INFLUENCE OF 5-HYDROXYTRYPTAMINE ON EXPERIMENTALLY INDUCED ATRIAL ARRHYTHMIAS IN DOGS

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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 resluts 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. Futher 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 adminstered 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.

Acetycholine-induced atrial fibrillation: This method based on the work of Sherf and Chick as modified by Schallck was followed (10,12). A small cotton pledget soaked in 5 percent

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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 soacked 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 pottassium 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

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

Dog No.	*Ach alone*	*Ach+5-HT*	*Dog No.*	*Aconitine alone*	*Aconitine+5-HT*
1	15	24	1	62	100
2	15	26	2	60	113
3	16	30	3	55	95
4	14	30	4	49	97
5	14	25	5	52	110
6	15	28	6	50	102
Mean	14.83 ±0.76	28 ±2.31		54.67 ±4.85	102.83 ±6.62
P value	<0.001				<0.001

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 28 min (Table I). The mean duration of aconitine induced arrhythmias was 54.67 min. Administration of 5-HT after the onset of fibrillation prolonged the duration of arrhythmia to 102.83 min (Table I). The rate of fibrillating auricle varied between 450-510/min.

Effect of reserpine: Reserpine treatment caused sedation, bradycardia and diarrhoea. Since all the animals were markedly depressed and less reactive after reserpinisation, 25 *mg/kg* of pentobarbitone sodium was sufficient to induce anaesthesia. The basal blood pressure was 40-60 *mm* Hg lower than those of the non reserpinised dogs. Intravenous infusion of 4 *ml/kg* of 0.9% saline was given immediately after surgery. Potassium was supplied to dogs during reserpine treatment, since preliminary studies revealed lowering of serum potassium levels after reserpinisation probably as a result of diarrhoea and dehydration. Hypokalemia could cause electrocardiographic abnormalities like appearance of U wave and changes in ST segment. Electrolyte levels for normal dogs were K, 4.5-5.4 mE/L and Na, 142-148 mE/L. Both K and Na were found to be within normal limits ranging from 4.5 to 6.0 and 142 to 150 mE/L respectively when checked at the onset of experiment.

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 $\mu g/kg$ doses prolonged the duration of these arrhymias but this duration of 8.9 min was less than that in non-reserpinised dogs where in it was 14.83 min (Table II). The rate of fibrillating auricle

TABLE II: Influence of 5-HT on the duration (min) of acetylcholine Ach and aconitine-induced atrial arrhythmias in dogs pretreated with reserpine.

Dog No.	*Ach alone*	*Ach+5-HT*	*Aconitine alone*	*Aconitine+5-HT*
1	3.5	12	22	48
2	2	7.5	21	41
3	1.75	8	22	49
4	2	10	22	49
5	1.75	7	19	43
Mean	2.2 ± 0.66	8.9 ± 1.85	21.2 ± 1.18	46 ± 3.35
P value		<0.001		<0.001

varied between 500 and 540/min. In reserpine treated dogs the duration of aconitine induced arrhythmia was also reduced significantly as compared to that in the control dogs. These arrhythmias continued only for a period of 21.2 min. When 5-HT was supplemented after application of aconitine plug, the resultant arrhythmias were more persistent, continuing for a

period of 46 min. Thus in reserpinised animals also, 5-HT exerted a facilitatory effect o atrial arrhythmias.

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

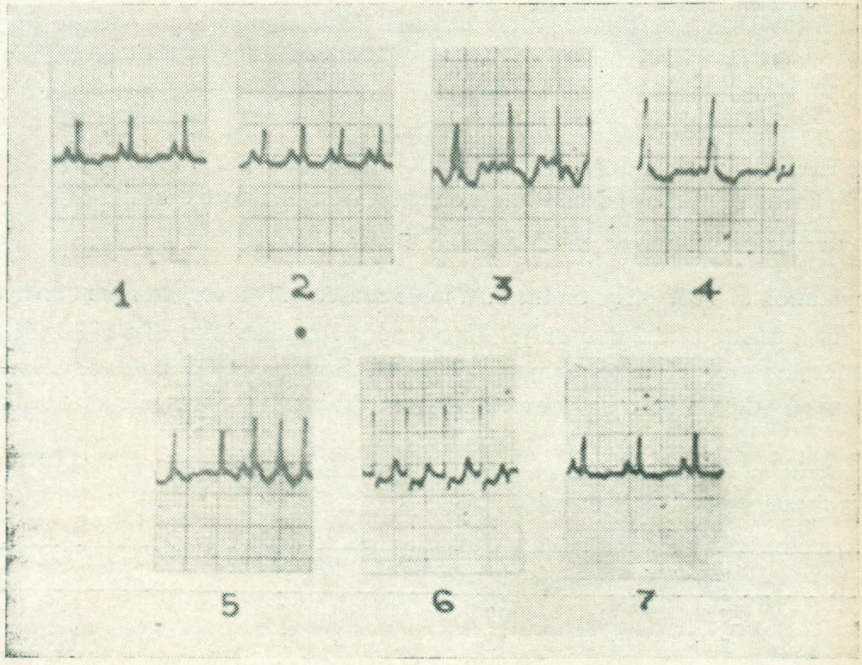

Fig. 1 : ECG Changes after injection of 5-HT into the area of S.A. node (1) Sinus rhythm (2) Initial tachycardia (3) Onset of atrial fibrillation (4) & (5) atrial fibrillation and (6) & (7) return of normal sinus rhythm.

DISCUSSION

The arrhythmogenic effects of aconitine and acetylcholine are attributed to the loca action of these agents (12,13). The duration of arrhythmias reported here is in confirmity wit the data of earlier workers. The present results indicate that 5-HT when supplimented to Ac and aconitine potentiated and significantly prolonged duration of atrial arrhythmias. Contro dogs, which were given the same dose of 5-HT, did not show any cardiac irregularities thoug

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 memberane or though 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.

Hashimete *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.

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