TETRAHYDROAMINACRIN AS A DECURARISING AGENT

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Tetrahydroaminacrin has marked anticholinesterase activity. It is a mild antagonist of tubocurarine, and this may be shown on the rat phrenic nerve diaphragm preparation. This antagonism is more marked in rats and dogs. Other pharmacological properties are described. THA has been used successfully to decurarise patients who have received tubocurarine or gallamine. Usually the administration of atropine is not necessary and recurarisation does not occur.

TETRAHYDROAMINACRIN (THA) was synthesised by Albert and others[1] and shown by Rubbo and others[2] to have no bacteriostatic properties. Later Shaw and Bentley[3] showed that the compound was a moderate antagonist of morphine but from experiments in the dog appeared to be too convulsant for use in man. These authors[4] also showed that smooth muscle was slightly contracted by THA and that it produced spontaneous contractions in the uterus of the guinea pig. On the intestinal musculature of rat or guinea pig, THA induced a 10 fold potentiation of the action of acetylcholine. Paradoxically, the drug, which itself has little action on the frog heart, abolishes the action of acetylcholine at that site. Thus, on one tissue, the intestine, it displays eserine-like activity and on another, the heart, it has atropine-like properties. Shaw and Bentley[4] also showed that THA was almost as powerful an anticholinesterase as eserine or neostigmine; it produced a 50 per cent inhibition of the hydrolysis of acetylcholine with a concentration of 10^{-7}M. This latter fact suggested that THA might act as a decurarising agent. With this purpose in mind a more complete investigation was undertaken.

METHODS

Toxicity. The general effect and LD50 were observed on rats, mice, dogs and rabbits. The drugs were injected intramuscularly.

Circulatory system. The effect on blood pressure and heart rate was observed on cats anaesthetised with pentobarbitone.

Antihistaminic activity. This was observed on the guinea pig intestine, which was bathed in Tyrode's solution.

Anticurare action. (*a*) Rat phrenic nerve diaphragm preparation (Bulbring)[5], (*b*) intact dog and cat. For details see later.

RESULTS

Toxicity

When THA is injected into rats and mice there is little effect other than some salivation until lethal doses are reached. At this stage the animal exhibits tremors, passes into clonic convulsions, which are not asphyxial and dies within a few minutes. The LD50 for mice is 33 mg./kg. with limits of 31 and 35 mg./kg.

Circulatory System

Doses up to 10 mg./kg. have little effect on the heart rate or blood pressure, a rise in pressure of up to 10 mm. Hg being recorded in some cases and a fall of similar magnitude in others. Robinson and McCaul (unpublished) found that in man the ECG was unaffected by THA, but in some cases it showed mild bradycardia presumably of vagal origin.

Antihistaminic Activity

THA has slight antihistaminic activity. A concentration of 10^{-3}M will prevent the action of histamine on the guinea pig ileum. The effect is, however, abolished in a few minutes when the drug is washed out.

Anticurare Action

(*a*) *Rat phrenic nerve-diaphragm preparation.* Figure 1 shows the moderate anticurare effect of THA at a dilution of 10^{-7}M. When the THA is added to the bath before the curare, the effects are variable. If the THA concentration is too high the preparation is damaged. On two occasions, however, the curare has had no effect in its presence at 10^{-7} and the contractions remained constant.

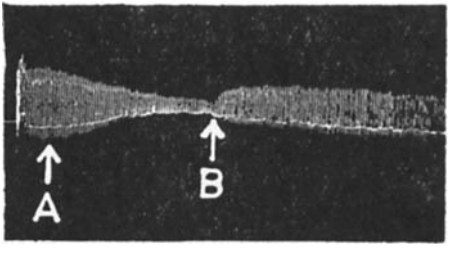

FIG. 1. The anticurare effect of THA. A. Tubocurarine 2×10^{-6}M. B. THA 10^{-7}M. Between A and B, 11 minutes. The preparation was stimulated once every ten seconds.

(*b*) *Intact animal.* (i) *Rat.* THA was given i.m. to 28 rats in doses from 5 to 40 mg./kg. Salivation occurred in 86 per cent of the animals. As the dose was increased the incidence of muscular tremors increased and a dose of 40 mg./kg. represented an LD100. Tubocurarine was given to 14 animals. It was found that 0·5 mg./kg. always produced death by respiratory paralysis.

Both drugs were given simultaneously to 17 animals to observe the antagonistic effect of THA against tubocurarine. The latter was given at a dose which always produced paralysis, viz., 0·5 mg./kg. It will be seen from Table I that about half the animals survived.

(ii) *Dog.* The dose of tubocurarine to produce muscular paralysis regularly was found to be 0·15 mg./kg. The LD100 was 0·25 mg./kg. THA when given alone to dogs in doses up to 5 mg./kg. i.m. produced no marked alterations in the animals behaviour. When given intravenously, however, doses of 2·0 mg./kg. cause respiratory stimulation together with marked panting but minimal or an absence of tremors or convulsions. This dose range also produced a bowel action in about half the animals to which it was given. Salivation did not occur in any of these animals when either compound was given alone.

THA and tubocurarine. Both compounds were given to 23 dogs of both sexes to observe the antagonising effect of THA in a dose range from 1·5 to 4·5 mg./kg. i.v. Hyoscine was given (0·5 mg./kg. i.m.) in some cases

to prevent salivation which was found to occur when THA was given after tubocurarine. Throughout these trials, when THA was given alone to the animal, no salivation resulted but when given to a curarised animal profuse salivation always occurred.

Tubocurarine followed by THA. Two dogs were given 0·15 mg./kg. tubocurarine i.v. This dose produced muscular paralysis. THA, 2·5 mg./kg., was then given intravenously when the signs of paralysis first became evident. This produced a dramatic return to normal level of muscle tone and restoration of respiration. A similar favourable result

TABLE I

SIMULTANEOUS ADMINISTRATION (I.M.) OF THA WITH 0·5 MG./KG. TUBOCURARINE

No. of rats	Dose THA mg./kg.	Results (No. died)
5	5	2
6	10*	3
1	20	1
2	25	1
1	35	—
2	20*	2

* Doses marked thus were administered against 1 mg./kg. dosages of tubocurarine.

was obtained in another dog which was given 0·2 mg./kg. of tubocurarine and 4·5 mg./kg. of THA. In this instance respiratory failure supervened before THA was given. Six animals were given 0·25 mg./kg. tubocurarine (lethal dose). When muscle hypotonia and failure of respiration was established 2·5 mg./kg. THA was given i.v. Respiration was immediately restored to normal. There was also a general improvement in muscle tone although the animals were still unco-ordinated in their movements for a few minutes.

Tubocurarine together with THA. Three dogs were given tubocurarine (0·15 mg./kg.) and THA (2·5 mg./kg.) mixed in the same syringe (i.v.). These animals showed neither loss of muscle tone nor depression of respiration. Three dogs were given a lethal dose of tubocurarine (0·25 mg./kg.) together with THA (2·5 mg./kg. i.v.). A slight degree of muscular paralysis was produced and the respirations were entirely diaphragmatic, but the animals did not die.

DISCUSSION

Tetrahydroaminacrin is a member of a series of compounds shown by Shaw and others[3] to reverse the narcotic activity of morphine, particularly in dogs. When further investigation of its pharmacodynamics was undertaken it was found to be a particularly effective anticholinesterase. Itwas now natural to investigate its anticurariform activity.

Its anticurare action on the rat phrenic nerve-diaphragm preparation was moderate. The action was variable, especially if the THA were added before the curare when it did prevent the action of curare on two occasions. However, it prevented curarisation in rats and dogs when the mixed drugs were administered simultaneously. Dogs with muscular and respiratory paralysis brought about by an injection of tubocurarine

were restored to almost normalcy by the intravenous administration of THA, provided respiratory paralysis had not proceeded too far.

In animals THA produces little salivation. Paradoxically salivation is sometimes seen in the curarised animal. This is not noted with therapeutic doses of THA and curare in man.

In animals death due to THA is accompanied by convulsions. Despite considerable use in clinical anaesthesia Robinson and McCaul (unpublished) have not noted convulsions in man.

Apart from its action on the central nervous system THA has little effect on other systems. The antihistaminic activity is weak. It has little effect on the heart or blood pressure.

Its decurarising action has been confirmed clinically by Robinson and McCaul (unpublished) who found that THA affected decurarisation of 200 patients who had received tubocurarine or gallamine. Unless large doses of THA were employed the patients were not atropinised. Recurarisation did not occur.

THA is also a mild non-specific respiratory stimulant. In many cases of respiratory failure occurring during operations on animals, breathing has been restarted by an intravenous injection of 5 to 10 mg./kg. This stimulant action has been confirmed clinically by Robinson and McCaul and by ourselves, the full details of which will be published later.

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