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Intravenous inoculation of silver-haired bat rabies virus, but not of a canine strain, elicits lethal encephalophathy in mice by fast brain invasion via neurosecretory hypothalamic fibers

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Neurotropic rabies virus (RV) is transmitted by saliva, most often through the bite of an infected canine, which leads to an always fatal encephalopathy by invasion of the CNS through nerve fibers innervating the affected muscle. In contrast, transfer by bat bites or scratches, the most frequent cause of human rabies in the USA, introduces RV in rather low amounts intradermally. In both scenarios, RV has also access – in addition to nerves – to lymph and blood. However, the effects of this vascularly distributed share of the viral inoculum have never been examined. Our study aimed to elucidate if RV circulating in the vascular system is able to directly invade the brain and if this postulated route is strain dependent. Furthermore, we wanted to identify putative entry ports by which hematogenously spread RV preferentially gains access to the brain.

Mice were infected intravenously (i.v.) with the canine strain DOG4 or the silver-haired bat-derived recombinant RV rSB and compared to mice inoculated intramuscularly (i.m.) with these two strains. Although both strains led to paralysis and death after i.m. inoculation, only rSB remained lethal after i.v. injection. rSB i.v. inoculation caused symptoms resembling those following intracerebral inoculation and not paralysis as seen after i.m inoculation. Furthermore, i.v. inoculated rSB infected the forebrain independently of viral presence in spinal cord or brainstem, with a preferred early affection of those hypothalamic nuclei connected to neurosecretory fibers of the neurohypophysis and median eminence. In contrast, DOG4 i.v. infected mice survived at least up to eight months and remained asymptomatic except for transient weight loss in the second week after inoculation.

Our study shows for the first time an astonishing strain dependent outcome of a strictly hematogenous RV infection route. Though the underlying mechanisms of this discrepancy are unclear and still under investigation, we propose that the broader cellular tropism of silver-haired bat rabies virus, compared to the narrow neurotropism of DOG4, enables the evasion of occurring immune responses by fast retrograde invasion of the CNS from the vascular system via neurosecretory fibers of the hypothalamus-pituitary output system.