EFFECTS OF 2,4-DINITROPHENOL ON THE ELECTROCARDIOGRAM IN THE FROG

I. P. Lapin

Department of Pharmacology (Head, Corresponding Member AMN SSSR Prof. V. M. Karasik) of the Leningrad Pediatric Medical Institute

(Presented by Active Member AMN SSSR V. V. Parin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 50, No. 8, pp. 97-100, August, 1960
Original article received August 17, 1959

The development of electrocardiography was just getting under way when it began to appear that particular components of the electrocardiogram (EKG), especially the T wave, are dependent on the state of metabolic processes in the myocardium [11, 17]. Analysis of a large volume of experimental and clinical data accumulated prior to 1936 gave G. F. Lang [5] grounds for the opinion that the T wave is based on biochemical processes in the myocardium, and that the use of the electrocardiographic method showed great promise for the study of cardiac metabolism.

The progress made by modern biochemistry in the study of the energetics of muscle tissue has aroused interest in the metabolism of energy-rich (macroergic) phosphorus compounds in the myocardium, and has led to the publication of works dealing with studies of this metabolism involving the use of electrocardiography. For example, it has been found that a reduction of ATPase activity in hypocalcemia results in prolongation of electrical systole (the Q–T interval), the most characteristic sign of so-called energetic-dynamic cardiac insufficiency [16]. Enhancement of the breakdown of macroergic compounds under the influence of epinephrine, and diminution of this breakdown under the influence of acetylcholine, are combined primarily with changes in the T wave [9]. In experimental hypertension in rabbits, a disturbance of energetic processes in the myocardium is manifested in the EKG through a reduction in the height of the T wave and a displacement of the S–T interval [10].

In electrocardiographic investigations extensive use has been made of the method, widely employed in experimental medicine, of toxic depression of respiratory and glycolytic phosphorylation with so-called inhibitors. Under the influence of agents that poison glycolytic phosphorylation-sodium monoiodoacetate and sodium fluoride, the amplitude of the slow component of the ventricular complex (T wave) increases; then the T wave assumes a diphasic form, becoming less diphasic as the action of the poisons is prolonged; at the same time the initial portion of the EKG, the R wave, remains unchanged [3]. Methylene blue, an agent that causes dissociation of respiration and phosphorylation, leads in high concentrations to prolongation of the S–T interval and to a slight elevation of the T wave in the EKG of the frog [4].

We have been unable to find published reports of changes produced in the EKG of the frog by 2,4-dinitrophenol (DNP), the substance most widely used for the purpose of dissociating respiration from phosphorylation. The present paper is concerned with an investigation of this phenomenon.

METHOD

Experiments were carried out in the fall and winter months. The frogs (Rana temporaria) were immobilized with curare or urethan. The DNP solution was injected into the femoral lymph sac. Since the cessation of pulmonary respiration that occurs in animals under the influence of curare or urethan markedly enhances the toxic effect of DNP [6, 7], we injected DNP in doses (5-20 γ/g) that produced no visible changes in intact animals, but were lethal for immobilized animals. We were forced to abandon attempts to record the EKG with nonpolarizing electrodes, in spite of the fact that, as is well known from special studies [15], bringing the electrodes close to the heart of the frog results in a fuller representation of the true nature of the heart's electrical activity. After some orienting experiments with the use of direct recording, we chose to record the EKG in the standard leads, using steel needles implanted under the skin of the extremities and connected by wires to an ÉKP-4M electrocardiograph. The choice of standard leads was dictated mainly by two considerations: 1) to record changes in the electrical activity of the heart under the influence of sublethal doses of DNP from the moment of injection of the poison to the onset of cardiac arrest, one must record for 3-4 hours; but $1\frac{1}{2}$-2hours after the heart is exposed, the distortions in the EKG, owing to a variety of causes (drying, etc.), become considerable [11, 12, 13]; 2) in the course of these experiments it was found that the exposed heart stops beating later than the nonexposed heart in DNP poisoning (this is evidently related to the diffusion of oxygen through the epicardium); under our experimental conditions this factor is not susceptible to precise quantitative evaluation, and so complicates the method. By comparing the three standard leads we established that the waves were more pronounced in lead III (left forelimb — left hindlimb); consequently, we thereafter recorded the EKG in lead III in all the frogs (40 experiments on 51 animals, of which 11 were controls). The over-all form of the EKG of curarized (or urethanized) frogs in our experiments was quite similar to those cited in published reports [8, 14].

RESULTS

The initial changes produced by DNP are slowing of the heart rate (before poisoning, 36-52 beats/min) shown by a lengthening of the R—R interval, and a marked elevation and deformation (diphasic form) of the T wave (Fig. 1). In the terminal period the form of the T wave returns to normal, or nearly so. As the toxic condition develops, the bradycardia progresses. Subsequently, there occurs a prolongation of the P—R interval (slowing of atrioventricular conduction) and the R—T interval (slowing of electrical systole), developing much more intensively than the slowing of the rate (before poisoning, the duration of these intervals was 0.35-0.42 sec and 0.65-0.92 sec, respectively). Thus, on comparison of frames 4 and 5 in Fig. 1, we see that, against the background of developing bradycardia, some acceleration of heart rate has occurred, and the duration of the R—T interval has increased. In those cases in which the S peak was distinctly evident before poisoning, it decreased in amplitude or disappeared as the poisoning progressed. The Q wave, in agreement with published data [1, 17], was not seen in the normal frog EKG in our experiments. All the EKG changes described were also seen in experiments with preliminary atropinization.

The almost constant invariability of the R wave observed in DNP poisoning of the heart provides a basis for the assumption that the process of depolarization, of which the R wave is the reflection, and the subsequent polarization of the heart, are relatively independent of the state of respiratory phosphorylation (an analogous assumption is made in regard to the glycolytic process). Just before cardiac arrest, the splitting of the ventricular complex described by E. I. Borisova and V. S. Rusinov [2]

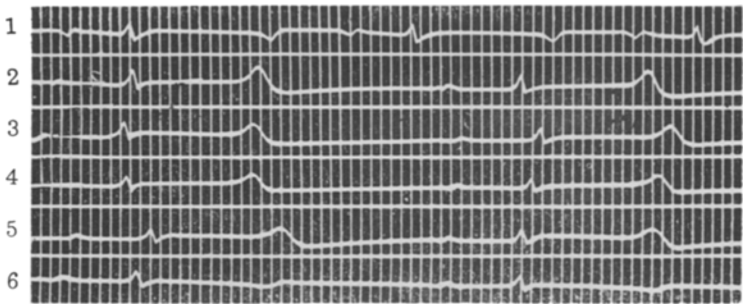

Fig. 1. Changes in the EKG of the frog under the influence of DNP. Time marker, 0.05 seconds. 1) Background (frog immobilized with curare, 2 γ/g; heart rate 35 beats/min); 2, 3, 4, 5, 6) 15, 47, 60, 90, and 120 minutes, respectively, after injection of DNP, 20 γ/g (heart rate 26, 24, 24, 28, and 28 beats/min, respectively).

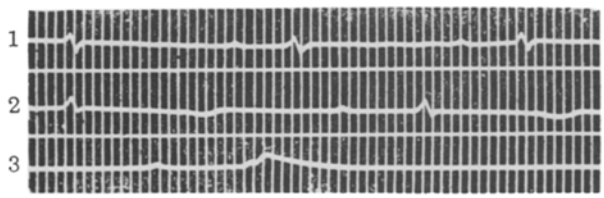

Fig. 2. Changes in the EKG of the frog under the influence of DNP. Time marker, 0.05 seconds. 1) Background (frog immobilized with urethan, 3 mg/g; heart rate 52 beats/min); 2, 3) 60 and 90 minutes, respectively after injection of DNP, 20 γ/g (heart rate 33 and 16 beats/min, respectively). Splitting of ventricular complex, of the type seen in longitudinal dissociation of single-chambered ventricle.

was observed, of the type seen in longitudinal dissociation of a single-chambered ventricle (3, Fig. 2).

These principal changes in the EKG produced by DNP gives evidence that when respiratory phosphorylation is depressed, the primary disturbances are disturbances in sinus automatism, in the restorative processes (of which the T wave is an expression) that ensure the spread of excitation, in atrioventricular conduction, and in electrical systole.

SUMMARY

The principal changes produced in the EKG of the frog by 2,4-dinitrophenol, an agent that dissociates respiration from phosphorylation, are (1) progressive slowing of the heart rate, (2) marked elevation and deformation of the T wave (it becomes diphasic), (3) lengthening of the P–R interval (slowing of atrioventricular conduction) and the R–T interval (slowing of electrical systole), and (4) diminution or disappearance of the S wave, developing much more rapidly than the slowing of the heart rate.

LITERATURE CITED

1. E. I. Borisova and V. S. Rusinov, Byull. Éksp. Biol. Med. 10, 337 (1940).
2. E. I. Borisova and V. S. Rusinov, Fiziol. Zhur. SSSR 2, 216 (1949).
3. N. A. Kelareva, Fiziol. Zhur. SSSR 1, 74 (1959).
4. E. A. Kyandzhuntseva, in: Materials on Experimental and Clinical Electrocardiography [in Russian] (Moscow, 1953) p. 173.
5. G. F. Lang, Problems of Circulatory Pathology and of Clinical Aspects of Cardiovascular Diseases [in Russian] (Leningrad, 1936) chap. 1.
6. I. P. Lapin, Byull. Éksp. Biol. Med. 41, 54(1956).*
7. I. P. Lapin, The Effect of Chemical Agents That Disturb Coupled Phosphorylation on the Principal Functions of the Frog Heart [in Russian] (Author's abstract, Cand. Diss. (Leningrad, 1959).
8. D. A. Lapitskii and G. R. Britanishskii, in: Mechanisms of the Pathological Reactions [in Russian] (Leningrad, 1949) chap. 11-15, p. 308.
9. M. E. Raiskina, Farmakol. i Toksikol. 1, 31 (1951).
10. M. E. Raiskina, Byull. Éksp. Biol. Med. 39, 36 (1955).
11. A. Samojloff, Arch. ges. physiol. 135, 417 (1910).
12. A. Samojloff, Arch. Anat. u. Physiol., Physiol. Abt. Suppl. 207 (1906).
13. L. I. Fogel'son and I. A. Chernogorov, Med.-Biol. Zhur. 6, 15 (1928).
14. G. Arsenescu et al., Stud. cer. de fisiologie 2, 373 (1957).
15. H. W. Diserens and R. W. Ware, Am. J. Physiol. 175, 191 (1953).
16. H. Grauer, Helvet. med. acta 14, 394 (1947).
17. H. Straub, Ztschr. Biol. 53, 499 (1910).

*See English translation.