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ACTION OF DECAMETHONIUM IODIDE (C 10) ON THE DEMARCATION POTENTIAL OF CAT'S MUSCLE.

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It has been observed [PATON & ZAIMIS, 1949] that decamethonium iodide (α : ω-bistrimethylammonium decane diiodide : also called C_{10}) causes neuromuscular block, but that its properties differ in several important respects from those of *d*-tubocurarine chloride. Thus, C_{10} elicits a contracture of frog's rectus ; its paralysing action is antagonized by its pentane homologue (C_5), but not by antiesterases; and the previous administration of *d*-tubocurarine chloride also reduces its action. Consideration of these properties suggested that C_{10} might act differently from *d*-tubucurarine chloride and that this might involve a depolarizing activity.

This communication presents the results of experiments studying the action of C_{10} and other drugs on the resting potential of mammalian muscle. In cats anaesthetized with chloralose, demarcation potential (DP) was recorded from the tibialis muscle [BROWN & GOFFART, 1949]; the muscle was prepared for close arterial injection and was burned at the distal end; in some experiments, twitch tension in response to maximal nerve shocks was recorded simultaneously.

It was observed that the intraarterial injection of 2μg. of C_{10} produced a fall of 30 to 50 p. 100 of the recorded demarcation potential, proceeding rapidly for 10-15 seconds, then slowly for 5-10 minutes, with recovery in 20-30 minutes roughly parallel to the neuromuscular paralysis. Similar falls followed 30-40 μg./kg. intravenously. No dose, however big, caused a depression exceeding 60 p. 100 of the demarcation potential. Small doses (0.2-0.5 μg. intraarterially) which caused only potentiation of the muscle twitch, elicited also a small but definite fall in DP.

Because C_{10} has a distinct anticholinesterase action, we have tested t effect of eserine and prostigmine on the DP. These two substances, in do producing a large increase of the twitch tension and causing strong fasci lations, did not depress the demarcation potential significantly.

We have also compared the action of potassium chloride by this techniq with that of C_{10}. At least 1 to 2 mg. KCl intraarterially were necessary produce a decrease of DP comparable to that caused by 2 μg. C_{10}.

Pentamethonium iodide (C_5) by itself did not alter the DP, even in la doses. It had, however, a weak antagonistic effect on the action of C_{10}; given first it will diminish (but not prevent) the fall of DP caused by C and if given during such a fall, it moderated it slightly. But these effe require big doses, and are small in magnitude compared with the effect such doses on the neuromuscular block due to C_{10}.

D-tubocurarine chloride, in paralysing doses, induced occasionally a sm increase (not more than 5 p. 100) in the DP, but often did not affect and never reduced it. On the other hand, in doses of 20-200 μg. int arterially, it prevented the depolarizing action of C_{10}; and, if injected dur a fall of DP due to C_{10}, could reverse this fall and accelerate recove Its actions therefore resemble those of C_5, but it is considerably more ef tive.

The localization of the depolarization which we have observed in tibi was studied on the cat's gracilis, which offers a simple muscle preparat with localized end-plate regions and a nerve-free distal extremity [Brc and Burns, 1949]. We observed that, in the uninjured muscle, after injection of C_{10} a potential difference appeared between the end-plate reg and the neighbouring parts of the muscle, the end-plates becoming relati negative. We have found, further, that in the presence of this depolariza of the end-plate region, the muscle fibre stimulated directly gave rise to action potential propagated as far as the end-plate region, but that the ac potential did not pass this point. After a dose of *d*-tubocurarine chlo producing an equally profound neuromuscular block, conduction along muscle fibre was unaltered.

These experiments will be published in full elsewehre.

CONCLUSIONS.

C_{10} presents a definite and typical depolarizing action on skeletal mu which is localized to the end-plate regions. The fact that this depolariza prevents propagation of the action potential along the muscle fibre sug that it is also responsible for the neuromuscular block caused by C_{10}. the other hand, the lack of parallelism between the antagonisms of C_5 to on neuromuscular block and on demarcation potential indicates that relation between the block and the depolarization is not a simple one.

REFERENCES.

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DISCUSSION.

Beccari. — The very interesting researches of Drs. Burns, Paton and Vianna Dias on the depolarizing action of $[C_{10}]$ upon the neuromuscular regions, claim our attention to the chemical behaviour of the quaternary ammonium iodides. Containing nitrogen in the excited state $s_2 p_3$, such compounds are highly reactive and may play a part not only in respiratory processes involving pyridinic enzymes, but also in transmethylation equilibria, redox equilibria, and, if nitrogen passes into the non excited state $s\, p_3$, they become soluble in lipoids producing a change in the partition coefficient at the interfaces. These considerations may furnish a possible explanation of the puzzling gauntlet of antagonisms observed between $[C_{10}]$ and $[C_5]$, curare and $[C_{10}]$, curare and acetylcholine, etc., upon different effectors, though the depolarizing action of such agents with respect to the membranes might appear to be the same.

Therefore it would be of interest to see if molecules of very low chemical reactivity, or non reacting at all with the living matter, would be able to act upon the membrane polarization in the synaptic junctions. We have found two series of metal complexes with α-α'-dipyridil and with orthophenanthroline, of the coordinative form $[Me(C_{10}H_8N_2)_3]^{++}$ and $[Me(C_{12}H_8N_2)_3]^{++}$, which seem to satisfy these conditions. The iron compounds have been used for a basal series of experiments.

On the synaptic activity of the spinal cord they demonstrate excitatory effects akin to those produced by drugs which are considered to increase depolarization (strychnine, curarine, eserine) : the dorsal and ventral root potentials are enhanced, summation may occur and long lasting spike discharges up to continuous activity have been observed. On the contrary, the neuromuscular transmission is completely blocked : all the features described for the end plate potentials in curarized muscles have been found with the iron complexes; however the time during which the « supernormal effect » due to a second nerve volley may be obtained, exceeds largely, up to 20-30 folds, the « supernormal period » of curare at 20 C. room temperature. Nerve fibres, even after soaking 48 hours in N/100 solutions, are still able to conduct impulses; it seems therefore that only the synaptic membranes are particularly accessible to the compounds mentioned.

Keeping in mind that neither the metal nor the complexogenic bases no longer be detected by their specific reagents, and that the compl injected into frogs and mammals, are eliminated unchanged by the kid one must conclude that they do not react at all with the living matter that if changes of polarization occur at synapses, they are probably purely physical kind.

A more detailed investigation of such action, especially by means of mi techniques upon isolated axons or nerve-muscle effectors, could pro valuable information upon the mecanisms involved in depolarization, the above complexes might perhaps become a better tool for the physiolo than for the pharmacologist, by clearing up the processes of synaptic tr mission.

KUFFLER. — The recent new techniques developed by the Hamps group have already been very fruitful in making possible experiments mammals which could previously be performed on isolated preparat only. Their work on C_{10} and C_5 compounds has, amongst others, a shown the specificity of the neuromuscular junctions.