

Antibodies inhibit prion propagation



**ASSIGN
BUSTER**

Critical Essay of “ Antibodies inhibit prion propagation and clear cell cultures of prion infectivity.”

Background Information

Prions are the actual action centers of nervous system diseases (Selkoe, 2005, 193). They are a dendritic package that replicates and spreads neural diseases (Selkoe, 2005, 193). They also can be considered the pathways or pathogenic agents that help to transmit various nervous system diseases such as scrapie and bovine spongiform encephalopathy (Peretz, 2001, 741). Bovine spongiform encephalopathy or “ Mad Cow Disease” is spread throughout the brain by the misfolding of important proteins, and is directly linked to the prions of the brain because without the process of prion replication the disease would not be able to disperse and persist in the body of the infected animal (CDC, 2004, 1282). There are many ways in which the nervous system carries out reactions, however most reactions consist of one major type of mechanism to cause a specific action. This mechanism is known as synthesis and is carried out by many of the nervous system’s components. In synthesis, there are two important components that must be present, the reactant and the reactor. The reactant can be anything such as a compound, an element, or a specific kind of chemical. In many cases in the human nervous system, the reactant is sodium. In the case of muscle contraction, the structures on the opposite side of the synaptic gaps (proteins) will have a specific binding site or action site that the sodium must connect to in order to complete a reaction and cause an action. The action sites of these structures are very specific; and have particular shapes. Much like a lock will only allow a specific key to be inserted into it, only specific

cofactors can bind to the action site of the protein (Yaun et al, 2005, 655).

The reactant will not allow just any reactor to bind to its action site, and so is a very effective control for mutation in the synaptic gap. Sometimes, though, more than one cofactor will fit into the reactant's action site due to the molecular and chemical similarities of various reactor compounds/chemicals. If a different reactor binds to the action site of the protein, then there are many possible outcomes. The protein could change shape and not complete its task, or it could perform a completely different task than it was intended for, or it could completely disseminate and not perform any task. The aforementioned competition is known as inhibition because the true reactor is inhibited from reacting with the protein by the invading reactor. There are many types of inhibition, including direct inhibition, indirect, and allosteric inhibition. Direct inhibition is when the protein's action site is blocked from the cofactor because of an invasive cofactor binds directly to the action site. This prevents the cofactor from reacting with the action site to begin a reaction. Indirect inhibition takes place when a chemical does not bind directly to the action site of a protein but instead binds to another part of the protein, thereby changing the overall shape of the protein and consequently the shape of the action site. In most cases this will then make it impossible for the cofactor to bind to the action site, either stopping the reaction entirely or making it possible for another undesirable cofactor to bind to the action site. Indirect inhibition can occur from reagents binding to either the protein or the cofactor, creating numerous ways to actually inhibit the reaction from taking place. Allosteric inhibition is when the protein's function is changed by an indirect sequence of events that takes place across the synaptic gap (5).

<https://assignbuster.com/antibodies-inhibit-prion-propagation/>

In the currently accepted model of prion replication, the prions interact with a specific prion-protein cofactor that interrupts the replication of prions and in turn creates a “mutated” or infectious prion (Peretz, 2001, 741). However, if this process is interrupted by another cofactor (essentially direct inhibition) then the infectious prions do not have a chance to form and cannot spread the disease. In some cases the interruptors of this process are antibodies produced by the body naturally. It is believed that if the body were caused to produce the antibodies that can inhibit the action of certain nervous system diseases by the addition of certain chemicals (read: antibiotic medicines) to the circulatory system, then it would be possible to treat or even prevent the diseases all together.

Critique and Overview of Methods

The authors (Peretz et al) of the article propose very exciting and interesting answers to numerous age old problems. The observations of the experiment suggest that there is evidence that particular antibodies can actually inhibit and negate the effects of certain infectious prions in the body (Peretz, 2001, 741). The overall purpose of the study was to provide preliminary information supporting earlier findings that antibodies are an important defense against nervous system diseases. The authors also sought to identify a particular region of PrP^C for drug targeting by further experimental practices. If it were possible to actually target this particular region for drug testing, then it is possible that degenerative diseases that were incurable in the past might be able to be treated and even cured with the right medicines in the future.

In order to study the inhibition demonstrated on prion propagation by antibodies, the researchers used several recombinant prion specific Fabs. Varying concentrations of each of the antibodies (Fabs) were added to infectious prion cultures for a test period of seven days, after which cells from each test culture were collected and the level of PrP^{Sc} was analyzed by utilizing immunoblotting (Peretz, 2001, 741). To then determine whether or not PrP^{Sc} remains undetectable after the removal of the antibodies, the authors made a subculture that was treated with the Fabs and then allowed to continue culturing for one more week following the removal of the antibodies. This would allow the researchers to decide if the antibodies were actually producing a lasting affect on the infected prions or if they were simply inhibiting the infection when the Fabs were present. Of course each of the above experiments was performed with a control group of cultures in which no antibodies were added to ensure accuracy of the results. Finally, as a concluding test of the authors' hypothesis, bioassays of infected mice were taken after a period sufficient for disease formation and then examined to determine the amount of infection that was present in the tissue.

The authors have done a fantastic job of "covering their bases" so to speak and have carried out all of the processes that would be necessary for a sufficient idea of how well their theory of prion inhibition by antibodies worked. By providing information on the cultures and subcultures of prions the actual inhibition of propagation is shown and serves as evidence that the researchers have reached accurate conclusions.

The results of the study suggest that it is possible that the introduction of antibodies to infectious prions will inhibit the further production of infection. The exact Fabs that showed reduction of infectious prions are D13, D18, R1, and R2. These Fabs indicated a reduction in infectious prion propagation when compared with the control groups of the experiment, successfully suggesting that there is a negative relationship between the amount of antibodies present versus the amount of infected prions. This relationship is basically defined as antibody concentration increases, the infectious prion propagation decreases. This finding supports the authors hypothesis and appears to be a reasonable explanation of the results obtained by this study.

The researchers that produced this study have drawn the conclusion that it is probable that if the prion propagation of a disease is inhibited by a cofactor (such as antibodies) then it is possible to cure or at least treat the disease itself (Peretz, 2001, 741). The researchers used their results to come to the conclusion that prion propagation inhibition is the key to making numerous diseases (especially neurological diseases) curable. The researchers also concluded that there was a specific area of PrP^C that should be targeted when developing new drugs to treat the various nervous system diseases. They determined this particular are from the information that was provided by tests done on the subcultures of prions that were treated with Fabs and then allowed to continue to grow without the Fabs being present (Peretz, 2001, 741). Finally, the researchers determined that none of the antibodies tested had a competitive effect on any of the other antibody types. They concluded that due to this fact a combination of antibodies could be used

when battling a disease so that the most effective inhibition effect could be possible (Peretz, 2001, 741).

Overall, assumptions made by the researchers were valid and well backed up. The conclusion that diseases could be battled by inhibiting the prions produced by the disease is well documented and makes perfect scientific sense (Guyer, 2005, 2). Prions are the actual cause of the replication and spread of the disease in the animal's body (brain) and thus if they are inhibited this would then slow if not stop the disease sprawl in the body (Guyer, 2005, 2). Also, the determination of the area to target new drug testing is very interesting, but well established due to the approach that the authors took to this problem. By culturing and then subculturing the prions, the authors were able to take several variables out of the equation on the quest for an answer as to where to begin looking for a particular area of importance. It is a fair assumption that the area of antibody/prion interaction that the authors chose was accurate and is a good place to begin testing for new prion propagation inhibiting drugs. The most intriguing (at least in my opinion) finding that the researchers obtained was that none of the antibodies produced inhibiting effects *on the other antibodies*, meaning that there could be several antibodies used in an effort to produce the largest propagation inhibition possible. The researchers really nailed the important factor in this experiment on the head when they concluded that more than one antibody could be released at the same time to produce the optimal inhibition of the prions' propagation. In order for further research to be truly successful it will be helpful to at least have a beginning place for the future experiments to begin.

In general the researchers have done a good job of laying the framework for the further study of prion propagation and how that relates to the cures of neurological diseases. The work was of high quality and well performed. All of the methods were very well documented and thoroughly researched before being carried out in an effort to provide the best understanding of how antibodies actually affect prion propagation. In general, Peretz et al did a fantastic job on this experiment and should be commended for providing the necessary information for the future research of what may very well be the biggest scientific and medical breakthrough since the discovery of modern antibiotic medicine as we know it today.

Literature Cited

Center for Disease Control. 2004. Bovine Spongiform Encephalopathy in a Dairy Cow- Washington State, 2003. MMRW Weekly. 52(53); 1280-1285

Grasbon-Frodl, E.; Schmalzbauer, R.; Weber, P.; Krebs, B.; Windl, O.; Zerr, I.; Kretzschmar, H. A. 2004. A novel three extra-repeat insertion in the prion protein gene (PRNP) in a patient with Creutzfeldt-Jakob disease. Neurogenetics (Heidelberg) 5(4). p. 249-250

Guyer RL. 2005. Prions: Puzzling Infectious Proteins. Research in the News. Available: science-education. nih. gov/nihH. Pg. 1-3.

Pan, T; Wong, P; Chang, B; Li, C; Li, R; Kang, S; Wisniewski, T; Sy, M. 2005. Biochemical fingerprints of prion infection: Accumulations of aberrant full-length and N-terminally truncated PrP species are common features in mouse prion disease. Journal of Virology 79(2). p. 934-943

<https://assignbuster.com/antibodies-inhibit-prion-propagation/>

Peretz D, Williamson RA, Kaneko K, Vergara J, Lecrerc E, Schmitt-Ulms G, Mehlhorn IR, Legname G, Wormald MR, Rudd PM, Dwek RA, Burton DR, Prusiner SB. Antibodies inhibit prion propagation and clear cell cultures of prion infectivity. *Nature*. 2001 Aug 16; 412(6848): 739-43

Selkoe, D J. 2005. Defining molecular targets to prevent Alzheimer disease. *Archives of Neurology* 62(2). p. 192-195

Yuan, J; Kinter, M; McGeehan, J; Perry, G; Kneale, G; Gambetti, P; Zou, W. 2005. Concealment of epitope by reduction and alkylation in prion protein *Biochemical and Biophysical Research Communications* 326(3). p. 652-659