Actions of Prolactin and Frusemide on Heart Rate and Rhythm

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Summary

Rat hearts with coronary circulations perfused by the Langendorff technique were studied. Recordings were made of the electrical and mechanical activity. Once the rate and rhythm of each heart had stabilized it was perfused with Ringer-Locke solution for 90 minutes; frusemide (40 μg/ml) was added to the perfusate during the last 30 minutes of this period. Eighteen experiments were performed—six controls, six in which prolactin at a concentration of 50 ng/ml was added to the perfusate for the whole 90 minutes, and six in which a prolactin concentration of 200 ng/ml was used.

With the controls heart rate and rhythm remained steady, but there was a slow decline in amplitude of the contraction. With a prolactin concentration of 50 ng/ml the heart rate rose to about 40% above control during the first hour and after an initial sharp increase the contraction amplitude declined more rapidly than in the controls. The prolactin concentration of 200 ng/ml produced a decline of about 25% in heart rate over the first hour and amplitude behaved much as in the controls. Frusemide had no clear effect on the rate of beating of the controls, but it tended to reverse both the acceleration produced by 50 ng/ml prolactin and the slowing produced by the higher dose. Both the doses of prolactin consistently caused disturbances of rhythm. These effects occur at concentrations of prolactin found in human plasma in various pathophysiological conditions.

Introduction

Human plasma prolactin levels may be raised during exercise and surgery and after myocardial infarction (Frantz *et al.*, 1972; Friesen *et al.*, 1972; Horrobin *et al.*, 1973). At these times the risk of cardiac dysrhythmias is increased, and because of its effects on potassium metabolism it has been suggested that prolactin may contribute to this risk (Horrobin, 1973). Prolactin concentrations similar to those found in human plasma during exercise, surgery, and treatment in a coronary-care unit can increase the excitability of arterial and arteriolar smooth muscle (Manku *et al.*, 1973 a). We therefore investigated the actions of prolactin on a rat perfused-heart preparation.

Methods

Hearts taken from 10-12 week-old white laboratory rats were perfused with oxygenated Ringer-Locke solution at a temperature of 35°C by the Langendorff technique. The perfusion rate was kept constant throughout the experiment. Mechanical activity was recorded via a hook through the tip of the heart connected to an isometric force transducer. Electrical activity was picked up by two electrodes, one near the top of the right ventricle and one near the bottom of the left ventricle. These allowed consistent recording of a clear QRS complex but satisfactory P waves were only occasionally picked up. The heart rate tended to slow down over the first 15-45 minutes and the preparation was observed until two heart-rate recordings at 10-minute intervals gave the same value (± 5%). Hearts which had not achieved a stable rate after 60 minutes or which continued to show any form of dysrhythmia, including single ectopics, were discarded. Once the heart had achieved a stable rhythm and rate the perfusion was carried out for a further 90 minutes. Three types of experiment were performed.

Controls.—Six hearts with a mean starting frequency of 138/min ± 4·9 S.E. of mean were perfused with Ringer-Locke solution alone for the first 60 minutes and then Ringer-Locke solution containing 40 μg/ml frusemide for a further 30 minutes. This concentration has been estimated to be at the upper end of the therapeutic range of frusemide concentrations in body fluids (Blair-West *et al.*, 1973).

Prolactin 50 ng/ml.—Six hearts with a mean starting frequency of 140/min ± 5·0 S.E. of mean were perfused with Ringer-Locke solution containing 50 ng/ml ovine prolactin (Ferring, Malmö) for 60 minutes and with the same concentration of prolactin plus 40 μg/ml frusemide for a further 30 minutes.

Prolactin 200 ng/ml.—Six hearts with a mean starting frequency of 137/min ± 13·7 S.E. of mean were treated the same as the prolactin 50-ng/ml group except that the prolactin concentration was 200 ng/ml.

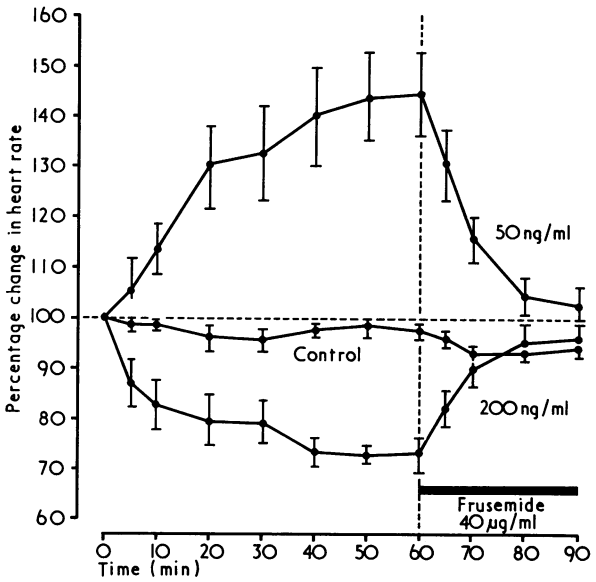

FIG. 1—Effects of prolactin and frusemide on heart rate. Results expressed as mean percentage changes from heart rates at beginning of experiment. Bars indicate S.E. of mean.

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Results

The changes in rate and amplitude of contraction in all three groups are shown in figs. 1 and 2. After 60 minutes the heart rates in both experimental groups were significantly different from those of the controls ($P < 0.01$). After five minutes the amplitude of contraction in the 50-ng/ml group was significantly different from the others ($P < 0.01$).

Controls.—The heart rhythm remained steady throughout. One heart showed occasional ectopic beats with a frequency of less than 1 in 500.

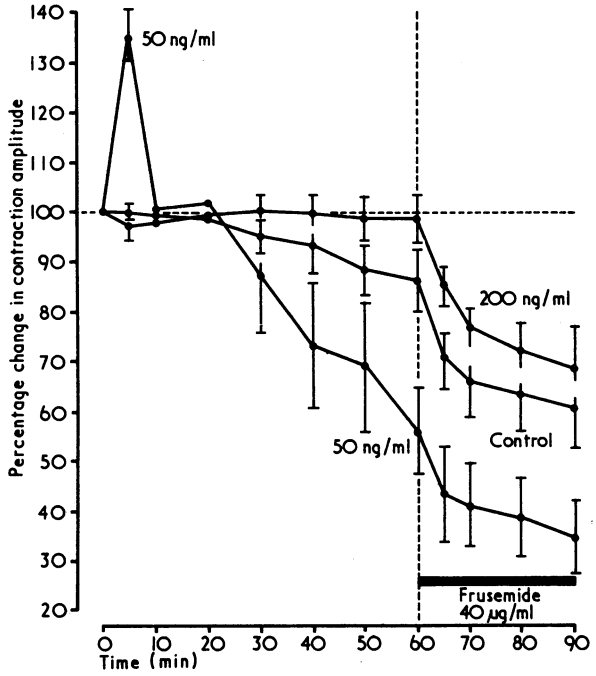

FIG. 2—Effects of prolactin and frusemide on the amplitude of contraction as recorded from the tip of the ventricle. Bars indicate S.E. of mean.

Prolactin 50 ng/ml.—Five out of six hearts showed prolonged runs of dysrhythmia starting 2-50 minutes after the beginning of the prolactin infusion and lasting for 5-10 minutes (fig. 3). Spontaneous reversion to a normal rhythm occurred before the frusemide infusion began. The sixth heart showed repeated ectopic beats. In five hearts the dysrhythmic QRS complexes were similar to the normal QRS waves suggesting a supraventricular origin; in these hearts the abnormal beats were for the most part coupled to a previous normal beat suggesting a re-entry phenomenon. In the sixth heart the highly irregular pattern of both the mechanical activity and the E.C.G. suggested a ventricular origin of the activity.

Prolactin 200 ng/ml.—Five out of six hearts showed rhythm disturbances, this time a slow form of coupled beat of supraventricular origin (fig. 4).

Discussion

Surgery, exercise. and other forms of stress, including admission to a coronary-care unit, can raise plasma-prolactin levels from the normal values of about 10 ng/ml up to 200 ng/ml (Frantz *et al.*, 1972; Friesen *et al.*, 1972; Horrobin *et al.*, 1973). Our experiments showed that similar prolactin levels may have marked cardiac actions. As Manku *et al.* (1973 a) have already shown that prolactin can modify the responses of cardiovascular smooth muscle to noradrenaline and to angiotensin our findings reinforce the suggestion that prolactin may have important physiological and pathophysiological effects on the cardiovascular system (Horrobin, 1973). The opposite effects of the 50 ng/ml and the 200 ng/ml prolactin levels on heart rate were particularly interesting in view of the similar reversal of prolactin effect on arteriolar responsiveness to noradrenaline and angiotensin (Manku *et al.*, 1973 a).

The effects of frusemide on heart rate supported the suggestion that at least some of the actions of frusemide may be dependent on an inhibition of the effects of endogenous pro-

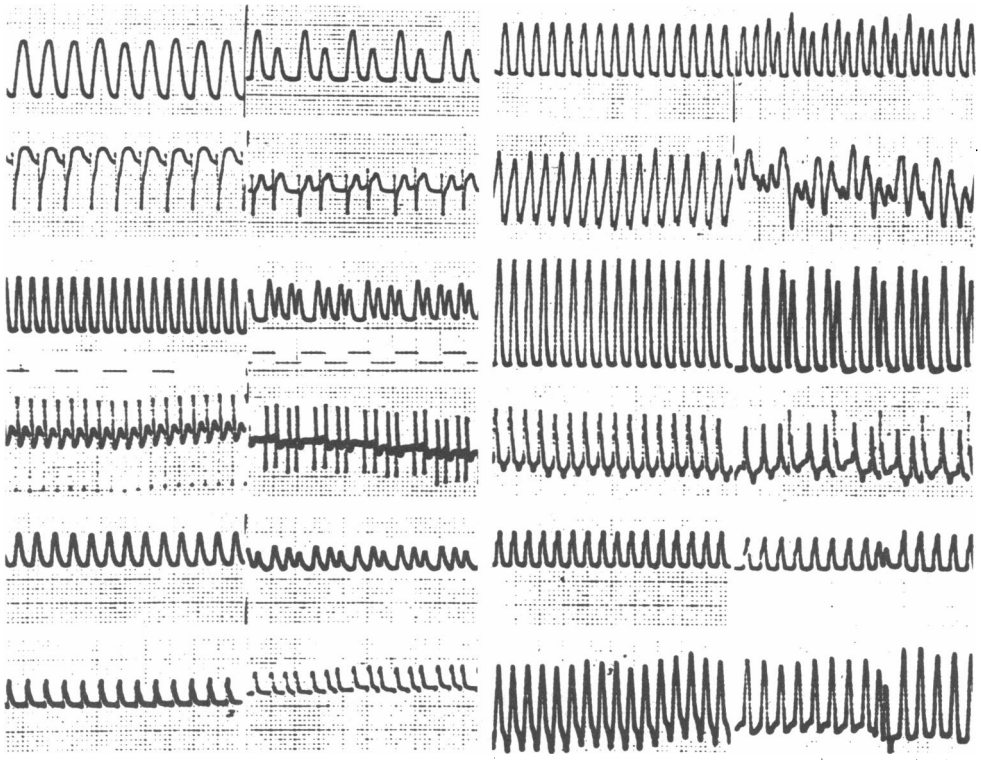

FIG. 3—Changes in mechanically recorded contractions and in E.C.G. before and during perfusion with 50 ng/ml prolactin. Each small square on horizontal scale represents 0·1 sec. Each block of four recordings came from one heart. Two records on left in each case (mechanical above, E.C.G. below) were taken during the control period while two on right were taken during infusion of 50 ng/ml prolactin.

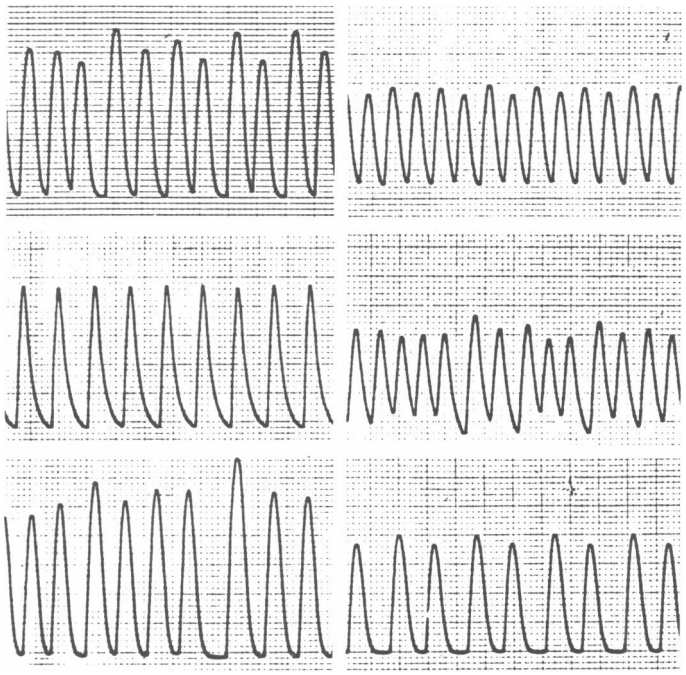

FIG. 4—Mechanically recorded contractions during perfusion with 200 ng/ml prolactin. Each small square on the horizontal scale represents 0·1 sec. Contractions during the control period had been of constant amplitude. E.C.G. changes are not shown, but in all five cases dysrhythmia indicated a beat of supraventricular origin.

lactin (Horrobin, 1973; Manku *et al.*, 1973 b). The lack of effect of frusemide in the absence of prolactin and its reversal of both the cardiac acceleration produced by 50 ng/ml and the slowing produced by 200 ng/ml suggested a specific interference with prolactin action rather than a non-specific effect on heart rate.

The most striking feature in respect of amplitude was the initial highly significant increase with the 50 ng/ml prolactin concentration ($P < 0.01$). We have no explanation for this as yet though an effect on ion movements is the obvious possibility. For the period between 10 and 60 minutes the differences in amplitude between the three groups might possibly have been related to differences in rate, with the slowest hearts showing the largest amplitude recordings. Rate changes could not, however, account for the small but consistent fall in amplitude in all three groups on the addition of frusemide. The contrast between the effects of frusemide on rate and amplitude suggested that the two were not mediated by the same mechanism.

There are several potential clinical implications of our finding. Prolactin may contribute to the risk of dysrhythmia developing in surgery, exercise, and the post-infarction state. The slowing effect of the higher prolactin levels suggests that it may perhaps play a part in post-infarction sinus bradycardia. There are reports in the literature of fatal dysrhythmias arising unexpectedly in patients on methyldopa, tricyclic antidepressants, phenothiazines, and reserpine (Kelly *et al.*, 1963; Salonen, 1968; Giles and Modlin, 1968; Goldstein, 1969; Coull *et al.*, 1970; Robinson, 1973; Sydney, 1973). It may be relevant that all these drugs stimulate prolactin secretion (Horrobin, 1973).

The changes in rate and rhythm produced by prolactin have some features in common with the dysrhythmias of digitalis intoxication. Gynaecomastia may be a side effect of digitalis therapy and it has been suggested that the drug may have oestrogen-like actions (LeWinn, 1953). Oestrogens stimulate prolactin secretion, and plasma radioimmunoassay of a small series of samples taken from patients on digitalis therapy has shown raised prolactin levels (Boyns and Cole, 1973). The inotropic and dysrhythmic effects of digitalis may be due to separate mechanisms (Fisherman, 1971). If this is so then a trial of digitalis in combination with a prolactin-suppressing drug may be worthwhile.

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