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Balcar V J & Johnston G A R. The structural specificity of the high affinity uptake of L-glutamate and L-aspartate by rat brain slices. *J. Neurochemistry* 19:2657-66, 1972.
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About two hundred compounds, selected on the basis of their chemical structure and pharmacological characteristics, were tested against high affinity uptake of L-glutamate by brain slices. The significance of the results for the physiology, pharmacology, and biochemistry of glutamatergic synaptic transmission is discussed. [The *SCI*® indicates that this paper has been cited in over 370 publications.]

Chemical Aspects of Synaptic Excitation

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I came to Canberra in February 1971, and as far as I can recall I got very few experimental results before about May—progress at a snail's pace by the standards of a novice research student. I regretted having turned down offers of scholarships from the UK and Canada, and I felt particularly bitter about a prestigious California institution which, after a very promising initial correspondence, did not even bother to reply to my formal application. Had I not been in Australia, where, as I found quickly, things like sunshine, squash, or spearfishing could be equally important as, say, structural specificity of high affinity uptake of L-glutamate, the life would have been gloomy, indeed.

Eventually, my PhD supervisor, Graham A.R. Johnston, taught me a technique using brain slices (described by L.L. Iversen and M.J. Neal[1]), and a few simple tricks turned it into a smoothly running large-scale machine producing a steady stream of data. I immediately started ransacking Graham's treasure of fine chemicals and, suddenly, the mysteries of synaptic physiology began to crumble before the onslaught of chemical expertise. When the prestigious California institution finally offered me a fat scholarship, it was I who did not bother to reply. Our progress came to a halt when a heat wave arrived at Christmastime. The water bath would no longer stay at 25°C, and [^{3}H]L-glutamate in brain slices was in danger of being metabolized. We had to start writing a paper. Some difficulties were encountered with getting the manuscript past the head of the department and, I seem to remember, there was a mail strike, too, but the *Journal of Neurochemistry* accepted it swiftly. I received over 400 reprint requests from 31 countries on five continents—but none from Australia.

Some 18 years later, I am still amazed how such a straightforward—and an essentially chemical—approach could penetrate into the complexities of glutamatergic synaptic function. Our work demonstrated that glutamate uptake and glutamate receptors were two distinct entities (not so obvious to everybody before 1971!), and we identified the strongest substrates/inhibitors of glutamate uptake (threo-3-hydroxyaspartate, L-cysteine sulphinate, L-cysteate, and D-aspartate). [^{3}H]D-Aspartate was subsequently shown to be indeed a substrate for glutamate uptake[2] and has since been used extensively in autoradiographic studies as a metabolically stable marker for glutamatergic structures.[3] Variations in the ionic composition of the incubation medium contributed to the debate on the mechanism and stoichiometry of the L-glutamate-Na^+ cotransport.[4] The information on the structural specificity helped in the search of compounds that could distinguish between the glial and neuronal compartments for glutamate uptake.[5,6] Finally, the sheer number of compounds tested (nearly 200, including some exotic drugs, poisons, and environmentally hazardous substances) means that our work is sometimes noticed in realms of science very remote from our own spheres of interest.

My initial motivation in 1971 was to deal with glutamate uptake as fast as possible so that I could move on to something more exciting. In 1989 I believe that I should have felt rather privileged for having the opportunity to work on one of the most important physiological mechanisms in the central nervous system.

1. **Iversen L L & Neal M J.** The uptake of [^{3}H]GABA by slices of rat cerebral cortex. *J. Neurochemistry* 15:1141-9, 1968. (Cited 450 times.)
2. **Davies L P & Johnston G A R.** Uptake and release of D- and L-aspartate by rat brain slices. *J. Neurochemistry* 26:1007-14, 1976. (Cited 180 times.)
3. **Storm-Mathisen J.** Autoradiographic and histochemical localization of high affinity glutamate uptake. (Roberts P J, Storm-Mathisen J & Johnston G A R, eds.) *Glutamate: transmitter in the central nervous system.* New York: Wiley, 1981. p. 89-116.
4. **Wheeler D D & Graves J S.** A model of the sodium and membrane potential dependence of high affinity glutamic acid transport in rat cortical synaptosomes. *J. Theor. Neurobiol.* 2:1-22, 1983. (Cited 10 times.)
5. **Fonnum F.** Glutamate: a neurotransmitter in mammalian brain. *J. Neurochemistry* 42:1-11, 1984. (Cited 365 times.)
6. **Balcar V J, Schousboe A, Spoerri P E & Wolff J R.** Differences between substrate specificities of L-glutamate uptake by neurons and glia, studied in cell lines and primary cultures. *Neurochem. Int.* 10:213-7, 1987.

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