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SUSCEPTIBILITY OF LABORATORY AND WILD RODENTS TO RATTUSOR APODEMUS-TYPE HANTAVIRUSES

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Summary. - Adult Wistar rats (*Rattus norvegicus*), *Apodemus agrarius*, *Meriones unguiculatus*, *Clethrionomys rufocanus*, and *Apodemus argenteus* were inoculated with *Rattus*-type (SR-11, KI-262, and TB-314) or *Apodemus*-type (Hantaan 76-118) hantaviruses. Production of serum antibody to the inoculated virus (IAHA titres of 1:32 to 1:4 096) was obsersved in all rodent species 10 weeks after virus inoculation. *Rattus*-type virus was detected in some organs of all the rodent species employed except of *Apodemus agrarius*. *Apodemus*-type virus was found only in some organs of *Apodemus agrarius*. Newborn Wistar rats induced antibody in high titres to both *Rattus*- and *Apodemus*-type hantaviruses. *Rattus*-type virus was detected in all the organs examined for up to 6 weeks after inoculation, whereas *Apodemus*-type virus disappeared from all organs except of brain and lung tissues. The virulence of the three *Rattus*-type viruses to newborn rats was different. These findings indicate that the susceptibility of rodents may vary depending on the combination of rodent species and virus strains; they also suggest that the various species of rodents may be the reservoir animals of hantavirus infection in nature.

Key words: hantavirus; HFRS; experimental infection; susceptibility; immunostaining

Introduction

Haemorrhagic fever with renal syndrome (HFRS) is a rodentborne viral febrile disease characterized by renal disorder in man (Cohen, 1982). The causative virus was first isolated from *Apodemus agrarius coreae* in Korea by Lee *et al.* (1978) and named Hantaan virus. Until now, more than 50 antigenically related viruses have been isolated from various rodent hosts or patients in

various countries (Yanagihara and Gajdusek, 1987). They are classified in the *Hantavirus genus* of the *Bunyaviridae* family by morphologic (McCormick *et al.*, 1982; White *et al.*, 1982) and genetic characteristics (Schmaljohn *et al.*, 1985). Hantaviruses are antigenically further divided into four serogroups, each of which is closely related to rodent species, such as the *Apodemus* type (derived from *Apodemus agrarius*), the *Rattus* type (derived from *Rattus norvegicus*), the *Clethrionomys* type (derived from *Celthrionomys glareolus*), and the *Microtus* type (derived from *Microtus pennsylvanicus*). The representative viruses in each serogroup are the Hantaan virus, the Seoul virus, the Puumala virus, and the Prospect Hill virus, respectively (Sugiyama *et al.*, 1984; Lee *et al.*, 1985).

In China and Korea, it has been reported that *Apodemus agrarius* and *Rattus norvegicus* are reservoir animals of Hantaan virus and Seoul virus, respectively (Lee *et al.,* 1978; 1982; Song *et al.*, 1984); both have caused human HFRS endemics. In Japan, however, HFRS outbreaks have occurred mainly in medical institutions and have been caused by laboratory rats (Kawamata *et al.*, 1985), and several endemic foci among *Rattus norvegicus* without cases of human illness were found (Morita *et al.*, 1983; Suzuki *et al.*, 1984; Arikawa *et al.*, 1985; 1986). Epidemiologic studies of hantavirus infection among wild rodents in the European part of the U.S.S.R. revealed that, in addition to *Clethrionomys glareolus,* various species of small mammals may serve as reservoir hosts (Yanagihara and Gajdusek, 1987). To obtain basic information concerning the ecology of the hantavirus among rodents, the susceptibility of laboratory and wild rodents to hantaviruses isolated from Apodemus or Rattus was studied on the basis of the detection of viral antigen and the antibody production in experimentally infected animals.

Materials and Methods

Cell culture and virus. The E6 clone of Vero cells (ATCC C1008, CRL 1586) was grown in Eagle's minimum essential medium (Eagle's MEM, Nissui, Co., Tokyo, Japan) supplemented with 5% foetal calf serum (FCS) and 2 mmol/l of L-glutamine. The following hantaviruses were used: 1. Hantaan virus strain 76 - 118, derived from *Apodemus agrarius coreae* (Lee *et al.*, 1978); 2. Seoul virus strain SR-11 (Kitamura *et al.*, 1983), derived from laboratory Wistar rat; 3. strains TB-314 and KI-262. derived from *Rattus norvegicus* captured at dumping grounds in Tokyo Bay in Tokyo and Kami-iso town in Hokkaido, Japan (Arikawa *et al.*, 1985; 1986). Viruses were inoculated into the Vero E6 cell monolayers and maintained with the same medium described above with a reduced amount of FCS (3%).

Animals. Six-week-old or newborn specific-pathogen-free Wistar rats (JCL, Shizuoka Laboratory Animal Centre, Shizuoka, Japan) were used in this experiment. Adult *Meriones unguiculatus* and *Apodemus agrarius jejensis* were kindly provided by Dr. H. Tamura of Teikyo Medical College, Japan, and Dr. K. Tsuchiya of Miyazaki Medical College, Japan, respecitvely. *Clethrionomys rufocanus bedfordiae* and *Apodemus argenteus* were captured in a forest in the suburbs of Sapporo, Japan. They were bled by tail cut using the filter paper method (Arikawa *et al.*, 1986). Before the experiment, the animals were checked for seronegativity to hantavirus. All the animals inoculated with hantavirus were kept in isolators equipped with a HEPA filter. The experiments were carried out in a room with class P3 facilities.

Experimental infection. All animals were inoculated by intraperitoneal (i. p.) route with 0.1 ml o virus suspension ($10^{4.0}$ focus-forming units, FFU/ml). Serum specimens were obtained from newborn rats on days 0,21, and 42 after virus inoculation or from 6-week-old rats on days 0, 7, 14 21, 28, 42, and 70 after inoculation.

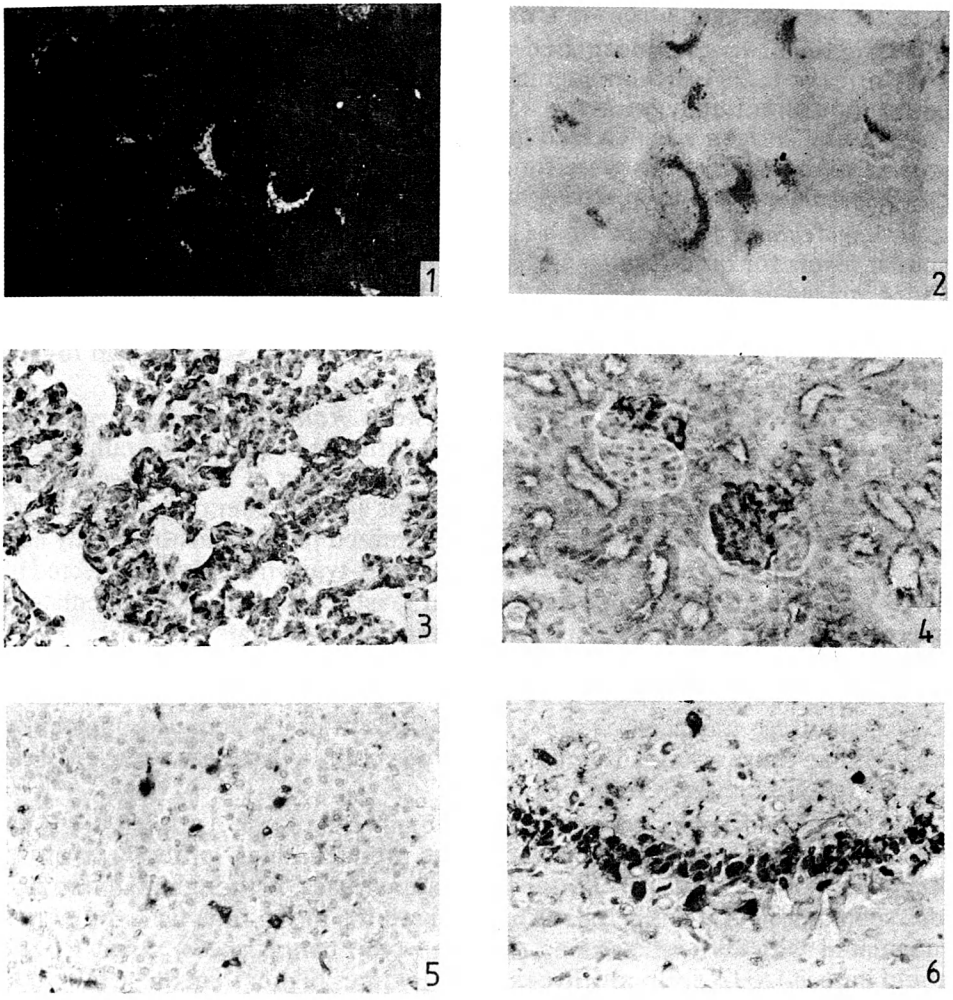
Detection of viral antigen in organs from infected animals. Internal organs from infected animal were collected and fixed with 4% paraformaldehyde for the detection of viral antigens using th immunohistological method (Zhang *et al.*, 1988). Formalin-fixed internal organs were embedde into paraffin by standard procedures. Tissue sections (4 μ m each) were deparaffinized in xylen and incubated with 0.25 % trypsin PBS at room temperature for 30 min to activate antigenicity b the method of Hondo *et al.* (1982). Viral antigen was detected by the avidin-biotin complex (ABC method (Vectastain ABC Kit, Vector Laboratories, Inc. Burlingame, CA. U.S.A.) with immun rabbit antiserum to strain SR-11.

Immune adherence haemagglutination (IAHA) test. Antibody titres of animal sera were measure by the IAHA test using essentially the same method as described previously (Sugiyama *et al* 1984).

Results

A monolayer culture of Vero E6 cells infected with strain SR-11 was fixe with acetone and examined for the presence of viral antigen by the IFA or b the ABC technique. Both techniques gave a well-defined, dot-like cytoplasmi staining with the anti SR-11 rabbit immune serum (Fig. 1). Since virtuall similar patterns and intensities of staining were obtained with the tw methods, they were considered to have similar levels of specificity and sensiti vity for the detection of viral antigen. Using formalin-fixed tissue sections a antigen, the IFA test required at least twice as long incubation period with th primary antibody to obtain the same intensity of staining as the ABC metho (data not shown). Therefore, the ABC method was applied for the detection o viral antigen in tissues of experimentally inoculated rodents. Fig. 2 show examples of the immunohistological detection of viral antigen in nerve cell alveolar cells of lung, glomerulus of kidney and gland cells of salivary glands o newborn rats experimentally infected with strain SR-11.

To examine the susceptibilities of various species of field rodents, adult *M unguiculatus, C. rufocanus, and A. argenteus* were inoculated i. p. with strai SR-11, KI-262, TB-314 or Hantaan 76–118. At ten weeks post-inoculation (p. i the production of serum antibody and the presence of viral antigen in tissue were compared with those in the adult Wistar rat and *A. agrarius*. As shown i Table 1, all the animals formed antibody to each hantavirus inoculated and vir antigen was also detected in some organs of the Wistar rat, *A. agrarius, M unguiculatus*, and *C. rufocanus* but not in organs of *A. argenteus*. Antibody titre and the distribution pattern of antigen in the organs varied depending on th combinations of animal species and virus strains. Thus, Wistar rats develope higher antibody titres to all the *Rattus*-type virus (SR-11, KI-262, and TB-31 than to *Apodemus*-type strain Hantaan 76–118. In the Wistar rats inoculate with strain SR-11 or strain TB-314, one showed viral antigen in the lung tissu In one rat from those inoculated with strain KI-262, viral antigen was found i



Figs. 1 - 6

Strain SR-11 virus antigen in Vero E6 cells (1 and 2) and in tissues of newborn rats 25 days after intraperitoneal inoculation (3 through 6) detected by immunohistological methods. Infected Vero E6 cells were fixed with acetone and were stained by the indirect immunofluorescent antibody technique (1) or the avidin-biotin complex (ABC) method (2). Deparaffinized tissue sections were treated with trypsin before the ABC staining. Antigen is shown in epithelial cells and alveolar macrophages of the lung (3), epithelial cells of glomerulus (4), Kupffer cells (5), and neurons of the hippocampus (6). Original magnification, x400 (1 and 2), x200 (3, 4, 5, and 6), reduced to 0.65 fold

the lung, heart, liver, and spleen. However, no virus-specific staining was detected in any organs from rats inoculated with strain Hantaan 76-118.

Two of the *A. agrarius* inoculated with strain Hantaan 76-118 had IAHA antibody titres of 1:128 to a homologous strain but *Rattus*-type virus (strain SR-11) could induce antibody with low (1:32, 32, 64) titres though only Hantaan 76-118 viral antigen was detected in some organs of *A. agrarius*. Thus, *Rattus norvegicus* and *A. agrarius* were found to be more highly susceptible to their original isolates than to heterologous ones.

M. unguiculatus produced high (1 024 to 4 096) IAHA antibody titres with similar levels for both *Rattus*- and *Apodemus*-type hantaviruses. *C. rufocanus* and *A. argenteus* showed similar but low IAHA antibody titres to all the strains inoculated. Viral antigens of *Rattus*-type strains could be detected in some organs of *M. unguiculatus* and *C. rufocanus* rodents whereas no Hantaan 76-118 antigen was found in any organs from these rodents.

To see the difference in virulence between *Rattus* and *Apodemus*-type hantaviruses, newborn rats were inoculated with one of the three strains of the *Rattus*-type (SR-11, KI-262, and TB-314) or one strain of the *Apodemus*-type (Hantaan 76-118) hantavirus. The distributions and persistence periods of viral antigens in various internal organs were examined immunohistologically and the results summarized in Table 2. All the *Rattus*-type viruses were detected in every organ examined and persisted for at least for 42 days post inoculation except in the case of strain SR-11 since all the inoculated rats died on day 25. In the rats inoculated with strain Hantaan 76-118, viral antigen was also found in various organs at least for 21 days p.i. However, the intensity of immunohistological staining, which may reflect to the amount of antigen, was apparently weaker than those obtained from *Rattus*-type strains. Also, only brain and lung tissues retained antigen for 42 days p. i.

IAHA antibody titres were measured up to 42 days p. i. Antibody titres on day 42 are listed in Table 2. Newborn rats produced high antibody levels to *Apodemus*-type as well as to *Rattus*-type hantaviruses. Although no difference was seen among the antigen distribution patterns in the organs from the rats inoculated with different strains of *Rattus*-type hantaviruses, strain KI-262 could induce IAHA antibody titres at least 16 times higher than those from rats (1:512) inoculated with strain TB-314.

Discussion

The use of the IAHA method and ABC technique has enabled a better understanding of the infection of rodents by hantaviruses and has demonstrated the high susceptibilities of various species of rodents to *Apodemus*- and *Rattus*-type hantaviruses. Previous studies in Europe have shown that *C*

Table 1. Antibody production and distribution of virus antigen in organs of adult rodents experimentally infected with *Rattus* or *Apodemus*-type hantaviruses

Animal Species	Virus strains	Number of animals	IAHA titres	Number of organs possessing antigen					
				Brain	Lung	Heart	Liver	Spleen	Kidney
Wistar rat	SR-11	2	4 096	0	1	0	0	0	0
	KI-262	3	2 048 - 4 096	0	1	1	1	1	0
	TB-314	2	4 096	0	1	0	0	0	0
	HTN-76-118	2	512	0	0	0	0	0	0
A. agrarius	SR-11	3	32 - 64	0	0	0	0	0	0
	HTN-76-118	2	128	0	1	0	1	0	0
M. unguiculatus	SR-11	2	2048	0	1	0	1	0	0
	KI-262	3	2 048 - 4 096	1	2	0	1	0	0
	HTN-76-118	2	1 024	0	0	0	0	0	0
C. rufocanus	SR-11	2	256	1	1	0	0	0	0
	KI-262	3	128	0	1	0	1	1	0
	HTN-76-118	2	128	0	0	0	0	0	0
A. argenteus	SR-11	2	64 - 128	0	0	0	0	0	0
	HTN-76-118	2	256	0	0	0	0	0	0

Table 2. Antibody titres and distribution of virus antigen in organs of newborn rats inoculated with *Rattus*- or *Apodemus*-type hantaviruses*

Virus strain	Days after inoculation	Tissues** examined for viral antigen							IAHA antibody titres
		Br.	Lun.	Hea.	Kid.	Spl.	Liv.	Sal.	
SR-11	21	++	+++	++	++	++	++	++	256
		++	+++	++	++	++	++	++	256
		++	+++	++	++	++	++	++	128
	25	+++	+++	++	++	++	+++	++	1024
		+++	+++	++	++	++	+++	++	512
		+++	+++	++	++	++	+++	++	512
		+++	+++	++	++	++	+++	++	N.T.
		+++	+++	++	++	++	+++	N.T.***	N.T.
		+++	+++	++	++	++	+++	N.T.	N.T.
KI-262	21	+++	+++	++	++	++	+++	++	512
		+++	+++	++	++	++	+++	++	512
		++	++	++	++	++	+++	++	512
	42	++	++	++	++	++	++	++	>4096
		++	++	++	++	++	++	++	>4096
		++	++	++	++	++	++	++	>4096
		++	++	++	++	++	++	++	>4096
TB-314	21	+++	+++	++	++	++	+++	++	256
		+++	+++	++	++	++	+++	++	256
		+++	+++	++	++	++	+++	++	256
	42	++	++	++	++	++	++	++	512
		++	++	++	++	++	++	++	512
Hantaan 76-118	21	++	++	+	++	++	+	+	1024
		++	++	+	++	++	+	+	512
		++	++	+	++	+	+	+	256
	42	++	+	-	-	-	-	-	2048
		++	+	-	-	-	-	-	2048
		+	+	-	-	-	-	-	2048

*Newborn rats were inoculated i.p. with 10^4 FFU of *Apodemus*- or *Rattus*-derived hantaviruses. Internal organs were collected 21 or 42 days p.i. Viral antigen in tissues was examined by the ABC method and scored as -: negative, +: weak positive, ++: positive, and +++ strong positive.

**Br. - brain, Lun. - lung, Kid. - kidney, Spl. - spleen, Liv. - liver, Sal. - salivary gland.

***N.T. - Not tested

glareolus is the main reservoir of a *Clethrionomys*-type hantavirus (Puumala virus), but several other species of rodents were also found to be seropositive or antigen-positive (Yanagihara and Gajdusek, 1987). The epidemiologic findings and studies reported here suggested that a variety of rodent species could be involved as reservoirs of hantaviruses in nature.

Since no viral antigen of strain SR-11 was detected in any organs of experimentally inoculated *A. agrarius* and *A. argenteus*, the infection was confirmed only from the serological evidence of low IAHA antibody titres (1:32 to 64). Nuzum *et al.* (1988) reported in their animal experiment that i.m. inoculation of $1.3 \times 10^{6.0}$ PFU of inactivated strain Hantaan 76–118 could induce only negligible antibody titres. In our experiment, animals were inoculated with only 1.0×10^{3} PFU of the virus. Therefore, the low IAHA antibody titres had to be induced by the actual infection.

Yamanouchi *et al.* (1984) reported that strain Hantaan 76–118 derived from *A. agrarius* had higher virulence to suckling mice than to suckling rats, while *Rattus*-derived strain B-1 was more virulent to suckling rats than to suckling mice on the basis of mortality, persistency of viral antigen in the tissues or gain of body weight. Our present study using suckling rats as well as adult Wistar rats and *A. agrarius* also demonstrated that *Rattus* and *A. agrarius* showed higher susceptibility to their own isolates than to strains isolated from different rodent species. This difference may reflect the passage history of these strains in *Rattus* or *Apodemus spp.* of rodents in nature.

M. unguicuratus showed high (more than 1:1 024) IAHA antibody titres to both *Rattus*- and *Apodemus*-derived strains. It has been reported that *Meriones* shows higher susceptibility to *Rattus*-type, *Apodemus*-type and *Clethrionomys*-type hantaviruses (Zhu *et al.*, 1984; Yanagihara *et al.*, 1985). Our results also confirmed that the animal was highly susceptible to *Rattus*-type strains isolated in Japan. *C. rufocanus* and *A. argenteus*, on the other hand, demonstrated the poor ability to produce antibodies to both *Rattus*- and *Apodemus*-type hantaviruses. Thus, susceptibilities of rodents may vary according to the combination of rodent species and virus strains.

All newborn rats inoculated with strain SR-11 died on day 25 p. i., while strains KI-262 and TB-314 did not cause any symptoms in newborn rats. Furthermore, strain KI-262 induced an antibody titre in rats more than 16 times higher than that of strain TB-314, although the distribution pattern and quantity of antigen in tissues were similar in the two strains. These results indicated that virulence among *Rattus*-type hantaviruses was heterogeneous.

In the present study, we applied the ABC method for the detection of viral antigen in the organs of experimentally infected animals. Since viral antigen in the formalin-fixed tissue sections was activated by brief treatment with trypsin and detected easily by application of the avidin-biotin system, this technique provided a quite accurate and safe procedure for the diagnosis of infection. In addition, the IAHA test does not employ the complicated system necessiated by the species-specific second antibody used in the IFA test. The combination

of immunohistological and serological techniques may be a useful tool for epizootiological studies of viral zoonosis among different rodent species.

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