ON THE COMBINED ACTION OF CAFFEINE AND STROPHANTHIN

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The significance of the basic functional state of the central nervous system in determining the effect of therapeutics introduced into the system is accepted generally. Directed action on the central link of the reflex apparatuses, causing this or that pharmacological effect, is a perceptive, but until now rarely used, method of changing the qualitative and quantitative aspects of a given effect.

The present work is an attempt to establish to what extent stimulation of the central nervous system, caused by caffeine, affects the specific action of the cardiac glycosides.

The solution of this problem is of great pratical interest in connection with the frequent use of this combination in clinical practice. However, the problem of the expediency of this combined use of caffeine and cardiac glycosides has not been resolved, since investigations in this area are not numerous, while the results are contradictory.

P. M. Subbotin [5] established the considerable increase in the activity of the cardiac glycosides during simultaneous administration of caffeine (from 109 to 226.5%). A. M. Preobrazhensky noted an increase in the minimum lethal dose of the cardiac glycosides during their administration together with caffeine. In connection with this, the hypothesis has been made that caffeine in small doses (2-50 mg) diminishes the action of the cardiac glycosides, while it raises their activity in large ones (160-170 mg). The reinforcement of the specific action of strophanthin when combined with caffeine was connected with an increase in the absorption of the cardiac glycosides. The reinforcement of the action of digitalis under the influence of caffeine was also noted by M. P. Nikolaev [2]. The majority of the experimental data cited above was obtained using the method of standardizing the cardiac glycosides biologically on narcotized animals under acute experimental conditions. Caffeine and strophanthin were administered intravenously and simultaneously, which is excluded in clinical pratice. However, we did not find in the literature available to us any clinical observations confirming the fact that the action of the cardiac glycosides is reinforced under the influence of caffeine. The expediency of the combined use of caffeine and digitalis is ascribed by clinicians to the vasodilatory action of caffeine (or its derivatives) on the coronary vessels [1, 4] or to its effect on the tonus of the blood vessels in general [6].

Thus, the experimental and clinical data on the question of the combined application of caffeine and cardiac glycosides are contradictory and need to be made more precise and supplemented.

EXPERIMENTAL METHODS

The experiments were carried out on 8 rabbits and 2 dogs. The animals were first accustomed to the experimental surroundings. The preparations under study were administered in the following order: first, caffeine solution was administered subcutaneously to the animal; then, 10 minutes later, strophanthin solution was administered intravenously at a constant rate of flow (1 ml in 30 seconds). The electrocardiogram record was made with the three standard leads 5, 20, and 40 minutes after the strophanthin injection. As a control caffeine,

strophanthin and isotonic sodium chloride solution were administered to the animals in part of the experiments.

In experiments on rabbits, caffeine was used in dosages of 8 mg/kg, 16 mg/kg; strophanthin – in dosages of 0.02 mg/kg, 0.04 mg/kg and 0.06 mg/kg. These doses were also used when the administration was combined. With dogs, caffeine was tested in a dosage of 12.5 mg/kg, strophanthin – in a dosage of 0.03 mg/kg. In the work 20% solution of caffeine and sodium benzoate was used and 0.05% solution of K-strophanthin. In all, 58 experiments were set up, 14 of these on dogs.

Experiments on Rabbits

In order to discover the changes made in an electrocardiogram by the administration of caffeine, 12 experiments were set up. The administration of 8 mg/kg of caffeine to rabbits did not change the cardiac rhythm at all significantly; the configuration of the electrocardiogram remained stable, in only two cases was an insignificant deviation of the S – T segment from the isoelectric line observed, the maximum increase of the $R - R_1$ interval consisted of 0.015 seconds.

In a dosage of 16 mg/kg caffeine caused some slowing of the cardiac rhythm. The P – Q interval remained unchanged in all cases, the Q – T segment was extended by 0.01-0.02 seconds in two experiments out of four. In two experiments an enlargement in the T deflection was observed and a rise of the S – T segment in one. The administration of strophanthin (12 experiments) regularly caused a slowing of the cardiac rhythm. With a dose of 0.02 mg/kg of strophanthin the $R - R_1$ interval increased 0.005 seconds on the average, at a doubled dose the slowing of the cardiac rhythm was more significant, averaging 0.02 seconds. The administration of 0.06 mg/kg of strophanthin gave the most sharply evidenced increase of the $R - R_1$ interval, 0.03 seconds on the average. The P – Q interval increased insignificantly in a number of cases: in one case with the injection of 0.02 mg/kg of strophanthin, in 2 experiments out of four with the administration of 0.04 mg/kg. A dosage of 0.06 mg/kg of strophanthin did not change the atrio-ventricular conductivity in any significant way. More constant and uniform was the increase in the Q – T segment, although within the limits of the tested dosages of strophanthin it was not possible to observe a parallel between the intensity of the changes of the Q – T segment and the size of the dosage. The T deflection usually did not change, only with the administration of 0.04 mg/kg of strophanthin was its tendency to decrease observed. The most typical changes in the electrocardiogram under the influence of strophanthin were, along with an increase in the Q – T segment, a lowering of the S – T segment, which, however, was not apparent in all the experiments. When a dose of 8 mg/kg of caffeine was combined with a dose of 0.02 mg/kg of strophanthin a sharper slowing of the cardiac rhythm was observed, averaging 0.025 seconds. The atrio-ventricular conductivity decreased in all the experiments. The electrical systole lengthened. The changes of the T deflection were also more evident, and only its lowering was observed. In three experiments a distinct lowering of the S – T segment was observed, typical of the action of strophanthin.

The facts presented indicate that the preliminary administration of caffeine considerably increases the specific action of strophanthin (Fig. 1). When the dosage of strophanthin was increased, the changes were more pronounced.

Thus, a toxic effect was observed in three experiments out of four with the administration of a dosage of 0.06 mg/kg of strophanthin, while the electrocardiogram was severely distorted in these cases (Fig. 2). It should be noted especially that the use of caffeine eliminated the lowering of the S – T segment typical of the picture of the strophanthin effect.

In the same way, the preliminary administration of caffeine increased the sensitivity of the rabbits also to the middle of the tested dosages of strophanthin – 0.04 mg/kg.

When the caffeine dosage was increased to 16 mg/kg combined with strophanthin (0.04 mg/kg, 0.06 mg/kg) neither a lowering of the atrio-ventricular conductivity nor an increase in the period of electrical systole was observed, which are observed with the isolated action of strophanthin. The changes in the T deflection and the S – T segments were less evident than with the action of strophanthin alone, while the changes in the T deflection correlated better with the action of caffeine than of strophanthin. Typical also is the fact that with the use of a dosage of 0.06 mg/kg not once were toxic effects observed in the animals.

Thus, with an increase of the caffeine dosage from 8 mg/kg to 16 mg/kg the strophanthin effect becomes less evident; consequently, the functional synergistic relationship between strophanthin and caffeine is replaced by an antagonistic relationship.

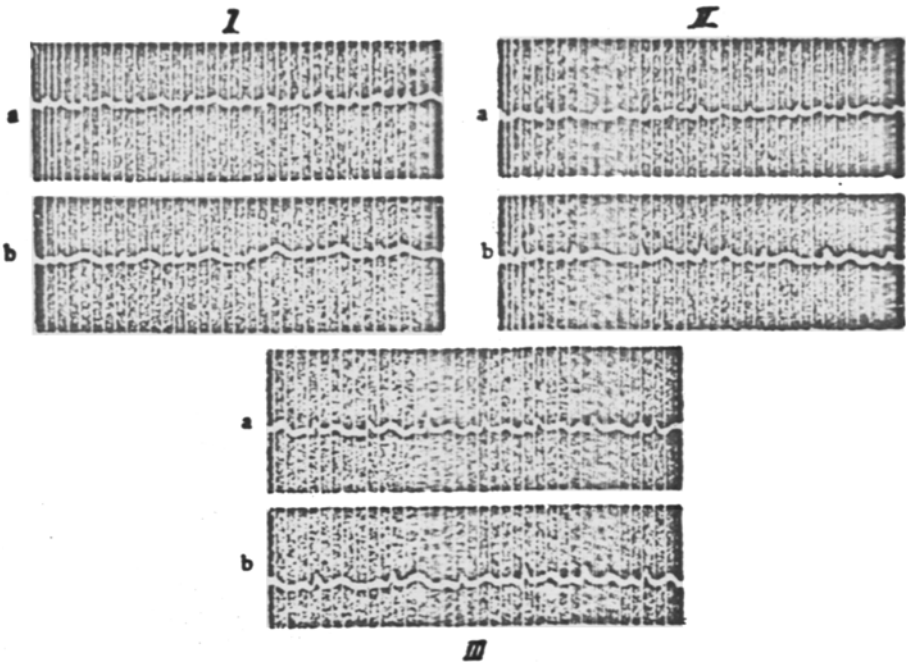

Fig. 1. Changes in the electrocardiogram of a rabbit with the administration of: I) caffeine (8 mg/kg): a) normal, b) 30 minutes after administration; II) strophanthin (0.02 mg/kg): a) normal, b) 20 minutes after administration; III) with the combined action of caffeine and strophanthin: a) normal, b) 20 minutes after administration of strophanthin (10 minutes before the administration of strophanthin, caffeine was administered).

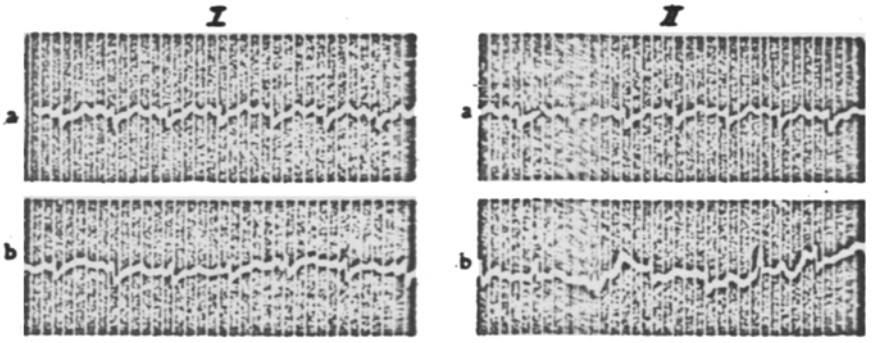

Fig. 2. Changes in the electrocardiogram of a rabbit with the administration of: I) strophanthin (0.06 mg/kg): a) normal, b) 20 minutes after administration; II) with the combined action of caffeine (8 mg/kg) and strophanthin (0.06 mg/kg): a) normal, b) 20 minutes after administration of strophanthin (caffeine was administered 10 minutes before the strophanthin).

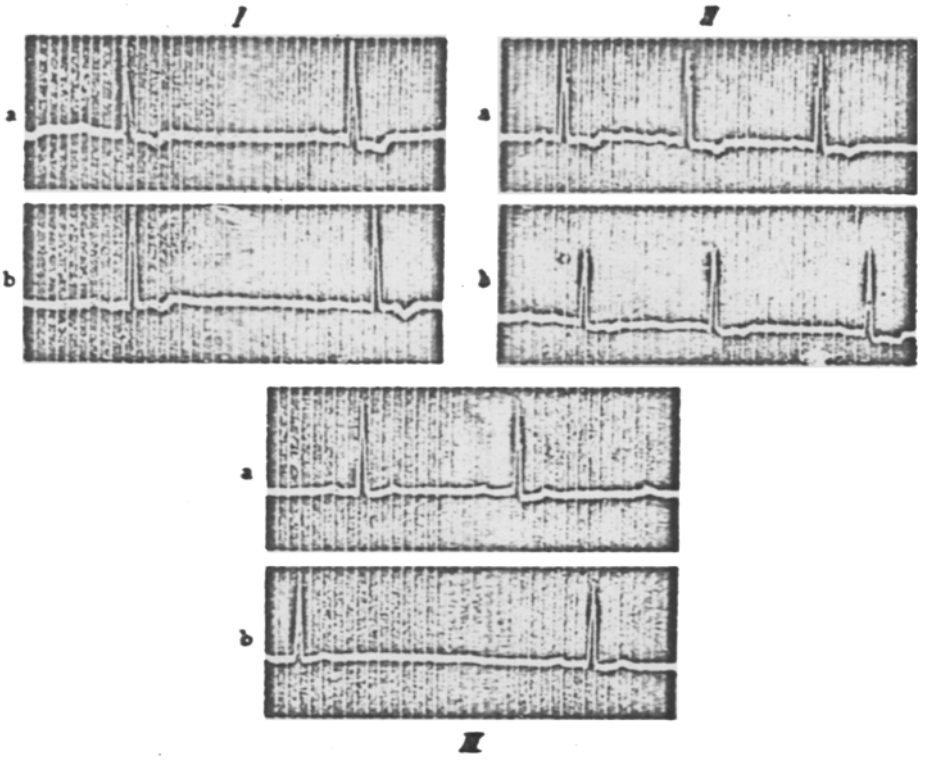

Fig. 3. Changes in the electrocardiogram of a dog with the administration of: I) caffeine (12.5 mg/kg): a) normal, b) 30 minutes after administration; II) strophanthin (0.03 mg/kg): a) normal, b) 20 minutes after administration; III) with the combined action of caffeine and strophanthin: a) normal, b) 20 minutes after administration of strophanthin (caffeine was administered 10 minutes before the strophanthin).

Caffeine in a dosage of 12.5 mg/kg caused a slight slowing of the cardiac rhythm and a tendency to smooth out the T deflection in dogs. The rest of the elements of the electrocardiogram remained stable. Strophanthin in a dosage of 0.03 mg/kg led to an insignificant shortening of the Q–T segment and sometimes to an increase in the negative T deflection. The atrio-ventricular conductivity decreased in only one experiment out of six. Evident slowing of the cardiac rhythm was not observed.

The combined administration of caffeine and strophanthin in the indicated dosages caused a distinct arhythmia in all the experiments: the $R-R_1$ interval varied from 0.5 to 1.5 seconds (dog Zhuk) and from 0.5 to 2.5 seconds (dog Fedot).

In three experiments out of four the atrio-ventricular conductivity decreased noticeably. The electrical systole shortened somewhat (Fig. 3). Thus in experiments on dogs also, preliminary administration of caffeine caused an increase in the vagotropic effect of strophanthin.

The synergism between small doses of caffeine and strophanthin observed in our experiments should be regarded as the result of the sensitization of the vagus mechanism by caffeine to the subsequent action of strophanthin. I. P. Pavlov pointed out the double action of caffeine, depending on the dosage: in small doses, caffeine raises the vagal tonus, while large doses lead to the functional exclusion of the cardiac branches of the vagus nerves. Since strophanthin has a distinct vagotropic action, it is natural that the vagotropic effect is increased when it is used with small doses of caffeine. Against a background of the action of large doses of caffeine, however, this effect of strophanthin decreases or disappears completely, which can be connected with the parabiotic state of the vagus nerves.

The role of the vagus nerves in the combined action of strophanthin and caffeine is confirmed also by experiments on atropinized frogs, which were carried out in our laboratory by A. I. Zolotarev, in which an absence of any effect from the preliminary administration of caffeine on the action of strophanthin was observed.

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