EFFECTS OF A FEW QUATERNARY AMMONIUM COMPOUNDS ON THE CARDIO-VASCULAR RESPONSES OF ACETYL CHOLINE IN DOG.

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Decisive evidence for acetyl-choline as a chemical transmitter has accumulated during the last 20 years. Chemically acetyl-choline is a quaternary ammonium compound and it is but natural to expect that substances analogous to this chemical grouping would have actions of preserving, mimicking or antagonising the natural chemical transmitter at the receptors sensitive to it. This is found to be correct and as a consequence thereof, a host of quarternary ammonium compounds have been prepared and tested. These compounds have been found varied in their actions. Decamethonium, d-tubocurarine etc. resemble acetyl-choline very closely at the neuromuscular junctions. On the contrary, Tetraethyl ammonium chloride, Hexamethonium and others antagonise it specifically at the ganglionic synapses.

In view of the varied nature of these drugs viz., augmenting or blocking the actions of acetyl-choline at different sites, their inter-relationship with this physiological transmitter appears to be very interesting. An active acetyl-choline like but not an effective anti-esterase action of Decamethonium on the denervated cat muscle has been reported by Paton and Zaimis (1949). A weak atropine-like action of Tetra-ethyl ammonium chloride has been claimed by Kulz and Arch (1922) which was subsequently denied by Hunt and Ranshaw (1925), Acheson and Moe (1946). Thus the issue has remained unsettled. Hexamethonium has been claimed to antagonise the stimulant effects of acetyl-choline and the like drugs in the experiments conducted on the isolated skin preparations where peripheral synapses, however, do not exit (Douglas and Gray 1953). The problem has not been amply explored and substantiated with experimental evidence and needs further elucidation.

In the light of the above contradictory observations, and in view of evaluating the antagonistic effects of Hexamethonium and Tetraethyl ammonium chloride further, the present study was made on the cardio-vascular system which is the principally effected system and at the same time contains ganglionic synapses. The experiments were conducted on dogs as similar work on this species of animal had not been published so far.
MATERIAL AND METHODS

Dogs of either sex weighing about 2.5 Kg were used. Anaesthesia was induced with ether and the animal was secured on the operation table. Femoral vein was cannulated and sodium barbitone 225 mg/Kg in 10% solution was injected in the vein to maintain the anaesthesia. Blood pressure was recorded from the carotid artery. For recording myocardial contractions, chest was opened and artificial respiration was started. The heart was exposed and the pericardium was divided in the middle by a vertical incision and the two edges were stitched on either side of the chest wall so as to make a pericardial bed. Curved pins were fastened in the auricular and ventricular muscles separately and were connected to the heart levers directly by thread. Tracings of auricles and ventricles were taken separately on the slowly moving kymograph. Care was taken to keep the heart moist. All the drugs were given through the cannulated femoral vein.

The following substances were used:

Decamethonium iodide (C10)-80 vg/Kg Tetra-ethyl ammonium chloride (TEAC) 8 mg/kg Hexamethonium bromide (C6) 4 mg/kg and acetylcholine in three different doses of 40,100 and 200 vg/Kg administered before and after the test drugs in each animal. Due care was taken to repeat the doses of A. ch after the test drugs only when the blood pressure and the myocardial contractions attain the original level. This time interval was varying with the individual drugs studied viz., about 10-15 min. with TEAC, 20-30 min. with C6 and negligible with C10. The effects on the vasodepressor

Fig. 1.
responses were tabulated. The mean difference in the responses of different doses of acetyl-choline on B.P. after the test drugs were calculated and then worked out on percentage basis as shown in the table.

Fig. 2.

RESULTS

C 10:—An increase in the response of A. ch by about 12.5% on the blood pressure of anaesthetised dogs was observed as shown in the table. (Fig. 1) Similar response was obtained on the myocardial contractions. (Fig. 2)
ACETYL CHOLINE IN DOGS.

TEAC:—A decrease in the response of A. ch by about 10% on the blood pressure was observed (Fig. 3). Similar effects on the myocardial contractions were also noted. (Fig. 4).

C 6:—A considerable decrease about 22.5-25% in the vasodepressor response of A. ch on the B.P. was observed as shown in the table and fig. 5. A likewise effect on the myocardial contractions was also recorded. (Fig. 6).

Table showing the effect of C 10,-TEAC and C 6 on the Vasodepressor response of acetyl choline.

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug of mean fall with animals of B.P. with doses used.</th>
<th>Ac. ch doses in micrograms in A. ch per Kg. before drug</th>
<th>B. P. with A. ch after drug + increase</th>
<th>m.m. Hg. animal m.m. Hg. mean fall in B. P. with A. ch after drug difference</th>
<th>mean % increase or decrease in response.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 10</td>
<td>80 vg</td>
<td>4 17.0 100 19.2 +2.2 13%</td>
<td>4 24 250 26.9 +2.9 12.5%</td>
<td>4 29.1 500 32.5 +3.4 12.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 18 100 16.3 -1.7 9.8%</td>
<td>4 25 250 22.5 -2.5 10%</td>
<td>4 30 500 27.1 -2.9 10%</td>
<td></td>
</tr>
<tr>
<td>TEAC</td>
<td>8 mg</td>
<td>4 24 100 17.4 -6.6 22.5%</td>
<td>5 26.6 250 17.8 -6.8 25.5%</td>
<td>5 30 500 22.5 -7.5 25%</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

The evidence shows that C10 potentiates the actions of A. ch on the blood pressure and the myocardial contractions of anaesthetised dogs. Barlow and Ing (1948) observed that bis-onium salts of the series of bis-trimethyl ammonium, increase the size of the contractions of the rat diaphragm to maximal stimuli. A very weak anti-cholinesterase action of the drug has been reported in vitro experiments by Paton & Zaimis (1949). Its activity is mostly limited to the 'true' enzyme and has been found to be 200 times more
potent than the 'pseudo' variety. This potentiation in the response of A. ch could be attributed to the anti-cholinesterase action of the drug, but for its action of low magnitude. The anti-cholinesterase activity of the drug, however, has been worked out in the vitro experiments. The possibility, therefore, stands to reason that anti-cholinesterase action of the drug becomes more manifest in the intact animal because of its lack of affinity for the 'pseudo'

![Fig. 4.](image)

cholinesterase in plasma. Additional evidence is provided from the observation of Paton and Zaimis (1949) regarding the potentiation of the twich during the early stages of the block produced by the drug, which is similar to that well established for eserine and DFP.

The evidence shows that the response of the blood pressure and myocardial contractions of anaesthetised dogs to A. ch after the administration of TEAC and C6 decreased which is in contrast to that obtained with Cl0. There had been a decrease to the magnitude of about 25% with C6 but to a
much lesser extent (about 10%) with TEAC. Slight decrease in the vasodepressor actions of ac. ch after C6 on the cat's blood pressure has been observed by Paton & Zaimis (1949). But in the experiments undertaken, the decrease in the response has been considerable to the magnitude of 25% on the blood pressure with a similar effect on the myocardial contractions. An atropine-like action of the drug has been denied but a little decrease in the depressor responses of carbamyl-choline has been described (Wein & Mason, 1951). Similar observations have been made by other workers. Douglas & Gray (1953) have noticed antagonism of C6 to the stimulant effects of ac. ch and

![Diagram](image)

**Fig. 5.**

the like drugs in the experiments conducted on the isolated skin preparations where no peripheral synapses exist. It is also established that C6 has no local anaesthetic actions and does not produce any disorders of sensations in man. These observations have led them (Douglas & Gray, 1953) to believe that C6 not only prevent the excitation of the ganglionic cells by A. ch released at the preganglionic nerve endings but also prevents such excitation of nervous tissue wherever it could be achieved. Observations made on the cardio-vascular system where ganglionic synapses also exit, amply substantiates their belief.

TEAC has also been found to decrease the cardio-vascular responses of ac. ch but to a lesser extent. A weak atropine-like action of the drug which could possibly explain this decrease in the response of A. ch has been claimed
and refuted by various workers (Kulz & Arch 1922, Hunt & Ranshaw 1925, Acheson & Moe 1946). From the experiments conducted, ample support is available to the findings of the earlier workers (Kulz & Arch, 1922). The atropine-like action of the drug may explain the decrease in the cardiovascular responses of ac. ch but the possibility of a direct depressant action of the drug like that of C6 on the nervous tissue can not be ruled out. The depression of the central nervous system in the albino rats observed while working out the toxicity of the drug speaks in favour of it.

**SUMMARY**

1. Members of the quaternary ammonium group alter the cardio-vascular responses of A. ch in anaesthetised dogs.
2. C10 increase the cardio-vascular responses of A. ch possibly due to a weak anti-cholinesterase action.

3. TEAC and C6 decrease the cardio-vascular responses A. ch possibly by rendering the effector cells less sensitive to the actions of A. ch.

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REFERENCES