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THE EFFECTS OF OXYTOCIN AND MILK REMOVAL ON MILK SECRETION IN THE GOAT

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SUMMARY

1. When goats were milked each hour after being given a dose of synthetic oxytocin within the range thought to be released by the pituitary, there was a progressive rise in milk yield becoming statistically significant by 5 hr. The effect was reduced if the milk was not removed from the gland each hour.

2. Milking transplanted glands each hour without injecting oxytocin also increased milk yield. The yield of the unmilked glands on the same animals was not affected. Massaging the transplanted glands had no effect on the milk yield.

3. Oxytocin treatment and, to a lesser extent, frequent milking without oxytocin, altered milk composition. [Na], [Cl] and [non-casein protein] increased; [K] and [lactose] decreased.

4. Oxytocin infusions permitted the leakage of [^{14}C]lactose from milk to plasma and [^{14}C]sucrose from plasma to milk.

5. In some goats very small doses of oxytocin caused changes in milk composition and in one such animal these changes were mimicked by the close arterial infusion of bradykinin.

6. Reasons are given for believing that the changes in composition are incidental to the main action of oxytocin in expelling milk and could be caused by a small number of leaks between the tight junctions connecting secretory cells.

7. The increase in the rate of milk secretion following milk removal is probably of greater physiological significance than the small changes in milk composition and supports Levy's idea of a local negative feed-back via a chemical component of milk.

INTRODUCTION

In 1910, Ott & Scott discovered that posterior pituitary extracts cause a rapid but temporary increase in milk flow in the goat and a number of workers then studied the mechanism (see Harris, 1958). The main consensus of opinion was that the action was on muscular tissue (later identified as myoepithelial cells) which squeezed out preformed milk, but a number of workers believed that pituitrine also increased the rate of milk formation (Hammond, 1913; Simpson & Hill, 1915; Maxwell & Rothera, 1915). Following the discovery of the milk ejection reflex the latter opinion was discredited. However, more recently there have been reports that oxytocin can cause an increase in milk yield in cows (Knodt & Petersen, 1942; Smith, 1947; Adams & Allen, 1948; Sprain, Smith, Tyler & Fosgate, 1954; Donker, Koshi & Petersen, 1954; Lakshmanan, Shaw, McDowell, Ellmore, & Fohrman, 1958; Morag, 1968), goats (Denamur, 1953), sheep (Denamur & Martinet, 1961; Morag & Fox, 1966) and rats (Morag & Brick, 1969). Similarly, effects of oxytocin on the composition of the aqueous phase of milk have been reported (see, for example, Wheelock, Rook & Dodd, 1965). However, in nearly all these experiments, large or very large doses of oxytocin were used so that there is doubt about their physiological significance.

In many experiments on lactation, oxytocin has been injected in order to obtain all the milk that has been secreted and which is stored in the gland. Thus although this can be accomplished with small doses it is important to know: (*a*) whether oxytocin and the act of milking have effects on the mammary glands other than aiding the evacuation of milk; and (*b*) whether such effects occur with doses that might be released by the pituitary in response to normal suckling or milking. The present results suggest that it does.

METHODS

Animals. The experiments were conducted on Saanen goats, in which a mammary vein and a carotid artery were exteriorized in loops of skin (Linzell, 1960, 1963*a*). Some also had one mammary gland transplanted to the neck with the artery and vein anastomosed to the exteriorized carotid artery and jugular vein (Linzell, 1963*b*) respectively. This enabled cannulation and close-arterial infusion to be carried out without further surgery by Seldinger's (1953) technique under local anaesthesia. All goats were routinely milked at 9.30 and 16.30 and the yield of each gland recorded.

Conduct of experiments. The experiments were all carried out in the animal's own pen. The goat was accustomed to wearing a light leather harness to which catheters and the infusion apparatus were attached (Linzell, 1966). Thus no restraint was necessary, and stress, which can interfere with the action of oxytocin on milk ejection (see Cross, 1953), was avoided. Milking during experiments was carried out by a person known to the goats but who was not the usual milker. This was to avoid the complication of a release of oxytocin by a conditioned reflex (see Zaks, 1962). Furthermore, some goats become restless and excited when the normal milker approaches, probably in anticipation of food.

Analytical methods. These were as previously described (Linzell, 1967). Latterly many of the methods were adapted to the Technicon autoanalyser. Measurement of ^{14}C and ^{3}H was carried out in a liquid scintillation spectrometer using a Triton X-100-toluene based scintillator (see Peaker, 1971).

Calculations. The rate of milk secretion in ml. hr^{-1} was calculated from a knowledge of the milk yield and the time of each milking. When expressed as a percentage this was calculated by dividing the yield during an experiment by the mean yield immediately before the experiment, integrated over 3–10 days.

In our goats, the rate of milk secretion varies from day to day. However, the small changes usually occur on both sides equally. Therefore the *relative milk yields quotient* calculated as shown below should equal 1 if both sides behave identically. This was calculated for five goats in early, mid and late lactation giving a mean figure of $0{\cdot}998 \pm 0{\cdot}002$. Thus calculation of this term can be used to detect a unilateral effect on milk yield.

$$\text{Relative milk yields quotient} = (l.j^{-1})(k.i^{-1})^{-1} \tag{1}$$

$$= (l.i)(j.k)^{-1}, \tag{2}$$

where i = total volume of milk from gland A on day 1,
j = total volume of milk from gland B on day 1,
k = total volume of milk from gland A on day 2,
l = total volume of milk from gland B on day 2.

In the work to be presented, gland B is the one which was milked hourly during the experimental period and the volumes of milk were those obtained between morning and evening milkings, i.e. the afternoon milk yield.

RESULTS

Effects of milking hourly using oxytocin. Linzell (1967) found that when goats were milked every hour instead of twice or thrice daily, the yield of milk was very similar to or even slightly higher than the mean yield for 3–10 days before the experiment and concluded that this technique can be used in short-term experiments on factors affecting milk secretion. The oxytocin used initially was the natural product (Pitocin, Parke Davis). However in 1963, the manufacturers changed to synthetic oxytocin without changing the name of the product. When this was discovered it was realized that Linzell's (1967) data were not necessarily homogeneous, and when they were re-examined it appeared that with synthetic oxytocin there was a greater rise in milk yield. Further experiments were done and analysis of forty-three experiments on fifteen goats showed that hourly milking for 8–9 hr using synthetic oxytocin in physiological doses (50–100 m-u. I.V.) usually caused a progressive rise in milk yield (Fig. 1) becoming statistically significant after 4 hr ($P < 0{\cdot}001$). Furthermore, on the day of the experiment the total milk obtained was significantly greater than that on the preceding and succeeding days (Fig. 2). The effect did not persist nor was it merely the result of obtaining more preformed milk since the mean hourly yield during the night after the experiment was almost identical to that during the night preceding the experiment (Fig. 2). As reported previously (Linzell, 1967) there were changes in milk composition; [fat] rose initially, due to the removal of residual milk, known to be rich

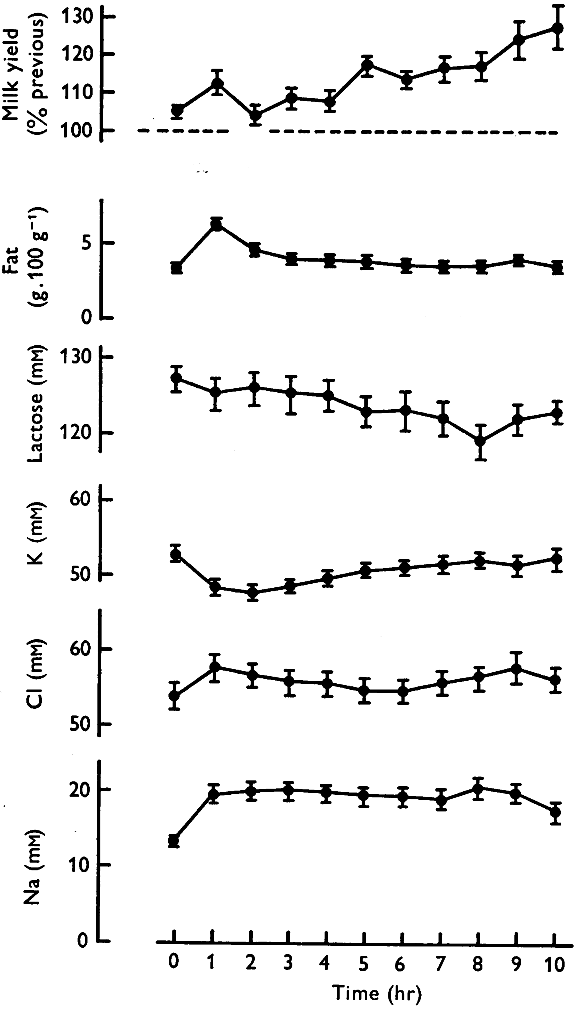

Fig. 1. The effect on milk yield and composition of hourly milking. On the day of the experiment, the udder was evacuated thoroughly after morning milking and the minimum effective dose of oxytocin determined (50–100 m-u. I.V. via an indwelling catheter). Thereafter this amount was injected each hour before milking. The yield is expressed as a percentage of the mean yield on twice daily milking for a stable period immediately before the experiment (3–10 days). Milk 0 was the overnight yield immediately before the experiment, the residual milk obtained was not included. The rise in yield at 1 hr may be due to incomplete emptying of the udder at morning milking. By the fifth hour the yield was significantly raised ($P < 0{\cdot}001$). The concentrations of lactose and ions are expressed as m-mole/l. fat-free milk. Mean ± S.E. Forty-three experiments on fifteen goats.

in fat, [lactose] tended to fall whereas [Na] and [Cl] rose and [K] fell abruptly, although [K] and [lactose] tended to recover (Fig. 1).

The effect on milk yield may, in part, be local since in ten goats where one gland was milked hourly after injecting 100 m-u. oxytocin and the other milked only at the end of the experimental period, the yield of the gland milked hourly was significantly higher than that of the other (Fig. 3).

Hourly milking without oxytocin. Linzell (1967) found that the pituitary cannot release effective amounts of oxytocin in response to frequent milking because when goats are milked hourly without injecting oxytocin, 50–90 % of the milk secreted is not removed. In order to ensure that oxytocin was not involved, experiments were conducted on transplanted, i.e. denervated glands which were milked not by the usual milker and not in the usual place, in order to decrease the chances of a release of oxytocin by a conditioned reflex. This procedure does not cause the characteristic rise in milk pressure of the control gland *in situ* (Linzell, 1963*b*).

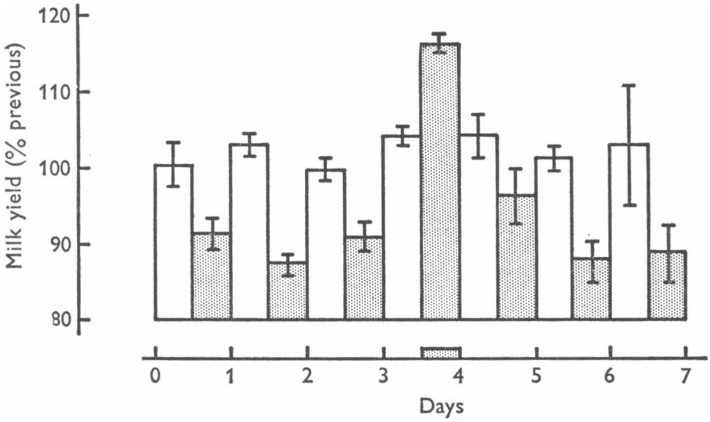

Fig. 2. A comparison of the total yield obtained on milking hourly between morning and evening milkings (see Fig. 1) with the morning and afternoon yield before and after the experiment (black bar). The residual milk obtained with oxytocin at the morning milking on the day of the experiment was excluded.

When the transplanted gland was milked hourly in four animals, the yield each hour was much less than expected although there was a progressive rise (Fig. 4). The shape of the curve may be explained as follows. Although the myoepithelium will contract effectively in response to massaging this is seldom comparable to the co-ordinated contraction induced by oxytocin which affects all parts of the gland simultaneously (Linzell, 1955, 1963 *b*). In the absence of such complete evacuation only a small proportion of the total milk secreted each hour would be removed. However, with time a gradual accumulation of milk would occur which would eventually completely fill the secretory portions of the gland, i.e. alveoli and small ducts. After this time the milk secreted each hour would displace an equal volume into the large ducts from which it could be removed by milking. In our experiments this point was reached after about 6 hr.

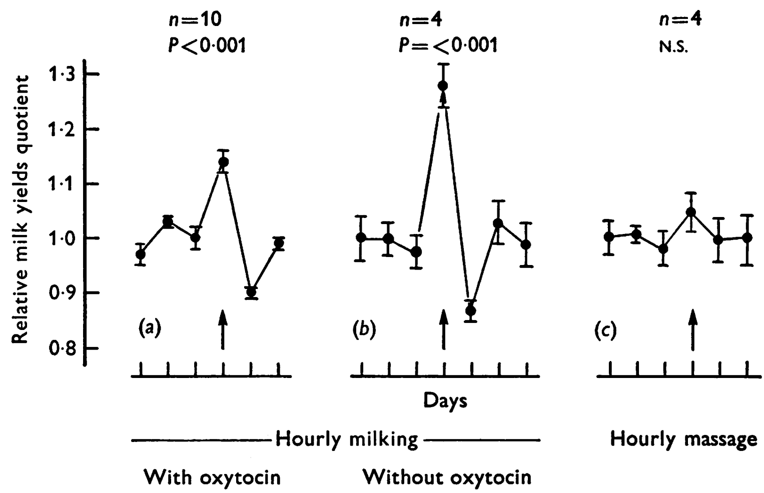

Fig. 3. The local stimulation of milk secretion by milk removal. The relative milk yields quotient (see Methods) for afternoon yield shows (*a*) that the yield on hourly milking with oxytocin was greater for the gland which was milked, (*b*) milking hourly without oxytocin also increased the yield of the milked gland compared with the non-milked and (*c*) that massaging had no significant effect. The fall in the quotient on the day after the experiment indicates a return to the previous yield and not a fall in absolute yield (see Methods).

When the total yield on hourly milking was added to the evening yield obtained by the normal milking of both the control and transplanted glands, the yield of the transplanted gland in three animals was 15, 20 and 21 % higher than on the previous 2–4 days and in all four the relative Milk Yields Quotient (see Methods) was significantly raised (Fig. 3). There were also changes in the composition of the milk similar to but smaller than those seen when using oxytocin (Fig. 4). In similar experiments, the transplanted gland was massaged every hour in a manner similar to milking but the milk was not removed. The relative milk yields quotient was not affected by such treatment (Fig. 3).

Effects of oxytocin alone. In three goats oxytocin was infused into the artery of a transplanted gland at 10 m-u./min for 5 hr. In these goats the milk yield of both the transplanted and the control glands fell and in two there were changes in milk composition as before (Fig. 5). Tissue permeability was increased because [^{14}C]sucrose passed from the plasma into the milk in one experiment and in another [^{14}C]lactose passed from milk into the blood; this does not occur normally (Fig. 6). There was also a large rise in non-casein protein in milk.

Oxytocin has been reported to have an insulin-like action in mammary tissue in high doses. Annison & Linzell (1964) found that 400 m-u. every

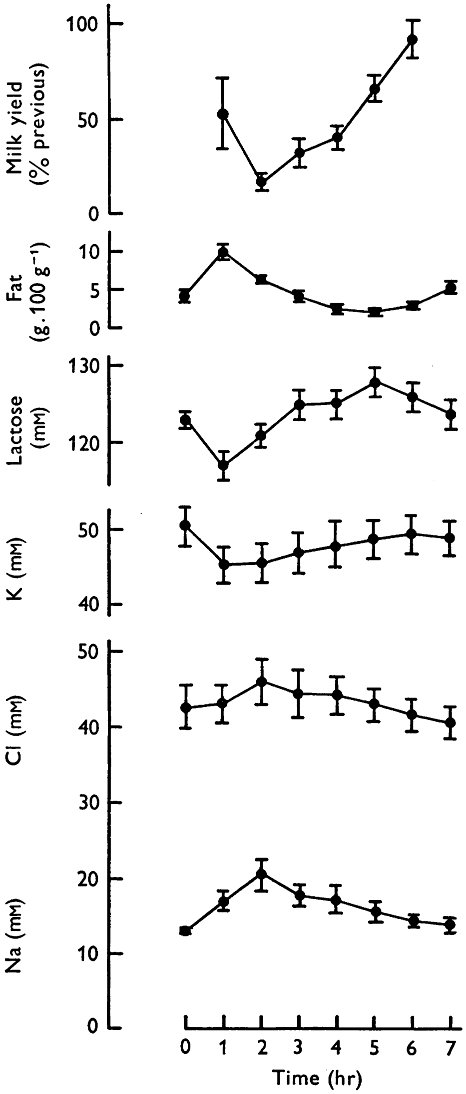

Fig. 4. The effect of hourly milking the transplanted glands of four goats. Oxytocin was not injected. Results plotted as in Fig. 1.

hour had no effect on the whole body turnover and mammary uptake of glucose in lactating goats and in the present experiments there were no changes in arterial concentrations or mammary A–V differences of free fatty acids, volatile fatty acids, glucose, oxygen, carbon dioxide, Na, K or Cl either across the control gland or across the transplanted gland which received a higher dose.

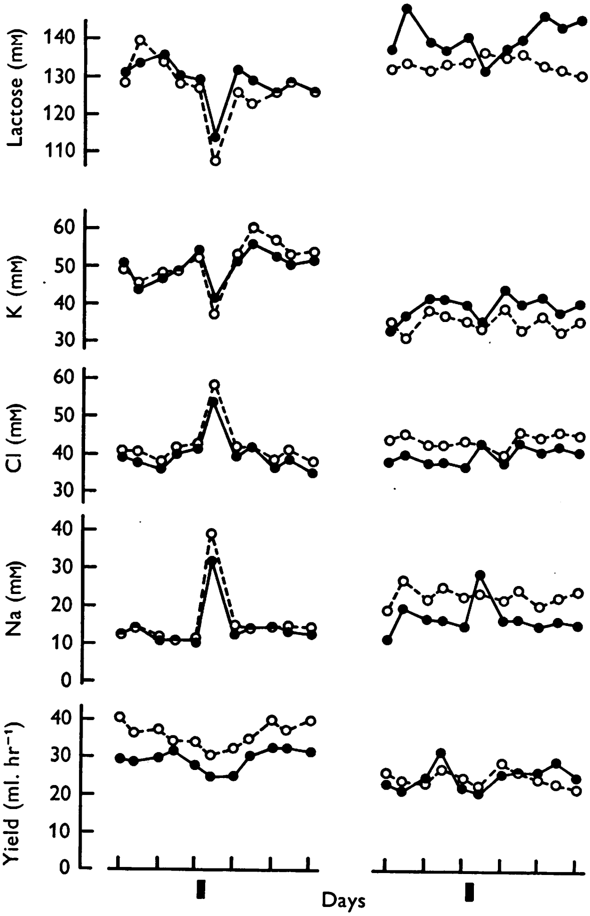

Fig. 5. The twice daily record of milk yield and composition of goat Polly who was very sensitive to oxytocin. *Left*: effect of infusing oxytocin I.A., 10 m-u./min for 5 hr. *Right*: effect of infusing bradykinin I.A., 100 ng/min for 4 hr. ●, Autotransplanted gland; ○, control gland *in situ*.

Some goats are very sensitive to oxytocin. For example, goat Polly showed small but significant rises in milk [Na] and a fall in [K] at evening milking following a single I.V. injection of 100 m-u. after morning milking

8 hr previously. Both glands were affected but when 20 m-u. was injected into the artery of the transplanted gland the effect was confined to this gland.

Since chloretone is used to preserve the oxytocin used in these experiments, the effect of this substance on milk composition has been investigated, but no effects were apparent when injected every hour for 5 hr in an amount equivalent to giving 200 m-u. oxytocin.

Effects of oxytocin on the relation between ions and lactose in milk. Previous

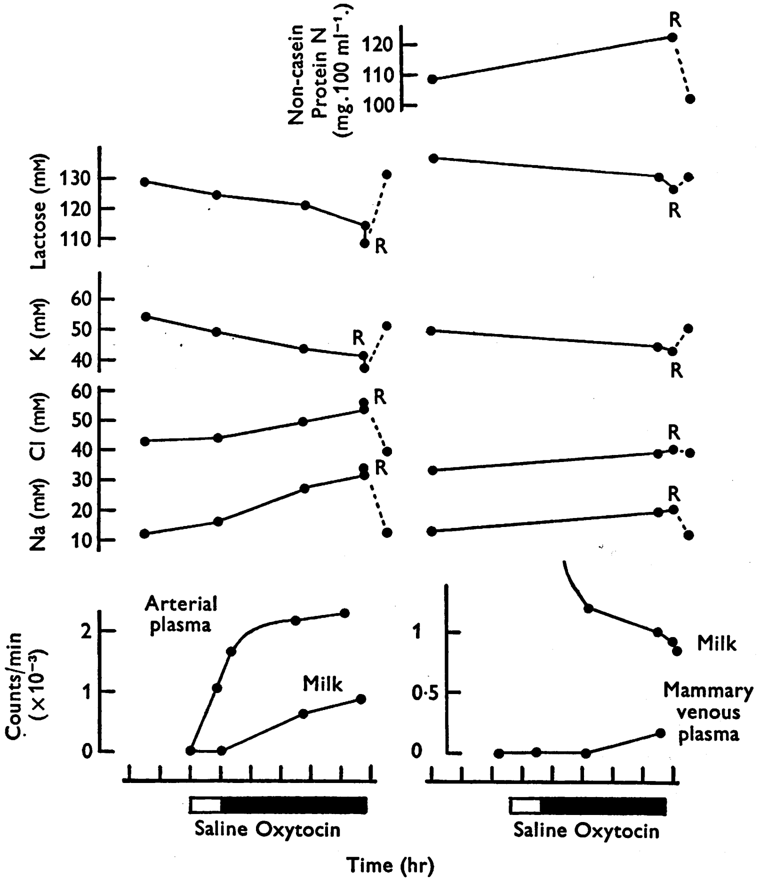

Fig. 6. Permeability changes produced by oxytocin in goat Polly. *Left*: passage of [^{14}C]sucrose from plasma into milk during an infusion of oxytocin (100 m-u./min) I.A. (black bar). Isotope infusion was started 1 hr before the oxytocin infusion. *Right*: passage of [^{14}C]lactose from milk to plasma during an infusion of oxytocin (100 m-u./min) I.V. (black bar). The isotope was injected into the teat 3 hr before the oxytocin infusion was started. Note the characteristic changes in milk composition which were greater in the last milk out after oxytocin (R); the last point (i.e. after the dashed line) is the milk removed next morning.

workers have noted that in different cows, there are correlations between the concentrations of lactose and monovalent ions in milk (Barry & Rowland, 1953; Rook & Wood, 1958, 1959; Walsh & Rook, 1964). We confirm that there are such relationships in the goat but also show that oxytocin, even when injected in low dosage, can alter the ratios of constituents in a way quite different from the normal random variations occurring from day to day.

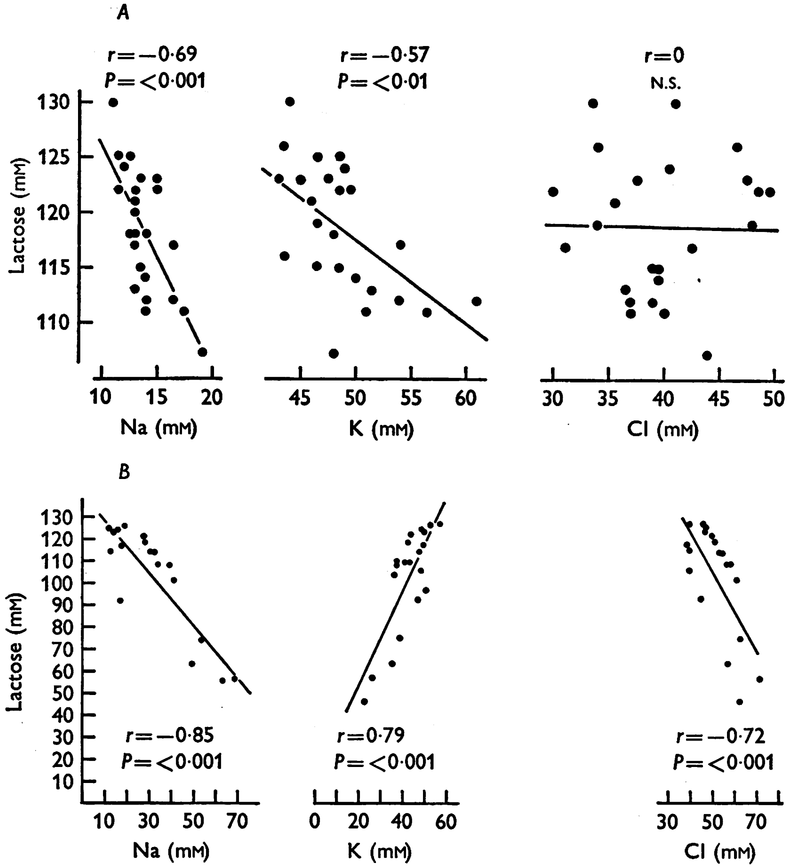

Fig. 7. Relationship between lactose and ion concentrations in the milk of a goat from day to day (A) and on days when oxytocin was given (*B*).

Fig. 7 shows for goat Polly the day-to-day variations in milk [lactose] in relation to [Na], [K] and [Cl]. [Na] and [K] rise and fall together and can be seen to be inversely related to [lactose] and there is no correlation between changes in [Na] or [K] and [Cl] which agrees with our hypothesis that Na^+ and Cl^- normally pass into milk by different mechanisms (Linzell & Peaker, 1971*c*). On days when the animal was treated with oxytocin, there were much larger changes in composition and, on those days, as [Na] and [Cl] increased, [lactose] and [K] decreased significantly.

Site of alteration of milk composition. Linzell & Peaker (1971*a*, *b*) have recently shown that the mammary ducts are probably normally impermeable to ions. To investigate whether the changes in ionic composition which occur in response to oxytocin involve a change in permeability of the ducts or the alveoli, 100 m-u. oxytocin was given to a goat, 2 hr and 2·5 hr after morning milking. 30 min later, a sample was taken from the teats and the glands milked by hand to obtain the milk that was lying in the ducts. At the end of hand milking, a final sample (strippings) was taken and 100 m-u. oxytocin injected, after which the milk that had been in the alveoli and was ejected by the oxytocin was removed. Analysis of these milk fractions showed that the composition of the milk present in the alveoli had changed (increase in [Na] and [Cl] decrease in [K] and [lactose]) but not that in the ducts, indicating that the effects of small doses of oxytocin on milk composition are brought about by changes in the alveoli only.

Histamine and bradykinin. Histamine (0·1 and 1·0 μg/min) had no effect when infused for 3·5 hr into the artery of a transplanted gland, except that the skin of the glands became pink. In goat Polly, bradykinin infused I.A. at 100 ng/min for 4 hr had similar effects on milk composition to oxytocin infusion (rise in [Na] and [Cl] and fall in [K] and [lactose]), but only a small effect at 4 ng/min (Fig. 5). At the start of the infusion there was a small, temporary increase in blood flow and the skin of the gland infused became oedematous. There was no effect on arterial blood pressure, heart rate or on the composition of the milk of the control gland or on the milk yield of either gland.

DISCUSSION

There is no shortage of papers on the effects of large doses of oxytocin on milk yield and composition. Many report an increase in milk yield of up to 30 % and, when studied, the milk composition changed in a characteristic fashion, namely a fall in [lactose] and [K] and a rise in [Na] and [Cl]. The amount of oxytocin which will effectively remove the residual milk, i.e. evacuate the alveoli, is very much smaller than is mostly used. In our laboratory the minimum effective dose in the goat is about 50–100 m-u. and in the sow and cow 0·5–1 u. (about 1–2 m-u. kg^{-1} body weight). These data are in excellent agreement with estimates of the amount of oxytocin released in response to suckling in these species (see Denamur, 1965). In contrast, the doses mostly used in the cow have been 10–20 u. and in the goat and sheep 1–5 u. Doses down to the physiological level were included in the studies on milk yield by Denamur & Martinet (1961) in the sheep and by Morag (1968) in the cow, but the composition of the milk was not reported.

Milk yield

The present results show that removal of milk from the mammary gland every hour following the I.V. injection of a physiological dose of oxytocin, sufficient to evacuate the udder (Linzell, 1967) results in a progressive rise in milk yield. The increase in yield may at least in part be related to the removal of milk rather than to a specific effect of oxytocin, since the removal of milk every hour from a transplanted, denervated gland without injecting oxytocin increased the yield of that gland compared with the unmilked gland *in situ*. Massaging the gland had no effect, which suggests that the glands respond to milk withdrawal rather than to the actual process of milking or suckling. These findings are very similar to those of Denamur & Martinet (1961) in the sheep. They injected 0·1–5 u. of oxytocin after each milking and found an increase in milk yield but only if they removed the additional alveolar milk ejected from the alveoli by the action of the exogenous oxytocin. If this extra milk was left in the gland there was no increase in yield and on average the 'milked' gland gave 27 % more than the control, a figure very similar to that seen by us when a denervated gland was milked hourly (24 %). These results suggest that the complete evacuation of the alveoli by whatever means and the removal of the milk is the factor concerned and imply a local negative feed-back mechanism within the gland itself.

The evidence for a local regulation of milk secretion does not rule out additional systemic factors. Hourly milking using oxytocin has been found to cause a sustained rise in plasma prolactin concentrations (Bryant, Greenwood & Linzell, 1968; Bryant, Linzell & Greenwood, 1970) which supports the hypothesis of Benson & Folley (1957) that oxytocin may have a physiological role in maintaining and perhaps regulating the rate of milk secretion by releasing prolactin. Therefore two mechanisms could be involved, the first, a central hormonal route initiated by the milk ejection reflex and responding to the frequency of milking or suckling and the second, a local action depending on the actual removal of milk. The two processes would of course have a similar effect of adjusting the rate of milk secretion to the size and nutritional requirements of the young at different stages of lactation. In a number of species it is well known that each of the young feeds from the same teat at each suckling. Therefore the local control mechanism may be involved in regulating the amount of milk secreted for young of different sizes in any one litter, whereas it seems likely that the central mechanism affects all glands equally provided that they are producing milk.

The mechanism by which the local effect is exerted is not known but two possibilities are (i) the mechanical presence of milk in the gland, i.e. milk pressure may inhibit milk secretion, (ii) that milk secretion may be inhibited by a chemical factor in stored milk. While extreme pressures do inhibit milk secretion when milking is stopped (see Linzell, 1959) it is not known whether or not small fluctuations influence the rate under normal conditions. Our results suggest that the pressure in the alveoli may not be implicated since in the experiments involving hourly milking with oxytocin, a local effect was seen when one gland was milked hourly compared with the other in which milk was left to accumulate during the experimental period. In the mouse the secretory tissue can be observed through the thin capsule of the gland. When the glands contain only small amounts of milk, 1–2 hr after suckling, oxytocin causes widespread alveolar contraction and the milk is completely ejected into the ducts where it remains. Only after 12 hr when the glands are very full, does milk run back into the alveoli as the myoepithelium relaxes (Linzell, 1955). The goat differs from the mouse in that relative to the size of the whole gland the large ducts and cistern are extremely capacious so that it might be expected that the time at which milk starts to run back into the alveoli would be much later than in the mouse. Thus it might be argued in the goat that the relief of pressure in the alveoli every hour would be the same on the two sides whether the milk was removed from the ducts or not. Some milk might re-enter the alveoli by elastic recoil of the myoepithelium but this would not involve a raised intra-alveolar pressure. Therefore it is possible that some local humoral factor may be involved in the local regulation of the rate of secretion. Another local effect which may assist in increasing the rate of milk secretion is the process of milking or suckling since Reynolds, Linzell & Rasmussen (1968) found that massage results in a local increase in blood flow although this, in itself, did not alter the rate of secretion in the present experiments.

The suggestion that a chemical factor in milk is involved in regulating the rate of secretion by a negative feed-back action is not new. Levy (1963*a*, *b*) showed that in the rat, the ability of the mammary tissue to synthesize fatty acids from acetate decreased as the glands filled with milk following teat obstruction. He also found that mammary gland acetyl CoA carboxylase was inhibited by rats' milk and by milk fatty acids of chain length 10, 12 and 14 C atoms (capric, lauric and myristic acids). Although there is lipase in milk (Korn, 1962) the majority of milk fatty acids are esterified so that it is not known whether this mechanism could account for a local regulation of milk secretion under normal conditions of frequent milk removal. The activity of other milk constituents is possible but a lipid substance might be a good candidate in view of their known ability to pass from milk to blood through the cell membranes (Rogers & Kleiber, 1957; Patton & McCarthy, 1963; Linzell & Peaker, 1971*a*, *b*). It would appear that substances like lactose to which the apical cell membrane is impermeable (Linzell & Peaker, 1971*c*) are unlikely to be involved. Ca^{2+} which passes from milk to blood (Azimov, Orlov & Belugina, 1961) could also be involved since Greenbaum, Gumaa & McLean (1971) found that rat mammary tissue distended with milk had a very high Ca content which persisted for 2 hr after suckling started.

Milk composition

The changes in milk composition induced by even small doses of oxytocin in some goats are quite clear and similar to those reported by other workers in cows and goats using large doses of oxytocin. Wheelock *et al.* (1965) suggested that since [Na] and [Cl] increased together with an increase in concentration of non-casein protein in cows' milk, the effects of large doses of oxytocin could be to permit the entry of extracellular fluid into milk. Our results in the goat are in agreement and, in addition, we have obtained objective evidence for this. The mammary epithelium does not normally allow the passage of significant amounts of labelled lactose from milk into plasma or labelled sucrose to pass from plasma to milk (Linzell & Peaker, 1971*a*, *b*, *c*). However, during an infusion of oxytocin, large amounts of these sugars passed in both directions. The site of alteration of milk composition appears to be in the alveoli since after oxytocin treatment only the milk in the alveoli was affected and the normal impermeability of the ducts (Linzell & Peaker, 1971*a*, *b*) seems not to have been changed. It seems likely that oxytocin can disrupt the secretory epithelium sufficiently to permit the passage of a little extracellular fluid in one direction and milk in the other between the tight junctions which connect the cells towards their apices. Even with large doses this is not a serious condition since once the administration of oxytocin and hourly milking is stopped, the milk composition quickly returns to normal (Linzell, 1967).

The mechanism by which oxytocin allows the entry of E.C. fluid into milk is not known, but the changes in composition could be due to its effective expulsion of milk which results in the rapid compression of the alveoli involving a change in shape of the secretory cells (Richardson, 1947). The less effective compression produced by massage and milking the transplanted glands, where oxytocin is not released, could have a similar effect, particularly as, in some goats, the myoepithelial cells will contract in response to massage (Linzell, 1963*b*). Linzell (1967) reported that the frequent milking of goats, given oxytocin before each milking, produced a large increase in the numbers of cells and cell fragments in the milk. Subsequently Wooding, Peaker & Linzell (1970) identified these fragments as pieces of secretory cell epithelium devoid of a nucleus. Forces capable of causing this detachment of the apex of a few of the cells might well be expected to affect tight junctions of some as well. Quite small leaks of extracellular fluid into milk with low Na and Cl concentrations could alter milk composition. Thus in the goats milked hourly without oxytocin (Fig. 4) the empty glands were 500–900 ml. in volume and were yielding 40–70 ml. milk per hr. It may be calculated that a leak of extracellular fluid equivalent to 1 ml. lymph at each milking would be sufficient to account for the observed rise in milk [Na] and [Cl]. In the case of the fall in [lactose] and [K], the addition of this quantity of fluid would not be sufficient to lower these by simple dilution alone. But since the concentration gradients are very high for these components, a similar small leak in the opposite direction could account for the changes observed. Since oxytocin does not alter the ionic composition of mammary cells (Linzell & Peaker, 1971*c*), the leaks may be presumed to occur in between the cells, as the experiments with labelled lactose and sucrose imply.

Bradykinin has been found to mimic the effects of oxytocin, and the possibility that oxytocin treatment may result in the formation and release of this other peptide in the mammary gland may have to be considered. Kallikrein is found in mammary tissue and bradykinin will cause milk ejection (Reynaert, Peeters, Verbeke & Houvenaghel, 1968) but, as with oxytocin, it is not known if the pressure exerted by the myoepithelial cells causes the change in milk composition or whether the secretory epithelium is affected directly.

It seemed possible that the variation in sensitivity of different goats could be the result of differences in the levels of circulating antibodies to exogenous oxytocin since many of the goats had been given oxytocin a number of times previously. However, Mr A. S. McNeilly could find no evidence of antibodies to oxytocin either in the plasma of a goat which was very sensitive to oxytocin or in one which was not. Since no differences in sensitivity to oxytocin in respect of milk composition have been apparent at different stages of lactation, it seems that the differences are the result of genuine biological variation between individuals.

Of the effects described in this paper, the greatest physiological significance would appear to be attached to the effect of milk removal in stimulating the rate of secretion by a possible local humoral mechanism. The effects on milk composition are small and probably only incidental to the main, and, in some species, the vital action of oxytocin in evacuating the mammary gland at suckling.

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