EFFECT OF SEROTONIN ON CARDIAC ACTIVITY

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Intravenous injection of serotonin (2 mg/kg) caused a biphasic response in unanesthetized rabbits. The first phase was characterized by strengthening of parasympathetic influences on the heart and by an increase in excitability of the anterior portions of the hypothalamus, and the second phase with strengthening of sympathetic influences on the heart and lowering of the excitability of the anterior hypothalamus and also by an increase in excitability of the posterior hypothalamus.

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The heart of animals and man is known to be highly sensitive to serotonin. The mechanism of the effects of serotonin on the heart is complex. Some authors attribute the effect of serotonin on the heart to its direct action on the myocardium and its conducting system [13, 14, 18, 21, 22, 24]. Other authors describe findings indicating reflex mechanisms in the cardiovascular effects of serotonin [1, 5, 7, 12, 20, 27].

Little attention has been paid to the study of changes in the central regulation of the heart under the influence of serotonin. For this reason, in the present investigation attention was concentrated on the nervous mechanisms of the changes in cardiac activity arising under the influence of serotonin.

EXPERIMENTAL METHOD

Experiments were carried out on 20 male rabbits weighing 2.5-3 kg with electrodes implanted into the brain, the localization of the electrodes being verified histologically after the end of the experiments. In chronic experiments on unanesthetized animals the effect of serotonin was studied on cardiac activity and compared with its effect on the functional state of the different parts of the hypothalamus. This state was assessed on the basis of its electrical activity and changes in the excitability of the hypothalamic structures in response to direct electrical stimulation (90/sec, 1 msec, 1-4 V), producing changes in the EEG and in the heart rate. Simultaneous recordings of the respiration, the EEG in three standard and two chest leads, and the cortical and hypothalamic electrical activity were made during the experiments on a "Galileo" Polyphysiograph. These indices were recorded continuously throughout the experiment (which began 1-1.5 h before injection of serotonin and ended 2-3 h after injection). The electrodes were implanted in the various hypothalamic nuclei by means of a stereotaxic technique 5-7 days before the beginning of the experiment with injection of serotonin. At the same time cortical electrodes were implanted epidurally into the bones of the skull above the visual and sensorimotor areas of the cortex. Serotonin in doses of between 60 μg/kg and 2 mg/kg, dissolved in physiological saline in a concentration of 1 mg/ml, was injected intravenously. To determine the mechanism of action of serotonin on the heart experiments were carried out in which the drug was injected against the background of the action of atropine (1.5 mg/kg) and after division of the vagus nerves.

EXPERIMENTAL RESULTS

Intravenous injection of small doses of serotonin (60-150 μg/kg) caused no significant changes in cardiac activity in the experimental rabbits. The animals developed only a slight increase in the respiration rate and an increase in hypothalamic electrical activity. Injection of large doses of serotonin (1-2 mg/kg) led to biphasic changes in the heart rate and in hypothalamic function. The first phase of the effect of serotonin on cardiac activity, which lasted for several seconds, was marked by the appearance of bradyarrhythmia, leading in most experiments to transient asystole, and by increased excitability of the anterior portions of the hypothalamus (the anterolateral, lateral, and medial preoptic region). No significant changes took place in the excitability of the posterior hypothalamus. The second phase of action of

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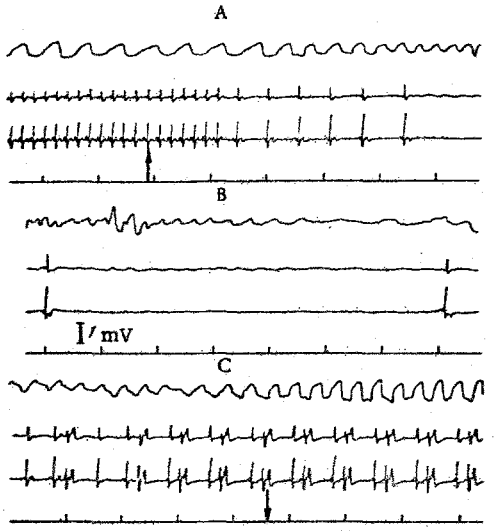

Fig. 1. Changes in the cardiac rhythm and respiration of a rabbit following intravenous injection of serotonin (1 mg/kg). A) Beginning of injection (marked by arrow); B) asystoles at end of injection (end of injection marked by arrow); B and C) continuation of A. From top to bottom: respiration, ECG standard load II and chest lead P_4, time marker (1 sec).

serotonin, which was more prolonged, was marked by a gradual increase in the heart rate accompanied by a decrease in excitability of the anterior hypothalamic structures mentioned above. Both phases of changes in cardiac activity caused by serotonin were accompanied by a sharp increase in the respiration rate. The slowing of the heart rate in the first phase of action of serotonin began 1.5-5 sec after the beginning of injection of the drug and reached its maximum as a rule after 10-20 sec. The R–R interval was greatly lengthened, the voltage of the P waves was reduced, and in addition, in several experiments changes were observed in the waves of the ventricular complex of the ECG (Fig. 1A and B). These changes took the form of an increase in the amplitude of the R wave and, in some experiments, a decrease in amplitude of the S wave. Changes in the T wave were variable. In some cases the T wave was variable. In some cases the T wave was enlarged while in others it became biphasic or negative. The changes in the ECG described above, characteristic of strengthened vagus effect on the heart, coincided in time with increased excitability of of the anterior hypothalamus. This increase in hypothalamic excitability was shown by the fact that subthreshold local electrical stimulation (1.5-2 V) of the hypothalamus, producing no changes in cardiac activity or the EEG before injection of serotonin, became threshold in magnitude after injection of serotonin and caused slowing of the cardiac contractions and an EEG activation reaction (Fig. 2A and B). The second phase of action of serotonin began a few seconds after the end of its injection and took the form of a gradual increase in the heart rate. The appearance of ectopic ventricular contractions separated from preceding nomotopic contractions of the heart by shortened intervals, indicating that they were extrasystoles, was observed under these circumstances. These were single or grouped in character and were observed for a period of 1-1.5 min (Fig. 1C).

The changes in cardiac activity during the second phase of action of serotonin described above were accompanied by a decrease in excitability of the structures of the anterior hypothalamus mentioned. This was shown by the fact that threshold electrical stimulation of the hypothalamus, causing changes in the cardiac rhythm and EEG before injection of serotonin, was no longer accompanied by these changes. To produce the previous effect, a much higher voltage of the stimulating current was required (from 4 to 6.5 V).

Against the background of pharmacological blocking of parasympathetic effects on the heart (atropinization) or after vagotomy, serotonin did not cause bradyarrhythmia. This suggests that the initial effect of the action of serotonin on the heart is connected with strengthening of the vagus nerve influence.

The coincidence in time between strengthening of vagus influences on the heart in the first phase of action of serotonin and increased excitability of the anterior hypothalamus (where the centers of the parasympathetic innervation of the heart are located) suggests that the effect of serotonin on the cardiac rhythm may be mediated through these centers. The second phase of serotonin action was manifested by a gradual increase in the heart rate. This could be due either to weakening of the parasympathetic or strengthening of the sympathetic influences on the heart. Evidence of strengthening of sympathetic influences on the heart during the second phase of serotonin action was given by the appearance of ventricular extrasystoles against the background of commencing increase in heart rate, accompanied by a decrease in excitability of the anterior hypothalamus.

The conclusion that adrenergic effects on the heart are strengthened under the influence of serotonin is confirmed particularly clearly by the results of our experiments in which serotonin was injected into rabbits with an idioventricular cardiac rhythm caused by severe diphtheritic myocarditics. The idioventricular cardiac rhythm is insensitive to vagus effects but highly sensitive to sympathetic nervous influences [8]. Against the background of an idioventricular rhythm, serotonin increased the activity of the ventricular rhythm of the heart. In addition, increased automatism of the sinus node was observed. These results are

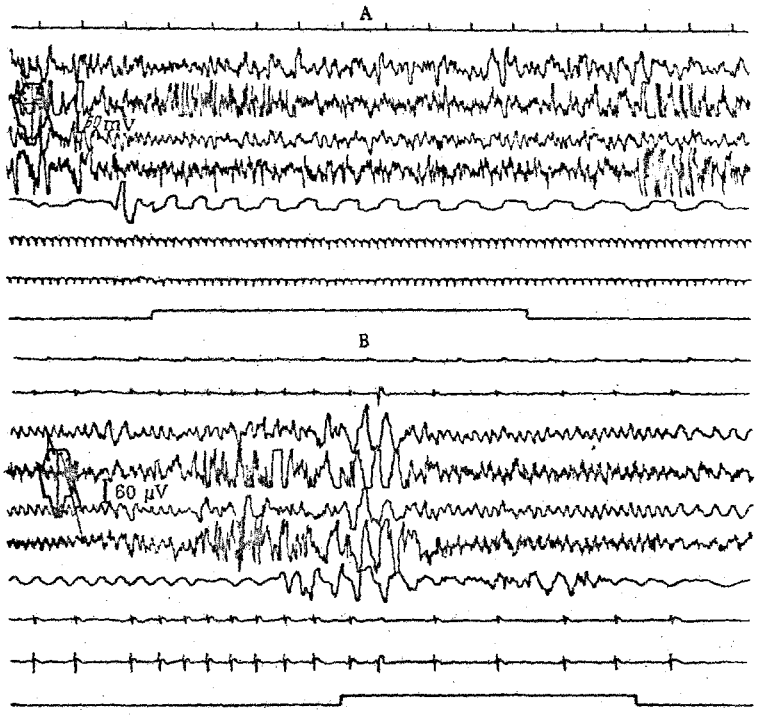

Fig. 2. Changes in the ECG, EEG, and respiration of a rabbit during stimulation of the lateral preoptic region of the hypothalamus (2 V, 90/sec, 1 msec) in phase I of the action of serotonin injected intravenously (2 mg/kg). A) Before injection; B) immediately after injection. From top to bottom: time marker (1 sec), EEG of right occipital and motor cortex, left occipital and motor cortex, respiration, ECG (standard lead II and chest lead P_4), marker of stimulation (elevation of bottom line). In B, standard lead III of the ECG is shown below the time marker.

described fully elsewhere [2, 4]. The possibility cannot be ruled out that functional changes in the autonomic centers in the second phase were the result of the direct action of serotonin on the hypothalamus, where the blood-brain barrier is more permeable to biogenic amines [28].

A direct action of serotonin on the heart cannot be ruled out, as has been conclusively demonstrated on isolated organs by several workers [15, 18, 23, 25, 26]. However, in our experiments biphasic changes in cardiac activity were found under the influence of serotonin, accompanied by changes in the thresholds of electrical stimulation of the hypothalamus in relation not only to its descending effects (on the heart), but also its ascending effects (on the cerebral cortex). This suggests that the effect of serotonin on the heart is mediated through its hypothalamic regulatory centers, and possibly also through the autonomic nuclei and the dorsal nucleus of the vagus nerve in the medulla, which are directly connected with the hypothalamic structures by the bundle of Schutz [6, 9]. Experiments in which serotonin was injected into vagotomized animals, in which the characteristic changes in cardiac activity produced by serotonin, i.e., bradyarrhythmia, were absent strengthen the conclusion that the effect of serotonin on the heart is mediated through the central levels of cardiovascular regulation. Endogeneous serotonin may evidently participate in the regulation of cardiac activity. Comparison of the results now obtained with published data concerning the formation of endogeneous serotonin and its high concentration in the hypothalamus [10, 11, 13, 16] suggests that the intensity of its biosynthesis and metabolism in this part of the brain may be one of the mechanisms of the central regulation of cardiac activity.

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