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Prions: the danger of biochemical weapons

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Abstract

The knowledge of biotechnology increases the risk of using biochemical weapons for mass destruction. Prions are unprecedented infectious pathogens that cause a group of fatal neurodegenerative diseases by a novel mechanism. They are transmissible particles that are devoid of nucleic acid. Due to their singular characteristics, Prions emerge as potential danger since they can be used in the development of such weapons. Prions cause fatal infectious diseases, and to date there is no therapeutic or prophylactic approach against these diseases. Furthermore, Prions are resistant to food-preparation treatments such as high heat and can find their way from the digestive system into the nervous system; recombinant Prions are infectious either bound to soil particles or in aerosols. Therefore, lethal Prions can be developed by malicious researchers who could use it to attack political enemies since such weapons cause diseases that could be above suspicion.

Keywords: Prions; biochemical weapons; Prion diseases; Prions danger to the environment; Prions risk alert.

1 Introduction

People have had a passion for weapons of mass destruction since the government military agencies search for chemical weapons culminating with the use of poisonous gases in the First War. During the Cold War, there were many rumors of research on biochemical and biological weapons since intelligence agencies of North America and Russian, used different types of weapons, such as radioactive, poison and contagious disease weapons, agaist their political enemies because these weapons cause diseases that could be above suspicion. It is important to emphasize that Prions also have this characteristic. Therefore it is plausible that Prion weapons can be used not only by governments but also by terrorists.

Furthermore, hypothetically, if Prions were used as a biochemical weapon, they could damage not only humans and animals, but the worldwide economies; therefore, even if Prions do not kill instantly a target, they can be a very persuasive object for those who have access to it.Prion diseases include a group of fatal neurodegenerative and infectious disorders in humans such as Creutzfeldt-Jacob disease (CJD), a variant form of CJD (vCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and kuru, fatal familial insomnia (FFI); in animals, they include: scrapie of sheep and goats, chronic wasting disease (CWD) of mule deer and elk, and bovine spongiform encephalopathy (BSE) of cattle (Prusiner, 1996). The central feature of these disorders is the conformational change of the host encoded, cellular Prion protein (PrPc), see figures (Figure 1A and Figure 2B, C) to an abnormal, partially proteinase K resistant and infectious isoform (PrPSc) with an aggregation propensity accumulating in the brain of diseased individuals (Figure 1B and Figure 2D) (Gambetti et al., 2003; Tatzelt & Schätzl, 2007). Cases of vCJD in Great Britain and France raised the possibility that BSE has been transmitted to humans (Bateman et al., 1995; Cousens et al., 1997). Macaque monkeys and marmosets both developed neurologic disease several years after inoculation with bovine Prions (Baker et al., 1993; Ono et al., 2011). These experiments clearly show that the inoculation of Prions is potentially fatal, and the fact that Prion strains are transmitted between species raised the possibility that a large section of the population is at high risk as a result of exposure to BSE Prions (Anderson et al., 1996; Sweeting et al., 2010; Bruce et al., 1997; Collinge et al., 1996; Griffin, 1997; Lasmézas et al., 1996; Scott et al., 1993).

Prions have key features which help them to survive in the environment for long periods, such as the resistance to protein degradation, "partially resistant to proteinase K" (Bolton et al., 1982; Prusiner, 1991), high resistant when exposed to irradiation, heat, and harsh chemical treatments (Plum, 1997), plus the fact that they can be attached to soil (Johnson et al., 2006; Saunders et al., 2011a) and spread through air, and therefore they are extremely hazardous (Denkers et al., 2010). Although Prions are just only a polypeptide sequence, they are resistant to heat since people who consumed contaminated meat after preparation got sick; this raised the possibility that a particular conformation of bovine PrPSc was selected for heat resistance during the manufacture of meat and bone meal (MBM). Therefore, it is believed that MBM is the source of Prions responsible for BSE (Prusiner, 1997).

Therefore, hypothetically, Prions can be manufactured based on the molecular characteristics of the Prion protein to make deadly biochemical weapons. The study on how the conversion of PrPC (the normal cellular protein) into PrPSc (the abnormal disease-causing isoform) (Supattapone, 2010) can generate polypeptide sequences designed exclusively to kill. Basically, an ideal Prion polypeptide sequence to be used as a biochemical weapon must be easily recombined and produced in large scale (Supattapone, 2010), be resistant to cold and heat, be fatal in very small quantities, and be transmitted through air, as demonstrated by (Denkers et al., 2010; Haybaeck et al., 2011), and through water, food and soil, as demonstrated

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by (Saunders et al., 2009; Saunders et al., 2011a), Gough & Maddison (2010) and (Smith et al., 2011). If Prions do not meet all specifications necessary of a biochemical weapon to kill, they at least have key features such as surviving through the digestive system, as demonstrated by Sales (2006), resistance to high temperatures during food preparation processes (Prusiner, 1997), recombinant Prions are infectious, as demonstrated by (Wang et al., 2010; Legname et al., 2004; Makarava et al., 2010), and lastly, a few molecules can produce a chain reaction in the conversion of PrPc into PrPSc causing a fatal neurodegenerative disease (Rigter et al. 2009).

2 Prion molecular factors involved in the conversion of the native form PrPc into the infective form PrPSc, which could be explored for evil plans

The basic mechanisms involved in the conversion PrPc into PrPSc are mainly achieved in four routes: the first includes the conformational mechanisms; the second includes the structural mechanisms; the third is related to the environmental pH; and fourth is the pathologic route.

The first route is associated to the lethality of the peptides, which involves a conformational change, through which the alfa (α)-helical content diminishes and the amount of beta (β)-sheet increases (Pan et al., 1993). PrPSc formation is a posttranslational process involving only a conformational change in PrPC. A comparison of the secondary structures shows that PrPc is 42% α-helical with a very low (3%) β-sheet content, whereas PrPSc consists of 30% α-helices and 43% β-sheets (Figure 1). Although the precise physiological role of PrPSc and the chemical differences between PrPSc and normal Prion protein (PrP) remain unknown, it appears that the differences are conformational (Prusiner, 1998). The Prions conformational transition from PrPc to PrPSc is accompanied by profound changes in the properties of the protein: PrPc is soluble in nondenaturing detergents, whereas PrPSc is not (Meyer et al., 1986) and PrPC is readily digested by proteases, whereas PrPSc is partially resistant (Kocisko et al., 1994; Hsiao et al., 1989) (Figure 1B). However, it is not fully known how disease-causing Prions arise in patients with sporadic forms; the main hypothesis is the horizontal transmission of Prions from humans or animals (Haley et al., 2011). Therefore it seems that the diseases caused by Prions are diseases of dietary origin, raising a great possibility that the PrPSc conformation is highly resistant to the mechanisms of animal polypeptides digestion, which is a key feature for a biochemical weapon (Sales, 2006). The second route is the structural mechanisms, which are associated with the basic structural transition from PrPc to PrPSc. Peptide fragments corresponding to Syrian hamster PrP residues 90 to 145 and 109 to 141, which contain the most conserved residues of the Prion protein and the first two putative α-helical regions, were studied using infrared spectroscopy and circular dichroism. The peptides could be induced to form α-helical structures in aqueous solutions and in the presence of organic solvents such as trifluoroethano or detergents such as sodium dodecyl. On the other hand, NaCl at physiological concentration or acetonitrile induced the peptides to acquire substantial β-sheet. The results suggest that perturbation of the packing environment of the highly conserved residues is a possible mechanism for triggering the conversion of PrPc into PrPSc where α-helices appear to be converted into β-sheets (Zhang et al., 1995). However, no atomic-resolution structure of the fibrillar state, which is likely to be infectious, has been reported to date because characterizing the structure of PrPSc has been challenging due to the difficulty in studying it through Nuclear magnetic resonance (NMR) or X-ray crystallography methods (Wasmer et al., 2008). However, there is a structural model based on solid-state nuclear magnetic resonance restraints for amyloid fibrils from the Prion-forming domain (residues 218 to 289) of the HET-s (het-s/S locus) that occur naturally in the filamentous fungus Podospora anserine (Figure 2D) (Wasmer et al., 2008; Dalstra et al., 2005). Nevertheless, the basis of PrPSc conversion has been elucidated. Some models with the earliest conversion events involving PrPSc have been established suggesting that the formation of the disease-causing isoform involves refolding in two of the PrPc NH2-terminal (N-terminal) α-helix (H1 and H2) into β-sheets or the two β-strands (S1 and S2) and proposing to "seed" β-sheet elongation as the short α-helix H1 (Figure 1) (Huang et al., 1996; Muramoto et al., 1996); the single disulfide bond joining COOH-terminal helices (C-terminal) would remain intact because the disulfide is required for PrPSc formation (Figure 1) (Pan et al., 1993; Muramoto et al., 1996).

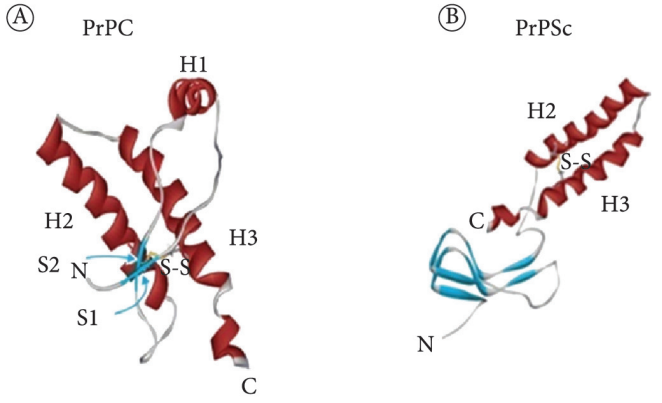

Figure 1. (**A**) Normal Human Prion protein (HuPrP) with 43% of α-helix, sensitive to proteinase K treatment without forming aggregates. The NH2-terminal (letter N in Figure) region (residues 23–124) is flexible, and the COOH-terminal (letter C in Figure) region (residues 125–228) that contains the globular domains is well structured the structures contain intramolecular disulfide bridge (S-S yellow trace in Figure), three α-helices, (H1), (H2), and (H3), red color, and a short double-stranded β-sheet (S1) and (S2). (H) and (S) indicate α-helix and β-strand, respectively (indicated by the blue arrows), and a disulfide bridge S-S (trace). (**B**) Human Prion protein infectious isoform (HuPrPSc) with 30% of α-helix and 43% of β-sheet, resistant to proteinase K treatment and capable of forming aggregates. The two β-strands (S1) and (S2) are proposed to "seed" β-sheet elongation (gray and blue colors) as the short α-helix (H1) unfolds and is converted into the PrPSc conformation. (H2) and (H3) remain stabilized via linkage of a disulfide bridge (yellow trace). (**B**) α-helix (red color), β-sheet elongation (gray and blue colors), and disulfide bridge S-S (yellow trace). Courtesy of Cayman Chemical Company. Ann Arbor, Michigan. USA.

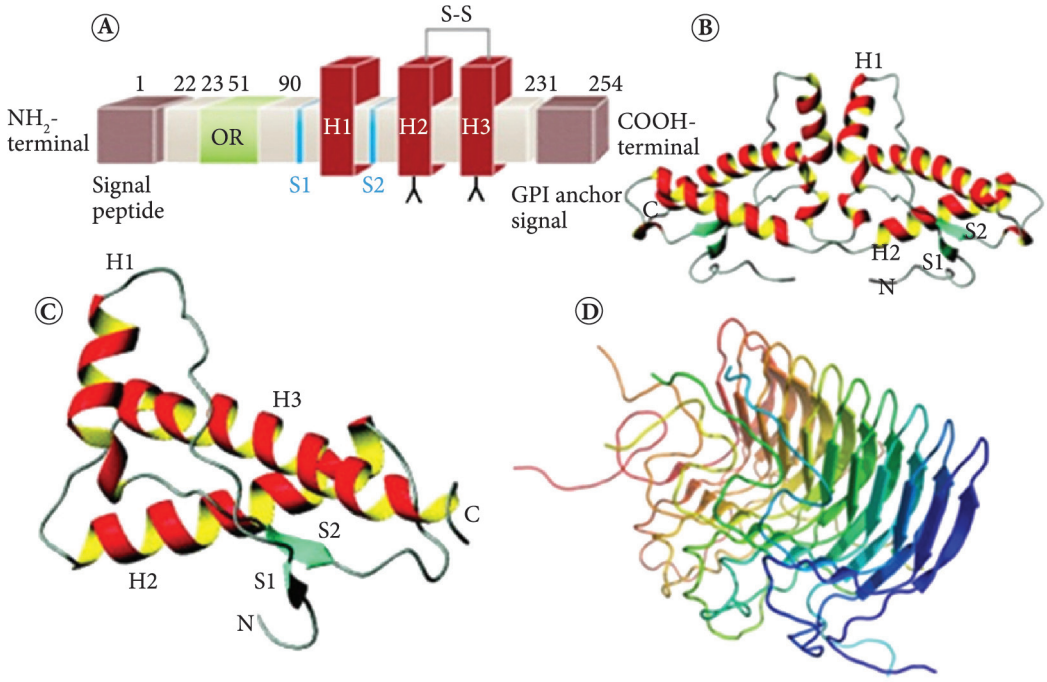

Figure 2. (**A**) Illustration of the normal structure of human Prion protein gene (PRNP). PrPc is synthesized from a 254 amino acid precursor. The nascent peptide is cleaved at both the N-and C-terminal in the Endoplasmic Reticulum (ER). A glycosylphosphatidylinositol anchor (GPI) (purple) is attached to the C-terminus at position 231 of PrPc that helps link it to the extracellular membrane (lipid bilayer).In the Golgi, PrPc is N-glycoslyated at positions 181 and 197. Mature PrPc consists of the amino acid residues 23-231 and is expressed as a membrane glycoprotein anchored to the cell surface by a GPI moiety. (H) and (S) indicate α-helix and β-strandregions, respectively. (S-S) and (Y) "inverted" indicate a disulfide bond and N-glycosylation sites, respectively. (OR) specific octapeptide repeat. (**B**) Mature PrPc dimer. Under native conditions, part of the native bovine PrPc exists as a monomer-dimer equilibrium. It is theorized from this dimeric structure that the dimerization is the first step in amyloid formation and the presence of these dimers could possibly speed up the aggregation of PrPSc. (**C**) The mature human PrPc protein. (**B and C**) NH2-terminal (letter N in Figure), COOH-terminal (letter C in Figure), α-helix (H1-H3) and β-strand (S1 and S2 in Figure). (**D**) A model for fibrils of fungal HET-s Prion forming domain. Since no structural data for PrPSc have been reported to date, this is shown for comparison. The organization of this fibril is a left-handed β-solenoid with dense, parallel β-sheet packing. The β-solenoid fold has been proposed for PrPSc. (**A**) Courtesy of Cayman Chemical Company. Ann Arbor, Michigan. USA. (**B-C**) Adapted From: Sekijima, M. Molecular dynamics simulation of dimeric and monomeric forms of human Prion protein: insight into dynamics and properties. Biophys J. With permission. (**D**) Adapted From: Wasmer, C. Amyloid fibrils of the HET-s(218-289) Prion form a beta solenoid with a triangular hydrophobic core. Science. With permission.

Theoretically, the high β-sheet content of PrPSc was predicted based on its ability to polymerize into amyloid fibrils (Prusiner et al., 1983; Caughey et al., 1991). Studies have found that the deletion of each of the four predicted helices prevented PrPSc formation, as did the deletion of the stop transfer effector region and the C178A mutation. The removal of a 36-residue loop between helices 2 and 3 did not prevent formation of protease-resistant PrP; the resulting scrapie-like protein, designated PrPSc106, contained 106 residues after cleavage of an N-terminal signal peptide and a C-terminal sequence for glycolipid anchor addition.The addition of the detergent Sarkosyl to cell lysates solubilized PrPSc106, which retained resistance to digestion by proteinase K. These results suggest that the regions of a proposed secondary structure in PrP and the disulfide bond stabilizing helices 2 and 3 are required for PrPSc formation (Rogers et al., 1993; Fischer et al., 1996; Muramoto et al., 1996). The third route is related to the pH environment. The pH seems to be important for the change of conformation because human PrPc has a pH-dependent conformational change. The α-helical intermediate formed at pH 4.1 can convert into the β-sheet conformation at pH 3.6 but not vice versa a loss of α-helix since the gain of β-sheets and a number of PrPSc-like conformations can be generated by incubating recombinant PrPc at low pH, indicating that the protonation of key residues is likely to destabilize PrPc facilitating its conversion to PrPSc. Fold stability of human PrPc as a function of pH is significantly reduced by the protonation of two histidine residues, His187 and His155. Mutation of His187 to an arginine imposes a permanently positively charged residue in this region of the protein and has a dramatic effect on the folding of PrPc resulting in a molecule that displays a markedly increased propensity to oligomerize. The oligomeric form is characterized by an increased β-sheet content, loss of fixed side chain interactions, and partial proteinase resistance. Therefore, the protonation state of H187 appears to be crucial in determining the conformation of PrP; the unprotonated form favors native PrPc, while the protonated form favors PrPSc-like conformations (Hosszu et al., 2010; Gerber et al., 2008; Hosszu et al., 2009). If these conditions are relevant, as there is considerable evidence that endosome-like organelles or

lysosomes, with their locally acidic environments are plausible locations for PrPSc propagation (Arnold et al., 1995), these models of Prions for these molecular regions are crucial for the development of disease via PrPSc, and theerefore the structure of these regions of the molecule can be exploited as a catalytic core for elaboration of new lethal Prions. Exploring mechanisms that allow the Prions to be captured by the airways as an aerosol microparticles; thus lesser amounts of Prions can be dispersed through the air and contaminate the water, soil, plantations, and very large regions. The fourth route is the pathologic route. Another mechanism of infection that could be very well explored is the pathogenesis. Prions could be related to microspheres directed to specific target cells and be embraced and activated by the endosomes pathway of many types of cells (Arnold et al., 1995). Pathogenesis can be divided into natural or congenital transmission and external transmission. The native or natural pathogenesis of Prion disease varies including mutation in human Prion protein gene (PRNP) and external transmitted causes (Tranulis et al., 2011). Figure 2A shows a normal structure of PRNP gene (Manson & Tuzi, 2001). Missense mutations and expansions in the octapeptide region (OR) result in familial forms of Creutzfeldt-Jakob disease (fCJD) and GSS (Beck et al., 2010; Jansen et al., 2011; Kovács et al., 2002). On the other hand, FFI is caused by the D178N mutation, the disease progresses quickly, and the patient dies within a few months after the onset of symptoms sleep disorders with agitation, fractionated sleep, snoring, and daytime sleepiness (Ayuso Blanco et al., 2006; Montagna et al., 2003). The inheritable familial forms of all Prion diseases (fCJD, GSS, and FFI) are inherited as autosomal-dominant disorders (Mastrianni, 2003). The polymorphism coding for methionine (M) or valine (V) at codon 129 of the Prion protein gene (PRNP M129V) plays a pivotal role in the susceptibility to CJD, influencing familial, transmitted, and sporadic forms of the disease (Alperovitch et al., 1999), homozygosity for methionine at position 129 (met/met at codon 129) predisposes susceptibility and earlier age of onset of disease (Kretzschmar & Illig, 2009; Mead et al., 2009). Therefore, the PRNP polymorphisms is related to specific clinical forms of Prion diseases, and polymorphism in the regulatory region of PRNP is associated with increased risk of sporadic CJD (Sanchez-Juan et al., 2011).

The pathogenesis of external transmission. In theory, vCJD can be transmitted by ingestion of contaminated meat derived from cows with BSE. PrPSc may be the major pathological mechanism to be explored because it survives the digestion process (Sales, 2006) and is hypothesized to be amplified by follicular dendritic cells and tingible body macrophages in gut-associated lymphatic tissue, such as Peyer patches. PrPSc eventually reaches draining lymphatics and the spleen by migrating to follicular dendritic cells (Aguzzi & Sigurdson, 2004). Hypothetically, PrPSc reaches the brain via the sympathetic nervous system from lymphatic tissues, and PrPSc propagation in the brain causes accumulation resulting in neurodegeneration (Harris & True, 2006; Aguzzi et al., 2008; Aguzzi et al., 2001; Venneti, 2010). Thus, theoretically, the conformation of Prions is pH dependent in endosome-like organelles or lysosomes with acidic environments. Dendritic cells (DCs) are obvious candidates, but DCs might not account for all of the transport of Prions, and other cells, including tingible-body macrophages (phagocytic cells in lymphoid germinal centers) are plausible locations for PrPSc propagation (Arnold et al., 1995; Aguzzi & Sigurdson, 2004) since PrP is captured by phagocytes of the immune system.Therefore, the conformational convertion of PrPc into PrPSc can be triggered by endocytosis of a Prion particle, and a phagocytic cell may trigger the disease with a particle reaching the brain by the sympathetic nervous system from the lymphatic tissues (Harris & True, 2006; Aguzzi et al., 2008; Aguzzi et al., 2001; Venneti, 2010). Therefore, the immune system is a target of lethal Prions, which could be added to adjuvants that are intended to perform phagocytosis by DCs to increase their efficiency and thus be transmitted through small wounds or scratches on the victim's skin.

3 Discussion

Recombinant Prions with fatal features could be developed in relatively simple laboratories using animals such as rats, mice, and monkeys (Supattapone, 2010; Wang et al., 2010; Legname et al., 2004; Makarava et al., 2010). Ricin has already been used as a weapon (Augerson, 2000; National Security Notes, 2004), for example in the case that caught the full attention of international media and was described by Papaloucas et al (2008) and which was about a political dissident that was killed by a supposed KGB agent using a single ricin-tipped umbrella as a weapon. Consequently, the same mechanism can be used to deliver Prions using simple objects without giving the victim a chance to receive a vaccine, treatment, or a specific anti-serum injection. Some political enemies must be eliminated and Prions can be a possible alternative to the use of venoms, precisely because Prions do not kill instantly and make the investigation process very difficult to trace the assassin agent. Another class of venom that have been used before and can be substituted by Prions are the radioactive venom (Jordan & Finn, 2006) because Prions can cause the same effect. One advantage is leaving no traces detectable by anti-gama radiation equipment, such as Geiger counter, and another advantage is being less dangerous to the assassin agent willing to use it.

The psychological effect caused by the use of Prions to extinguish rivals could be as powerful as the radioactive effects, and it can send a strong message such as "Do not play with the government interests". The use of such weapons seems to have strong personal issues involved because it would be easier to kill someone simply using a gun, but with Prions, the victim agonizes for months before dying (Papaloucas et al., 2008). The most frightening possibility would be the use of Prions to get rid of enemies in large regions of ongoing conflicts or political separatist wars. In theory, it would not raise any suspicion by the international community because of its silence mechanisms, but after years a lot of people would start dying presenting the same symptoms and the alert would have come too late. If Prions are made in laboratories with the purpose to be spread in the air, it could kill a large number of people since it has been demonstrated that CWD can be dispersed as aerosol (Denkers et al., 2010; Haybaeck et al., 2011; Ford et al., 2002). In addition, the decontamination of the environment can be a

huge problem if Prions are not rapidly degraded in the soil by microorganisms; some studies have demonstrated that the soil is as possible reservoir of scrapie and CWD agents, which can persist in the environment for years. Attachment to soil particles likely influences the persistence and infectivity of Prions in the environment (Smith et al., 2011; Gough & Maddison, 2010; Saunders et al., 2009).

The evidence that soil and other environmental surfaces can play a role as reservoir of Prions dissemination contributes to the imminent threat these particles can represent if they are released into the environment (Maddison et al., 2010; Saunders et al., 2011b). Finally, the impact that Prions could cause to wildlife, especially mammals, is terrifying; people who had been in contact to contaminated environments or had ingested inoculated animals could die in days, months, or years.

The long effects of Prion contamination can be terrible and are similar to radioactive effects. Concluding, it is utmost important to alert the scientific community scientific community, agencies, and governments worldwide to discourage, inhibit, and investigate those who have this evil intention.

4 Final conclusions

Bioterrorism is as emerging threat that is growing with the development of biotechnology. The risk of biochemical weapons falling into wrong hands can be devastating; it could contaminate cattle, humans and many other animal species leading to thousands of deaths and would lead to a global pandemic and economic crisis too.

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