Host range of zoonotic hepatitis E viruses

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Abstract

Based on a proposed classification, the family Hepuviridae is divided into two genera: Orthohepevirus and Piscihepevirus. The genus Orthohepevirus, divided into seven species, contains the fast majority of HEV strains identified so far: Orthohepevirus A, B, C and D. Within Orthohepevirus A genotype HEV-1 and HEV-2 infect only humans; for genotype HEV-3 and HEV-4 the predominant host species are pig, wild boar, rabbit, deer, mongoose and human. Genotype HEV-5 and HEV-6 infect wild boar and genotype 7 and 8 camel. Orthohepevirus B infect chicken, Orthohepevirus C infect rat and ferrets and Orthohepevirus D infect bat. In this review article epidemiological aspects of HEV due to crossing species barriers based on infectivity studies are assessed.

Background

Hepatitis E virus (HEV) is a small (approximately 27-34 nm in diameter), non-enveloped virus with a positive sense, single-stranded RNA genome. HEV is, however, a quasi-enveloped virus with a lipid layer when collected from cell culture or from blood. In faeces, the lipid layer is removed by the bile [1,2].

HEV is a major cause of acute clinical hepatitis among humans throughout the world. Acute hepatitis E in humans in developing countries is caused by the HEV genotypes 1 (HEV-1; occurrence mainly in Asia) and 2 (HEV-2; occurrence mainly in Africa and Mexico) with a host range restricted to humans [3]. These genotypes are transmitted primarily by the faecal/oral route (primarily by contaminated water). The human associated as well as zoonotic genotypes of HEV are grouped into the species Orthohepevirus A, which includes a total of 8 genotypes, originating mostly from pig, wild boar, rabbit, and camel species. Orthohepevirus B consists of avian hepatitis E virus species, whereas Orthohepevirus C viruses were isolated from rodents (rats, voles, and shrew) and carnivores (such as ferrets, mink and foxes). HEV from bats are classed in the species Orthohepevirus D and fish-related HEV belongs to genus Piscihepevirus [4] (compare Table 1).

Interspecies Infection of HEV

Autochthonous HEV infections in industrialized countries have been identified over the last years triggered primarily by food borne infections caused by HEV genotypes 3 and 4. Pigs and wild boars have been recognized as main reservoir for these genotypes. Besides pigs, wild boars, rabbits, deer and mongoose, some further animal species are reported to be infected by HEV, frequently by further HEV genotypes.

Transmission of HEV from animals to humans are reported frequently, primarily via swine and wild boar [11-14], especially by undercooked pork [15-21]. As, besides suidae, further animals, such as rabbits, cows, bison, deer, hare, goat, sheep and equines as well as camel [4,22-29] are infected by Orthohepevirus A, the interspecies transmission of HEV should be studied carefully in order to define risk mitigating strategies to avoid, or at least minimize, the transmission of HEV to humans from other sources than pork. Prevalence and partly incidence of HEV in naturally infected animals were also reported: e.g., for rabbits [30], deer [28,31-33], mink and ferrets [34-35], rodents (rats, mice, voles, squirrel) [36-38], wild and domestic carnivores (raccoons, raccoon dogs, dogs and cats) [36] and zoo animals including non-human primates [40-42].
In contrast to naturally occurring interspecies transmissions of HEV, experimental transmission studies are performed under defined conditions as standardized test animals, inoculum and inoculation route, and follow-up for infection markers. Such experimental infectivity studies provide information of the infectious dose of the experimental host and, if the experimental animal is suitable regarding sensitivity to HEV infection and clinical markers, a small animal model as an alternative to pigs (and non-human primates) may be an appropriate basis for vaccine development and antiviral drug testing.

Therefore, studies were performed to infect laboratory animals as rabbits, mice and rats with a human pathogenic HEV variant, commonly from infected pigs or wild boars. A study covering the above-mentioned parameters was performed employing a liver suspension from a wild boar with a known HEV RNA concentration and for some further studies HEV from bile and faeces with a known HEV RNA concentration [43]. This material was inoculated in rabbits, Wistar rats and mice demonstrating a very effective transmission to European rabbits, limited transmission to rats and no transmission to mice (diverse mouse strains) as shown in Table 2.

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Inoculation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit †</td>
<td>Liver homogenate: 7.3 x 10^6 copies of HEV gt 3 (i.v.)</td>
<td>Number of animals inoculated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>immunized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive control</td>
<td>PBS</td>
<td>2</td>
</tr>
<tr>
<td>negative control</td>
<td>PBS</td>
<td>2</td>
</tr>
<tr>
<td>Wistar rats</td>
<td>Liver homogenate: 1.8 x 10^6 copies of HEV gt 3 (i.v.)</td>
<td>8 ‡</td>
</tr>
<tr>
<td>naïve</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification based on published data [4-10].

**Table 1:** Classification of Hepeviruses.
The data reported by Schlosser et al. [43] demonstrated that rabbits are sensitive for HEV-3 isolated from a wild boar: The virus was detected in faeces of naïve rabbit after being infected and seroconverted; however, HEV RNA could not be detected in serum samples. In one of two rabbits HEV RNA was detected also in the liver and gall bladder at necropsy (the naïve rabbits were the positive control animals (non-vaccinated animals) in this study employing two different vaccines, either rat HEV capsid protein or HEV-3 capsid protein. Further studies with a larger number of animals have to confirm the tendency that the rat HEV capsid containing vaccine does not protect rabbits as effectively as HEV-3 capsid protein when challenged with infectious HEV-3. In Wistar rats no clinical symptoms were observed and only in a small number of inoculated animals the markers of HEV infection (HEV RNA in faeces or seroconversion) could be detected. Immunosuppression by dexamethasone had no impact on improved susceptibility of rats to a HEV infection. Wild-type and immunodeficient (interferon-alpha/beta receptor-, CD4- and CD8- negative and BALB/c nude mice) mice were resistant to HEV infection. These data are in line with published data demonstrating a high sensitivity of rabbits to HEV infection. However, the rabbits showed minimal clinical symptoms. For rats, divergent results are published [44-46] and mice are considered to be resistant to HEV infection [47]; however, for Balb/c nude mice different results were reported [48]. Table 3 compiles results from experimental infectivity studies using Orthohepevirus A genotype 3 and 4.

Table 2: Sensitivity of animal models for hepatitis E virus genotype 3.

<table>
<thead>
<tr>
<th>Immunosuppressive treatment</th>
<th>Liver homogenate: 1.8 x 10⁶ copies of HEV gt 3 (concurrently i.v. and orally)</th>
<th>PBS</th>
<th>8</th>
<th>No HEV infection markers and no clinical symptoms detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative control</td>
<td>PBS</td>
<td>12*</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td>Mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild-type C57BL/6</td>
<td>Liver homogenate: 1.8 x 10⁶ copies of HEV gt 3 (concurrently i.v. and orally)</td>
<td>2</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td>CD4⁻ mice</td>
<td>Faeces suspension: 2.8 x 10⁵ copies of HEV gt 3 (concurrently i.v. and orally)</td>
<td>2</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td>CD8⁻ mice</td>
<td>PBS</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFNAR⁻ mice</td>
<td>Liver homogenate: 1.8 x 10⁶ copies of HEV gt 3 (orally)</td>
<td>3</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td></td>
<td>Liver homogenate: 1.8 x 10⁶ copies of HEV gt 3 (i.v.)</td>
<td>3</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BALB/c nude (nu/nu)</td>
<td>Liver homogenate: 5.8 x 10⁵ copies of HEV gt 3 (i.v.)</td>
<td>4²</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td></td>
<td>Faeces suspension: 8.8 x 10⁵ copies of HEV gt 3 (i.v.)</td>
<td>4²</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td></td>
<td>bile: 2.3 x 10⁴ copies of HEV gt 3 (i.v.)</td>
<td>4²</td>
<td></td>
<td>No HEV infection markers and no clinical symptoms detected</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Results from 2 independent experiments compiled; †vaccinated with rat HEV capsid protein; ‡vaccinated with HEV gt 3 capsid protein; †pretreatment with dexamethasone (0.15 mg/kg Voren Suspension®, Boehringer Ingelheim; subcutaneously); ‡plus one additional rat co-habited (contact exposure control); 8 naïve animals and 4 immunosuppressed animals; †1 control animal per group.
Conclusion

The risk of zoonotic HEV infection of humans is virtually restricted to *Orthohepevirus A* genotypes 3 and 4 and food-borne transmission of HEV, primarily due to consumption of undercooked meat, appears to be a major route [57,58]. Primarily immunocompromised patients may also be infected by the rat HEV (*Orthohepevirus C*, HEV–C1) [59-61] but also by camel HEV (*Orthohepevirus A*, HEV-7) [62]. Epidemiological surveillance in a wide range of animals such as rabbits, hare, deer, wild boar, pigs and rodents should be performed to assess the risk of HEV transmission to humans. These studies should also include animal manure applications and runoff contaminating surface water as well as irrigation causing concomitant contamination of products such as vegetables, berries and shellfish [57]. Risk mitigation strategies to avoid or minimize the infection of humans is improved hygiene, avoiding rodent droppings and preparing food properly (heating) or inactivate HEV contamination otherwise.

Cross-species transmission studies can assess the increased risk of HEV contamination in the environment and define the most appropriate small animal model for vaccine and antiviral drug development.

References


47. Li TC, Suzuki Y, Ami Y, Tsunemitsu H, Miyamura T, Takeda N. Mice are not susceptible to hepatitis E virus infection. Journal of Veterinary Medical Science. 2008;70(12):1359-62.


