6498

The Effect of Ouabain on the Oxygen Consumption of Cardiac Ventricular Muscle.

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Recently David[1] has reported that strophanthin in concentrations of 1-8 in 10^6 depresses equally both the frequency of beat and rate of oxygen consumption of the frog's auricle. Eismayer and Quincke[2] found that a low concentration (1×10^{-7}) of this substance increased the oxygen consumption of beating hearts about 20%, while high concentrations (1×10^{-5}) reduced it about 30%. But the latter concentration brought the heart to systolic standstill. The first studies on the influence of strophanthin on the oxygen consumption were those of Rhode and Ogawa,[3] who found that a heart arrested in systole by this drug consumed more oxygen than a normal beating heart. Otherwise the increase was proportional to the work done. In the reports mentioned, the drug was used in serum or Ringer's solution and the hearts were working. Clark[4] has shown the action of digitalis is dependent upon the presence of calcium ions.

In this experiment attempts were made to study the action of ouabain upon the oxygen consumption of resting cardiac muscle. The effects of this drug in sucrose and Ringer's solution were compared to see whether ions influenced the metabolic response.

Methods. The oxygen consumption measurements were done by means of the Thunberg differential volumeter modified by Fenn.[5] Each bottle had a capacity of about 15 cc. The capillary volume was about 2.5 cmm. per centimeter. The experimental bottle was fitted with 2 side-arms set at right angles to one another. The smaller one held a few drops of NaOH solution to absorb CO_2 and the larger contained the substance whose effect was to be determined. In all experiments the tissue was placed in the bottle without any solution bathing it. Four-tenths of a cc. of the reagent to be investigated were placed in the side-arm and tipped on the tissue at will. The bottles were filled with pure oxygen but were not shaken.

[1] David, J. C., *J. Pharm. and Exp. Therap.*, 1930, **40**, 229.

[2] Eismayer, G., and Quincke, H., *Arch. f. exp. Path. u. Pharm.*, 1930, **150**, 308.

[3] Rhode, E., and Ogawa, S., *Arch. f. exp. Path. u. Pharm.*, 1912, **69**, 200.

[4] Clark, A. J., *Proc. Roy. Soc. Med.*, 1912, **5**; *Therap. and Pharm.*, Sec., 181.

[5] Fenn, W. O., *Am. J. Physiol.*, 1927, **80**, 327.

The cardiac ventricular muscle of *Rana pipiens* was used. The ventricle of the heart was removed along the atrioventricular groove and cut longitudinally through the apex into 2 parts of as nearly equal size as possible. After blotting with filter paper to remove adherent blood, the muscle was immediately placed in the experimental bottle. The temperature was 22.5° C. and controlled to within .01°. The Ringer's solution contained NaCl, 0.65%; KCl, 0.0075%; and $CaCl_2$, 0.01%. No buffer was used. The sucrose solution was 6.5%.

There were 12 ouabain experiments, 3 in each group, using concentrations of 10^{-5}, 3×10^{-5}, and 10^{-4} in isotonic sucrose. Three experiments were done using the drug in a concentration of 3×10^{-5} in Ringer's solution. Experiments with isotonic sucrose alone were done simultaneously. The results were consistent in every case. Control experiments on the addition of Ringer's solution were also included.

Results. The graphs in Fig. 1 represent experiments in which crystalline ouabain was added to ventricular muscle in concentrations of 10^{-4}, 3×10^{-5}, and 10^{-5} in isotonic sucrose.*

Ouabain, in a concentration of 10^{-4} in isotonic sucrose causes an immediate but gradual increase of the rate of oxygen consumption; this rate falls very slightly after about an hour, yet always remains above the original level. In a concentration of 3×10^{-5} in isotonic sucrose, the metabolic rate increases more slowly, but reaches that of the tissue bathed in 0.1 mg. ouabain per cc. The muscle bathed in a sucrose solution containing ouabain in a concentration of 10^{-5} first shows a fall in metabolic rate, probably due to the action of sucrose, but after an hour the rate increases so that 2 hours after treatment it is above normal. In these experiments the influence of ions other than those supplied by the tissue is excluded. At the end of the experiments the muscles exposed to ouabain were contracted, firm, non-irritable, and their cut surfaces curled toward one another.

* The frog dose was found to be 0.003 mg. of ouabain per gm., 0.001 mg. per gm. stopped the heart in systole in 10 minutes. Assuming the blood volume of a 30 gm. frog to be 3 cc. and concentration of drug in circulation does not change during observation, then the frog dose is 0.009 mg. for the frog or 0.003 mg. per cc. of the blood. In the frog dose the drug bathes heart muscle in a concentration of about 3×10^{-6}. The solution containing ouabain in a concentration of 10^{-5} is equivalent to a dose producing systolic arrest in the frog in 10 min. These assumptions are made because only heart muscle and red blood cells adsorb digitalis.[6]

[6] Clark, A. J., *J. Pharm. and Exp. Therap.*, 1913, **4**, 399.

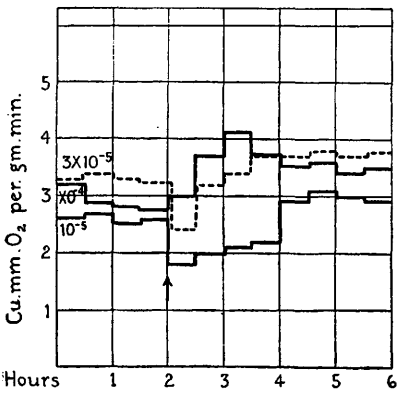

Fig. 1

Effects of ouabain in concentrations of 10^{-4}, 3×10^{-5} and 10^{-5} in isotonic sucrose solution on the oxygen consumption of resting cardiac ventricular muscle of the frog. In the 2 lower concentrations there is an immediate fall in the oxygen consumption, probably due to the action of the sucrose solution. Arrow marks the addition of the solutions.

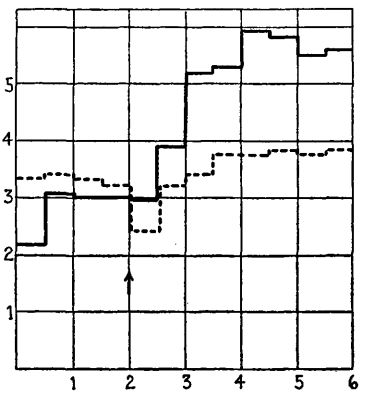

Fig. 2

Comparison of the effects of ouabain in a concentration of 3×10^{-5} in Ringer's (solid line) and isotonic sucrose solution (dotted line). The response is greater in Ringer's solution. The time for increasing the oxygen consumption is the same in both. The arrow marks the addition of the solutions.

Ouabain in Ringer's solution in a concentration of 3×10^{-5} *produces a striking increase in respiration of almost* 100% *in contradistinction to the same amount of drug in sucrose.* (Fig. 2 and Table

TABLE I.

Conc. of Ouabain	Rate of O Consumption mm.³/gm./min. Initial	After Addition of Drug	Time for Onset of Inc. O Use, min.	% Inc. of O Cons.	Ave.
10^{-5}	2.5	3.1	140	24	
in sucrose	3.8	4.0	180	5	13
	2.7	3.0	100	11	
3×10^{-5}	3.2	3.8	30	19	
in sucrose	1.9	3.7	35	95	51
	3.3	4.6	10	39	
10^{-4}	2.7	4.2	0	56	
in sucrose	2.2	4.2	5	91	76
	3.1	5.6	9	81	
3×10^{-5}	2.3	5.0	15	117	
in Ringer's	3.0	5.9	30	96	93
	3.0	5.0	30	67	
Isotonic Sucrose	1.9	1.5		—21	
(control)	3.7	2.4		—35	—29
	2.6	1.8		—32	
Ringer's	1.9	1.7		— 9	
(control)	2.9	3.1		6	— 4
	3.0	2.7		—10	

I.) An antagonism exists between the effects of sucrose and ouabain on the oxygen consumption and tone of heart muscle. Sucrose decreases the tone and oxygen consumption of cardiac ventricular muscle[7] (Table I). In the concentration used the effects of isotonic sucrose are readily overcome by ouabain.

The relationship between the concentration of ouabain in isotonic sucrose and Ringer's solutions and the time for the metabolic response is apparent from both the graphs and the table; the more concentrated the drug, the more rapid the increase. The presence of the ions in Ringer's solution does not seem to influence the time for response, but does increase the total metabolic response. However, if the depressing effect of the sucrose solution on the oxygen consumption (average 29%) be added to the metabolic increase (average 51%), caused by the drug in a concentration of 3×10^{-5} in this solution, the difference between the total increase (80%) in this and in Ringer's solution (average 93%) is decreased.

Summary. The oxygen consumption of the resting frog's heart is about one-fourth that of the working heart.[8] Ouabain, as one of the digitaloid drugs, brings the heart to a standstill and simultaneously increases the oxygen consumption. This effect is greater in Ringer's than in sucrose solution. In certain concentrations this effect may be masked by a decrease in work, which results from cessation of beating. The time for the action of this drug on the oxygen consumption is inversely proportional to its concentration and does not seem to be affected by the presence of ions.

[7] Victor, J., *Am. J. Physiol.*, in press.

[8] Clark, A. J., and White, A. C., *J. Physiol.*, 1928, **66**, 185.