EFFECT OF 1-ADAMANTYL RADICALS ON CURARE-LIKE ACTIVITY

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The importance of hydrophobic 1-adamantyl radicals (Ad) for curare-like activity was investigated in a series of polymethylene bis-ammonium salts $R(CH_3)_2N^+(CH_2)_nN^+(CH_3)_2R \cdot 2I^-$ ($R = CH_3$ or Ad). Introduction of Ad radicals into the cationic groups of depolarizing agents (n = 9-11) changed the mechanism of their action and lowered their activity. Addition of Ad radicals to the quaternary nitrogen atoms of antidepolarizing agents (n = 5 and 6) sharply increased their curare-like activity. The results are evidence of the existence of hydrophobic zones in nicotinic cholinergic receptors of skeletal muscles.

KEY WORDS: Cholinergic receptor, curare-like activity; adamantyl radicals in polymethylene bis-ammonium salts.

Introduction of 1-adamantyl (Ad)† radicals into the molecules of nicotinic cholinomimetics may have an effect in two different directions. On the one hand, because of their hydrophobic properties, they create additional points for fixation of substances to the cholinergic receptor (CR), leading to definite stabilization of the existing conformation of the receptor protein. Changes are thereby produced in the mechanism of neuromuscular block: depolarizing agents are converted into antidepolarizing [3, 4]. On the other hand, the considerable volume of the Ad radical (seven to eight times larger than the methyl group) may create steric hinderances preventing interaction between the active center of the agent and the CR. This must be manifested as a decrease in the activity of the compounds. Increased activity has not been observed after the introduction of Ad radicals.

In this connection it was important to discover whether, in principle, curare-like activity of compounds can be increased by introducing hydrophobic radicals into their structure. This amounts essentially to the creation of compounds with sufficiently complementary properties relative to CR. The investigation described below was carried out for this purpose.

EXPERIMENTAL METHOD

The activity and mechanism of action of the substances were investigated‡ mainly in experiments on cats, pigeons, and the isolated frog rectus abdominis muscle [5].

The hydrophobic character of the compounds was judged from their interaction with polyacrylic acid [2]. Potentiometric titration curves were used to determine the degree of electrostatic binding of the substances with polyacrylic acid (θ), which depends on the hydrophobic properties of the compound.

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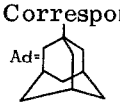
† Ad= 

‡The pharmacological investigations were carried out in conjunction with B. N. Ibadova. A. P. Arendaruk, N. V. Klimova, L. N. Lavrora, N. V. Smirnova, and M. I. Shmar'yan participated in the work of synthesizing the compounds.

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TABLE 1. Cholinergic Properties of Bis-quaternary Ammonium Compounds $(CH_3)_2\overset{+}{N}(R)-(CH_2)_n-\overset{+}{N}(R)(CH_3)_2 \cdot 2\,I^-$

R	Parameters	n							
		5	6	7	8	9	10	11	
$-CH_3$	Stimulant effect on isolated frog rectus abdominis muscle (conventional units of activity)	~0	0,1	1,3	7,1	36	71	91	Acetylchlorine 1500
	Transmission of impulses from sciatic nerve to tibialis anterior muscle in cat inhibited by 95% (doses in mg/kg, intravenously)	>40	>40	1,9	0,16	0,036	0,03	0,06	Tubocurarine chloride 0,3
—Ad	Blocking effect on transmission of impulses from sciatic nerve to gastrocnemius muscle in cat (doses in mg/kg, intravenously)	0,8—1,2	0,12—0,2	0,2—0,25	0,09—0,12	0,45—0,55	0,25—0,3	0,45—0,55	Tubocurarine chloride 0,18—0,23

[1]Activity of compound for which n = 12 is taken as 100 [9].

[2]See [9].

EXPERIMENTAL RESULTS AND DISCUSSION

A factor of importance to nicotinic cholinolytic action is the localization of the Ad radical. For example, for acetylcholine derivatives the compound was more active if the Ad radical was as far as possible from the quaternary nitrogen atom.

$$R^3—CH_2—CO—O—CHR^2—CH_2—\overset{+}{N}(CH_3)_2\cdot R^1\cdot I^-$$

a) R^1=Ad; R^2=R^3=H; b) R^2=Ad; R^1=CH_3; R^3=H;
c) R^3=Ad; R^1=CH_3; R^2=H. (I)

They can be arranged in the following order of activity Ic > Ib > Ia. They produced flaccid paralysis in pigeons in doses of 2.5–4, 5–6, and 9–10 mg/kg, respectively.

A different pattern was observed for dicarboxylic acid derivatives (II).

$$(CH_3)_2\overset{+}{N}-CH_2-\underset{R^1}{CH}-O-CO-Y-CO-O-\underset{R^2}{CH}-CH_2-\overset{+}{N}(CH_3)_2\cdot 2i^-$$

a) R^1=Ad; R^2=H; Y=—CH_2—CH_2—
b) R^2=Ad; R^1=CH_3; Y=—CH_2—CH_2—
c) Y=—Ad—; R^1=CH_3; R^2=H
d) Y=Ad—CH<; R^1=CH_3; R^2=H.

The compound IIa, with N—Ad radicals, was most active (it blocked neuromuscular transmission in cats in doses of 0.25–0.35 mg/kg, intravenously).

Compound IIb was 30–40 times weaker. It had a blocking effect if injected in doses of 11–13 mg/kg. Compounds IIc and IId were less active still (their blocking doses exceeded 20 and 30 mg/kg, respectively).

It is difficult to analyze the results because two parameters changed simultaneously: the mechanism of action and the activity. Accordingly, introduction of the Ad radical into the molecule of antidepolarizing agents is very interesting. For this purpose a series of polymethylene bis-trimethyl ammonium salts was used (Table 1). This series is interesting because compounds with n = 5 and 6 are antidepolarizing agents, whereas the higher homologues (n = 9–11) have marked depolarizing properties [9, 10].

It will be clear from Table 1 that replacement of one methyl group attached to each quaternary nitrogen atom by an Ad radical gives all the compounds antidepolarizing properties. They produce flaccid paralysis in pigeons, exhibit nicotinic cholinolytic activity on the frog rectus abdominis muscle, block neuromuscular transmission in cats without preliminary facilitation and muscle fasciculations, and neostigmine acts as their antagonist.

Comparison of compounds with R = CH_3 and R = Ad shows that when n = 5–8 the curare-like activity of the Ad analogues is higher than that of the corresponding bis-trimethyl ammonium salts. On introduction of Ad radicals into the cationic groups of depolarizing agents (n = 9–11), the mechanism of their action is modified and their activity reduced. Addition of Ad radicals to quaternary nitrogen atoms of antidepolarizing agents increases activity tenfold when n = 5, and a hundredfold when n = 6. Compounds with n = 7 and 8, which evidently have admittedly mild nicotinic cholinomimetic properties, occupy an intermediate position (experiments on hens and on the isolated frog rectus abdominis muscle). The activity of their N—Ad analogues also was increased, but less so than when n = 5 and n = 6 (by 8–10 times for n = 7 and by 1.5 times for n = 8).

Consequently, the differences in activity were particularly great for hexamethonium (n = 6). The reason was most probably the high-hydrophobic character of the Ad radicals providing additional fixation points on the subsynaptic membrane and stabilizing ionic (ion—dipole also) bonds. Considering that n = 6 is not the optimal interonium distance for neuromuscular blocking agents, the possibility cannot be ruled out that hexamethonium interacts only with one anionic group of the CR. The second cationic group may form an ion—dipole bond with partial charges (δ^-) of the CR.

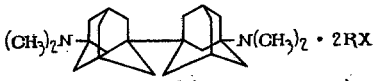
The importance of Ad radicals is also seen in the case of the bis-tertiary analogue of hexamethonium (III):

$$H_3C—\underset{R}{N}—(CH_2)_6—\underset{R}{N}—CH_3\cdot 2HBr$$

a) R=CH_3; b) R=Ad. (III)

The bis-tertiary salt (IIIa) does not inhibit neuromuscular synapses, whereas the corresponding Ad derivatives (IIIb) blocks the transmission of impulses from the sciatic nerve to the gastrocnemius muscle in the cat in a dose of 10-12 mg/kg.

After the introduction of Ad radicals into the central part of the molecule (IV), compounds with an interonium distance similar to that of hexamethonium were sufficiently active antidepolarizing, curare-like agent (neostigmine acted as their antagonist).



a) RX = CH_3I; b) RX = C_2H_5I; c) RX = HCl. (IV)

The compound with RX = CH_3I (IVa) blocked neuromuscular transmission in the cat in a dose of 0.7-0.8 mg/kg, and that with RX = C_2H_5I (IVb) did so in a dose of 0.6-0.7 mg/kg. It is noteworthy that the bis-tertiary amine (IVc) induced neuromuscular block in a dose as low as 2.5-3.5 mg/kg, i.e., only 3-4 times greater than for the corresponding bis-quaternary salt (IVa).

The Ad derivatives of hexamethonium (Table 1, n = 6, R = Ad and IVa), in muscle-paralyzing doses, produce virtually no change in the arterial pressure and have no effect on the transmission of excitation in the superior cervical ganglion.

Essential differences in the hydrophobic properties of hexamethonium and N–Ad analogue can be judged from the much higher degree of electrostatic binding of the latter with polyacrylic acid. The strongly hydrophobic character of the Ad radicals, as these results show, stabilizes the resulting substance–polyelectrolyte complex.

Besides Ad analogues of hexamethonium, there are also other active curare-like agents in which the cationic centers are separated by hexamethylene chains. These include qualidil [1], mylaxen, and other compounds [6-8]. The hydrophobic properties of these substances undoubtedly also play an essential role. However, it is difficult to assess them because of the existence of conjugated bonds in the rings and the possible role of dipole–dipole interaction of the substances with the CR on account of the formation of partial charges.

Hydrophobic radicals thus affect not only the mechanism of action, but also the activity of cholinergic substances, including strengthening of their curare-like properties. These findings confirm the presence of hydrophobic zones in the nicotinic CR of skeletal muscles.

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