Decrease in Susceptibility of Mice to Passive Anaphylaxis Following Avoidance-Learning Stress (24811)

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A variety of procedures including adrenalectomy(1,2) sensitization with adjuvants(3) and treatment with *B. pertussis* antigens(4) has been employed to increase susceptibility of mice to anaphylaxis. Conversely, anaphylaxis in sensitized mice can be prevented by prior administration of cortisone and related steroids, by lysergic acid and by chlorpromazine and other tranquilizers(5). As part of a study of emotional stress and nonspecific resistance to infectious disease, we have employed an avoidance-learning shuttlebox to increase susceptibility to infection with the virus of herpes simplex in mice(6). To further evaluate the nature of the host response to shuttlebox stress, stressed mice were tested for susceptibility to passive anaphylaxis by intravenous injection of a mixture of bovine plasma albumen, BPA, and anti-BPA mouse serum.

Methods. In a preliminary experiment, stressed mice sensitized to bovine plasma albumen, BPA, appeared to be less susceptible than were controls to a shocking dose of antigen. The difference in response of the stressed mice could have been due either to impaired immunologic response or to a decrease in susceptibility to the chain of events following combination of antigen and antibody. In the following experiments the former possibility was excluded by subjecting stressed mice to passive anaphylaxis employing procedures adapted from those developed by Sobey *et al.*(7,8) for production and quantitative scoring of anaphylaxis. Anti-BPA mouse serum was prepared by injecting normal 5-6-week-old mice with 2 mg of alum precipitated BPA contained in 0.1 ml of physiological saline. The mice were bled 2 weeks later and the sera harvested, pooled and stored at 4°C or −20°C until used. 4- 5-week-old male or female mice were subjected to avoidance-learning stress in shuttleboxes for 6 hours a day for periods of 1 day or 4 weeks as described(6). Immediately following the last period of stress, each mouse was injected intravenously in the tail vein with 0.5 ml of a freshly prepared mixture of equal parts of undiluted anti-BPA mouse serum and 0.02% BPA, the optimal shocking dose as determined by Sobey and Adams(8). Severity of shock was scored on a relative basis as follows: (a) fatal shock, 4; (b) severe shock with complete prostration and failure to respond to stimuli followed by recovery, 3; (c) moderate shock with crouching and prostration but responsive to stimuli, 2; (d) mild shock with scratching and agitation, 1; and (e) no signs of shock, 0.

Results. The results of 3 experiments, Table I, show that anaphylaxis was more severe in controls of either sex than in stressed mice, with fatal shock in 17/26 controls and in only 2/26 in the combined stressed groups. The chi square for this difference in mortality is 16.3, significant beyond the .001 level.

Because changes in susceptibility to herpes simplex had been observed only following periods of stress of 2 to 4 weeks in our previously reported experiments(6), the influence of shorter periods of stress on anaphylaxis was not initially tested. In a second series of experiments mice subjected to avoidance-learning stress for a single period of 6 hours were tested for susceptibility to passive anaphylaxis induced as described above. In the first of 2 experiments 8 of 8 stressed mice survived and in the second 7 of 9 survived shocking doses of BPA and BPA antiserum lethal to 8 of 10 controls in the first and 18 of 18 controls in the second experiment. Many of the survivors exhibited mild to moderate shock but, even so, the differences in severity scores were highly significant.

Discussion. Shocking mixtures of antiserum and BPA were clear. Faint precipi-

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TABLE I. Severity of Passive Anaphylaxis in Mice Subjected to Chronic Avoidance-Learning Stress.*

No.	Exp. 48 ♀		Exp. 54A ♀		Exp. 54B ♂	
	Stressed	Controls	Stressed	Controls	Stressed	Controls
1	0	3	1	1	1	2
2	0	4	1	2	1	2
3	0	4	1	2	1	2
4	0	4	2	2	1	2
5	0	4	2	4	2	4
6	1	4	2	4	2	4
7	1	4	2	4	2	4
8			2	4	3	4
9			2	4	4	4
10			4			4
P level of diff. in scores†	P = .000		P = .10		P = .05	
P level of diff. in scores of all exp.†			P = .002			

* Severity of anaphylaxis scored as follows: 0 = no signs of shock; 1 = mild shock; 2 = moderate shock; 3 = severe shock with recovery and 4 = fatal shock.
† Computed by Mann-Whitney U test (two tailed test).

tates were seen by ring tests with antigen solutions containing from 0.1 to 0.001% BPA but precipitates suitable for antibody nitrogen determination(9) were not obtained even with a wide range of antigen concentrations above and below those used to cause anaphylaxis. Shocking mixtures presumably consisted of soluble antigen-antibody complexes formed with antibody of low valence; the possibility that solubility and shocking activity depended in part on excess antigen was not excluded(10, 11).

In contrast to experiments with herpes simplex(6) in which increased susceptibility was observed only after 2 to 4 weeks of stress, the increase in resistance to anaphylactic shock appears after a single period of shuttlebox stress. The rapidity of the response together with known increased susceptibility of mice to anaphylaxis following adrenalectomy(1) and decreased susceptibility following cortisone (5) suggest that increased adrenal cortical activity is responsible for the increased resistance in stressed mice. Whatever the mechanism, the change in susceptibility to anaphylactic shock following an avoidance-learning procedure provides additional evidence for the influence of environmental stress upon host response to infectious and allergic disease.

Summary. Mice subjected to chronic or acute shuttlebox stress were less susceptible than unstressed controls to passive anaphylactic shock induced by intravenous injection of a mixture of BPA and anti-BPA mouse serum.

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