

## CHAPTER III

### RESULTS

#### 1. Effects of 5-HT on isolated rat atria

##### 1.1 Positive chronotropic effect.

Contractile responses of the right atria when exposed to different concentration of 5-HT (0.20 µg/ml to 7.75 µg/ml) were measured in Locke solution for a period of 15 min after addition of each concentration of 5-HT to the bathing fluid. As shown in Fig.1, 5-HT caused a concentration-dependent increase of the spontaneous rate. Doses of 0.2 µg/ml and 0.8 µg/ml produced a slight increased. Some experiments have been studied at high dose 7.75 µg/ml which also produced a dose dependent. The time to maximum peak effects were relatively to the doses (see Fig.1), but they showed a prolonged chronotropic effects more than 15 min. In Fig.1, collection of the effects of a dose 2.00 µg/ml have been demonstrated. In this study a dose of 2.00 µg/ml was used to investigated for the mechanism of 5-HT antagonists. The positive chronotropics effects at this dose was about 10% increase from normal rate. The average normal right atrial rate collected in this study from 75 rats was  $266.4 \pm 22.3$  beats/min. No cardiac arrhythmias was observed in all experiments.

## 1.2 Positive inotropic effect

The inotropic effect of 5-HT on a constant left atrial force have been investigated. As shown in Fig.2, 5-HT produced dose-dependent increased in contractile force. The peaks to maximum effect were about 3 min after addition of drug which faster than those observed on the right atrial rate (about 5-10 min depend on doses). As shown in Fig.2, higher doses produced faster decline after peak-effects. No cardiac arrhythmias was observed in all experiments.

## 2. Antagonism of 5-HT effects on right atrial rate and left atrial isometric tension by 5-HT antagonists.

### 2.1 Antagonism of 5-HT effect on right atrial rate and left atrial contractile force by one 5-HT antagonist.

Cyproheptadine 0.02  $\mu\text{g/ml}$  caused slight reduction on right atrial rate and left atrial isometric tension. As shown in Fig.3, a small reduction occurred 1 min after addition of cyproheptadine and then sustained at that level for a period of more than 15 min. In Fig.4, there was no change in left atrial force of contraction during 3 min after administration and then a small gradually reduction was observed which differed from the right atrial rate.

Prior administration of cyproheptadine 0.02  $\mu\text{g/ml}$  (5 min before addition of 5-HT) could reduce the positive chronotropic effects of 5-HT about 50% at each period (Fig.3), but not statistically significant ( $P > 0.05$ ). As shown in Fig.4 prior administration of cyproheptadine 0.02  $\mu\text{g/ml}$  (5 min before addition of



5-HT) could significantly ( $P < 0.05$ ) reduce the positive inotropic effect of 5-HT which differed from those observed on the right atrial rate.

Methysergide 0.47  $\mu\text{g/ml}$  caused slight reduction (2-3% from control) on both right atrial rate (see Fig.5) and left atrial force of contraction (see Fig.6). The pattern of a reduction were similar to those produced by cyproheptadine.

In Fig.5, prior administration of methysergide (5 min before 5-HT) could significantly ( $P < 0.05$ ) reduce the positive chronotropic effect of 5-HT at every periods except at 15 min ( $P > 0.05$ ). The percentage of these reduction was about 50% from the effect of 5-HT alone. Again, in Fig.6 prior administration of methysergide (5 min before 5-HT) could significantly reduce ( $P < 0.05$ ) the positive inotropic effect of 5-HT. At 15 min the average percentage change was only  $101.6 \pm 1.7$  but was not statistically significant ( $P > 0.05$ ). AS shown in Fig.5 and Fig.6, methysergide showed a greater reduction in the effect of 5-HT on left atrial force of contraction than on the right atrial rate.

### 3. Effects of a beta-blocking agent (propranolol) on positive chronotropic and inotropic actions of 5-HT

A dose of 0.15  $\mu\text{g/ml}$  of propranolol was selected to investigate in this study. It could abolish the positive chronotropic effect of norepinephrine (0.4  $\mu\text{g/ml}$ ) which produced chronotropic effect equal to 5-HT (2.0  $\mu\text{g/ml}$ ). As shown in Fig.7 and 8 propranolol 0.15  $\mu\text{g/ml}$  caused no significant reduction on both right atrial rate and left atrial force of contraction. Prior administration of propranolol (5 min before 5-HT) could reduce the



positive chronotropic effect of 5-HT on the right atrial rate (see Fig.7). The average percentage of reduction were about 50% but are not statistically significant at all periods ( $P > 0.05$ ). The peak maximum effects of 5-HT after administration of propranolol was about 1 min after administration which faster than the effects of 5-HT alone (about 3-5 min) and also differed from the effects after cyproheptadine (Fig.3) and methysergide (Fig.5).

The results observed in Fig.8 was clearly showed that propranolol 0.15  $\mu\text{g/ml}$  could not antagonize the positive inotropic effect of 5-HT on left atria.

#### 4. Effects of 5-HT antagonists and beta-blocking agent on positive chronotropic and inotropic actions of 5-HT

##### 4.1 Effects of cyproheptadine and propranolol on positive chronotropic and inotropic actions of 5-HT.

Combination of propranolol 0.15  $\mu\text{g/ml}$  and cyproheptadine 0.02  $\mu\text{g/ml}$  caused a slight reduction (about 2-3%) on right atrial rate (see Fig.9) and also 2-3% on the left atrial isometric tension (see Fig.10). Prior administration of both propranolol and cyproheptadine (5 min before 5-HT) could significantly reduce ( $P < 0.025$ ) the positive chronotropic effect of 5-HT. This combination antagonists effect was greater than a single effect produced by single drug. Again the result in Fig,10, prior administration of combined propranolol and cyproheptadine, showed a statistically significant ( $P < 0.005$ ) on reducing the left atrial force of contraction. The peak maximum effect was  $101.6 \pm 1.3\%$  at 3 min after addition of 5-HT. This maximum effects was closed to the



effects antagonized with cyproheptadine alone ( $101.1 \pm 1.1$  at 3 min, see Fig.4) but differed from the antagonizing effect of propranolol alone (see Fig.8).

#### 4.2 Effects of methysergide and propranolol on positive chronotropic and inotropic effects of 5-HT

The combination of methysergide ( $0.47 \mu\text{g/ml}$ ) and propranolol ( $0.15 \mu\text{g/ml}$ ) caused a very small reduction on right atrial rate (see Fig.11) and left atrial force of contraction (see Fig.12). Prior administration of both methysergide and propranolol (5 min before 5-HT) could mitigate positive chronotropic effect (see Fig. 11) induced by 5-HT, positive inotropic effect (see Fig.12) and also the reduction effect was completely and all of the points were highly significant difference ( $P < 0.005$ ).

#### 5. Effects of 5-HT antagonists on isolated reserpinized rat atria

The rats were pretreated with reserpine  $5 \text{ mg/kg i.p.}$  2 days before experiment. The average body weight was decreased about  $43.72 \pm 1.49 \text{ gm.}$  ( $n = 32$ ). Normal right atrial rate collected from 32 rats was about  $263.4 \pm 18.4 \text{ beats/min}$  which was similar to non-treated rats ( $266.5 \pm 22.3$ ,  $n = 75$ ). As shown in Fig.13, the pattern of chronotropic effect of 5-HT on right atrial rate in reserpinized rats are similar but less than those observed from non-treated rats. However, they are not statistically significance.

Similar results were also observed (see Fig.14) on the effects of 5-HT on left atrial isometric tension between reserpinized and non-reserpinized rats.

As shown in Fig.15 the effects of cyproheptadine (0.02  $\mu\text{g}/\text{ml}$ ) on the right atrial rate was similar to those observed in non-reserpinized rats. Prior administration of cyproheptadine (5 min before 5-HT) could significantly antagonized ( $P < 0.05$ ) the positive chronotropic effect of 5-HT. However, the antagonized effect of cyproheptadine was gradually reduced after 5 min and were not statistically difference at 10 and 15 min ( $P > 0.05$ ).

Prior administration of cyproheptadine also significantly antagonized ( $P < 0.05$ ) the positive inotropic effect produced by 5-HT at every periods of investigation (see Fig.16).

Methysergide 0.47  $\mu\text{g}/\text{ml}$  showed very slightly change on right atrial rate (see Fig.17) and left atrial isometric tension (Fig.18) from control values. But 5-HT 2.0  $\mu\text{g}/\text{ml}$  caused increased in both right atrial rate and left atrial contraction similar to non-reserpinized rats. Prior administration of methysergide (0.47  $\mu\text{g}/\text{ml}$ ), 5 min before 5-HT, could completely antagonized the positive chronotropic and inotropic effects of 5-HT (see Fig.17 and 18).

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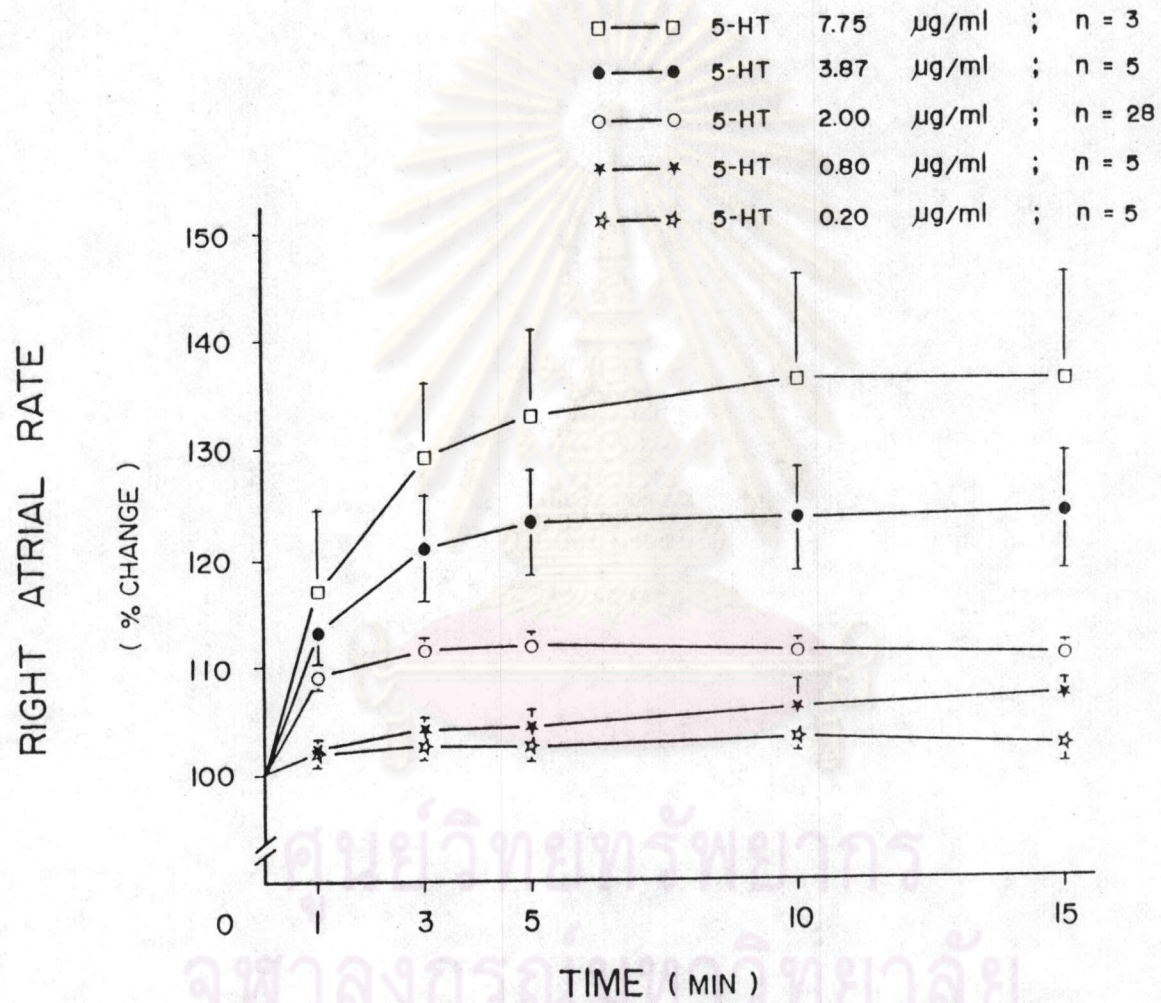


Fig. 1 Dose-response curves of 5-HT on the isolated rat right atrial rate. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

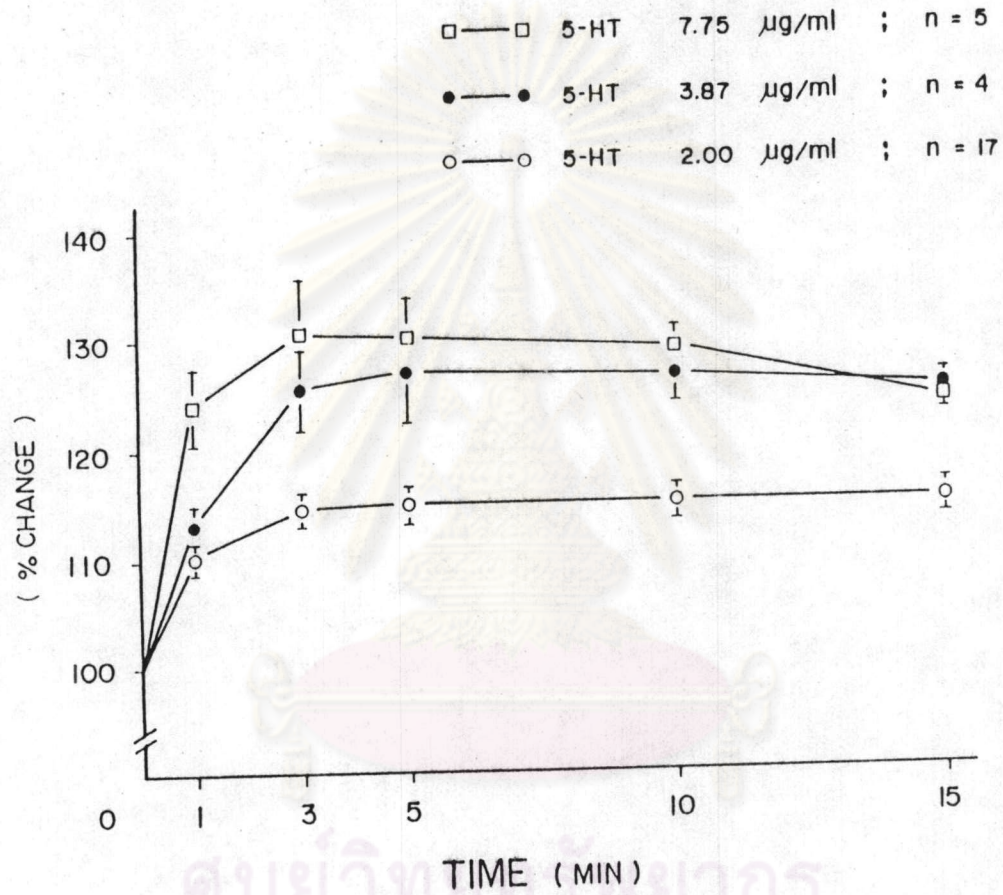


Fig. 2 Dose-response curves of 5-HT on the isolated rat left atrial isometric tension. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.



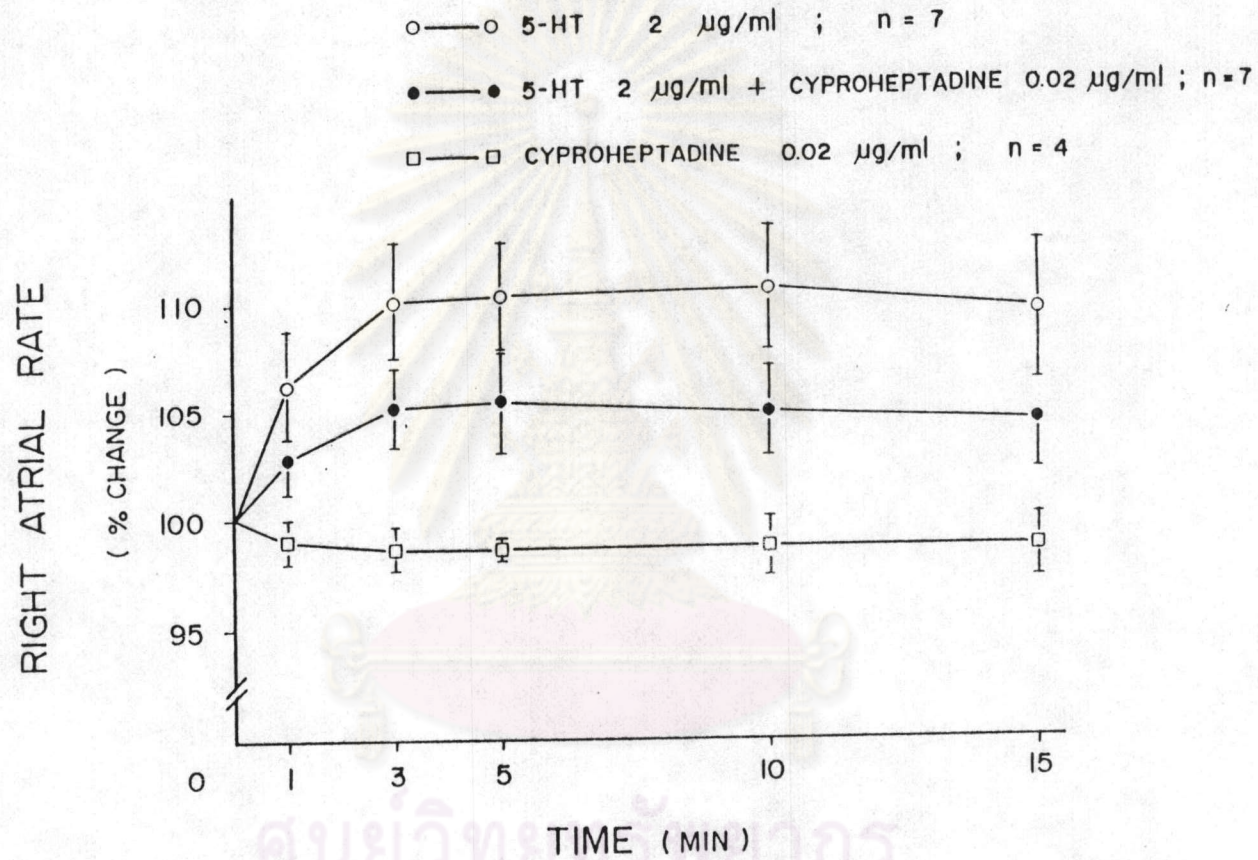


Fig. 3 The effect of 5-HT 2.0 µg/ml, cyproheptadine 0.02 µg/ml and 5-HT 2.0 µg/ml + cyproheptadine 0.02 µg/ml upon the rat right atrial rate. Each point on the curves represents the mean value ± S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

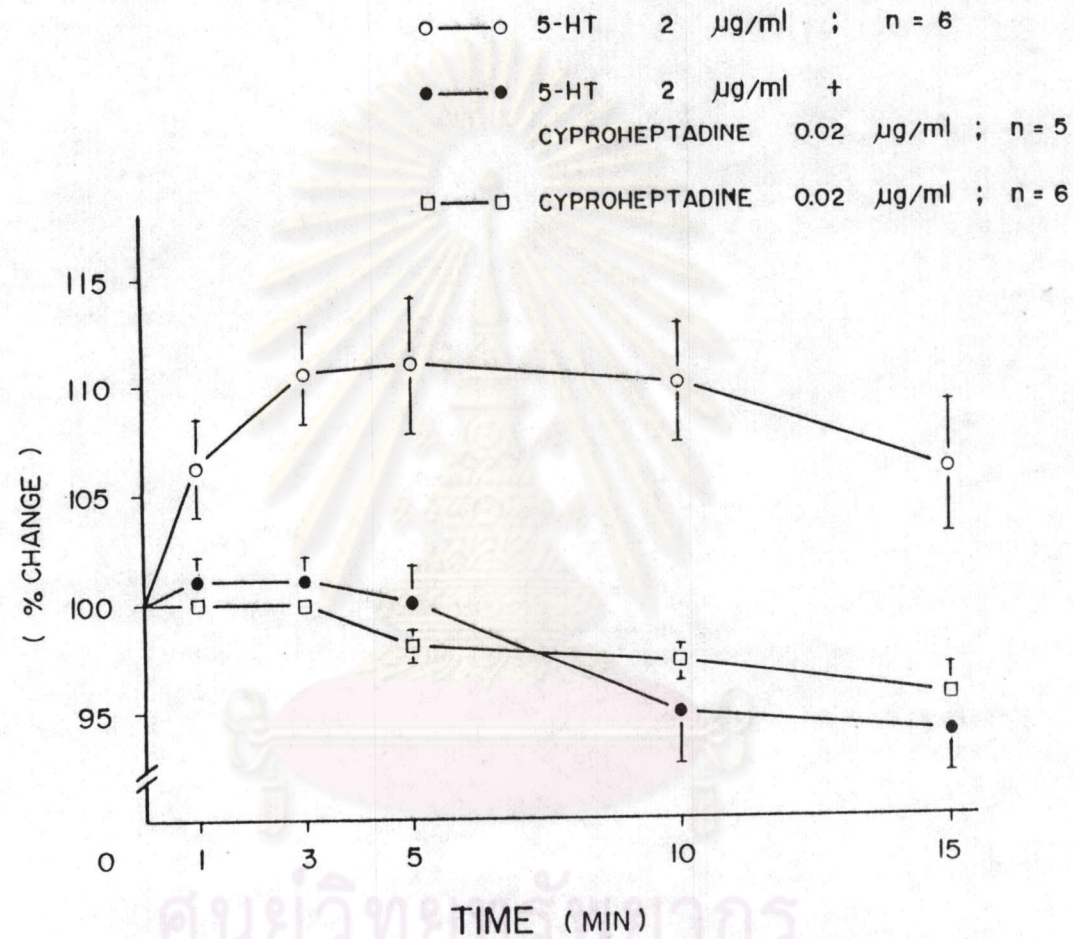


Fig. 4

The effect of 5-HT 2.0 µg/ml, cyproheptadine 0.02 µg/ml and cyproheptadine 0.02 µg/ml + 5-HT 2.0 µg/ml, upon the isolated rat left atrial isometric tension. Each point on the curves represents the mean value ± S.E.M. of the percentage change from the control values.



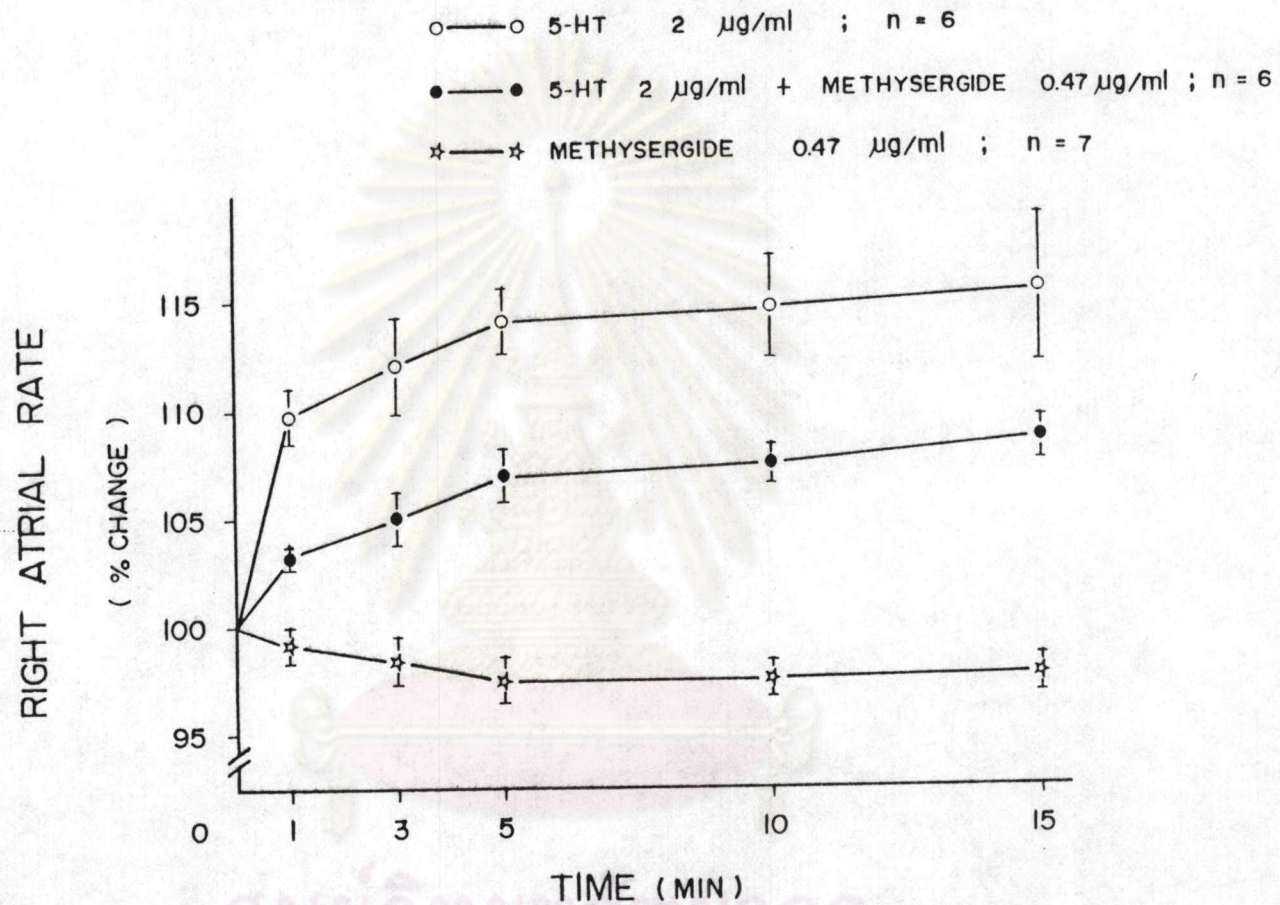


Fig. 5 The effect of 5-HT 2.0 µg/ml, methysergide 0.47 µg/ml and methysergide 0.47 µg/ml + 5-HT 2.0 µg/ml, upon the isolated rat right atrial rate. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

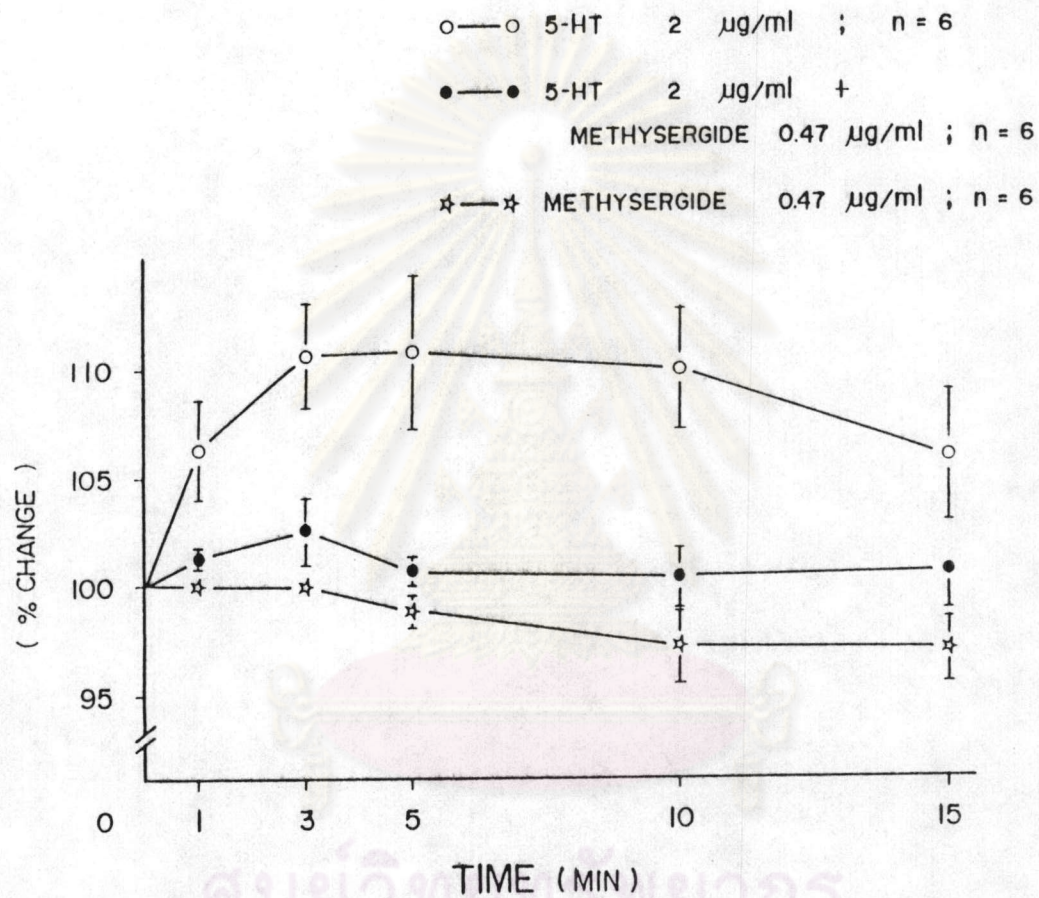


Fig. 6 The effect of 5-HT 2.0 µg/ml, methysergide 0.47 µg/ml and methysergide 0.47 µg/ml + 5-HT 2.0 µg/ml, upon the isolated rat left atrial isometric tension. Each point on the curves represents the mean value ± S.E.M. of the percentage change from the control values.



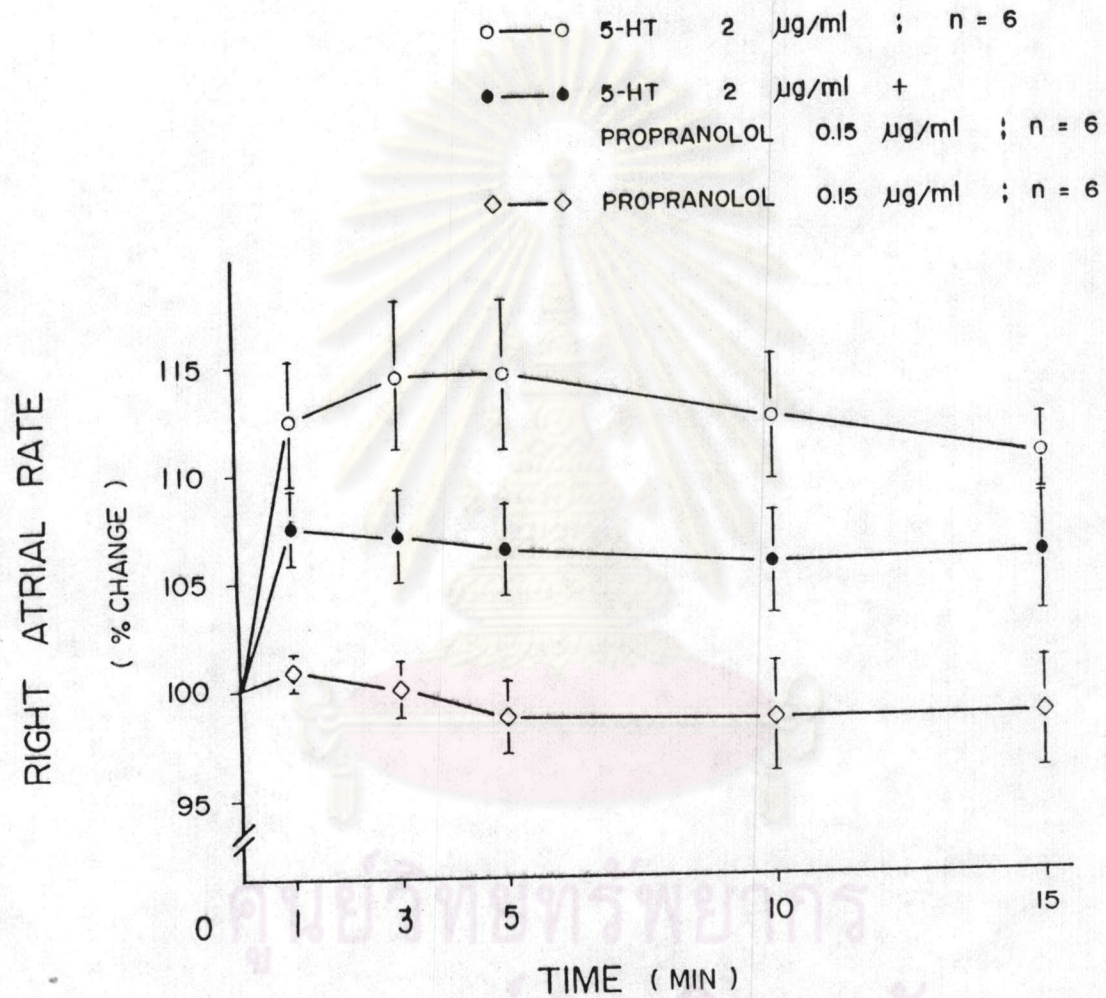


Fig. 7 The effect of 5-HT 2.0 µg/ml, propranolol 0.15 µg/ml and propranolol 0.15 µg/ml + 5-HT 2.0 µg/ml, upon the isolated rat right atrial rate. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

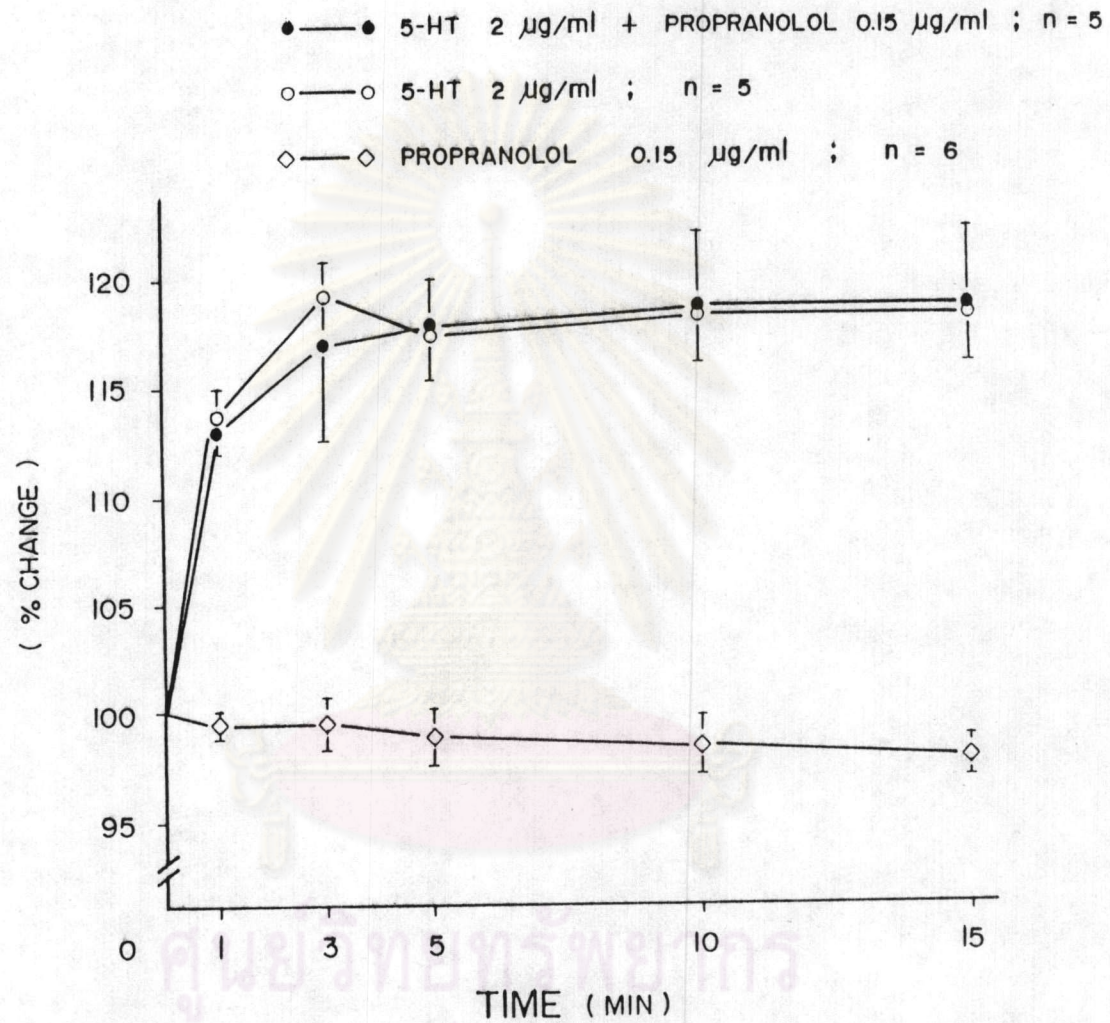


Fig. 8 The effect of 5-HT 2.0  $\mu\text{g/ml}$ , propranolol 0.15  $\mu\text{g/ml}$  and propranolol 0.15  $\mu\text{g/ml}$  + 5-HT 2.0  $\mu\text{g/ml}$ , upon the rat left atrial isometric tension. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.



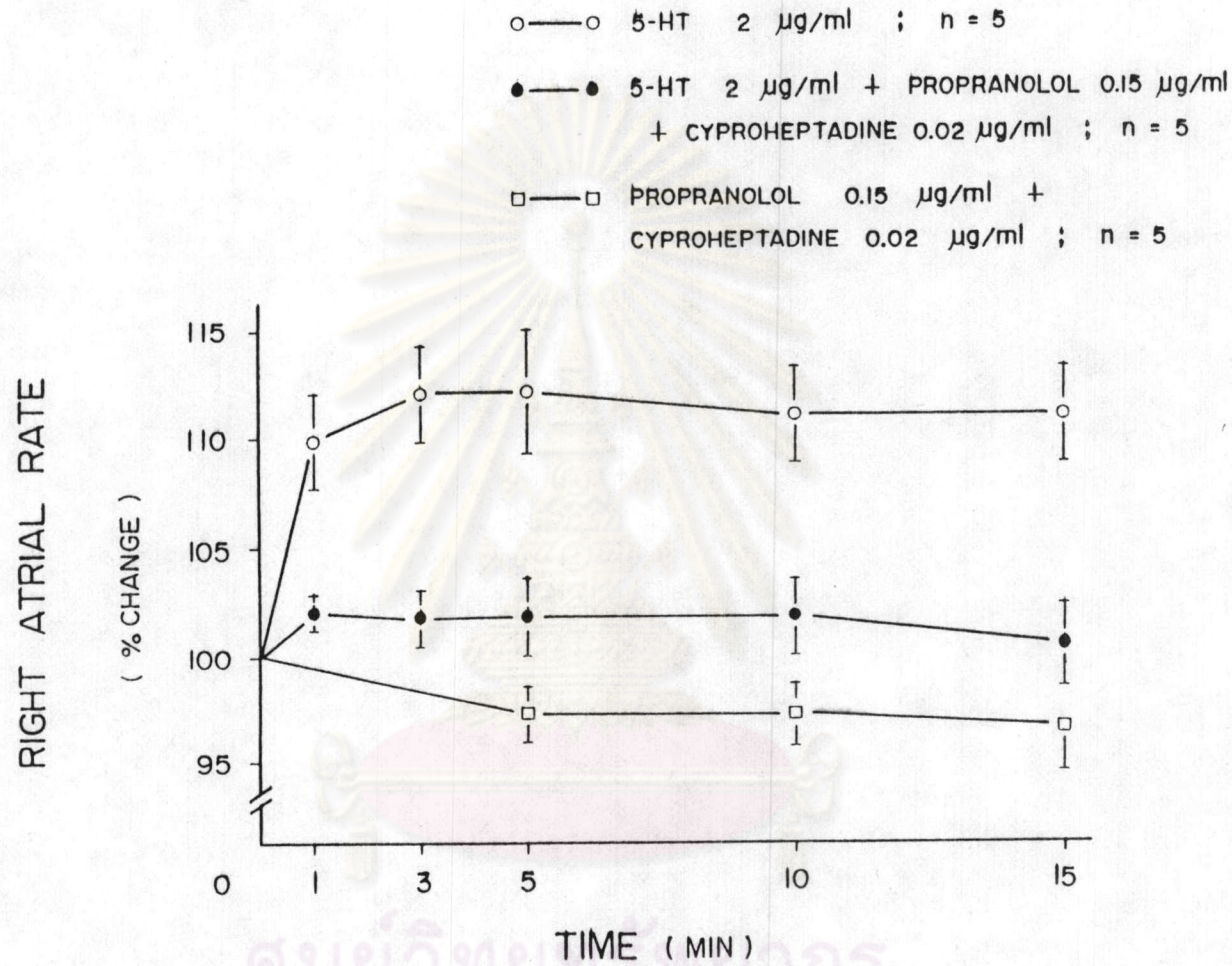


Fig. 9 The effect of 5-HT 2.0  $\mu\text{g/ml}$ , propranolol 0.15  $\mu\text{g/ml}$  + cyproheptadine 0.02  $\mu\text{g/ml}$  and propranolol + cyproheptadine + 5-HT, upon the isolated rat right atrial rate. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.



LEFT ATRIAL ISOMETRIC TENSION

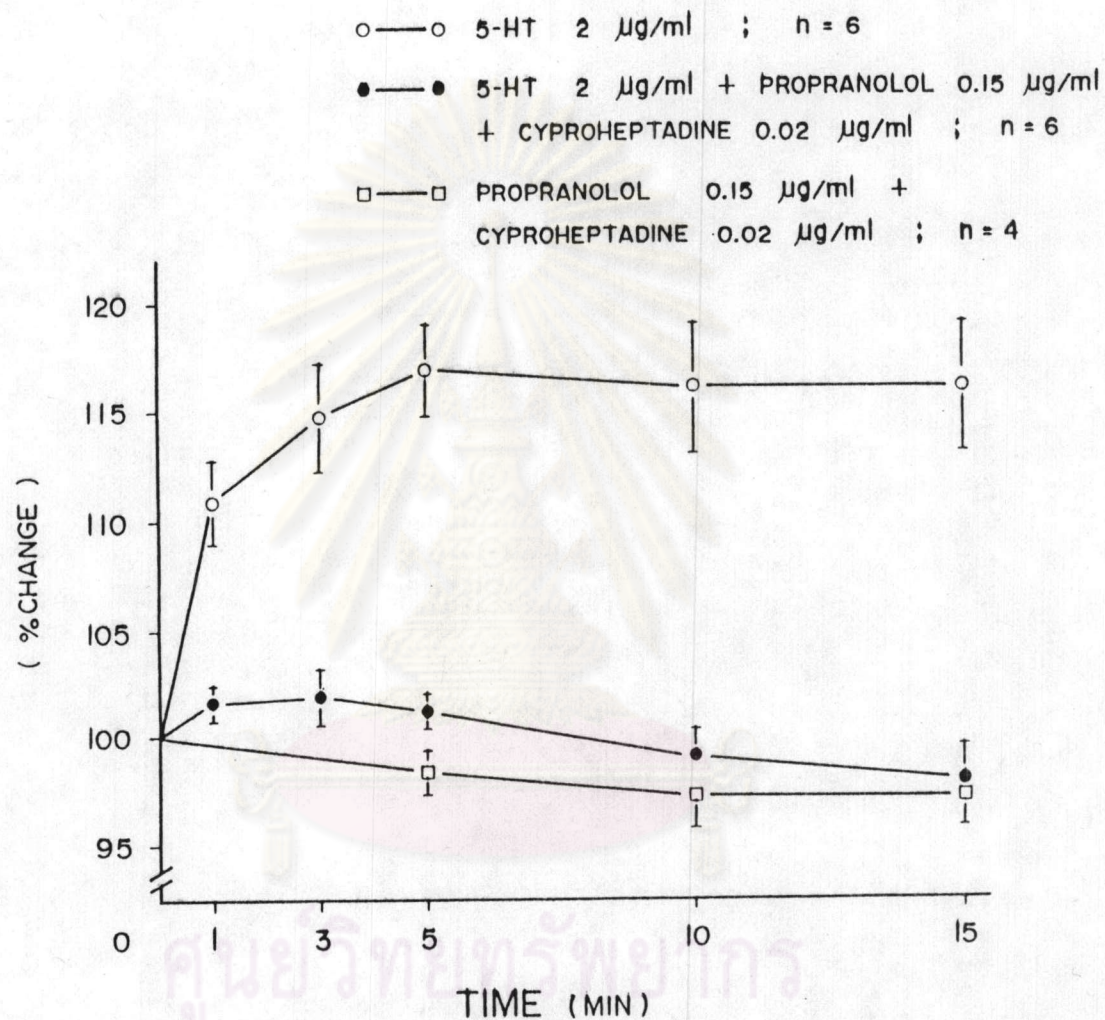


Fig. 10 The effect of 5-HT 2.0  $\mu\text{g/ml}$ , cyproheptadine 0.02  $\mu\text{g/ml}$  + propranolol 0.15  $\mu\text{g/ml}$  and propranolol + cyproheptadine + 5-HT, upon the isolated rat left atrial isometric tension. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.



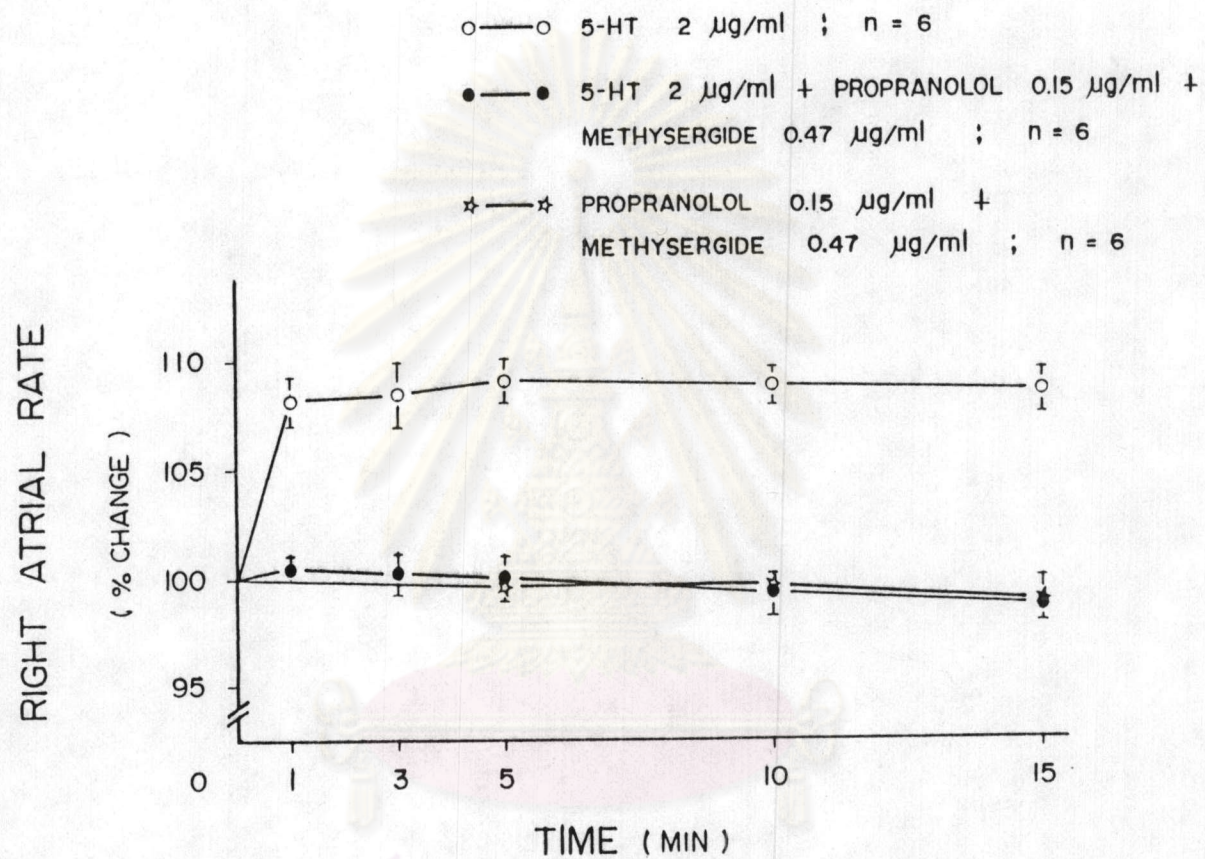


Fig. 11 The effect of 5-HT 2.0  $\mu\text{g/ml}$ , methysergide 0.47  $\mu\text{g/ml}$  + propranolol 0.15  $\mu\text{g/ml}$  and methysergide + propranolol + 5-HT, upon the isolated rat right atrial rate. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

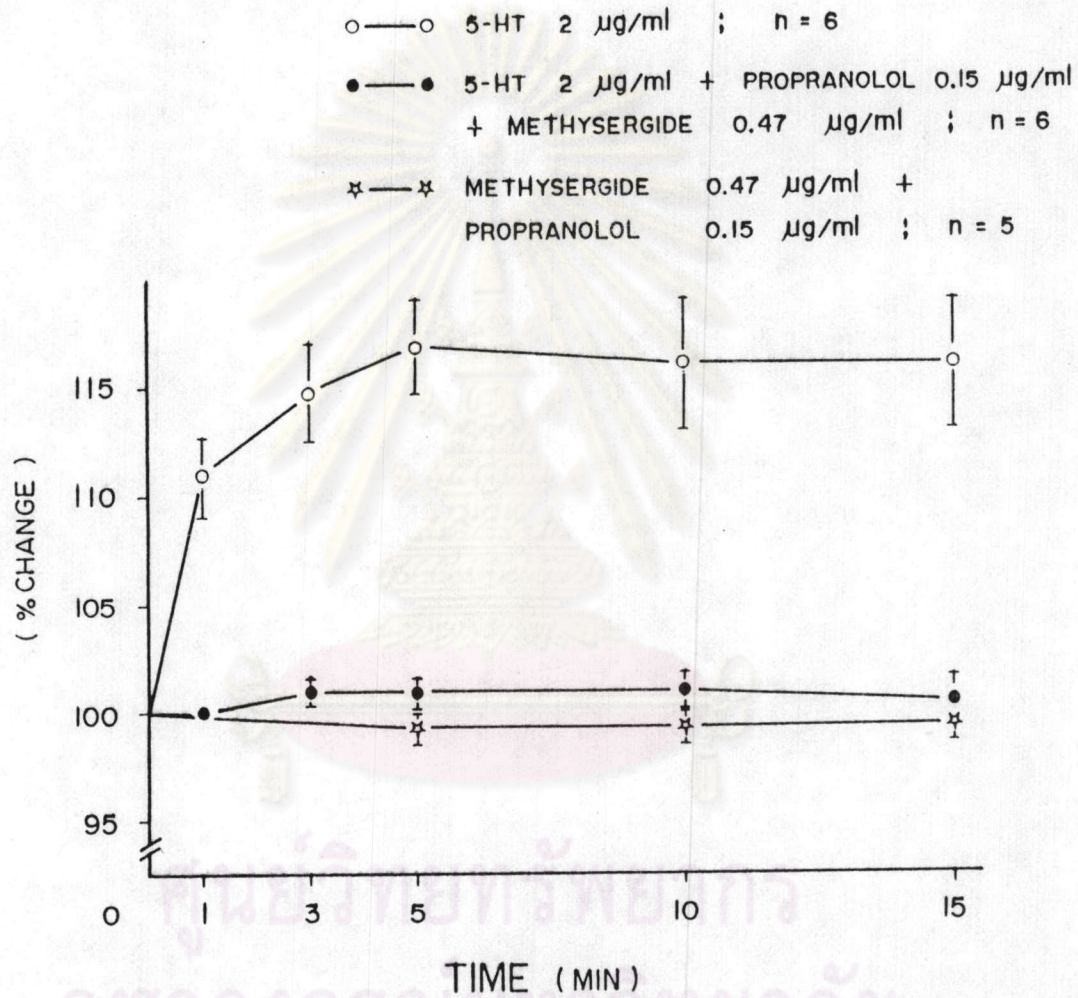


Fig. 12 The effect of 5-HT 2.0  $\mu\text{g/ml}$ , methysergide 0.47  $\mu\text{g/ml}$  + propranolol 0.15  $\mu\text{g/ml}$  and methysergide + propranolol + 5-HT, upon the isolated rat left atrial isometric tension. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.



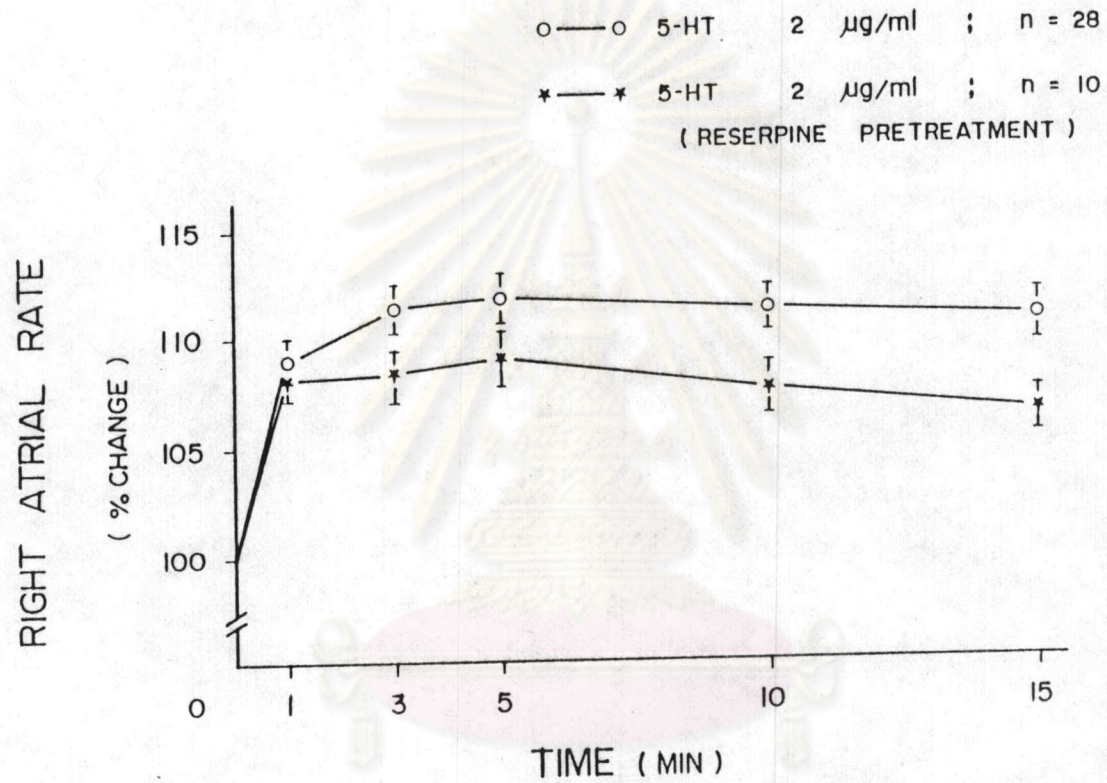


Fig. 13. Comparison the effect of 5-HT 2.0 μg/ml in non-reserpinized rat ○—○, and reserpinized rat \*—\*, upon the isolated rat right atrial rate. Each point on the curves represents the mean value ± S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

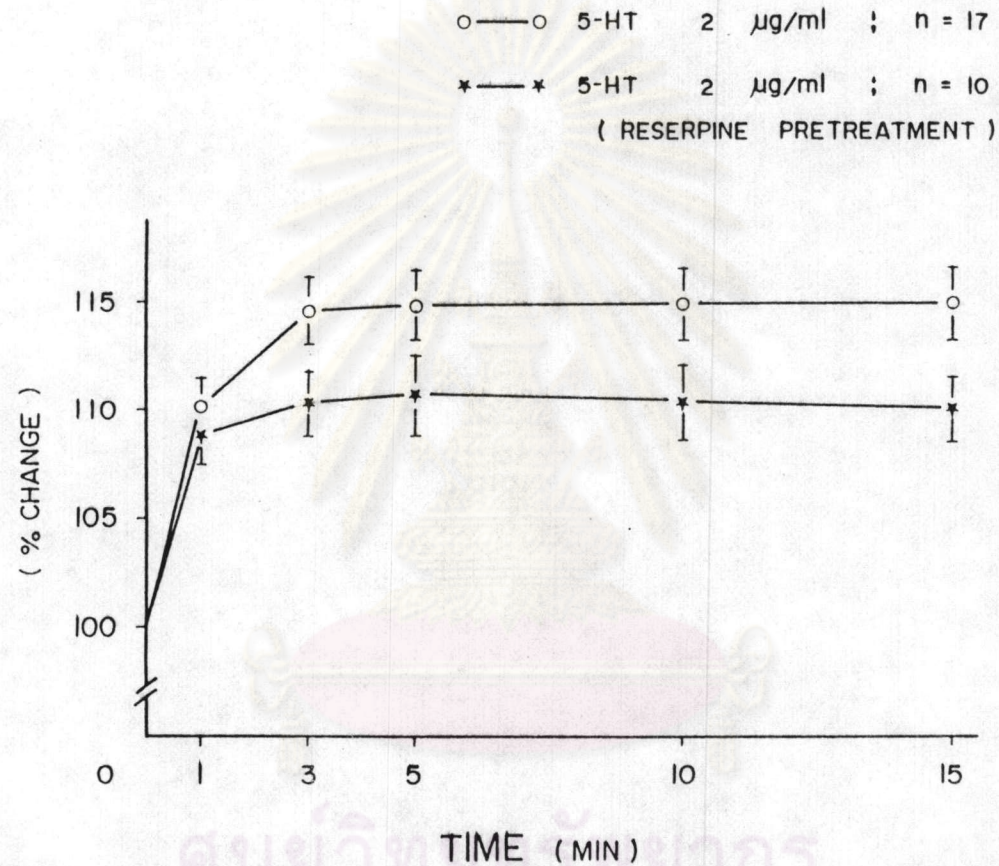


Fig. 14 Comparison the effect of 5-HT 2.0  $\mu\text{g/ml}$  in non-reserpinized rat ○—○, and reserpinized rat ★—★, upon the isolated rat left atrial isometric tension. Each point on the curves represents the mean value  $\pm$  S.E.M. of the percentage change from the control values.



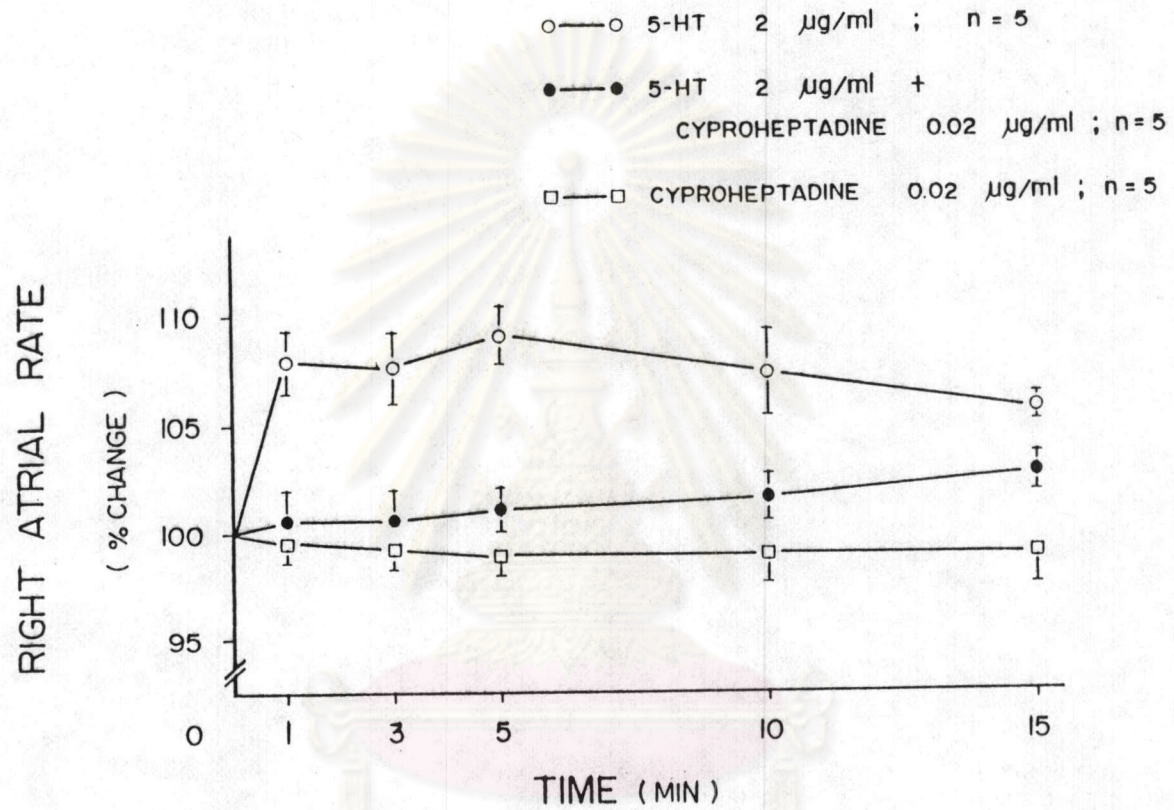


Fig. 15 The effect of 5-HT 2.0 µg/ml, cyproheptadine 0.02 µg/ml and cyproheptadine 0.02 µg/ml + 5-HT 2.0 µg/ml, upon the isolated reserpinized rat right atrial rate. Each point on the curves represents the mean value ± S.E.M. of the percentage change from the control values.

LEFT ATRIAL ISOMETRIC TENSION

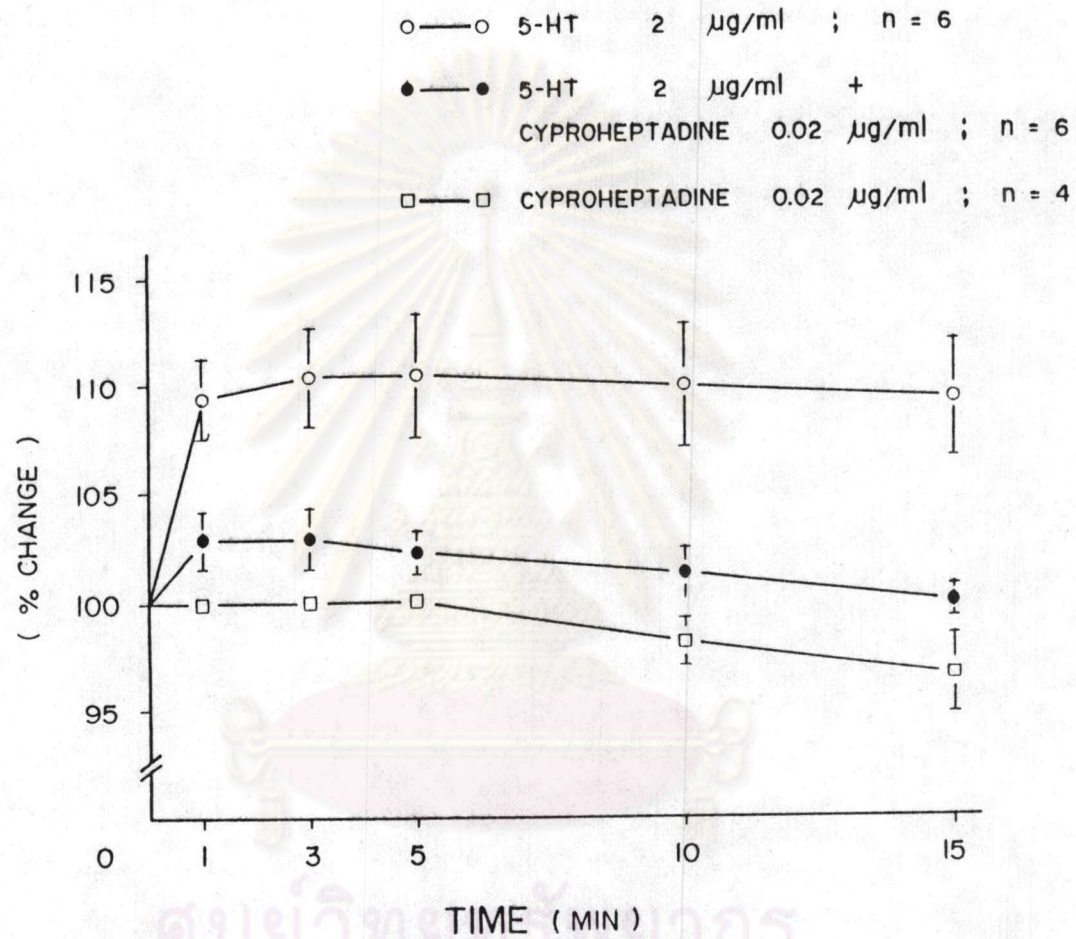


Fig. 16 The effect of 5-HT 2.0 µg/ml, cyproheptadine 0.02 µg/ml and cyproheptadine 0.02 µg/ml + 5-HT 2.0 µg/ml, upon the isolated reserpinized rat left atrial isometric tension. Each point on the curves represents the mean value ± S.E.M. of the percentage change from control values.



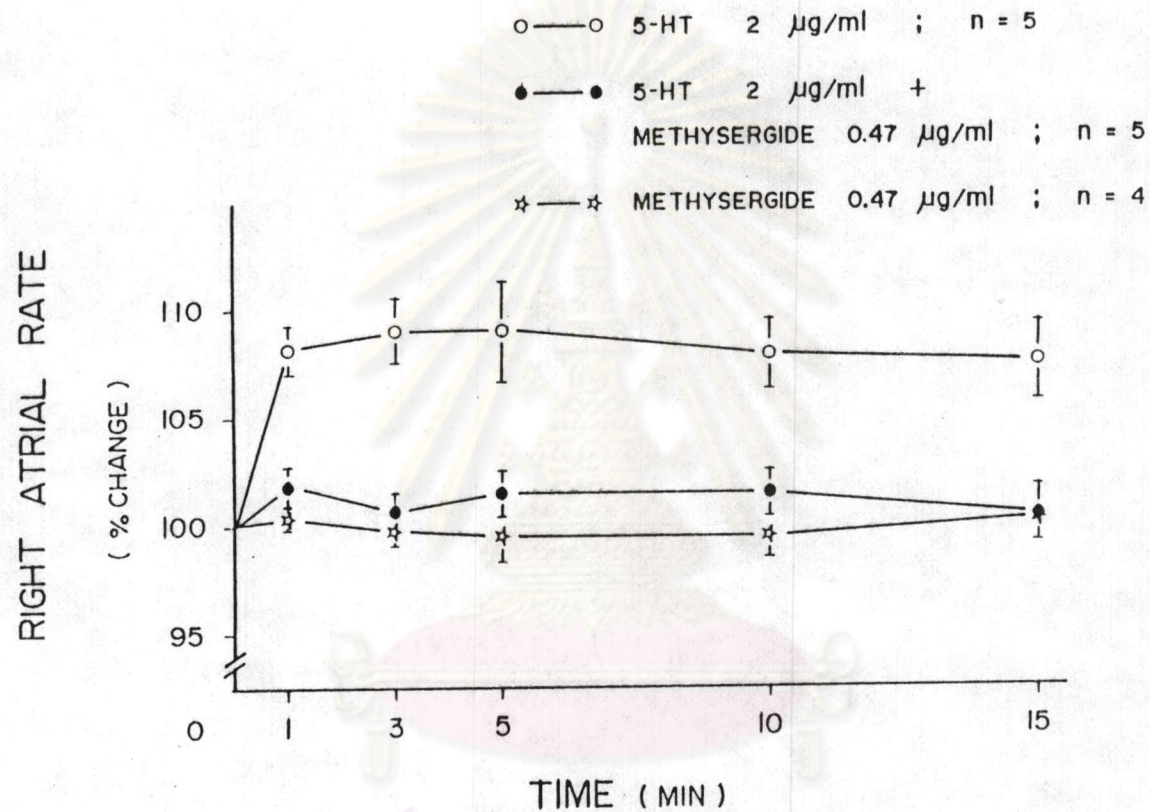


Fig. 17 The effect of 5-HT 2.0 µg/ml, methysergide 0.47 µg/ml and methysergide 0.47 µg/ml + 5-HT 2.0 µg/ml, upon the isolated reserpinized rat right atrial rate. Each point on the curves represents the mean value ± S.E.M. of the percentage change from control values.

LEFT ATRIAL ISOMETRIC TENSION

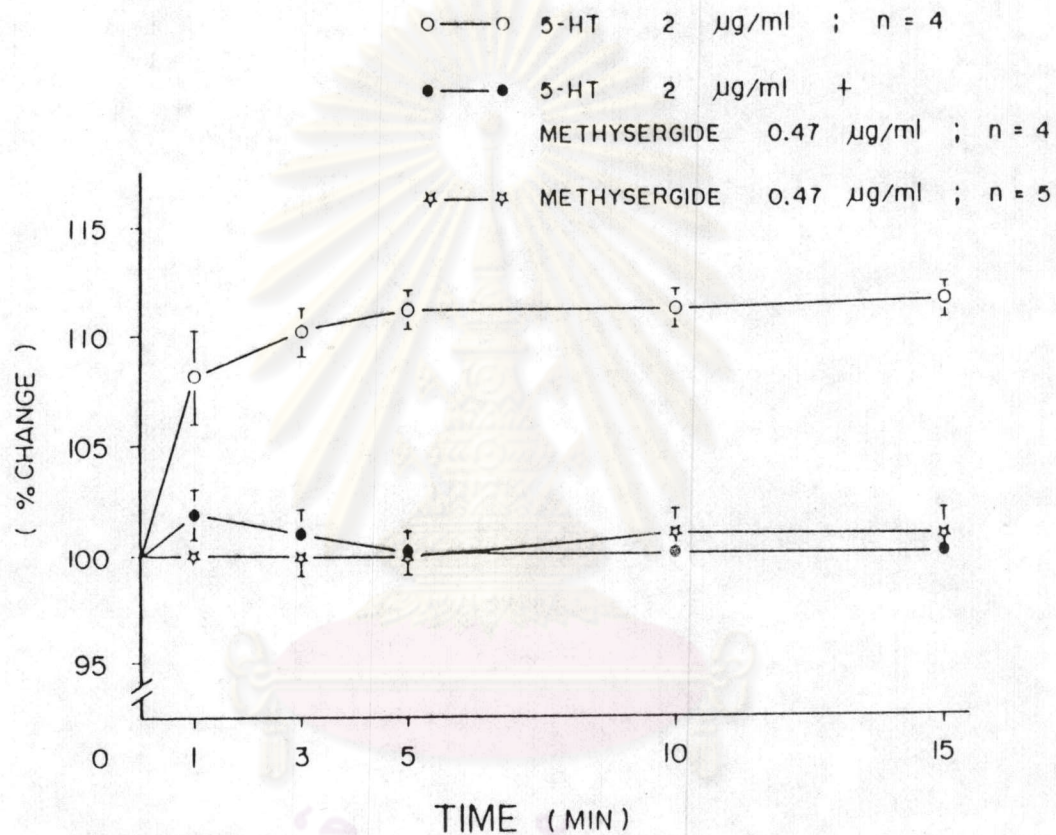


Fig. 18 The effect of 5-HT 2.0 µg/ml, methysergide 0.47 µg/ml and methysergide 0.47 µg/ml + 5-HT 2.0 µg/ml, upon the isolated reserpinized rat left atrial isometric tension. Each point on the curves represents the mean value ± S.E.M. of the percentage change from control values.

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