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Genetic effects on susceptibility to histidine induced teratogenesis in the mouse

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Summary

In the mouse histidinaemia has a teratogenic effect. Animals subjected to high levels of histidine *in utero* may develop inner ear and behavioural abnormalities typical of the 'shaker–waltzer' syndrome. Selection procedures for abnormalities and relaxation of selection have resulted in two histidinaemic strains: the Cambridge strain in which abnormalities occur in over 80% of animals, and the Edinburgh strain in which the penetrance of abnormal behaviour has declined to about 1%. Breeding experiments suggest that the differences are largely due to differences in the genetic backgrounds which modify foetal susceptibilities to the teratogenic effects of high histidine levels. High susceptibility appears to be dominant over low susceptibility in the present strains. There appears to be no interaction of maternal histidinaemia with the *dreher* mutation which is considered to induce inner ear malformation as a result of an early neural tube abnormality.

1. Introduction

Histidinaemia is an inborn error of metabolism occurring in both mouse and man and characterized by very low histidine ammonia lyase activity (HAL; E.C. 4.3.1.3) in liver and skin. As a result of this reduction in enzyme activity (less than 5% of normal) large accumulations of histidine and its imidazole derivatives are found in urine, liver, skin, plasma and brain, although no overt phenotypic effects are seen (Bulfield & Kacser, 1974; Rosenmann *et al.* 1983; Coulombe *et al.* 1983). In both species the condition is due to an autosomal recessive gene; in the mouse the mutant allele (designated *his*) has been shown to be a null allele at a structural or regulatory locus for the HAL protein and has been mapped close to *Steel* (*Sl*) on chromosome 10 (Wright *et al.* 1982). Heterozygotes in both species show about 50% of normal HAL activity but have almost normal levels of plasma histidine (Bulfield & Kacser, 1974; Kacser, Bulfield & Wright, 1979).

Apart from the demonstrable effects on enzyme activities and on tissue metabolic concentrations, there appear to be no other overt phenotypic differences in the three genotypes (Scriver *et al.* 1983; Kacser, Bulfield & Wright, 1979). In contrast, some sub-strains of histidinaemic mice showed a variable incidence of behavioural abnormalities. This was traced to the effect of high levels of histidine or its derivatives in pregnant females on the development of the embryos in these strains (Kacser *et al.* 1977). Such mice, when exposed *in utero* to maternal histidinaemia (whether genetically or nutritionally induced) during the second trimester of gestation, showed deafness and behavioural abnormalities similar to those induced by the 'shaker–waltzer' group of mutants. Further investigation revealed that affected animals had varying degrees of malformation of the inner ear, involving otoliths, semi-circular canals and cochlea (Kacser *et al.* 1973, 1977, 1979). This teratogenic effect occurred regardless of whether the mother was normal or balance-affected provided that she was histidinaemic during the relevant period of gestation. The effect was also independent of offspring or paternal genotype at the *his* locus.

During our work on the histidinaemia in the colony held in Edinburgh, it was noticed that the incidence of balance-affected offspring declined over the years although the histidinaemia (and the homozygosity, *his/his*) was not altered. In contrast, the stock held in Cambridge, which was now also *his/his*, continued to show high incidence. This paper shows the results of investigations into the differences between these two stocks.

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Table 1. *Results of intercrosses between CAM-K and EDI histidinaemic (his/his) stocks in 1976 (from Kacser, Mya Mya & Bulfield, 1979)*

Type of mating	Parents		% abnormal offspring
	Female	Male	
1. Pure strain crosses	CAM-K	× CAM-K	72·6
	EDI	× EDI	6·6
2. Intercrosses	CAM-K	× EDI	7·9
	EDI	× CAM-K	6·3
3. Backcrosses	INT[a]	× CAM-K	58·1
	INT[a]	× EDi	13·6

[a] INT = offspring of intercross between EDI and CAM-K.

2. Materials and Methods

(i) *Animals*

Histidinaemic (*his/his*) animals were obtained from a stock descended from wild mice trapped in Peru in 1962 (Wallace, 1970). A behavioural abnormality occurred sporadically in this stock. After receipt of the stock in Edinburgh, attempts to isolate the 'gene' for abnormality resulted in the discovery of the segregating *his* mutation in the stock and the finding that only offspring from *his/his* mothers showed the abnormality (Kacser *et al.* 1973). Outcrosses to C57BL/6 were carried out in these early experiments and recovery of the *his/his* and +/+ genotypes effected by backcrosses to the Peru stock.

Edinburgh stock (EDI): +/+ and *his/his* lines maintained as random-breeding, closed colonies since 1971. The +/+ line never showed abnormalities. In the absence of direct selection for behavioural abnormalities, the incidence of such defects in the offspring of *his/his* animals declined from over 80% in 1971 to the present level of about 1%, although the histidinaemia was maintained in all tissues.

Cambridge stock (CAM): was maintained by Dr E. M. Wallace in Cambridge (as a pure *his/his* stock, once the nature of the lesion had been established (Kacser, Bulfield & Wallace, 1973)) by selection for high incidence of balance-affected animals. It was reintroduced to Edinburgh in 1976 with 73% penetrance of behaviour defects and designated CAM-K. As a result, however, of problems due to the poor mothering abilities of affected females, Cambridge-born animals were again imported during 1981. Although penetrance remained high (80–90%) it transpired that, due to breeding problems at Cambridge, the colony had been outcrossed several times since 1976, rescuing both histidinaemia and high penetrance of behaviour defects each time. As a result, the present CAM stock, designated CAM-J, has been found to differ from the previously used CAM-K in some respects. (see Results)

The DR stock, in which the *dreher* (*dr*) mutation was segregating, was obtained from Dr G. Truslove, University College, London in 1981 and was derived from wild mice trapped in Germany (Falconer & Sierts-Roth, 1951).

(ii) *Behavioural scoring*

Animals were routinely tested at weaning and again three weeks later for deafness, leaning and circling behaviour. The procedure involved observing the animals' behaviour for a few minutes in a clear plastic tank. Animals were scored as deaf if no reaction was observed in response to a sudden loud noise nearby.

(iii) *Urine testing*

At 5–6 weeks of age mice were tested for histidinaemia by testing urine with ferric chloride reagent strips (Phenistix, Ames Co.). The abnormally high concentrations of imidazole derivatives of histidine which are excreted in the urine of histidinaemics react with ferric chloride to produce a change in colour from yellow to grey-green or black.

(iv) *Crosses*

Throughout the series of crosses all EDI animals used were able to hear and had normal behaviour. CAM-J males were all behaviourally abnormal. The CAM-J females used, however, were chosen to be either normal or only mildly abnormal in order to maximise the chances of successfully rearing litters. This restricted the number of females available for breeding purposes. Whenever possible, two or three weaned litters were obtained from each mated pair.

3. Results

(i) *Crosses of EDI and CAM*

The original stock containing behaviourally abnormal animals was obtained from Cambridge (Wallace, 1970, 1973) and a colony established in Edinburgh

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Table 2. *Summary of crosses between EDI and CAM-J (1983).* (All animals had *his/his* genotypes)

Type of mating	Parents		Offspring		
	Female	Male	N[a]	Ab[a]	% Ab
1. Pure strain crosses	CAM-J	CAM-J	41	285	87
	EDI	EDI	156	2	1
2. Intercrosses[b]	EDI or CAM-J	CAM-J or EDI	127	78	38
F_1 intercrosses	F_1	F_1	87	42	33
3. 1st backcrosses[b]					
1BC (CAM)	F_1	CAM-J	125	122	49
1BC (EDI)	F_1	EDI	29	17	37
F_2 intercrosses	F_2	F_2	52	34	40
4. 2nd backcross					
2BC (CAM)	1BC (CAM)	CAM-J	73	180	71
2BC (EDI)	1BC (EDI)	EDI	16	0	(0)
5. 3rd backcross					
3BC (CAM)	2BC (CAM)	CAM-J	5	91	95
6. Intercrosses of backcross	1BC (CAM)	1BC (CAM)	23	68	75
offspfing (BC (CAM) only)	2BC (CAM)	2BC (CAM)	0	8	(100)
	3BC (CAM)	3BC (CAM)	2	16	(89)

[a] In this, and all following tables, N refers to normal animals while Ab refers to behaviourally abnormal animals. Numbers in parentheses indicate results based on samples of less than 20 animals.
[b] All intercross and backcross data are from both reciprocal crosses.

Table 3. *Maternal effect of histidinaemia*

Maternal genotype	Paternal genotype	Expected offspring genotype	Total no. offspring	N	Ab	% Ab
EDI +/+	CAM-J *his/his*	*his/+*	133	133	0	0
EDI/CAM *his/+*	CAM-J *his/his*	1:1 *his/+* : *his/his*	292	292	0	0
		Totals	425	425	0	0
EDI *his/his*	CAM-J *his/his*	*his/his*	120	62	58	48

(see Materials and methods). While the Cambridge stock (CAM) was maintained by selection for high incidence of the behaviour abnormality, the Edinburgh stock (EDI) was maintained as a 'random breeding' closed colony once the homozygosity of the *his/his* genotype had been established. It was noted that the incidence of behaviourally abnormal offspring in EDI gradually declined from over 80% in 1971 to 7% in 1976 and to about 1% in 1983. In both EDI and CAM stocks the high level of histidine in the tissues remained unaltered and both stocks were homozygous *his/his* at that locus.

In a series of intercrosses between these two histidinaemic stocks (Table 1 and Kacser, Mya Mya & Bulfield, 1979), the identity of the incidence in the reciprocal intercrosses (cross 2) indicated that the difference in incidence of abnormal animals in EDI and CAM crosses (cross 1) did not result from differences in intra-uterine conditions but must have been due to differences in susceptibilities of the offspring to the same maternal histidinaemia. The crosses indicated that 'high' susceptibility (in CAM) was recessive to 'low' (in EDI) but failed to show how many loci might be involved.

By 1980 the incidence of abnormal animals in the EDI line had declined to around 1%. The CAM stock was reintroduced to Edinburgh in 1980, by which time it had undergone several 'rescue' outcrosses in Cambridge (see Materials and methods). This stock was designated CAM-J to distinguish it from the stock used previously in the crosses of Table 1 (CAM-K).

The results of a series of intercrosses and backcrosses are presented in Table 2. Since, again, no significant differences were found between reciprocal crosses ($P < 0{\cdot}05$) the results of the crosses are not shown separately but have been combined in Table 2 for ease of reading. Table 3 gives the results of crosses involving non-histidinaemic mothers, from which it can be confirmed that the abnormal behaviour of the offspring is conditional on the histidinaemic status of the mothers. In previous publications (Kacser *et al.*

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Table 4. *Results of histidinaemia × dreher crosses*

Type of mating	Maternal genotype	Paternal genotype	Offspring N	Offspring Ab[a]	Offspring % Ab[a]
1st intercross	EDI *his/his* +/+	DR +/+ *dr/dr*	60	4	6
F_1 intercross	F_1 *his/+ dr/+*	F_1 *his/+ dr/+*	343	81	19
F_2 intercross	F_2 *his/his* +/?	F_2 +/? *dr/dr*	96	34	26
F_3 intercross	F_3 *his/his dr/+*	F_3 *his/his dr/+*	9	31	78
F_4 intercross	F_4 *his/his* +/?	F_4 *his/his* +/?	0	12	(100)
Backcross to EDI	EDI *his/his* +/+	F_2 *his/+ dr/dr*	58	1	2
Intercross to CAM-J	CAM-J *his/his* +/+	F_2 (all genotypes)	28	75	73

[a] Abnormalities are reported irrespective of whether they were due to *dreher* or maternal histidinaemia. The two types could be distinguished (see text).

1977; Kacser, Mya Mya & Bulfield, 1979) it was shown that *his/+* mothers could only produce abnormal offspring if their diet during pregnancy was supplemented with histidine so that their tissue histidine levels were elevated to those of *his/his* mothers.

From Table 2 it can be seen that in the first intercrosses the incidence of affected individuals is much higher than in comparable crosses from 1976 (Table 1) and is considerably higher than the current EDI incidence of 1%. Furthermore, any possible maternal differences do not determine penetrance since mothers from both high penetrance CAM and low penetrance EDI strains produced offspring with similar incidences of abnormalities when mated to reciprocal males. Thus penetrance differences in the 'pure' strains must be due to differing offspring susceptibilities to a common histidinaemic maternal environment. It is also clear that the high susceptibility alleles must have been introduced into the genotype of the offspring of the EDI mothers from the CAM males.

Comparing Tables 1 and 2, the results of the 1st intercrosses suggest that the high susceptibility in CAM-J is no longer recessive to the low susceptibility in EDI as it was in CAM-K. Taking the recent history of the CAM stock into consideration, it is hardly surprising that high penetrance of the behaviour defects is no longer a recessive trait. Indeed, the outcrossing of the strain in Cambridge, followed by reselection for high penetrance, is more likely to result in the accumulation of dominant or semi-dominant susceptibility alleles. If such alleles existed in the outcross strain, selection would clearly tend to fix these alleles more rapidly than recessive alleles. The EDI stock, meanwhile, has never been outcrossed since its first isolation but the decline in penetrance from 7% (Table 1) to the present level of 1% suggests the continued loss of high susceptibility alleles, and this cannot, therefore, account for increased penetrance in the F_1 offspring of EDI × CAM-J intercrosses, compared to the EDI × CAM-K crosses.

As can be seen in Table 2, F_1 and F_2 intercrosses produced incidences of affected animals of around 35%, similar to the incidence in the 1st intercrosses. Backcrossing to CAM-J animals increased penetrance until, after the 2nd and 3rd backcrosses, it was comparable to the pure CAM-J incidence. All pairs in these backcrosses produced affected offspring. Backcrossing to EDI, which was initiated at a later stage using fewer crosses, appeared to reduce penetrance to the level of the EDI strain after two backcrosses to the EDI strain. The results of the backcrosses, which show penetrance gradually returning to the level of the backcross strain, suggest codominance of high and low susceptibility alleles or segregation of a number of loci.

(ii) *Crosses of histidinaemia and dreher*

Inner ear mutants of the shaker–waltzer type are mainly recessive although they often show variable penetrance or expressivity in the homozygous condition. It was considered possible that the susceptibility alleles might be 'mild' alleles of such mutants whose penetrance was enhanced by the presence of high levels of maternal histidine.

Maternal histidinaemia appears to interfere only with early stages of inner ear development (Kacser *et al.* 1977; Kacser, Mya Mya & Bulfield, 1979; Mya Mya, 1978) and only in embryos that are genetically susceptible to its teratogenic effects. In any case it was possible that susceptibility might be influenced by the presence of an inner ear mutant allele in heterozygous conditions. The mutant chosen to test this hypothesis was *dreher* (*dr*) since the published effects on the inner ear in adults (Fischer, 1956), were similar to those of maternal histidinaemia, as were some aspects of its embryology (Deol, 1964). It was possible that *dreher* alleles affected the 'same' developmental pathway as that affected by maternal histidinaemia.

The results of crosses between EDI, CAM-J and *dreher* are shown in Table 4. In the crosses of EDI females × *dr/dr* males all offspring were *his/+*, *dr/+* and born to mothers with histidinaemia. The penetrance of abnormal behaviour in these crosses is not

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Table 5. *Results of C57BL/6 × CAM-J crosses*

Type of mating	Maternal genotype	Paternal genotype	Offspring N	Ab	% Ab
1st intercross	C57BL/6 +/+	CAM-J *his/his*	56	0	0
F_1 intercross	B6/CAM F_1 *his*/+	B6/CAM F_1 *his*/+	107	0	0
F_2 intercross	B6/CAM F_2 *his/his*	B6/CAM F_2 *his/his*	4	16	80
	+/?	+/?	12	0	(0)
Backcross to C57BL/6	B6/CAM F_2 *his/his*	B6 +/+	11	5	(31)

significantly different from that observed in the EDI strain, as shown in Table 2. There is thus no evidence to suggest that the *dr* allele in heterozygous condition might increase susceptibility to the effects of high maternal histidine levels. At the same time it shows that the DR stock did not contain any dominant high susceptibility alleles such as the CAM-J stock contained.

In F_1 intercrosses all parental mice were *his*/+, *dr*/+ (i.e. non-histidinaemic), hence no maternal effects were expected. On the other hand some *dr/dr* offspring were expected to segregate. Examination of whole mounts of the bony labyrinth (by the method of Lyon, 1958) had previously established that *dr/dr* inner ears could be distinguished from others with histidine-induced abnormalities. In all cases, malformations in *dreher* inner ears were more severe than in the most severely abnormal histidinaemic inner ears. In particular, the semi-circular canals and crus commune tended to be very much shorter and narrower and the ampullae and vestibule more grossly distended than in histidinaemia induced abnormalities. Histidinaemia and *dreher* segregated independently in the F_2 offspring, as expected for unlinked genes: all abnormal offspring were *dr/dr* but none of the *his/his* offspring showed abnormalities unless they were *his/his, dr/dr*.

Further crossing of F_2 non-*dreher* *his/his* females × F_2 *dr/dr* males resulted in about 26% of F_3 animals showing abnormal behaviour, similar to the F_2 incidence. Some of these animals, however, were only mildly affected and examination of inner ears revealed defects more typical of maternal histidinaemia than of *dreher*. This suggested that genes in the genetic background of the DR stock could influence susceptibility to the maternal effect of histidinaemia, although the *dr* allele itself apparently had no effect. To confirm this, F_3 *his/his* animals were intercrossed, mating normal (*dr*/+) females with presumed *dr*/+ males (normal or mildly affected). All matings produced some offspring with abnormalities typical either of *dreher* or of maternal histidinaemia (78% abnormal progeny). An F_4 intercross of normal females × mildly abnormal males resulted in 12 F_5 progeny, all of which showed behavioural and inner ear abnormalities characteristic of maternal histidinaemia.

Backcrossing of F_2 animals to EDI reduced the penetrance of abnormal behaviour to the level of the EDI stock.

The results of the EDI × *dreher* crosses, in general, suggest that, although the genotype at the *dr* locus itself has no effect on susceptibility to maternal histidinaemia, other genes in the genetic background of the DR strain do increase susceptibility. These DR background genes appear to be recessive to alleles in EDI, from the backcross results. The intercrosses of F_2 animals to CAM-J confirms the dominance of CAM-J alleles.

(iii) *Crosses to C57BL/6*

Crosses of CAM-J and C57BL/6 animals were made in order to establish the dominance relations of CAM-J alleles for high penetrance of histidine-induced behaviour abnormalities with those of a strain known to carry no endogenous susceptibility to such effects (Kacser & Bacon, unpublished results). The results are shown in Table 5.

As expected, no abnormal offspring were obtained from non-histidinaemic mothers whatever the genetic background. All *his/his* mothers did produce some affected offspring. The effects on behaviour varied from only mild leaning to severe leaning, circling and deafness. Comparison of the F_2 *his/his* and +/? intercrosses indicates that the abnormalities result from an effect of histidinaemia, while the backcross to C557BL/6 again suggests a dominant effect of CAM-J alleles on penetrance.

4. Discussion

A number of crosses have been carried out which give information about the genetics of susceptibility to histidine teratogenesis. It can be unequivocally stated that abnormalities of the inner ear occur only in animals subjected *in utero* to high levels of histidine or its derivatives, but the incidence of abnormalities is independent of genotype at the *his* locus. It is also true that genetic changes have apparently occurred within the two histidinaemic stocks, CAM and EDI, over the last few years, such that high susceptibility, which was recessive in the original stock (CAM-K) to low, is now dominant or codominant in CAM-J. Nevertheless,

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these results can provide no more than general indications of the genetic basis of susceptibility. Although susceptibility to teratogenesis is dependent on genes in the genetic background and does segregate, it is not possible to specify exactly how many loci might be involved. Inspection of Table 2 indicates that a major 'dominant' allele in CAM-J is segregating. By the 2nd or 3rd backcross to CAM-J, the incidence is virtually the same as in the pure CAM-J. Similarly, the second backcross to EDI shows reversion to the incidence of the pure EDI strain. It is not possible to exclude differences in one or more minor susceptibility alleles between EDI and CAM-J because of the nature of the scoring. Classification of animals as 'abnormal' masks a wide range of severity of abnormalities, both in the inner ear and behaviour. This variation in abnormalities, seen within strains, litters and even between the two ears of an individual suggests that, while maternal histidinaemia is a necessary precondition, it has only a triggering effect and is not the only factor involved in the teratogenic effect. The inner ear and behavioural phenotypes are far removed from the original defect and are subject to a great deal of modification during development. Since some adults exhibit unilateral abnormalities in the ear, and it is unreasonable to suppose that major differences in histidine concentration can exist between the two otic vesicles of a $9\frac{1}{2}$–$11\frac{1}{2}$ day embryo, it is obvious that some apparently genetically susceptible embryos may not develop obvious inner ear or behavioural abnormalities and in such a case penetrance will not reach 100%.

In effect, we propose that major gene differences may affect induction of a primary lesion early in the development of the inner ear. Differences in penetrance of abnormalities between histidinaemic stocks and in outcrosses, however, may be viewed as variation in the level of developmental buffering by the action of modifying genes in the genetic background which can influence both the incidence of behaviour defects and the degree of malformation of the inner ear.

Unfortunately we do not know what the initial lesion in histidine teratogenesis is. Observations of inner ear malformations and behaviour in a number of shaker-waltzer mutants have led Deol (1966*a*, *b*, 1968, 1976) to suggest that in many cases inner ear malformations and behavioural defects may be independent effects of an initial abnormality in the hind brain or neural tube early in development.

In histidinaemia the critical period of histidine action and the range of abnormalities which can be seen as early as $14\frac{1}{2}$ days of gestation point to early interference with otic development during the period when the hind brain and acoustic ganglion are the dominant influences on inner ear morphogenesis, and a previous study (Kacser, Mya Mya & Bulfield, 1979) indicated that a hind brain abnormality was indeed present in $9\frac{1}{2}$–$11\frac{1}{2}$ g.d. embryos. Attempts to confirm this (data not shown) suggest, however, that this was a dissection artefact and does not occur in embryos fixed *in utero* (Burns & Kacser, manuscript in preparation). No differences can be seen in sections of EDI and CAM-J embryos before 13–$13\frac{1}{2}$ g.d. (Mya Mya, 1978). Nevertheless, it is still possible that an initial, morphologically undetectable, abnormality is induced in the neural tube, with secondary effects on ear morphology and behaviour.

The relationship of the *dreher* mutant and maternal histidinaemia is of interest in this respect. In *dreher* the neural tube is clearly abnormal from an early stage and the inner ear later develops abnormally (Deol, 1964). Unlike histidinaemia, however, the abnormalities are fully penetrant, more severe and much less variable, and in the presence of maternal histidinaemia the *dreher* phenotype persisted unaltered. This suggests an epistatic relationship, with the *dreher* phenotype masking any teratogenic effects of the high histidine environment. Such a situation would arise if *dreher* induced abnormalities of greater severity, and possibly earlier in development, than the action of histidinaemia, with less opportunity for modifying genes to produce a normal phenotype after the initial lesion. This would be consistent with the embryology of both *dreher* (Deol, 1964) and the inner ear in maternal histidinaemia (Kacser, Mya Mya & Bulfield, 1979).

We have demonstrated that a variety of alleles (and loci?) exist in different strains of mice which can affect the developmental impact of histidinaemia, from zero penetrance (in C57BL/6) through high penetrance recessive to low (in CAM-K) to high penetrance dominant over low (in CAM-J). Because CAM-K no longer exists we are unable to comment on the possible allelism to CAM-J. These observations may not be irrelevant to the homologous human maternal histidinaemia where sporadic association with speech defects and mental retardation occurs (Scriver *et al.* 1983; Rosenmann *et al.* 1983; Coulombe *et al.* 1983). In the absence of breeding experiments, the possible genetic basis would not be ascertainable.

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