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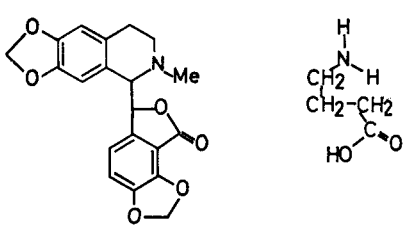
LETTERS TO THE EDITOR

The inhibitory transmitter: GABA or its choline ester?

Recently, Curtis, Duggan & others (1970) reported studies on the action of the alkaloid bicuculline on the central nervous system; they claimed that this alkaloid was a relatively selective antagonist of γ-aminobutyric acid (GABA). Since their pharmacological evidence indicated that GABA was likely to be a transmitter at certain inhibitory synapses, the possible interaction of bicuculline with synaptic GABA receptors was discussed in the light of a comparison of Drieding stereomodels of GABA and the alkaloid. The comparison showed that GABA was indeed isosteric with part of the bicuculline molecule (Fig. 1), and this, of course, supported the view that bicuculline antagonizes the action of GABA by competing for the GABA receptors.

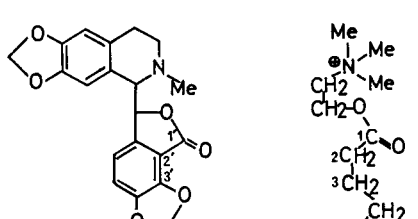
Examination of Drieding stereomodels of esters of choline, however, shows that many of these compounds also bear a close resemblance to that part of the bicuculline molecule which Curtis & others (1970) suggest bears a resemblance to GABA; in particular Drieding models of γ-aminobutyrylcholine (GABACh) and bicuculline demonstrate that the GABACh molecule corresponds particularly well also with that part of the alkaloid molecule under consideration (Fig. 2). The GABACh molecule matches exactly with the bicuculline molecule as far as the C-2 of the acid moiety of the choline ester, and there is only a slight discrepancy in the position of the C-3 of this part of the ester. It is obvious also that simple choline esters such as acetylcholine and propionylcholine will be isosteric with the same portion of bicuculline, but these simple esters possess no chemical group that would interact in the same way as the methylene di-oxy ring of the alkaloid. The nitrogen of bicuculline would be expected to be positively charged at physiological pH, as would the quaternary nitrogen of GABACh, and it is likely too that the methylene carbon atom of the methylene di-oxy ring would carry a partial positive charge as a result of the electron withdrawing effect of the oxygen atom. It is also likely that as the methylene di-oxy rings of the alkaloid will repel one another, forcing the bicuculline molecule into a linear form, the spatial arrangement of its nitrogen and its ester groups will then correspond well with the preferred conformation of acetylcholine esters (see for example Chothia, 1970; Inch, Chittenden & Dean, 1970). Thus, it might be suggested that bicuculline would react with a receptor for GABACh and in some ways (cf. Figs 1 and 2) could be expected to have more affinity for such a receptor than for a GABA receptor.

The possible role of GABACh in the mammalian central nervous system has been neglected by comparison with that of GABA; even though it is more than ten years since the presence of GABACh was first demonstrated in brain tissue and it was



BICUCULLINE GABA

FIG. 1



BICUCULLINE GABA CH

FIG. 2

proposed as an inhibitory transmitter (Kuriaki, Yakushiji & others, 1958; Kewitz, 1959a, b), there have been only a limited number of publications concerned directly with this compound. This paucity of information about GABACh could possibly be due to the lack of a specific assay for the ester and the lack of readily-available radioactively-labelled GABACh. However, it should be noted that the true role of GABA has still not been established definitively despite intensive study and much evidence for its relation with the activity of inhibitory neurons (Krnjević, 1970).

Since GABACh is known to exhibit inhibitory activity in certain parts of the cns (Takahashi, Nagashima & Koshino, 1958; Ashida, Takeuchi & others, 1965), the possibility that it might be an inhibitory transmitter should not be overlooked; this choline ester might even be the active form of GABA in inhibitory transmission. Although many of the requirements for a transmitter are apparently satisfied in the case of GABA (Krnjević, 1970), the extensive involvement of this compound in brain energy and ammonia metabolism found by Krnjević and its high concentration in brain tissue compared with that of acetylcholine (Kewitz, 1959a) could suggest that it is not the true transmitter. If this is so, some of the observed effects of GABA on inhibitory pathways might be explained by factors such as the release of stored GABACh, the enhanced synthesis of GABACh or the decreased breakdown of ester in the presence of added GABA (or both). Thus, in view of the known activity of GABACh (Takahashi & others, 1958; Ashida & others, 1965; Asano, Noro & Kuriaki, 1960) and of the still ill-defined function of GABA in the central nervous system, (Krnjević, 1970), these simple observations with molecular models prompt the question "Is the inhibitory transmitter GABA or its choline ester"?

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