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REVIEW ARTICLE

Exploiting the Combinatorial Therapeutic Approach in Glutamate toxicity induced neurodegenerative diseases – A mini review

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Abstract

Glutamate toxicity is implicated in various neurodegenerative diseases which share diverse pathological features, and among these oxidative stress, inflammation and excitotoxicity play leading role in their progression. Since glutamate toxicity involves activation of multiple pathways, merely blocking a single component may be ineffective to modulate the process. So, no single drug effectively abates glutamate toxicity associated neurodegeneration. Therefore, combination therapy aimed at inflammatory, stress and non-inflammatory mechanisms involved in various neurodegenerative diseases may prove to be successful and effective therapy to combat these diseases in comparison to monotherapies including anti-inflammatory drugs (AIDs). In conclusion, further studies need to be designed to elucidate the potential of combination therapy to target cross talk between various stress mechanisms to ameliorate glutamate toxicity, in comparison to monotherapies. This mini review evaluates research findings, not only with the aim of recognition of scope of combinatorial therapeutic approach for the cure of various neurodegenerative diseases but also for its translation into the clinical arena.

INTRODUCTION

Combination therapy is the use of multiple therapies or medications to treat a single disease. Recent research focuses on the new therapeutic strategy based on the administration of the combination of multiple therapies mimicking biological concentration to ameliorate diverse diseases. Often all the therapies used in combinatorial therapeutic approach are pharmaceutical, but it may sometimes involve non-medical therapy, e.g. the combination of medications and talk therapy to treat depression. Pharmaceutical combination therapy may involve administration of separate drugs, or sometimes, dosage forms containing several active ingredients (such as fixed-dose combinations). The combination therapies own a main advantage of reduced development of drug resistance, and hence possess enhanced efficacy. Moreover, combination therapies also possess advantages of lower treatment failure rate, lower case-fatality ratios, slower development of resistance and consequently less money needed for the development of new drugs. Additionally, combinatorial approaches can be used in the optimization of in-vitro survival and differentiation, synthetic genomics, delaying of aging and improvement of physiological performance **(Jacob et al., 2009).** Moreover, combinatorial therapeutic approach increases the chance of effective treatment by eliminating development of resistance to drugs in comparison to monotherapy **(Natalia & Richard, 2013)**.

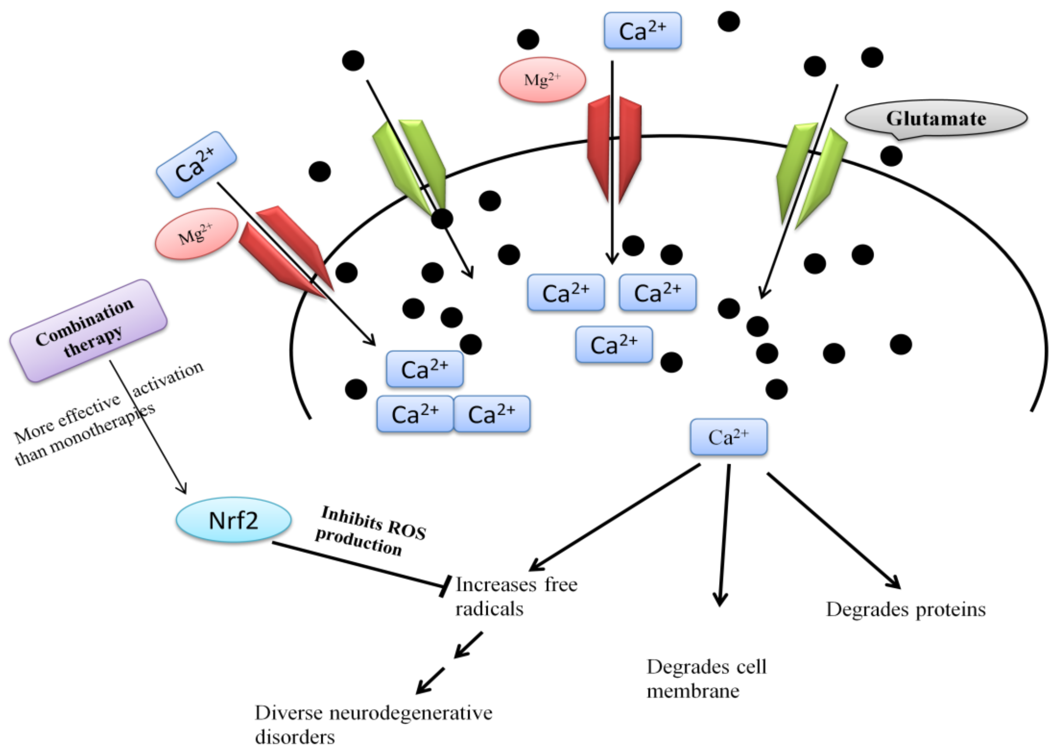
Combinatorial therapeutic approach in treatment of various diseases

Multi-targeted drugs are supposed to replace therapies which aim at a single target **(Wermuth, 2004)**. Modulating multiple targets has been hypothesized to be an asset in the treatment of a number of disorders **(Morphy, Kay, & Rankovic, 2004).** Most multiple-action drugs in clinical use today were discovered serendipitously and their mode of action elucidated retrospectively. Combinatorial therapeutic approach has been successfully applied for the amelioration of several diseases like cancers, malaria etc. Combination therapy has been reported to show enhanced anti-tumor activity in certain cancers **(Stritzker & Szalay, 2013).** A combinatorial radiotherapy and biotherapy approach with the expression of radio-sensitizing molecules and proteins or the delivery of prodrug-converting enzymes shows increased anti-tumor effect in comparison to monotherapies **(Stritzker, Pilgrim, Szalay, & Goebel, 2008)**. Recently, a combination therapy using radiolabeled antibodies bound to tumor-colonizing bacteria has been seen to increase therapeutic efficacy in a model of metastatic pancreatic cancer in mice **(Quispe-Tintaya et al., 2013).** New presurgery combination therapy, which involves chemotherapy prior to surgery, may possibly improve outcomes of triple-negative breast cancer in women **("New presurgery combination therapy may improve outcomes for women with triple-negative breast cancer," 2013).** Artemisinin combination therapy, which combines an artemisinin derivative with another longer-lasting drug has brought a revolution in the alleviation of malaria and over 90% of people have been benefitted by this combination therapy **(Adjuik et al., 2004)**. Combination therapy reduces associated problems of rheumatoid arthritis, such as heart attack and stroke. Furthermore, combination therapy using drug decitabine before chemotherapy and a cancer vaccine has been observed to be more effective in treating recurrent ovarian cancer in women **(Whiteman, 2014).** However, the combination of two or more effective drugs with different mechanisms of action cannot be simply assumed to always improve results as compared with monotherapy **(Johnson, MacDougall, Ostrosky-Zeichner, Perfect, & Rex, 2004)**. One study suggests benefits of broad spectrum lactam monotherapy in the treatment of patients with fever and neutropenia in comparison to combination therapy **(Mical, Karla, & Leonard, 2003).**

Neurodegenerative diseases and combination therapy

Neurodegeneration is a general term for the progressive loss of structure or function of nerve cells, including their death **(Bredesen, Rao, & Mehlen, 2006).** The incidence of neurodegenerative diseases is on rise and are extremely devastating, affecting millions of people worldwide **("Cognitive impairment in neurodegenerative diseases & preclinical models." 2013).** Neurodegenerative diseases are a group of complex diseases that are becoming world’s most alarming public health challenges. It is estimated that over the next two decades, the incidence of these diseases including AD and MS will increase upto 50%. In fact, the mechanisms leading to neurodegeneration are not properly understood, so the diseases arising from it have no treatment so far. Glutamate neurotoxicity has been implicated in stroke, Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Multiple sclerosis (MS) and other neurodegenerative conditions **(Hughes, 2009; A. H. Kim, Kerchner, & Choi, 2002).** So, the reduction of glutamate toxicity is one of the most essential therapeutic strategy for the treatment of these disorders **(Gardoni & Di Luca, 2006; K. Kim et al., 2011).** However, the molecular mechanisms responsible for glutamate induced cell death have not been fully elucidated **(Wang & Qin, 2010).** A crosstalk between various inflammatory, non-inflammatory, oxidative stress and excitotoxicity mechanisms have been hypothesized, which ultimately leads to diverse neurodegenerative conditions. Till date, there are no cures for these diseases and the drugs that target these diseases treat only their symptoms and not the cause. Various AIDs have been seen to modulate neuro-inflammation, but due to the other complex mechanisms involved in addition to neuroinflammation, a need for the better therapy arises for improved efficacy. Moreover according to the oriental medicine, the pathogenesis of neurodegenerative disorders is characterized by the loss of kidney essence or the blocking of the brain channel by blood stasis or both. Therefore, the main ways to treat neurodegenerative disorders are tonification of kidneys, removal of the phlegm, elimination of blood stasis and stimulation of revitalization **(Chen & Zhang, 1997)**. So, combination therapy should be designed such that the multiple molecular structures and receptors in the central nervous system are targeted in a single package. But the design of multiple ligands is attaining a balanced activity at each target of interest while simultaneously achieving a wider selectivity and a suitable pharmacokinetic profile. This therapeutic strategy offers the opportunity to selectively modulate the glutamate toxicity which is implicated in a wide range of neurodegenerative diseases.

Combinatorial therapy also possesses better blood brain barrier (BBB) penetration and minimal adverse effects. Also, MS has no known cure, but it can be managed by combination therapies **(Compston & Coles, 2002).** Furthermore, several in-vitro and in-vivo studies suggest the involvement of inflammatory mechanisms in Parkinson's disease but the neuro-inflammatory mechanisms leading to this disease are not fully understood. So it is likely that combination therapies with drugs targeting both inflammatory and non-inflammatory mechanisms may prove to be more effective for the treatment of this disorder **(Klegeris, McGeer, & McGeer, 2007).** However, unfortunately little work has been done in evaluating effect of this combinatorial therapeutic approach in combating neurodegeneration. A novel drug combination consisting of an HMG-CoA reductase inhibitor and a selective Cyclooxygenase-2 (COX-2) inhibitor has been reported to delay the onset of Alzheimer's disease **(Guilford, Kindness, & Schumm, 2002)**. Thus combination therapy with antioxidants or multi-potent drugs may represent an attractive and effective strategy to treat diverse neurodegenerative pathologies as compared to conventional monotherapies **(Gilgun-Sherki, Melamed, & Offen, 2006).** It is hypothesized that combination therapy may provide protection in CNS trauma and neurodegenerative disorders **(Sharma, Muresanu, & Sharma, 2013).** It has been reported that combination of drugs already developed against specific disease with constituent groups of active molecules into a single therapeutic agent can represent a new therapeutic strategy **("Drug Combinations Key In Treating Neurodegenerative Diseases. ," 2009).** Combination treatment in mice has been reported to show promising beneficial therapeutic strategy to combat a fatal neurological disorder in kids, Batten disease **("Combination treatment in mice shows promise for fatal neurological disorder in kids ", 2012).** Furthermore, in a study carried out in our laboratory we have observed modulation of index inflammatory marker iNOS and its by-product-NO, which are the root cause of most neurodegenerative conditions, by combination therapy using ethyl pyruvate and methanolic extract of Rheum emodi (*Unpublished work of our laboratory*). This drug combination is hopefully expected to be beneficial in combating glutamate toxicity (A schematic for Glutamate effects on cell are shown in the diagram below). Further, evaluating the effect of this drug combination on other parameters associated with neurodegeneration will help to validate our data.



Schematic representation of glutamate entry into the cell and its consequences. Glutamate enters the cell through receptors and as a result intracellular calcium increases which in turn leads to different effects and ultimately death of neurons and diverse neurodegenerative conditions. Combination therapy has been observed to be more effective in treating different neurodegenerative conditions than monotherapies partly by impairing production of ROS through Nrf2 activation.

● Glutamate NMDA Glutamate receptor (Green) Non-NMDA Glutamate receptor (Red)

CONCLUSION

The discovery of novel combination therapy may pave way for successful treatment of various diseases. For the better management and cure of glutamate toxicity, newer and promising strategies are needed as inflammation, oxidative stress and excitotoxicity have been hypothesized to act synergistically and exacerbate glutamate toxicity associated neurodegeneration. Monotherapies used for the cure of diverse neurodegenerative diseases aim at single target. Subsequently, there is a need to search for new possible combination therapies that would much more effectively abate various stress responses implicated in various neurodegenerative diseases. Screening drugs that have already been developed to address very specific disease targets and come up with new ways to combine their constituent molecules into a single therapeutic agent could represent a new frontier for pharmacology. However, it cannot be simply assumed that the use of two or more effective drugs with different mechanisms of action will produce an improved outcome compared to the results seen with a single agent. Combination therapy could reduce clinical efficacy, increase potential for drug interactions and drug toxicities, and carry a much higher cost for antifungal drug expenditures without proven clinical benefit **(Lewis & Kontoyiannis, 2001).** The real success of this combination therapy will lie in balancing of in-vitro and in-vivo activities with optimizing the pharmacokinetic and safety profiles. Further attention should be paid to issues of dose response and dose selection for these trials.

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