sec with trains of supramaximal 2·0 msec pulses, one at a frequency of 200 Hz (fast) and the other at 20 Hz (slow). HC3 or THPC3 (40 μg/kg intravenously) caused a progressive blockade of transmission which commenced after a delay of 10–15 min. The muscle receiving the "fast" stimulation was most rapidly and strongly affected. The block by either substance was antagonized by choline (25–50 mg/kg intravenously) if given before it became too deep. The respiration was similarly affected and its progressive deterioration, although delayed, always preceded the changes in the responses of the gastrocnemius muscles.

From these results it would appear that TPHC3, although slightly more potent, has essentially the same pattern of action as HC3 notwithstanding the difference in structure.

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Actions of a cholinergic antagonist on mammalian skeletal muscle

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The compound N-ethyl 2-pyrrolidylmethylphenylcyclopentyl glycollate (PMCG) has both peripheral and central atropine-like properties (Abood & Biel, 1962). Brimblecombe & Green (1968) found it to be 4 times less active than atropine peripherally and 5 times more active centrally. In addition, Abood & Biel (1962) reported that at 10^{-6}M the drug increased by 50% the isometric twitches of the isolated, indirectly stimulated frog sartorius muscle in Ringer solution but inhibited spontaneous twitches of the muscle in calcium-free system. They suggested that PMCG affected muscle depolarization by interfering with the movement of ions, notably Ca^{++} and Mg^{++}. The drug possesses only very weak anti-cholinesterase activity (pI50 against acetylcholinesterase=1·5, and against cholinesterase=4·0).

PMCG was therefore studied on the rat phrenic nerve diaphragm preparation *in vitro* and on fast and slow hind limb muscles of the cat *in vivo*. In the cat, twitch and tetanus characteristics of a typical fast muscle (flexor hallucis longus, FHL) and a typical slow muscle (soleus) were recorded essentially by the method of Buller & Lewis (1965a, b). Drugs were injected intra-arterially into a branch of the femoral artery.

Twitches of the rat diaphragm were increased by up to 47% by PMCG at a bath concentration of 10 μg/ml. In both cat muscles, lower doses (0·25 to 10 mg) potentiated, and higher doses (10 mg and above) depressed twitches. Potentiation was more marked in FHL than in soleus (increases of up to 200% and 70% respectively) and occurred in both indirectly and directly stimulated muscles, the latter curarized. Increases in twitch tension were characterized by increases in the time to peak (up to 50%) and in the maximum rate of rise of tension (up to 85%).

Transition from potentiation to depression occurred over a narrow dose range, soleus being more susceptible to depression than FHL. High doses completely blocked twitches of both cat muscles stimulated indirectly. Directly stimulated curarized muscles were less depressed. There was also depression of twitches of the rat diaphragm at higher concentrations.

Doses of PMCG which potentiated twitch also potentiated low frequency tetani (5–30 Hz for soleus, 10–50 Hz for FHL), had little effect on intermediate frequency tetani (40–60 Hz and 80–100 Hz respectively), and depressed high frequency tetani (80 Hz and above and 150 Hz and above respectively). Tension at the higher frequencies was not maintained after PMCG. Doses sufficient to block twitch also reduced or abolished tetanic responses at all frequencies. Essentially similar results were obtained with the rat diaphragm.

It is concluded that, in low doses, PMCG potentiates contraction of skeletal muscle by an action mainly on the muscle membrane and not via the neuromuscular junction and that higher doses depress twitches (and tetani) by a similar action and probably partly by a curare-like action, similar to that of atropine (Bulbring, 1946).

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Observations on the neuromuscular blocking action of 2-(4-phenylpiperidino)-cyclohexanol (AH 5183)

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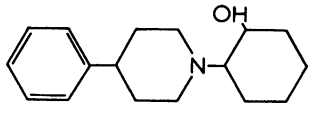
Oral administration of 2-(4-phenylpiperidino)-cyclohexanol (AH 5183), 10–20 mg/kg to mice, caused paralysis and death from respiratory arrest. As these effects resembled those seen after intravenous injection of neuromuscular blocking agents the effects induced by AH 5183 could have been mediated through similar mechanisms. This would be a novel property in a simple piperidine tertiary base.



AH 5183

In cats anaesthetized with chloralose maximal twitches of the tibialis anterior muscles were elicited by stimulation of sciatic nerves. In most experiments the contractions of both muscles were recorded simultaneously, one being excited once every second the other once every 10 sec. The neuromuscular block induced by AH 5183 varied with the frequency of stimulation; for example, AH 5183 (0·1 mg/kg intravenously) inhibited the twitches of the more rapidly stimulated muscle by 78%