γ-Aminobutyrylcholine and central inhibition

On the basis of possible structural similarities between bicuculline and γ-aminobutyrylcholine (GABACh), the reported depressant effects of GABACh on the electrical and convulsive activity of the cerebral cortex (Takahashi, Nagashima & others, 1958; Ashida, Takeuchi & others, 1965), and the presence of GABACh in the brain (Kewitz, 1962), the question has been posed (Howells, 1971) whether γ-aminobutyric acid (GABA) or its choline ester is the transmitter at inhibitory synapses in the mammalian central nervous system which are blocked by bicuculline (Curtis, Duggan & others, 1970a, 1971a,b; Curtis & Felix, 1971).

There is, however, much relevant information not quoted by Howells (1971) to explain why GABACh has not gained general acceptance as a central inhibitory transmitter. Topically administered GABACh appears not to have a reproduceable depressant effect on the electrical responses of the cerebral cortex (Honour & McLennan, 1960; Hance, Winters & others, 1963). Furthermore, electrophoretically administered GABACh has little or no depressant action on the firing of either spinal interneurons (Curtis & Watkins, 1960; Curtis, Phyllis & Watkins, 1961) or neurons of the cerebral cortex (Crawford & Curtis, 1964; Krnjević, 1964), in contrast to the powerful depressant action of GABA. On the other hand GABACh did influence the excitability of spinal Renshaw cells and has, in addition, a delayed excitant action on these cells (Curtis & others, 1961). These and other observations (Kuriaki, Yakushiji & others, 1958; Asano, Noro & Kuriaki, 1960; Holmstedt & Sjoqvist, 1960; Hagiwara & Kusano, 1961; Kewitz, 1962; Hance & others, 1963) suggest that the pharmacological actions of GABACh are related to cholinergic systems rather than to those involving GABA.

Any antagonism between GABACh and bicuculline could be accommodated by our original model regarding structural similarities between GABA, muscimol and bicuculline (Curtis & others, 1970a), which has been extended to include imidazole-4-acetic acid (Curtis & others, 1970b) and 4-aminotetrolic acid (Beart, Curtis & Johnston, 1971). According to Howells' alternative model (1971) acetylcholine resembles bicuculline: yet bicuculline does not influence the excitation of Renshaw cells by acetylcholine (Curtis & others, 1971a). A number of other compounds of pharmacological interest, including dopamine and *S*(+)-noradrenaline, also show structural similarity to bicuculline.

Thus, although GABACh should not be overlooked as a possible transmitter in the central nervous system, this ester is unlikely to be as important as GABA as the transmitter at bicuculline-sensitive inhibitory synapses.

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Sleep-inducing effects of L-tryptophan

We have demonstrated that L-tryptophan in doses of 4–10 g has hypnotic effects in man. In one study a group of insomniac patients showed significantly increased total sleep, and significantly reduced sleep latency and number of awakenings by behavioural criteria (Hartmann, Chung & Chien, 1971a). In a group of normal subjects (eleven subjects studied over a total of 101 nights) all night eeg recordings showed that L-tryptophan produced significantly shorter sleep latency than placebo; total sleep time and desynchronized sleep time was slightly but not significantly increased (Hartmann, 1970; Hartmann, 1967; Hartmann & others, 1971a). Others have found similar reduction in sleep latency, though there is disagreement about effect on sleep stages (Oswald, Ashcroft & others, 1966; Wyatt, Engleman & others, 1970; Griffiths, Lester & others, 1971).

We have now studied the effects of several dose levels of L-tryptophan on recorded sleep in the rat. All rats were implanted with cortical, hippocampal and with nuchal muscle electrodes and were studied approximately once per week after placebo or after tryptophan feeding over six months, after adaptation to the laboratory.

In a preliminary study with multiple 6–8 h recordings in six animals, tryptophan, 150 and 300 mg, produced little change in waking, or synchronized sleep, and a slight but not significant decrease in desynchronized sleep. Sleep latency could not be accurately measured. Eleven rats with implanted electrodes were in the principal experiment. After adaptation to the laboratory, each received oral placebo on at least three occasions and oral L-tryptophan on three occasions, at doses of 300, 450, and 600 mg/kg in random order. Four of these rats were normals and seven had brain catecholamine concentrations lowered to 40% of normal by a previous injection of 6-hydroxydopamine two weeks before the experiment. (We were interested here in possible interactions between L-tryptophan and the catecholamines.) Rats were studied for on 8 h recording every week for four months. Results are in Table 1. L-Tryptophan produced a dose-dependent reduction in sleep latency in both groups of animals. There was no significant change in amount of time spent in waking, synchronized sleep or desynchronized sleep and there was no difference in the number of awakenings. The cycling or architecture of sleep was relatively normal. There was no clear interaction between 6-hydroxydopamine and L-tryptophan. (The effects of 6-hydroxydopamine itself on sleep have been discussed elsewhere (Hartmann, Chung & others, 1971).