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Meldrum B S. Epilepsy and γ-aminobutyric acid-mediated inhibition.
Int. Rev. Neurobiol. 17:1-36, 1975.
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This paper reviewed the evidence for the pre- and post-synaptic inhibitory action of γ-aminobutyric acid (GABA) and linked drug effects on GABA synthesis, agonist and antagonist receptor action, re-uptake, or further metabolism to convulsant and anticonvulsant mechanisms. [The *SCI*® indicates that this paper has been cited in over 285 publications.]

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Enthusiasm for a possible role of GABA in epilepsy reached an early peak at a conference held in 1959.[1] This followed demonstrations by T. Hayashi that GABA applied to the canine motor cortex could arrest an epileptic discharge and by K. Killam that certain convulsant hydrazides blocked the synthesis of GABA. However, in the following 10 years, the concept fell out of favour because many studies showed a lack of correlation between brain GABA levels and convulsant and anticonvulsant drug action. In 1969 I began working with Robert Naquet on the pharmacology of photically induced epilepsy in the baboon, *Papio papio*, using drugs that modified the metabolism of GABA and some recently defined post-synaptic GABA antagonists, and with Roger Horton on regional brain GABA changes related to drugs inhibiting glutamic acid decarboxylase and GABA-transaminase. It became clear that impairment of GABAergic inhibition correlated with convulsant drug action and enhancement of GABA-mediated inhibition with an anticonvulsant effect. The many negative or conflicting findings in the literature of the previous 10 years could be explained in terms of an enzyme inhibitor acting on both the synthesis and further metabolism of GABA or by convulsant and anticonvulsant drug effects not related to GABA. GABA levels were a poor guide to inhibitory function.

My review was completed by November 1973 and just missed the deadline for the 1974 volume. However, it appeared at a fortunate time, encouraging others to explore this area when new pharmacological tools had become available. Subsequently, several drug companies developed novel anticonvulsant drugs designed to enhance GABA-mediated inhibition, such as Vigabatrin, an irreversible inhibitor of GABA-transaminase that has been shown in several recent trials to decrease seizures in patients otherwise resistant to drug therapy. Attempts to prove a primary failure of GABA-mediated inhibition as the causal factor in human epilepsy have however met with rather less success. The possibility exists that by focussing attention on the role of inhibition in epilepsy this review delayed exploration of the role of excitatory mechanisms.[2]

At least five volumes have reported conferences on GABA and the nervous system or GABA and benzodiazepine action since 1975. Recent reviews include chapters emphasising electrophysiological[3] or pharmacological aspects[4] of GABA in epilepsy.

1. **Roberts E, Baxter C F, Van Harreveld A, Wiersma C A G, Adey W R & Killam K F,** eds. *Inhibition in the nervous system and gamma-aminobutyric acid.* New York: Pergamon Press, 1960. 591 p.
2. **Meldrum B.** Possible therapeutic applications of antagonists of excitatory amino acid neurotransmitters. *Clin. Sci.* 68:113-32, 1985.
3. **Krnjević K.** GABA-mediated inhibitory mechanisms in relation to epileptic discharges. (Jasper H H & van Gelder N M, eds.) *Basic mechanisms of neuronal hyperexcitability.* New York: Liss, 1983. p. 249-80.
4. **Meldrum B S.** GABA and other amino acids. (Frey H-H & Janz D, eds.) *Antiepileptic drugs.* Berlin: Springer-Verlag, 1985. p. 153-88.

