DIRECT EVIDENCE FOR THE INTIMATE RELATIONSHIP BETWEEN THE UPTAKE OF DIGITOXIN AND AN ACTIVITY OF GUINEA PIG HEART

SUMIKO FUJINO, HIDEYO OHISHKA, YUKO MOCHIDA AND MAMORU TANAKA

Department of Pharmacology, Sapporo Medical College, Sapporo

Received for publication June 24, 1964

Though the view, that there would be an intimate relationship between the cardiac action of digitalis glycosides and the uptake of the drugs by heart, has been often regarded as a well-established basis in understanding of the mechanism in the cardiac action of the drugs (1, 2), direct evidence for its validity is not yet given. The present communication is concerned with the direct demonstration of this evidence and shows a highly intimate relationship between the uptake of digitoxin and the cessation of beating in guinea pig heart.

Upon the addition of digitoxin of $2 \times 10^{-7}$ g/ml, the automatically driven guinea pig heart stops beating in 100 min under the condition of normal Ringer-Locke solution (a) and in 40 min under the potassium-deficient condition (b), whereas under the potassium-rich condition the heart continues to beat even in 250 min (c), as is shown in Fig. 1-A. At the time of cessation of beating, no response to electric shock given was detected. These mechanical and electrocardiographical results as such are not new; and such phenomena have been already reported (3-6). It is, however, very noteworthy that, when the uptake of digitoxin by heart is determined at the time of the cessation of beating, a new relationship on the cardiac action of digitoxin is recognizable: As is shown in columns a and b of Fig. 1-C, the uptake of digitoxin upon the cessation of beating is strikingly similar between the normal condition and under the potassium-deficient one, in spite of the considerably marked difference between their total volumes of perfusion fluid (Fig. 1-B). In accord with this intimate relationship, the column c of Fig. 1-C on the potassium-rich condition demonstrates that the uptake of digitoxin, which was determined before the cessation of beating, is smaller.
than the cases of cessation, in spite of its considerably large volume of perfusion fluid (column c in Fig. 1-B).

This highly intimate relationship between the uptake of digitoxin by heart and its toxic action is not only of significance in relation to the well-known but speculated basis in understanding of the cardiac action of digitalis glycosides (1, 2), but also of interest with respect to the explanation of the well-established phenomenon that the toxic action of digitoxin on heart is effected by the increase or decrease in concentration of potassium (3-6). Namely, the present relationship shows that the appearance of the toxic action of digitoxin relates directly to the uptake of the drug of a certain quantity, of which level is always constant regardless of the potassium concentrations in milieu, and that potassium in modified concentrations can only regulate the process of uptake.

How the uptake of digitoxin can determine the appearance of the toxic action is at present not yet understood. A biochemical analysis such as the search of intracellular components responsible for the uptake could, however, give a clue to elucidate the problem and lead to the solution of the mechanism in the whole cardiac actions of digitalis glycosides.

REFERENCES