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Note on the cardiac effects of nystatin

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Nystatin, a polyene antifungal antibiotic, induces systolic arrest of the isolated hearts of the frog, rat or rabbit. In the frog, heart failure induced by raising venous pressure was antagonised and the cardiac outflow was increased. Coronary flow in the perfused heart of the rat or rabbit was decreased.

ARORA & Baghchi (1963) reported the cardiotonic activity of nystatin in the perfused frog heart. The present report communicates the results of experiments on the effects of nystatin on the hearts of the frog, rat and rabbit.

Methods and results

A 0·5% solution of nystatin in propylene glycol at 85° was diluted as necessary. Since it lost cardiotonic activity completely in 2 to 3 hr, it was freshly prepared before each experiment.

Frog hearts were perfused as described by Burn (1952). In 6 experiments, failure was induced by raising perfusion pressure in steps of 1 cm before perfusing with drug. In another 6 experiments, failure was not induced before perfusion. Cardiac outflow was measured through a cannula in the aorta. Comparisons were made with ouabain and with control preparations without any drug.

Langendorff's preparation of the albino rat and the rabbit heart was set up as described earlier (Arora & Arora, 1963) and the effects of perfusion with nystatin were compared with those produced by ouabain and propylene glycol.

In both kinds of preparation, the Ringer-Locke solution used before beginning drug perfusion contained the same amount of propylene glycol as the Ringer-Locke solution containing nystatin.

In the non-failing perfused frog heart, nystatin, 2×10^{-5} g/ml, induced systolic arrest in 20 to 30 min. There was an initial slight decrease in the amplitude of contraction and cardiac outflow followed by an increase in the amplitude of contraction and cardiac outflow and then a gradual increase in the diastolic tone and a decrease in cardiac outflow terminating gradually in systolic arrest (Fig. 1a). Changes in the heart rate were variable but generally a slight initial increase was followed by a gradual reduction. In the perfused frog hearts where failure had been induced, perfusion with nystatin 2×10^{-5} g/ml, produced effects similar to those seen in the non-failing heart (Fig. 1b). In 6 experiments with ouabain, 2×10^{-5} g/ml, effects were essentially similar to those seen with nystatin although the systolic arrest was not as complete as with nystatin, i.e., the ventricles did not become as contracted, white and button-like as with nystatin. In 6 experiments with propylene glycol, a progressive decrease in the amplitude of contraction and cardiac outflow followed the induction of failure.

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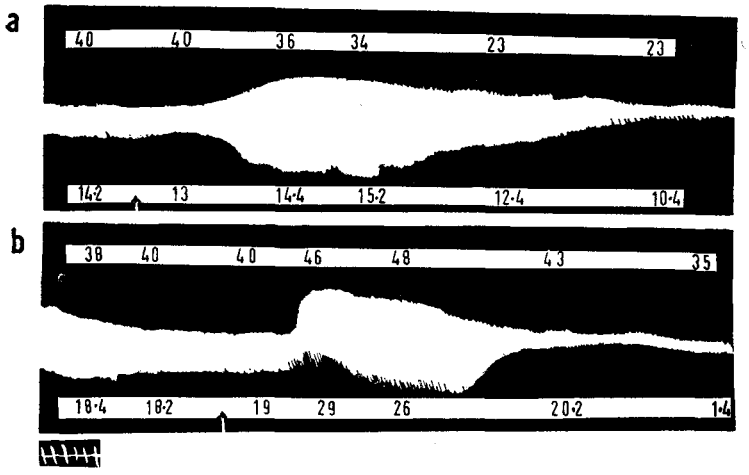

FIG. 1. Effects of nystatin, 2×10^{-5} g/ml, on the perfused frog heart. a, effects on the normal heart; b, effects after inducing failure by increasing perfusion pressure. Drug perfusion was started at arrow. The records from above downwards are: heart rate/min, contractions of the heart, cardiac outflow ml/min. Time tracing in 30 sec intervals.

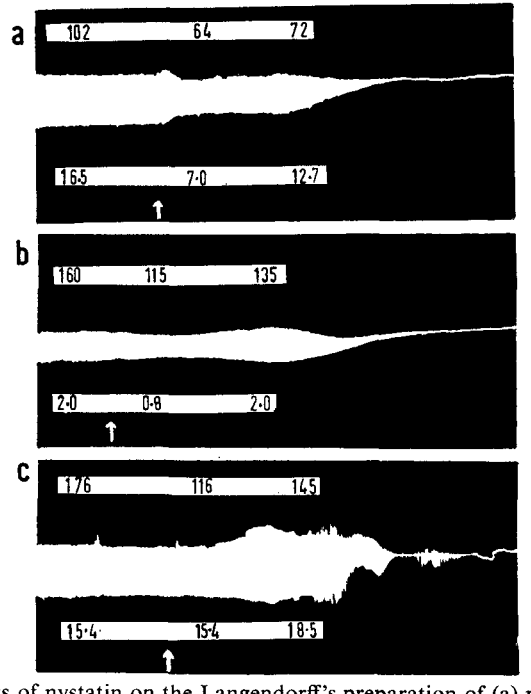

FIG. 2. Effects of nystatin on the Langendorff's preparation of (a) rabbit heart and (b) rat heart. Concentrations used were (a) 4×10^{-5} g/ml and (b) 3×10^{-5} g/ml. (c) shows the effects of ouabain, $2{\cdot}5 \times 10^{-6}$ g/ml, on the perfused rabbit heart. Drug perfusion was started at arrow. The records from above downwards are: heart rate/min, tracings of contractions of the heart, coronary flow ml/min.

In 7 experiments on the rat heart, using nystatin, 3×10^{-5} g/ml, and 6 experiments on the rabbit heart using nystatin, 4×10^{-5} g/ml, changes were essentially similar. An initial decrease in the amplitude of contraction was followed by a partial or complete recovery terminating in systolic arrest in 10 to 15 min (Fig. 2). Coronary flow decreased markedly immediately after starting nystatin perfusion followed by a partial recovery towards normal. In one experiment each on the rat and the rabbit heart, recovery in coronary flow was complete. In all but one experiment on the rat and the rabbit heart, where no change in the heart rate could be seen, there was an initial decrease in the heart rate which was followed either by a partial recovery and then again a decrease and finally cessation of ventricular activity, or by a progressive decrease terminating in ventricular arrest. In all cases, the auricles continued to beat after the ventricles had stopped.

In 6 experiments on the rat heart, ouabain, 10^{-5} g/ml, failed to have any action on the heart rate, coronary flow or the amplitude of contraction. However, in 5 experiments on the rabbit heart, $2{\cdot}5 \times 10^{-6}$ g/ml, induced systolic arrest in 10 to 15 min. Unlike nystatin, there was an increase in the amplitude of contraction above normal level from the start without any initial decrease (Fig. 2). The coronary flow also increased above control values in 3 out of 5 experiments. In one experiment on the rabbit heart auriculo-ventricular block was seen.

Discussion

Nystatin thus resembles hamycin and trichomycin in its ability to induce systolic arrest of the heart in various species. Certain differences with ouabain, however, exist such as those on the amplitude of contraction and coronary flow. It is interesting to note that nystatin, a polyene antifungal antibiotic, is a tetraene (Vining, 1960) while hamycin and trichomycin are heptaenes and yet they all share the cardiotonic activity. Unlike hamycin and trichomycin, nystatin solution is highly unstable in its cardiotonic activity. The significance of the cardiac effects of nystatin remains to be established.

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