ELECTROPHYSICAL EFFECTS OF SEROTONIN ON ATRIOVENTRICULAR AND INTRAVENTRICULAR CONDUCTION IN DOGS

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When studying the effect of serotonin on hemodynamic parameters in dogs, the writers previously [1] noted changes in duration of the cardiac cycle and of the PQ interval on the ECG (Fig. 1). Other workers [7] found that serotonin acts as mediator of the arrhythmogenic effect of digitalis. No data on the action of serotonin on atrioventricular (AV) and intraventricular conduction could be found in the literature.

The aim of this investigation was to investigate the effect of serotonin, if any, on the AV conducting system of the dog's heart under acute experimental conditions.

EXPERIMENTAL METHOD

Altogether 15 experiments were conducted on 12 anesthetized mongrel dogs of both sexes, weighing 27.4 ± 1.3 kg. Animals were anesthetized with 0.5-1% halothane and nitrous oxide with the addition of oxygen, depending on the blood gas composition. The ECG was recorded throughout the experiment in standard lead II and used to determine the heart rate (HR). A thin-ended piezoelectric probe ("Miller," USA) was inserted through the left femoral artery into the ascending aorta to measure the cardioaortic pressure. This same parameter was used to evaluate changes in the hemodynamics during treatment with serotonin, in accordance with criteria described previously [1]. The left femoral vein was cannulated for injecting drugs. Tetrapolar electrode catheters ("USCI," USA) were introduced into the heart through the dissected right femoral vein with the aid of three separate introducers of "Desilest-Hoffman" type (diameter 6F) into the heart. Their precise location was verified roentogenologically and electrocardiographically. The first electrode catheter was introduced into the upper part of the right atrium and was used to record the atrial electrogram (EG; proximal pair of electrodes) and for atrial stimulation (distal pair of electrodes), the second, near the medial (septal) cusp of the tricuspid valve, was used to record the His bundle EG [12], the third was located inside the left ventricle near the apex, and was used for electrical stimulation. Quickening atrial stimulation was used to evaluate 1:1 AV conduction (Wenckebach's point) and the appearance of a functional block of intraventricular conduction was determined [6]. Refractory periods of the AV conducting system were measured by applying premature atrial extrastimuli (ST) immediately before basic atrial stimulation, with a cycle 300 msec in duration [4].

To study antigrade AV conduction the following parameters were estimated with the same sequence of measurements at different stages of the experiment:

1) Intraatrial conduction time (PA interval) was measured from the beginning of the P wave of the ECG to the beginning of the atrial complex (A) on the EG recorded from the superior part of the right atrium.

2. The conduction time of the A—H interval through the AV node was counted from the beginning of the atrial complex A until the beginning of the His bundle potential (H) on the intracardiac EG.

3. The conduction time along the the His—Purkinje system and the H—V interval was measured from the beginning of the H potential to the earliest appearance of ventricular activity (V) on one EG or surface ECG.

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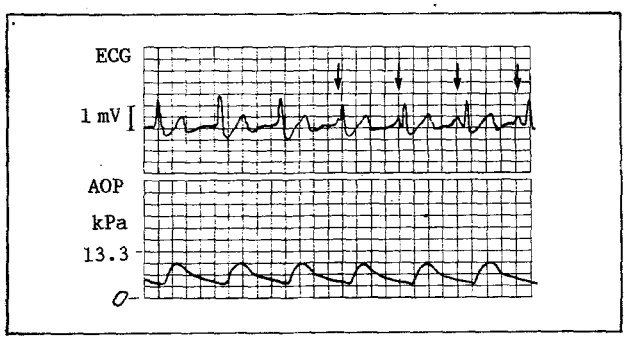

Fig. 1. Recording of typical ECG (lead II) and aortic pressure curve (AOP) at height of action of serotonin. Arrows indicate changes in PQ intervals.

4. The effective refractory period (ERP) of the AV node was determined as the longest A_1-A_2 coupling interval for which the A_2 extrastimulus did not spread to the bundle of His.

5. The functional refractory period (FRP) of the AV node was determined as the shortest A_1-A_2 coupling interval for which the H_1-H_2 interval did not exceed the A_1-A_2 coupling interval.

6. The appearance of His bundle branch block (BB) during increasingly frequent atrial stimulation was determined as the longest ST—ST interval for which aberrant ventricular QRS complexes were observed as a result of functional BB, and conduction through the AV node remained 1:1.

7. The Wenckebach point was determined during quickening atrial stimulation as the longest ST—ST stimulation interval before the appearance of the Wenckebach rhythm.

Parameters were recorded on a "Mingograf-62" automatic writer ("Siemens-Elema," Sweden) with paper winding speed of 50 to 200 mm/sec, An electrocardiostimulator ("Biotronik UHD-10," GFR) was used for programed stimulation. All intervals determined above were measured by means of an interactive computer program. Curves were digitalized by means of a light pen on the graph table of a "Hewlett-Packard 9826" microcomputer (USA).

All electrophysiological and hemodynamic data were obtained in the initial state and in the new hemodynamic steady state induced by serotonin. Serotonin (No. H-5755; 5-hydroxytryptamine hydrochloride, from "Sigma," USA) was injected intravenously by means of an infusion system in a dose of 50 μg/kg·min for 30 min. The initial recordings were made not later than 40 min after the end of infusion. In view of data on the hemodynamic effects of serotonin [1], the stable state was achieved about 5 min after the beginning of infusion. The results are given in mean values (M ± m). The effect of serotonin was compared with the control state by Student's test.

EXPERIMENTAL RESULTS

Serotonin in a dose of 50 μg/kg·min significantly increased HR from 142 ± 21.9 to 167 ± 23.7 beats/min (17.8%; $p < 0.01$). The mean intra-aortic pressure was lowered by 22.9%, i.e., from 12 ± 0.546 to 9.19 ± 0.599 kPa.

Mean values of the duration of the cardiac cycle and also the parameters of AV conduction under the influence of serotonin and in the control group are given in Fig. 2.

Serotonin was found to significantly shorten the AH interval of AV conduction from 51.9 to 43.9 msec ($p < 0.05$). Shortening of the PA and HV intervals was not significant.

The results of investigation of quickening atrial stimulation under the influence of serotonin and in the control group are given in Fig. 3. During administration of serotonin, a functional BB and Wenckebach phenomenon appeared in response to shortening of the ST—ST intervals. The mean value of the ST—ST interval for BB to appear was significantly shortened under the influence of serotonin by 19 msec ($p < 0.010$, whereas the ST—ST interval for the appearance of a Wenckebach rhythm was shortened by 20 msec, but not significantly.

It will be clear from Fig. 3 that after injection of serotonin ERP of the AV node was significantly ($p < 0.01$) shortened from 144 ± 15 to 138 ± 16 msec, whereas FRP was shortened correspondingly from 252 ± 31 to 224 ± 37 msec ($p < 0.01$).

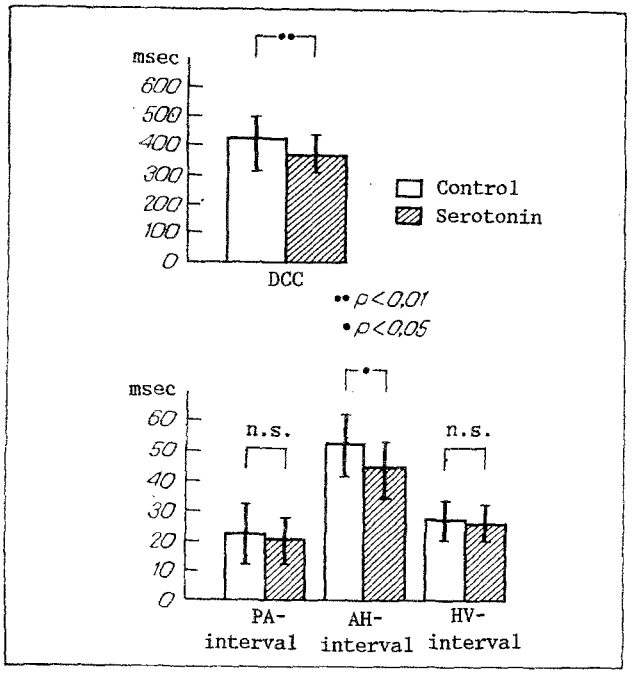

Fig. 2

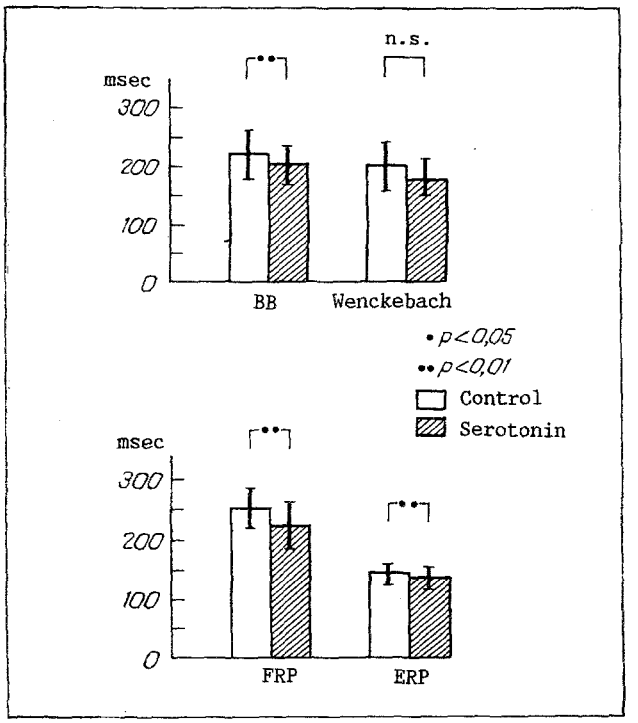

Fig. 3

Fig. 2. Duration of cardiac cycle (DCC) in intervals of AV conduction (PA-, AH-, and HV-intervals) in control state and at height of action of serotonin. Here and in Fig. 3: M ± m, n = 15; n.s.) not significant.

Fig. 3. Appearance of BB and Wenckebach's phenomenon, and also FRP and ERP of AV node in control state and at height of action of serotonin.

Changes in HR and the mean aortic pressure arising under the influence of serotonin, similar to our own findings, were observed by certain other authors [8]. Our electrophysiological data indicate that serotonin increases AV conduction. Meanwhile, quickening of idioventricular pacemakers was not observed. This effect is typical for drugs acting on the sympathetic nervous system [13]. The properties of idioventricular pacemakers cannot be estimated definitely because of the increase in HR under the influence of serotonin. Since changes in autonomic tone have a powerful influence on AV conduction, estimation of its true function is disputable [10]. The effect of serotonin on the autonomic nervous system remains the subject of discussion. It has been found [14] that serotonin inhibits noradrenalin release from adrenergic nerve endings, whereas other investigators found that it has a direct stimulating effect on the sympathetic nerves of the heart [5]. It can thus be tentatively suggested that in our experiments, as a result of injection of serotonin, sympathetic tone increased, as shown by reduction of the aortic pressure. The increase in HR could have been due to the indirect action of serotonin on pressure receptors, and also to the stimulating effect on serotonin receptors in the myocardium [9]. Some workers [8] consider that the positive ino- and chronotropic effects of serotonin are independent of catecholamine release. It has recently been shown [11] that ketanserine, a blocker of serotonin receptors (of the S_1 type), lengthens the action potential in the guinea pig papillary muscle. It can accordingly be postulated that shortening of intervals of AV conduction, observed in the present investigation, was due to the direct action of serotonin, and also to the increased action of the sympathetic nervous system.

Objective evaluation of the action of serotonin on AV and intraventricular conduction was made even more difficult by the quickening of the heart at the ERP and FRP of the AV node. Data in the literature on this subject are contradictory. On the one hand, it has been shown that with an increase in HR, ERP is lengthened but FRP is shortened [2]. Another investigation revealed shortening of both ERP and FRP in separate cases of an increase in HR [3]. It thus remains unclear to what degree changes in refractory periods of AV-node conduction are due to the direct action of serotonin, and to what degree to its effect on HR.

In conclusion it has to be pointed out that besides the marked hemodynamic effect of serotonin, we observed acceleration of the sinus node pacemaker and also improvement of AV conduction, due to both direct and indirect mechanisms. According to our data, serotonin does not increase the frequency of idioventricular pacemakers, at least in the dosage of the drug which we used. Further investigations must be aimed at excluding the influence of changes in autonomic tone by means of pharmacologic and (or) surgical denervation of the heart. It must also be discovered what type of serotonin receptor is involved in the electrophysiological action of serotonin discussed above.

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