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AN ELECTROENCEPHALOGRAPHIC STUDY OF THE BLOCKING ACTION OF SELECTED TRANQUILIZERS AS A FUNCTION OF TERMINAL METHYL AMINE GROUP

W. G. STEINER AND H. E. HIMWICH

Thudichum Psychiatric Research Laboratory,
Galesburg State Research Hospital, Galesburg, Ill., U.S.A.

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Abstract—Nine compounds representing variations in terminal methyl structure were studied for block of EEG alerting in the rabbit. The desmonomethyl (secondary amine) compounds acted more rapidly in depressing the EEG alerting response to handclap but were not so potent as the compounds having a dimethyl (tertiary amine) terminal structure in depressing the EEG alerting evoked by pain. The desdimethyl (primary amine) ending was found to be the least active of the three terminal forms, being relatively ineffective in modifying the EEG alerting produced by peripheral stimuli, particularly pain. The piperazinyl terminal structure was found to resemble the dimethyl structure when attached to the chlorpromazine nucleus but it may be more similar to the desdimethyl structure when attached to other nucleus configurations such as that of imipramine or amitriptyline. It is concluded that variations in drug activity as measured by block of EEG alerting are associated with modifications in the terminal chemical structure of the side chain.

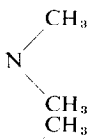
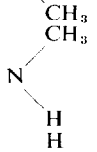
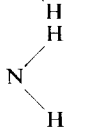
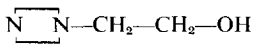
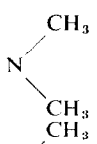
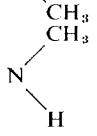
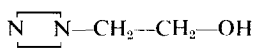
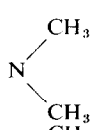
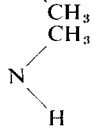
THE terminal methyl amine group is present in the structure of a variety of psychoactive agents, and our laboratory has just completed a study of this N,N-dimethyl configuration in derivatives of chlorpromazine.[1] The purpose of this report is to provide additional data on the role of the terminal methyl group in the imipramine and amitriptyline structures, in addition to that of chlorpromazine, as a demonstration of the generality of findings for this terminal molecular configuration. Nine compounds were selected for study, which represent three types of nuclei (chlorpromazine, imipramine, and amitriptyline), and four types of terminal amine structure (dimethyl, tertiary amine; desmonomethyl, secondary amine; desdimethyl, primary amine; and piperazinyl). Table 1 presents a schematic summary of the structural similarities and dissimilarities of the nine compounds.

METHOD

Forty-five adult New Zealand male albino rabbits, ranging in weight from 2 to 3 kg, were employed in experiments with the nine compounds. Animals were tracheotomized under ether and local pontocaine anesthesia, curarized, and artificially respired prior to the administration of the drugs.[2] Each of the compounds was studied on a separate group of five rabbits; the drugs were administered by femoral vein at the rate of 1·0 mg/kg every 4 min until the animals succumbed. Compounds were given at a concentration of 10 mg/ml in distilled water. Monopolar EEG recordings were

obtained from the cortex (anterior and posterior), caudate nucleus, thalamus (VPL), hippocampus, amygdala, and the reticular substance just cephalad to the pons. Histological examinations were not undertaken since no attempt was made to localize drug effects to a particular brain structure.

TABLE 1. SUMMARY OF VARIATIONS IN TERMINAL STRUCTURE BY TYPE OF NUCLEUS

Compound designation	Nucleus S-position	Nucleus N-position	Radical 2-position	Terminal group
Chlorpromazine[a]	S	N	Cl	
Desmonomethyl[b]	S	N	Cl	
Desdimethyl[c]	S	N	Cl	
Piperazinyl[d]	S	N	Cl	
Imipramine[e]	CH_2—CH_2	N	H	
Desmonomethyl[f]	CH_2—CH_2	N	H	
Piperazinyl[g]	CH_2—CH_2	N	H	
Amitriptyline[h]	CH_2—CH_2	C	H	
Desmonomethyl[i]	CH_2—CH_2	C	H	

[a] Chlorpromazine (Thorazine), Smith Kline & French Labs.
[b] Desmonomethylchlorpromazine (SKF 4515), Smith Kline & French Labs.
[c] Desdimethylchlorpromazine (SKF 4577), Smith Kline & French Labs.
[d] Perphenazine (Trilafon), Schering Corp.
[e] Imipramine (Trofranil), Geigy Pharmaceuticals.
[f] Desmonomethylimipramine (Pertofrane), Geigy Pharm.; (DMI), Lakeside Labs.
[g] (G 33006), Geigy Pharmaceuticals.
[h] Amitriptyline (Elavil), Merck Sharp & Dohme, Inc.
[i] Desmonomethylamitriptyline (Aventyl), Eli Lilly & Co.; (desmethylamitriptyline), Merck Sharp & Dohme, Inc.

The normal resting EEG pattern of the curarized, artificially respired rabbit consists of high amplitude slow wave activity interspersed with spindle formations of 14-cycle/sec activity. Under conditions of peripheral stimulation such as noise or pain, the EEG tracing undergoes a change of pattern in all areas being recorded. The high amplitude slow waves are replaced by lower amplitude fast activity, and the spindle formations are no longer evident in the EEG tracing. This EEG alerting or activation normally lasts from 10 to 20 sec. Tranquilizing agents depress this activation response. In the present experiment, animals were stimulated peripherally at the end of each 4-min drug period, and the occurrence of EEG alerting was recorded. Stimulation consists of a vigorous clapping of hands; after recovery, the animal's footpad was squeezed. Both types of stimuli normally elicit intense EEG alerting; this response was considered to be blocked when the stimuli failed to elicit a change in the EEG pattern. Since all drugs were administered serially at a relatively rapid rate (4 min), no attempt was made to repeat the stimuli for each dose level. The block of EEG alerting was attributed to the total dose level the animal had received at the time the block occurred. Under a different rate of administration, the total dose needed to produce these effects would undoubtedly change.

RESULTS AND DISCUSSION

Table 2 presents the average milligram per kilogram dose at which each of the nine compounds modified the EEG alerting reaction to the extent that no perceptible changes were noted in the EEG tracing in response to peripheral stimulation by handclap and by squeezing the footpad of the hind paw. As can be noted, the cortical response was abolished for all compounds at a drug level lower than that required for a block of EEG alerting for all recording areas studied, and more drug was required to produce this effect for the pain stimulus than for that of handclap. The hippocampus was invariably the last of the structures studied to undergo modification for each type of stimulus, and a complete block across all recording areas of the alerting elicited by pain was not obtained by the compound having a piperazinyl terminal group attached to the imipramine nucleus.

It seems clear from the data of Table 2 that variations in drug activity as measured by block of EEG alerting are associated with variations in the terminal amine structure of the side chain. The difference in activity can be directly attributed to the terminal amine structure since the several compounds with a given type of nucleus differ only in the structural configuration of the end group. The slight difference in molecular weight (about 2·5% per methyl) would not account for the wide differences in activity noted in Table 2. The secondary amine compounds (desmonomethyl) consistently produced a block of EEG alerting for handclap at lower dosages than either the tertiary (dimethyl) or primary (desdimethyl) amine compounds, the primary amine structure being the least active of the three terminal forms in terms of block of EEG alerting. On the other hand, the conventional dimethyl compounds were found to be more active in effecting a complete block of EEG alerting elicited by pain stimuli since this effect was achieved in less time and with less drug than those required for the other terminal configurations.

It appears, then, that the secondary amine compounds act more quickly but not so potently as the tertiary amine compounds since modifications in the EEG response to pain indicate a greater degree of central nervous system depression than is the case

Table 2. Variation in drug activity (EEG block) as a function of terminal structure*

Type of stimulus	Degree of EEG block	Type of compound	Terminal structure			
			Dimethyl (mg/kg)	Desmonomethyl (mg/kg)	Desdimethyl (mg/kg)	Piperazinyl (mg/kg)
Handclap	Cortical	Chlorpromazine	2·0	1·2	3·6	2·0
		Imipramine	4·2	1·6		7·8
		Amitriptyline	2·4	1·6		
	All areas recorded	Chlorpromazine	3·5	2·8	6·8	2·5
		Imipramine	5·4	2·8		22·5
		Amitriptyline	2·6	3·0		
Pain	Cortical	Chlorpromazine	2·8	5·2	8·7	3·2
		Imipramine	8·0	11·4		no block
		Amitriptyline	2·4	4·8		
	All areas recorded	Chlorpromazine	7·0	8·4	11·7	5·4
		Imipramine	10·5	13·6		no block
		Amitriptyline	4·2	5·4		

* Values represent average dose required to produce a given degree of EEG block by stimulus. All drugs were administered by femoral vein at a rate of 1·0 mg/kg every 4 min.

for modifications in the EEG response to handclap. The more rapid action of the desmonomethyl drugs suggests either a more rapid rate of penetration of the brain for this chemical configuration or a slower rate of detoxification. The short time period involved (5 to 12 min for block of handclap stimuli) would favor a more rapid rate of penetration. Brune *et al.*[1] found approximately a twofold difference in the brain level of the desmonomethyl derivative of chlorpromazine as compared with chlorpromazine in the rat—a difference that could provide the basis for the more rapid action of the desmonomethyl compounds in blocking the EEG alerting response to handclap. On the other hand, Brune *et al.*[1] found that approximately three times as much desmonomethyl chlorpromazine was required in the brain to produce the same degree of depression of reactivity in the rat as that of chlorpromazine, thus indicating substantial differences in potency of the two methyl configurations as well. Although the species, dosage, and time values of the two studies differ, the findings are not inconsistent with each other, and it may be concluded that the conventional dimethyl (tertiary amine) terminal configuration is clearly the most potent of the terminal configurations studied even though the desmonomethyl (secondary amine) compounds effect mild degrees of central nervous system depression at lower drug values.

The relationship just described between the terminal methyl configurations appeared to be independent of the type of nucleus studied. Animals required more desmonomethyl drug before a block of the EEG alerting to pain was obtained, regardless of whether it was the desmonomethyl form of chlorpromazine, imipramine, or amitriptyline. This was not the case with the piperazinyl end-group structure. While the piperazinyl form of chlorpromazine was effective in producing a block of EEG alerting to pain, the piperazinyl form of imipramine was lacking in such an action. The action of the piperazinyl terminal structure, then, does appear to be dependent in part upon the structure of the nucleus.

No general conclusions can be drawn from the present data on the effects of the desdimethyl (primary amine) structure since only one nucleus was represented with this terminal configuration. It can be concluded, however, that the desdimethyl compound was a phenothiazine of weak action from the viewpoint of blocking the EEG alerting produced by peripheral stimuli.

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