Resistance to Endotoxin After Protection Against Initial Lethal Challenge with Adrenocorticosteroids or Chlorpromazine. (23297)

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Previous investigations have established that mice may be protected against lethal doses of brucella endotoxin by both adrenocorticosteroids(1,2) and chlorpromazine(3). It has also been observed that injection of a single sublethal dose of brucella endotoxin confers resistance to subsequent challenge with lethal amounts of endotoxin(4). Such resistance was found to develop within 2 weeks and to persist for approximately 6 months. The studies reported here were done to determine if therapy with steroids or chlorpromazin interfered with the development of subsequent resistance to the lethality of endotoxin.

Materials and methods. Male ABC mice weighing 20 to 25 g were housed 5 to 10 animals per cage in an air-conditioned room and had free access to tap water and Purina Fox Chow. The endotoxin was prepared from *Brucella melitensis* by a modified Boivin technic(5). A saline suspension was injected intraperitoneally. Appropriate dilutions with saline of the protective agents were given intramuscularly.

Results. Various groups of mice were treated with either cortisone acetate, 9-alpha-fluorohydrocortisone acetate, or chlorpromazine by the schedules outlined in Table I. These groups, along with control groups given injections of sterile saline at the same intervals, were then challenged with 2 LD_{50} amounts of brucella endotoxin. With each agent, significant protection against endotoxin lethality was observed. Following this initial challenge, the survivors from each treatment group were then subsequently challenged with a lethal amount (2 LD_{50}) of endotoxin at either 2 or 4 weeks. Again, untreated mice of the same approximate weight were challenged as controls. The results (Table I) indicate that the protected animals developed resistance to endotoxin lethality by 2 weeks and that this resistance persisted at least 4 weeks.

Discussion. These findings show that protection against an initial lethal dose of endotoxin with adrenocorticosteroids or chlorpromazine does not interfere with the development of resistance to endotoxin. Such an observation might have significance in the treatment of serious infections due to Gram-negative micro-organisms. It is now well established that the febrile and toxic state that occurs in such infections can be controlled and subdued with adrenocorticosteroids, though the mechanisms responsible for this beneficial effect are not understood(6).

Summary. Mice protected against an initial lethal challenge with brucella endotoxin by treatment with cortisone acetate, 9-alpha-fluorohydrocortisone acetate, or chlorpromazine develop resistance to subsequent challenge to endotoxin.

TABLE I.

Agent	Schedule of treatment	Endotoxin mortality* Initial challenge Treated	Controls	2 wk later Treated	Controls	4 wk later Treated	Controls
Cortisone	.5 mg I.M. 3 hr†	8/20	8/10	3/ 9	10/10		
"	*Idem* 2 hr†	10/45	14/15	1/15	9/12	1/15	8/10
9-alpha-fluoro-hydrocortisone	.05 mg I.M. 2 hr†	15/25	10/10	2/ 9	10/10		
Chlorpromazine	.2 mg I.M. every 4 hr × 4	2/10	7/10			2/ 8	10/10

* No. dying/No. challenged. † Before challenge.

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Dehydrogenase Enzyme Studies in Experimental Renal Hypertension.* (23298)

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Previous investigations(1,2,3) have demonstrated that the kidney, adrenal, thyroid and pituitary play a role in development and maintenance of experimental renal hypertension. In the present investigation one facet of metabolic activity of these organs was measured in an attempt to determine if an abnormal metabolism within one or more of them could be related to the etiology of experimental renal hypertension, while cardiac muscle was likewise studied to observe any effects of high blood pressure levels on this portion of the cardiovascular system. Since reserpine effectively lowers the hypertensive blood pressure level in experimental renal hypertension(4), it was decided also to study the above mentioned tissues in hypertensive animals under active reserpine therapy. The area of tissue metabolism studied was the endogenous dehydrogenase enzyme activity. This was quantitated employing the tetrazolium technic.

Methods. Both male and female rats of the Denver strain were used. During the years this colony has been employed for cardiovascular problems in our laboratory, the normal, mean arterial blood pressure, measured directly under general anesthesia, has been determined to range from 100-140 mm Hg. With this information available the lower limit for a hypertensive blood pressure level was set at 150 mm Hg. Experimental renal hypertension was produced in 3 different ways. Constriction of the remaining kidney by means of a figure 8 ligature after unilateral nephrectomy(5), feeding a choline deficient diet early in life(6), and encapsulation of one kidney followed by removal of the contralateral kidney(7) were the methods employed. For the latter procedure a butylmethacrylate polymer plastic dissolved in acetone was used to construct the capsule. Blood pressures were measured indirectly using the "Infraton" sphygmograph system(8) and recorded on a direct writing Sanborn E.C.G. Readings were obtained with animals under light ether anesthesia. Measurements using this method were found to agree favorably with simultaneously recorded direct blood pressure measurements. Only animals which were acutely hypertensive were employed for the endogenous dehydrogenase enzyme determinations. Following the first complete week in which an animal presented a consistently elevated mean arterial pressure, as measured every 2 days, the animal was sacrificed or placed upon reserpine therapy for 14 days before being sacrificed. A dose of 100 μg/kg/day of reserpine was necessary to reduce the elevated blood pressure to a stabilized level within 14 days. Pure powdered reserpine was used.‡ It was dissolved in a minimum of glacial acetic acid and brought to the

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