Advances in scrapie research

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Summary
The bovine spongiform encephalopathy (BSE) crisis clearly demonstrated the need to keep animal transmissible spongiform encephalopathies (TSE) under control in order to protect animal and human health. Scrapie is the most widespread TSE of livestock in the world. For this reason, health authorities in different countries have elaborated plans that aim towards scrapie eradication. The unusual nature of the scrapie agent and the fragmented status of scientific knowledge about it, along with the limitations of currently available diagnostic tools, make it unlikely that the objective of eradication will be achieved in the near future. Scientific research is focused on acquiring the knowledge that will improve the efficiency of these efforts.

Keywords

Introduction
Scrapie is a fatal, progressive neurodegenerative disease of sheep and goats that is one of the transmissible spongiform encephalopathies (TSE), also known as prion diseases. It was first reported in Great Britain in 1730 and then later in France and Germany (33). In the last fifty years intense research activity has been aimed at explaining the different and sometimes contradictory features of this disease.

The nature of the scrapie agent has been a mystery for a long time. In the 1980s it was considered to be an atypical virus belonging to the slow virus group (95). Later studies by Alper et al. (4) and Prusiner (90) dismissed the viral theory. Prusiner formulated a new theory called ‘the protein only hypothesis’, and suggested that the scrapie agent is a pathogenic protein with infectious features, that he called a prion (91).

The recent bovine spongiform encephalopathy (BSE) crisis clearly demonstrated the need to keep animal TSE under control in order to protect animal and human health. For this reason, health authorities in different countries have elaborated plans that aim towards scrapie eradication, which combine the reinforcement of surveillance activities with breeding programmes to increase the genetic resistance of sheep (40). The nature of scrapie and the fragmented status of current knowledge make it unlikely that this objective will be achieved within a short time frame. Scientific research is focused on acquiring knowledge to improve the efficiency of these efforts. The present article aims to update the scientific information available on this issue, which is of current interest for public and animal health.

Geographical distribution of scrapie

Figure 1 shows countries in which scrapie was identified between 1996 and 2004. The chart is based on data...
obtained from the ongoing surveillance performed by Member States of the European Union (EU) (43) and information available from the OIE database Handistatus II (since 2004 Handistatus II has been replaced by the World Animal Health Information Database [WAHID], but information from Handistatus II is still available at http://www.oie.int/hs2/report.asp?lang=en). Scrapie is endemic in large parts of Europe, mainly in Western Europe. Several cases were reported in Sweden in 2004 and 2005, after a long period of absence. The disease is also present in Canada, the United States of America, Brazil, Ethiopia, and Japan. It has been reported in Israel since 1993. At the beginning of the 1950s scrapie was reported in Australia and New Zealand, however, these countries have successfully eradicated the disease using rigorous health measures and they are currently considered to be ‘scrapie free’ (33). Similarly, scrapie was reported in South Africa for the last time in 1972. In numerous countries scrapie has never been reported, and in others the information available is incomplete for the period under study. It is important to underline the fact that huge differences exist in the intensity and effectiveness of surveillance activity organised in various countries.

Aetiology

The ‘protein only hypothesis’ proposed by Prusiner suggests that the TSE agent originates from prion protein, or PrP. Prion protein exists in two different forms: one is cellular PrP (PrP\textsuperscript{C}), a glycoprotein normally associated with the cell membrane and encoded by the PRNP gene; the other is scrapie-associated PrP (PrP\textsuperscript{Sc}), which accumulates in the brains of affected animals. The two isoforms share the same amino acid sequence, but they differ in the folding of the molecule. Prusiner’s theory proposes that PrP\textsuperscript{Sc} molecules, spontaneously generated in the organism or derived from a contaminated external environment, are able to induce a conformational change of PrP\textsuperscript{C} to PrP\textsuperscript{Sc}, which triggers a pathological refolding chain reaction. The central role of PrP in TSE has been demonstrated by the use of knockout PrP\textsuperscript{0/0} mice. Inactivation of the PRNP gene renders mice completely resistant to experimental challenge with TSE agents (24). Prusiner’s theory has been the subject of considerable controversy. Recently, two scientific studies have been published that provide strong evidence in support of the protein only hypothesis. In the first, Legname \textit{et al.} synthesised an artificial peptide in \textit{Escherichia coli} that corresponded to the 89–230 fragment of mouse PrP (MoPrP\textsuperscript{89–230}). Once folded into a beta-sheet rich conformation, the peptide was able to induce neurological dysfunction at between 380 and 660 days after infection when inoculated intracerebrally into transgenic mice expressing MoPrP\textsuperscript{89–231}. Brain extracts from these animals were able subsequently to transmit the disease to wild-type mice in 150 days (74). In 2005, Castilla and colleagues reported the in \textit{vivo} conversion of PrP\textsuperscript{C} to PrP\textsuperscript{Sc} using a technique called protein misfolding cyclic amplification (PMCA), which resulted in indefinite amplification of PrP\textsuperscript{Sc}. The in \textit{vivo} generated forms of PrP\textsuperscript{Sc} showed similar properties to PrP\textsuperscript{Sc} derived from diseased brain tissue, and, when inoculated into wild-type hamsters, led to a scrapie-like disease that was similar to the illness produced by infectious brain material (27).
Genetics of susceptibility to scrapie in sheep and goats

The influence of genetics on scrapie susceptibility in sheep has been studied for many years (36). Polymorphisms in the key positions 136 (63, 72), 154 (16) and 171 (50) of the ovine PrP chain are strongly associated with the overall susceptibility to natural and experimental scrapie and experimental BSE. The allele ARQ, which carries alanine (A) at codon 136, arginine (R) at 154 and glutamine (Q) at 171, is considered to be the wild type. The amino acid substitutions A136V, R154H, Q171R and Q171H generate allelic forms with variable degrees of susceptibility to the disease, ranging from high susceptibility to very strong resistance (16, 28, 100, 103). The susceptibility of different genotypes has been assessed in relation to the risk of developing the clinical signs of scrapie (11, 13, 84, 102). In accordance with the British National Scrapie Plan (NSP), the European Commission (40) has grouped the PrP genotypes of sheep into five classes representing different levels of risk:

- NSP1: the most resistant genotype, ARR/ARR
- NSP2: genotypes with high resistance, ARR/ARQ, ARR/ARH, ARR/AHQ
- NSP3: genotypes with low resistance; this class is further divided into ‘NSP3 ARQ/ARQ’ and ‘NSP3 others’: AHQ/AHQ, ARH/ARH, ARH/ARQ, AHQ/ARH, and AHQ/ARQ
- NSP4: the genetically susceptible genotype, ARQ/VRQ
- NSP5: genotypes with high susceptibility: ARQ/VRQ, ARH/VRQ, AHQ/VRQ, and VRQ/VRQ.

Prion protein allele frequencies vary with sheep breeds. In Europe, a generally high prevalence of ARQ and ARR alleles has been observed, but some breeds show a significantly high frequency of VRQ, ARH and AHQ (37, 41).

In general, when scrapie arrives in a flock the first animals affected are those carrying the VRQ/VRQ genotype. The disease is especially associated with the ARQ/ARQ genotype in sheep breeds where the VRQ allele is rare or absent. It has been reported recently that in the Massese (108) and Steigard (17) breeds, the ARQ/ARQ and ARQ/AHQ genotypes are the main target of the scrapie agent, even in the presence of animals carrying the VRQ allele. In Mediterranean countries (Greece, Spain and Italy) most cases are in ARQ/ARQ animals (43). This difference seems not only to be due to a greater frequency of the ARQ/ARQ genotype in sheep from these countries, but to a greater relative susceptibility of the ARQ/ARQ genotype. To explain this finding, two hypotheses have been proposed:

- different genetic targeting of the particular scrapie strain involved in the outbreak
- the effect of genetic factors other than PRNP in the various sheep breeds affected, which are able to modulate their susceptibility to scrapie (12).

In 2005, Diaz et al. (34) estimated that about 20% of the overall genetic susceptibility to scrapie is controlled by genes other than PRNP. The existence of genes with quantitative effects (quantitative trait loci [QTL]) that influence the incubation period of scrapie in infected animals has been demonstrated in mice (78, 80, 98), and in sheep (30). Several chromosome regions have been identified in which such genes are thought to be located.

The role of different strains of scrapie in influencing the genetic susceptibility of sheep to scrapie, has been known for a long time. Cheviot sheep with the ARQ/ARQ genotype were found to be resistant to experimental challenge with the SSBP/1 scrapie strain (50) but were susceptible to the CH1641 strain (43). More recently, the preferential targeting of the BSE agent to the ARQ/ARQ genotype has been demonstrated in experimentally infected sheep (50).

Cases of natural scrapie are reported in heterozygous VRQ/ARR sheep but are rare when the ARR allele is accompanied by other non-VRQ alleles. Knowledge gathered during recent decades from surveillance and experimental investigations led to the belief that ARR/ARR sheep were resistant or had an extremely low susceptibility to scrapie (6, 39, 53, 55, 66, 106). Up until 2006 only one unconfirmed case of scrapie had been found in ARR/ARR sheep (64). However, the recent detection of ‘atypical’ forms of TSE affecting resistant sheep genotypes has brought such beliefs into question and raised doubts about the effectiveness of sheep breeding programmes for genetic resistance to scrapie (14, 25, 81, 86).

Less knowledge is available regarding the genetic susceptibility of goats to scrapie. Several mutations in the open reading frame (ORF) of goat PRNP have been identified. Among them, the 12 most frequent have been detected in different goat breeds, they are: G37V, T110P, G127S, I142M, H143R, R154H, P168Q, Q222H, Q222K, and S240P. Other mutations are rare and seem to be specific to particular breeds or to geographical regions (1, 2, 18, 51, 70, 87, 104, 112). The effect of PrP alleles on scrapie susceptibility in goats has been evaluated by studying natural outbreaks. A significant association is observed between scrapie and the wild-type PrP allele. In contrast, it has been observed that the H142M (51), H143R, R154H (18), N146S, N146D (87) and Q222K (1, 104) polymorphisms have a pronounced protective effect. Moreover, Goldmann et al. have described an allelic variant of PrP that is composed of three instead of...
the usual five octapeptide repeats, which seems to be associated with prolonged incubation time in goats experimentally inoculated with the SSBP1 strain of scrapie (49).

Transmission and pathogenesis

Scrapie is transmissible under natural conditions. However, its transmission routes are still unknown. The scrapie agent is able to persist for a long time in soil (19, 68). Environmental contamination and infected fetal membranes probably transmit the disease from ewe to lamb and among adult sheep (54, 59). The presence of PrPSc in the placenta has been studied by Andreoletti et al. (7) and Alverson et al. (5). They have demonstrated that the presence of PrPSc in cotyledons depends on the genotype of the lamb. In fact, PrPSc was detectable only in the placenta of fetuses carrying susceptible genotypes (VRQ/VRQ, ARQ/VRQ or ARQ/ARQ).

The scrapie agent probably enters the organism by the oral route (33, 89), as occurs with other types of human and animal TSE such as BSE and variant Creutzfeldt-Jakob disease (vCJD). The latter is the human TSE that has been associated with the consumption of BSE-infected foodstuffs (23, 29). Iatrogenic transmission of TSE is also well documented in humans; indeed, more than 200 cases are recorded as having originated from neurosurgery and treatment with cadaver-derived growth hormone (20). Since December 2003, three individuals have been identified with vCJD infection that was probably acquired from blood transfusion (77, 88, 111). In animals, iatrogenic transmission of scrapie occurred in England in 1936 via contaminated louping ill vaccine (92). More recently, an epidemiological association was observed in Italy between scrapie outbreaks and the administration of a formol-inactivated vaccine against contagious agalactia that was prepared using brain and mammary gland homogenates of sheep infected with Mycoplasma agalactiae (3, 26).

After entering via the oral route, it has been proposed that transportation of the scrapie agent across the intestinal mucosa could occur via the M cells, which are cellular elements specialised in the uptake of macromolecules from the enteric lumen (56), or across the absorptive epithelium of intestinal villi into the lacteals (65). Jeffrey et al. observed that at this stage the PrP genotype does not influence the uptake of prion from the enteric lumen (65).

In early preclinical stages, PrPSc accumulates in gut associated lymphoid tissue (GALT), in particular in the palatine tonsils and Peyer’s patches (6, 107). PrPSc is observed in the germinal centres of lymphatic follicles, associated with follicular dendritic cells (FDC) and macrophages (79, 105) (Fig. 2). Then, gradually, the infectious agent colonises the whole GALT system and subsequently spreads to non-GALT regions of the lymphoreticular system (LRS) and central nervous system (CNS). Colonisation of the LRS precedes by many months the appearance of clinical signs; however, it has been observed that PrPSc accumulation in the LRS is not indispensable for neuroinvasion (76, 93, 94, 105). The possibility of early detection of PrPSc in the lymphoid tissue of the rectal mucosa has been demonstrated recently (52). This represents a significant improvement towards the ante-mortem identification of scrapie-infected animals by analysing tissue samples that are readily accessible for biopsy.

Differences in the LRS distribution of PrPSc between different genotypes of sheep have been observed. In VRQ/VRQ and ARQ/ARQ sheep, a similar pathogenic pathway has been observed, although it appears that PrPSc accumulation in the LRS of ARQ/ARQ sheep happens more tardily than in VRQ/VRQ animals (53, 66). The VRQ/ARR genotype is often associated with a lack of lymphatic involvement (71).

The enteric nervous system (ENS) represents one of the gateways through which the scrapie agent enters the nervous system. The scrapie agent, progressing into the CNS along the nerve fibres, enters the spinal cord and brain stem (Fig. 3). It is probable that other routes exist that allow the scrapie agent to reach the brain, such as nerves from lymphoid organs or haematogenous spread (79, 107).

The presence of the infectious agent in blood has been demonstrated through the successful experimental transmission of scrapie and BSE to sheep by blood transfusion (60, 62). In recent years efforts have been concentrated on the attempt to develop diagnostic tests that allow the detection of the scrapie agent in live animals.
Several tests that are under development are described as having a demonstrated or potential capacity to detect PrPSc in blood (111).

Ruminant tissues are grouped by the World Health Organization (WHO) into two major categories of infectivity in relation to the demonstration of PrPSc and/or infectivity (111). The CNS and those tissues that are anatomically associated with the CNS are considered to be high-infectivity tissues. The lower-infectivity tissues are: the peripheral nervous system, lymphoreticular system, bone marrow, gut, liver, kidney, adrenal gland, pancreas and placenta. Infectivity has also been found in blood vessels, skeletal muscles, tongue, salivary gland, nasal mucosa and body fluids such as blood and cerebrospinal fluid. Infectivity or PrPSc has not been detected in other organs or tissues.

The pathogenesis of BSE in sheep has been studied by inducing experimental infection by the oral (6, 15, 67), intraperitoneal (9) and intracerebral routes (61). In contrast to BSE in cattle, where infectivity is mainly concentrated in the CNS (110), infectivity or PrPSc is widely diffused in sheep tissues, as is the case with scrapie. Sheep with the ARQ/ARQ genotype are the most susceptible to BSE (61). Strikingly, Houston et al. reported that 3 out of 19 intracerebrally inoculated ARR/ARR sheep, but none of the inoculated ARQ/ARR sheep, showed clinical signs of BSE after long incubation periods (61). Intracerebral inoculation is extremely effective at inducing the infection; therefore, this result does not necessarily imply that ARR/ARR sheep are susceptible to BSE under natural conditions. Nevertheless, Andreoletti and colleagues recently detected the accumulation of PrPSc in the spleen of one out of six ARR/ARR sheep that had been orally infected with BSE (8). Overall, the reports of atypical scrapie cases in resistant genotypes, together with the findings obtained in ARR/ARR sheep, challenged with the BSE agent, demonstrate that genetic resistance is not an absolute concept and that there are circumstances in which animals that are supposed to be genetically resistant could indeed be susceptible. This demands examination of the impact of ARR/ARR susceptibility on the progress of breeding programmes currently ongoing in different European countries and on their likely success in controlling or, possibly, eradicating TSE in sheep.

Prion strains

The existence of different scrapie strains was reported for the first time in the late 1960s (35, 46, 47). In experimentally inoculated mice, strains determine the specific duration of the incubation period, as well as the characteristic distribution and intensity of neurological lesions (the lesion profile). These characteristics are maintained upon serial passage in the same mouse line (22, 35). Classically, the procedure for strain typing is based on the inoculation of a defined panel of inbred mice lines in which the incubation time and the lesion profile give the specific ‘signature’ of a strain (21). However, the excessive length of the incubation period, or even the failure of transmission upon inoculation of wild-type mice, may prevent the efficient characterisation of many scrapie isolates. Recently, a number of improved animal models for scrapie have been developed. Transgenic mice expressing ovine PrP (31, 109) and the bank vole, a rodent species which has proved to be very susceptible to a number of animal and human TSE agents (82), appear among the most promising models for characterising scrapie isolates. Recently, the risk of the circulation of BSE in small ruminant populations and the need to develop analytical
methods for rapid and efficient discrimination between scrapie and BSE led to the investigation of the molecular properties of PrPSc, and the eventual demonstration that the properties can vary depending on the TSE strain involved (96). These properties are usually analysed by protease K digestion and immunoblotting, which allow the measurement of the molecular weight and glycoform ratios of the protease-resistant core of PrPSc. Several reports have shown that experimental BSE in sheep is characterised by the accumulation of a distinctive PrPSc, which can be discriminated from that of scrapie on the basis of molecular weight and glycoform pattern (9, 57, 58, 83, 99). In fact, PrPSc from most scrapie cases has a higher molecular weight and a lower glycoform ratio than that from sheep BSE, while a minority of the scrapie cases so far reported have been characterised by an electrophoretic mobility even higher than that of BSE (58). The molecular features of ovine BSE are similar to those found in BSE in cattle and several BSE-related prion diseases (29, 57). The low apparent molecular weight of BSE-related PrPSc is a consequence of the protease K cleavage site of PrPSc, which is slightly closer to the C-terminal compared with that of scrapie PrPSc. Based on this finding, Stack et al. (96) recently demonstrated that the epitope of the P4 monoclonal antibody, which is at the N-terminus of PrP (amino acids 93–98 of ovine PrP), is indeed usually cleaved by proteinase K in ovine BSE and spared in ovine scrapie. These findings have paved the way for the development of discriminatory immunoblotting methods (75, 101).

In 2005 the first case of naturally-occurring BSE in a goat, which was slaughtered in 2002, was confirmed in France by the combined use of bioassays and molecular strain typing (38). This is the only case of BSE that has been identified in small ruminants, to date.

In recent years, our knowledge of the extent of TSE strain variability that occurs under natural conditions in small ruminants has improved significantly. In 1998 a novel form of scrapie caused by a new strain of the agent, or perhaps a novel TSE, was reported in sheep in Norway (17). This form of the disease, named Nor98, can be differentiated from classical scrapie by its pathology, epidemiology, form of the disease, named Nor98, can be differentiated by the combined use of bioassays and molecular strain typing (96). These properties are usually analysed by protease K digestion and immunoblotting, which allow the measurement of the molecular weight and glycoform ratios of the protease-resistant core of PrPSc. Several reports have shown that experimental BSE in sheep is characterised by the accumulation of a distinctive PrPSc, which can be discriminated from that of scrapie on the basis of molecular weight and glycoform pattern (9, 57, 58, 83, 99). In fact, PrPSc from most scrapie cases has a higher molecular weight and a lower glycoform ratio than that from sheep BSE, while a minority of the scrapie cases so far reported have been characterised by an electrophoretic mobility even higher than that of BSE (58). The molecular features of ovine BSE are similar to those found in BSE in cattle and several BSE-related prion diseases (29, 57). The low apparent molecular weight of BSE-related PrPSc is a consequence of the protease K cleavage site of PrPSc, which is slightly closer to the C-terminal compared with that of scrapie PrPSc. Based on this finding, Stack et al. (96) recently demonstrated that the epitope of the P4 monoclonal antibody, which is at the N-terminus of PrP (amino acids 93–98 of ovine PrP), is indeed usually cleaved by proteinase K in ovine BSE and spared in ovine scrapie. These findings have paved the way for the development of discriminatory immunoblotting methods (75, 101).

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Recently, a few cases of TSE in sheep in France, the UK and Cyprus have shown unusual molecular features which seem to be intermediate between BSE and scrapie. After transmission to transgenic ovinised mice (TgOvPrP4) it has been observed that some of the isolates from France have characteristics similar to those of the scrapie isolate CH16+1 (10, 42, 97).

Conclusions

Only a few years ago, all TSE cases in small ruminants were identified as scrapie. The situation that has been revealed by the progress of research appears much more complex: BSE has been identified in a goat, Nor98 and atypical cases have been described, and, more recently, sheep TSE cases with molecular features in common with BSE have been found. Moreover, evidence exists that biological variability is detectable even among isolates of ‘classical’ scrapie (21). Such complexity has important implications for diagnostic and epidemiological surveillance, and has an impact on risk assessment, with consequences for the intensity of control and prophylactic measures. The possibility of control in such a multifaceted situation requires a further increase of knowledge obtained by integrating surveillance with experimental activities.

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Les progrès de la recherche sur la tremblante

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Résumé
La crise liée à l’épizootie d’encéphalopathie spongiforme bovine (ESB) a clairement établi la nécessité de contrôler les encéphalopathies spongiformes transmissibles (EST) des animaux afin de protéger la santé animale et la santé publique. La tremblante est l’EST la plus répandue parmi les animaux d’élevage. En conséquence, elle fait l’objet de programmes d’éradication dans plusieurs pays. En raison des caractéristiques atypiques de l’agent causal, des lacunes dans les connaissances scientifiques s’y rapportant et des insuffisances des outils diagnostiques actuellement disponibles, l’éradication à court terme de la tremblante paraît improbable. La recherche scientifique est actuellement axée sur les connaissances nécessaires pour améliorer l’efficacité des efforts entrepris.

Mots-clés

Avances en la investigación sobre el prurigo lumbar

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Resumen
La crisis de la encefalopatía espongiforme bovina (EEB) puso claramente de manifiesto la necesidad de mantener bajo control las encefalopatías espongiformes transmisibles (EET) en los animales para proteger la salud tanto de éstos como de las personas. El prurigo lumbar es la EET más frecuente en el ganado, y por este motivo las autoridades sanitarias de distintos países han elaborado planes para erradicarlo. La singularidad de su agente patógeno y el carácter fragmentario de los conocimientos científicos al respecto, junto con las limitaciones de los instrumentos de diagnóstico hoy por hoy disponibles, hacen poco probable que en un futuro próximo se pueda cumplir el objetivo de la erradicación. La investigación científica está centrada en obtener los conocimientos necesarios para que esas iniciativas resulten más eficaces.

Palabras clave
References


