医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2007 年 1 月 12 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	FDA proposes barring certain cattle material from medical products as BSE Safeguard. FDA News, 11 January 2007	公表国 米国	
販売名(企業名)						

研究報告の概要

ウシ海綿状脳症(BSE)の原因となる物質のヒトへの伝播リスクをさらに減少させるために，米国食品医薬品局(FDA)はヒトへの使用を目的とした一部の医薬品(薬剤，ワクチン及び医療機器)ならびに反芻動物への使用を目的とした薬剤でのウシ由来原料の使用を制限することを提案した。この新しい規制では，罹患ウシにおいて最高濃度の BSE 因子を含むことが確認されている部位すべてと，以下のものが禁止される：

・30 ヵ月齢以上のウシの脳，頭蓋，眼及び脊髄
・月齢又は健康状態を問わず，全てのウシの扁桃腺及び小腸の一部
・歩行不能な「ダウナー」牛の全部位
・食用の検査を受けていないウシ，及び合格していないウシの全部位
・本規則案での禁止部位による汚染を防ぐための適切な処置を行っていないウシ胎仔血清
・本規則案での禁止部位由来の獣脂で，0.15%を超える不溶性不純物を含有する場合
・機械によって加工された牛肉

確実にこれらの禁止事項を企業に従わせるため，FDAは医薬品の原料として，あるいは製造工程の一部として使用されるウシの全部位が規制要件を満たすことを明示する記録の保管要求を提案している。

使用上の注意記載状況・その他参考事項等

BYL-2007-0268

www.fda.gov/bbs/topics/NEWS/2007/NEW01545.html

報告企業の意見	今後の対応
1997 年以降，BSE リスクを低減するために FDA は厳重な措置(例えば，反芻動物由来飼料の使用禁止)を取っている。これまでの BSE 報告件数がわずかであることから，事実上のリスクは非常に小さく，これらの措置は有効であると考えられる。	現時点で新たな安全対策上の措置を講じる必要はないと考える。

FDA News

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FDA Proposes Barring Certain Cattle Material From Medical Products As BSE Safeguard

The U.S. Food and Drug Administration is proposing to limit the materials used in some medical products in order to keep them free of the agent thought to cause mad cow disease, also known as bovine spongiform encephalopathy or BSE.

This is the latest in a series of BSE safeguards that would bar material that has been found to harbor the highest concentrations of this fatal agent in infected cattle. These materials would be prohibited from use as ingredients in medical products or elements of product manufacturing.

The proposed rule would cover drugs (prescription, over-the-counter, and homeopathic), biologics (such as vaccines) and medical devices intended for use in humans as well as drugs intended for use in ruminant animals like cattle and sheep. Cattle can get mad cow disease, while sheep can get a similar disease known as scrapie.

"These measures build on a series of barriers FDA and the U.S. Department of Agriculture have erected to further protect humans from exposure to the fatal agent linked to BSE," said Andrew von Eschenbach, M.D., Commissioner Food and Drugs. "This proposed rule adds one more safeguard that will reduce the risk of transmission even further."

The cattle materials prohibited in the proposed rule are those that pose the highest risk of containing infectious material and include:

- the brain, skull, eyes and spinal cords from cattle 30 months and older;
- the tonsils and a portion of the small intestines from all cattle regardless of their age or health;
- any material from "downer" cattle–those that cannot walk;
- any material from cattle not inspected and passed for human consumption;
- fetal calf serum if appropriate procedures have not been followed to prevent its contamination with materials prohibited by this proposed rule;
- tallow that contains more than 0.15 percent insoluble impurities if the tallow is derived from materials prohibited by this proposed rule and;
- mechanically separated beef.

To ensure that companies comply with these prohibitions, FDA proposes to require that records be kept to demonstrate that any cattle material used as an ingredient in these medical products or as part of their manufacturing process meet the rule's requirements.

Since 1996, strong evidence has accumulated for a causal relationship between ongoing outbreaks of mad cow disease in Europe and a disease in humans called variant Creutzfeldt-Jakob (vCJD) disease. Both disorders, which are thought to be caused by an unconventional transmissible agent, are invariably fatal brain diseases with incubation periods typically measured in years. Transmission of the BSE agent to humans, leading to vCJD, is believed to occur via ingestion of cattle products contaminated with the BSE agent; however the specific products associated with this transmission are unknown.

About 200 cases of vCJD have been identified worldwide, including three cases in the U.S. However, there is no evidence that those three patients contracted the BSE agent in the U.S.

FDA and USDA's efforts to help protect the public from vCJD have included several other significant steps such as the FDA's 1997 ruminant feed regulation, which forbids the use of certain mammalian-origin proteins in ruminant feed. Also, a 2005 interim final rule bans the use of certain high-risk cattle material in food, dietary supplements and cosmetics.

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識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2006 年 11 月 1 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Isolation from cattle of a prion strain distinct from that causing bovine spongiform encephalopathy. Béringue, V. et al., PLoS Pathog., 2, 956-963 (2006)	公表国 フランス	
販売名 (企業名)						

研究報告の概要

ヨーロッパにおいて伝染性海綿状脳症 (TSEs) のために死亡及び屠殺した畜牛の大規模な検査が行われた結果，電気泳動上 BSE 因子の PrP とは異なる，異型 PrP (PrP^{res}) プリオンタンパク (H 型と呼ばれる) が発見された。フランスの畜牛から分離された 7 種のプリオンタンパクをトランスジェニックマウス (Tg) マウスへ脳内接種し比較することにより，H 型 PrP^{res} の伝播性を評価した。マウスには，ウシ (tgBov) 及びヒツジ (tgOv) PrP のいずれかを発現させるようにした (本系統ではマウス PrP は発現していない)。全てのマウスで神経症状が発症し，tgBov Tg マウスは 400 日の間に，tgOv Tg マウスは 600 日の間に海綿状脳症で死亡した。次世代マウスでは，平均生存時間は 100 日間まで減少した。ウシ海綿状脳症 (BSE) または異型クロイツフェルト・ヤコブ病 (vCJD) 因子に感染すると，PrP^{res} は tgOv Tg マウスの脾臓内でウエスタンブロット法で検出可能なレベルまで蓄積した。一方，H 型プリオンを接種した tgOv Tg マウスでは，脾臓内に PrP^{res} は検出されなかった。罹患したマウスの脳切片の分析によると，H 型 PrP^{res} と BSE PrP^{res} の構造上の一致は一部分のみで，神経解剖学的には異なる病変が判明した。さらに，H 型プリオン感染マウスでは重度の海綿状態が観察された。イタリアのヒツジのスクレピー分離株で行われた同様の実験によって，現時点では H 型プリオンは tgOv Tg マウスに接種した全ての TSE 分離株と関連性がなく，したがってこれは新型のプリオンであるという結論になった。
著者らは複数のプリオン株の存在，あるいはいくつかの動物においてプリオンが分岐進化している可能性を示唆した。しかしながら，その起源とヒトの健康への潜在的リスクは今日現在，未知のままである。

報告企業の意見	今後の対応
本調査結果から，TSE に関与するプリオンは当初考えられていた以上に多様性に富み，またヒトへの感染はプリオンの種類によって異なることが示唆された。これは，ウシ由来製品を含有する血漿分画製剤の製造工程におけるプリオン除去工程を評価する際に考慮が必要となる可能性がある。	弊社の血漿分画製剤の製造工程において，これまでに同定されている種々のウシプリオンに対してプリオン除去工程は効果的であることが確認されている。 現時点で新たな安全対策上の措置を講じる必要はないと考える。引き続き関連情報の収集に努める。

使用上の注意記載状況・その他参考事項等

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57

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Isolation from Cattle of a Prion Strain Distinct from That Causing Bovine Spongiform Encephalopathy

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To date, bovine spongiform encephalopathy (BSE) and its human counterpart, variant Creutzfeldt-Jakob disease, have been associated with a single prion strain. This strain is characterised by a unique and remarkably stable biochemical profile of abnormal protease-resistant prion protein (PrP^{res}) isolated from brains of affected animals or humans. However, alternate PrP^{res} signatures in cattle have recently been discovered through large-scale screening. To test whether these also represent separate prion strains, we inoculated French cattle isolates characterised by a PrP^{res} of higher apparent molecular mass—called H-type—into transgenic mice expressing bovine or ovine PrP. All mice developed neurological symptoms and succumbed to these isolates, showing that these represent a novel strain of infectious prions. Importantly, this agent exhibited strain-specific features clearly distinct from that of BSE agent inoculated to the same mice, which were retained on further passage. Moreover, it also differed from all sheep scrapie isolates passaged so far in ovine PrP-expressing mice. Our findings therefore raise the possibility that either various prion strains may exist in cattle, or that the BSE agent has undergone divergent evolution in some animals.

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Introduction

While transmissible spongiform encephalopathies (TSEs) in small ruminants and humans are believed to involve distinct prion strains [1,2], a single prion strain has been associated so far with bovine spongiform encephalopathy (BSE) and its human counterpart, variant Creutzfeldt-Jakob disease (vCJD) [3–6]. In particular, the abnormal, protease-resistant form of prion protein (PrP^{res}) that accumulates in the brains of infected individuals [7] shows a consistently unique electrophoretic profile in immunoblots [8]. However, the biochemical testing of the brains of slaughtered and fallen cattle, which was intensified since 2000 in European countries as a means to protect the consumers, has led to the discovery of positive samples that showed distinct PrP^{res} profiles. These atypical profiles have been sorted into two groups so far, provisionally termed H-type when the size of the protease resistant fragments is higher than for BSE, and bovine amyloidotic spongiform encephalopathy, or L-type, when it is lower [9,10]. These observations raise the possibility that as yet unrecognised prion strains may exist in cattle as in other species [11], and have potential implications in terms of public health. Unlike bovine amyloidotic spongiform encephalopathy isolates, which derive from animals with defined histopathological abnormalities [10], precise information corroborating a prion disease is lacking for H-type cases. It was therefore crucial to determine through experimental transmission whether such cases reflect some alteration in PrP metabolism, possibly in aging animals, or involve a truly infectious agent.

In this study, we report the transmission of a TSE-like disease by inoculation of French cattle isolates identified as H-type variants to two lines of PrP transgenic mice. Furthermore, we provide compelling evidence that this agent has unique features compared to epizootic BSE and other related agents. We also establish that there is no link with ovine TSE isolates transmitted so far to these models.

Results

H-Type Isolates Are Transmissible to Mice

Two transgenic mouse lines were used as recipient for transmission experiments. The tg540 line is a newly established line that expresses bovine PrP (Protocol S1), resulting in an enhanced susceptibility to BSE agent compared to conventional mice [6,12]. The tg338 line, expressing the VRQ ($Val^{136}Arg^{154}Gln^{171}$) allele of ovine PrP, has allowed an efficient transmission of natural scrapie isolates from sheep and goat [13,14]. The rationale for including tg338 mice in this study was the possibility that characterisation of a prion

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Abbreviations: BSE, bovine spongiform encephalopathy; PrP^{res}, protease-resistant prion protein; TgBov, bovine tg540; TgOv, ovine tg338; TSE, transmissible spongiform encephalopathies; vCJD, variant Creutzfeldt-Jakob disease

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Synopsis

Prions are unconventional agents of proteic nature that are formed of abnormal conformations of the host-encoded prion protein (PrP). They cause fatal neurodegenerative diseases in both animals and humans and can be transmitted between species as exemplified in humans by the emergence of variant Creutzfeldt-Jakob disease following the epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom, since diagnosis of prion infection is only possible once the central nervous system has been invaded. Brains of slaughtered or fallen cattle are routinely screened in Europe to protect the consumers from BSE. This has unexpectedly led to the discovery of unprecedented PrP conformations that were distinct from the single one associated so far with BSE or BSE-related diseases. To precisely determine their etiology, the authors have studied the transmissibility of these new conformations, termed H-type, to transgenic mice expressing either bovine or ovine PrP. They show that these cases are highly pathogenic for these mice. The authors also demonstrate that they are not directly related to the agent involved in the BSE epidemics. Overall, the new data on isolation of a new prion strain from cattle, whose prevalence and associated zoonotic risk should be carefully monitored in the future,

accidentally passed from small ruminants to cattle might be facilitated on such mice, by comparison with the ovine isolates transmitted so far. Tg540 (tgBov) and tg338 (tgOv) mice overexpress PrP in the brain at similar levels (~8- to 10-fold). Both lines have a normal lifespan, the same as $PrP^{0/0}$ mice on which the transgenes were introduced. H-type isolates representative of a series of seven samples identified in France were inoculated intracerebrally to tgBov and tgOv mice (Table 1). Typical BSE agents from cattle and from other species was inoculated to the same mice for the sake of comparison. Remarkably, all H-type isolates induced a neurological disease on primary transmission, with a 100% attack rate in both mouse lines. The mean survival times observed with cases no. 1 and no. 2 in tgBov mice, ~400 d, appeared to be prolonged compared to those for cattle, sheep, goat BSE, and human vCJD inocula, which ranged from ~250 to 380 d. Such a discrepancy could reflect a lesser infectivity of H-type samples, consistent with their comparatively lower PrP^{res} content [9]. Moreover, the survival time was reduced by ~100 d on subpassage, approaching that for BSE from cattle or other sources on secondary passage, or on primary passage for inocula of presumably higher titre (i.e., producing no substantial reduction of survival time on subpassage: BSE no. 3 and ARQ [$Ala^{136}Arg^{154}Gln^{171}$] no. 1). Upon transmission to tgOv mice, the mean incubation period produced by the four H-type cases was strikingly homogeneous (586–612 d), consistent with a potentially unique agent (Table 1). This was comparable to or even shorter than the incubation periods of epizootic BSE or related inocula on the same mice (560–792 d). As illustrated in Figure 1, the relative incubation periods observed on tgOv and tgBov mice appeared to differ significantly among the H-type and BSE-type agents. In addition, the reduction in incubation period observed upon secondary transmission of H-type (case no. 2) on tgOv mice was significantly less dramatic than that observed for vCJD and sheep BSE inocula (Table 1). Overall, these suggested that H-type and BSE might be different TSE agents.

H-Type PrP^{res} Profile Is Preserved in Transgenic Mice

The brains of diseased mice were analysed by immunoblotting for the accumulation of abnormal PrP. PrP^{res} was readily detected in all mice tested since the first passage, consistent with the efficient transmission observed in both lines (10/10 and 33/33 positive brains for tgBov and tgOv mice, respectively). The PrP^{res} molecular profile was fairly uniform

Table 1. Transmission of Bovine Molecular Variant Cases (H-Type) to Transgenic Mice Expressing Bovine or Ovine PrP

Isolate	Case Number	Passage	Mean survival time, d ± SEM (n/n_0)[a]	
			tgBov Mice	tgOv Mice
H-type	1	First	414 ± 10 (5/5)	612 ± 26 (10/10)
		Second	317 ± 6 (8/8)	ND
	2	First	401 ± 9 (5/5)	595 ± 18 (8/8)
		Second	296 ± 3 (9/9)	319 ± 10 (6/6)
	3	First	ND	607 ± 12 (6/6)
	5	First	ND	586 ± 15 (9/9)
BSE	1	First	377 ± 22 (6/6)	ND
	3	First	298 ± 7 (9/9)	704 ± 36 (7/7)
		Second	283 ± 10 (5/5)	NA
Sheep BSE[b]	ARQ 1	First	278 ± 2 (6/6)	560 ± 60 (5/5)
		Second	263 ± 6 (6/6)	178 ± 2 (4/4)
	ARQ 3	First	339 ± 25 (5/5)	ND
	ARR 1	First	340 ± 8 (7/7)	ND
Goat BSE[c]	CH636	First	253 ± 9 (6/6)	590 ± 43 (4/4)
		Second	291 ± 27 (5/5)	NA
Variant CJD	NHBY0/0003	First	343 ± 8 (5/5)	792 ± 22 (6/6)
		Second	293 ± 11 (6/6)	195 ± 9 (6/6)
Control	Sheep brain	First	793 ± 26 (0/9)	835 ± 15 (0/6)

NA, not available; ND, not done.
[a]Intracerebral inoculation with 2 mg brain tissue equivalent; n/n_0: diseased/inoculated.
[b]Experimental cases.
[c]Field case.
DOI: 10.1371/journal.ppat.0020112.t001

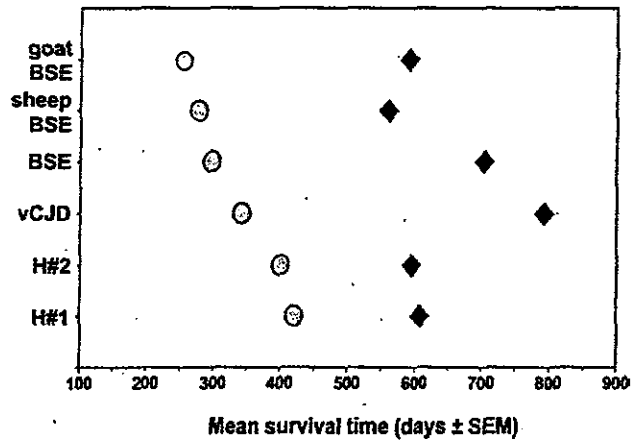

Figure 1. Survival Time in Transgenic Mice Infected with H-Type and BSE-Type Agents

Mean survival times (days ± SEM) upon primary transmission are shown for tgBov (grey circles) and tgOv (black diamonds) mice inoculated with H-type cases, BSE, and related isolates (see Table 1). The intervals between the incubation times on each line are significantly different for H-type and BSE agents ($p < 0.0002$, Fisher test).

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among the isolates. Remarkably, like the BSE agent for which the typical signature was conserved whatever the donor species (≥ 3 brains analysed per combination), the H-type agent essentially retained its biochemical phenotype upon serial transmission to tgBov as well as to tgOv mice expressing a heterologous PrP^C (Figure 2 and below). Compared to BSE PrP^{res}, it was characterised by a significantly higher apparent molecular mass (difference measured for unglycosylated species: 0.9 ± 0.05 kDa and 0.7 ± 0.06 kDa in tgBov and tgOv mice, respectively) and the relative proportions of glycoforms were essentially similar. A further difference was the lack of detectable PrP^{res} in the spleen of H-type diseased tgOv mice (three to five spleens tested per isolate), while this accumulated at substantial levels after BSE or vCJD infection (Figure 2B).

H-Type and Epizootic BSE Agents Exhibit Distinct Neuropathological Features

We next examined the PrP^{res} targeting and the vacuolation in the brain, which are known to exhibit a strain-dependent variation [6,15,16]. This was performed on tgBov mice since they express a PrP^C homologous to that of the donors, including the number of octarepeats [17], thus providing a relevant context for comparing H-type and epizootic BSE isolates. H-type isolates showed a similar distribution of PrP^{res} deposits on both primary and

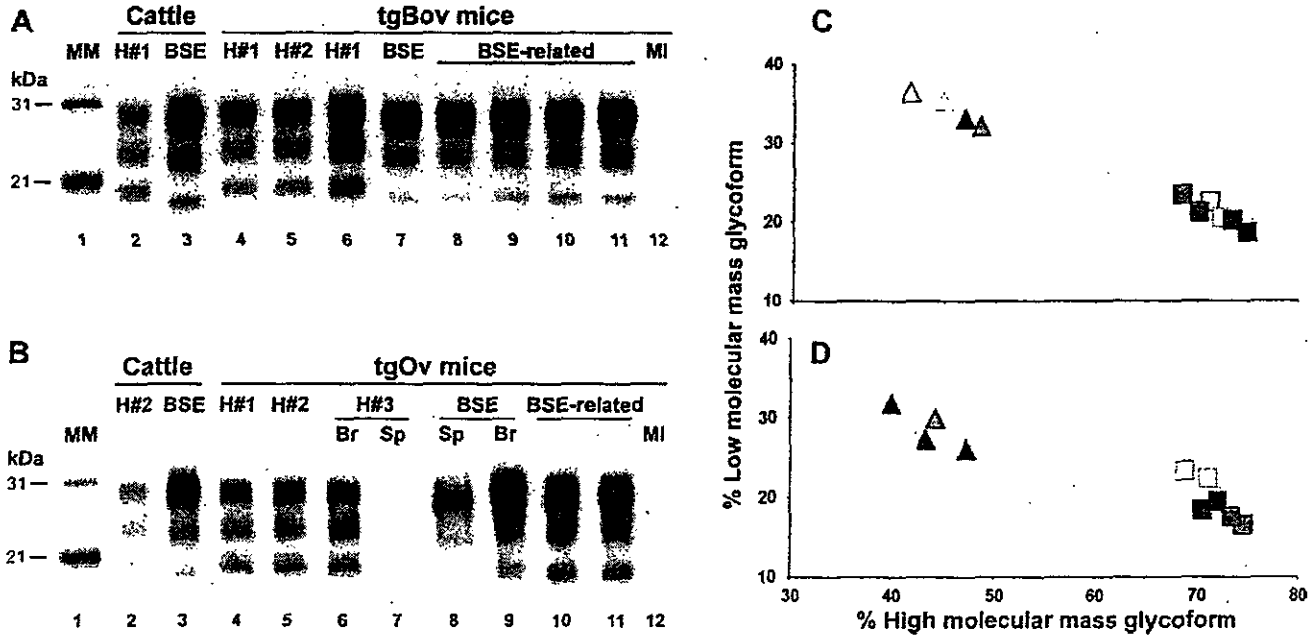

Figure 2. Western Blot Analysis of PrP^{res} in the Brains of Transgenic Mice Infected with H-Type or BSE-Type Agents

(A) Primary or secondary (lane 6) transmission to tgBov mice. BSE-type inocula include cattle BSE no. 3 (lanes 3 and 7), sheep BSE ARQ no. 1 and ARR no. 1 (lanes 8 and 9), goat BSE (lane 10), and vCJD (lane 11). The PrP^{res} profiles of both H-type and BSE agents in cattle (lanes 2 and 3) are essentially similar to those in tgBov mice (lanes 4–11). Brain tissue equivalent loaded: 2.5 mg in lane 2; 0.15 mg in lane 3; 0.5 mg in lanes 4–12. MI, mock-infected brain; MM, molecular markers.

(B) Primary transmission to tgOv mice. H-type agent shows a distinct PrP^{res} pattern in the brain (Br) compared to BSE agents (lane 9, BSE no. 3; lane 10, goat BSE; lane 11, vCJD). Note the lack of PrP^{res} signal in the spleen (Sp) of H-type–infected mice (lane 7), unlike that in BSE-infected mice (lane 8). Brain or spleen tissue equivalent loaded: 3 mg in lane 2; 0.15 mg in lane 3; 0.5 mg in lanes 4–6; 2 mg in lanes 7–12.

(C and D) Ratio of high- and low-molecular-mass PrP^{res} glycoforms in the brains of tgBov (C) and tgOv (D) mice following challenge with H-type or BSE agents (data plotted as means ± SEM). H-type isolates are represented as triangles (no. 1, blue; no. 2, orange; no. 3, pink; and no. 5, black) and BSE agents as squares (BSE no. 3, red; sheep BSE ARQ no. 1, grey; sheep BSE ARR no. 1, yellow; goat BSE, brown; and vCJD, light blue). Secondary transmissions are represented by unfilled symbols of the same colour. Note the strikingly distinct glycoform ratio between H-type and BSE groups in both mouse lines, as reported in cattle [9].

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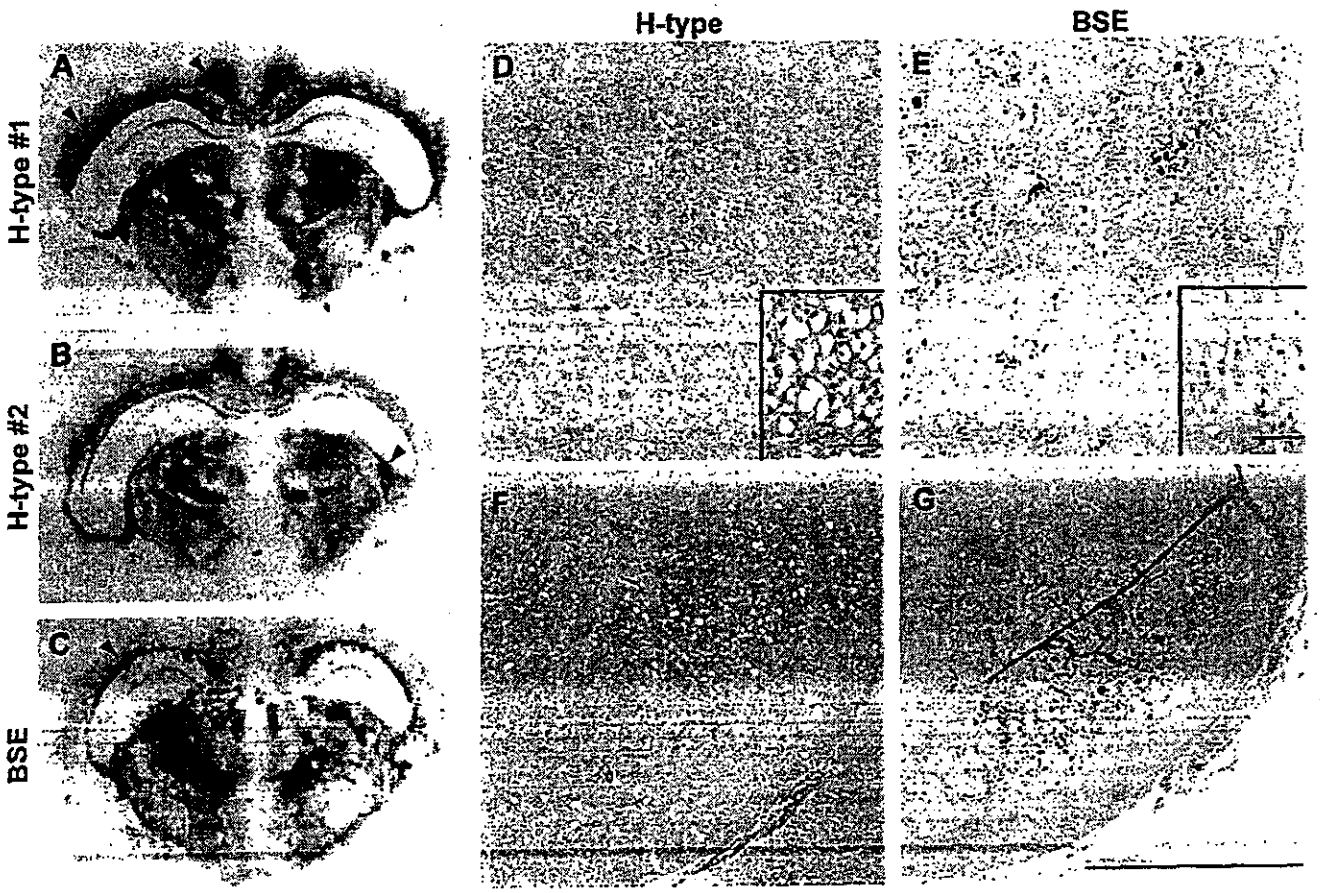

Figure 3. Regional Distribution of PrP^{res} and Vacuolar Changes in the Brains of Bovine Transgenic Mice Infected with H-Type or BSE Agents

Histoblots of representative coronal sections of tgBov mouse brains at the levels of the hippocampus are shown. The distribution of PrP^{res} deposits was similar among H-type isolates (A) (B), and different from that of cattle BSE (C) in several areas indicated by arrowheads, such as the cortex, the corpus callosum and dorsal commissure, alveus, fimbria, and stratum oriens of the hippocampus. Note that intensity of PrP deposition markedly differed between H-type and BSE agents. Illustration of how this appears by immunohistochemistry in the striatum (D) (E) and substantia nigra (F) (G), H-type–infected mice being less intensively labelled than those infected with BSE agent. By contrast, spongiosis was much more severe in H-type–infected brains. Bars: 30 μm; insert: 7 μm.

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secondary transmission, as assessed by histoblotting on brain coronal sections (Figure 3A–3B). The staining did not differ from that seen with cattle BSE in several regions, such as the striatum and several nuclei of the thalamus, including the geniculate, ventral postero-lateral and -medial as well as the brain stem (Figure 3A–3C and data not shown). However, other areas such as the cerebral cortex, the corpus callosum including the cingulum, the dorsal commissure, the alveus, and fimbria of the hippocampus were predominantly stained with H-type, whereas BSE PrP^{res} was rather confined in the stratum oriens of the hippocampus (Figure 3A–3C). Moreover, the overall intensity and aspect of PrP deposition markedly differed between the two types of agents. While immunochemistry revealed various types of PrP deposits in both cases, thin diffuse PrP deposits were predominant in H-type–infected brains, whereas the most frequent type was granular in BSE-infected mouse brains. In several areas, including the striatum and the substantia nigra (Figure 3D–3G), there was a striking lack of correlation between the intensity of PrP deposition and the severity of the vacuolation. Overall, the vacuolation was much more intense in the case of H-type variant (Figures 3 and 4): areas such as the septum, hypothalamus, hippocampus, and cortex showed severe spongiosis, accompanied by a pronounced reactive glial astrocytosis based on GFAP staining (not shown), while BSE-induced vacuolation was moderate in the same areas.

H-Type Agent Is Distinct from the Ovine TSE Isolates Transmitted so Far to tgOv Mice

We finally examined whether H-type isolates may have an ovine TSE origin. The majority of typical and atypical sheep scrapie isolates we have studied so far transmits before a year to tgOv mice ([13,14] and our unpublished data). Only a group of sheep scrapie isolates from Italy (SSit) was found to infect tgOv mice after a prolonged survival time within the range of H-type cases. Indeed three of them, SSit cases no. 5, no. 7, and no. 8, induced a typical neurodegenerative disease with a mean survival time of 698 ± 20 d (5/5 animals affected), 659 ± 31 d (7/7), and 569 ± 37 d (4/4), respectively. Case no. 5 incubation time was still longer than H-type case no. 2 on subpassage (417 ± 20 d, 6/6 animals affected). The PrP^{res} molecular profile observed in the brain of SSit-diseased mice