Br. J. Pharmac. (1970), **40**, 68–77.

A comparison between the blocking actions of 2-(4-phenylpiperidino) cyclohexanol (AH 5183) and its N-methyl quaternary analogue (AH 5954)

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Summary

1. The neuromuscular blocking activities of AH 5183 (2-(4-phenylpiperidino) cyclohexanol) and its N-methyl quaternary analogue (AH 5954) were compared in rapidly stimulated nerve-skeletal muscle preparations of the rat, chicken and cat.

2. The evidence indicated that in isolated preparations the neuromuscular block produced by both AH 5183 and AH 5954 was primarily pre-junctional in origin. That produced by AH 5954 was readily reversible either by washing the tissue or by reducing the stimulation frequency, whereas that produced by AH 5183 was difficult to reverse in these ways.

3. Low doses of AH 5954 sensitized the rat hemidiaphragm preparation to the neuromuscular blocking action of choline. The neuromuscular block produced by choline was reversible by tetraethylammonium but not by neostigmine. This suggested that the blocking action of choline is at least partly pre-junctional in nature.

4. In anaesthetized cats AH 5954 possessed a biphasic neuromuscular blocking action. The initial phase was rapid in onset, suggestive of a post-junctional action, whereas the second phase was prolonged and reversible by choline, suggestive of a prejunctional inhibitory action on the choline transport mechanism. AH 5183 produced no initial blocking action and was irreversible by choline.

5. Both AH 5183 and AH 5954 possessed local anaesthetic and α-adrenoceptor blocking actions. These actions and the neuromuscular blocking action were affected to different degrees by quaternization, suggesting that the three main actions of the two drugs are independent.

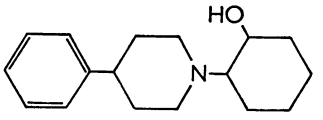
6. It was concluded that AH 5954 and AH 5183 act at different pre-junctional sites at the neuromuscular junction, AH 5954 acting extraneuronally by inhibiting choline transport and AH 5183 intraneuronally at the level of the synaptic vesicle membrane.

Introduction

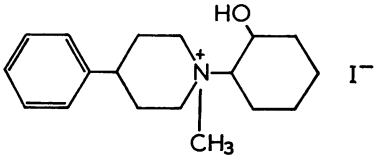
The blocking actions of the tertiary base 2-(4-phenylpiperidino) cyclohexanol (AH 5183) on various cholinergic and adrenergic preparations have been studied in some detail (Brittain, Levy & Tyers, 1969a, b ; Marshall, 1970). AH 5183 proved

to have three separate actions, an α-adrenoceptor blocking action, a local anaesthetic action, and an inhibitory action at cholinergic neuroeffector junctions. Previous studies from this laboratory (Marshall, 1970) suggested that AH 5183 impairs neuromuscular transmission primarily through a pre-junctional action which is possibly exerted within the nerve ending axoplasm at the level of the synaptic vesicle membrane.

The present studies were undertaken to determine the effects of quaternizing the tertiary nitrogen of AH 5183 on its pharmacological actions. The chemistry of AH 5954, the N-methyl quaternary analogue of AH 5183, has recently been described by Peel (1970).



AH 5183



AH 5954

Methods

The actions of AH 5954 were compared with those of AH 5183 on the following preparations.

(*a*) The isolated phrenic nerve-hemidiaphragm of the rat (Bülbring, 1946).

(*b*) The isolated chick biventer cervicis muscle preparation stimulated through its motor nerve (Ginsborg & Warriner, 1960).

(*c*) The isolated phrenic nerve of the rat.

(*d*) The isolated intestine of the rabbit to which the periarterial nerves were stimulated (Finkleman, 1930). The details of methods *a, b, c* and *d* were fully described in a previous paper relating to the actions of AH 5183 (Marshall, 1970).

(*e*) The drug was injected intraperitoneally into conscious chicks.

(*f*) The tibialis anterior muscle of cats anaesthetized with a mixture of chloralose (80 mg/kg) and pentobarbitone sodium (2·5 mg/kg). Maximal twitches of the tibialis anterior muscles of both legs were elicited by stimulation of the sciatic nerves with rectangular pulses of 100 μs duration. Isometric contractions were recorded by Grass FT03C force transducers connected to an ink-writing dynograph. One tibialis anterior muscle was stimulated every 10 s, while the contralateral muscle was stimulated once every second via a stimulus isolation unit. Arterial blood pressure was recorded in mmHg (1 mmHg$\equiv$1·333 mbar) from a common carotid artery by a Statham pressure transducer and respiration was measured by a thermistor probe in the trachea.

Drugs. Carbachol chloride, choline chloride, chloralose, tetraethylammonium bromide (B.D.H.), neostigmine methylsulphate (Roche), pentobarbitone sodium

(Abbott), (−)-phenylephrine, sodium adenosine-5′-triphosphate (Sigma), isoprenaline bitartrate (Wyeth). The doses quoted refer to the salts or the bases.

Results

Rat phrenic nerve-hemidiaphragm preparations

(a) Effects of stimulation frequency

The quaternary derivative (AH 5954), in concentrations of 30–40 μg/ml, produced a slowly developing block of hemidiaphragms stimulated at 1 Hz, after a latent period of 10·0 ± 3·1 min (mean ± S.E.M.) following the first addition of the drug to the bath. These doses were without effect on the contralateral preparation stimulated at 0·1 Hz. Block of the more slowly stimulated preparation was not produced until concentrations of 200 μg/ml or more were added to the bath. The tertiary compound (AH 5183) produced a similar selective block of the more rapidly stimulated preparation but was 5 to 10 times more potent (Marshall, 1970). During block in transmission produced by AH 5183 or AH 5954 in the more rapidly stimulated preparation, the tension of a tetanus (50 Hz for 10 s) was reduced and rapidly waned during the period of stimulation. Some effect on a tetanus was also evident in the contralateral more slowly stimulated muscle, although never to the extent that it was in the more rapidly stimulated preparation.

Slowing the stimulation rate to 0·1 Hz during block of transmission produced a rapid recovery of twitch tension in the continued presence of AH 5954. Alterna-

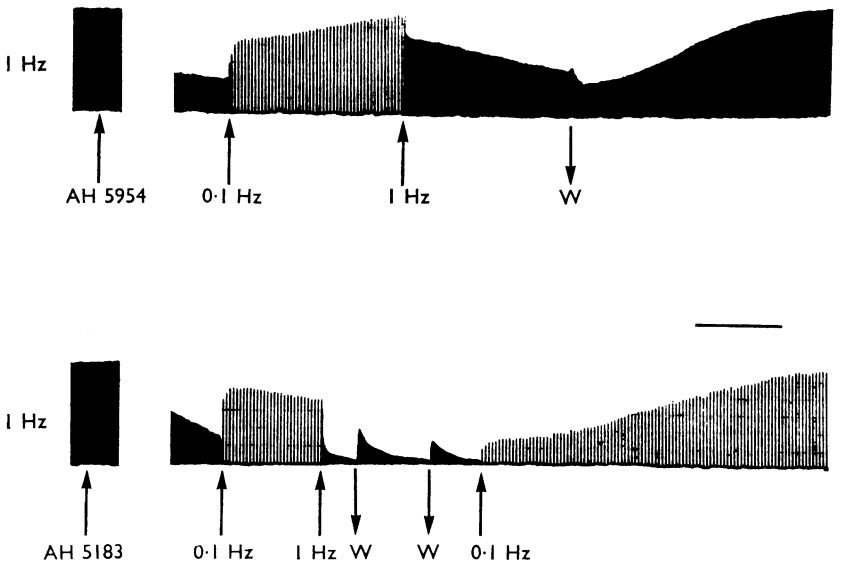


FIG. 1. Rat phrenic nerve-hemidiaphragm preparations. The upper and lower records are from different experiments. Contractions are upwards. Both preparations were stimulated at 1 Hz and periodically the stimulation rate was slowed to 0·1 Hz where indicated. At W, the preparations were washed for 30 s with fresh Krebs-Henseleit solution. In the upper preparation AH 5954 (30 μg/ml) was added to the bath at the marked arrow, and in the lower preparation AH 5183 (4 μg/ml) was added to the bath. Thirty minutes later the blocking action of AH 5954 was relieved either by slowing the stimulation rate or by washing, whereas that of AH 5183 was not relieved by either procedure alone, but required a combination of both. The horizontal bar corresponds to 5 min.

tively, washing the tissue with fresh Krebs-Henseleit solution, without slowing the stimulation frequency, also produced full recovery from the block of transmission (Fig. 1). In contrast, with AH 5183 a combination of both procedures was required before even a slow recovery commenced (Fig. 1).

(b) Changes in ionic concentrations

As was found for AH 5183 (Marshall, 1970), elevated calcium and depressed magnesium levels shortened the latent period and hastened the rate of development of block produced by AH 5954. Figure 2 illustrates the effect of elevated Ca^{2+}. Elevated magnesium and lowered calcium levels produced the opposite effects.

(c) Antagonists

The anti-tubocurarine drugs neostigmine (0·1–0·5 μg/ml) and tetraethylammonium (TEA, 200 μg/ml) produced only a transient reversal of transmission failure due to AH 5954 or AH 5183. After the initial brief reversal, TEA accelerated the rate of development of the block.

Choline (10–60 μg/ml) added during transmission failure produced by AH 5954 or AH 5183 was either without effect or, in the larger concentrations (30–60 μg/ml), deepened the block. Pretreatment of the tissue with choline (30–200 μg/ml) enhanced the blocking action of both AH 5954 and AH 5183. Further investigation of this interaction revealed that the degree of enhancement of the AH 5954 block was dependent on the dose of choline, and that the characteristics of the neuromuscular block produced by a large dose of choline (100–200 μg/ml) together with a small dose of AH 5954 (10–20 μg/ml) differed from those of AH 5954 alone. As noted above, slowing the stimulation frequency to 0·1 Hz produced full recovery from block due to AH 5954 alone. In contrast, slowing the stimulation frequency in a tissue treated with AH 5954 plus choline produced only a partial reversal of the block. The block then either redeveloped slowly, or the twitch height remained

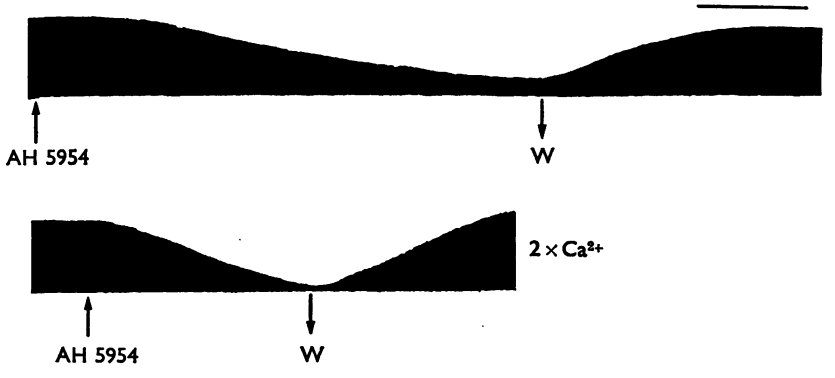


FIG. 2. Rat phrenic nerve-hemidiaphragm preparations stimulated at 1 Hz as in Fig. 1. In both traces, at the marked arrows AH 5954 (30 μg/ml) was added to the bath. The lower trace was recorded in Krebs-Henseleit solution containing twice the normal concentration of calcium ions. At W, the preparations were washed for 30 s. Note the short latent period and rapid development of neuromuscular block in the presence of excess calcium ions. The horizontal bar corresponds to 10 min.

constant at a reduced amplitude (Fig. 3). This phase of block differed from that produced by AH 5954 alone in that it was partially and transiently reversed by neostigmine (0·5 μg/ml) and rapidly and completely reversed by TEA (200 μg/ml, Fig. 3). Control experiments showed that choline itself has little neuromuscular blocking activity in this preparation at the dose levels used (100–200 μg/ml). However, the block produced by larger concentrations of choline (1–1·5 mg/ml) bore a strong resemblance to that produced by other depolarizing substances in this preparation, for example succinylcholine, decamethonium (Freeman, 1968a, b) and DMPP (Marshall, unpublished observations), being reversible by TEA (Fig. 3). Thus it appears that the block produced by AH 5954 plus choline is due primarily to choline, and that AH 5954 sensitizes the tissue to the blocking action of choline.

Cat

AH 5954 (5–10 mg/kg) injected intravenously produced a fall in general arterial blood pressure which lasted for approximately 10–15 min. As these doses had little lasting effect on neuromuscular transmission, it was necessary to inject small doses at regular intervals in an attempt to obtain cumulative effects on neuromuscular transmission, whilst minimizing the depressor effects.

The doses used (5–10 mg/kg) produced a period of twitch augmentation in the tibialis anterior muscle stimulated at 0·1 Hz and a rapid block of twitch height in the contralateral muscle stimulated at 1 Hz. Recovery from the blocking action of AH 5954 in the preparation stimulated at 1 Hz proceeded in two phases. Initially

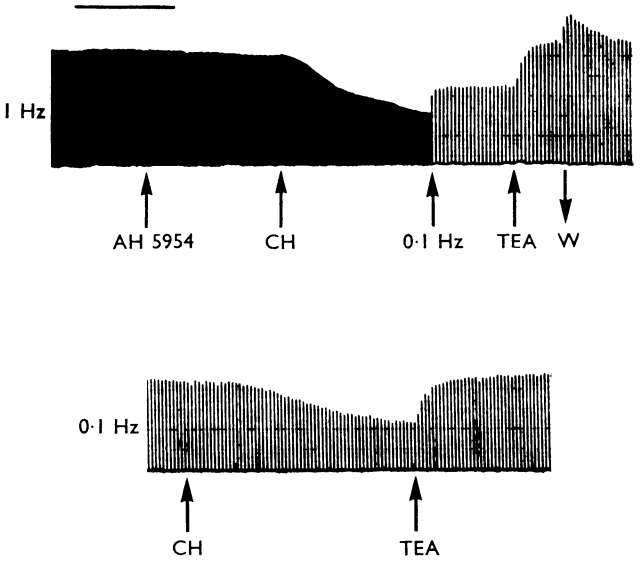


FIG. 3. Rat phrenic nerve-hemidiaphragm preparations as in Fig. 1. In the upper trace at the marked arrow AH 5954 (10 μg/ml) was added to the bath. This dose was insufficient to produce neuromuscular block. At CH, choline (200 μg/ml) was added to the bath. Previous experiments had shown this dose of choline to have little blocking action of its own. The neuromuscular block produced by the combination of AH 5954 and choline was only partially reversed by slowing the stimulation rate to 0·1 Hz, but was completely reversed by TEA (200 μg/ml). In the lower trace the neuromuscular blocking action of choline (1·5 mg/ml) was antagonized by TEA (200 μg/ml). The horizontal bar corresponds to 5 min.

it was rapid but at about the level of 50% recovery the rate slowed. With the initial doses of AH 5954, recovery was complete within 10 min, but at a cumulative dose level of 20–25 mg/kg the twitches remained constant at a depressed amplitude for 20–25 min (Fig. 4). This two-phase blocking action was similar to that produced by compounds known to possess both pre- and post-junctional actions on neuromuscular transmission (Bowman & Hemsworth, 1965 ; Marshall, 1968a, b ; Dowd, Jennings, Marshall & Tracy, 1968). The second phase of block was reversible by choline (Fig. 4), although two injections, each of 5 mg/kg, were required, in contrast to the single injection of 5 mg/kg necessary to reverse the blocking action of most straight-chain choline analogues in this preparation (Bowman & Rand, 1961 ; Bowman & Hemsworth, 1965 ; Bowman, Hemsworth & Rand, 1967 ; Marshall, 1968a, b ; Dowd *et al.*, 1968). Nevertheless, choline reversal was more convincing than that observed for hemicholinium-3 in the same preparation (Bowman & Rand, 1961).

As described previously (Marshall, 1970), AH 5183 did not produce an immediate block. With this compound, block was of slow onset and development and of long duration. Recovery was not enhanced by the injection of choline.

Domestic fowl

(a) Injection into conscious chicks

Intraperitoneal injection of AH 5954 (40 mg/kg) produced a flaccid paralysis of slow onset. The rate of onset of paralysis was hastened when the birds were exercised by continually attempting to elicit righting reflexes (Bowman & Rand, 1961). The muscles of the neck were particularly sensitive to the actions of AH 5954, since at a stage when the birds could still stand they experienced difficulty in holding up their heads. At no stage of the paralysis was any spasticity produced.

(b) Chicken biventer cervicis muscle preparation

The blocking actions of AH 5954 in this preparation were similar to those seen in the rat hemidiaphragm preparation. In the biventer cervicis preparation the differences between AH 5183 and AH 5954 evidenced by slowing the stimulation

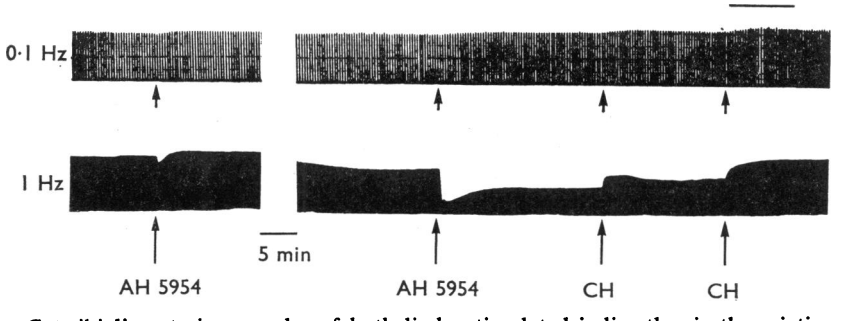


FIG. 4. Cat tibialis anterior muscles of both limbs stimulated indirectly via the sciatic nerves. In the upper record the muscle was stimulated at a frequency of 0·1 Hz while in the lower record the muscle was stimulated at a frequency of 1 Hz. At the marked arrows AH 5954 (10 mg/kg) was injected intravenously. At CH, choline (5 mg/kg) was injected intravenously. Note the two-phase block produced by AH 5954 in the rapidly stimulated muscle, which was fully reversed by a total of 10 mg/kg of choline. The upper horizontal bar corresponds to 5 min and the lower bar indicates the time period between the records.

frequency or washing the tissue were more striking than in the rat hemidiaphragm. Recovery of twitch height after AH 5183 was extremely slow, taking 1–2 h to full recovery, even at a stimulation frequency of 0·1 Hz, whereas after AH 5954 recovery proceeded at a similar rate to that observed in the rat hemidiaphragm.

Previous experiments have shown that post-junctionally active blocking drugs of the tubocurarine type reduce responses to carbachol to a greater extent than they reduce responses to electrical stimulation (Marshall, 1969). AH 5954 (20–40 μg/ml) produced a greater reduction of twitch height than of carbachol contractures (Fig. 5), indicating that a substantial component of its blocking action was pre-junctional in origin.

Local anaesthetic activity

Concentrations of 150 and 250 μg/ml of AH 5954 reduced the amplitude of the action potentials recorded from the rat phrenic nerve *in vitro* by 35% and 50% respectively. These concentrations were 2–3 times greater than those of AH 5183 found to produce the same effect.

Rabbit intestine

AH 5954 (3–5 μg/ml) reduced responses to added phenylephrine (0·02 μg/ml) to approximately the same degree as it reduced responses to periarterial nerve stimulation, whereas it had no effect on the comparable responses produced by ATP (0·25 μg/ml) or isoprenaline (0·05 μg/ml). These effects are indicative of a blocking action on α-adrenoceptors (Bowman & Hall, 1970) and are identical to those obtained using AH 5183 (Marshall, 1970).

Discussion

The results show that the effects of AH 5954, like those of the parent compound AH 5183, are not confined to cholinergic neuro-effector junctions, but consist of three apparently separate actions—an α-adrenoceptor blocking action, a local anaesthetic action and an inhibitory action at cholinergic junctions. At the adrenergic

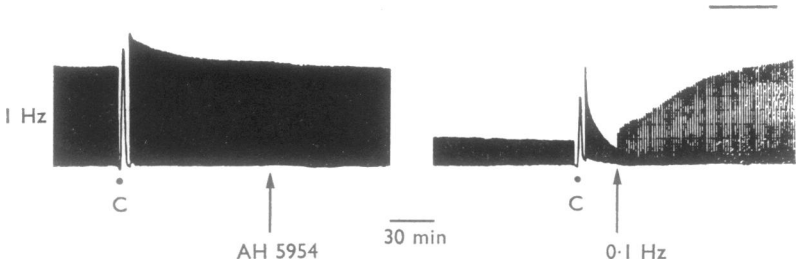


FIG. 5. Maximal twitches of a chick biventer cervicis muscle stimulated indirectly at 1 Hz. At C, electrical stimulation was temporarily stopped and carbachol (2·5 μg/ml) was added to the bath for 90 s. (Paper speed was slowed during carbachol responses.) At the marked arrow AH 5954 (20 μg/ml) was added to the bath. Forty-five minutes later the carbachol response was blocked to a lesser degree than was maximal twitch height. At 0·1 Hz the stimulation frequency was slowed from 1 Hz to 0·1 Hz. This procedure produced reversal of the neuromuscular block, in the continued presence of AH 5954. The horizontal bar corresponds to 5 min.

junctions studied, AH 5954 proved similar both in potency and mechanism to AH 5183, quaternization having no effect on the α-adrenoceptor blocking action. Quaternization has also been found not to modify the action of some other α-adrenoceptor blocking drugs (Ariens & Simonis, 1969).

Quaternization reduced the local anaesthetic activity by two to four times and the neuromuscular blocking activity eight to tenfold. Thus the three main pharmacological activities of AH 5183 are affected quantitatively to different degrees by quaternization, supporting the suggestion that these activities are unrelated (Marshall, 1970).

Additionally, quaternization produced some important differences in the neuromuscular blocking action of the two compounds. In the rat hemidiaphragm and the chick biventer cervicis muscle preparation, the evidence suggested that the blocking actions of AH 5954 and AH 5183 were primarily prejunctional in nature, being similar in most characteristics to those of hemicholinium-like drugs (see Schueler, 1960 ; Bowman *et al.*, 1967 ; Bowman & Marshall, 1970, for reviews). However, in the rapidly stimulated cat tibialis anterior muscle, an initial blocking action of rapid onset and short duration was noted using AH 5954, suggestive of an initial postjunctional action. The lack of contracture in the chicken biventer cervicis muscle indicates that this action is non-depolarizing in nature.

In the isolated preparations from the rat and chicken the actions of AH 5954 and AH 5183, although different in potency, were in most respects similar qualitatively. However, the ease with which the blocking action of AH 5954 could be reversed by reduction of the stimulation frequency, or by washing the tissue, was in marked contrast to that of AH 5183, which was extremely difficult or impossible to reverse in these ways. In view of the impermeability of biological membranes to quaternary compounds, and the ease of reversal of AH 5954 block, it was considered possible that AH 5954 was exerting its pre-junctional action at an extraneuronal site, possibly by a hemicholinium-like action on the choline transport mechanism. It was not possible to demonstrate reversal of AH 5954 block by choline *in vitro*, but the second prolonged phase of block in the cat tibialis anterior muscle was reversible by choline, thus supporting the above suggestion.

The striking reduction of neuromuscular blocking potency on quaternization is an unexpected feature in drugs acting at the neuromuscular junction although activity of the erythroidine alkaloids is affected in a similar way by quaternization (Unna, Kniasuk & Greslin, 1944), and this reduction lends weight to the argument that AH 5183 and AH 5954 act at different sites, the former acting intracellularly and the latter extracellularly. Alternatively, AH 5954 being a quaternary compound presumably would have greater difficulty in attaining access to intracellular sites of acetylcholine metabolism than AH 5183 and it could be argued that AH 5954 is also acting intracellularly and that its low activity is due to poor penetrability. However, this seems unlikely in view of the ease of reversal of AH 5954 block compared with that of AH 5183. Most of the compounds which inhibit choline transport are quaternary ammonium compounds (Bowman & Marshall, 1970) and there is no evidence to indicate that tertiary compounds have a greater affinity for the choline transport mechanism than do quaternary compounds (Martin, 1969 ; Hemsworth & Bosmann, personal communication, 1970). Thus the earlier suggestion that AH 5183 may possess a non-competitive blocking action on the choline transport system in nerve terminals (Marshall, 1970) appears unlikely.

Drugs acting on the choline transport system sensitize tissues to subsequent administration of other types of neuromuscular blocking drugs (Hemsworth, 1965). The sensitization of the rat hemidiaphragm by AH 5954 to the neuromuscular blocking action of choline was marked, and the characteristics of the neuromuscular block were similar to those observed with other " depolarizing " drugs, to which has been ascribed a pre-junctional action on transmitter release (Freeman, 1968a, b). The present experiments lend weight to the possibility that depolarizing drugs exert a pre-junctional action on this tissue, since choline block was poorly reversed by neostigmine, but was reversed by TEA, whose main action at the neuromuscular junction is to increase the release of acetylcholine (Collier & Exley, 1963). It appears possible that AH 5954 sensitizes the tissue to this pre-junctional action of choline by indirectly inhibiting acetylcholine synthesis and hence reducing the safety margin of transmission.

The evidence presented on the pre-junctional blocking actions of AH 5954 and AH 5183 at the neuromuscular junction suggests that the drugs act at different sites and provides additional evidence for the suggestion that AH 5183 exerts its neuromuscular blocking action at an intracellular site, probably at the level of the synaptic vesicle membrane, by inhibiting the uptake of newly synthesized acetylcholine into the vesicles.

I am grateful to Dr. R. T. Brittain of Allen & Hanbury's Ltd. for gifts of AH 5183 and AH 5954 and to Professor W. C. Bowman for discussion of the manuscript. Part of this work was supported by a grant from the British Egg Marketing Board.

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(*Received April* 13, 1970)