泌乳ラットにおけるインスリン分泌の低下

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Decrease in Insulin Secretion in Lactating Rats

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ABSTRACT. Changes in plasma insulin concentrations in the pregnancy, lactation and after-weaning period in female rats were investigated. Plasma insulin concentrations increased as pregnancy progressed, but there was a sharp decrease before parturition and the values remained at 20 to 30% of those in virgin rats throughout the lactation period. The concentrations again returned to the same levels as in virgin rats 3 days after completion of lactation. Decreased plasma insulin concentrations during the lactation period were seen in the portal and abdominal veins and in the carotid artery. Plasma insulin concentrations in lactating rats decreased in dose-dependent manner with increased litter sizes, but they returned to the values in the virgin rats when the litter sizes were decreased and lactation stopped. Since the same amounts of insulin secretion as in virgin rats were observed in lactating rats after administration of glucose, it was evident that insulin secretion from the pancreas is suppressed in lactating rats. Because plasma insulin concentrations were not decreased in rats with the galactophores sectioned beforehand even when a sucking stimulus was applied, and there were dose-dependent decreases in the blood glucose levels in abdominal vein and simultaneous stepwise decreases in the portal insulin levels in lactating rats as the litters become larger, it was assumed that drops in peripheral blood glucose levels with milk secretion have an effect on the decreased plasma insulin concentrations in lactating rats.—KEY WORDS: blood glucose, insulin, lactation, litter size, mammary gland.

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Milk secretion is controlled mainly by the maternal nutritional state and hormones. Insulin and many other hormones including prolactin and corticosteroids are considered to be indispensable for lactation [16, 25]. It has long been known that the plasma insulin concentration increase in female rats as pregnancy progresses [7, 13, 23]. However, recently, it has been reported that the plasma insulin concentration in pregnant rats decrease during the latter half of pregnancy [3, 27, 28], and significantly decreased insulin concentration continue during the lactation period [2, 8, 9, 28].

Flint [4] reported that the numbers of insulin receptors in mammary cells increased in female rats during the lactation period, and the decreased plasma insulin concentrations observed in the lactation period is considered to be caused by increased uptake of insulin by peripheral tissue such as the mammary gland and by the liver [22]. In the recent report we have described experiments which showed that the low plasma insulin concentration in lactating rat was restored by the removal of pups and these rises due to pups-removal was not prevented by prolactin administration [20]. Thus, these data suggested that milk production presumably served to suppress insulin secretion from pancreas. Indeed, in the cow, an inverse relationship between plasma insulin concentration and milk yields was observed [11].

In the present experiments, detailed changes in the plasma insulin and glucose concentration in the portal vein and in the secretory response of insulin after glucose injection in lactating rats were investigated, and the effects of varying amounts of

lactation on the plasma insulin and glucose levels were investigated.

MATERIALS AND METHODS

Animals. Crj: CD (SD) female rats from Charles River Japan, Inc., weighing 180–230 g were used. The animals given standard pellets (CE-2, Nihon CLEA, Tokyo) and water *ad libitum.* They were reared in a room with the temperature controlled at 25±1°C, the relative humidity at 55±5% and the lights on 7:00 and off 19:00. The rats were mated and the day following mating was considered as day 0 of pregnancy. The date of birth of the pups was considered as day 0 of lactation and the period of lactation was 21 days following parturition.

Measurement of insulin and blood glucose. Blood was collected from the portal and abdominal veins and the carotid artery under sodium pentobarbital anesthesia and from the tail vein without anesthesia. The blood was collected between 11.00 and 13.00 with heparinized syringe. The samples were immediately centrifuged at 0°C, and the plasma samples were frozen at −20°C for subsequent determination of insulin and glucose. Plasma insulin was determined by a double antibody assay by using ^{125}I-insulin and antiserum that cross-reacted to the same extent with rat, pork and human insulin (from CEA SORIN data). The procedure used was essentially that described in the insulin RIA kit supplied by CEA-IRE-SORIN, France. Results were expressed in terms of μU of a human insulin standard (40 ng/lmU). Sensitivity of assay is 2 μU/m*l*. Blood glucose was measured by enzymic method using a kit supplied by Wako Pure Chemical, Tokyo.

Experiment I: (a) Changes in the plasma insulin concentrations in the pregnancy, lactation and after-weaning periods of female rats were investigated. Blood was collected simultaneously from the carotid artery and abdominal and portal vein under anesthesia and the insulin concentrations in plasma were measured. Pregnant animals with less than 10 fetuses were excluded from the experiment, and the litter size during the lactation period was adjusted 10 on the day of parturition.

(b) For a more detailed investigation of changes in insulin concentration, blood was collected from the tail vein of six other rats at shorter interval, and the change in insulin concentration were studied.

Experiment II: To examine the glucose tolerance during the pregnancy, lactation and after-weaning periods in female rats, the intravenous glucose tolerance test (ivGTT) was performed by the authors' own method [19] using rats on the 21st day of pregnancy, 14th day of lactation and 14 days after weaning. Glucose (1.0 g/kg; 50%, w/v) was administered into the tail vein and blood was collected from the abdominal artery 0, 4, 16 and 28 minutes after administration. The half-time of blood glucose (T 1/2) and total insulin secretion were obtained.

Experiment III: Two experiments were performed to investigate the effect of varying amounts of lactation on plasma insulin concentrations. In the first experiment, changes in the maternal plasma insulin concentrations with the litter sizes adjusted to four or 10 or all of the pups removed immediately after parturition were examined using blood collected from the tail vein. In the second experiment, changes in insulin concentration were investigated in dams with galactophores sectioned. The galactophores were sectioned 3 days before parturition. Under ether anesthesia, the galactophores of all mammary glands were exposed by means of a small incision near the teats and they were sectioned so as not to damage the nerves. After parturition, the litter size was adjusted to 10, and all pups

were exchanged once a day between the intact lactating control group and the galactophore sectioned group to provide the same sucking stimulus as in the intact lactating control group. Successful sectioning was confirmed by determining that there was no increase in the body weight of pups before and after nursing. Blood was collected from the tail vein.

Experiment IV: To examine the plasma glucose levels in the pregnancy, lactation and after-weaning periods in female rats, blood was collected from the abdominal and portal veins and the carotid artery under anesthesia at one week intervals after mating. Plasma glucose levels were also measured in blood collected from the abdominal vein 14 days after parturition in dams with the litter sizes adjusted to two, five, ten or 15, or all pups removed immediately after parturition to investigate the effect of varying amounts of lactation on blood glucose.

Statistics: All results were expressed as mean±SEM.

Significance difference in mean value between groups were determined by unpaired student's *t*-test. *P* values of less than 5% were considered significant.

RESULTS

Changes in plasma insulin concentrations in the pregnancy, lactation and after-weaning periods:

Insulin concentrations in plasma from the abdominal vein increased with the progress of pregnancy, and the value on 14th day of pregnancy was significantly higher than that in virgin rats. However, the value on the 21st day of pregnancy was significantly lower. The plasma insulin levels in the lactation period following parturition continued to be less than 10 μU/m*l* and significantly less than the values in virgin rats. At the end of the period of lactation on day 21,

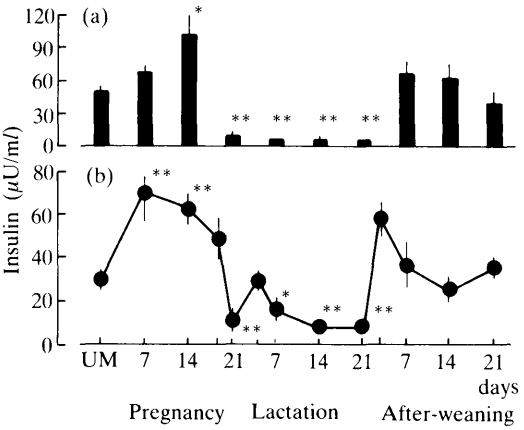

Fig. 1. Changes in plasma insulin concentration during pregnancy, lactation and after-weaning period. Blood were taken from abdominal vein (a) or tail vein (b). Points and columns are mean values, with their standard errors represented by vertical bars, for seven to nine observations. Statistical significance of difference between unmated and others. *; $p<0.05$, **; $p<0.01$.

the plasma insulin concentration increased sharply and was the same as that of virgin rats on the 7th day of the after-weaning period. More detailed changes in plasma insulin concentrations were obtained by examining blood collected from the tail vein of same animals at shorter intervals. The plasma insulin concentrations maintained their high values until at least 2 days before parturition, and returned to the same values as in virgin rats 3 days after the pups were weaned after the 21 day lactation period (Fig. 1).

Plasma insulin concentrations in portal vein showed changes similar to those observed in the abdominal and tail veins. These values during lactation period were all significantly lower than that in virgin rats. Plasma insulin concentrations in the carotid artery also showed the same changes as those seen in the portal and tail veins except that there was no significant difference on the 7th day of lactation (Fig. 2.a). The differences in insulin concentrations between in the carotid artery and in the portal vein are shown in Fig. 2(b). Although the

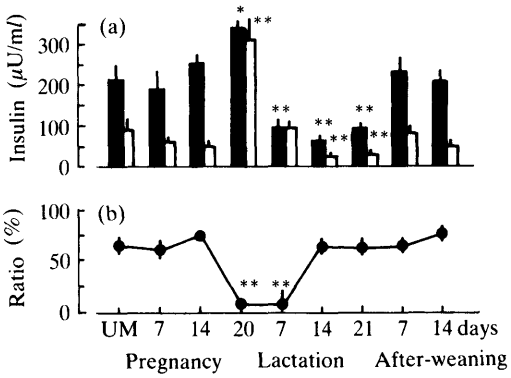

Fig. 2. Changes in plasma insulin concentration and insulin disappearance ratio during pregnancy, lactation and after-weaning period. (a), Blood were taken from portal vein (black column) and carotid artery (white column). (b) Disappearance ratio were calculated by the difference between the concentration in portal and in carotid. Values are means, with their standard errors represented by vertical bars, for seven to nine observations. Statistical significance of difference between unmated and others. *; $p<0.05$, **; $p<0.01$.

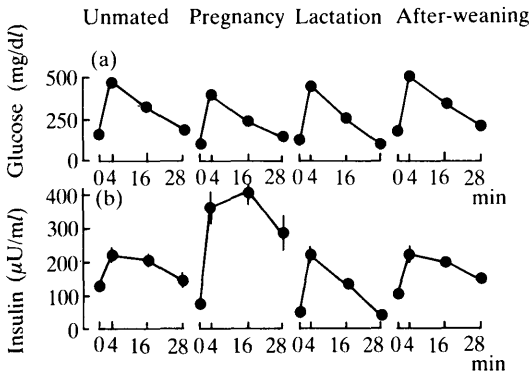

Fig. 3. Changes in plasma glucose and insulin concentrations during intravenous glucose tolerance test (ivGTT). Glucose injection (1 g/kg b.w.) was performed at 0 min in unmated rats, pregnant, lactating and after-weaning rats. Points are mean values, with their standard error represented by vertical bars, for six to eight observations.

ratios on the 20th day of pregnancy and the 7th day of lactation were significantly lower than that of virgin rats, there were no differences from the virgin values at any other time.

Glucose tolerance test (ivGTT):

The ivGTT was performed on virgin rats and on the rats on the 21st day of pregnancy, the 14th day of lactation and the 14th day of the after-weaning period (Fig. 3). There were no difference in plasma glucose levels in the virgin and lactating rats before administration of glucose, but plasma insulin concentration in lactating rats were significantly lower than those in virgin rats. However, the same insulin concentration patterns were seen in both the virgin and lactating rats after glucose administration. As seen in Table 1, total insulin secretion during 28 minutes after glucose administration in pregnant rats was significantly greater than that in virgin rats, but there were no significant differences between virgin and lactating rats. However, the T1/2 value in lactating rats was significantly shorter than that in virgin rats. On the other hand, the T1/2 value for pregnant rats did not differ from that of virgin rats in spite of the increased total insulin secretion.

Effects of litter size and lactation changes on plasma insulin concentrations:

When the pups were removed immediately after parturition, plasma insulin concentrations in the dams returned to the level in virgin rats after 3 days (Fig. 4). In lactating rats for which the litter sizes were reduced to four pups immediately after parturition, the plasma insulin concentration were basically midway between those of rats for which the litter size adjusted to 10 and those of rats with all of the pups removed.

When all of the galactophores were sectioned 3 days before parturition, there was no decrease in plasma insulin concentrations such as that observed in intact lactating control rats in spite of the application of the same sucking stimulus as that in intact lactating controls (Fig. 5).

Changes in plasma glucose levels in pregnancy, lactation and after-weaning periods:

Plasma glucose levels showed no marked changes up to the 14th day of pregnancy,

Table 1. Blood glucose concentration and glucose disappearance rate during ivGTT in unmated, pregnant, lactating and after-weaning rats.

Physiological state	n	T1/2[a] (min)	Glucose[b] (mg)	Insulin[c] (μU)
Unmated	8	21.2±1.8[d]	4123±421	1951± 368
Pregnancy	6	19.7±1.7	4103±455	7117±1075**[e]
Lactation	6	16.0±0.5**	3866±229	2273± 206
After weaning	6	22.5±2.5	4516±345	2441± 653

a) Glucose disappearance rate after glucose load.
b) Total incremental glucose concentration during ivGTT.
c) Total insulin secretion during ivGTT.
d) Mean±SEM of n observation.
e) Statistical significance of difference between unmated and others, **; $p<0.01$.

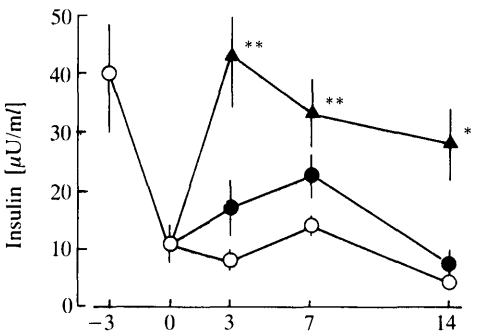

Fig. 4. Effect of litter reduction on maternal plasma insulin concentrations. Number of pups per litter were adjusted ten (control, ○) or four (●), or all pups were removed (▲) on day 0 of lactation. Points are mean values, with their standard errors represented by vertical bars, for seven observations. Statistical significance of difference between control and others. *; $p<0.05$, **; $p<0.01$.

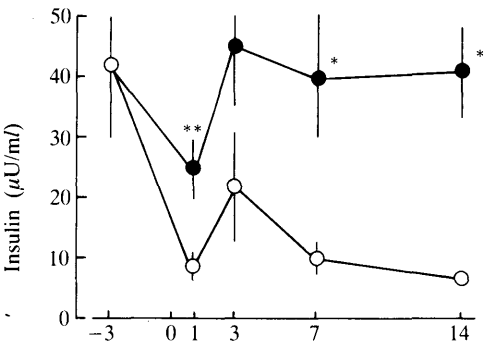

Fig. 5. Effect of section of galactophores on maternal plasma insulin concentrations. Section of galactophores was carried out on three days before parturition and the number of pups per litter were adjusted to ten on day 0 of lactation. Points are mean values, with their standard errors represented by vertical bars, for seven observations. Statistical significance of difference between control (○) and sectioned (●). *; $p<0.05$, **; $p<0.01$.

but they were significantly lower than in virgin rats in portal and abdominal veins and the carotid artery on the 20th day of pregnancy (Table 2). Plasma glucose levels in the abdominal vein of lactating rats were lower than those in virgin rats throughout the lactation period. However, the levels in the portal vein and carotid artery did not differ from those of virgin rats except for decreases on the 7th and 14th days of lactation. After being decreased throughout the 21 day lactation period, the plasma glucose levels in the abdominal vein again returned to that of virgin rats after completion of lactation.

Plasma glucose levels in the abdominal vein on the 14th day of lactation were compared among lactating dams with the litter sizes adjusted to 2, 5, 10 or 15 on the

Table 2. Changes in blood glucose concentration in V. portal, A. carotid and V. abdominal during pregnancy, lactation and after-weaning period.

	Unmated	Pregnancy			Lactation			After-weaning	
		7	14	20	7	14	21	7	14 days
n	6	6	6	5	6	5	6	6	5
Portal	156.0[a)]	156.2	153.0	107.8**[b)]	138.0*	142.0	142.7	145.7	153.6
Vein	6.1	6.3	7.9	8.4	2.4	12.3	6.5	10.5	11.5
Carotid	133.8	139.2	133.8	88.3**	130.2	118.0*	131.7	126.5	123.1
Artery	1.9	6.0	9.5	6.3	4.2	6.4	5.7	3.3	4.9
Abdominal	145.5	147.3	143.8	121.4*	119.0**	122.6*	128.5*	138.0	158.6
Vein	4.8	6.2	3.4	6.3	3.2	7.0	4.0	5.8	9.9

a) Upper and lower values represent the mean and SEM, respectively.
b) Statistical significance of difference between unmated and others; *; $p<0.05$, **; $p<0.01$.

day of parturition and dams with all pups removed. As the litter size increased, the levels tended to decrease dose-dependently (Table 3). Plasma insulin concentrations in portal vein investigated simultaneously also decreased dose-dependently with increasing litter sizes similarly to the changes observed in plasma glucose levels.

Table 3. Effect of changes in littter size on abdominal vein concentration of glucose and portal vein concentration of insulin.

Group[a)]	n	Glucose[b)] (mg/dl)	Insulin[c)] (μU/ml)
Unmated	7	176.2±8.2[d)]	172.2±16.8
Removed	5	189.2±2.9	–
2 pups	5	148.2±1.5	196.0±43.7
5 pups	5	123.0±1.9*[e)]	69.6±22.5*
10 pups	5	133.4±3.5**	50.6±17.6**
15 pups	5	129.6±8.7**	36.8±13.5**

a) Litter size were adjusted 2, 5, 10, 15 or all pups were removed on day 0 of lactation.
b) Blood were taken from V. abdominal on day 14 of lactation.
c) Blood were taken from V. portal on day 14 of lactation.
d) Mean±SEM of n observations.
e) Statistical significance of difference between unmated and others: *; $p<0.05$, **; $p<0.01$.

DISCUSSION

Plasma insulin concentrations in female rats increased as pregnancy progressed and decreased in the late period of pregnancy. The present result, however, differed from those in the previous reports [3, 23, 27, 28] with respect to the time of the start of the decrease. In the present experiments, plasma insulin concentrations showed high values until just before parturition. This difference might have been due to the maternal nutritional state, i.e., whether or not they were starved or fed before blood collection [15].

Following the decrease just before parturition, the plasma insulin concentrations fell to 20 to 30% of the levels in virgin rats throughout the lactation period. Two reasons for this drop in plasma insulin concentration can be considered. One is a decrease in insulin secretion from the pancreas and the other is increased insulin uptake by the liver and peripheral tissue. Robinson *et al.* [22] assumed the decrease in plasma insulin concentration observed in lactating rats is due to increased insulin uptake by liver and peripheral tissue. When the uptake was estimated from the differences in insulin concentrations between the portal vein and carotid artery, the insulin uptake on the 7th day of lactation was less than that in virgin rats, there was no

difference in uptake from that of virgin rats from the 14th day of lactation, and it does not appear that insulin uptake by liver increases in lactating rats. In cows, it has been reported that insulin uptake by the liver was 85% in non-lactating dairy cows compared with 65% in lactating dairy cows, i.e., the insulin uptake dropped during the lactaion period [14]. It seems that the decreased plasma insulin concentration observed in lactating rats is due to reduced insulin secretion from the pancreas. The basis for this is that, as observed in the present experiments, the decreased plasma insulin concentrations in lactating rats were observed not only in peripheral sites but also in the portal vein.

There is no injury to B-cell in lactating rats because the same amount of insulin secretion as in virgin rats was seen in lactating rats after glucose administration. This suggested that insulin secretion is suppressed for some reason in lactating rats. In normal state, the major control of insulin secretion is exerted by a feedback regulation of the portal glucose level. It has been reported that blood glucose levels of abdominal vein are significantly lower in lactating rats than in virgin rats [1, 22], and glucose level in portal vein of lactating rats is significantly lower at day 12 of lactation [2]. In the present experiments, the authors made a detailed examination of changes in blood glucose levels in the portal and abdominal veins and the carotid artery of lactating rats and found no reductions in portal glucose levels except in the initial period of lactation.

Since plasma insulin concentrations increased when litter sizes were decreased and returned immediately to the levels in virgin rats when lactation stopped, it can be assumed that the sucking stimulus or milk secretion plays a role in inhibition of insulin secretion. Hart *et al.* [11] showed the inverse relationship between plasma insulin concentration and milk yields in the cow. It has been reported that prolactin secretion also increases with increased sucking stimulus due to larger litters, but prolactin decreases plasma insulin concentrations in lactating rats [1, 4, 22]. The decrease of plasma insulin concentrations by prolactin in these reports is based on experimental results showing that the decreased insulin concentrations in lactating rats returned to the levels in virgin rats after administration of CB-154. The authors also found that the administration of CB-154 increased plasma insulin levels in lactating rats [20]. However, we assumed that prolactin dose not directly suppress insulin secretion, but milk secretion maintained by the action of prolactin suppresses the secretion of insulin from the pancreas. This is clear from experimental results showing that plasma insulin concentrations were not decreased when sucking stimulus was applied to rats with only the galactophores sectioned so as not to damage the nerves, i.e., when only milk secretion was stopped without inhibiting prolactin secretion.

The mechanism or the reason why milk secretion inhibits insulin secretion is not clear. Jones *et al.* [12] suggested that increase in mammary gland insulin sensitivity in lactation causes an increased flux of glucose towards the mammary gland and that a fall in plasma insulin concentration occurs as a result of a decrease in the plasma glucose concentration by the increasing extraction of glucose by the mammary gland. Insulin secretion is greatly influenced by changes in portal glucose levels, but the autonomic nervous system is also known to play a role in regulation of insulin secretion [5, 6, 10, 18]. Recently, it has been reported that there is a glucoreceptor in the small intestine [17] and liver [21]. Previous study in the cow and in the goat have shown that glucose uptake by the mammary gland represents 60% of the total glucose turnover

rate. Indeed, glucose turnover was increased from 3 days of parturition on in lactating rats compared with nonlactating rats [2]. As was clear from the present experiments, peripheral glucose levels showed a stepwise decrease when the litter size was increased in lactating rats and this resulted in a stepwise decrease in insulin concentrations in the portal vein. Therefore, there is a possibility that drops in blood glucose levels in peripheral tissue at the time of milk production inhibit insulin secretion.

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要　約

泌乳ラットにおけるインスリン分泌の低下：溝口順二・今道友則[1)]（食品薬品安全センター秦野研究所，[1)]動物繁殖研究所）—— 雌ラットの血漿インスリン濃度は，妊娠の経過に伴って上昇したが，分娩2日前に急激に低下し，泌乳期間中は有意に低下して処女ラットの20-30％であった．泌乳期間終了後3日には再び処女ラットの値に戻った．インスリン濃度の低下は末梢血のみならず門脈血においても認められ，乳仔数が増加すると用量反応的に低下し，泌乳中断により処女ラット値に戻った．グルコース投与後には処女ラットと等しいインスリン分泌量がみられることから，泌乳ラットではインスリン分泌が抑制されていると考えられた．さらに，乳管切断ラットでは，吸乳刺激が加えられてもインスリン濃度の低下はみられず，乳仔数増加により末梢血糖は用量反応的に低下することから，泌乳ラットにおけるインスリンの分泌低下には乳生産に伴う末梢血糖の低下が関与していると推察された．