Antiviral Research 95 (2012) 282–292

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

The Syrian hamster model of hantavirus pulmonary syndrome

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ARTICLE INFO

Article history:
Received 28 April 2012
Revised 30 May 2012
Accepted 1 June 2012
Available online 15 June 2012

Keywords:
Hantavirus pulmonary syndrome
Andes virus
Bunyavirus
Hamster
Animal model

ABSTRACT

Hantavirus pulmonary syndrome (HPS) is a relatively rare, but frequently fatal disease associated with New World hantaviruses, most commonly Sin Nombre and Andes viruses in North and South America, respectively. It is characterized by fever and the sudden, rapid onset of severe respiratory distress and cardiogenic shock, which can be fatal in up to 50% of cases. Currently there are no approved antiviral therapies or vaccines for the treatment or prevention of HPS. A major obstacle in the development of effective medical countermeasures against highly pathogenic agents like the hantaviruses is recapitulating the human disease as closely as possible in an appropriate and reliable animal model. To date, the only animal model that resembles HPS in humans is the Syrian hamster model. Following infection with Andes virus, hamsters develop HPS-like disease which faithfully mimics the human condition with respect to incubation period and pathophysiology of disease. Perhaps most importantly, the sudden and rapid onset of severe respiratory distress observed in humans also occurs in hamsters. The last several years has seen an increase in studies utilizing the Andes virus hamster model which have provided unique insight into HPS pathogenesis as well as potential therapeutic and vaccine strategies to treat and prevent HPS. The purpose of this article is to review the current understanding of HPS disease progression in Syrian hamsters and discuss the suitability of utilizing this model to evaluate potential medical countermeasures against HPS.

Contents

1. Introduction

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are a large group of viruses which are associated with two clinical syndromes in humans: hemorrhagic fever with renal syndrome (HFRS), and hantavirus pulmonary syndrome (HPS). Both HFRS and HPS are associated with vascular leakage with HFRS mainly affecting the kidneys and HPS preferentially targeting the lungs. Case fatality rates for HFRS can reach as high as 15% and for HPS can exceed 40% (Jonsson et al., 2010). Currently, the ICTV recognizes 23 unique species of hantaviruses, at least half of which are medically important to humans (ICTV, 2009). In nature, pathogenic hantaviruses are primarily maintained in specific rodent hosts which dictate the geographic regions of endemicity for individual viruses. HFRS

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0166-3542/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.antiviral.2012.06.002

occurs throughout Europe and Asia and is caused by Old World hantaviruses including Hantaan and Puumala viruses (HTNV and PUUV), while HPS occurs in the Americas and is associated with infection of New World hantaviruses, primarily Sin Nombre and Andes viruses (SNV and ANDV). Humans are predominantly exposed to hantaviruses via inhalation or ingestion of contaminated rodent excreta or secreta, although direct transmission through rodent-bites and human-to-human transmission have also occasionally been documented (Martinez et al., 2005; Padula et al., 1998; St Jeor, 2004; Torres-Perez et al., 2010).

Based on the high mortality rates and the capacity to spread via aerosolization, hantaviruses are considered Category A priority pathogens by the National Institute of Allergy and Infectious Diseases. At present there are no FDA-approved medical countermeasures to treat or prevent HPS or HFRS, therefore the development of safe and effective vaccines and antivirals to reduce the threat of hantaviruses globally is imperative. A major impedance to developing appropriate interventions has been a lack of practical animal models of disease. To date, researchers have had to rely on testing therapeutics in suckling mice or natural rodent hosts, neither of which are models for HFRS or HPS. In 2001 a lethal model for HPS was described in Syrian hamsters (Hooper et al., 2001). The purpose of this article is to review the current literature on the ANDV hamster model and discuss its appropriateness for use in evaluating medical countermeasures for HPS.

2. Animal models of HFRS and HPS

The development of animal models of HFRS and HPS has been an intense area of research since their respective discoveries (Tables 1 and 2). Currently no animal model exists which reflects the disease manifestations of severe HFRS. Non-human primates often provide good models for studying hemorrhagic fever viruses, and therefore have been assessed as potential models for HFRS, though with limited success (Gowen and Holbrook, 2008; Yanagihara et al., 1988). The lone exception is Cynomolgus macaques which develop a mild disease (i.e., lethargy, proteinuria, and microhaematuria) suggestive of acute nephropathy following inoculation with wild-type PUUV (Klingstrom et al., 2002; Sironen et al., 2008). Several small laboratory animals have also been experimentally infected with numerous Old World

Table 1
Summary of animal models for Old World hantaviruses.

	Virus	Brief description
Natural hosts		
Striped field mouse	Hantaan	Subclinical, persistent infection with transient viremia between days 7 and 12 p.i. and infectious virus and/or antigen detected in organs between days 10 and 360 p.i. Horizontal transmission, primarily associated with infectious virus in urine, was observed for 360 days p.i.[a]
Bank Vole	Puumala	Subclinical, persistent infection with transient viremia between days 10 and 14 p.i. and infectious virus/antigen detected in organs between days 14 and 270 p.i. Horizontal transmission observed between days 14 and 42 p.i. [b]
Norway (brown) rat	Seoul	Subclinical, most likely persistent, infection with viral RNA detected in organs for 40 days p.i.[c,d]
Laboratory animals		
Juvenile rat	Hantaan	Subclinical infection with transient viremia between days 10 and 13 p.i. and persistent detection of virus/antigen in organs. Horizontal transmission was observed for up to 63 days p.i.[e]
Suckling mouse	Hantaan	Acute, disseminated infection with neurological signs of disease and lethality rates between 88 and 100% at 13–14 days p.i.[f,g,h]
Suckling mouse	Seoul	Disseminated infection with 100% lethality between days 18–24 p.i. [i]
Suckling mouse	Dobrava	Disseminated infection associated with increased levels of nitric oxide that is fatal in up to 88% of mice between days 18–26 p.i.[j]
Juvenile mouse	Hantaan	Acute, disseminated infection with primarily pulmonary disease manifestations which are fatal in approximately 25% of mice[k]
Adult mouse	Hantaan	Acute, disseminated infection resulting in lethal encephalitis in 100% of infected mice[l]
Mongolian Gerbil	Seoul	Subclinical, disseminated infection of unknown duration[m]
	Hantaan	Subclinical, disseminated infection of unknown duration[m]
Syrian hamster	Puumala	Subclinical, disseminated infection with viral antigen detected for at least 56 days p.i.[n,o,p,q]
Syrian hamster	Hantaan	Subclinical, disseminated infection with viral antigen/RNA detected for >30 days p.i.[o,p,q]
Syrian hamster	Seoul	Subclinical, disseminated infection with viral antigen/RNA detected for >30 days p.i.[o,q,r]
Syrian hamster	Dobrava	Subclinical, disseminated infection with viral antigen/RNA detected for >30 days p.i.[o]
Cynomolgus macaque	Puumala	Self-limiting infection resulting in low grade fever, serum biochemical changes, mild proteinuria and microhematuria as well as transient viremia and renal inflammatory infiltrates similar to a mild form of HFRS known as Nephropathia epidemica[s,t]

[a] Lee et al. (1981).
[b] Yanagihara et al. (1985).
[c] Klein et al. (2001).
[d] Easterbrook et al. (2007).
[e] Lee et al. (1986).
[f] Kurata et al. (1983).
[g] McKee et al. (1985).
[h] Ebihara et al. (2000).
[i] Yoo et al. (1993).
[j] Klingstrom et al. (2006).
[k] Seto et al. (2012).
[l] Wichmann et al. (2002).
[m] Xu et al. (1992).
[n] Sanada et al. (2011).
[o] Hooper et al. (2001).
[p] Schmaljohn et al. (1990).
[q] Kamrud et al. (1999).
[r] Hooper et al. (1999).
[s] Klingstrom et al. (2002).
[t] Sironen et al. (2008).