Applied Cell Biology

ISSN : 2320-1991 Online
ISSN : 2320-1983 Print
Volume 9 Issue 2

Research Article
Appl Cell Biol, 9(2), 2021 [43-48]

Exploring Drug and Antibody-Based Treatment Options for Creutzfeldt-Jakob Disease

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ABSTRACT

Creutzfeldt-Jakob Disease (CJD) is a neurodegenerative disease characterized by mutant PrP prion proteins, which accumulates and impairs the function of wild-type PrPc proteins. The interaction of prion proteins with wild-type proteins converts the PrPc proteins to mutant PrP proteins. These mutant prion proteins lead to neural tissue degradation and other nervous system problems that can eventually lead to death. The use of antibodies to target and destroy prion proteins can be used to decrease PrP levels that can stop CJD progression. The binding affinities of different anti-PrP Fab antibodies are analyzed to determine which antibody best binds to PrP proteins and targets them for destruction. Through antibody-based targeting of prion proteins, potential treatment methods could be developed for CJD. In addition, the use of drugs, such as quinacrine and doxycycline, also show short-term effects in decreasing the progression of CJD. These drugs extend the average lifespan of tested subjects with CJD but also lead to the development of drug-resistant prion proteins that eventually cause the death of the subject affected by CJD.

Keywords

Neurodegenerative
Antibody
Doxycycline
Prion

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is an extremely rare and fatal neurodegenerative disorder which affects about only one in one million people worldwide each year [1]. CJD is classified as a type of prion disease. Prions (PrP) are a variant type of infectious protein that causes normal prion proteins in the brain to fold abnormally, leading to brain damage that occurs rapidly [2]. Although many forms of prion disease occur in animals and humans, CJD occurs exclusively in humans [2]. Most commonly, the disease has been seen to occur on average around the age of 60, and due to its extremely rapid progression, most individuals die within one year [1]. Since CJD causes brain damage, many of the early symptoms that occur are mental changes. These include behavioral and personality changes, anxiety, memory loss, changes in vision, and difficulty speaking and swallowing [2]. In the later stages of the disease, severe brain deterioration ultimately causes individuals to slip into a coma [1]. Similar to other physical problems such as broken arms, neurological diseases such as CJD can leave families and patients with higher levels of depression post-diagnosis [2,3]. The disease can be diagnosed through MRI scans of the brain or electroencephalography (EEG) in most cases [1].

CJD can be classified into three different subtypes [4]. These subtypes are dependent upon the way in which an individual develops the disease. The first type is sporadic CJD, in which the disease appears for no specific reason and accounts for a majority of CJD cases--almost 85% [4]. The second type is

hereditary CJD, and this occurs when individuals test positive for a genetic mutation related to CJD and a family history of the disease. This accounts for around 10-15% of cases [4]. Finally, acquired CJD occurs when an individual has been exposed to infected human tissue, typically via a medical procedure, and the disease is transmitted through contamination to the individual; this occurs very rarely, accounting for only around 1% of cases [4]. This type of acquired CJD can also result in variant CJD (vCJD), in which an individual consumes meat from infected cattle with mad cow disease (another type of prion disease within animals). Currently, there is no definite cure for any CJD, and research is being conducted to determine the exact pathophysiology of the disease and possible treatments [1]. As of now, those affected with CJD mainly receive supportive care for symptoms they experience.

In order to understand the disease, it is crucial to gain a deeper understanding of the mechanism by which CJD propagates. PrPc protein is a normal cellular prion protein that is found on cell membranes of all types of body cells in healthy individuals. This protein serves complex functions that are still not fully understood [1]. An issue arises when these proteins misfold and accumulate. There exists an infectious isoform of PrP protein termed PrP scrapie, also referred to as PrPsc. This protein induces the healthy PrPc proteins to change conformation and turn into the infectious PrPsc form as well [1]. Over time, the PrPsc isoform proteins accumulate, and neural issues arise due to the lack of healthy PrP and due to the buildup of PrPsc plaques.

It is still not completely understood how the conformational change from PrP to the PrPsc isoform occurs on a molecular level [5]. One hypothesis is that there exist two stable conformations, so making that transition easier results in the production of more PrPsc isoforms [5]. The protein is made of a long, flexible amino acid chain consisting of 3 alpha-helices and two sheets forming antiparallel beta-strands [5]. The PrPc protein has been analyzed because it is soluble and does not aggregate. However, the PrPsc is difficult to purify and isolate in a soluble, non aggregated form, so it has not been completely imaged and understood. However, it is understood that the PrPsc form includes regions that promote stabilization of the PrPc core structure through hydrogen bonding, leading to a conformational change to the PrPsc form [6].

CJD occurs because of two reasons: the lack of properly functioning PrPc proteins and the buildup of infectious PrPsc proteins. The PrPsc proteins accumulate in insoluble plaques, which waste space in nervous tissue and lead to neural degeneration. Additionally, there is progressively less and less PrPc protein available to perform its normal functions [7]. Over time, the disease worsens, and increasing amounts of PrPc proteins are converted, and the plaques build.

Although CJD is a rare disorder, its fatality requires research to be conducted in finding a promising treatment for those affected by the disease. Currently, there have been multiple approaches to find a cure for CJD. Many of these approaches aim to prevent or minimize abnormal prion protein production in the brain. One technique is the use of RNA interference within scrapie-infected (type of prion disease) mice, and it has been shown to increase survival time [8]. Antisense oligonucleotides have also been shown to extend prion-infected mouse lifetimes by preventing prion protein production [9]. However, despite ongoing research, no cure has still been found for CJD since it proves to be increasingly complex to target misfolded prion proteins in the brain. Many limitations include the difficulty of accurately delivering treatments to specifically the brain and extrapolating treatments that have worked in mice to humans since they experience a different type of prion disease. One type of current treatment that is emerging to be a promising avenue involves antibodies. Antibodies are the immune system's prime agent in marking for the destruction of foreign invaders that could be harmful to the body. The antibodies themselves function by blocking PrPsc replication. The antibodies do this by binding to specific regions of generic PrP proteins and prevent PrPsc replication by preventing interactions between PrPsc and PrPc [10]. When they cannot interact, PrPsc does not have a chance to induce a conformational change in PrPc. Antibodies also decrease levels of both PrPc and PrPsc. Thus, they cannot be used extensively [10]. If too much PrPc is destroyed, negative outcomes may also result. Thus, it is also important to consider safety and outcomes in living organisms.

The purpose of this literature review is to analyze potential methods for treating CJD. The largest challenge in treating CJD with antibodies is that it is challenging for antibodies to cross the blood-brain barrier (BBB), presenting a gap in knowledge. Thus, it is imperative to locate a drug that can cross this barrier to cause effects in the region of the body that needs it: the brain. This research aims to analyze an antibody that can cross the blood-brain barrier, is effective in slowing the rate PrPc to PrPsc conversion, and is safe and effective in clinical trials. The literature review also focuses on analyzing the efficacy rates of different drug treatments in combating prion production in CJD and the ability of these drugs to cross the BBB to generate an effective solution.

METHODS

By using a wide array of research journals and online sources, a search was conducted using keywords "Creutzfeldt-Jakob disease", "antibodies", "blood-brain barrier", "drug treatment", "PrP", "prion", "PrPc". Searches related to the blood-brain barrier and drugs yielded potential treatment options of drugs that could effectively cross the BBB and provide improvement in CJD symptoms. These sources were filtered for drugs that could reduce the amount of PrP proteins without producing harmful side effects in the brain. Searches related to antibodies and the BBB resulted in information regarding potential methods through which antibodies could be transported across the BBB for treatment against infectious prion proteins. Sources related to these topics were also analyzed to identify other novel practices being researched to improve conditions for CJD patients. Literature sources regarding drugs and antibodies unable to cross the BBB or produce adverse side effects were noted during analysis. The data regarding antibody binding constants were compiled into a table and analyzed for efficacy in the treatment of CJD. The data relating to drug efficacy were also compiled in separate tables and analyzed to determine which drug produces the most improvement in CJD symptoms.

DATA

Table 1: Dissociation rate constant (k_{off}) and equilibrium constant (KD) of the Fabs that bind to PrP (Senatore et al., 2020).

Fab	k_{off} (1/s)	KD (M)
Fab_POM1	2.96E-04	2.01E-09
Fab1	2.88E-03	1.21E-08
Fab2	1.58E-03	1.01E-08
Fab3	2.46E-03	7.72E-09
Fab4	1.93E-03	1.41E-08
Fab6	1.44E-03	9.89E-09
Fab7	2.41E-03	1.76E-08
Fab8	3.62E-03	1.79E-08
Fab10	2.61E-03	1.41E-08
Fab12	3.20E-03	1.71E-08
Fab13	4.98E-03	4.56E-08
Fab15	3.76E-03	1.27E-08
Fab25	2.42E-03	4.71E-08
Fab28	1.08E-03	1.28E-08
Fab29	3.15E-03	1.04E-08
Fab30	1.76E-03	4.76E-09
Fab32	2.90E-03	1.50E-08
Fab35	2.29E-03	1.75E-08
Fab41	2.65E-03	1.95E-08
Fab44	3.18E-03	1.21E-08
Fab46	3.39E-03	1.46E-08
Fab48	2.45E-03	1.06E-08
Fab52	4.12E-03	2.98E-08
Fab53	1.73E-03	9.79E-09
Fab61	3.97E-03	2.06E-08
Fab69	1.36E-02	9.50E-08
Fab71	2.45E-03	6.20E-09
Fab72	2.14E-03	7.14E-09
Fab74	1.57E-02	4.85E-08
Fab75	3.67E-03	2.64E-08

Table 2: Incubation periods for prion-infected MDR0/0, FVB and CD1 mice orally treated with 40 mg/kg/day of quinacrine.

Mouse line	Treatment initiated (dpi)	Treatment duration (d)	Incubation period (days ± SEM)
$MDR^{0/0}$	30	60	135 ± 4
	30	30	143 ± 1*
	60	30	128 ± 3
	60	20	141 ± 2*
	60	10	141 ± 2*
	60	Until death	115 ± 2
	0	Until death	115 ± 4
	Untreated	-	124 ± 3
FVB	60	30	128 ± 1*
	60	Until death	118 ± 2
	Untreated	-	121 ± 2
CD1	105	Until death	121 ± 2
	95	30	129 ± 5
	95	Until death	129 ± 3
	80	30	116 ± 4
	80	Until death	121 ± 2
	70	30	145 ± 5*
	70	60	131 ± 5
	70	Until death	121 ± 2
	Untreated	-	127 ± 2

*Statistically significant (P<.01) prolongation of the incubation period compared to untreated controls. For all experiments, n = 9 mice. https://doi.org/10.1371/journal.ppat.1000673

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Table 3: Effect of Doxycycline in Treatment of CJD in Human Population.		
Baseline characteristics of the ITT population by treatment	**Doxycycline**	**Placebo**
Patients	62	59
Sex		
Male	24 (39%)	27 (46%)
Female	38 (61%)	32 (54%)
Age		
mean (years)	62.7 (9.9)	63.3 (10.4)
<60 years	24 (39%)	24 (41%)
≥60 years	38 (61%)	35 (59%)
Disease duration		
Mean (months)	5.9 (6.3)	5.1 (4.1)
1-4 months	38 (61%)	37 (63%)
≥5 months	24 (39%)	22 (37%)
Codon 129 PRNP genotype*		
MM	28 (49%)	25 (45%)
MV	18 (32%)	13 (24%)
VV	11 (19%)	17 (31%)
PSWC in EEG †		
Present	35 (59%)	27 (52%)
Absent	24 (41%)	25 (48%)
14-3-3 Detection in CSF ‡		
Positive	55 (92%)	53 (90%)
Negative	5 (8%)	6 (10%)
Data are mean (SD) or number (%). ITT=intention-to-treat. M=methionine. V=valine. PSWC=periodic sharp wave complexes. EEG=electroencephalogram. *Nine patients with missing data. †Ten patients with missing data. ‡Two patients with missing data.		

RESULTS

The human phage display libraries were used to identify the anti-PrP Fab antibodies that had binding affinities for CJD prion proteins. These antibodies were screened and compiled in a table based on the best binding affinities. Three rounds of phage display were used to screen for human Fab phage antibodies with short and long complementary chains to the proteins of interest. Fab antibodies that either lacked strong binding affinities or presented sequences that did not bind to the protein of interest were omitted. The selected Fab antibodies were compiled in Table 1.

The drugs that were used in this research includes quinacrine, doxycycline, and flupirtine. These drugs were tested in either human patients affected with CJD or experimental mice that had prions injected into their brains to cause CJD. The drug quinacrine was tested in three different types of mice, and the drugs doxycycline and flupirtine were tested in human patients with CJD. The orally treated mice (MDR0/0), wild-type outbred mice (CD1), and wild-type inbred mice (FVB) were all injected with prions, and the survival time was measured. Their survival times were compared to determine the efficacy of the drug in treating or improving CJD conditions.

The efficacy of doxycycline was analyzed based on a study conducted on the European population, with participants from Italy and France. The sex and age of the participants were selected to represent the epidemiological CJD population of Europe. By collecting tissue samples, the type of PRNP gene that each individual had was analyzed, and individuals were selected based on certain mutations in the gene that led to CJD. The severity of CJD progression was determined by monitoring the progression of dementia by analyzing periodic sharp wave complexes on an electroencephalogram (EEG). The severity of dementia helped determine the efficacy of the drug in improving CJD symptoms. The survival rates of the patients in the trial were also compared between the placebo and the drug. The study was halted after 104 of the 121 patients died due to disease progression. An autopsy was performed on 39 of the patients to collect further information about CJD progression.

LITERATURE REVIEW

Immune system has one aspect which is used to recognize and get rid of foreign substances from the body through antibodies. Antibodies can be produced against many antigens, including PrP, which is seen in CJD. Finding suitable antibody treatments for neurological diseases like CJD has been difficult in the past because of the neurotoxic side effects and challenges of the antibody crossing the blood-brain barrier (BBB) [11]. Researchers have recently identified antibodies directed against the flexible tail region of infectious PrP using a synthetic human antibody (Fab) phage library [12]. Of the thousands of anti-PrPs that targeted the different epitopes of the PrP, 49 were characterized in detail, including the kinetics and binding affinities [11]. The Fabs with the best affinity to PrP are listed in Table 1.

However, the possibility of these antibodies in crossing the blood-brain barrier was not addressed. Treatment through a possible antibody treatment design will focus on accessing and administering drugs to the BBB. PrP contains a globular C-terminal domain (GD) that is highly conserved and a flexible N-terminal tail region (FT) [13]. The Trojan horse method is a method by which a compound that is specific to the target site

is conjugated to the therapeutic drug. The Trojan horse method can be used with the highest affinity Fab anti-PrP antibodies to cross the BBB by conjugating the antibody to a peptide that is specific to a receptor on the BBB [14]. Transferrin has been identified as a receptor-mediator transporter for large molecules across the BBB [14]. Therefore, there is potential that the BBB can uptake the transferrin-anti-PrP antibody (TAP) to have its therapeutic effect in the brain. With modern medical technology, however, neurologists are limited to finer neurotherapeutic processes centered around the cellular makeup of the blood-brain barrier.

The impact of designing antibody treatments to surpass the blood-brain barrier is that potential paracellular transport through tight junctions will need to be overcome. This relates to the gap in knowledge of deriving a cure for CJD as the most probable and effective mechanism would be traversing the blood-brain barrier. The use of antibodies to propose a promising treatment for CJD is impactful because we can use what we know to cure CJD in accordance with treating other diseases that currently do not have cures. For example, Alzheimer's Disease and Parkinson's Disease are two neurocognitive disorders that are a result of tau protein tangles and beta-amyloid plaques, respectively. If neurobiologists are able to extend the life of prion-infected mice, then perhaps they can use these same treatment methods to cure patients with other neurocognitive diseases. It is important to understand and comprehend these treatment methods as innovative strategies to conquer these neurocognitive disorders.

None of the drugs showed potential cure for CJD. However, each drug demonstrated different efficacy rates that either slowed down the progression of CJD or improved symptoms related to CJD. These improvements eventually led to the development of drug-resistant prions that increased CJD progression and led to the death of associated participants. The data given on the efficacy of quinacrine in Table 2 showed that mice treated with quinacrine resulted in extending incubation periods compared to the controls that were not given with the drug [15]. These short-term extensions in incubation periods that are statistically significant ($p<0.01$) are indicated with an asterisk in Table 2. However, these effects did not last long as these mice eventually developed drug-resistant prion proteins, which were discovered by dissecting dead mice and finding elevated PrPSc levels in the brain [15]. This shows that quinacrine does not significantly alter the progression of CJD. The study also demonstrated that quinacrine lacks the ability to cross the blood-brain barrier effectively, which led to the study having to inject the drug intracerebrally for the mice in the study [16]. These limitations prevent the widespread use of the drug for treating the human population affected by CJD. More research needs to be conducted on human patients with improvements in methods to make the drug cross the blood-brain barrier effectively to address these limitations.

The efficacy of the drug doxycycline was also limited in its ability to treat CJD permanently. The patients in this study eventually died, but the adverse effects are not believed to be caused by the drug due to similar outcomes in the placebo group [14]. The results of the study do indicate that patients treated with doxycycline have extended short-term lifespans than the placebo group [14]. As seen in Table 2, a higher percentage of individuals that were treated with doxycycline lived greater than a period of 5 months than individuals that received the placebo [14]. On average, patients that received the drug had a greater disease duration average than patients that received the placebo [14]. However, most of the patients ended up dying due to disease progression. An autopsy was performed on patients from both groups to check for differences in conditions and ensure that the drug did not create any harmful side effects that led to the death of the patients [14]. The extent of spongiform degeneration and gliosis present in CJD were similar between both groups [14]. The study did show that the drug had a better ability to cross the blood-brain barrier [14].

Based on both study outcomes, it appears that doxycycline does have a better ability to cross the blood-brain barrier. However, as both studies were not performed on humans, it can be challenging to accept this comparison of the drug for human use. Similarly, while doxycycline does have beneficial effects, as the population tested was mainly people part of the European region, the findings of the doxycycline study cannot be generalized to other patients in non-European regions of the world. Maybe future research can be conducted using artificial intelligence to address some of the issues with this drug [17]. Additionally, further research could be done to investigate chemical and physical forces in the body that could help understand more about the pharmacodynamics and the pharmacokinetics of the body [18-20]. These limitations need to be addressed in further research to improve the widespread use of the drug.

CONCLUSION

Based on this study, it is clear that there are no treatment options that can permanently cure CJD. The studies conducted on antibodies show potential for developing a treatment method that identifies antibodies with strong binding constants to target PrP proteins. This could help reduce prion levels

significantly enough to treat CJD. While certain drugs have been discovered and experimented with for treating CJD, none of them cause significant reductions in prion levels in the brain to improve CJD symptoms. Most studies reported patients developing drug-resistant PrP proteins, which led to the death of test subjects. As the two main drugs, quinacrine and doxycycline, analyzed in this research were not both tested in humans, the efficacy of the drugs cannot be compared against each other. However, in each of the studies, quinacrine and doxycycline extended the short-term lifespan of the test subjects. Further research needs to be carried out on such drugs to improve efficacy rates and treatment potential for CJD.

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Citation: Senthilraja V, Lou E, Nakka A, Karamian P, Aslam I, et al. (2021) Exploring Drug and Antibody-Based Treatment Options for Creutzfeldt-Jakob Disease. Appl Cell Biol, 9(2), 2021 [43-48]