

STUDY OF THE EFFECTS OF TRANQUILLIZERS ON THE ACETYLCHOLINE, 5 HYDROXYTRYPTAMINE, ADRENALINE AND NOR-ADRENALINE RESPONSES OF THE CARDIAC, SMOOTH AND SKELETAL MUSCLE¹

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Meprobamate and reserpine potentiate while chlorpromazine blocks the acetylcholine response of the skeletal muscle. Meprobamate, reserpine and chlorpromazine block the action of acetylcholine and 5 HT on the intestinal and heart muscles. Phenobarbitone in large doses blocks the intestinal response and potentiates the cardiac response of 5 HT. The actions of adrenaline and nor-adrenaline were not influenced by these drugs.

Attempts have been made by various workers to differentiate some of the centrally acting drugs by showing a specificity of action against acetylcholine and 5-hydroxytryptamine (5HT) responses of the peripheral excitable tissues. Costa (1956), showed a difference in tranquilizers and hallucinogens on 5HT responses of rat uterus. Schaumann et al. (1952) and Medakovic (1958) showed a parallelism between the analgesic potency of morphine and related compounds to their anti-acetylcholine and anti-5HT activity on guineapig ileum. Quilliam (1955) has classified barbiturate and nonbarbiturate groups of hypnotics by showing a difference in the acetylcholine responses of skeletal muscle.

The present study was undertaken with a view to find out if chemically different tranquillizers possess any difference on acetylcholine, 5HT, adrenaline and nor-adrenaline (local hormones) responses of the peripheral excitable tissues and if, such a study could further add to our knowledge about the mechanism of action and assessment of these drugs.

METHODS

The drugs used in the present study were phenobarbitone sodium, meprobamate, chlorpromazine hydrochloride and reserpine. One per cent solution of phenobarbitone sodium and meprobamate was made in distilled water and propyleneglycol respectively. Chlorpromazine and reserpine were obtained as injectable solutions in the ampules from the local market.

The frog rectus muscle preparation was made by the method as described by Burn (1952). Submaximal concentrations of acetylcholine (2.5×10^{-7} to 5×10^{-7})

1. This paper was presented at the Annual Conference of Association of Physiologists and Pharmacologists of India, held at Jaipur, in December, 1963.

were allowed a contact of 2 minutes and the contractions recorded. Drugs were added and allowed to act for 5 minutes and the same doses of acetylcholine repeated. Experiments were repeated in eserinised (10^{-6}) frog ringer solution.

Isolated rabbit and guinea pig intestines were put up as per usual techniques. Submaximal concentrations of acetylcholine (2.5×10^{-7} to 5×10^{-7}), 5HT (5×10^{-8} to 2.5×10^{-7}) and adrenaline (1×10^{-7} to 2.5×10^{-7}) were allowed a contact for 90 sec. and the responses were recorded. Drugs were added and allowed a contact of 5 min. before repeating the same doses of these local hormones.

Isolated frog heart was perfused through a venous cannula put in the sinus venosus and suitable doses of acetylcholine (0.5–1.0 ug.), 5HT (80–100 ug.), adrenaline (0.5–1.0 ug.) and noradrenaline (0.5–1.0 ug.) were injected through an indwelling polyethylene tube inserted 2.5 cm. above the cannula in the rubber tubing and the responses were recorded. The heart was then perfused with ringer solution containing the drug. The maximum effect of the drug was seen in 5 min., when the effects of the same doses of local hormones were again studied.

RESULTS

Phenobarbitone even in concentration of 2×10^{-5} was not found to possess any significant effect on the acetylcholine response of frog rectus muscle. Meprobamate (1×10^{-4}) and reserpine (1×10^{-8}) were found to potentiate while chlorpromazine (1×10^{-8}) to block the acetylcholine response of frog rectus muscle (Fig. 1).

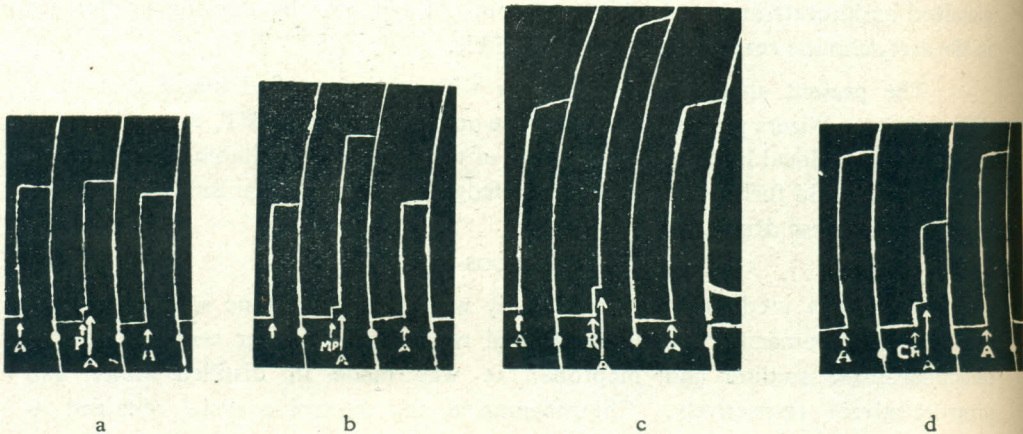


Fig. 1. Effect of (a) P—phenobarbitone sodium 2×10^{-5} , (b) M—meprobamate 1×10^{-4} , (c) R—reserpine 1×10^{-8} and (d) Ch—chlorpromazine hydrochloride 1×10^{-8} on acetylcholine response of frog rectus. All contractions are due to 5×10^{-7} of A—acetylcholine, Dot indicates wash,

Potentiation of acetylcholine response by meprobamate and reserpine was also seen in eserinised ringer.

5 HT, adrenaline and noradrenaline even in concentrations upto 2×10^{-3} were not found to produce any action on the rectus muscle.

All the drugs under present study were found to block the 5HT response of the guinea pig intestine (Fig. 2).

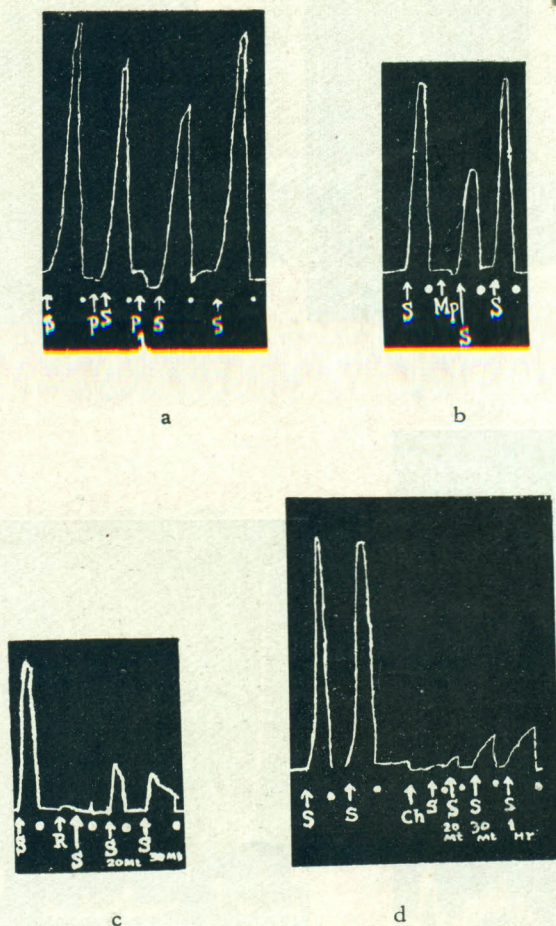


Fig. 2. Effect of (a) P—phenobarbitone sodium 1×10^{-5} , P₁—phenobarbitone sodium 2×10^{-5} , (b) meprobamate 1×10^{-4} , (c) reserpine 1×10^{-8} and (d) chlorpromazine hydrochloride 1×10^{-8} on 5HT response of guinea pig ileum. All contractions are due to 5×10^{-8} of S-5 HT. Dot indicates wash.

The acetylcholine induced contraction of rabbit ileum was antagonised by meprobamate, reserpine and chlorpromazine but, not modified by phenobarbitone (Fig. 3).

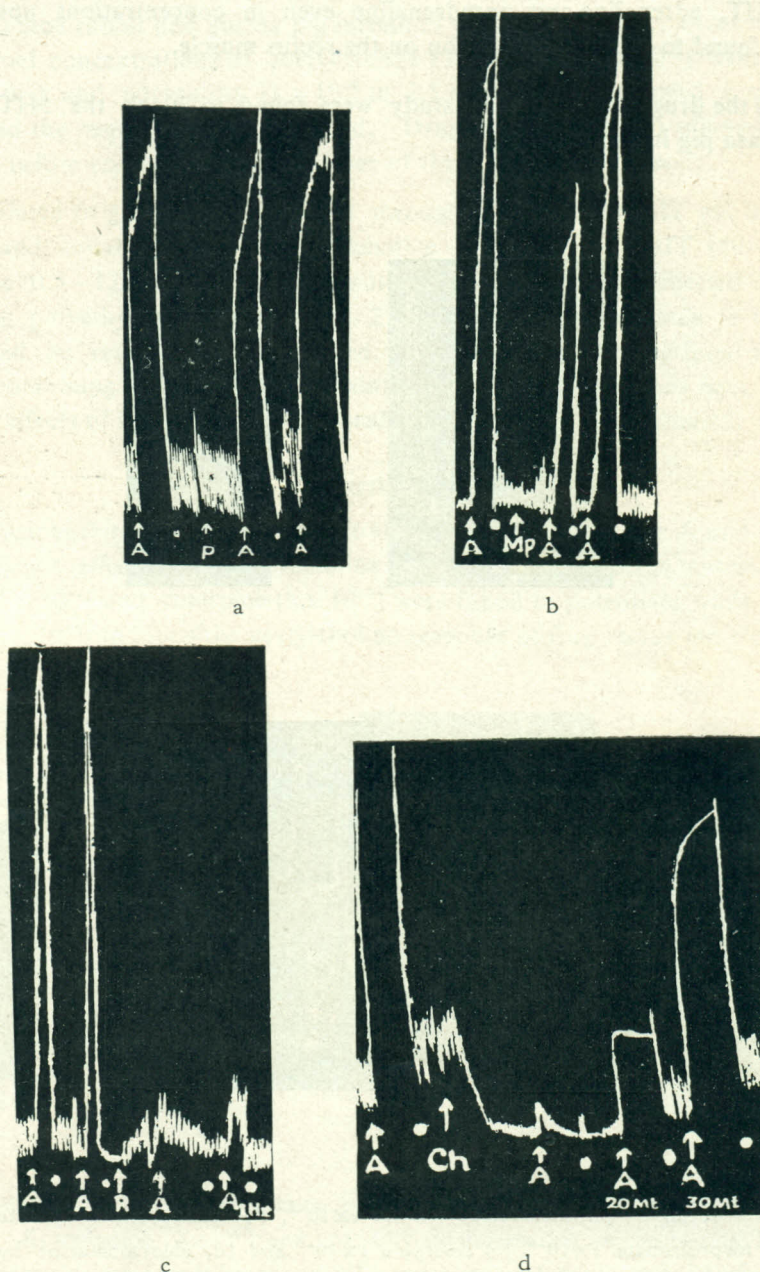


Fig. 3. Effect of (a) phenobarbitone sodium 2×10^{-5} , (b) meprobamate 1×10^{-4} , (c) reserpine 1×10^{-8} and (d) chlorpromazine hydrochloride 1×10^{-8} on acetylcholine response of rabbit ileum. All contractions are due to 2.5×10^{-7} of acetylcholine. Dot indicates wash.

Reserpine (1×10^{-8}) and chlorpromazine (1×10^{-8}) were found to possess more potent anti-5 HT and antiacetylcholine actions and also delay the recovery of the normal responses of 5 HT and acetylcholine (Fig. 2 and 3).

The action of acetylcholine on the frog heart was blocked by all the drugs (Fig. 4).

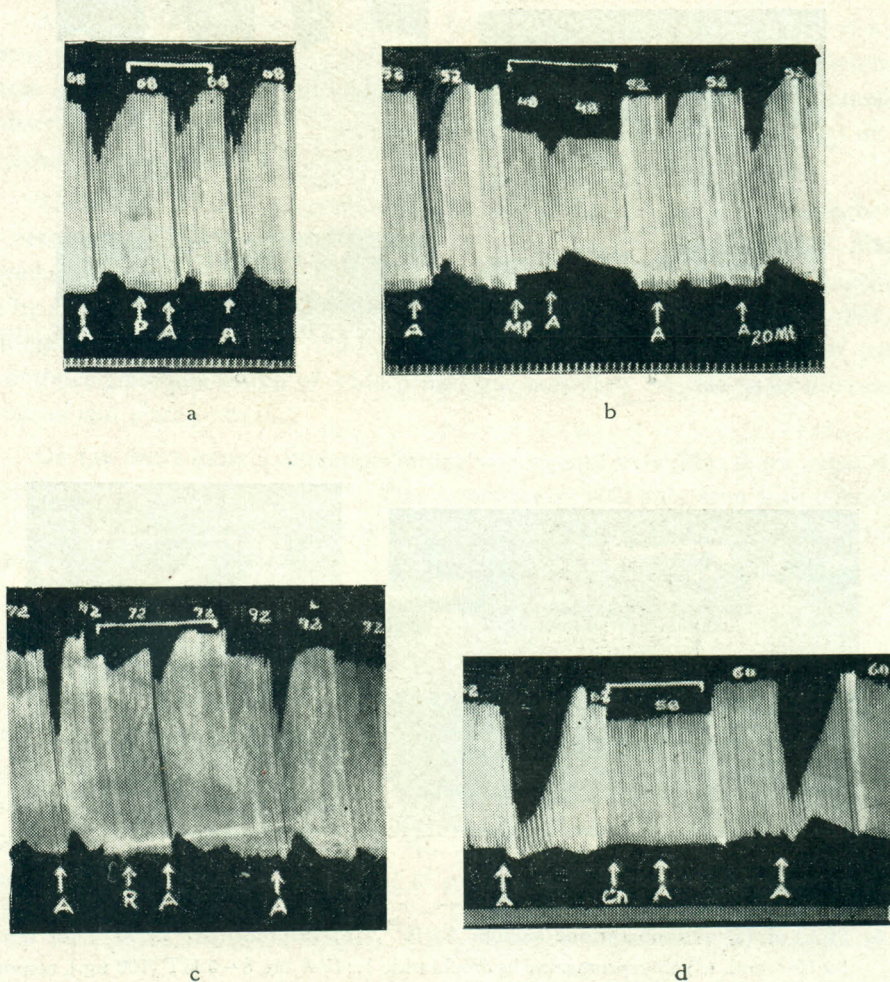


Fig. 4. Effect of (a) phenobarbitone sodium 2×10^{-5} (b) meprobamate 1×10^{-4} (c) reserpine 1×10^{-8} and (d) chlorpromazine hydrochloride 1×10^{-8} on acetylcholine (0.5 ug.), response of heart muscle; Bracket indicates the perfusion with the drug. Heart rate per minute is indicated above the tracings. Time interval=3 seconds.

✓ Meprobamate, reserpine and chlorpromazine were found to block the action of 5 HT on the frog heart while phenobarbitone in large doses (2×10^{-5}) potentiated 5 HT response of frog heart (Fig. 5).

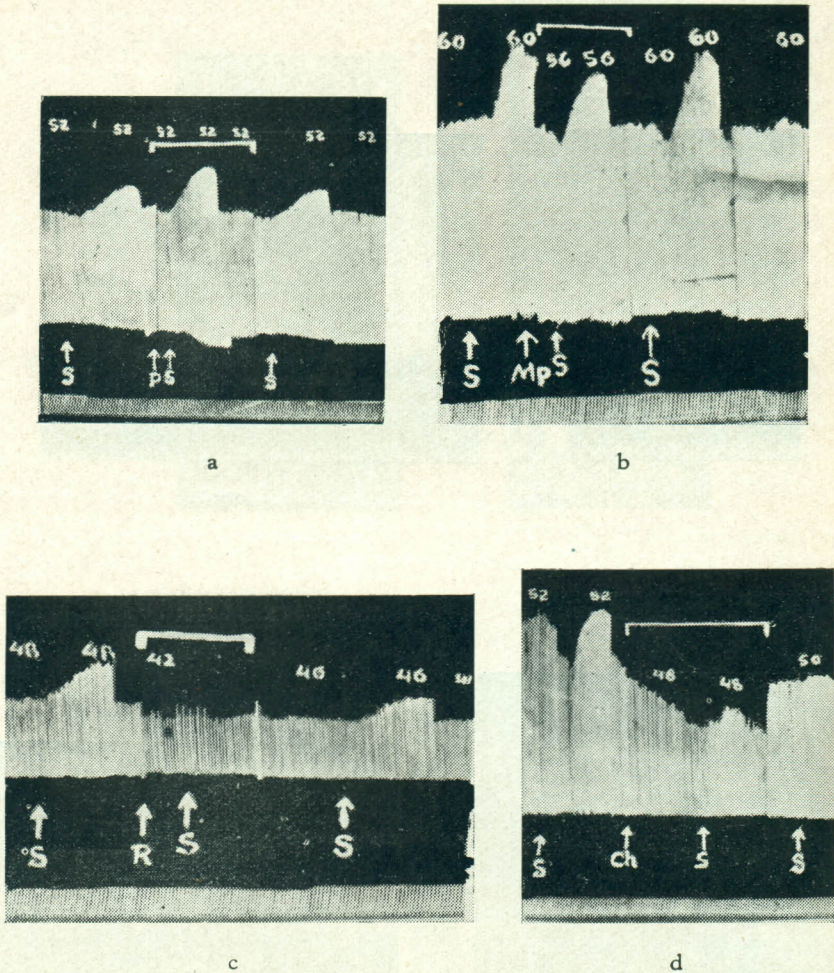


Fig. 5. Effect of (a) phenobarbitone sodium 2×10^{-5} , (b) meprobamate 1×10^{-4} , (c) reserpine 1×10^{-8} and (d) chlorpromazine hydrochloride 1×10^{-8} on S-5 HT (100 ug.), response of heart muscle; Bracket indicates the perfusion with the drug. Heart rate per minute is indicated above the tracings. Time interval=3 seconds.

The action of adrenaline on the intestinal muscle and that of adrenaline and noradrenaline on the heart muscle was not modified in presence of the drugs under present study.

DISCUSSION

At the moment, the present study does not substantially add to our knowledge about the mode of action of the drugs employed. The anti-acetylcholine and anti-5 HT actions of the drugs, under present study, may be due to a direct action on the receptors. The interesting findings, however, are a differential behaviour of these drugs on acetylcholine response of the rectus muscle and 5 HT response of the heart muscle.

Meprobamate and reserpine have been found to increase the acetylcholine content while chlorpromazine to cause an insignificant decrease in the acetylcholine content of rat brain (Agarwal and Bhargava, unpublished data). It is interesting to observe similar differences in the action of these tranquillizing drugs on the acetylcholine response of frog rectus muscle.

The potentiation of acetylcholine response on the frog rectus by meprobamate and reserpine may be due to a direct sensitization of the motor end plate to acetylcholine, since these drugs do not possess any anti-cholinesterase activity as seen by experiments in presence of eserinated ringer. Burn (1954) and Kopra and Armitage (1954), have found chlorpromazine to potentiate the action of curare. The anti-acetylcholine action of chlorpromazine may thus be due to its diminishing the size of end plate potential.

On the heart muscle, phenobarbitone was found to differ from other drugs in potentiating the action of 5 HT. This potentiation was only seen with concentration of 2×10^{-5} of phenobarbitone which, if calculated on weight basis for human beings, would result in hypnosis.

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