. The excitation and inhibition of crustacean muscle by amino acids. *J. Physiol.—London* 148:39-50. 1959.
[Department of Pharmacology, College of Physicians and Surgeons, Columbia University, New York, NY]

Of 47 compounds tested, several neutral amino acids (e.g., γ-aminobutyric acid (GABA), β-alanine, and taurine) inhibited contraction of crayfish muscle, while some acidic ones (i.e., L-glutamic, L-aspartic, and L-cysteic acids) caused excitation. The most potent of the latter was L-glutamic acid, which was proposed as the excitatory neurotransmitter. [The *SCI*® indicates that this paper has been cited in more than 105 publications.]

L-Glutamate as Neurotransmitter—Origin of the Concept

Jay H. Robbins
Dermatology Branch
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892

July 19, 1990

During my senior year at Harvard College, I began a project under William G. Van der Kloot, instructor in biology, on the effect of picrotoxin, a convulsant, on the function of the inhibitory neuron to the opener muscle in the crayfish claw. I finished the project during a summer fellowship from the College of Physicians and Surgeons in Bill's laboratory after he had moved to the Cornell University (Ithaca) Department of Zoology. We reported[1] that picrotoxin blocked inhibition of the opener muscle.

I then chose for my medical school research elective to study the effects of amino acids on crayfish muscle rather than on the mammalian nervous system. Others had shown that the amino acid GABA (which affected mammalian preparations) inhibited contraction of the crayfish claw, likely the transmitter of the inhibitory neuron. I reasoned that the transmitter of the excitatory neuron might also be an amino acid. I discussed my ideas with S.C. Wang, professor of pharmacology and a strong proponent of independent student-research projects, who sponsored my project even though it was far removed from his own interests.

I tested 47 compounds. The most potent excitatory amino acid was L-glutamic acid, which facilitated, caused, and blocked contraction in a concentration-dependent manner. I suggested that L-glutamate could be the excitatory transmitter. I am pleased that this paper has become a *Citation Classic.*

In 1959 A. Van Harreveld and M. Mendelson, at the California Institute of Technology in Pasadena, also reported that L-glutamate excited crayfish muscle.[2,3] Although their papers clearly indicated that L-glutamate could be the excitatory transmitter, they considered it more likely that the actual transmitter was a substance chemically related to L-glutamate. D.R. Curtis, J.W. Phillis, and J.C. Watkins, at the Australian National University in Canberra, also reported in 1959 the excitatory activity of L-glutamate on spinal neurons in the cat,[4] but they considered the activity "nonspecific" and not that of a transmitter.

These 1959 publications by three independent laboratories launched the field of excitatory amino acid research. My paper and those of Van Harreveld[2,3] led others (notably A. Takeuchi, N. Takeuchi, J. Dudel, and P.N.R. Usherwood) to establish L-glutamate as an excitatory transmitter in invertebrates.[5] Furthermore, Watkins has stated that our observations concerning L-glutamate in the crayfish, together with his and his coworkers' observations in the cat, led to the synthesis of N-methyl-D-aspartate,[6] which revolutionized study of L-glutamate by defining its most important receptor in the mammalian nervous system.[7]

The conflict concerning the transmitter status of L-glutamate, which raged for two decades before being resolved,[5,7] has been reviewed by Usherwood,[5] who commented on how "...sections of the scientific community react to a new concept which threatens to undermine established ideas." He recounted how "...against a consensus view...in the early 1960s the concept of...metabolites such as L-glutamate and L-aspartate serving a neurotransmitter role seemed distinctly untenable if not outright heretical." Today, L-glutamate is the likely transmitter at the majority of excitatory synapses in the mammalian central nervous system and, in excess, may be responsible for neuronal dysfunction or death in a variety of human neurologic and psychiatric disorders.[7]

I left the field of invertebrate neuropharmacology to complete my medical education and training. However, my subsequent research[8] has led to another hypothesis concerning the human nervous system, namely, that DNA repair is required for neurons to survive and that some neurodegenerations (e.g., Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis) are due to defective DNA repair in neurons. How ironic it is to find that one of the most attractive competing hypotheses is that the nerve cell death in some of these diseases is due to L-glutamate!

1. **Robbins J & Van der Kloot W G.** The effect of picrotoxin on peripheral inhibition in the crayfish. *J. Physiol.—London* 143:541-52. 1958. (Cited 65 times.)
2. **Van Harreveld A.** Compounds in brain extracts causing spreading depression of cerebral cortical activity and contraction of crustacean muscle. *J. Neurochem.* 3:300-15. 1959. (Cited 140 times.)
3. **Van Harreveld A & Mendelson M.** Glutamate-induced contractions in crustacean muscle. *J. Cell. Comp. Physiol.* 54:85-94. 1959. (Cited 80 times.)
4. **Curtis D R, Phillis J W & Watkins J C.** Chemical excitation of spinal neurones. *Nature* 183:611-2. 1959. (Cited 50 times.)
5. **Usherwood P N R.** Amino acids as neurotransmitters. *Advan. Comp. Physiol. Biochem.* 7:227-309. 1978. (Cited 85 times.)
6. **Watkins J C.** The synthesis of some acidic amino acids possessing neuropharmacological activity. *J. Med. Pharm. Chem.* 5:1187-99. 1962. (Cited 50 times.)
7. **Olney J W.** Glutamate, a neurotoxic transmitter. *J. Child Neurol.* 4:218-26. 1989.
8. **Robbins J H, Kraemer K H, Lutzner M A, Festoff B W & Coon H G.** Xeroderma pigmentosum: an inherited disease with sun sensitivity, multiple cutaneous neoplasms, and abnormal DNA repair. *Ann. Intern. Med.* 80:221-48. 1974. (Cited 460 times.) [See also: **Robbins J H.** Citation Classic. *Current Contents/Clinical Medicine* 15(18):12, 4 May 1987 and *Current Contents/Life Sciences* 30(18):12, 4 May 1987.]

1A·22