A Kiss of a Prion: New Implications for Oral Transmissibility

Bianca Da Costa Dias and Stefan F. T. Weiss

School of Molecular and Cell Biology, University of the Witwatersrand, Johannesburg, South Africa.

(See the report by Maddison et al, on pages 1672–1676.)

There is no doubt about it: prions—infectious particles composed mainly if not entirely of misfolded protein (scrapie-type prion protein [PrPsc]), which are the causative agents of transmissible spongiform encephalopathies (TSE) such as scrapie, variant Creutzfeldt-Jakob Disease (vCJD), and bovine spongiform encephalopathy (BSE)—are transmissible [1–3]. These agents may be introduced via intracerebral, intravenous, intraperitoneal, or intraventricular infection, and recent research indicates that oral transmission may also occur. The last mode of transmission is of particular interest because it indicates that the consumption of meat and other products derived from animals experiencing prion disorders may pose a real risk to humans. Recent reports suggest that, in addition to meat, bodily fluids such as blood, saliva, feces, and milk may well be risk factors for possible transmission of TSEs to humans. Successful oral transmission among different animal species (interspecies) has been demonstrated. However, species specificity, the “species barrier,” and the mode of transmission must be taken into account and may explain why cattle, sheep, goats, mink, and mice are successfully orally infected with bovine scrapie-type prion protein (bovPrPsc), whereas the ingestion of bovPrPsc by pigs, poultry, and cervids such as elk and deer fails to cause disease [1]. Humans are also thought to be susceptible to oral infection by bovPrPsc by means of contaminated bovine products (eg, meat pies), and this is believed to be the manner in which the zoonotic disease vCJD originated [4].

But where do prions hide in the body? They replicate primarily in the central nervous system, particularly in the brain and the lymphoreticular system [4], as well as in other tissues such as muscle [5]. Furthermore, the presence of these infectious agents in bodily excretions and secretions is a major cause for concern, because it enhances the risks of transmission. Prions have been identified in feces of asymptomatic deer [6] and in the blood, saliva, and urine of deer with chronic wasting disease [7, 8]. PrPsc has also been detected in the salivary glands of scrapie-affected sheep [9].

The report by Maddison et al [10] in this issue of the Journal describes for the first time, to our knowledge, the secretion of prions into the oral cavity of sheep. The authors used silicon dioxide (SiO2) to concentrate prions, in conjunction with serial protein misfolding cyclic amplification, or sPMCA, a method to amplify and detect prions in body fluids such as blood from scrapie-infected hamsters [13]; the last example succeeded even in the presymptomatic phase [14]. Maddison et al [10] used this technique to demonstrate that prions are present in buccal swab samples obtained from sheep with preclinical scrapie infections.

However, one must pose the following question: how do ingested infectious PrPsc prions reach the mucus and saliva? After oral ingestion, prions are thought to be taken up first by Peyer patches before they disseminate through gut-associated lymphoid tissues, the lymphoreticular system, the vagus nerve, and the enteric nervous system, after which they enter the central nervous system [15]. Internalization of prions in the intestine is thought to be performed by M-(microfold) cells [16] and by enterocytes, which internalize bovPrPsc dependent on the prion receptor LRP/LR [17]. Maddison et al [10] suggest, according to their data, that prions are able to spread from the small intestine to the oral salivary glands and epithelia within a period of 9 months. This route explains the occurrence of prions in saliva and the shedding of prions into the oral cavity.

The transmissibility of scrapie among sheep (intraspecies) is well recognized. It must be emphasized that horizontal transfer (from one individual to another) of scrapie is the main route of infection, because vertical transmission of disease from mother to offspring via milk or placental tissue occurs infrequently. Thus, in view of the report by Maddison et al, the oral transmissibility of prions among sheep...
may serve as a major route for horizontal scrapie transfer. This occurrence is plausible because sheep often lick each other. Maddison et al [10] indicate that, because of the similarities in prion tissue distribution, their implications for the oral transmission of ovine scrapie might be true for other prion diseases, such as chronic wasting disease and human vCJD. If this is true for humans, a kiss of a prion may sometimes have lethal consequences.

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References