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Prenatal and Postnatal Maternal Effects on Body Weight in Cross-fostering Experiment on Two Subspecies of Mice

Edy KURNIANTO[1,*)], Akihisa SHINJO[2)], and Daisuke SUGA[2)]

[1)]*The United Graduate School of Agricultural Sciences, Kagoshima University, 1–21–24 Korimoto, Kagoshima 890-0065,* [2)]*Faculty of Agriculture, University of the Ryukyus, 1 Senbaru, Nishihara-cho, Okinawa 903-0129, and *Permanent address: Faculty of Animal Sciences, Diponegoro University, Campus Tembalang-Semarang, Indonesia*

Abstract: *A cross-fostering experiment was conducted on two quite distinct subspecies of mice, domesticated laboratory mouse of $CF_{\#1}$ (Mus musculus domesticus) and Yonakuni wild mouse (Yk, Mus musculus molossinus yonakuni), to estimate the prenatal and postnatal maternal effects on body weight of offspring. Mating was done between subspecies, two or three females being mated to a male at nine-ten weeks of age. Two dams of different subspecies that littered at the same day were used as a group of foster dams. Litters were standardized to six young mice in order that a dam nursed three mice of her own litter and three mice from that of another subspecies dam. The litters were weaned at 3 weeks of age. The body weight of individual mice was determined at 1, 3, 6 and 10 weeks of age. The result demonstrated that prenatal maternal effects were more important than postnatal maternal effects in contributing to the variation in body weight at all ages examined. Prenatal maternal effects accounted for 61–96% and 35–92% of total variance in males and females, respectively; whereas postnatal effects accounted for 1–7% for males and 3–23% for females. Analysis for between postnatal within prenatal, and between prenatal within postnatal indicated that expression of the body weight of offspring was limited by the genetic type of their prenatal dam and influenced by the postnatal environment of nursing dam. The greatest body weight was attained by offspring born to prenatal $CF_{\#1}$ dams and nursed by postnatal $CF_{\#1}$ dams, followed by $CF_{\#1}$ offspring born to $CF_{\#1}$ dams and nursed by Yk dams, Yk offspring born to Yk dams and nursed by $CF_{\#1}$ dams and the lightest ones were Yk offspring born to Yk dams and nursed by Yk dams.*

Key words: *body weight, cross-fostering technique, mice, prenatal and postnatal maternal effect*

Introduction

In the common procedure for the cross-fostering experiment, a dam is given its own young mice plus the young from each of the other dams included in a group. By this procedure, the variation in F_1 offspring performance may be divided into prenatal and postnatal components.

Cross-fostering techniques have been used to compare the performance of several populations of mice

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Address corresponding: A. Shinjo, Faculty of Agriculture, University of the Ryukyus, 1 Senbaru, Nishihara-cho, Okinawa 903-0129, Japan

[9]. White *et al.* [16] conducted an investigation to characterize the magnitude and nature of lines differences into the prenatal and postnatal maternal effects on growth and maternal ability in three lines of mice, two of which had been subjected to long term selection for six weeks (H_6 and L_6), and unselected control (C_2). Moore *et al.* [8] examined the relative importance of genetic effects, uterine effects and postnatal maternal effects in causing growth differences by using two lines of mice selected for high (H_6) and low (L_6) body weight by means of embryo transfer and cross-fostering at birth.

Many studies have shown that postnatal maternal performance of the dam was responsible for a large portion of the variation in the preweaning weight of offspring [2, 3], and some carry-over postnatal maternal effects were present after weaning [4]. Numerous experiments previously reported have used laboratory mice of a similar genetic type.

In this study we examined the relative importance of prenatal and postnatal effects on the body weight of two quite distinct subspecies of mice at 1, 3, 6 and 10 weeks of age.

Materials and Methods

Animals: Two subspecies of mice, the $CF_{\#1}$ domesticated laboratory mouse (*Mus musculus domesticus*) and the Yonakuni wild mouse (Yk, *Mus musculus molossinus yonakuni*), were used in this study. $CF_{\#1}$ is described as an outbred albino mouse with pink eye, and known as a European mouse. This mouse has large body, males weighing 41 g and females 34 g at maturity, and apparently prolific with a litter size of about 12 mice. Yk is a wild mouse originating in the Ryukyu Islands (southern islands of Japan) and has gray skin. The body weight of the Yk is about 12–13 g at maturity and not so prolific with a mean litter size of 4 mice [12, 13].

Mating between subspecies was done when they reached nine to ten weeks of age. A male was mated with two or three females, and they remained together for 16–21 days. The pregnant females were taken and placed in separate cages until littering. Two females of different subspecies that littered on the same day were used as the foster dams for each other in a group. Litters were standardized to six mice as nearly as possible, and randomly recombined so that each dam nursed three mice from her own litter and three mice from other subspecies dams in a group. The standardization of litter size was important to eliminate the effects of the number in litters suckled. Litters were weaned at three weeks of age. After weaning, males and females were caged separately.

Individual body weights were determined at 1, 3, 6 and 10 weeks of age with Sartorius portable (model PT-1200, 0.1 g scale). Only first litters were used. Water in drinking bottles and food pellets (CE-2, Clea Japan Inc.) were provided *ad libitum*. Room temperature was maintained at approximately 24°C and 76% relative humidity with 12 hr light and 12 hr darkness.

By restricting the group to two dams littering at least six mice on the same day, 16 $CF_{\#1}$ and 16 Yk dams were used and the number of offspring was 191 mice.

Statistical analysis: Body weights were analyzed by the General Linear Model (GLM) of SAS [11]. A mathematical model used to analyze body weight data as follows:

$$Y_{ijkl} = \mu + s_i + a_j + p_k + (sa)_{ij} + (sp)_{ik} + (ap)_{jk} + (sap)_{ijk} + e_{ijkl}$$

where:

Y_{ijkl} = an observation on the l^{th} mouse of the i^{th} sex, j^{th} prenatal and k^{th} postnatal,

μ = the general mean,

s_i = the effect of sex with variance σ^2_s (i=1,2),

a_j = the effect of prenatal with variance σ^2_a (j=1,2),

p_k = the effect of postnatal with variance σ^2_p (k=1,2),

$(sa)_{ij}$, $(sp)_{ik}$, $(ap)_{jk}$ and $(sap)_{ijk}$ = the accompanying interaction effects with σ^2_{sa}, σ^2_{sp}, σ^2_{ap} and σ^2_{sap} variances, respectively,

e_{ijkl} = the effect of differences among full-sibs born and reared alike.

Interaction effects which exist in the ANOVA were examined by using a technique described by Shinjo [14].

Figure 1 shows the schemes used to examine prenatal and postnatal effects on F_1 body weight. Differences between body weight of offspring born by prenatal dams represent the effects common to individuals before birth (prenatal effects). Differences between body weight of offspring nursed by postnatal dams represent the effects common to individual nursed by the same dam after birth (postnatal effects).

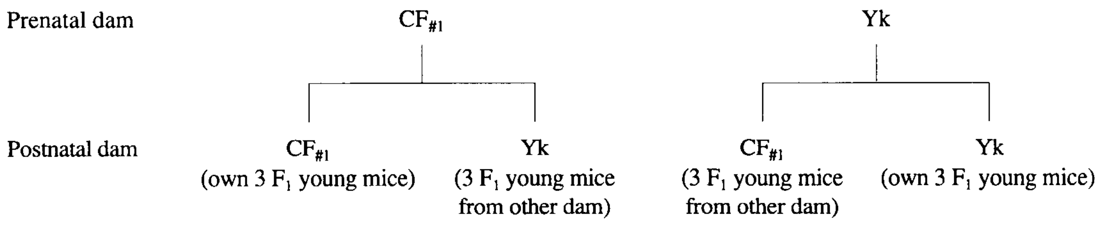

Fig. 1. Schemes used in examining the prenatal and postnatal effects.

Table 1. Analysis of variance by mean squares for pooled sexes for body weight at 1, 3, 6 and 10 weeks of age

Source of variation[1]	df[2]	Mean squares at weeks			
		1	3	6	10
Pre	1	49.25**	661.59**	7018.24**	9198.77**
Post	1	23.19**	131.92**	130.91**	225.91**
Sex	1	5.27*	55.70**	736.16**	927.10**
Pre × Post	1	5.93*	38.42**	137.85**	114.99**
Pre × Sex	1	5.95**	24.55**	277.50**	275.94**
Post × Sex	1	2.05	5.35	1.37	0.06
Pre × Post × Sex	1	0.72	5.28	0.33	2.96
Error	183	0.89	3.47	3.21	4.64

[1]Pre: Prenatal, Post: Postnatal. [2]Degree of freedom. *Significant at $P<0.05$, **Significant at $P<0.01$.

Results

Analysis of variance was utilized to examine the magnitude of the source of variation into prenatal, postnatal and sex components and accompanying effects interacting components. Mean squares of body weight resulting from pooled sex are shown in Table 1. Prenatal, postnatal, sex, prenatal and postnatal interaction, and prenatal and sex interaction had important effects ($P<0.05$–$P<0.01$) on variation in body weight at all ages examined.

Since the sex factor significantly contributed to body weight performance, a further analysis was conducted for each sex. Tables 2 and 3 show analysis of variance contains mean squares, components of variance and the percentages they represent of total variance in the body weight of male and female, respectively. Both Tables 2 and 3 showed that the variance for the individual body weight can be partitioned into four components, namely prenatal, postnatal, prenatal and postnatal interaction, and error components. The prenatal component (σ^2_a) includes the variance due to genetic differences between individuals in body weight present among individuals before birth as well as variance resulting from the environmental effects of the dam that provided for the litters in the uterus. The postnatal component (σ^2_p) includes the variance arising from the direct maternal effects on the body weight of the litters following parturition during the suckling period. The interaction of two main effects includes the result of genetic and environment interaction (σ^2_{ap}) in which the effects of individual litter performance and the dam's milk contribute to this component. All effects not included in the above components contribute to the error component (σ^2_e).

The prenatal effects apparently increased with age, which accounting for 61 to 96% and for 35 to 92% of total variance for males and females, respectively. Postnatal effects decreased from 7 to 1% for males and 23 to 3% for females. These results indicated the great importance of prenatal maternal effects of the dam to the variation in the body weight of offspring during the

Table 2. Analysis of variance for individual body weight at 1, 3, 6 and 10 weeks of age at F_1 male

Source of variation1)	df2)	Age (weeks) 1	3	6	10
Mean Square					
Pre	1	41.57**	437.51**	4689.56**	5886.39**
Post	1	5.33**	23.49**	49.07**	108.33**
Pre × Post	1	1.18*	2.44**	58.02**	71.99**
Error	91	0.89	4.33	3.27	4.92
Component of variance and as a percentage of the total					
Pre (σ^2_a)		1.66	17.70	191.51	240.35
		(60.58)\$	(75.48)	(96.29)	(95.29)
Post (σ^2_p)		0.18	1.42	1.87	4.23
		(6.57)	(6.06)	(0.94)	(1.68)
Pre × Post (σ^2_{ap})		0.01	−0.08#	2.24	2.74
		(0.36)	(0.00)	(1.13)	(1.09)
Error (σ^2_e)		0.89	4.33	3.27	4.92
		(32.48)	(18.47)	(1.64)	(1.95)

1)Pre: Prenatal, Post: Postnatal; 2)Degree of freedom. *Significant at $P<0.05$, **Significant at $P<0.01$. \$Values in the parentheses are the components of variance as percentage of the total. #Negative estimates of the component assumed as zero.

Table 3. Analysis of variance in individual body weight at 1, 3, 6 and 10 weeks of age in F_1 female

Source of variation1)	df2)	Age (weeks) 1	3	6	10
Mean Square					
Pre	1	11.34**	233.21**	2436.15**	3400.76**
Post	1	21.10**	102.96**	85.99**	118.28**
Pre × Post	1	5.83*	55.25**	81.96**	43.84**
Error	92	0.89	2.76	3.16	4.42
Component of variance and as a percentage of the total					
Pre (σ^2_a)		0.47	8.10	85.47	119.32
		(35.07)\$	(49.93)	(90.63)	(92.43)
Post (σ^2_p)		0.31	3.52	2.91	4.01
		(23.13)	(21.70)	(3.09)	(3.11)
Pre × Post (σ^2_{ap})		0.17	1.84	2.77	1.36
		(12.69)	(11.34)	(2.94)	(1.05)
Error (σ^2_e)		0.39	2.76	3.16	4.40
		(29.10)	(17.02)	(3.35)	(3.41)

1)Pre: prenatal, Post: postnatal; 2)Degree of freedom. *Significant at $P<0.05$, **Significant at $P<0.01$. \$Values in the parentheses are the components of variance as percentage of the total.

prenatal period.

Significant interactions between prenatal and postnatal effects were found at all ages studied, which indicated that genetic differences among litters before birth as well as the influence of the prenatal dam and presumably the large amount of nutrition provided by the postnatal dam contributed to the variation in body weight at the respective ages. This also indicated that the prenatal and postnatal factors were not independent, so that further analysis of prenatal and postnatal

Table 4. Significance test of effect of between postnatal within prenatal for F_1 body weight

Sex	Postnatal dam	N1)	Age (weeks) 1	3	6	10
				Prenatal $CF_{\#1}$ dam		
Male	$CF_{\#1}$	24	6.3 ± 0.5**2)	15.6 ± 1.2**	35.9 ± 1.5**	41.6 ± 1.8**
	Yk	24	5.3 ± 1.7	13.4 ± 3.9	31.8 ± 2.8	36.2 ± 3.3
Female	$CF_{\#1}$	23	5.8 ± 0.9**	14.4 ± 1.2**	27.7 ± 2.2**	32.0 ± 3.4**
	Yk	24	3.9 ± 1.6	9.7 ± 3.4	22.9 ± 2.7	27.4 ± 1.9
				Prenatal Yk dam		
Male	$CF_{\#1}$	24	4.1 ± 0.1^{NS}	9.2 ± 0.7^{NS}	14.2 ± 1.0^{NS}	17.2 ± 1.7^{NS}
	Yk	24	3.8 ± 0.8	7.8 ± 0.6	14.4 ± 1.5	16.7 ± 1.6
Female	$CF_{\#1}$	24	4.1 ± 0.2^{NS}	8.4 ± 0.4^{NS}	12.3 ± 0.7^{NS}	14.8 ± 0.8^{NS}
	Yk	24	3.7 ± 0.7	7.7 ± 0.5	12.2 ± 0.9	13.7 ± 0.9

1)Number of mice used. 2)Values are the means ± standard deviation. **Two means within each age column for each sex are significantly different at $P<0.01$. ^{NS}Not significant ($P>0.05$).

Table 5. Significance test of effect of between prenatal within postnatal for F_1 body weight

Sex	Prenatal dam	N1)	Age (weeks) 1	3	6	10
				Postnatal $CF_{\#1}$ dam		
Male	$CF_{\#1}$	24	6.3 ± 0.5**2)	15.6 ± 1.2**	35.9 ± 1.5**	41.6 ± 1.8**
	Yk	24	4.1 ± 0.1	9.2 ± 0.7	14.2 ± 1.0	17.2 ± 1.7
Female	$CF_{\#1}$	23	5.8 ± 0.9**	14.4 ± 1.2**	27.7 ± 2.2**	32.0 ± 3.4**
	Yk	24	4.1 ± 0.2	8.4 ± 0.4	12.3 ± 0.7	14.8 ± 0.8
				Postnatal Yk dam		
Male	$CF_{\#1}$	24	5.3 ± 1.7**	13.4 ± 3.9**	31.8 ± 2.8**	36.2 ± 3.3**
	Yk	24	3.8 ± 0.8	7.8 ± 0.6	14.4 ± 1.5	16.7 ± 1.6
Female	$CF_{\#1}$	24	3.9 ± 1.6**	9.7 ± 3.4**	22.9 ± 2.7**	27.4 ± 1.9**
	Yk	24	3.7 ± 0.7	7.7 ± 0.5	12.2 ± 0.9	13.7 ± 0.9

1)Number of mice used. 2)Values are the means ± standard deviation. **Two means within each age column for each sex are significantly different at $P<0.01$.

maternal effects is important. Table 4 shows the significance test for between postnatal within prenatal factors, and Table 5 shows the significance test for between prenatal within postnatal factors.

It can be seen in Table 4 that the body weight of offspring born to the prenatal $CF_{\#1}$ dam and nursed by the postnatal $CF_{\#1}$ dam was greater ($P<0.01$) than that of nursed by the Yk postnatal dam for both sexes at all ages studied. There was no significant body weight difference ($P>0.05$) between the two groups of offspring born to the Yk dam and nursed by the postnatal $CF_{\#1}$ and Yk dams. These results indicated that body weight depended partly on the animals's own genetic factors. The genetic potential of the Yk offspring to have a lighter body weight was less than that of $CF_{\#1}$ offspring in the environment provided by the postnatal dam.

The body weights of offspring born to the prenatal $CF_{\#1}$ dams were heavier ($P<0.01$) than those born to the Yk prenatal dams and nursed by the postnatal $CF_{\#1}$ dams at all ages examined for both sexes (Table 5). A similar result ($P<0.01$) was obtained when offspring in these two groups were nursed by the Yk postnatal dams. Moreover, the body weight of offspring, regardless of genotype, nursed by the postnatal $CF_{\#1}$ dams was heavier than that of those the nursed by Yk dams. These results indicated that a good environment, for example, possibly the greater milk yield of postnatal $CF_{\#1}$ dams, gives better performance.

As shown in Tables 4 and 5, the heaviest means body weights were attained by offspring born to the prenatal $CF_{\#1}$ dams and nursed by the postnatal $CF_{\#1}$ dams. The second heaviest means body weight was attained by offspring born to the prenatal $CF_{\#1}$ dams and nursed by the postnatal Yk dams. The third rank were offspring born to the prenatal Yk dams and nursed by postnatal $CF_{\#1}$ dams. The lightest means body weights were those of offspring born to the prenatal Yk dam and nursed by the postnatal Yk dams.

Discussion

The results of our study showed that prenatal maternal effects accounted for higher percentages of variance in body weight than postnatal maternal effects in all ages examined (see Tables 2 and 3). The results of the present study were not in agreement with those reported by Brandsch and Kadry [1] and Cox *et al.* [2]. They demonstrated that postnatal maternal effects were the more important in contributing to variation in the body weight of offspring during the suckling period. Brandsch and Kadry [1] used mice that came from an unselected base population which was formed by crossing four highly inbred strains of mice of similar body weight. Cox *et al.* [2] used mice from the an unselected control group of a colony formed by crossing two F_1 stock (CAF_1, AKF_1) representing four different inbred lines. They found that prenatal maternal effects accounted for 6–11% and 13–18% of total variance in 21 and 42 days of age, respectively; whereas postnatal maternal effects accounted for 49–60% and 14–26% at the above ages.

Differences between their study [1, 2] and the present one may be due to differences in strains and the number of mice used. We used two subspecies of mice which widely differed in genetic type and phenotype. Our previous study showed that the average body weight of $CF_{\#1}$ at maturity was 41 g for males and 34 g for females; whereas that of Yk was 13 g and 12 g for males and females, respectively. In addition, differences due to cross-fostering and the analysis system should be taken into consideration. A common approach in cross-fostering has been to form a group with three dams and their offspring, born within 12 hr, and allow each dam to nurse two of her own young and two from each of two other litters in a group [7]. In the present study, foster dam groups were formed according by restricting the dam to nursing three of her own young and three from another subspecies dam, and all of these offspring should be born within one day period.

It is important to note that the dam can have an unique influence on the offspring during embryonic development in the uterus and during the suckling period. In the cross-fostering experiment, the growth of offspring is influenced by both their own dam (prenatal dam) and the foster dam (postnatal dam) [7]. The prenatal dam transmits a sample half of its genes to each young mouse and gives maternal effects which are expressed directly in the uterus during the period from ovulation to parturition. The postnatal dam has an environmental influence on the young through the nutrient in the milk during the suckling period.

It has been recognized that the influence of a dam on her offspring was a combination of prenatal and postnatal factors [6, 10, 17]. The interaction between prenatal and postnatal factors means that one postnatal environment permits the expression of the genetic characteristics in a strain, but another does not. The best possible inheritance will not result in superior performance unless the proper environment is also provided, so that the animal can attain the limit determined by their inheritance.

As far as we know, no analysis of prenatal and postnatal effects has previously been reported. For that reason we conducted this analysis. In this analysis prenatal and postnatal effects can be interpreted separately.

In mammals it usually is the offspring and the dam that contribute components to a trait [7, 17]. In the present study, in the prenatal period both the genes of the offspring and maternal effects, expressed directly in the uterus from ovulation to parturition, influence body weight. After birth, the body weight of offspring in the suckling period mainly depends on the milk production of the dam and her mothering ability as well as the offspring's own gene.

As a quantitative trait, body weight may show vary greatly because some of the many genes involved may express themselves phenotypically in either an additive or a nonadditive manner, but non additive genetic variation is relatively unimportant. The influence of the genes at each locus on the phenotype is usually quite small relative to the influence of the total genotype [15].

It is clear that the limit to performance is set by the animals's own genetic characteristics and the best possible environment will not cause that individual to exceed its own genetic potential [6]. The $CF_{\#1}$ mouse is two to three times as heavy as the Yk mouse, and apparently the above results show that the genetic potential of the $CF_{\#1}$ was greater than that of the Yk. Offspring born to $CF_{\#1}$ mice were heavier, whether nursed by a postnatal $CF_{\#1}$ dam or a Yk dam. In contrast, even when offspring born to Yk prenatal dams were nursed by a $CF_{\#1}$ postnatal dam, the Yk offspring did not exceed their own genetic potential in heavier body weight.

The postnatal maternal effects are those arising from the influence of the dam on the offspring during the suckling period [6]. The present study demonstrated that individuals of similar genetic type, whether born to a large ($CF_{\#1}$) or small dam (Yk), when nursed by a large dam were heavier than those nursed by a small dam. This is not surprising because most of the offspring nursed by a large dam were probably receiving more milk from this postnatal dam.

In conclusion, the present study demonstrated that there was an interaction between prenatal and postnatal effects in determining the body weight of F_1 offspring. Moreover, prenatal maternal effects had a greater influence than postnatal maternal effects in contributing to variation in body weight. This suggests that offspring born to a large prenatal dam will be heavier than those born to a small dam whether nursed by a large or by a small postnatal dam.

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