Influence of 5-Hydroxytryptamine on Experimentally Induced Atrial Arrhythmias in Dogs

Alice Kuruvilla and Ranita Aiman*
Department of Pharmacology, Christian Medical College, Vellore

Summary: 5-hydroxytryptamine when administered intravenously prolonged and potentiated acetylcholine and aconitine-induced atrial arrhythmias in dogs significantly. In reserpinised animals, which are depleted of adrenergic transmitters, 5-HT produced similar prolongation of acetylcholine and aconitine induced arrhythmias. 5-HT when injected directly into the area of S.A. node caused tachycardia, extrasystoles and fibrillation. These results suggest that facilitatory effect of 5-HT is probably mediated through a direct action on heart rather than through sympathetic mediators.

Key words: atrial arrhythmias acetylcholine and aconitine-induced effect of 5-hydroxytryptamine

INTRODUCTION

5-hydroxytryptamine (5-HT) is normally present in the cardiac tissue and is known to exert a variety of actions on the heart (7,15). Madan et al. (8,9) have reported that during the occurrence of atrial and ventricular arrhythmias, the 5-HT content of the cardiac tissue is increased and after treatment with quinidine and reversion of these arrhythmias, the 5-HT content is reduced. Further more 5-HT antagonists, methysergide and cyproheptadine have antiarrhythmic activity in experimentally induced arrhythmias (1,11). These observations indicate that 5-HT is implicated in the mechanism underlying the occurrence of ectopic beats in cardiac tissue. This study was, therefore, undertaken to evaluate the influence of exogenously administered 5-HT on experimentally induced atrial arrhythmias in dogs. Since excitatory actions of 5HT on the heart are considered to be mediated through adrenergic mechanisms (4,5), some experiments were also carried out in reserpinised animals.

MATERIALS AND METHODS

Thirty one healthy mongrel dogs of either sex weighing between 9.5 and 16.5 kg were used for the present study. They were anaesthetised with pentobarbitone sodium (30 mg/kg iv). Under positive pressure respiration, the chest was opened by a midline sternum-splitting incision, and the heart exposed. Bipolar limb lead II recordings were arranged on Siemens Cardiomat, single channel direct writing electrocardiogram. Blood pressure recordings were made on a kymograph from a cannulated right carotid artery. To study the influence of 5-HT on cardiac arrhythmias, the following procedures were selected.

Acetylcholine-induced atrial fibrillation: This method based on the work of Sherf and Chick as modified by Schalck was followed (10,12). A small cotton pledget soaked in 5 percent
acetylcholine (Ach) was placed directly over the area of sino-atrial node. One min later fibrillation was produced by pinching the atrium with a pair of forceps and its duration noted.

**Aconitine-induced atrial fibrillation:** As described by Scherf (13), a cotton pledget soaked in 0.05 percent solution of aconitine nitrate was placed on the auricle. Within 3-4 min, persistent atrial fibrillation was produced. The time for spontaneous reversal with a 1:1 rhythm and rate below 200 beats per min was noted.

5-HT creatinine sulphate was given intravenously in doses of 10 μg/kg after the onset of fibrillation. In 4 control dogs, the effect of this dose of 5-HT on B.P. and electrocardiogram was noted. The time for spontaneous reversion of arrhythmia was noted in each dog with and without 5-HT.

In order to deplete catecholamines, animals were pretreated with reserpine 0.5 mg/kg intraperitoneally for two consecutive days and employed for the experiments on the third day. Potassium was given to the reserpinised dogs daily (1 g of potassium chloride) along with food. Serum Na and K levels were estimated in these dogs before using them for the experimental study.

To study the direct effect on cardiac rhythm, 5-HT was injected directly into the area of S.A. node subepicardially both in reserpinized and control animals.

**RESULTS**

In control dogs intravenous administration of 10 μg/kg of 5-HT alone failed to produce any arrhythmia. Changes in systemic blood pressure observed after 5-HT were characteristically biphasic—initial rise (5-10 mm Hg) followed by fall (10-20 mm Hg) which continued for a period of 3-4 min. Administration of higher doses of 5-HT (50 μg/kg) caused ECG changes like reduction of P-Q interval and depression of ST segment.

The mean duration for the spontaneous reversal of Ach induced arrhythmia was 14.83 min (Table I). The rate of fibrillating atrium varied between 400 and 480/min. The blood pressure remained normal and the sinus rhythm was given the mean of aconitine induced fibrillation prolonging auricle varied.

**Effect of reserpine:** All the animals were given pentobarbitone sodium (6 mg/kg) intraperitoneally for two consecutive days and employed for the experiments on the third day. Saline 0.9% was given intravenously in doses of 10 μg/kg after the onset of fibrillation.

To study the direct effect on cardiac rhythm, 5-HT was injected directly into the area of S.A. node subepicardially both in reserpinized and control animals.

**TABLE I:** Influence of 5-HT on the duration (min) of atrial arrhythmias induced by acetylcholine (Ach) and aconitine

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Ach alone</th>
<th>Ach+5-HT</th>
<th>Dog No.</th>
<th>Aconitine alone</th>
<th>Aconitine +5-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>24</td>
<td>1</td>
<td>62</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>26</td>
<td>2</td>
<td>60</td>
<td>113</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>30</td>
<td>3</td>
<td>55</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>30</td>
<td>4</td>
<td>49</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>25</td>
<td>5</td>
<td>52</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>28</td>
<td>6</td>
<td>50</td>
<td>102</td>
</tr>
</tbody>
</table>

| Mean    | 14.83     | 28       | 54.67   | 102.83         |
|         | ±0.76     | ±2.31    | ±4.85   | ±6.62          |

**P value** < 0.001 < 0.001
April 1977
Ind. J. Physiol. Pharmac

... of the atrial node. One min later, a cotton pledget soaked in 5-HT was inserted into the area of

... duration noted. Within 3-4 min, persistent atrial arrhythmias with a 1:1 rhythm and a rate of

... of 10 μg/kg after the onset of fibrillation caused ECG abnormalities like appearance of U wave and

... the duration of fibrillation and the spontaneous reversal was always heralded by a gradual rise of blood pressure towards prefibrillation level. The sinus rhythm rate of the heart was the same before and after fibrillation. When 5-HT was given, the mean duration of resultant arrhythmia was 54.67 min. The mean duration of acetylcholine (Ach) induced arrhythmias was 28 min (Table I). The mean duration of aconitine-induced arrhythmias was 14.83 min. When 5-HT was supplemented after application of Ach plugs on the S.A. node caused only a very transient arrhythmia which continued for a period of 2.2 min only. Intravenous administration of 5-HT in 10 μg/kg doses prolonged the duration of these arrhythmias by 14.83 min (Table II). The rate of fibrillating auricle varied between 500 and 540/min. In reserpine-treated dogs, the duration of atrial arrhythmias was also reduced only for a period of 21.2 min. When 5-HT was supplemented after application of Ach plugs, the resultant arrhythmias were more persistent, continuing for a period of 21.2 min.

... was always heralded by a gradual rise of blood pressure towards prefibrillation level. The sinus rhythm rate of the heart was the same before and after fibrillation. When 5-HT was given, the mean duration of resultant arrhythmia was 54.67 min. The mean duration of acetylcholine (Ach) induced arrhythmias was 28 min (Table I). The mean duration of aconitine-induced arrhythmias was 14.83 min. When 5-HT was supplemented after application of Ach plugs on the S.A. node caused only a very transient arrhythmia which continued for a period of 2.2 min only. Intravenous administration of 5-HT in 10 μg/kg doses prolonged the duration of these arrhythmias by 14.83 min (Table II). The rate of fibrillating auricle varied between 500 and 540/min. In reserpine-treated dogs, the duration of atrial arrhythmias was also reduced only for a period of 21.2 min. When 5-HT was supplemented after application of Ach plugs, the resultant arrhythmias were more persistent, continuing for a period of 21.2 min.

The blood pressure remained low by 25-35 mm Hg throughout the period of fibrillation and the spontaneous reversal was always heralded by a gradual rise of blood pressure towards prefibrillation level. The sinus rhythm rate of the heart was the same before and after fibrillation. When 5-HT was given, the mean duration of resultant arrhythmia was 54.67 min. The mean duration of acetylcholine (Ach) induced arrhythmias was 28 min (Table I). The mean duration of aconitine-induced arrhythmias was 14.83 min. When 5-HT was supplemented after application of Ach plugs on the S.A. node caused only a very transient arrhythmia which continued for a period of 2.2 min only. Intravenous administration of 5-HT in 10 μg/kg doses prolonged the duration of these arrhythmias by 14.83 min (Table II). The rate of fibrillating auricle varied between 500 and 540/min. In reserpine-treated dogs, the duration of atrial arrhythmias was also reduced only for a period of 21.2 min. When 5-HT was supplemented after application of Ach plugs, the resultant arrhythmias were more persistent, continuing for a period of 21.2 min.
period of 46 min. Thus in reserpinised animals also, 5-HT exerted a facilitatory effect on atrial arrhythmias.

**Effect of 5-HT applied on the S.A. node:** A total dose of 9 \( \mu g/kg \) of 5-HT in a small volume of 0.05 ml was injected in the area of S.A. node. In all the five dogs, electrocardiographic changes observed were atrial tachycardia, extrasystoles and fibrillation which lasted for a period of 90-105 sec after which normal sinus rhythm was established. Lower dose (5-6 \( \mu g/kg \)) of 5-HT caused only tachycardia, but no fibrillation. Injection of the same volume of normal saline in the same manner did not cause any such E.C.G. changes. In five reserpinised dogs which were treated with atropine (100 \( \mu g/kg \)) sufficient to block the muscarinic effect of ACh, injection of 5-HT into the area of S.A. node caused similar electrocardiographic changes.

---

**DISCUSSION**

The arrhythmogenic effects of aconitine and acetylcholine are attributed to the local action of these agents (12,13). The duration of arrhythmias reported here is in conformity with the data of earlier workers. The present results indicate that 5-HT when supplemented to ACh and aconitine potentiated and significantly prolonged duration of atrial arrhythmias. Control dogs, which were given the same dose of 5-HT, did not show any cardiac irregularities though minimal changes were blood pressure could this facilitatory effect on cell membrane.

In reserpinised significantly lower than (6) that catecholamines 
long intervals of the
Hashimoto et al. (3) 
induction of atrial animals augmented 
5-HT appears to enable that its effect is
mechanisms.

This is further node subepicardial were treated with action on cell me 
Weatherall et al. fibrillatory activity, 
vagal fibres in car frequency of imp 
inhomogeneity in 
established arrhy 

Grateful a 
land for the gene 
for diligent tech 

---

1. Achari, G. and *Pharmacologia* 
2. Dawes, G. S. 
3. Hashimoto, K. 
5-HT exerted a facilitatory effect on minimal changes were observed in the blood pressure. It is unlikely that these small changes in blood pressure could influence the arrhythmia considerably. As suggested by Madan et al. (9) this facilitatory effect of 5-HT on atrial arrhythmias may be due to its direct depolarising action on cell membrane or through the liberation of catecholamines.

In reserpinised animals, the duration of both Ach and aconitine-induced arrhythmias was significantly lower than in control animals. This is in conformity with our previous observations (6) that catecholamines are essential for the maintenance of aconitine induced arrhythmias for long intervals of time.

Hashimote et al. (3) have also observed that adrenergic mechanisms may be playing a role in the induction of atrial fibrillation by Ach. Intravenous administration of 5-HT in reserpinised animals augmented the duration of Ach and aconitine induced arrhythmias significantly. Since 5-HT appears to exert a facilitatory effect on arrhythmias in reserpinised animals also it is possible that its effect is due to a direct action on the heart rather than through catecholamine mechanisms.

This is further confirmed by our observations on injecting 5-HT directly into area of S.A. node subepicardially. Since these changes were also observed in reserpinised animals which were treated with atropine, it is likely that 5-HT produces these rhythm changes by a direct action on cell membrane independent of cholinergic and adrenergic factors. As reported by Weatherall et al. (16) 5-HT has depolarising action on cell membrane which could enhance fibrillary activity. Schneider et al. (14), have recorded action potentials from afferent pulmonary vagal fibres in cats after intravenous injection of 5-HT which showed a sudden increase in the frequency of impulses from these fibres. The depolarising effect can induce an irregularity or inhomogeneity in the excitability of cardiac tissues which would allow perpetuation of an already established arrhythmia.

ACKNOWLEDGEMENTS

Grateful acknowledgement is made to Dr. Taeschler of Sandoz Limited, Basle, Switzerland for the generous supply of serotonin creatinine sulphate. Mr. S.I. Chandranath is thanked for diligent technical assistance.

REFERENCES


SUMMARY: The effect was investigated. Chlorpromazine antagonised phenytoin time/extension time, ralolin, tolbutamide or chlorpromazine.

Key words: enzymes, phenobarbital, umarol and griseofulvin, quinidine (9). As far as its interaction with enzyme-inducers have been reviewed.

Phenobarbital and umarol and griseofulvin were administered intraperitoneally. The experiments were conducted to define the action of phenytoin in the presence of diazepam or chlorpromazine, defined as the abolition of the convulsion.

Adult male albino mice were used. The flexor and extensor convulsions were timed and calculated according to the formula of approximately 0.2 for 4 days. Thirty six mice were used. Saline injections and phenobarbital was calculated.