J. Comp. Path. 2011, Vol. 144, 25–40

ELSEVIER
www.elsevier.com/locate/jcpa

REVIEW

Experimental Encephalomyocarditis Virus Infection in Small Laboratory Rodents

K. Doi[*,†]

** Nippon Institute for Biological Science, 9-2221-1, Shin-Machi, Ome, Tokyo 198-0024 and † Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1, Yayoi, Bunkyo, Tokyo 113-8657, Japan*

Summary

Encephalomyocarditis virus (EMCV) is a cardiovirus that belongs to the family Picornaviridae. EMCV is an important cause of acute myocarditis in piglets and of fetal death or abortion in pregnant sows. Small rodents, especially rats, have been suspected to be reservoir hosts or carriers. This virus also induces type 1 diabetes mellitus, encephalomyelitis, myocarditis, orchitis and/or sialodacryoadenitis in small laboratory rodents. This paper reviews the pathology and pathogenesis of experimental infection with EMCV in small laboratory rodents.

Keywords: encephalomyocarditis virus; pathogenesis; pathology; small laboratory rodents

Contents

Introduction

Encephalomyocarditis virus (EMCV) is a cardiovirus that belongs to the family Picornaviridae (Matthews, 1979). The virus was first isolated from non-human primates (Helwig and Schmidt, 1945) and then from pigs (Murane *et al*., 1960). EMCV is an important cause of lethal acute myocarditis in piglets and of fetal death or abortion in pregnant sows (Acland, 1989; Kim *et al*., 1989; Paschaleri-Papadopoulou *et al*., 1990; Koenen *et al*., 1999). Small rodents, especially rats, have been suspected to be reservoir hosts or carriers (Hill *et al*., 1985; Acland and Littlejohns, 1986; Zimmerman, 1994). EMCV has a wide host range among domestic and wild animals (Simpson *et al*., 1977; Hubbard *et al*., 1992; Grobler *et al*., 1995) and has a worldwide distribution (Billinis *et al*., 1999; King *et al*., 2000).

EMCV was first classified into two main variants based on its organ tropism in mice (Craighead, 1966a). The first is neurotropic (designated E) and produces a rapidly fatal infection and the second is cardiotropic (designated M) and usually causes non-fatal illness with a few signs of central nervous system (CNS) involvement. The M variant was also shown to induce diabetes mellitus in particular strains

Correspondence to: K. Doi (e-mail: kunio-doi@nibs.or.jp).

0021-9975/$ - see front matter
doi:10.1016/j.jcpa.2010.05.001

of mice (Craighead and McLean, 1968). Since Yoon *et al.* (1980) established the highly diabetogenic variant (designated D) and non-diabetogenic variant (designated B) by repeated plaque-purification of the M variant, many studies of diabetes mellitus have been done with mice infected with the D variant of EMCV (EMCV-D).

The dominant target organs of EMCV are the CNS, heart and pancreas (Doi *et al.*, 1988; Matsuzaki *et al.*, 1989b). In addition, EMCV induces sialodacryoadenitis in mice (Craighead, 1966b) and orchitis in Syrian hamsters (Hirasawa *et al.*, 1991) and mice (Shigesato *et al.*, 1994).

This paper reviews the pathology and pathogenesis of experimental infection with EMCV in small laboratory rodents.

Susceptibility to EMCV

Five species of small laboratory rodents are reported to be susceptible to EMCV infection. Among them, mice, Mongolian gerbils and Syrian hamsters are highly susceptible (Matsuzaki *et al.*, 1989b) and guinea pigs are slightly susceptible (Petruccelli *et al.*, 1991).

Rats are suspected to be reservoir hosts or carriers of EMCV. Kilham *et al.* (1955) reported that albino rats infected by the intracerebral (IC) route with three different strains of EMCV-M isolated from primates developed degenerative changes and inflammatory cell infiltration in the brain, spinal cord and muscles. In contrast, Findlay and Howard (1951) reported inapparent infection in rats infected experimentally with EMCV. Matsuzaki *et al.* (1989b) reported that intraperitoneal (IP) inoculation of adult rats with EMCV-D failed to produce clinical disease, or pathological changes, and that no viral replication could be demonstrated in any of the organs examined (brain, heart, lungs, liver, spleen, pancreas and kidney). Subsequently, Ikegami *et al.* (1997) reported that when laboratory rats were inoculated IP or IC with EMCV-D when younger than 14 days of age, lesions were restricted to the brain, although viral replication was detected in the brain, heart and pancreas. These authors suggested that an age-related decrease in the susceptibility of rat brain to EMCV infection may reflect an age-related change in the susceptibility of neurons themselves, as well as in the maturation of the immune system. Su *et al.* (1999, 2003) suggested from the results of studies of rat brain slice cultures and rat primary neuron cultures that an age-related decrease in the susceptibility of rat brain to EMCV-D was less related to the maturation of the immune system than to that of the neuron.

Spyrou *et al.* (2004) reported that two European strains of EMCV (Greek strain 424/90 and Belgian strain 279/95) isolated from myocardial lesions of pigs were readily transmitted by contact among rats under experimental conditions. Psalla *et al.* (2006a) reported that experimental infection of rats with these two European strains of EMCV was inapparent, but that virus was isolated from faeces and several organs and that EMCV antigen was detected in the cytoplasm of cardiac muscle cells, pancreatic acinar cells and hepatic endothelial cells, and in macrophages of lymphoid organs. These authors proposed that the presence of EMCV in cardiac muscle cells without lesions supported the hypothesis that the rat is a natural reservoir host species of EMCV and that the persistence of virus in the macrophages of the thymus may represent a mechanism of perpetuation and reactivation, under immunosuppressive conditions, of the infection.

Doi *et al.* (1993) examined the transmissibility of EMCV-D in mice and reported that mice inoculated with EMCV-D by the intranasal (IN), oral or IP routes showed marked viraemia and prominent pancreatic lesions at 2 days post inoculation (dpi), and excreted virus in faeces from 2 to 8 dpi. However, being different from the rat (Spyrou *et al.*, 2004), only a small population of control mice housed with EMCV-D-inoculated mice for 10 days developed viraemia and pancreatic lesions.

Nakayama *et al.* (2004a, b) examined the susceptibility of pregnant mice to EMCV-D infection. In pregnant BALB/c mice inoculated by the IP route with EMCV-D at 11, 13 or 15 days of gestation (DG), the virus replicated predominantly in trophoblast cells and giant cells in the spongiotrophoblast layer of the placenta in all inoculation groups and also in fetal myocardium and liver in mice inoculated at 11 DG. The virus titre was elevated earlier and was higher in the placenta than in the fetus. These authors suggested that placental damage as well as the direct effect of virus on fetuses might be a cause of fetal death. In this connection, Abzug (1994) examined the mode of infection of Theiler's murine encephalomyelitis virus (TMEV), a picornavirus, in pregnant mice, and reported that TMEV infected the majority of the placenta and fetus following early gestation (6–7 DG) inoculation, and most placentas except for the labyrinth layer and almost no fetuses after middle (9–10 DG) or late gestation (12–13 DG) inoculation, respectively. In addition, Abzug (1993) showed that giant cells were the earliest predominant targets of TMEV infection following early gestational inoculation, and that giant cells appeared to be an integral part of the pathogenesis of gestational murine virus infection.

Encephalomyelitis

The susceptibility of the rat brain to EMCV infection is discussed above. Syrian hamsters showed viral