Penetration of Infectious Prion Protein in the Intestine During the Lactation Period

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Abstract: Prion diseases are fatal neurodegenerative zoonotic foodborne disorders, which are caused by an abnormal isoform of prion protein (PrP^{Sc}) derived from the cellular isoform of prion protein (PrP^{C}). According to epidemiological surveillance and *in vivo* experiments, exposure to the PrP^{Sc} during the weaning period is fraught with risk, suggesting that, during development, the intestinal defenses and the immune system are involved in PrP^{Sc} infection susceptibility. Although it remains unclear how PrP^{Sc} passes through the natural biological barriers during its invasion of intestinal cells, the 37 kDa/67 kDa laminin receptor is suspected to be one of the receptors involved in PrP^{Sc}-incorporation. In addition, we have recently shown that the neonatal Fc receptor (nFcR), which contributes to the uptake of maternal antibodies into the intestine, may play an important role in PrP^{Sc} incorporation. In this review, recent studies on PrP^{Sc} uptake and models of PrP^{Sc} incorporation into the intestine *via* the laminin and Fc receptors are described.

Keyword: Prion disease, PrP^{Sc} uptake, Fc receptor.

INTRODUCTION

Prion diseases or transmissible spongiform encephalopathies are fatal neurodegenerative diseases and include bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and Creutzfeldt-Jakob disease (CJD) in humans [1, 2]. The appearance of variant CJD (vCJD) has raised public health concerns that BSE might be transmissible to humans across species through dietary exposure to BSE-contaminated foodstuffs [3]. In addition, human cases of vCJD are still emerging in the UK, many years after the emergence of BSE, because of the extremely long incubation period of prion diseases [2].

The pathogenic event of prion disease consists in the accumulation in the neural and lymphoid tissues of the abnormal form of prion protein (PrP^{Sc}) [6], which is structurally distinct from the normal or cellular prion protein (PrP^{C}) [4, 5]. Interestingly, the main structure of PrP^{C} is an alpha helix, whereas that of PrP^{Sc} is a beta-sheet. Notably, this conformational change affects the physic-chemical properties of PrP^{Sc}, characterized by detergent-insolublity, high propensity to aggregated, and resistance to protease digestion [1, 2, 3]. Although the site of PrP^{Sc}-invasion is disputed, natural infection can occur orally, especially through the gastrointestinal tract [7, 8]. In this review, recent studies on PrP^{Sc} uptake and a model of PrP^{Sc} incorporation into the intestine *via* the laminin and Fc receptors are described.

INTESTINAL PRION ENTRY

Parts of PrP^{Sc} can be digested but most of its structure can withstand degradation by the gastric juices and enzymes in the gastrointestinal tract [9]. Therefore, PrP^{Sc} is able to reach intestinal epithelia [10, 11], and penetrates the intestinal epithelial barrier as well as other biological barriers before reaching the central nervous system (CNS) [12, 13]. However, the mechanism of its incorporation and the route by which PrP^{Sc} moves from the intestine to the CNS remains unclear. According to experiments using animal models such as mink, mice, sheep, and non-human primates, PrP^{Sc} invasion through the intestinal epithelial barrier is the first important step in the oral route infection, but the actual mechanisms of epithelial cell invasion are poorly understood [14-17]. When PrP^{Sc} transmigrates from the intestine to the lymphoid tissues, it accumulates around the follicular dendritic cells (FDC) of the gut-associated lymphoid tissue (GALT) and in the tangible-body macrophages of lymphoid nodules [18]. In addition, PrP^{Sc}-positive cells were detected in the dome region of intestinal Peyer's patches [19], suggesting that M cells in the follicle-associated epithelium are the entry site of these transmissible agents [20].

In summary, there are two main hypotheses to explain the penetration of prions into the intestinal barrier: the M cell-dependent pathway and the M cell-independent pathway [21, 22]. The former route, which is thought to be the main one, PrP^{Sc} passes through dendritic cells and accumulates in mesenteric lymph nodes, prior to invade neural tissue. In the M cell-independent pathway, PrP^{Sc} is taken up by epithelial cell transport mechanisms and starts accumulating in the enteric nervous system (ENS). Until now, lactoferrin, which is widely present intracellularly and in secretory fluids such as milk and saliva, is reported to inhibit prion accumulation [23]. Furthermore, while prion-soil interactions can vary with solution chemistry, prions bound to soil containing SiO_2 and bentonite clay are capable of maintaining the ability of transmitting prion diseases for months in the environment [24]. Only a few reports, so far, have investigated exogenous compounds or host factors capable of inhibiting the penetration of PrP^{Sc} into cells.

MOLECULAR MECHANISMS OF THE ENTRY OF PRP^{Sc} *VIA* RECEPTORS

The molecular mechanisms of PrP^{Sc} entry *via* putative receptors are also disputed. In the case of vCJD, a 37-kDa laminin receptor precursor (LRP) was proposed as a receptor that aids the entry of PrP^{Sc} [25, 26]. LRP is incorporated into the 67-kDa mature laminin

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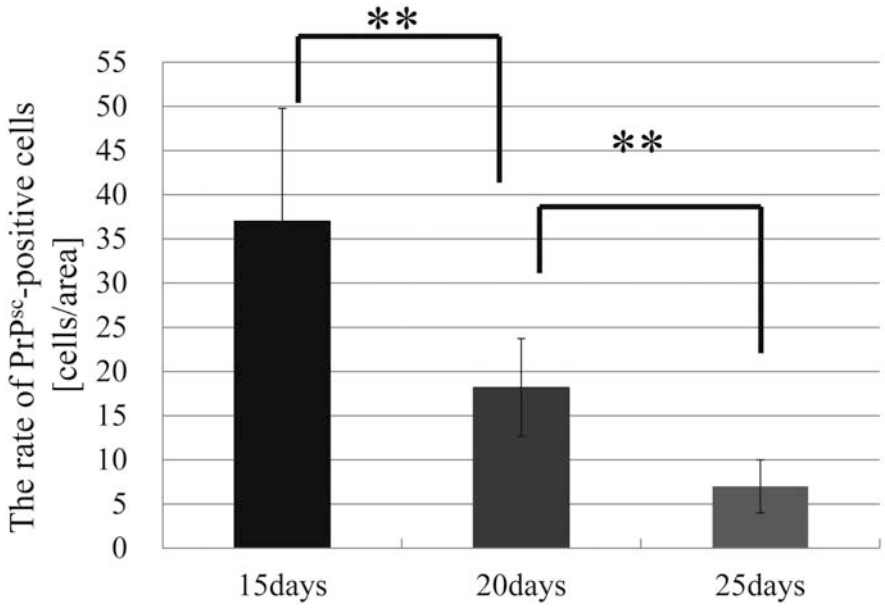

Fig. (1). Age-dependent incorporation of PrP^{Sc} in CD-1 mice
PrP^{Sc} was readily incorporated into the villi of 15-day-old and 20-day-old mice, whereas it was only partially incorporated in 25-day-old mice. The number of ileal epithelial cells incorporating PrP^{Sc} was significantly higher in 15-day-old mice than in 20- or 25-day-old mice. Results are expressed as mean ± S.D. Statistical differences were determined using the Student's t-test. **, P<0.01. This figure is reproduced from Fig. (**4**) of Ano *et al.* [32] with permission from Spandidos Publications Ltd.

receptor, which is expressed in the brush border surface of 40% of the human intestine [27]. It was reported that human CaCo-2/TC7 cells (an epithelial line derived from an intestinal carcinoma) are capable of endocytosing PrP^{Sc} from BSE brain homogenates. However, this uptake was reduced but not inhibited completely by blocking the 37 kDa/67 kDa laminin receptor with an anti-laminin receptor antibody [28]. The results suggested that other receptor(s) were involved in the incorporation of PrP^{Sc}.

Epidemiological studies of the BSE epidemic in Great Britain, have shown that feed was the major route of PrP^{Sc} infection [29], and through simulation models that most infected animals had been exposed to the agent within the first 6 months of life [30, 31]. This suggests that specific biological mechanisms acting in early life play an important role in infection by PrP^{Sc}.

In the suckling period, growth factors and immunoglobulins, which are present in large amounts in maternal milk, are incorporated by specific or non-specific receptors such as neonatal Fc receptors (nFcR), which are abundantly expressed on the villous epithelium before weaning [30]. In addition, suckling cows do not have fully developed intestinal epithelial barriers against foreign substances [33]. Therefore, these animals are particularly susceptible to prion agents. In a previous study by our group, intestinal sections of CD-1 mice were observed using immunohistochemistry after the administration of PrP^{Sc} in order to determine the relationship between PrP^{Sc} incorporation and age [34]. It was shown that PrP^{Sc} was incorporated into the villous epithelium and the lamina propria of 15-day-old mice fed with milk containing PrP^{Sc}. On the other hand, it was demonstrated that PrP^{Sc} was present on the luminal surface of villous epithelial cells but was hardly found in villous columnar epithelial cells in 20-day-old mice. PrP^{Sc} could not be detected in 25-day-old mice. Significantly more PrP^{Sc} was incorporated into the villous epithelium in the 15-day-old mice than in 20-day old mice [34] (Fig. **1**), suggesting that some factors expressed during the suckling period may play important roles in the incorporation of PrP^{Sc}. Interestingly, in CD-1 SCID mice which lack maternal immunoglobulins, the incorporation of PrP^{Sc} into villous epithelial cells was significantly reduced compared with that in wild type CD-1 mice. In contrast, PrP^{Sc} uptake into the villi of CD-1 SCID mice fed with PrP^{Sc} and abundant mouse IgG was enhanced compared with what observed in CD-1 SCID mice administered PrP^{Sc} alone. This indicated that maternal immunoglobulins and/or nFcR play an important role in the penetration of PrP^{Sc} into epithelial cells. It was also reported that the oral route of PrP^{Sc} infection was enhanced by its binding to soil particles [35], suggesting that the association of PrP^{Sc} with soil minerals and organic carbon enhanced the oral transmissibility of prion disease relative to the unbound agent.

Fc RECEPTOR INHIBITION INFLUENCES PrP^{Sc} ENTRY

Our studies suggested that the binding of PrP^{Sc} to maternal immunoglobulins can enhance the enteric invasion of PrP^{Sc} relative to unbound PrP^{Sc}.

We therefore examined the role of the FcR in PrP^{Sc} incorporationm by using. Z-ε-aminocaproic acid (ZAA) as a blocker of the Fc receptor [36]. ZAA (Fig. **2A**) is a derivative form of ε-aminocaproic acid that is believed to inhibit and/or interact with the Fc receptors (patent No.: WO2004/058747). The compounds such as 3-(3-cyanopropylsulfanil) benzoic acid (Fig. **2B**) and 3-(2-hydroxyphenyl) butene-2- carboxylic acid (Fig. **2C**)

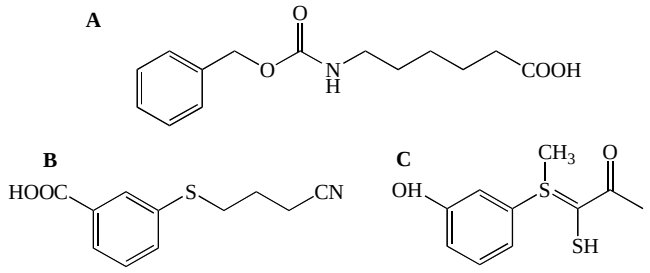

Fig. (2). Structure of Z-ε-aminocaproic acid (ZAA) and other compounds predicted to bind the Fc receptor
Z-ε-aminocaproic acid (**A**) is a derivative form of ε-aminocaproic acid, an analogue of the amino acid lysine. This Fig. (**2A**) is reproduced from Fig. (**1**) of Uraki *et al.* [34] with permission from the Public Library of Science. 3-(3-cyanopropylsulfanil) benzoic acid (**B**) and 3-(2-hydroxyphenyl) butene-2- carboxylic acid (**C**) are also predicted to bind and inhibit the Fc receptor.

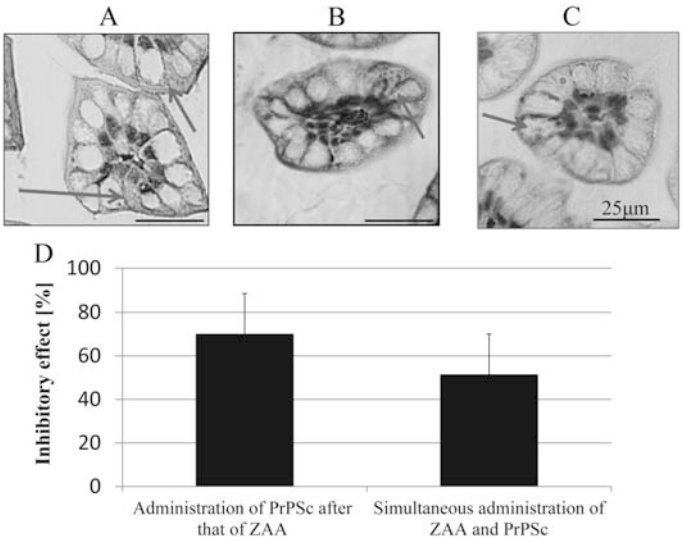

Fig. (3). Incorporation of PrP^{Sc} through intestinal villi in CD-1 mice
Histochemical analysis of PrP^{Sc} in the intestinal villi of 15-day-old mice that had been orally administered PrP^{Sc} (**A**), PrP^{Sc} after ZAA treatment (**B**), or PrP^{Sc} and ZAA at the same time (**C**). Arrows indicate PrP^{Sc}-positive cells. The inhibitory effect of PrP^{Sc} incorporation was calculated using the following formula: (percentage of ileal epithelial cells incorporating IgG or PrP^{Sc} with ZAA treatment) / (percentage of ileal epithelial cells incorporating IgG or PrP^{Sc} without ZAA treatment) ×100. Inhibitory effects of 70.1% and 51.5%, respectively, were seen during ZAA treatment (**D**). This figure is reproduced from Fig. (**3**) of Uraki *et al.* [34] with permission from the Public Library of Science.

were predicted to have a bioactivity similar to that of ZAA. In our previous study [36], we confirmed that ZAA has the potential to block the Fc receptor by administering ZAA together with mouse IgG. Upon showing a blocking effeect of ZAA on PrP^{Sc} penetration, the relationship between PrP^{Sc} and the epithelial Fc receptor was analyzed. As expected, the incorporation of PrP^{Sc} into the villi was significantly reduced in the group of mice in which PrP^{Sc} was administered after treatment with ZAA as well as in the group in which PrP^{Sc} and ZAA were administered at the same time. The results suggested that ZAA may suppress the incorporation of PrP^{Sc} by inhibiting FcR (Fig. **3**). Our results were consistent with previous observations and indicated that the neonatal Fc receptor plays a role in the uptake of PrP^{Sc}. However, Klein and co-workers [37] concluded that the Fc receptor has a minimal effect on prion pathogenesis using mice genetically deficient in Fcγ receptors I, II, and III. Vein and co-workers reported that the lack of expression of nFcR in epithelial cells correlates with the onset of intestinal resistance to mouse mammary tumor virus (MMTV) through lactation [38]. In this model, however nFcR was not required for infection, since β-2m-deficient newborn mice remained susceptible to MMTV infection. Resistance to MMTV infection after weaning may also reflect the postnatal maturation of digestive functions of the gastrointestinal tract with the appearance of acid secretion in the stomach and secretion of digestive enzymes both in the stomach and the gut [38]. As the reason for this discrepancy remains unclear, further *in vivo* experiments using mice treated with ZAA before and after prion administration will allow to determine the effect of blocking Fc receptors on disease progression. The interaction between LRP and the Fc receptor during the incorporation of PrP^{Sc} into villous cells also remains to be elucidated.

CONCLUSION

In this review, we described recent studies investigating the mechanism of the oral transmission of PrP^{Sc} using *in vitro* and *in*

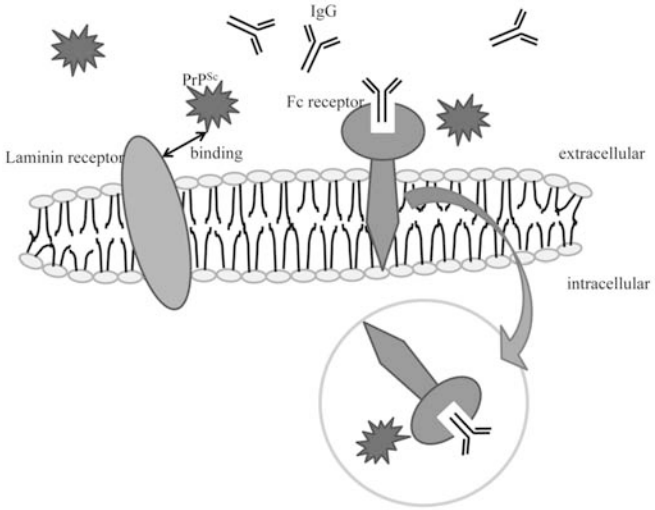

Fig. (4). Possible model of PrP^{Sc} uptake *via* the laminin and Fc receptors in the intestinal cells
Although the laminin receptor has been identified as a possible PrP receptor that binds to PrP^{Sc} and PrP^{C} directly, Fc receptors expressed on the surface of epithelial cells may also play important roles in PrP^{Sc} incorporation. An appealing mechanism is that PrP^{Sc} can be incorporated throughout IgG binding to the Fc receptor.

vivo models. From these studies, the following model of PrP^{Sc} uptake can be proposed (Fig. **4**). After oral challenge with PrP^{Sc}, M cells and villous columnar epithelial cells are involved in the first step of PrP^{Sc} incorporation. Though the presence of the prion receptor LRP, which is expressed on the surface of intestinal epithelial cells, may represent a risk factor for prion diseases, the expression of Fc receptors has been shown to enhance the uptake of PrP^{Sc}. Finally, it should be noted that other routes of infections are plausible. Haybaeck *et al.* recently reported that aerogenic exposure to prions leads to direct neuroinvasion bypassing an obligatory replicative phase in lymphoid tissues [39]. These findings spur further researches on airborne transmission and not only on the oral route leading to the development of preventive measures and new treatments for prion disease.

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