EFFECT OF LITHIUM COMPOUNDS ON CARDIAC ARRHYTHMIAS INDUCED BY COMPRESSION OF THE COMMON CAROTID ARTERIES*

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In cases when ventricular arrhythmias develop against a background of potentiation of discharges in the sympathetic nerves of the heart, as a result of the central action of strophanthin, intravenous injection of lithium preparations have been shown [1] to reduce the level of sympathetic activity (SA) and to restore the sinus rhythm (SR). These results suggested that the antiarrhythmic action of lithium is linked with its ability to depress hyperactivity of the sympathetic nervous system.

To test this hypothesis the effect of lithium compounds was studied on arrhythmias arising in cats with divided vagus and aortic nerves in response to compression of the common carotid arteries. According to some observations [3], the development of arrhythmias in this case is due to enhancement of activity of the sympathetic nervous system in connection with removal of the inhibitory effect of impulses from baroreceptors of the cardio-aortic and carotid sinus reflexogenic zones on it. To assess changes in activity of the sympathetic system during compression of the common carotid arteries and in response to injection of lithium compounds discharges were recorded in the inferior cardiac or renal nerve, which are postganglionic sympathetic nerves.

EXPERIMENTAL METHOD

Experiments were carried out on 18 cats weighing 2.6-3.4 kg, anesthetized with chloralose (30 mg/kg) and urethane (500 mg/kg) intravenously.

Division of the vagus and aortic nerves (together with the cervical sympathetic nerve) and subsequent clamping of the common carotid arteries were carried out at the level of the larynx. The common carotid arteries were clamped in all animals three or four times at intervals of 15-30 min depending on the effect. The renal nerve (left) was exposed extraperitionally, divided, and its central end was placed on bipolar platinum electrodes. The right inferior cardiac nerve was exposed near the stellate ganglion, after preliminary removal (without injury to the dura) of the first two ribs, and it was placed without dividing it on the same electrode. To prevent possible movement of the nerves relative to the electrodes on account of respiration, pneumothorax was induced distally to the fourth rib. To prevent drying and cooling of the nerve, the hollow formed by surrounding tissues was filled with warm mineral oil. The animals were immobilized with succinylcholine (150 µg/kg/min intravenously) and artificially ventilated. The tidal volume was determined from the animal's body weight by means of nomograms [5]. The body temperature (rectal) was maintained by a heater at 36-38°C. The arterial blood pressure (BP) was measured with an electromanometer through a polyethylene catheter introduced into the femoral artery. Potentials of sympathetic nerves, their mean in-

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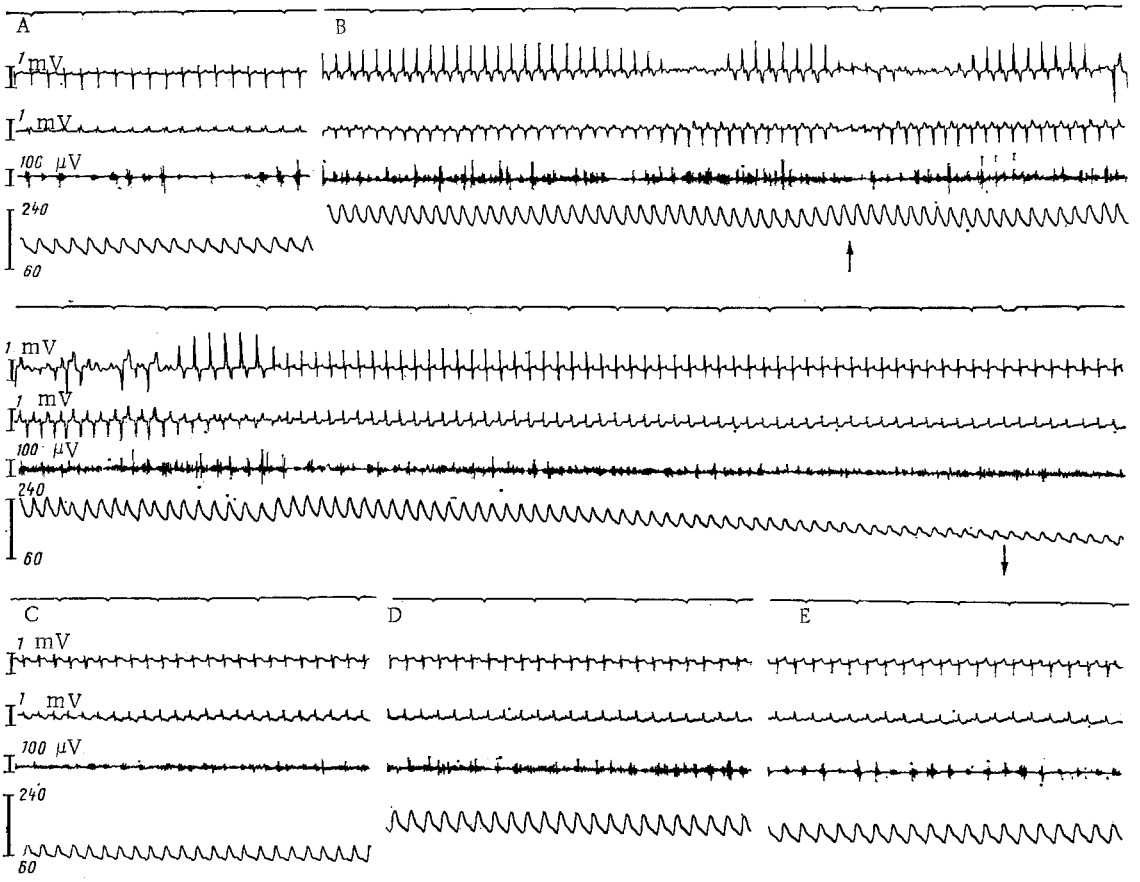

Fig. 1. Development of arrhythmia after compression of common carotid arteries and antiarrhythmic action of lithium hydroxybutyrate (400 mg/kg). A) original state (after division of vagus and aortic nerves); B) 40 sec after compression, VT; arrows indicate beginning and end of injection of lithium hydroxybutyrate; C) 15 sec after end of injection of compound; D) 1 min after injection; E) 30 sec after removal of clamp. Here and in Fig. 2, from top to bottom: time marker 1 sec, ECG in thoracic lead and in standard lead II, discharges in inferior cardiac nerve, BP (in mm Hg).

tensity, BP, and the ECG in standard lead II and chest leads, were recorded on the RM-86 polygraph (Nihon Kohden, Japan). Lithium chloride (200 mg/kg) and lithium hydroxybutyrate (200 or 400 mg/kg) were injected intraveously as 10% solutions.

EXPERIMENTAL RESULTS

After division of the vagus and aortic nerves BP and the cardiac frequency (CF) were 120-180 mm Hg and 180-260 beats/min, respectively.

During compression of the common carotid arteries 14 of the 18 animals developed arrhythmias; in half of the animals they recurred when compression was repeated. In six cats ventricular extrasystoles (VES) appeared 15-30 sec after the beginning of compression, and by the end of the first minute they changed to ventricular tachycardia (VT) or to an idioventricular rhythm (IVR), often against the background of atrioventricular dissociation. In the remaining animals arrhythmias began immediately with VT or IVR, but not until 30 sec after the time of compression of the carotid arteries (five experiments) or later still, at the beginning of the second minute (three experiments). Arrhythmias were always preceded by an increase in SA, which began immediately after compression. In 11 animals SA reached its maximal value 10-20 sec after the beginning of compression, and thereafter it was maintained at the same level or fell slightly. In three cases activity increased by a further 5-7% by the time of appearance of VT. The maximal increase in SA was 170-230% (in four experiments), 60-100% (in seven experiments), and 20-40% (in three experiments). This great difference in the magnitude of responses of SA to compression of the common carotid artery could not be attributed to the fact

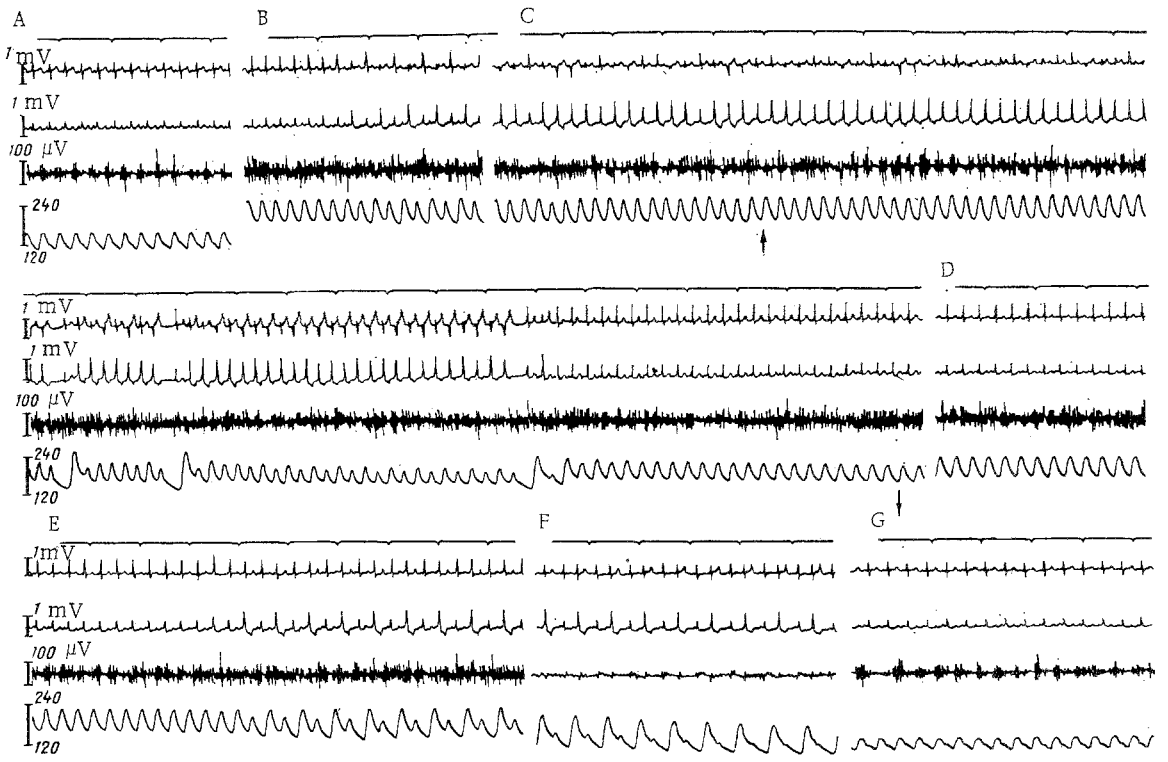

Fig. 2. Antiarrhythmic effect of lithium hydroxybutyrate (200 mg/kg) in arrhythmias induced by compression of common carotid arteries. A) original state (after division of vagus and aortic nerves); B) 25 sec after compression, appearance of VES; C) 1 min after compression ; injection of lithium hydroxybutyrate (beginning and end of injection indicated by arrows); restoration of SR at end of injection; D) 15 sec after end of injection of compound; E) 1 min after end of injection, appearance of late VES of bigeminy type; F) 10 sec after removal of clamp; G) 30 sec after removal of clamp, SR.

that discharges were recorded in different sympathetic nerves. The increase in activity was accompanied by an increase in BP by 33-55% (in 11 cats) or by 60-80% (in 3 cats) from the initial level, and also by an increase of 13-33% in CF. In seven control animals the arrhythmias continued throughout the period of arterial compression (from 1 to 5 min); SR was restored 10-15 sec after removal of the clamps. Only in one experiment did SR recover after 3 min, while the clamps were still *in situ* (the maximal increase in SA in this experiment was 20% of the initial level). During the first 30 sec after removal of the clamps SA was sharply inhibited and BP and CF fell rapidly. By the 3rd-5th minute SA, BP, and CF were established at close to their initial levels.

In four experiments no disturbances of rhythm appeared during compression of the common carotid arteries. The maximal increase in SA was observed in these animals 15-40 sec after the beginning of compression, and amounted on average to 27%. BP and CF were increased on average by 45 and 6%, respectively.

SA fell rapidly after injection of lithium chloride or hydroxybutyrate (6 experiments). The greatest fall was observed 20-40 sec after the beginning of injection of the compounds, when it amounted to 34-92% (relative to the highest level attained during compression). The greatest fall in SA (to 22-56% of its initial level) was produced by injection of lithium hydroxybutyrate in a dose of 400 mg/kg. When lithium hydroxybutyrate was injected in a dose of 200 mg/kg SA fell by the smallest amount and remained 65% higher than the initial level in this case (experiment 1). Parallel with the fall in SA, in all experiments BP and CF fell usually by 25-70 and 5-34%, respectively. SR was restored in all animals 30-35 sec after the beginning of injection of lithium preparations (Fig. 1). The case when VP developed 10 sec after the beginning of injection of lithium chloride, with a change to ventricular fibrillation, and SR was restored at the beginning of the first minute after a short period of IVR, was an exception. In the experiments in which the fall in SA was minimal, 1 min after the

end of injection of lithium hydroxybutyrate (200 mg/kg), VES of bigeminy type appeared against the background of SR, and it disappeared 15-20 sec after removal of the clamps (Fig. 2). In cases (4 experiments) when the lithium compounds were injected during repeated clamping of the carotid arteries, SR was restored in the same way and between the same time limits.

Injection of lithium preparations without preliminary compression of the common carotid arteries did not cause significant changes in SA, BP, or CF.

The results of these investigations show that compression of the common carotid arteries leads to the development of arrhythmias in cases when it evokes a significant and rapid rise in SA, accompanied by an increase in BP and CF. If the increase in activity was small or developed comparatively slowly, arrhythmias did not appear. This suggests that the strengthening of SA is a pathogenetic link in the chain of development of ventricular tachyarrhythmias. A relative increase in SA compared with the initial level, which evidently depends both on the state of the centers responsible for realization of the inhibitory effect of impulses from baroreceptors on SA and also on the state of the baroreceptors themselves, is an important factor. The fact that a marked increase in SA was observed in cases when pulse modulation of the discharges in the sympathetic nerves was sufficiently clearly expressed is in agreement with this proposition. It has been reported [4] that ventricular arrhythmias may appear in response to frequent repeated compressions of the common carotid arteries. The disagreement between these data and the results of the present experiments can probably be attributed to the significantly shorter period of compression (15 sec) or the less deep anesthesia in the experiment by the authors cited.

Injection of lithium preparations against the background of arrhythmias evoked by compression of the common carotid arteries led in all experiments to a decrease in SA, BP, and CF and to restoration of SR. SA, BP, and CF could subsequently rise, but the arrhythmias did not return. Only in one experiment, in which lithium hydroxybutyrate was injected in a dose of 200 mg/kg and the fall in SA was minimal, did VES reappear against the background of SR. This could be associated with the relatively low lithium content in this dose of the drug, for injection of lithium hydroxybutyrate in a dose of 400 mg/kg (the lithium content in 400 mg of lithium hydroxybutyrate corresponds approximately to its content in 200 mg of lithium chloride) led to the greatest fall in SA, and repeated arrhythmias did not arise in these experiments even during prolonged compression of the carotid arteries.

Considering the stronger depression of SA by lithium hydroxybutyrate, the particular features of its antiarrhythmic effect in strophanthin-induced arrhythmias [1, 2], and the tranquilizing properties of hydroxybutyrate, lithium hydroxybutyrate can be expected to be more effective than lithium chloride in clinical practice.

LITERATURE CITED

1. E. V. Lukoshkova, E. G. Kryzhanovskaya, and M. N. Karpova, Byull, Eksp. Biol. Med., 91, No. 1, 35 (1981).
2. A. A. Stolyarchuk, N.N. Samoilov, A. V. Rychko, et al., Farmakol. Toksikol., No. 1, 37 (1979).
3. C. Y. Chai, T. F. Huang, and S. C. Wang, Am. J. Physiol., 215, 1316 (1968).
4. C. Y. Chai, T. M. Lee, and S. C. Wang, Arch. Int. Pharmacodyn., 219, 180 (1976).
5. L. I. Kleinman and E. P. Radford, J. Appl. Physiol., 19, 360 (1964).