CHARGE DELOCALISATION IN RELATION TO NEUROMUSCULAR BLOCKING ACTIVITY OF CERTAIN TETRAALKYLAMMONIUM COMPOUNDS

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HOLMES, Jenden and Taylor (1947) related the curariform activity of certain quaternary compounds to the charge delocalisation in the molecule. The amount of charge delocalisation is dependent on the electronegativity of the alkyl groups linked to the central nitrogen atom. They postulated that if the density of charge on the central atom fell below a critical level, the compound would be pharmacologically inactive at the neuromuscular junction. Their evidence was based on dissociation constants of aliphatic amines and carboxylic acids. It is well known that the ionisation constants of bases are dependent not only on the inductive effect, but also on the steric effects of those substituents. The dissociation constants of carboxylic acids would seem to reflect most closely the inductive effects of alkyl substituents.

Holmes and his colleagues were limited by lack of reliable values for the dissociation constants required and by their scant pharmacological data. They used neuromuscular blocking potencies taken from the work of Ing and Wright (1934) who measured the time for complete paralysis of frog sartorius muscles. Further work was clearly indicated.

Our work uses cats and the method, depending on the depth rather than the rate of onset of paralysis, would seem more reliable in relation to this theory. An attempt has been made to extend the studies of Holmes and others and to determine the relationship, if any, between the charge delocalisation and pharmacological activity at the neuromuscular junction, for a series of six simple quaternary ammonium compounds.

METHOD

Contractions of the left gastrocnemius muscle of spinal atropinised cats were recorded using a Brown-Schuster myograph. The sciatic nerve was stimulated by supramaximal rectangular pulses (6 per min., 0·5 msec. duration). Retrograde injections were made into the right iliac artery so that drugs were carried with the blood stream down the left leg.

Drugs. The compounds studied were tetramethylammonium iodide (TMA), tetraethylammonium iodide (TEA), tetra-n-propylammonium iodide (TPA), tetra-n-butylammonium iodide (TBA), tetra-n-amylammonium bromide (TAA) and tetra-n-hexylammonium bromide (THA). TMA and TEA were obtained from commercial sources; TPA, TBA, TAA and THA were isolated and purified by Dr. E. R. Clark in this laboratory. All doses are expressed in terms of the chemical base.

Results and Discussion

After intra-arterial injection of doses up to 12 mg. of drug, all the compounds except TEA interfered with neuromuscular transmission in the cat (Fig. 1); TEA was inactive in these doses. Results from four experi-

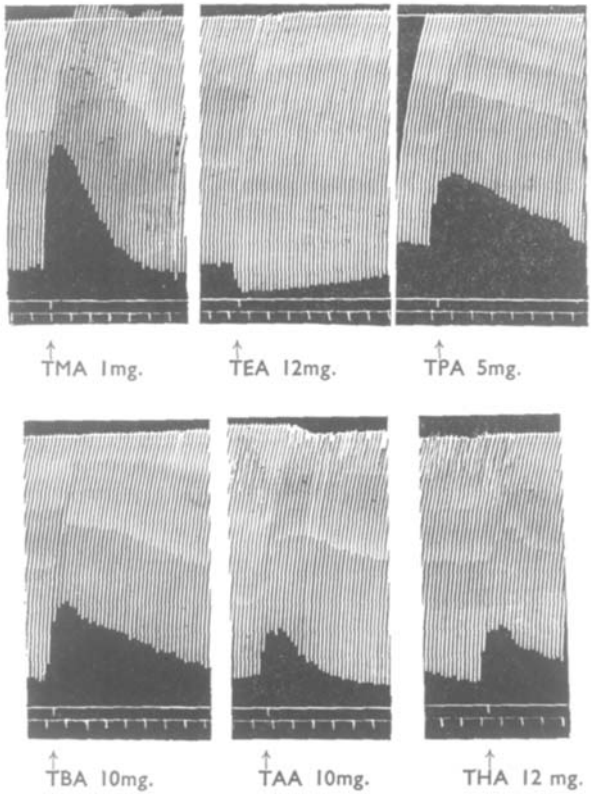

FIG. 1. Cat, spinal, atropine. Contractions of left gastrocnemius muscle in response to sciatic nerve stimulation (6 shocks/min., 0·5 msec. duration). Drugs injected into the right iliac artery as indicated. Time signal, 60 sec.

ments clearly show the order of potency to be TMA > TPA > TBA > TAA > THA > TEA. Table I shows K_a values for the appropriate carboxylic acids (Ingold, 1953).

TABLE I

THERMODYNAMICALLY CORRECTED ACIDITY CONSTANTS FOR CERTAIN CARBOXYLIC ACIDS. (INGOLD, 1953)

Acid	Group – R of R–COOH	$K_a \times 10^5$
Acetic ..	.. CH_3-	1·75
Propionic	.. C_2H_5-	1·33
n-Butyric	.. C_3H_7-	1·50
n-Valeric	.. C_4H_9-	1·38
Caproic ..	.. $C_5H_{11}-$	1·32
n-Heptylic	.. $C_6H_{13}-$	1·28

Stronger acids (i.e., with higher K_a values) will reflect lower electropositivity (+I effect) for the alkyl group and therefore the order of +I is hexyl > amyl > ethyl > butyl > propyl > methyl. The greater the +I value, that is the greater ease with which they yield electrons towards an electron-attracting centre, the lower will be the density of charge on the central nitrogen atom in the corresponding tetra-alkylammonium compound. Therefore, according to the theory of Holmes and others, the order of pharmacological potency should be TMA > TPA > TBA > TEA > TAA > THA. Except for TEA this was the order of neuromuscular blocking activities found in this study. Of this series of compounds only TEA antagonises neuromuscular blocking agents (Collier and Exley, unpublished). This action of TEA is presynaptic in origin (Stovner, 1957) and probably involves the release of acetylcholine. It is likely that this presynaptic effect would reduce the blocking action of TEA on the postsynaptic membrane. Thus the exceptionally low neuromuscular blocking activity of TEA is not surprising.

Though there are undoubtedly many other factors influencing the biological activity of these compounds, the experimental results in cats support the theory that concentration of charge favours their neuromuscular blocking activity.

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