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Oral vaccination of dogs with recombinant rabies virus vaccines

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Abstract

Oral rabies virus (RV) vaccines are used to immunize a diversity of mammalian carnivores, but no single biological is effective for all major species. Recently, advances in reverse genetics have allowed the design of recombinant RV for consideration as new vaccines. The objective of this experiment was to examine the safety, immunogenicity and efficacy of recombinant RV vaccines administered to captive dogs by the oral route, compared to a commercial vaccinia-rabies glycoprotein (V-RG) recombinant virus vaccine. Animals consisted of naive purpose-bred beagles of both sexes, and were 6 months of age or older. Dogs were randomly assigned to one of six groups, and received either diluent or vaccine (PBS; V-RG; RV SN10-333; RV SPBN-Cyto c; RV SPBNGA; RV SPBNGAGA), with at least six animals per group. On day 0, 1 ml of each vaccine (or PBS) was administered to the oral cavity of each dog, at an approximate concentration of 10^8 to 10^9 $TCID_{50}$. After vaccination, dogs were observed daily and bled weekly, for 5 weeks, prior to RV challenge. No signs of illness related to vaccination were detected during the observation period. Excluding the controls, RV neutralizing antibodies were detected in the majority of animals within 1–2 weeks of primary vaccination. Thereafter, all dogs were inoculated in the masseter muscle with a street virus of canine origin. All control animals developed rabies, but no vaccinates succumbed, with the exception of a single dog in the V-RG group. Review of these preliminary data demonstrates the non-inferiority of recombinant RV products, as concerns both safety and efficacy, and supports the suggestion that these vaccines may hold promise for future development as oral immunogens for important carnivore species, such as dogs.
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Keywords: Rabies; Rabies virus; Rabies vaccination; Oral vaccination; Canine vaccination

1. Introduction

During the last 30 years, great progress has been made in the development of oral vaccines against rabies (Wandeler, 1991). The primary focus of these efforts has been towards application in control against wildlife rabies in Europe and North America, by the strategic distribution of vaccine-laden baits (Stohr and Meslin, 1996; MacInnes et al., 2001). For these activities, self-replicating virus vaccines are needed to contact the oral mucosa of a diversity of mammalian carnivores because large amounts of inactivated antigens are required for minimal protection (Rupprecht et al., 1992). Current vaccine production methods are cost-prohibitive to produce these products, which may require milligram concentrations of purified antigens, such as the rabies virus (RV) glycoprotein (G), at both high density and in a similar orientation as intact viral particles (Dietzschold and Schnell, 2002).

Depending upon the host species of interest, tens of millions of vaccine doses may be distributed annually in national campaigns by hand or via aircraft, at bait densities from 15 to 75 baits or more per km^2 (Aubert et al., 1994; Slate et al., 2002). Considering the opportunity for potential contact between non-target species, such as humans, domestic animals, endangered species, etc., and RV vaccines distributed

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in the environment, safety concerns have been paramount in the conceptual design of these biologicals (Wandeler, 2000). Historically, residual neurovirulence was assessed by the experimental inoculation of RV vaccine candidates into the brain of laboratory animals (Koprowski, 1996). Moreover, the first generation of RV vaccines intended for oral vaccination retained the opportunity to cause occasional disease, by the parenteral or oral routes (Winkler et al., 1976; Wandeler, 1988; Bingham et al., 1992; Vos et al., 1999). To minimize these drawbacks, additional research efforts concentrated upon other more attenuated RV and recombinant vaccines that would retain potency, but not induce rabies by the oral, peripheral or intracerebral routes in immune competent adult animals (Dietzschold et al., 1983; Wiktor et al., 1984; Preve et al., 1990; Schumacher et al., 1993; Xiang et al., 2003).

Over the past decade, significant insights have appeared into the function and mechanisms of action of individual viral genes in pathogenesis and immunity, after direct use of RV as an expression vector system (Conzelmann and Schnell, 1994; Schnell et al., 1994; Morimoto et al., 2001). To further test the applied feasibility of the reverse genetics approach in the development of new vaccines, the objective of this current work was to investigate both the safety and effectiveness of a variety of novel recombinant RVs (Dietzschold and Schnell, 2002). Preliminary research with these viruses in laboratory rodents has demonstrated comparable safety and effectiveness to other RV vaccines (Morimoto et al., 2001; Pulmanausahakul et al., 2001; Faber et al., 2002). However, no comparative data are available for proof of concept concerning effects after oral vaccination of more relevant species, such as dogs or other carnivores.

Dogs remain the primary reservoir for rabies in developing countries (Meslin et al., 1994). In addition, in developed countries that have eliminated canine rabies, dogs are an important non-target species because of their opportunity to consume vaccine-laden baits and subsequently expose people, as an obvious consequence of the close human–animal bond (Rupprecht et al., 2001). Specifically, in this study, we investigate the occurrence of adverse events, the induction of neutralizing antibody and the protective efficacy of recombinant RVs in captive beagles, compared to a commercial recombinant poxvirus vaccine used for rabies prevention and control in Europe and North America.

2. Materials and method

2.1. Animals

Forty-two purpose-bred beagles (not vaccinated against rabies), of mixed age and sex, were obtained from commercial sources. All dogs were individually housed, and identified by a unique tattoo. Dogs were quarantined a minimum of 30 days for general health observations, prior to initiation of this study. All animal care and experimental procedures were performed under an approved protocol in compliance with the Centers for Disease Control and Prevention Institutional Animal Care and Use Guidelines.

2.2. Vaccination

Dogs were assigned randomly to one of six groups. Of the 42 dogs in the study, 12 were assigned as controls. Of the remaining animals, six each were assigned to one of five vaccination groups, A–E (Table 1). Briefly, group A received a commercial vaccinia rabies-glycoprotein (V-RG) recombinant virus vaccine (Wiktor et al., 1984). Group B received RV SN10-333, generated from RV SN10, a non-pathogenic derivative of the RV vaccine strain SAD B19, as described (Schnell et al., 1994; Morimoto et al., 2001). The RV SN10-333, which contained an intact psi (Ψ) non-translated sequence, was constructed by site-directed mutagenesis, with the replacement of an arginine to a glutamine mutation (AGA → GAG) at RV G position 333 (Morimoto et al., 2001). Group C received RV SPBN-Cyto c, derived from RV SPBN (having a deleted Ψ), with the human cytochrome c gene introduced between the RV G and L genes, as described (Pulmanausahakul et al., 2001). Group D received RV SPBNGA, derived from RV SPBN, having a RV G with an arginine to a glutamine exchange (AGA → GAG) at position 333 (termed GA), as described (Faber et al., 2002). Group E received RV SPBNGA-GA, which contains two GA genes in tandem (Faber et al., 2002). Vaccines were stored at −80 °C, prior to use. On day 0, control dogs received per os 1.0 ml of sterile 0.01 M phosphate buffered saline (PBS) pH 7.5, whereas dogs in the vaccination groups received 1 ml of thawed vaccine per os, administered via needle-less syringe.

2.3. Rabies virus neutralizing antibody determination

After vaccination, dogs were bled weekly. The blood was allowed to clot and the serum was separated by low speed centrifugation. Serum samples were tested for evidence of RV neutralizing antibodies (RVNA), determined by the rapid fluorescent focus inhibition test (RFFIT), as described (Smith et al., 1996). A minimum positive RVNA result was defined as the neutralization of approximately 50 focus-forming $doses_{50}$ per 0.1 ml of RV (strain CVS-11, produced on murine neuroblastoma cells) at an initial serum dilution of 1:5 or higher. Once antibodies were detected, a four-fold rise in

Table 1
Rabies vaccines used in this study

Group	Vaccine	Concentration[a]	Number of dogs
A	V-RG	$1 \times 10^{8.9}$	6
B	SN10-333	$1 \times 10^{8.6}$	6
C	SPBN-Cyto c	$1 \times 10^{8.4}$	6
D	SPBNGA	$1 \times 10^{8.2}$	6
E	SPBNGA-GA	$1 \times 10^{8.6}$	6
Controls	None	None	12

[a] Tissue culture infectious $doses_{50}$ per ml.

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