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A *p*-terphenyl hemicholinium compound

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Hemicholinium No. 3 (HC3) is a derivative of diphenyl (Long & Schueler, 1954; Schueler, 1955), with high but somewhat variable toxicity. Death in small animals follows respiratory paralysis of delayed onset; this is usually explained as being the result of the inhibition of acetylcholine synthesis. There is evidence that HC3 can affect choline metabolism in other ways and has some actions which occur immediately after its administration (Gardiner, 1961; Domer & Gardiner, 1968). It is uncertain whether these other actions are involved in the lethal intoxication, so we are studying analogues of HC3 in which the balance between the various actions might be different. This communication reports some experiments with the *p*-terphenyl analogue (TPHC3) of HC3.

The LD50 following intraperitoneal injection into mice was 95 μg/kg for HC3 and 80 μg/kg for TPHC3. These values were determined simultaneously with groups of mice from common stock; on other occasions the values varied between 150 and 50 μg/kg for either substance.

Both HC3 (10^{-4}M) and TPHC3 (10^{-4}M) strongly inhibited the synthesis of acetylcholine by guinea-pig brain mince and with either the inhibition was less if choline (10^{-4}M) was present.

Inhibitory effects were produced by both substances on the responses of isolated tissues involving acetylcholine. The toad isolated rectus abdominis and the guinea-pig isolated ileum were immediately and reversibly depressed by concentrations greater than 10^{-6}M; the spontaneous activity of rabbit jejunum was more resistant, being affected when the concentration of HC3 or TPHC3 was raised to 10^{-4}M.

Either substance (0·5 mg/kg intravenously) in chicks produced an immediate curare-like paralysis of the legs and wings which was antagonized by choline (80–100 mg/kg). In the rat the effects on neuromuscular transmission were studied by recording the contractions of both gastrocnemius muscles in response to the stimulation of the sciatic nerves. The nerves were regularly stimulated every 5–10 sec for 0·2

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%).