Cardiac Glucosides and Lundsgaard Contracture

The striped muscle of vertebrates poisoned with monohalogeno acetate shows *when stimulated* a progressive, irreversible contracture and inexcitability. This contracture, the Lundsgaard phenomenon, is associated with the inhibition of carbohydrate metabolism. All the substances which react with the –SH groups of cysteine, glutathione, and proteins (i. e. "*thioloprive*" substances[1]), when applied to isolated amphibian muscle, give the same contracture curve when the muscle is stimulated: for instance, heavy metal ions, arsenic compounds[2], vesicants and lacrymators, maleic acid (but not fumaric) and oxidizing substances including quinones and peroxides.

Further work has shown that the Lundsgaard contracture is the physiological translation of any biochemical lesion of carbohydrate metabolism[3].

At first sight, nothing is closer to the Lundsgaard phenomenon than the contracture of the frog's heart poisoned with a cardiac glucoside, and this similarity is not accidental[1].

A series of papers of KRAYER, R. MENDEZ, and others[4] have shown the following facts:– (1) substances (synthetic or natural) containing the unsaturated lactone ring, which in the molecule of cardiac glucosides is essential for digitalis-like action, cause a progressive ventricular contracture of the isolated frog's heart; (2) ascorbic acid, which can be considered as an unsaturated lactone, has a digitalis-like action on the frog's heart, and this action is due to hydrogen peroxide formed during the oxidation of ascorbic acid; (3) besides H_2O_2 (a confirmation of RICHTER'S[5] observations), various sulfhydryl reagents applied to the frog's heart lead to progressive contracture and inexcitability.

Recent work in my laboratory has proved that isolated amphibian striped muscle, when poisoned with digitoxin, shows an incomplete contracture when periodically excited with KCl; but we have not observed a reaction *in vitro* between cardiac glucosides and sulfhydryl substances in an atmosphere of nitrogen.

Many substances have the same general effect (with quantitative differences) on striped and cardiac muscle; the digitalis ventricular contraction of the frog's heart may be considered as a particular case of the Lundsgaard contracture. The biochemical background of the Lundsgaard contracture is an inhibition of glycolysis by blocking of the SH enzymes; lactic acid is not produced; the phosphagen stores are rapidly exhausted.

Several investigations by various german authors show that cardiac glucosides inhibit glycolysis *in vitro*:– (1) strophanthin 0·001 to 0·1% decreases oxygen consumption and CO_2 production of mouse liver and guinea-pig's brain; anaerobic glycolysis is inhibited by strophanthin concentration as low as 0·001%[6]; (2) according to HAARMANN[7] and TOBBEN[8], lactic acid formation in hearts poisoned with strophanthin is nearly completely inhibited, although it might be increased when small concentrations of strophanthin are used. Further discussion of these facts is given by LENDLE[1]. In this field of biochemical action of cardiac glucosides, much more information is needed before reaching a definite conclusion; all that can be said at present is that already a few data are available by favour of the hypothesis which assimilates cardiac glucoside contracture to the Lundsgaard phenomenon on striped muscle.

Quite naturally, many arguments can be raised against this idea; conflicting observations are numerous. We agree with MENDEZ[2] when he stresses the point that therapeutic and toxic actions are very different phenomena in digitalis action; but we like to give a final clinical argument.

The typical disease where inhibition of carbohydrate metabolism (at the level of pyruvic acid) plays the dominant role is beriberi. Sudden death from cardiac failure and vasomotor collapse is common in human severe thiamin deficiency; it is usual in criminal digitalis intoxications. The T wave of the electrocardiogram is typically flattened or inverted in beriberi and in digitalis poisoning; this anomaly disappears when both conditions are cured; failure of the beriberi heart to respond to digitalis therapy has been noted, and considered as a criterium[3].

Thus, if one considers the pharmacological evidence, the clinical data and the little we know about the biochemical action of cardiac glucosides, one gathers without difficulty the elements of a sound working hypothesis which may be formulated as follows: the action of cardiac glucosides on the heart is the consequence of a discrete inhibition of carbohydrate metabolism, presumably by the indirect blocking of some –SH enzyme (or enzymes).

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Résumé

De nombreux arguments d'ordre pharmacologique, en accord avec quelques expériences biochimiques et des observations cliniques, montrent que la contracture cardiaque provoquée par les corps digitaliques peut-être assimilée à la contracture de Lundsgaard du muscle strié. Une hypothèse de travail est proposée, selon laquelle l'action des glucosides digitaliques sur le cœur est la conséquence d'une inhibition partielle du métabolisme des hydrates de carbone.

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Protecting Effect of Heparin on the Oxidation of Thrombin[1]

There can be found many statements in the widespread literature on heparin about its antithrombin–antiprothrombin–and antikinase effect.

[1] With the help of the «Roche»-Studienstiftung.