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ALZHEIMER´S DISEASE AND BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) CONNECTIONS

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Abstract text (PP-060)

Prion diseases, also called transmissible spongiform encephalopathies (TSEs), are a group of fatal neurodegenerative disorders affecting animals (BSE, scrapie…) and humans (CJD…). Until recently, TSEs encapsulated a distinct category of neurodegenerative disorder, exclusive in their defining characteristic of infectivity (prion diseases). It now appears sclerosis (ALS).that similar mechanisms of self-propagation may underlie other proteinopathies (prion-like diseases) such as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosir (ALS).

However, only prion disease has been established as the sole „bona fide infectious" disease among these protein misfolding disorders (neurodegenerative diseases). The misfolding and aggregation of endogenous proteins in the central

nervous system is a neuropathological hallmark of above mentioned neurodegenerative diseases. Prions („infectious“) are produced by recruiting the normal cellular prion protein (PrPc) and stimulating its conversion into the disease causing isoform PrPsc (derived from scrapie).

The new prion diseases that have emerged in the last 25 years are BSE and variant Creutzfeldt-Jakob disease (vCJD). The accepted cause of vCJD is that BSE spread from cattle to humans by the consumption of infected beef. However, the evidence that supports this is very thin. Despite probable widespread exposure of the UK population to BSE-contaminated food in the 1980s, there have been only fewer cases of vCJD, than researchers anticipated. The reasons for this are to date uncertain. The temporal relationship between BSE and vCJD (1990s) only coincidentally supported the notion that BSE caused vCJD, and as such is not evidence. The evidence other than this comes from research using mouse models and analysis of subtypes of abnormal prion protein. This supporting evidence was related to four papers published in high-ranking journals (1996- 1999).

These experimental mouse models were later supported by the mathematical BSE/vCJD models in about 13 scientific articles (1996- 2006). So these „infectious conclusions“ were finished in 2006, when it was found that „Alzheimer's may 'seed' itself like BSE”, if proteins taken from the brains of Alzheimer's patients and injected into the brains of genetically engineered mice trigger Alzheimer's-like lesions in the mouse brains.

Later, many other similar studies showed that the pathology of AD, PD and ALS can be transmitted to animals in a way similar to that by which a prion disease was transmitted with PrP inoculation. These neurological disorders can be produced by either peripheral (extracerebral) or direct brain (intracerebral) inoculation. Those findings provide evidence of cell-to-cell spread of pathologic proteins of neurological disorders in experimental animals, suggesting those pathological proteins may have seeding abilities, like prion diseases, to transmit pathology. Experimental studies have shown that the aggregation of the AD-associated proteins amyloid-β (Aβ) and tau, and of the PD-associated protein α-synuclein, can be stimulated in laboratory animal models by intracerebral injection of inocula containing aggregated species of the respective proteins.

Knowing that amyloid-β and similar proteins act like prions, researchers are left wondering why no one has recorded a case of the proteins passing from person to person, when on the basis of laboratory results, all neurodegenerative diseases should be infectious. However, to date, there is no direct evidence in humans indicating that the diseases caused by misfolded Aβ, tau, α-synuclein are infectious. Again, as in the case of BSE / CJD infection, reasons for this are uncertain.

Taken together, these results are consistent with the fact that BSE and scrapie (prion diseases) are not infectious (it has never been scientifically proven), as has been presented at the last World Veterinary Congresses (2008, 2013). Similarly, also other neurodegenerative diseases are not infectious, relevant connections mentioned above will be interpreted at the Congress.

Keywords: neurodegeneration, BSE, Alzheimer´s disease

Poster text;

Neurodegeneration- „infection" in animals and humans

Prion diseases, also called transmissible spongiform encephalopathies (TSEs), are a group of fatal neurodegenerative disorders affecting animals (BSE, scrapie…) and humans (variant Creutzfeldt-Jakob disease -vCJD…). Until recently, TSEs encapsulated a distinct category of neurodegenerative disorder, **exclusive in their defining characteristic of infectivity (prion diseases)**. It now appears that similar mechanisms of **self-propagation may underlie other proteinopathies (prion-like diseases) such as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS).** However, only prion disease has been established as the sole „bona fide infectious" disease among these protein misfolding disorders (neurodegenerative diseases). The misfolding and aggregation of endogenous proteins in the central nervous system is a neuropathological hallmark of above mentioned neurodegenerative diseases. Prions („infectious") are produced by recruiting the normal cellular prion protein (PrPc) and stimulating its conversion into the disease causing isoform PrPsc (derived from scrapie). The new prion diseases that have emerged in the last 25 years are **BSE and variant Creutzfeldt-Jakob disease (vCJD).** The accepted cause of vCJD is that BSE spread from cattle to humans by the **consumption of infected beef**. However, the evidence that supports this is very thin. Despite probable widespread exposure of the UK population to BSE-contaminated food in the 1980s, there have been **only fewer cases of vCJD, than researchers anticipated**. The reasons for this are to date uncertain. The temporal relationship between BSE and vCJD (1990s) **only coincidentally supported the notion that BSE caused vCJD,** and as such is not evidence. The evidence other than this comes from **research using mouse models** and analysis of subtypes of abnormal prion protein.

Supporting evidence about the „infectious neurodegeneration"

This supporting evidence was related to **four papers published in high-ranking journals (1996- 1999),** see some „citations" from these journals;

COLLINGE, J. et al; **Nature**, **1996**; 'New variant' Creutzfeldt-Jakob disease (vCJD) has strain characteristics…, consistent with BSE being the source of this new disease.

HILL, A.F. et al; **Nature**, **1997**; The same prion strain causes vCJD and BSE.

BRUCE, M.E.; WILL, R.G.; IRONSIDE, J.W. et al; **Nature**, **1997**; Transmissions to mice indicate that new variant CJD is caused by the BSE agent.

SCOTT, M.R.; WILL, R.G., IRONSIDE, J. et al; **PNAS**, **1999**; Our findings provide the most compelling evidence to date that prions from cattle with BSE have infected humans and caused fatal neurodegeneration.

See also other journals, mostly as the „mathematical BSE/vCJD models"(1996- 2006);

WILL, R.G. et al; **Lancet**, **1996**; A new variant of Creutzfeldt-Jakob disease in the UK.

PRUSINER, S. B; **Science**, **1997**; There is now considerable concern that bovine prions (BSE) may have been passed to humans, resulting in a new form of CJD.

WILL, R.G.**; Dev Biol Stand., 1998;** Current evidence strongly supports the hypothesis that there is a causal link between BSE and vCJD disease.

PRUSINER, S.B.; **PNAS**, **1998**; Prions are unprecedented infectious pathogens that cause a group of invariably fatal neurodegenerative diseases by an entirely novel mechanism.

COLLINGE, J.; **Lancet**, **1999**; It is clear that the prion strain causing BSE in cattle has infected human beings.

GHANI, A.C. et al; **Nature**, **2000**; Predicted vCJD mortality in Great Britain, the current mortality data are consistent with between 63 and 136,000 cases among the population known to have a susceptible genotype (about 40% of the total population).

WILL, R.G. et al.; **Ann Neurol**., **2000**; As of December 31, 1998, 35 deaths had been attributed to vCJD in the United Kingdom.

ANDREWS, N.J. et al; **Lancet**, **2000**; Incidence of vCJD disease in the UK.

D'AIGNAUX, J.N. et al; **Science**, **2001**; Predictability of the UK Variant Creutzfeldt-Jakob Disease Epidemic.

ANDREWS, N.J.; Lancet, **2003**; Deaths from variant Creutzfeldt-Jakob disease in the UK. We analysed data for deaths from vCJD since 1995 and estimated the underlying trend in mortality.

D'AIGNAUX, J.N. et al; **Stat Methods Med Res**., **2003**; The predictability of the epidemic of vCJD disease by back-calculation methods.

SMITH, P.G. et al; **Curr Top Microbiol Immunol**., **2004**; The epidemiology of vCJD.The modelling is limited by the absence of a test for infection with the vCJD agent.

LLEWELYN, C.A. et al; **Lancet, 2004**; Oour findings raise the possibility that this infection was transfusion transmitted. Infection in the recipient could have been due to past dietary exposure to the BSE agent**.**

WILL, R.G.; **Int J Epidemiol**., **2005**; Commentary: The risk of vCJD Disease: reassurance and uncertainty.

CLARKE, P; GHANI,A.; **J. Royal Soc. Inter**., **2005**; Projections of the future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility.

COLLINGE, J. et al; **Lancet**, **2006**; Kuru in the 21st century--an acquired human prion disease with very long incubation periods. **Incubation periods of infection with human prions can exceed 50 years.**

The designation of prions as infectious agents has become problematic

Above mentioned „infectious conclusions“ were finished in 2006, when it was found that **„Alzheimer's may 'seed' itself like BSE“**, if proteins taken from the brains of Alzheimer's patients and injected into the brains of genetically engineered mice trigger Alzheimer's-like lesions in the mouse brains (JUCKER and WALKER,2006).

Later, many other similar studies showed that the **pathology of AD, PD and ALS can be transmitted to animals in a way similar to that by which a prion disease (BSE…) was transmitted with PrP inoculation**. These neurological disorders can be produced by either peripheral (extracerebral) or direct brain (intracerebral) inoculation. Those findings provide evidence of cell-to-cell spread of pathologic proteins of neurological disorders in experimental animals, suggesting those **pathological proteins may have seeding abilities, like prion diseases,** to transmit pathology. Experimental studies have shown that the aggregation of the AD-associated proteins amyloid-β (Aβ) and tau, and of the PD-associated protein α-synuclein, **can be stimulated in laboratory**

animal models by intracerebral injection of inocula containing aggregated species of the respective proteins. Knowing that **amyloid-β and similar proteins act like prions,** researchers are left wondering why no one has recorded a case of the proteins passing from person to person, when on the basis of laboratory results, **all neurodegenerative diseases should be infectious.** However, to date, there is no direct evidence in humans indicating that the diseases caused by misfolded Aβ, tau, α-synuclein are infectious.

Now it is well established that prions are agents of disease, in that they can spread from host to host just like typical pathogens, so the **designation of prions as infectious agents has become problematic (WALKER and JUCKER, 2015).** They propose to define prions as „proteinaceous nucleating particles“ to highlight the molecular action of the agents, lessen unwarranted apprehension about the **transmissibility of noninfectious proteopathies**, and promote the wider acceptance of this revolutionary paradigm by the biomedical community.

Neurodegeneration and magnesium as naturally NMDA receptor antagonist

The neurodegenerative diseases, occurred to a greater extent, **only in ruminants (BSE, scrapie, chronic wasting disease**), because only in them, **magnesium** is not absorbed in the intestine, but in the rumen.

Researchers have found that a new **highly absorbable form of magnesium called magnesium-L-threonate** concentrates more efficiently in the brain, rebuilds ruptured synapses, and **restores the degraded neuronal connections observed in Alzheimer's disease** and other forms of memory loss in people (SLUTSKY et al. 2010). In experimental models, **magnesium-L-threonate induced improvements of 18% for short-term memory and 100% for long-term memory.**In addition, NMDA receptor antagonist **(Memantine**) is approved by the U.S. F.D.A and the European Medicines Agency for **treatment of moderate-to-severe AD** (2006).

A number of studies have clearly indicated that amyloid β toxicity in AD is mediated, at least in part**, by glutamate-mediated excitotoxicity, which involves activation of the glutamate N-methyl-D-aspartate (NMDA) receptors,** leading to elevated intra-cellular Ca^{2+} and consequent stimulation of a cascade of enzymes resulting in cell death.

In brain, one major action of Mg^{2+} is modulating the voltage-dependent block of glutamate NMDA receptors, controlling their opening during coincidence detection that is critical for synaptic plasticity (MAYER et al., 1984; NOWAK et al., 1984).

Altered neuronal calcium homeostasis affects metabolism of amyloid precursor protein (APP), leading to **increased production of β-amyloid (Aβ)**, and contributing to the initiation of AD.

Higher additional dietary Mg-supplementation in dairy cows as an European „phenomenon“ at the beginning of 1990s; and decrease of BSE incidence in the UK

The official scientific statement about the 5-years incubation period of the BSE is based on the **feed ban of meat and bone meal- MBM (1988) and the BSE incidence decrease,** in the UK cattle (after 1993). Putting this „phenomenon“ into the practical conditions; significantly **higher additional dietary Mg-supplementation** - can be a cause about the BSE incidence decrease in the UK, after 1993/94 period.

- See the article; „Providement for an optimum supply of sodium and magnesium to the feed rations of dairy cows and high pregnant heifers“ (HLASNY, 1989) published in Czechoslovak scientific journal „Biol. Chem. Vet.“ (Prague) and in other Czechoslovak scientific journal „Veterinary Medicine” (HLASNY, 1989) , see article „Evaluation of a new mineral supplement in young cattle feeding during winter season” (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2631375&dopt=Abstract).

These results were also published by the“Czechoslovak Patent Office“ in Prague (HLASNY, 1991), see „Mineral supplement for breeding cattle“, Patent No. 274 171. These recommendations that much more magnesium (by 180%) is necessary in dairy mineral supplements; really, it was **commonly realized in Europe, at the beginning of 1990s**.

The worldwide link between the BSE incidence and magnesium deficiency

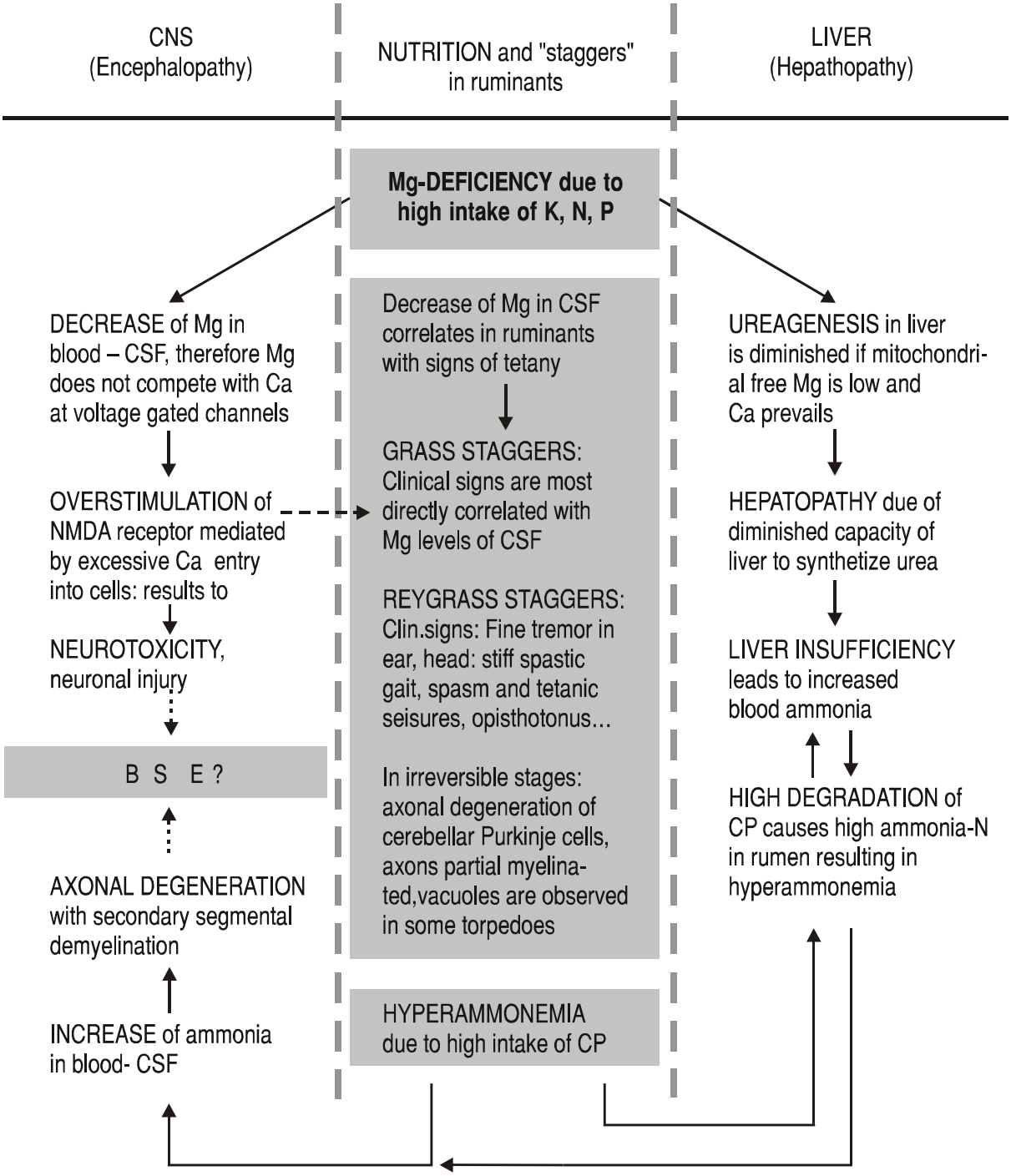
Why neurodegeneration in ruminants is not observed on warm season grasses? There is the explanation; these grasses are low in crude protein and potassium, and **higher in magnesium content** (hot weather- water stress is obvious)

On the other hand, in Britain- Ireland, a high intake of grasses (mostly ryegrass) in ruminants; available water capacity, high N -fertilization, cool and cold marine climatic region; these circumstances are ideal for the **subclinical (chronic) hypomagnesaemia in ruminants.** So higher ietary Mg was very effective about the **reducing BSE incidence in the UK.**

Based on this **„interpreted knowledge“ about** the **origin of the BSE** and a significant preventive effect of **magnesium**, should be similarly preventive do about the **Alzheimer's disease (AD).** The latest research results, shows on the above scenario. So, for example, a **„synthetic“ NMDA receptor antagonist memantine- Ebixa… (ROBINSON and KEATING, 2006),** is since 2006 approved in the US and the EU for the treatment of patients with moderate to severe dementia of the Alzheimer's type. Since 2010 (SLUTSKY et al.) it is known an effect of **magnesium“ (Mg-L-threonate) in AD,** an increase in brain Mg enhances both short-term synaptic facilitation and long-term potentiation and improves learning and memory functions. There the Mg acts **as a 'natural' antagonist of NMDA receptors.** In veterinary and medical practice is a long time, well-known **ketamine, which is an another „synthetic“ antagonist of NMDA receptors.** Ketamine, sold under the brand name Ketalar among others, is a medication mainly used for starting and maintaining anesthesia.

The mechanism of the influence of Mg deficiency and the emergence of the BSE incidence (HLASNY, J., 2001)

Nervous diseases and connections with nutrition in ruminants



CNS: Central nervous system • CSF: Cerebrospinal fluid • CP: Crude protein
NMDA: "N-Methyl-D-Aspartate" receptor.