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化粧品

識別番号・報告回数			報告日	第一報入手日 2005 年 7 月 19 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	①②ポリエチレングリコール処理人免疫グロブリン ③人免疫グロブリン	研究報告の公表状況	AABB WEEKLY REPORT,11(25),3,2005	公表国 カナダ		
販売名 （企業名）	①献血ヴェノグロブリン-IH ヨシトミ（ベネシス） ②ヴェノグロブリン-IH（ベネシス） ③グロブリン-Wf（ベネシス）					

研究報告の概要

カナダ Hema-Quebec は vCJD が地域の血液供給を介して伝播することのないよう数年前に実施に移された複数のドナー規制を緩和した。緩和は 2005 年 7 月 6 日より発効となり、新たな規制を説明する声明が発表された。Hema-Quebec の新たな基準は 1999 年～2001 年に制定された規制のいくつかを緩和し、「1980 年 1 月 1 日以降累計で，英国に 1 ヵ月以上またはフランスに 3 ヵ月以上滞在した全ての可能性のあるドナーを除外し、1980 年以降英国において輸血をうけた人および特定の西欧諸国に累計で 6 ヵ月以上滞在した全ての血液ドナーも不適格とする」を「1980 年 1 月 1 日～1996 年 12 月 31 日に累計で英国に 1 ヵ月以上またはフランスに 3 ヵ月以上滞在した人は献血が不適格とする」に変更予定である。加えて、1997 年 1 月 1 日以降の英国およびフランスへの訪問は西欧での滞在期間の累計に含まなくなる予定である。ただし 1980 年 1 月 1 日以降に特定の西欧諸国で血液、赤血球、血小板、血漿を輸血された人は依然として不適格である。この変更は、BSE に対する調査および管理措置が 1996 年以降英国およびフランスにおいて成功していると考えられること、および vCJD 患者数が極めて少ないことに基づいて、Hema-Quebec が vCJD に関連したドナー選定基準の妥当性を再評価した結果である。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
カナダHema-Quebecにおいて、vCJDに係る供血排除基準が緩和されるとの報告である。 これまで血漿分画製剤によってvCJDが伝播したとの報告はない。しかしながら、万一vCJD感染者の血液が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

Hema-Quebec Revises Donor Eligibility Criteria Related to vCJD

In an effort to increase the number of individuals in Quebec eligible to give blood, Hema-Quebec (Montreal, Canada) has eased several donor restrictions put in place years ago to help ensure variant Creutzfeldt-Jakob disease (vCJD) will not be transmitted via the province's blood supply. The changes became effective July 6, 2005, when the organization issued a statement to the press explaining its new policies.

Hema-Quebec's new criteria modify some of the restrictions that the organization instituted between 1999 and 2001, when the blood supplier opted to exclude all potential donors who, on a cumulative basis, had spent one month or more in the U.K. or three months or more in France since January 1, 1980. At the time, Hema-Quebec was also disqualifying all blood donors who, since that date, had spent six months or more, on a cumulative basis, in certain other Western European countries; as well as individuals who had received a blood transfusion in the U.K. since 1980.

Although the exclusion of donors who have spent six months or more in applicable Western European countries since January 1, 1980, is being maintained, for those who have visited the U.K. or France, the period of restriction has been reduced. Now, only those who have cumulatively spent one or more months in the U.K. or three or more months in France between January 1, 1980, and December 31, 1996, will be ineligible to give blood. The 1996 cut-off date applicable to stays in the U.K. and France had previously been recommended by Health Canada and is compliant with the Canadian Standards Association's (CSA) standards concerning blood and blood products.

In addition, visits to the U.K. and France since January 1, 1997, will no longer be included in the cumulative duration of time spent in Western Europe. However, any individual who has received a transfusion of blood, Red Blood Cells, Platelets or Plasma since January 1, 1980, in the applicable Western European countries, will still be disqualified from giving blood.

Hema-Quebec cites two reasons for willingly reassessing the relevance of its donor selection criterion as it relates to vCJD. According to the organization, surveillance and control measures for bovine spongiform encephalopathy (BSE)—a disease in cattle linked to vCJD in humans—have been deemed successful in the U.K. and France since 1996. Also, the prevalence of vCJD has been fairly low.

These policy changes will allow travelers who made their first visit to the U.K. or France since January 1, 1997, to donate blood, regardless of the length of their stay, opening up a new segment of donors for the organization.

To read more about Hema-Quebec's new policies, visit: www.hema-quebec.qc.ca/anglais/centredepresse/coms2005/20050706.htm.

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医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
一般的名称	インフリキシマブ（遺伝子組換え）		研究報告の公表状況	J Virol 79:8665-8668(2005) 2005年7月	公表国 スペイン	
販売名（企業名）	レミケード点滴静注用100（田辺製薬）					

研究報告の概要

問題点（トランスジェニックマウスモデルを用いた、BSEプリオンの母子伝達の評価）

ウシプリオン蛋白を発現するトランスジェニックマウス（雌）の脳内にBSEウシ由来の接種物を投与してBSEを感染させ、投与160日～223日後に健康な雄と交配させ妊娠させた。その結果、投与195日及び223日後に交配させたマウス（各1匹）では脳抽出物にウェスタンブロット分析で異常プリオン蛋白の強いシグナルが認められ、生まれた仔合計10匹のうち2匹の脳内に異常プリオンが検出された。対照的に、投与160日後に交配させた3匹のマウスのうち1匹のみに脳内異常プリオンの蓄積が認められ、その仔13匹のうち1匹に脳内異常プリオンが検出された。異常プリオンが認められなかった他の2匹から生まれた仔（総計40匹）の脳には異常プリオンは検出されなかった。今回のマウスを用いた実験で、BSEプリオンが中枢神経系から末梢組織に拡がり、母子感染することが明らかになった。

報告企業の意見	今後の対応
ウシプリオン蛋白を発現するトランスジェニックマウスを用いた実験で、BSEプリオンが母子感染するという報告であり、今後のBSE感染予防の観点からして重要な報告と考えられる。	今後も同様の報告に注意して調査・対応を行う。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
9）本剤の生産培地には、ウシの脾臓及び血液を加水分解した分子量1,000以下のアミノ酸及びペプチド等が添加されている。このウシの脾臓及び血液は、米国農務省の検疫により食用可能とされた健康な米国産ウシから得られている。米国では、伝達性海綿状脳症（TSE）の危険性を防ぐために臨床的・組織学的検査による動物の検査、動物性飼料のウシへの使用禁止及び輸入禁止措置等の防疫対策が取り続けられている。さらに製造工程での安全対策として、TSE伝播の原因である分子量約30,000のプリオン蛋白を除去できる工程として、限外ろ過処理を培地添加前に実施している。なお、この方法で実際にプリオンが除去できることを証明するために、意図的にウシ由来成分にプリオン蛋白を大量添加し、処理後にプリオン蛋白が除去されていることを、ヨーロッパや日本において食品の安全性を判断するために用いられているウエスタンブロット法で測定し、陰性であることを確認している。しかし、プリオン蛋白が存在する可能性は理論的には否定し得ないため、その旨を上記の安全性に関する対策とともに患者へ説明することを考慮すること。なお、本剤投与によりTSEをヒトに伝播したとの報告はない。

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Vertical Transmission of Bovine Spongiform Encephalopathy Prions Evaluated in a Transgenic Mouse Model

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In this work we show evidence of mother-to-offspring transmission in a transgenic mouse line expressing bovine PrP (boTg) experimentally infected by intracerebral administration of bovine spongiform encephalopathy (BSE) prions. PrP^{res} was detected in brains of newborns from infected mothers only when mating was allowed near to the clinical stage of disease, when brain PrP^{res} deposition could be detected by Western blot analysis. Attempts to detect infectivity in milk after intracerebral inoculation in boTg mice were unsuccessful, suggesting the involvement of other tissues as carriers of prion dissemination. The results shown here prove the ability of BSE prions to spread centrifugally from the central nervous system to peripheral tissues and to offspring in a mouse model. Also, these results may complement previous epidemiological data supporting the occurrence of vertical BSE transmission in cattle.

Prion diseases or transmissible spongiform encephalopathies (TSEs) belong to a class of infectious diseases characterized by the presence of an abnormally folded protein (PrP^{Sc}) that accumulates in the brains of affected individuals (24). TSEs may be of spontaneous, familial, or infectious origin. While spontaneous and familial etiologies have been described for the disease in humans (22, 23), infectious TSEs have been clustered mainly in domestic animals, from which sheep scrapie was the prototype of disease (17). The epidemic dimension of bovine spongiform encephalopathy (BSE) in the mid-1980s contributed to the spread of the disease to humans in the form of variant Creutzfeldt-Jakob disease (vCJD) (7, 8). It is now generally accepted that the consumption of contaminated meat and/or meat-derived products has been the most probable route of transmission of BSE prions to humans. Natural routes of transmission have been described for scrapie prions (16, 19, 20), although scant information is available regarding BSE natural routes of infection. The ability of scrapie prions to accumulate in placental tissues from genetically susceptible ewes (1, 25, 27) might be a contributing factor in scrapie epidemiology (16). However, this picture still remains diffuse for BSE. No PrP^{Sc} accumulation is detected in placentas from BSE-infected cattle (31), and neither blood nor milk from BSE-infected animals have yet been shown to be infectious, consistent with the apparent absence of the prion agent in peripheral tissues (3). Experiments to test maternal transmission in cattle showed that approximately 10% of calves born to cows with confirmed BSE developed disease (2). This transmission rate, however, was obtained in a scenario of disease prevalence, since some of the calves were born after the feed ban was fully effective.

The ability of prions to move from the central nervous system (CNS) through afferent nerve fibers has been described for several TSEs, including genetic and sporadic human prion diseases (14, 15)and scrapie (28), and was suggested for chronic wasting disease (CWD) (26). Recently, it has been shown how vCJD and Gerstmann-Sträussler-Scheinker syndrome (strain Fukuoka-1) prions retaining full infectivity can be detected in the blood of mice after intracerebral inoculation (6). To test the ability of BSE prions to spread from CNS to peripheral tissues, we studied the efficiency of BSE transmission from intracerebrally BSE-inoculated mothers to their offspring in a transgenic mouse line (boTg110) expressing bovine PrP (4). boTg110 mice express boPrP controlled by the mouse PrP promoter at a level eight times that of the level of bovine PrP in cattle brain as previously described (4). Groups of boTg110 females were intracerebrally infected with a BSE inoculum named BSE_1 consisting of a pool from 49 BSE-infected cattle brains (TSE/08/59) supplied by the Veterinary Laboratories Agency (New Haw, Addlestone, Surrey, United Kingdom). The titer of this inoculum was ~10^8 50% infective dose units per gram of bovine brainstem when measured in the boTg110 mouse line (data not shown). At different times postinoculation, infected female mice were mated with healthy homologous males (Table 1). Group I female mice (mated at 195 and 223 days postinoculation [d.p.i.]) showed a strong PrP^{res} signal as judged by Western blot analysis of brain extracts (data not shown). In contrast, only mouse 09 from group II (mated at 160 d.p.i.) showed detectable brain PrP^{res} accumulation, in good agreement with the kinetics of PrP^{res} deposition in this mouse model (4).

PrP^{res} was clearly detected by Western blotting in 2 out of 10 mice born from group I females (mated at 195 and 223 d.p.i.) but in only 1 out of 40 in group II (mated at 160 d.p.i.). The PrP^{res} banding pattern observed for group I positive brains was similar to that for brains from Tg110 mice intracerebrally challenged with the BSE_1 inoculum, and no differences could be observed in their relative molecular weight mobilities (Fig. 1A)

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TABLE 1. Vertical transmission of BSE in bo-PrP-Tg110 mice after intracerebral inoculation

Group	Inoculum	Mouse	d.p.i. to:				Clinical signs	PrP^{res} in mothers[a]	No. of offspring with PrP^{res}/total no. of offspring (d.p.i.)
			Mating	Offspring	Milking	Culling			
I	BSE_1	01	195	246	256	274	Yes	+++	1/5 (622)
I	BSE_1	02	223	250	258	274	Yes	+++	1/5 (613)
II	BSE_1	09	160	182	190	237	Yes	++	1/13 (536)
II	BSE_1	12	160	182	190	210	No	−	0/14
II	BSE_2	14	160	182	190	210	No	−	0/13
III	None (control)	03	220	246	256	276	No	−	0/12
III	None (control)	05	220	246	256	276	No	−	0/10

[a] +++, strong PrP^{res} signal; ++, PrP^{res} accumulation detectable in brain; −, no detectable PrP^{res} in brain.

Deglycosylation experiments with *N*-glycosidase F (PNGase F) confirmed this observation (Fig. 1B). However, differences in the amounts of immunoreactive PrP^{res} were found between group I and II: PrP^{res} levels in mouse 09/02 from group II were found to be clearly lower than those in mice from group I. This fact might be explained by the shorter survival time of this mouse (time to death, 536 d.p.i.) relative to those of mice from group I, which died at 622 and 613 days postinfection. Differences in the percentages of PrP^{res}-positive offspring among groups I and II (20% versus 2.5%; $P_{t\ test} = 0.098$) might be related to the time after intracerebral BSE prion inoculation after which mating was allowed. Thus, higher transmission rates, defined by the presence of detectable PrP^{res}, are obtained if the accumulation of pathogenic PrP in brain is allowed to reach certain nonpathological levels without disturbing the reproductive competence of female mice. The high percentage of PrP^{res}-negative littermates could be attributed to the limited sensitivity of the Western blot technique (5). In addition, exploring the presence of PrP^{res} depositions by immunohistochemistry in brains from mice negative for PrP^{res} by Western blotting was consistently unsuccessful (data not shown). The lack of PrP^{res} detection, however, cannot exclude completely the existence of subclinical infections in the PrP^{res}-negative offspring. This assumption can be supported by the statistically significant differences ($P = 0.020$) observed in the survival times between offspring from infected (585 ± 60, 589 ± 71, 583 ± 36, 566 ± 63 and 608 ± 20 d.p.i.) and control (637 ± 57 d.p.i.) mothers (Fig. 2). Moreover, there was no difference between the survival times of PrP^{res}-positive and PrP^{res}-negative offspring mice. To confirm the fact of subclinical infection, works on second-passage experiments are in progress.

The fact that BSE prions delivered into mice brains can be transmitted to a next generation is indicative of their intrinsic ability to centrifugally spread from the CNS to other peripheral tissues. In fact, the ability of prions to move from CNS through afferent nerve fibers has been also described for other TSEs, including genetic and sporadic human prion diseases (14, 15) and scrapie (28), and was suggested for chronic wast-

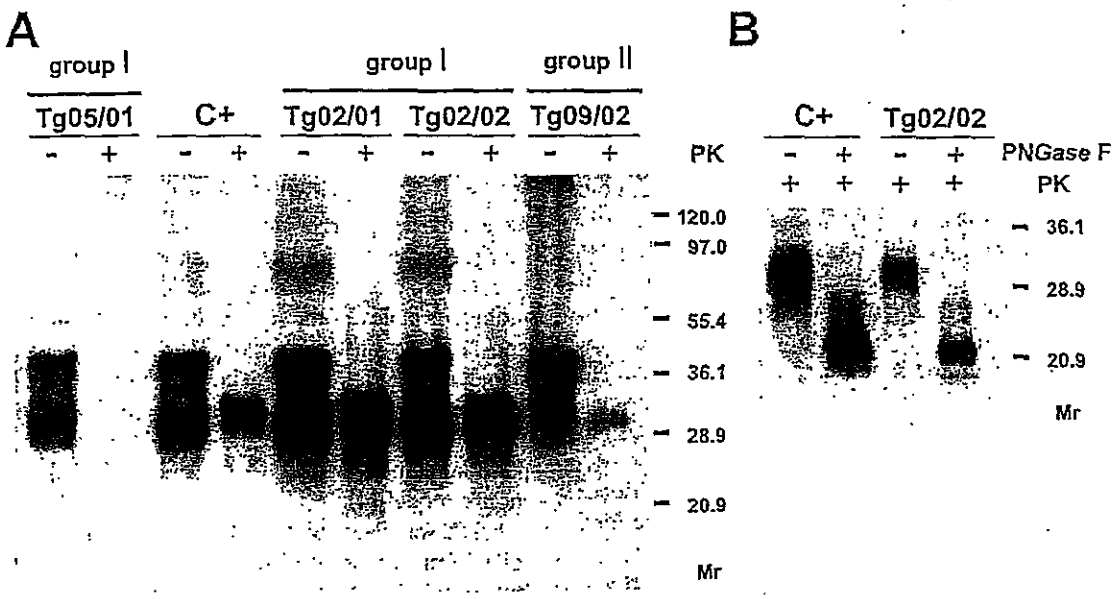

FIG. 1. (A) Comparison of Western blot profiles in brain detergent-insoluble fractions from PrP^{res}-positive offspring. Tg05/01, mouse born from the Tg05-uninfected female; Tg01/02 and Tg02/02, mice born from the Tg01 and Tg02 BSE_1 inoculum-infected females, respectively; Tg09/02, mouse born from the Tg09-infected female; C+, brain extract from a Tg110 mouse intracerebrally inoculated with BSE_1 inoculum; Mr, Relative molecular mass expressed in kilodaltons; PK, proteinase K treatment. Protein loads per lane are equivalent in progeny mice. In the Tg05/01 mouse the PK − lane shows soluble brain fraction. (B) Deglycosylation studies of PrP^{res} from control (C+) and progeny Tg02/02 brain extracts.

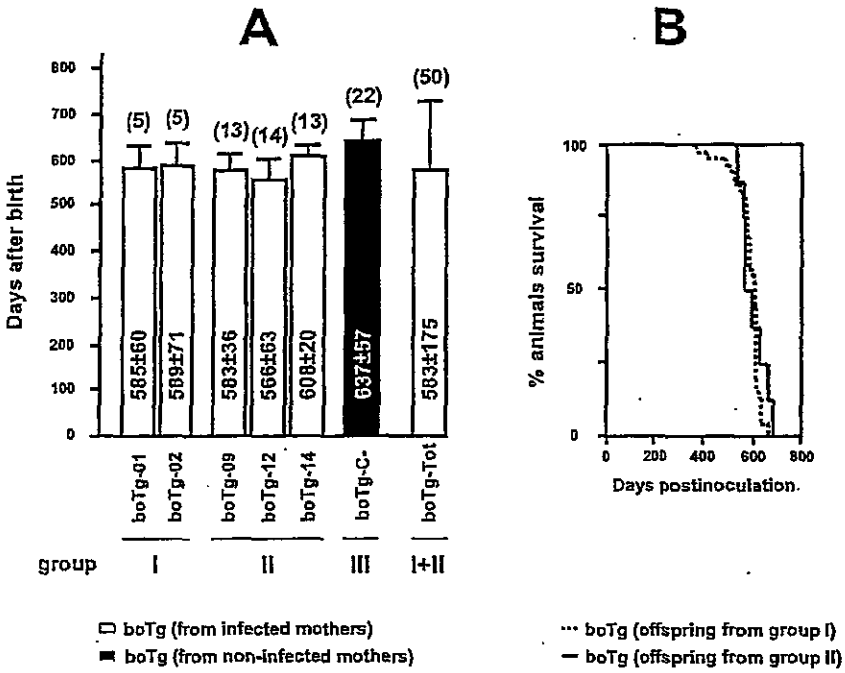

FIG. 2. Mean survival times of mice born from infected mothers. (A) Histograms showing survival times of the offspring of each female and of all offspring (boTg-Tot). BoTg-C-, offspring from uninoculated group III mothers. The values within the bars represent the days after inoculation ± standard deviations. The numbers of mice of each type inoculated are in parentheses. (B) Kaplan-Meier curves correspond to the overall groupings of the offspring (groups I and II)..

ing disease (CWD) (26). Recently it has been shown how vCJD and Gerstmann-Sträussler-Scheinker syndrome (strain Fukuoka-1) prions retaining full infectivity can be detected in the blood of mice after intracerebral inoculation (6). The role of blood in BSE prion dissemination became more evident after the demonstration of BSE transmission to sheep via blood transfusion even during the preclinical phase of an experimental oral BSE inoculation in sheep (18). Our results indicated that BSE prions could be transmitted to the offspring after intracerebral inoculation in a process that seems to be more efficient when detectable amounts of PrP^{res} are present in the brain. The way by which prion infectivity is transmitted through a next generation could be then, based on previous work, be identified as blood dissemination. Other investigated tissues (placenta, lymphoid tissues, and gastrointestinal tract) were negative for PrP^{res} either by Western blotting or by analysis with immunohistochemistry (data not shown). However, these negative results do not allow one to conclude that there is a lack of infectivity in these tissues. In our experimental model, other fluids cannot be disregarded as vehicles for prion spread. To asses whether the route of infection through milk feeding was involved, we carried out experimental inoculations of milk extracted from mothers. For this purpose, 0.5 ml of pooled milk extracted from both infected and uninfected mothers was delipidated and intracerebrally injected into boTg110 mice after a concentration step (centrifugation at 25,000 × *g* for 30 min). We estimate that the amount of milk used for the inoculations represents 25% of the milk intake during lactancy. Analysis of the survival times of mice inoculated or mock inoculated did not show any significant difference (Fig. 3). Brains from these mice were then analyzed with both histopathology and immunohistochemistry for the presence of PrP^{res}. Similarly, no PrP^{res} was detected (data not shown). This negative result does not exclude the potential of milk to transmit prions but suggests that the relevance of this fluid in infectivity might be very low if it exists at all. Thus, the centrifugal dispersion of prions together with the ability of blood to retain prion infectivity might account for the transmission of BSE prions to the offspring without excluding other possible ways.

With regard to BSE in cattle, previous fieldwork studies

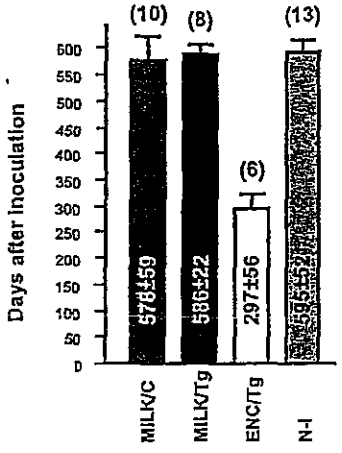

FIG. 3. Survival times of boTg110 mice inoculated with donor milk samples. Survival times for mice inoculated with milk from healthy female boTg110 mice (MILK/C) or milk (MILK/Tg) and brain (ENC/Tg) pools from BSE_1-infected female boTg110 mice are shown. The values within the bars indicate the days postinoculation ± standard deviations. The numbers of mice inoculated with each type of sample are indicated in parentheses.

suggested that the disease may be passed from cow to calf (29, 30). However, there has been controversy and uncertainties regarding whether or not maternal transmission has implications in the prevalence of this disease similar to those that it has for sheep scrapie (9, 10). Our results reveal an enhanced risk of disease in mice born from BSE-infected mothers at the end stage of the incubation time. The same type of risk may apply to the offspring from BSE-infected cattle, as has been suggested from the epidemiological data (9). However, it is necessary to point out here some differences between our transgenic mouse model and bovine species. Firstly, boTg110 mice express boPrP at a level eight times that of bovine PrP in cattle brain; therefore, there is more PrP^C substrate available for conversion to PrP^{Sc}. Secondly, there are some evident differences with respect to the architectural anatomies of mouse and cattle placentations. In cattle, the placenta is bridged to the uterus by a cotyledonary form of attachment, and the structure is of the syndesmochorial type, in which the embryo trophoblastic layer and the maternal uterine epithelium are not fused. In contrast, mouse embryonic and uterine epithelia are completely fused (hemochorial). This type of structure allows blood from the uterine endothelium to be in close contact with the fetal placenta, therefore facilitating the chances for prion dissemination and embryonic contamination.

The BSE agent can propagate efficiently in sheep (11), and the possibility of sheep flocks becoming infected with BSE was raised (21). However, in contrast to findings for sheep scrapie, no evidence of PrP^{Sc} has been found in the reproductive tissues of sheep infected with BSE (13), nor has BSE been reported in the offspring of experimentally infected ewes (12). Since transmission of BSE prions to the offspring occurs in the mouse model, it is reasonable to assume that host-specific restrictions may compromise the ability of BSE prions to be vertically transmitted.

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