Title: DO BARBITURATE RECEPTORS EXIST?

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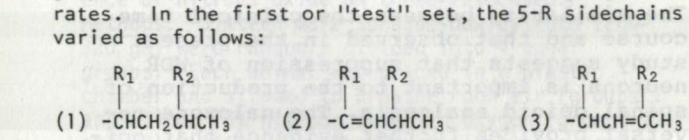
Introduction. Lipid solubility, rather than structural specificity, is commonly considered the operant factor governing clinical utility of the barbiturates. Yet numerous examples exist of significant differences in activity and/or potency between optical isomers of these drugs (whose lipid solubilities are identical), suggesting preferential attachment of one configuration (usually the "S") to putative sites of action ("receptors") in the CNS. Nor are the differences pharmacokinetically determined, since (1) plasma half-lives of the more potent "S" isomers are usually shorter than those of the companion "R" isomers and (2) brain concentrations of the two are equal or only marginally different.

Methods and Results. Since minor changes in barbiturate structure frequently result in dramatic switches between anticonvulsant and convulsant activity, it was decided to attack the receptor problem with a computer graphic study of two series of 5-ethyl, 5-R barbiturates. In the first or "test" set, the 5-R sidechains varied as follows:



with R_1 and R_2 being either H or CH_3. In the resultant group of 8 anticonvulsant and 4 convulsant barbiturates, features common to all are the barbiturate ring itself and the 5-ethyl substituent. Obviously then, the qualitative differences manifested are determined by the spatial configurations of the 5-R sidechains, each of which is capable of an endless variety of bends and twists. To quantify stereochemical comparisons of these variants, uniform placement of the barbiturate ring in the horizontal plane was assumed. Also, since the conformation with the methyl group of the 5-ethyl substituent located just below the ring is known to be always the lowest in energy (i.e., the most stable), this conformation was assumed throughout.

Calculations were then performed with a Cyber computer using the program COMOL while varying the torsion angles between adjacent carbon atoms two at a time at rotational intervals of 5°. From these data potential energy contour maps of all of the possible conformational surfaces were drawn using a modification of another computer program, KONTO. Each distinct valley in the contour map for any given barbiturate represents a single low energy conformation. Assuming as potentially active any conformation which classic energy calculations place within 10 kcal/mole of the global minimum, then for each barbiturate hundreds of accessible conformations can be obtained by varying the several torsion angles in increments of 30° within this range.

It was next posited that the position of the terminal methyl group of the 5-R sidechain may be critical for interaction with the anticonvulsant or convulsant binding sites. Starting with a single point in space to represent the terminal methyl group of each of these low energy configurations, low energy conformations of both anticonvulsant and convulsant barbiturates were found scattered through the entire accessible space, i.e., with the ring horizontal and the 5-ethyl below. To identify active pharmacophores within the space requires definition of (1) spatial regions containing at least one low energy conformation of each anticonvulsant or each convulsant and (2) regions accessible to all of the anticonvulsants but not the convulsants, or vice versa.

Superimposing all possible configurations of each anticonvulsant member of the test set generated only one region of space containing a low energy (stable) conformation of each, thus representing the most likely pharmacophore for this series. The region also includes one conformation of each of several convulsant barbiturates, suggesting that they may exert both anticonvulsant and convulsant activity, but to differing extents. (In fact, at subconvulsant doses they do indeed inhibit pentylenetetrazole-induced seizures.)

Since two methyl (or equivalent) groups seem to be required for convulsant activity, a similar spatial analysis of the convulsant barbiturates in the set was conducted using, instead of a point, a line connecting the two terminal methyl groups. The resultant convulsant region in space is not occupied by any of the anticonvulsant barbiturates, thus defining the probable convulsant pharmacophore.

These models were then tested by similar analysis of a second or "trial" set of 3 anticonvulsant and 4 convulsant barbiturates, in which the 5-R substituent included a variety of ring structures, hence altering their spatial geometry considerably. With each anticonvulsant, one low energy conformation fell within the proposed anticonvulsant region, but none fell in the convulsant region; the convulsants similarly fit the proposed convulsant pharmacophore.

Conclusions. Definition of two distinct regions of space containing the terminal group(s) of at least one low energy conformation of each barbiturate, anticonvulsants in one, convulsants in the other, strongly supports their role in interacting with anticonvulsant or convulsant binding sites respectively. Conversely, putative binding sites or receptors in the CNS involved in these activities must possess spatial configurations appropriate to accommodate the pharmacophores thus identified. By analogy, it seems reasonable to predict the existence of other structurally selective receptors mediating in dose-related fashion the sedative, hypnotic and "anesthetic" effects of barbiturates.

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