Maternal Effects on Mouse Brain Weight

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Abstract:
When BALB/cCF mice were crossed reciprocally with 4 other inbred strains, adult brain weights averaged 21.0 mg heavier for hybrid offspring with a BALB mother than those with a BALB father. Reciprocal backcrosses to BALB revealed that this effect was a consequence of the BALB maternal environment, not cytoplasmic or sex chromosomal influences. These findings demonstrate that BALB mice have heavier brains than those of several other inbred strains, partly because of chromosomal influences, but also because of their maternal environment, an environmental influence which usually functions as a component of heredity in studies comparing inbred strains. Backcrosses also revealed a maternal environment effect whereby offspring with an F_1 hybrid mother had adult brains averaging 9.0 mg heavier than those with a BALB mother.
Key words: inbred strain — cytoplasm — maternal environment — hybrid vigour

Article:

INTRODUCTION

It is well known that the size of the mouse brain depends upon hereditary factors[5,17] and that it is also influenced strongly by postnatal nutrition[1,14] and environmental[8] enrichment. However, there are certain circumstances, such as maternal environmental effects, where an influence on brain size is clearly significant, but cannot easily be attributed to either hereditary or environmental causes. The present study reveals two such maternal effects on brain size, one being the larger brains of F_1 hybrid mice having a BALB/c mother rather than BALB/c father, and the other being the larger brains of offspring of back-crosses having an F_1 hybrid rather than BALB/c mother.

To separate a maternal environmental effect from simple genetic influences on brain size of mammals, crosses must be done in a reciprocal manner[19]. If a BALB/c female mated with a C57BL/6 male yields offspring with larger brains than a C57BL/6 female mated with a BALB/c male, this could result from 3 things: (a) the sex chromosomes may be the site of genes exerting a positive influence on brain growth; (b) the cytoplasm of the egg of a BALB/c female may contain organelles or substances favourable for brain growth; (c) the BALB/c female may provide uterine and postnatal environments that are especially favourable for brain growth. These 3 possibilities can be examined separately using reciprocal backcrosses as indicated in Table I. The crosses B × BC and B × CB give the same maternal environment, cytoplasm (assuming the sperm contributes negligible cytoplasm) and distribution of non-sex chromosomes. Among male offspring, all receive the X chromosomes from B, but one group receives the Y chromosome from C and the other from B. Among female offspring, one group receives both X chromosomes from B and the other receives one X from each strain. The crosses BC × B and CB × B differ mainly with respect to the origin of the cytoplasmic organelles. The crosses B × BC and BC × B differ mainly in maternal environment, one being B and the other F_1 hybrid BC.

A series of reciprocal crosses of the strain BALB/cCF with 4 other inbred strains was done in order to study the mode of inheritance of deficient corpus callosum, a hereditary brain defect in the strains BALB/c and 1294J[20]. The results for corpus callosum size have been presented in detail elsewhere[21]. In the course of this study, two significant maternal effects on brain size were detected, and these are described in detail in the present report.

MATERIALS AND METHODS

Mice of the inbred strains A/J, C57BL/6J, DBA/2J and 129/J were procured from the Jackson Laboratory and then propagated at Waterloo using full-sib matings. As of November, 1979, the 129/J strain had been inbred for 83 generations and the other 3 strains had been inbred for at least 130 generations[7]. The BALB/cCF mice were purchased from Carworth Farms, which had obtained them from the Laboratory Animals Centre in the U.K. in 1968, which in turn had obtained BALB/cJ mice from Jackson in 1955 after 61 generations of inbreeding. By 1978 the strain had been inbred for over 100 generations[21] and is presently maintained at Waterloo using full-sib matings. Because the mice bred at Waterloo differ from their ancestors procured from Jackson and Carworth with respect to body and brain size[20], only data for mice bred at Waterloo are included in this report. Some of the inbred strain parents of F_1 hybrid mice were reared at Jackson Laboratories, but their data are not used because of the substantial supplier effect. Thus, data for inbred strains given in Table I do not comprise all the data for parents of F_1 hybrids.

Mice were housed in 29 cm × 18 cm × 13 cm opaque plastic mouse cages with `Betta-Chip' hardwood bedding, plus a few sheets of toilet tissue for nesting, and they were given free access to tap water and Master MLM rodent food (Maple Leaf Mills, Toronto, Canada). One male was mated with one to 3 females in a clean cage, and each female was isolated when she became visibly pregnant. The litters (unculled) were weaned at 30 days of age, and in several instances the parents were remated to produce a second litter. Data for first and second litters were pooled for analysis because a *t*-test on the 45 matched litters from the same mothers revealed no significant difference in brain weight ($P > 0.40$).

At various ages mice were anesthetized with pentobarbital sodium, weighed and then perfused intracardially with saline followed by buffered formalin. Fixed brains were removed from the skull, carefully trimmed and blotted, and then weighed to the nearest milligram. Parts trimmed away were those which were sometimes missing or of a variable size because of problems in extraction (olfactory bulbs, optic nerve, trigeminal nerve, paraflocculi and spinal cord). This procedure yields smaller within-group variance , but it also results in a slightly lower mean brain weight.

The 29 mating combinations done for this study are listed in Table I.

RESULTS

The present report involves data only for mice with corpus callosum of normal size (cross-sectional area at least 0.82 mm^2 or length at midplane at least 2.90 mm; see Wahlsten[20,21] for details) in order to be sure that effects on brain weight in no way reflect pathological conditions. Many mice of the strains BALB/cCF and 129/J showed absence or deficiency of transcortical axons in the corpus callosum. No F_1 hybrid mice showed the defect, but 39 of 997 mice in backcross groups had defective CC, most of which involved crosses with 129/J. Analyses reported herein were also done with inclusion of mice with abnormal CC, but results were essentially the same.

The vast majority of mice in backcross groups were perfused in an age range from 70 to 110 days, but many inbred and F_1 hybrid mice were perfused much later because they were used for breeding or held in reserve in case a littermate was infertile. For this reason, all data were corrected for variation in age at perfusion using a regression procedure described in detail by Wahlsten[20]. Linear and then quadratic regressions of body and brain weight on age were computed separately for each cross and sex, and where the regression was statistically significant ($\alpha = 0.05$) the measure for each mouse was transformed to values it would have had at 100 days of age. The common age of 100 days was used because it was near the median age of backcross mice and thus entailed the smallest change in mean scores because of the correction procedure. The actual regression equations are available from the author upon request.

Data corrected for age were analyzed in two ways in order to evaluate effects of different variables. First the data for all mice of each cross were pooled across litters in order to assess sex differences. However, there was evidence that mice from larger litters tended to have smaller brains. To assess the contributions of litter size effects to differences between crosses, an analysis of covariance was necessary, but this could only be done

using litter mean brain weight as the dependent variable because all mice in a litter had the same value for litter size. Sex differences could not be evaluated when litter means were used because many litters, especially the smaller ones, had all mice of one sex. Consequently, the analysis done on individual scores was repeated using litter mean scores.

TABLE I

Brain and body weights for male and female mice of 5 inbred strains, 8 reciprocal F_1 hybrid crosses and 16 reciprocal backcrosses

Abbreviations: A, A/J; B, BALB/cCF; C, C57BL/6J; D, DBA/2J; Ø, 129/J. In each cross the female parent is listed first; B × A indicates BALB/cCF female mated with A/J male. In backcrosses, a B × A hybrid offspring is symbolized BA. Both brain weights and body weights are given in grams.

	Brain weight						*Body weight*					
	Male			*Female*			*Male*			*Female*		
	n	*Mean*	*S.D.*	*n*	*Mean*	*S.D.*	*n*	*Mean*	*S.D.*	*n*	*Mean*	*S.D.*
Inbred strains												
A × A	42	0.405	0.019	24	0.417	0.026	42	19.6	3.1	25	19.3	3.2
B × B	854	0.477	0.023	938	0.481	0.023	855	24.8	2.1	938	21.4	2.4
C × C	41	0.477	0.017	34	0.463	0.014	41	23.6	1.8	34	18.9	1.4
D × D	23	0.411	0.009	26	0.399	0.023	23	22.5	1.3	26	18.9	2.0
Ø × Ø	17	0.444	0.013	8	0.438	0.012	17	23.2	1.5	8	16.5	1.4
F_1 hybrids												
B × A	36	0.452	0.018	32	0.447	0.018	36	23.5	2.1	32	19.7	2.1
A × B	27	0.429	0.019	25	0.432	0.017	27	22.3	1.5	25	19.3	1.8
B × C	23	0.498	0.019	11	0.494	0.018	23	27.8	4.1	11	24.2	1.6
C × B	26	0.483	0.021	28	0.482	0.019	26	26.1	2.2	28	22.2	2.0
B × D	18	0.496	0.018	10	0.514	0.019	18	31.6	2.2	10	28.0	1.2
D × B	12	0.476	0.009	22	0.488	0.009	12	29.8	1.8	21	24.8	1.5
B × Ø	38	0.476	0.016	36	0.487	0.017	38	23.7	2.0	35	20.7	2.0
Ø × B	4	0.474	0.010	1	0.455	0	4	23.5	2.2	1	20.6	0
Backcrosses												
B × BA	44	0.486	0.015	51	0.491	0.015	44	25.2	1.6	51	21.2	1.8
B × AB	40	0.482	0.023	55	0.479	0.029	40	25.3	2.7	55	21.1	2.5
BA × B	28	0.483	0.016	40	0.489	0.015	28	25.2	2.3	40	21.9	1.9
AB × B	25	0.494	0.019	37	0.492	0.026	25	26.9	2.2	37	23.1	2.4
B × BC	28	0.485	0.025	30	0.491	0.024	28	24.7	2.2	30	20.9	1.9
B × CB	32	0.487	0.016	55	0.489	0.017	32	24.7	2.7	55	21.0	2.2
BC × B	43	0.502	0.018	37	0.508	0.020	43	29.8	1.6	37	23.6	1.5
CB × B	19	0.498	0.021	18	0.496	0.025	19	29.6	1.5	18	20.9	2.2
B × BD	41	0.483	0.016	56	0.482	0.015	41	26.5	1.8	56	21.7	1.7
B × DB	20	0.486	0.019	25	0.494	0.016	20	25.3	1.9	25	22.8	1.7
BD × B	26	0.484	0.014	24	0.488	0.011	26	26.6	2.5	24	21.4	1.2
DB × B	14	0.496	0.023	24	0.496	0.018	14	26.8	2.6	24	22.1	1.9
B × BØ	23	0.484	0.023	26	0.493	0.026	23	25.0	2.1	26	21.2	1.9
B × ØB	19	0.491	0.028	19	0.486	0.031	19	22.8	2.6	19	21.3	2.5
BØ × B	23	0.509	0.026	25	0.506	0.017	23	27.1	2.0	25	22.4	2.1
ØB × B	7	0.507	0.021	5	0.494	0.025	7	27.7	2.6	5	23.0	2.2

Mean brain and body weights are given separately for males and females of each cross in Table I. Analysis of variance for data of the F_1 hybrids revealed highly significant effects of the strain to which the BALB mice were crossed for both brain weight ($P < 0.001$, $F = 185.8$; df = 3,331) and body weight ($P < 0.001$, $F = 178.3$; df = 3,329). The effect of strain was also significant in an analysis of data from backcrosses for both brain weight ($P < 0.001$, $F = 12.0$; df = 3,927) and body weight ($P < 0.001$, $F = 7.9$; df = 3,927), although the actual strength of the strain effect was much smaller among the back-crosses than the F_1 hybrids. There were no significant sex differences in brain weight among either the F_1 hybrid or backcross mice ($P > 0.10$), but body weights were obviously larger for males than females in all crosses.

Of particular interest was the large reciprocal F_1 hybrid effect. Mice with a BALB mother had brains that averaged 18.1 mg heavier than those with a nonBALB mother ($P < 0.001$, $F = 68.2$; df = 1,331), and they also had bodies that averaged 1.3 g heavier ($P < 0.001$, $F = 32.9$; df = 1,331). Because the interaction between the reciprocal effect and the strain effect was not significant for either brain or body weight, it was apparent that the reciprocal effect was of similar magnitude for mice derived from each of the 4 inbred strains. The cause of the reciprocal effect could not be determined from the F_1 hybrid data, however. Sex chromosome, cytoplasmic, and/or maternal environment influences could have resulted in a superiority of the BALB mothers. To separate

these effects, analysis of the backcrosses was necessary. This revealed that mice with an F_1 hybrid mother had brains that were 9.7 mg heavier than those with a BALB mother, a highly significant maternal environment effect ($P < 0.001$, $F = 51.4$; df = 1,927), but that there was no significant difference between brain weights of mice whose F_1 hybrid parent had had a BALB mother or non-BALB mother ($P > 0.10$). This latter finding means that in backcrosses with a BALB mother, for example B × BA and B × AB , it did not matter whether the father was a BA or AB hybrid, which persuasively exludes a sex chromosome effect; and in backcrosses with a BALB father, for example BA × B and AB × B, it did not matter whether the mother was a BA or AB hybrid, which argues against a cytoplasmic effect. If sex chromosome and cytoplasmic effects were not present in the backcrosses to BALB, they very likely were not present in the F_1 hybrids either, and hence the reciprocal effects in both F_1 hybrids and back-crosses must have resulted from effects of maternal environment. There was a significant interaction between the maternal environment effect and the strain effect among backcross mice ($P < 0.001$, $F = 5.2$; df = 3,927), which means that the magnitude of the maternal effect was not the same for backcrosses derived from all 4 non-BALB inbred strains. The differences in brain weights between mice with BALB and F_1 hybrid mothers were 5.2 mg, 13.8 mg, 4.1 mg and 17.6 mg for backcrosses involving the A, C57, DBA and 129 ancestral strains, respectively. A similar pattern of results occurred for body weight of backcross mice.

Although the maternal environment effects may have modified all components of body size, there was some indication that brain weight was especially sensitive to the maternal environment. Because there is no genetic variability within an F_1 hybrid group, the relation between brain and body size among group members must result from small variations in pre-and postnatal environments which affect the growth of brain and other organs similarly. Linear regression of brain weight on body weight done separately for each sex of each F_1 hybrid cross revealed that within an F_1 hybrid group a 1.0 g increase in body weight was associated with an average of 3.8 mg increase in brain weight (averaging regression coefficients for groups with more than 10 members). The magnitude of the BALB/c maternal effect, however, was substantially larger; for every 1.0 g increase in body weight resulting from the maternal effect, there was an average of 10.9 mg increase in brain weight (neglecting crosses with 129/J which had small sample size).

It is likely that the same pattern occurred within the backcross groups. The average regression coefficient of brain weight on body weight within each sex of each backcross group was 5.4 mg/g (neglecting the ØB × B groups), whereas the average magnitude of the F_1 maternal effect between the reciprocal backcrosses was 6.65 mg/g. Although these two linear relations are numerically similar, the within-group relation was probably inflated by genetic variation within the segregating backcross groups, and the environmental contribution to the relation was probably somewhat smaller than 5.4 mg/g.

Among the 52 F_1 hybrid litters, those with a BALB mother contained more mice on average than those with a non-BALB mother (7.4 and 6.0 mice per litter, respectively; $P < 0.01$, $F = 7.5$; df = 1,44), and brain weights tended to be slightly smaller in larger litters. Because there were no sex differences in brain weight, the mean brain weight was determined for each litter and then subjected to analysis of variance. The magnitude of the reciprocal F_1 hybrid effect (17.5 mg) derived from litter means was very similar to that derived above from individual scores and was statistically significant ($P < 0.001$, $F = 18.6$; df = 1,44). When the linear relationship with litter size was first removed with analysis of covariance, the reciprocal F_1 hybrid effect on brain weight was even larger (21.0 mg superiority of litters with a BALB mother).

Although there were no significant differences in litter size among the 146 backcross litters ($P > 0.10$), larger litters tended to have smaller brains. Analysis of variance on litter mean brain weights revealed a significant maternal environment effect (11.2 mg heavier brains for litters with an F_1 hybrid mother; $P < 0.001$, $F = 14.2$; df = 1,130) but no significant sex chromosome or cytoplasmic effects ($P > 0.7$). When litter size was used as a covariate, the magnitude of the maternal effect was somewhat smaller (9.0 mg; $P < 0.001$, $F = 11.0$; df = 1,129) but there were still no sex chromosome or cytoplasmic effects ($P > 0.6$).

In the course of analyzing litter means it was noticed that mice of a particular cross born in 1979 tended to have larger brains than others born in either 1977, 1978 or 1980. It was not possible to include year of birth as an independent variable in a single analysis of covariance for all F_1 hybrids or back-crosses because not all crosses were produced in each year. However, the reciprocal crosses derived from a particular ancestral strain were produced in the same years, which made it possible to do separate analyses on the 4 groups of F_1 hybrids and 4 groups of back-crosses derived from the 4 non-BALB inbred strains. This procedure made it possible to evaluate the magnitude of the maternal environment effect adjusted for both year of birth and litter size using the Multiple Classification Analysis procedure of the SPSS program package[15].

The magnitude of the BALB maternal effects estimated in this way were 18.1 mg, 12.5 mg, 24.7 mg and 33.2 mg for crosses with the A, C57, DBA and 129 strains, respectively. The effect for the crosses with C57 was of marginal significance ($P = 0.08$), which primarily reflects low power of the test resulting from small (9) degrees of freedom in analysis of covariance using litter means. The effect for the crosses with 129 should not be taken too seriously because there was only one litter in the Ø x B group owing to breeding difficulties. Nevertheless, the brains in this litter of 5 mice were unusually small for that litter size, which is quite consistent with the maternal effects observed for crosses with the other strains. The mean brain weights for the reciprocal F_1 hybrids adjusted for year of birth and litter size are presented in Fig. 1.

A similar analysis of covariance for the separate groups of backcrosses revealed maternal environment effects of 0.1 mg, 8.8 mg, 12.8 mg and 20.2 mg for the crosses with A, C57, DBA and 129, respectively. Only the first effect was not statistically significant ($\alpha = 0.05$). Means adjusted for year and litter size are given in Fig. 1 for backcross mice with BALB and F_1 hybrid mothers.

Thus, results of separate analyses of individual scores and litter means are very similar, the only noteworthy differences being the lack of a significant maternal environmental effect in backcross mice derived from the A strain and emergence of a large maternal effect for those derived from DBA when adjustments for both year of birth and litter size are made.

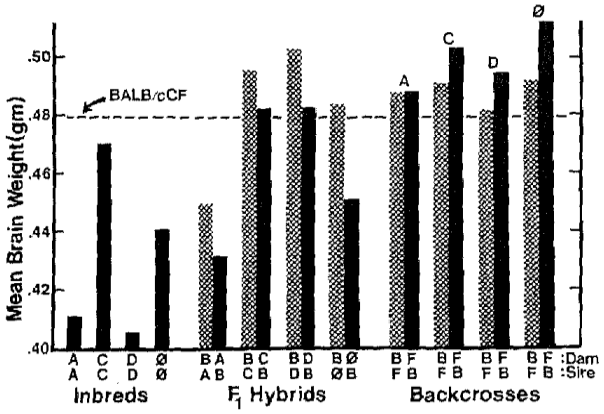

Fig. 1. Mean adult brain weights at 100 days of age for 5 inbred strains, 8 reciprocal F_1 hybrids involving BALB mice, and reciprocal backcrosses of the F_1 hybrids to BALB mice. The heredity of the mother or dam for each cross is given in the top row of letters, and the father or sire is given in the bottom row. Each mean for hybrids is derived by Multiple Classification Analysis which adjusts for effects of year of birth and litter size using analysis of covariance on litter mean brain weights, as explained in the text. In the backcrosses each mean represents two separate crosses involving reciprocal F_1 hybrids, with the strain to which the BALB mice were originally crossed being indicated by a letter at the top of each pair of bars. For example, the first backcross mean for B × F is actually the mean of two groups listed in Table I: B × BA and B × AB. Abbreviations: A, A/J; B, BALB/cCF; C, C57BL/6J; D, DBA/2J; Ø, 129/J.

DISCUSSION

These results indicate that BALB/cCF mice have larger brains than several other inbred strains because they inherit autosomal genes which increase brain size *and* because they are conceived and nurtured in a BALB/c maternal environment. Although the influence of the BALB/c maternal environment may in turn reflect autosomal genetic factors possessed by the mother, as has been shown for certain Mendelian gene mutations[10,16], the maternal environment effect on offspring development is not the same kind of genetic influence on the growing mouse as is the mouse's own set of genes inherited via egg and sperm. From the perspective of the growing mouse it is strictly an environmental influence, although some human theorists might prefer to see it as an indirect genetic influence. The fact is that the BALM mouse's own set of genes and its mother's environment are normally confounded in studies which simply compare inbred strains without doing reciprocal hybrid crosses. If the strains are maintained under identical housing and feeding conditions, it is appropriate to interpret significant differences between their brain sizes as expressions of differences in heredity, provided that one recognizes `heredity' to be an operationally defined entity which includes the usual direct chromosomal influence on brain growth, plus the less widely recognized differences in maternal environment.

Maternal effects in mammals have been reported several times previously[9,11,12], including a maternal effect on human IQ". In the present laboratory, hybrid maternal effects have been observed on the rates of mouse development observed both prenatally[23] and postnatally[24]. Reciprocal F_1 hybrid effects have also been noted for mouse brain size[6], although Hahn and Haber[6] were unable to distinguish sex linkage, cytoplasmic heredity and maternal environment; their data showed that F_1 hybrid males with a BALB/cJ mother had brains averaging 12 mg heavier than those with a BALB/cJ father. Of course, maternal effects on brain size are not always observed when the necessary reciprocal crosses are done[22], and hence the presence or size of such effects may be strain-specific.

Cytoplasmic effects on mouse brain or behavior are quite rare, there being only one such report in the literature[3], but attempts to detect them are also rare. Cytoplasmic effects on mouse embryogenesis have been reported recently[2,13]. A molecular study of mouse mitochondria) DNA suggests that there is no substantial variation between laboratory strains of *Mus domesticus*, although many wild populations differ markedly from laboratory mice[4]. Thus, it would be interesting to search for cytoplasmic effects on brain size using crosses of laboratory and wild mice.

Whether the maternal environment effects observed in the present study resulted from prenatal uterine environment, postnatal care or both remains to be determined using cross-fostering and possibly ovarian transplantation. It is also possible that the maternal effect was at least partly mediated by cytoplasmic factors, because much of the cytoplasm of the egg is actually derived from the maternal ovarian environment during oogenesis. In this sense the present results do not entirely exclude a cytoplasmic effect on brain weight, although they do exclude factors such as mitochondria which are inherited largely unchanged from the grandparents of the backcross mice. Cytoplasmic mediation of the maternal environment effect could be studied by transfer of fertilized ova. The BALB/c maternal effect on brain weight is sufficiently large to make such experiments quite feasible. In fact, the maternal effect of 21 mg or an increase in brain weight of about 4% is comparable to effects produced by environmental enrichment[8], although it is somewhat smaller than effects of protein malnutrition[1].

The data also revealed autosomal genetic influences on brain weight similar to those reported previously. As is evident in Fig. 1, the degree of dominance depended upon the strain to which BALB/c was crossed. Intermediate inheritance prevailed when BALB/c was crossed with the related A/J strain, which is not surprising in view of the fact that A/J mice are descended from a cross of the Bagg albino stock (ancestor of BALB/c) with Cold Spring Harbor albinos[7] done in 1921. The close relation between A/J and BALB/c mice may also account for the lack of a maternal effect in backcross mice derived from ALL Complete dominance was apparent in the cross with 129/J and overdominance in crosses with C57BL/6J and DBA/2J. In view of the prevalence of dominance in the F_1 hybrids, it is not at all surprising that there was little difference among

backcross groups derived from F_1 crosses with different strains. Although the backcross groups derived from A/J may appear exceptionally high in brain weight, it must be kept in mind that they benefited from both the BALB/c and F_1 hybrid maternal environments.

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