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Curtis D R & Johnston G A R. Amino acid transmitters in the mammalian central nervous system. *Ergeb. Physiol. Biol. Chem. Exp. Pharmakol.* 69:97-188, 1974. [Department of Pharmacology, John Curtin School of Medical Research, Australian National University, Canberra, Australia]

This article provided a comprehensive overview of the neurochemistry and neuropharmacology of individual amino acids of interest as possible transmitters in the mammalian central nervous system. In addition we reviewed the then available evidence that certain endogenous amino acids were the transmitters of identified inhibitory and excitatory pathways. [The *SCI*® indicates that this paper has been cited in over 955 publications, making it the most-cited paper from this journal.]

Investigating the Messages of Synaptic Events

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This 1974 review, which introduced the terms glycinergic, gabergic, aspartergic, and glutamergic (or more euphonious versions—of which GABAergic must surely be the least attractive!), was written when we were still flushed with excitement after discovering that bicuculline was an adequately selective gamma-aminobutyric acid (GABA) antagonist useful for investigating GABA-mediated synaptic events in the cat central nervous system.[1] This led to an accelerated worldwide interest in GABA-receptors, in compounds that modulated their receptivity, in GABA-activated ion channels, and in membrane transport processes. Bicuculline, like strychnine, which had earlier been demonstrated in Canberra to be a selective glycine antagonist,[2] rapidly joined the list of "classical" pharmacological antagonists: frequently used but with the original publications rarely cited, even in prestigious journals of high international standing.

Our review, as did that published earlier by J.C. Watkins and me,[3] also included amino acids that excite central neurones, again a field to which major contributions were made in Canberra. The lack of appropriately selective antagonists, however, prevented definitive evaluation of the role of aspartate, glutamate, and related endogenous amino acids as excitatory synaptic transmitters. With the recognition now of subtypes of excitatory amino acid receptors, based largely on the availability of a series of antagonists, many of which originated from the work of Watkins in Bristol,[4] this field of neuropharmacology is expanding. There does seem to be a preoccupation, however, with the details of receptor, channel, and intracellular mechanisms studied under *in vitro* conditions, often using cultured cells that have never experienced synaptic excitement, in an absence of an appreciation of the realities of the conditions that exist *in vivo*.

We remain grateful to the editors of *Ergebnisse der Physiologie, Biologischen Chemie und Experimentellen Pharmakologie* for providing us with the opportunity to review amino acid transmitters in the mammalian central nervous system on an anatomical and functional basis at a time when research in this area was burgeoning but not in such a complex fashion as at present.

1. **Curtis D R, Duggan A W, Felix D & Johnston G A R.** Bicuculline, an antagonist of GABA and synaptic inhibition in the spinal cord. *Brain Res.* 32:69-96, 1971. (Cited 600 times.)
2. **Curtis D R, Hosli L & Johnston G A R.** A pharmacological study of the depression of spinal neurones by glycine and related amino acids. *Exp. Brain Res.* 6:1-18, 1968. (Cited 330 times.)
3. **Curtis D R & Watkins J C.** The pharmacology of amino acids related to gamma-aminobutyric acid. *Pharmacol. Rev.* 17:347-92, 1965. (Cited 375 times.)
4. **Watkins J C.** Twenty five years of excitatory amino acid research. (Roberts P J, Storm-Mathisen J & Bradford H F, eds.) *Excitatory amino acids.* London: Macmillan, 1986. p. 1-39.