ACUTE AUTOIMMUNE ENCEPHALOMYELITIS IN MICE

II. Susceptibility is Controlled by the Combination of H-2 and Histamine Sensitization Genes*

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Genes controlling specific immune responses (Ir genes)[1] to various exogenous antigens have been identified and reside within the major histocompatibility complex (MHC) (1). Ir genes also influence susceptibility to a variety of experimental autoimmune diseases, most notably thyroiditis (2), myasthenia gravis (3), collagen arthritis (4), polyneuritis (5), and encephalomyelitis (6–18). Experimental automimmune encephalomyelitis (EAE) is an acute inflammatory and demyelinating disease mediated by the cellular component of the immune response. EAE has been well studied in a number of laboratory species ranging from rodents to primates, because it is easily induced with a single injection inoculum of purified myelin-basic protein (MBP) (19) in an oil-based adjuvant containing mycobacteria (e.g., Freund's complete adjuvant [FCA]). This disease is associated with a T cell-dependent delayed-type hypersensitivity (DTH) reaction to MBP (19). Both induction (20) and effector phases (21, 22) of the disease are T lymphocyte dependent. Transfer of EAE can be accomplished with MBP-sensitized T cells (22), but transfer with serum containing antibody to MBP has not been successful.

Studies using rats show strong association between susceptibility to EAE and MHC, but background (i.e., non-MHC) genes are also believed to be involved (14, 15). In guinea pigs, strain 13 is highly susceptible, whereas strain 2 is relatively resistant, and this finding correlates with in vivo and in vitro assessment of lymphocyte reactivity to MBP (10). A number of early investigators found it difficult to induce EAE in outbred and inbred strains of mice (6). The use of *Bordetella pertussis* vaccine accentuated the development of EAE in some strains of mice, but others remained resistant (7). Analysis of inbred strains (9, 12, 18) has suggested that two specific H-2 haplotypes, H-2^s and H-2^q, confer susceptibility, whereas others are refractory to the development of EAE.

Susceptibility to EAE appeared to be solely controlled by the appropriate H-2

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[1] *Abbreviations used in this paper:* CNS, central nervous system; DTH, delayed-type hypersensitivity; EAE, experimental autoimmune encephalomyelitis; FCA, Freund's complete adjuvant; Ir, immune response; HSF, histamine sensitivity factor of *B. pertussis* (pertussigen); MBP, myelin basic protein; MHC, major histocompatibility complex; MSCH, mouse spinal cord homogenate; VAA, vasoactive amines (serotonin and histamine); VAAS, VAA sensitization.

haplotype until the more recent use of H-2 congenic strains of mice to controversial results, in that not all H-2 congenic mice bearing responder H-2^s and H-2^q haplotypes were susceptible to EAE (12, 18). This suggests that other background or non-H-2 genes also play a role in EAE susceptibility.

We have determined that a combination of an appropriate H-2 haplotype and a second dominant gene, the gene for vasoactive amine sensitization (VAAS), confers susceptibility to acute EAE in mice. Susceptible strains bear *H-2^s* and *H-2^q* haplotypes and undergo VAAS with administration of *B. pertussis* (an adjuvant crucial to the development of acute EAE in mice); resistant strains are not sensitive to *B. pertussis* VAAS or lack the appropriate H-2 type. F_1 hybrids between H-2 nonresponder/VAAS-sensitive mice and H-2 responder/VAAS-resistant mice are fully susceptible to EAE and VAAS. The role of these genes on the expression of acute and chronic EAE in mice is discussed.

Materials and Methods

Animals. Mice used in these studies were obtained from several sources: Dr. Margaret Holmes kindly provided several inbred and congenic strains for the studies at The Walter and Eliza Hall Institute. Some recombinant strains were from the University of Southern California (USC) Immunogenetics mouse colony, and (SJL × BALB/c)F_1, (SJL × NZB)F_1, and (SJL × SWR)F_1 hybrid strains were obtained from The Jackson Laboratory, Bar Harbor, ME. Outbred (CFW) mice were obtained from Camm Labs; some inbred F_1 hybrids were produced in the USC Vivaria. The DDD strain was obtained from Dr. K. Susuki (University of Tokyo), and H-2 typed $K^sI^sD^?$ from Dr. S. Sakai (Natsuume) of the Cancer Research Institute of Kanazawa University and Ms. K. Sudo (University of Tokyo). Mice of both sexes at 6–10 wk of age were used for the studies.

Induction and Evaluation of EAE. Mice were immunized with mouse spinal cord homogenate (MSCH), 10 mg dry weight suspended in saline, emulsified in equal volume of FCA supplemented with 5 mg/ml *Mycobacterium tuberculosis* (H37RA; Difco Laboratories, Detroit, MI). All four footpads were injected, the total inoculum volume being 0.1 ml. For the complete "encephalitogenic challenge," two injections of *B. pertussis* (25×10^9 cells) were given immediately thereafter and again 48 h later. Mice were examined daily for signs of EAE scored on a scale of 0–3: 0, no disease; 1, tail atonia, slight hind limb weakness; 2, hind limb paralysis, incontinence of bladder; and 3, moribund state or death due to EAE. Histological assessment of EAE was made on mid-sagittal paraffin sections of brain and spinal cord, stained with hematoxylin and eosin. Without knowledge of the injection regime, the size and frequency of perivascular mononuclear infiltrates in the white matter of the central nervous systems (CNS) were graded on a scale of 0–3 as: 0, no lesions; 1, few lesions, mainly leptomeningeal and ependymal; 2, numerous infiltrates in the white matter of the brain stem, cerebellum and spinal cord; and 3, florid lesions throughout the brain and spinal cord white matter (23).

Vasoactive Amine (VAA) Sensitivity deteminations. B. pertussis has been demonstrated to cause a "hypersensitivity" to both VAA serotonin and histamine (24). For the sake of simplicity, we chose to test VAAS with only histamine. Histamine sensitization due to *B. pertussis* vaccine was determined by intraperitoneal injection of 1 mg histamine free base (denoted as challenge) in 0.2–0.5 ml saline 3–4 d after the initial inoculation of *B. pertussis* vaccine (25). Deaths (due to hypotensive and hypovolemic shock) were recorded for the next 2 h, and the results are expressed as number of deaths divided by the total number of animals challenged. Mice challenged with histamine without treatment with *B. pertussis* inoculation served as a negative control.

Results

VAA Sensitivity. Several strains of mice were examined for their natural sensitivity to VAA (histamine and serotonin) by titration of LD_{50} levels (Table I). Groups of

TABLE I

VAA LD_{50} Determinations on Normal Mice*

Mouse strain	Histamine		Serotonin	
	i.v.	i.p.	i.v.	i.p.
	mg		*mg*	
SJL	0.3	0.3	1.2	—
BALB/c	2.5	17.0	2.5	—
SWR	3.0	12.0	2.0	20.0
(SJL × BALB/c)F_1	2.5	15.5	2.5	15.0
(SJL × SWR)F_1	2.5	15.0	—	15.0
(SJL × NZB)F_1	3.0	20.0	4.0	20.0
B10.S(9R)	—	20.0	—	—

* Determinations were made using groups (N = 8) of normal mice (mean weight 20 g).

eight mice, average weight 20 g, were tested over a wide range of doses of histamine and serotonin by intravenous or intraperitoneal administration, and 2 h later the deaths (due to hypotensive and hypovolemic shock) were recorded. SJL mice were determined to be very sensitive to both VAA tested. For example, the LD_{50} for histamine intravenously in SJL mice is ~10 times lower than that determined for other strains. Other mouse strains tested (e.g., BALB/c) were fairly resistant to both VAA (e.g., histamine intraperitoneally LD_{50} = 12–20 mg, which is equivalent to ~600–1,000 mg/kg). The natural high level resistance to VAA induced shock is inherited in a dominant fashion as seen by the resistance of the (SJL × BALB/c)F_1 hybrids to shock.

B. pertussis-induced Histamine Hypersensitivity. The administration of *B. pertusis* or purified histamine sensitivity factor (HSF) to certain strains of mice will cause a "histamine and serotonin hypersensitivity" (23, 26). We tested a number of different strains and F_1 hybrids for induced histamine sensitivity after administration of *B. pertussis* or HSF; saline-treated mice served as controls (Table II). Of all the inbred strains tested, only SJL, DDD, and SWR showed increased histamine sensitivity after *B. pertussis* treatment. Outbred CFW mice also developed increased sensitivity. The susceptibility to *B. pertussis* or HSF-induced histamine sensitivity is inherited in a dominant fashion as indicated by the responses of (SJL × BALB/c)F_1 and (B10.Q × DDD)F_1 hybrids (B10.Q are not sensitive to HSF; see Table III).

Correlation of EAE and HSF Sensitivity. Inbred, outbred, and recombinant strains of mice were evaluated for EAE susceptibility and *B. pertussis*-induced histamine sensitivity (Table III). In each case histological and clinical indices of EAE are presented, and in separate experiments, histamine-induced deaths 3 d after administration of *B. pertusis* vaccine are recorded. SJL, SWR, and CFW all developed EAE and increased histamine sensitivity in response to *B. pertussis*. BALB/c, CBA, C57BL/6, and DBA/1 did not develop EAE nor histamine sensitivity. Outbred CFW mice developed both EAE and histamine sensitivity.

To determine if the susceptibility of EAE and VAAS is controlled by H-2 genes, several H-2 congenic and recombinant strains were examined. All strains resistant to EAE were also resistant to VAAS. However, in several strains such as B10.S, B10.T(6R), B10.S(7R), and B10.HTT, some individual mice developed EAE and

TABLE II

Histamine Sensitization in Mice Given HSF or B. pertussis Vaccine

Mouse strain	Number of deaths/total tested*				
	HSF			*B. pertussis* (5×10^{10})	Saline
	150	75	30		
		μg			
C57BL/6	0/5	0/5	0/5	0/5	0/5
AKR	0/5	0/5	0/5	0/5	0/5
CBA	0/5	0/5	0/5	0/5	0/5
A/J	1/5	0/5	0/5	0/5	0/5
BALB/c	0/5	0/5	0/5	0/5	0/5
SJL	5/5	2/6	2/5	9/12	0/10
CFW	6/6	3/5	—	9/10	0/5
DBA/1	0/10	—	—	1/10	0/8
SWR	—	—	—	6/6	0/6
DDD	1/6	2/5	—	6/7	0/6
(SJL × BALB/c)F_1	4/4	4/4	1/6	6/6	0/10
(SJL × SWR)F_1	6/6	5/6	—	6/6	0/4
(B10.Q × DDD)F_1	2/5	1/6	—	4/6	0/6

* Data are expressed as number of deaths/total tested 3 d after administration of HSF, pertussis, or saline; challenge was 1 mg histamine-free base i.p. with the exception of SJL, which was given only 0.1 mg.

some were sensitive to *B. pertussis*-induced histamine sensitivity; the reason for variation within the strain is not known. It is not possible to correlate the two in individuals because both traits cannot be tested in a single mouse.

The susceptibility to EAE and VAAS in F_1 hybrid mice was also examined (Table IV). Both EAE and VAAS appear to be inherited in a codominant fashion. SJL, SWR, and CFW hybrids with nonresponder strains (BALB/c or NZB) were determined to be susceptible to both EAE and VAAS. Hybrids produced between EAE-resistant/VAAS mice (e.g., DDD) and strains that were susceptible to neither EAE nor VAAS (e.g., B10.S, B10.HTT, or B10.Q) were susceptible to EAE and VAAS.

Discussion

The immune response to protein antigens are generally regulated in part by MHC genes, probably Ia antigens (1). However, in experimental autoimmune disease models, such as EAE, it is clear that non-MHC genes play an important role in the susceptibility to the disease (14, 15). EAE is complicated by the fact that the experimental readout is not merely the production of a single antibody or restricted cytotoxic T cell response. Rather, the overall expression of the disease is the result of a well orchestrated concert of effector cells, immune factors, and tissue responses. The mouse EAE model has been examined for almost 20 yr (6), and still there is great disagreement regarding the factor(s) that control the induction and expression of the disease.

In a companion paper, we have carefully documented the role that *B. pertussis* plays as an effector adjuvant in the expression of murine EAE.[2] In our laboratory this

[2] Linthicum, D. S., J. J. Munoz, and A. Blaskett. Acute experimental autoimmune encephalomyelitis in mice. I. The adjuvant action of *Bordetella pertussis* is due to vasoactive amine sensitization and increased vascular permeability of the central nervous system. Manuscript submitted for publication.

TABLE III

Incidence of Acute EAE and Histamine Sensitization in Inbred, Outbred, and Recombinant Strains of Mice

Strain	H-2 type	Composition of H-2 region						EAE index*		Histamine sensitization‡
		K	IA	IB	IC	S	D	Clinical	Histological	
Inbred										
C57BL/6	b	b	b	b	b	b	b	0.0 (0/10)	0.0 (0/10)	0/6
DBA/1	q	q	q	q	q	q	q	0.0 (0/3)	0.0 (0/3)	1/10
SJL	s	s	s	s	s	s	s	1.8 (7/10)	—	12/12
SWR	q	q	q	q	q	q	q	1.8 (3/5)	1.6 (4/5)	6/6
DDD	UD§	s	s	?	?	?	?	0.2 (2/12)	0.2 (2/12)	6/7
Outbred										
CFW	s/q	s	?	?	?	?	q	1.7 (9/15)	0.8 (8/14)	10/10
Recombinant										
A.SW	s	s	s	s	s	s	s	0.0 (0/20)	0.0 (0/20)	0/10
A.TH	t2	s	s	s	s	s	d	0.0 (0/5)	0.4 (1/5)	1/10
A.TL	t1	s	k	k	k	k	k	0.0 (0/20)	0.0 (0/20)	0/10
B10.S	s	s	s	s	s	s	s	0.0 (0/9)	0.2 (2/9)	6/11
B10.A	a	k	k	k	d	d	d	0.0 (0/4)	0.1 (1/4)	0/7
B10.Q	q	q	q	q	q	q	q	0.0 (0/14)	0.0 (0/6)	5/16
B10.HTT	t3	s	s	s	k	k	d	0.1 (1/14)	0.1 (1/14)	2/17
B10.T(6R)	y1	q	q	q	q	q	d	0.3 (2/11)	0.4 (3/10)	6/16
B10.S(7R)	t2	s	s	s	s	s	d	0.2 (4/22)	0.2 (3/20)	6/14
B10.S(8R)	as1	k	k	?	s	s	s	0.0 (0/7)	0.0 (0/7)	0/7
A.TFR-1	an1	s	k	k	k	k	f	0.0 (0/4)	0.0 (0/4)	0/6

* EAE indices are expressed as mean values (maximum = 3.0). Parenthetical values are numbers of affected individuals/total tested.

‡ Expressed as deaths/total tested after challenge with 1 mg histamine 3 d after administration of 10^{10} *B. pertussis* cells.

§ Undesignated.

adjuvant is crucial to the successful production of acute EAE and its success as an adjuvant relies upon the HSF content. With these aspects in mind we examined a wide variety of mouse strains for susceptibility to EAE and HSF sensitivity. The results presented herein clearly indicate that the susceptibility to EAE is conferred by the presence of the appropriate responder H-2 haplotype and the presence of a non-H-2 gene(s), which controls the susceptibility to HSF.

In Table V we have summarized the data from 11 publications (1, 2, 6, 7, 9, 11–13, 17, 18, 23), including this report, on murine EAE, and have compared these data with published reports (6, 9, 11, 13, 23, 24) on susceptibility to *B. pertussis*-induced histamine sensitivity. The overall analysis reveals a positive correlation between the two phenomena. There are a few disagreements regarding the susceptibility to EAE or HSF in certain strains, but these for the most part are in the minority of published reports (7, 11–13, 17, 18). Differences in results from different laboratories may depend upon the route of injection of the encephalitogen, source of the encephalitogenic material (allogenic or syngeneic spinal cord), and exact derivation of each mouse strain tested. In addition, of course, the nature of the adjuvant *B. pertussis* is quite variable; we have observed that different strains and batches can vary with respect to the amount of HSF activity. Furthermore, Munoz and Bergman (26) have determined that the degree of HSF responsiveness of CFW mice alters during the year, and can

TABLE IV

Incidence of Clinical and Histological EAE and Histamine Sensitization in F_1 Hybrid Mice

Strain	H-2 genotype	EAE index		Histamine sensitization
		Clinical	Histological	
(SJL × BALB/c)F_1	s/d	2.3 (10/11)	2.3 (9/9)	10/10
(SJL × NZB)F_1	s/d	2.3 (11/12)	2.4 (11/11)	10/10
(SJL × SWR)F_1	s/d	2.0 (9/12)	—	6/6
(SJL × CFW)F_1	s/s,q	2.8 (10/10)	2.9 (7/7)	9/9
(CFW × BALB/c)F_1	s,q/d	1.3 (5/8)	1.0 (4/7)	6/6
(CFW × B10.S)F_1	s,q/s	0.4 (3/10)	0.9 (7/10)	5/6
(CFW × A.SW)F_1	s,q/s	2.4 (9/9)	1.6 (4/5)	3/8
(SWR × A.SW)F_1	q/s	1.6 (5/8)	1.4 (4/7)	6/6
(SWR × B10.S)F_1	q/s	1.5 (6/8)	1.7 (6/6)	7/7
(DDD × B10.Q)F_1	$K^sI^sD^?$/q	1.2 (9/14)	2.0 (9/14)	4/6
(DDD × B10.S)F_1	$K^sI^sD^?$/s	1.5 (11/12)	0.8 (9/12)	—
(DDD × B10.HTT)F_1	$K^sI^sD^?$/t3	2.3 (15/16)	2.4 (15/16)	—
(C57Bl/6) × B10.Q)F_1	b/q	0.0 (0/4)	0.0 (0/4)	—

EAE index numbers are means for each group. Proportion of affected mice shown in parenthesis. Histamine sensitization numbers are expressed as deaths/total individuals tested by injection of 1.0 mg histamine i.p. 3 d after administration of *B. pertussis* (10^{10} cells).

vary with environmental stress and age of the animals. Genetic drift of the HSF response gene in each mouse colony may also account for different results between laboratories using the same strain over the years. With respect to the H-2 genetic contribution, it is clear that H-2 contributes to susceptibility. However, susceptibility is not expressed unless complemented with the HSF response gene. For example, Lando et al. (18) reported that SJL and (SJL × BALB/c)F_1 mice were susceptible to EAE, but that A.SW and B10.S and F_1 hybrids with BALB/c were not susceptible to EAE. They concluded that EAE was not influenced by H-2. We have observed that A.SW, B10.S, and BALB/c are fairly resistant to VAAS induced by *B. pertussis* and therefore, none of the F_1 hybrids produced with these parental strains have the HSF response gene, nor do they develop EAE, even though they possess the appropriate responder H-2 gene. Montgomery and Rauch (27) have also reported that EAE responsiveness is under the primary control of genes outside the H-2 complex and present data indicating that a maternal factor, sex hormone, or sex-linked gene(s) can modify EAE responsiveness. We have observed (unpublished) that SJL male mice subject to excessive fighting behavior do not develop EAE as readily as docile, age-matched, females, or docile, age-matched, castrated males.

In the present study, the H-2 control of susceptibility to EAE appears to be mediated by the D-end of the H-2 complex. For example, the DDD strain does not develop EAE, in spite of having $K^sI\text{-}A^s$ alleles, presumably because it lacks the appropriate D allele. However, F_1 hybrids between DDD and B10.S, B10.HTT, or B10.Q possess the D^s, D^d, or D^q allele, respectively, and are fully susceptible to EAE, suggesting that D^s, D^d, or D^q is necessary to confer susceptibility. This D region allelic requirement may control the overall response to the adjuvant used in the encephalitogenic challenge. Staruch and Wood (28) reported that murine responses to muramyl dipeptide were controlled by at least two genes, one inside and one outside the MHC; $H\text{-}2^d$ and $H\text{-}2^k$ were high responders to the muramyl dipeptide. We have recently produced EAE in the SJL × BALB/c recombinant inbred strain C × J1 (kindly

TABLE V

Summary of Published Observations on Murine EAE Susceptibility and B. pertussis-induced Histamine Sensitivity

Mouse Strain	H-2 type	EAE susceptibility	Reference	VAA hypersensitivity	Reference
A/J	a	−	7, 12, 18	−	23, 24*
BALB/c	d	−	7, 9, 12, 17, 18	−(+)	(24)*
C57Bl/6J	b	−(+)	23 (7, 12, 18)*	−(+)	(9)*
C57Bl/10	b	−	7, 17	?	
C57L/J	b	+	7	+	23
C3H/J	k	−(+)	7, 12, 23 (11, 13)	−	13, 24
CBA	k	−	7, 12	−	24*
DBA/1	q	−(+)	7, 9 (17)*	−	*
DBA/2	d	−	7, 18	−(+)	23 (24)
DDD	($K^sI^sD^s$)	−	11*	+	11, 13*
NBZ	d	−	1, 2, 12, 18	−	24
NZC	d	−	12	?	
SJL/J	s	+	7, 11, 12, 13, 17, 18*	+	11, 13*
SWR	q	+	7*	+	24*
CFW	s/q	+	7, 23*	+	23*
A.SW	s	−(+)	9, 11, 18 (12, 17)*	−	*
A.TH	th	−(+)	(12, 17)*	−	*
A.TL	tl	−(+)	(12, 17)*	−	*
A.TFR-1	an1	−	*	−	*
B10.A	a	−	7, 12, 18*	−	*
B10.S	s	±(+)	7, 9, 18 (17)*	±	*
B10.Q	q	−	7, 9, 18*	±	*
B10.HTT	t3	±	*	±	*
B10.T(6R)	y1	±	*	±	*
B10.S(7R)	t2	±	*	±	*
B10.S(8R)	as1	−	*	−	*
BRVR	k	−	6, 7, 12	−	6
BSVS	+5	+(−)	6 (7)	+	6

Observations for EAE susceptibility and VAA hypersensitivity induced by *B. pertussis* are recorded as + (positive) and − (negative). Where there are minor conflicting reports, the parenthetical observations and references are indicated.

* Indicates data presented in this paper.

provided by Dr. Mel Cohn, Salk Institute for Biological Studies), which is H-2^d and HSF sensitive (unpublished observations); these preliminary data support the notion that H-2^d is a responder haplotype, and, when complemented with the HSF response gene, confers susceptibility to EAE.

In mice, the expression of DTH responses is controlled by VAA, especially serotonin (29). The role of VAA is to allow the egress of sensitized T lymphocytes and nonsensitized mononuclear cells from the microvasculature to the antigen depot site (30). Most likely the same sequence of events is true for the action of VAA in the expression of murine EAE. The observations reported in a companion paper support this notion, in that we have demonstrated VAA antagonists such as cyproheptadine and methysergide can effectively block the development of acute EAE.[2] It must be noted that throughout this and the companion paper we have emphasized that *B. pertussis* and VAAS are important in the expression of acute EAE in mice. This point has been intentional, in that it has been reported by several laboratories (31) that

chronic EAE in mice can be produced in SJL mice only in the absence of *B. pertussis* or by giving the vaccine with the encephalitogenic emulsion intradermally. The different forms of EAE have been best documented for the rat (32), in which three well-recognized types of EAE exist: (*a*) hyperacute EAE, characterized by hemorrhage, fibrin deposition, edema, and presence of polymorphonuclear cells, and is dependent upon *B. pertussis*, more specifically HSF, which alters CNS vascular permeability (33); (*b*) acute EAE; and (*c*) chronic, relapsing EAE. In mice only two forms, acute and chronic EAE, have been reported. The acute EAE of mice, however, may be closely related to the "hyperacute" EAE observed in rats, in that the disease is dependent upon *B. pertussis*, especially HSF, the CNS vascular permeability increases, and some polymorphonuclear cells are occasionally present in the lesions. Chronic EAE has only been observed in the SJL mouse (31). As indicated in Table I, and supported by previous workers (24), the SJL mouse is a priori very sensitive to VAA- (both histamine and serotonin) induced shock, whereas other strains examined are highly resistant. The gene(s) controlling natural VAA sensitivity is probably different than that which controls HSF sensitivity, because SJL and SWR mice have different natural VAA sensitivities. We postulate that the SJL mouse does not require any additional VAA sensitization to develop chronic EAE, thereby accounting for the production of chronic EAE in the absence of *B. pertussis*. Because the inheritance of the natural resistance to VAA-induced shock is dominant, SWR and (SJL × BALB/c)F_1 hybrids should not develop chronic EAE, even though they are fully susceptible to acute EAE and HSF sensitivity. Chronic EAE, unlike acute EAE, is probably not accompanied by any detectable acute CNS vascular permeability change mediated by VAA antecedent to the cellular infiltration of the CNS, and may be due to the slow penetration of effector cells over a prolonged period of time.

Summary

The expression of acute experimental autoimmune encephalomyelitis (EAE) in mice is controlled by several dominant genes, H-2 and histamine sensitization genes. SJL/J and SWR/J, which are H-2^s and H-2^q, respectively, are susceptible to EAE and sensitive to *Bordetella pertussis* histamine-sensitizing factor (HSF), which produces a vasoactive amine hypersensitivity. Other H-2^s or H-2^q strains such as A.SW, B10.Q, and several others do not develop acute EAE and are not sensitive to *B. pertussis* HSF. One strain tested, DDD ($K^sI^sD^?$) is HSF sensitive but does not develop EAE (presumably because it lacks the appropriate responder H-2 haplotype). However, F_1 hybrids between B10.S and DDD are sensitive to HSF and develop EAE. The induction and effector phases of acute EAE are apparently controlled by the combination of H-2 and HSF genes. A combination of the correct H-2 hapotype and histamine sensitivity is required for the development of acute EAE.

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