

Hypothesis

The origin of bovine spongiform encephalopathy: the human prion disease hypothesis

Scrapie theory	Human theory	
(1) Comparison of TSE in putative primary species with BSE in field cattle—ie, direct comparison of the diseases as far as possible in their “natural” state		
Context	Natural scrapie compared with “natural” BSE	
Clinical features	Human TSEs compared with “natural” BSE	
Neuropathology*	Not relevant	
Molecular analysis	Not relevant	
Neuropathology*	The distribution and local patterns of PrP staining and vacuolation are very variable in sheep scrapie, and depend on the sheep PRNP genotype. ¹ Generally the neuropathology of BSE has been very consistent. ² Only one in 20 show amyloid plaques. Two atypical cases have been reported recently. ³	Human TSEs show wide variation in neuropathology. ^{4,7} The two atypical cases of BSE ³ showed (i) plaque-like deposits similar to sCJD MV with PrP type 2 and (ii) a distribution of severity across different brain regions that differed from typical BSE cases.
Molecular analysis	All natural scrapie strains tested differ from BSE in their Mr-ngc, although several show a similar glycoform ratio. ^{8,10} However, one laboratory scrapie strain (CH1641) shares both parameters with BSE. ^{8,9}	BSE shares its glycoform ratio with certain types of fCJD (E200K and D178N), and has a low Mr-ngc, similar to many sCJD cases, kuru, and iCJD. ^{11,13} One subtype of fCJD (E200K-129V) shares both parameters with BSE. ¹⁴ 2 cattle BSE cases, recently reported, show a western blot profile that differs from all previous BSE cases, which is similar to certain sCJD types. ¹
(2) Experimental transmission from putative primary species to cattle		
Context	Experimental scrapie in cattle, compared with natural BSE	
Clinical features, neuropathology, molecular analysis	All published attempts to transmit scrapie to cattle via the oral route have failed. ^{15,16} Clinical signs and neuropathology of scrapie transmitted to cattle intracerebrally are markedly different from BSE. ^{17,19}	Human TSEs transmitted experimentally to cattle, compared with natural BSE
(3) Reverse transmission of cattle BSE to putative primary species		
Context	Experimental BSE in sheep compared with natural scrapie	
Clinical features	Many sheep BSE cases have much shorter clinical course than scrapie, and only a few show signs of pruritus (pronounced in nearly all field scrapie cases). However clinical features of experimental BSE in sheep are very variable and some cases are similar to field scrapie. ^{2,20,21}	vCJD compared with other human TSEs
Neuropathology	One scrapie strain shows a similar distribution of vacuolation to BSE in sheep, ¹ but the distribution of PrP ^{Sc} differs between scrapie and sheep BSE. ^{1,20}	The younger age of onset, longer illness duration, and prominent affective features at onset help to distinguish vCJD from sCJD, but occasional sCJD cases show these features. ^{6,7,22,23,24} Furthermore, the age of onset of an acquired TSE depends on the age at transmission. In fCJD, there is wide variation in clinical features, not only between but also within genotypes, ^{6,24} many of which overlap with vCJD.
Molecular analysis	BSE transmitted to sheep exhibits an Mr-ngc different from all except 1 scrapie strain (CH1641), although its glycoform ratio resembles that of scrapie. ^{8,9}	Overall, within the wide variation in neuropathological features of human TSEs, there are some notable similarities between vCJD, kuru, and certain fCJD types. ^{6,7,23,4,5,24,25}
(4) Experimental transmission to a tertiary species: (i) mice transgenic for bovine PRNP		
Context	Scrapie transmitted to mice transgenic for bovine PRNP, compared with BSE transmitted to the same mouse line.	Human TSEs transmitted to mice transgenic for bovine PRNP, compared with BSE transmitted to the same mouse line
Clinical features, neuropathology, molecular analysis	Scrapie transmits intracerebrally to mice transgenic for bovine PrP, but resulting neuropathology is quite different from BSE and incubation periods tend to be shorter. No molecular analysis results were described. ²⁶	vCJD readily transmits to mice transgenic for bovine PRNP, ²⁶ producing incubation periods, neuropathology and molecular analysis identical to those following BSE transmission. It has been stated ²⁷ that sCJD does not readily transmit, but no published results are available. Further experiments are needed to provide more evidence relevant to the human hypothesis.
(5) Experimental transmission to a tertiary species: (ii) other mouse lines or other species		
Context	Scrapie transmitted to mice, compared with BSE transmitted to the same mouse line.	Human TSEs transmitted to a tertiary species, compared with BSE transmitted to the same species.
Clinical features	No sheep scrapie strains resemble BSE in the distribution of incubation periods in different mouse lines, nor in the distribution of neuropathology following transmission to mice. ^{15,28–31†} As above	Incubation periods following transmission of sCJD to mice are generally longer than following transmission of BSE or vCJD. ^{31,32†} Transmission of GSS (P102L) to mice (based on 15 GSS cases of which five transmitted ³² yields incubation periods close to transmission of vCJD, ³¹ although these are in different mouse lines.† Transmission from one patient with the E200K mutation occurred with a long incubation period, ³² similar to sCJD, although again this was in a different mouse line.†
Neuropathology	As above	The lesion distribution in mice infected with sCJD differs from those infected with BSE or vCJD. ^{31†} Similarly, neuropathology in macaque BSE and vCJD differs from that of macaque sCJD. ^{33,34} Both the mouse and macaque data are based on a very few sCJD cases.
Molecular analysis	Following transmission to non-transgenic mice, all scrapie strains tested, except for 87V, differ from BSE in their Mr-ngc, although several show a similar glycoform ratio. ^{35–37†}	Transmission of BSE and vCJD to non-transgenic and certain transgenic mice has in some instances yielded molecular analysis profiles that resemble the BSE signature, and therefore differ from the other human TSEs apart from E200K-129M. ^{31,38} However in other recipient mice, BSE (SJL,† RIIS,† and HuPrP ¹⁴ -Prnp ^{0/0} 129MM mice‡) and vCJD (HuPrP ¹⁴ -Prnp ^{0/0} 129VV mice‡) yield an Mr-ngc and a glycoform ratio identical to sCJD. ^{39,40}

Primary species=putative origin. Secondary species=natural recipient of transmitted infection (here cattle). Tertiary species=another species used for research. Here this is usually mice, to which infection from the primary or secondary species is transmitted. Glycoform ratio=proportions of glycosylated and non-glycosylated components following partial digestion by proteinase K. Mr-ngc=molecular mass of non-glycosylated component produced following partial digestion by proteinase K. *Neuropathology comparisons are only of limited value between different species, and are influenced by the dose and route of infection. Mouse lines used in strain comparisons: †non-transgenic mice;‡mice transgenic for human PrP.

Webtable: Scrapie and human theories of the origin of BSE: summary of evidence about disease and strain characteristics

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