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Resveratrol therapy for Alzheimer's disease

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Introduction

In 1993, the first FDA-approved drug for treating the neural or chemical deficiencies that underlie Alzheimer's disease (AD) was ushered into the clinical field of age-related dementias. Unfortunately, the drug, Tacrine (Cognex), has not been effective in reducing dementia, nor the disease progression (Fan et al., 2010). Given these and other limitations of current drug therapies, neuroscientists have been forced to search for new therapeutic strategies that might affect the underlying mechanisms of the disease. One such strategy is to treat the afflicted AD brain with resveratrol, a natural polyphenol found in grapes and red wine (Torres et al., 2008; Torres et al., 2011). In this brief review, we summarize the putative causes of AD, list the current therapeutic approaches to AD and discuss the rationale for using resveratrol in this and other neurodegenerative diseases.

The disease: Clinical symptoms

Alzheimer's disease is a progressive neurodegenerative disorder with a prevalence of approximately 5% of the USA population over the age of 65 (Grabowski, 2011). Afflicted individuals suffer from blunted cognitive ability and as the disease progresses, severe memory loss, disorientation and aphasia become more symptomatic. In the later stages of AD, the patient becomes severely disabled, immobile and mute. Death occurs mostly from inanition, malnutrition and/or pneumonia (Grabowski, 2011). Conclusive diagnosis of the disease is made post-mortem, with certain aberrant histopathological findings noted throughout the brain parenchyma (Fauzi et al., 2008). However, due to advanced computer-based neuroimaging techniques (e.g., high-resolution structural MRI scans) and sophisticated behavioral testing (e.g., Mini-Mental State Examination), most cases of AD can now be correctly diagnosed in vivo by well-trained neurologists (Kumar et al., 2010).

Pathology: Faulty brain circuits

Considerable evidence suggests that AD is multifactorial, involving several different etiopathogenic mechanisms. When the AD brain is examined post-mortem using highly-specific histopathological stains and visual-

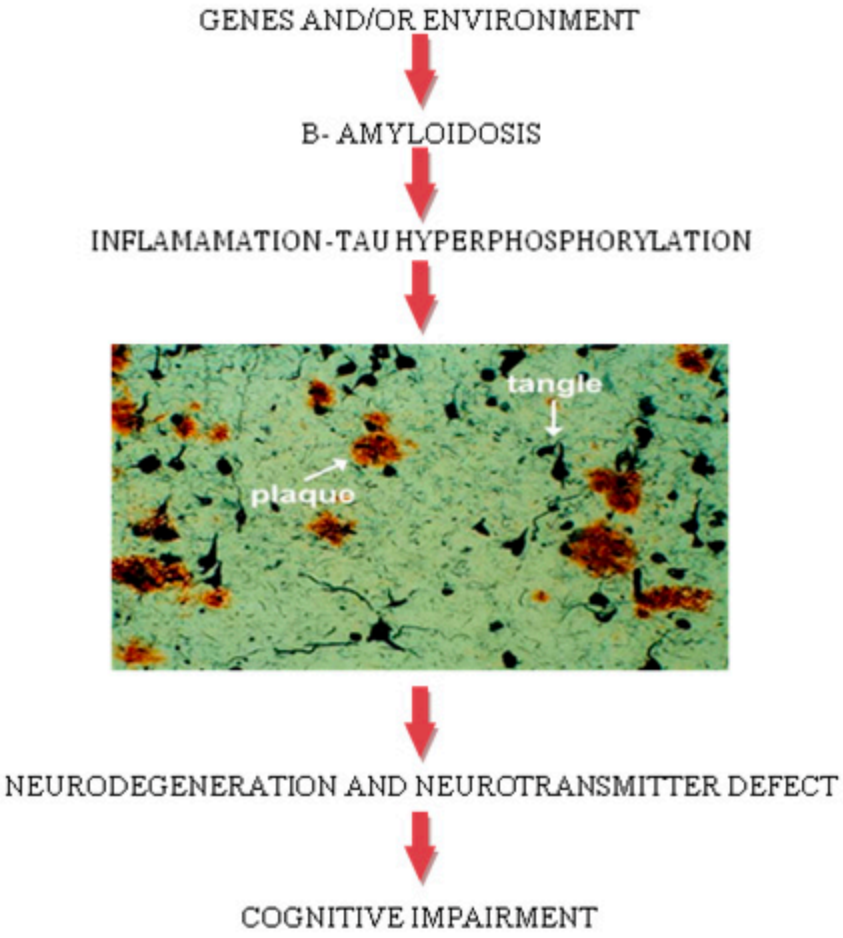

Fig. 1. It is proposed that mutated genes and/or environmental insults give rise to increased amounts of soluble and insoluble β-amyloid proteins. The inability of the AD brain to remove high levels of these proteins leads to insoluble plaques in cerebrocortical and hippocampal neurons (see depicted photomicrograph). Accumulation of this and other aberrant proteins (e.g., TAU) culminates in cell death and neurotransmitter deficit (e.g., acetylcholine). Progressive clinical dementia of the Alzheimer's type is the final outcome of this cascade of events. Figure modified from LaDu Alzheimer's Disease Research Laboratory, Department of Anatomy and Cell Biology at the University of Illinois, Chicago

ized under light microscopy, it is characterized by β-amyloidosis and neurofibrillary degeneration (Kumar et al., 2010). β-amyloidosis refers to the abnormal deposition of β-amyloid protein fragments (or plaques) in the brain parenchyma and cerebral blood vessels (i.e., congophilic angiopathy). On the other hand, neurofibrillary degeneration is a progressive retrograde neuronal degeneration that is seen as neurofibrillary tangles (i.e., dystrophic neurites) in cerebrocortical and hippocampal nerve cells (Fauzi et al., 2008; Schneider et al., 2011). Other pathological markers of the AD brain often include the abnormal phosphorylation of TAU proteins within neurons and activation of microglial cells, the brain's own immune cells (Wyss-Coray, 2006; Huang and Jiang, 2009). In general, the presence of the aforementioned mutant proteins in the brain parenchyma correlates with clinical diagnosis of amnestic cognitive impairment in apparently genetically-prone individuals (Bussiere et al., 2003; Fig. 1). It is conceivable therefore that extirpation of cerebrocortical and hippocampal neurons might disrupt vast connected networks of the brain involved in declarative and procedural memories. Indeed, neuroimaging techniques are revealing that faulty circuits or structural connections may underlie the pathogenesis of AD and other brain disorders. This view is now providing new insights into their underlying causes, which promises more objective methods of diagnosis and more rational targeted treatments.

Familial history of AD: Early diagnosis and genes

A few months ago, new guidelines for diagnosing AD were published by the National Institute on Aging. Among others, the new guidelines specify that the pathology, in particular, the plaques of extracellular deposits of

β-amyloid can be detected years (if not decades) before the patient experiences his/her first bouts of dementia (Jack et al., 2011; McKhann et al., 2011; Albert et al., 2011; Sperling et al., 2011). This preclinical or presymptomatic stage of diagnosis offers the opportunity to study the risk factors for disease, such as apolipoprotein E (APOE) ε4 or family history of AD (Driscoll et al., 2006). For instance, individuals who are symptom-free but carry the APOE ε4 allele are at substantial risk for early onset AD (Okonkwo et al., 2010). There is a considerable load effect of this gene as carriers show higher levels of β-amyloidosis and neurofibrillary degeneration in their brains than non-carriers of the APOE ε4 gene variant (Whitehair et al., 2010). It should be noted that APOE ε4 is not in itself a determinant of AD onset but instead is a factor that in combination with other rogue alleles and epigenetic variables define AD risk. In this regard, other genes catalogued as major risk factors for early onset AD include, presenilin 1 and presenilin 2. Finally, there is considerable evidence that maternal origin of family history risk is associated with a higher incidence of β-amyloid pathology than paternal origin (Mosconi et al., 2007). This finding suggests a differential expression of AD genotypes between males and females, a form of genomic imprinting. Another possibility for this differential expression might be a form of epigenetic transmission where some effects of the intrauterine environment could produce marked effects on disease-related traits to filial generations. Regardless, there is strong evidence of an interaction between gender, genes and ill-defined factors from conception to development in AD.

Current treatment for AD: Pharmacological actions

As previously noted, there is no cure for AD nor is there an FDA-approved drug that prevents β-amyloid deposition from forming or dismantling those already rooted in the brain parenchyma. Nevertheless, research completed in the early 1990s established the relationship between AD and diminished availability of acetylcholine in the synapse (Terry and Buccafusco, 2003). More recently, neuroscientists also demonstrated the involvement of glutamate in AD, as blocking the actions of this excitatory neurotransmitter appears to improve disease outcome. Accordingly, Aricept (Donepezil), Exelon (Rivastigmine) and Reminyl (Galantamine) work by preventing the breakdown of acetylcholine, whereas Namenda (Memantine) protects nerve cells from excessive glutamate release (Fan et al., 2010). The rationale for using Namenda is that cognitive function is impaired when high glutamate levels reach the synapse, as demonstrated in a wide range of experimental paradigms. (Schneider et al., 2011) Unfortunately, Tacrine (Cognex) is rarely used today because of its high toxicity profile.

Despite the vast pharmacological arsenal for the treatment of AD and other forms of clinical dementia, convincing evidence of an adequate level of efficacy and reliability on disease outcome is lacking (Lu et al., 2009). Moreover, drugs that target β-amyloid deposits in cerebrocortical and hippocampal neurons have failed in any measure of efficacy in clinical trials (Fan et al., 2010). Thus, there is a pressing need to develop new drugs with unconventional actions for treating age-related neurodegenerative diseases. Resveratrol, in this regard, is an unusual and interesting molecule.

Resveratrol: A potential therapeutic agent for AD

Resveratrol (3,5,4'-trihydroxystilbene) is a natural polyphenol found in grapes and red wine as well as in the roots of Japanese knotweed. Interest in using resveratrol for preventing a wide variety of illnesses began in the early 1990s when red wine consumption was reported to exert beneficial effects on cardiovascular function (Baur and Sinclair, 2006).

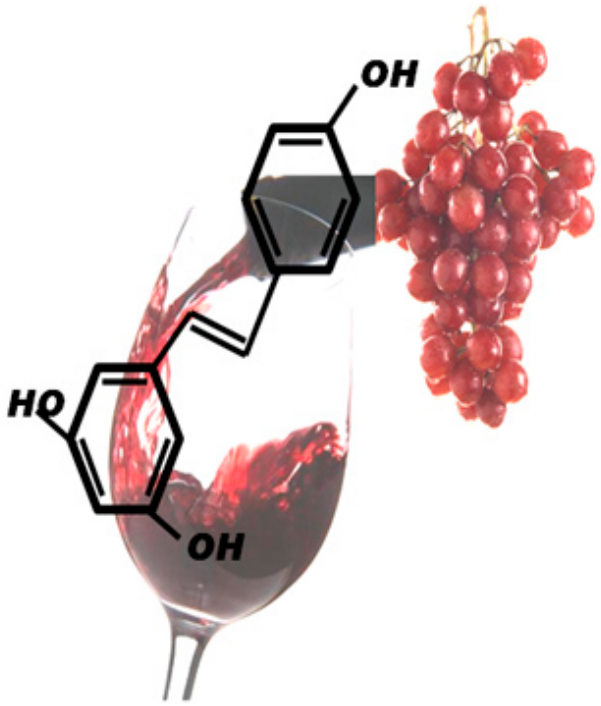

Fig. 2. Resveratrol is one of several experimental drugs that are currently being tested for reducing β-amyloidosis and neurofibrillary tangles. A growing body of in vivo and in vitro evidence indicates that resveratrol (see depicted chemical photomicrograph) reduces the toxic effects of insoluble aggregates found in several neurodegenerative diseases, including AD. Although circulating resveratrol penetrates the blood-brain barrier, it is rapidly metabolized by the liver. Our laboratory is working on this pharmacokinetic issue to assess whether resveratrol or its metabolites can be enhanced in vivo. Another line of research in our laboratory is to understand the mechanisms by which resveratrol affects disparate brain diseases.

Subsequently, resveratrol was found to inhibit platelet aggregation, stroke, brain damage and carcinogenesis at several stages (Della-Morte, 2009; Fig. 2).

Although the precise mechanisms by which resveratrol exerts its wide range of beneficial effects on disease are not yet clear, there is convincing evidence that resveratrol acts on a set of proteins known as sirtuins. Sirtuins are a conserved family of proteins found in all metazoans in which adult cells proliferate (Michan and Sinclair, 2007). One of these proteins is known as silent information regulator 1 (SIRT1), a mammalian transcription factor localized to the cell nucleus of most nerve cells of the brain, including cerebrocortical and hippocampal neurons (Michan and Sinclair, 2007; Zakhary et al, 2011).

SIRT1 is of significant interest to healthy aging as activation of this protein delays the aging process in experimental animals, including rodents. Not only does SIRT1 modulate the life span of cells, it also reduces the aggregation of toxic proteins (e.g., β-amyloids) that often accumulate in the senescent brain (Albani et al., 2010; Gan and Mucke, 2008). Thus, SIRT1 has been postulated to be a key molecule in regulating the steady-state level of normal aging and neurodegeneration. Thus, activation of sirtuin signaling pathways could delay certain aspects of the aging process and could also provide new therapeutic avenues for preventing neurodegenerative diseases (Fig. 3). From a therapeutic perspective, this duality of expression is of considerable importance, particularly if the activity of SIRT1 can be enhanced by lipid soluble molecules, such as resveratrol. Indeed, there is compelling evidence that resveratrol can pass the blood-brain barrier and activate SIRT1 signaling pathways in the adult brain (Torres et al., 2010). Resveratrol is therefore a true agonist of SIRT1.

There is no doubt that resveratrol can have a positive effect on the transcriptional signature of cerebrocortical and hippocampal neurons. The question to ask now is whether resveratrol can prevent the accumulation of insoluble aggregates (i.e., β-amyloids) in the AD brain. The answer to this question is encouraging. Rapidly emerging data from basic and clinical studies of resveratrol indicate that this polyphenol molecule can delay the toxic effects induced by aberrant proteins, both in vivo and in vitro (Baur, 2010) Furthermore, resveratrol is currently being evaluated for its therapeutic efficacy and safety in clinical trials of AD and cerebral ischemia (Baur and Sinclair, 2006). These data suggest that resveratrol is capable of exerting strong neuroprotective effects, most likely by acting upon

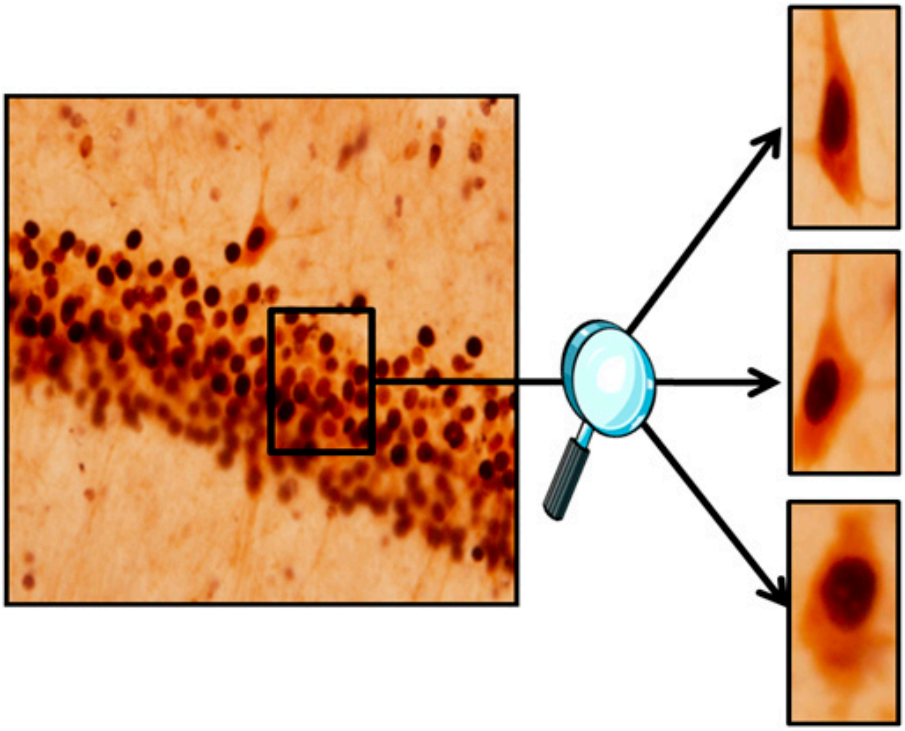

Fig. 3. The beneficial effects of resveratrol appear to involve the activation of SIRT1 signaling pathways. SIRT1 activity also increases in response to calorie restriction diet. SIRT1 is a transcription factor localized to the nucleus of mammalian hippocampal neurons (see depicted photomicrograph). Activation of SIRT1 by resveratrol represents a novel experimental approach for reducing plaque and neurofibrillary pathology in AD.

signaling pathways associated with protein homeostasis.

Conclusion

Aging societies face an increasing prevalence of neurodegenerative disorders for which no cure exists. Furthermore, it has come as an acute disappointment that most FDA-approved drugs for AD have failed to help patients. Thus, the use of resveratrol for AD and other neurodegenerative disorders (e.g., Parkinson's disease) looks promising. However, it is by no means a silver bullet. Most neuroscientists agree that AD treatment must include a combination of several drugs (a cocktail) to target not only β-amyloidosis and neurofibrillary degeneration but also hyperploidy (a state where neurons contain more than two set of chromosomes), and other secondary pathologies associated with clinical dementia. Thus, resveratrol in combination with other promising drug(s) could be a better way to treat AD than any single, current medication alone.

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Biographies

Dr. Brian H. Hallas (bhallas@nyit.edu) received his Ph.D. in neurobiology from Purdue University in 1979. He also holds an M.S. in biology from Purdue University, a B.A. in Psychology, and a B.S. in Biology from University of Hartford. He has been awarded numerous research grants and has authored many articles in scientific journals. He is the recipient of various honors and awards, most recently the prestigious Presidential Service Award from New York Institute of Technology in 2007. In 2004, he was awarded a fellowship by the Heritage Foundation Health Policy for Research in Health Policy based on stem cell research. From 2003 to 2007, he was Associate Dean of Research at the New York College of Osteopathic Medicine of New York Institute of Technology, where he is currently Chair and Professor of the Department of Neuroscience and Histology. He has published over 70 peer reviewed articles, several book chapters and 225 abstracts.

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Editor's Column

It is that time of year again. The Society for Neuroscience meetings are just around the corner. The Society now has over 40,000 members and is growing steadily. The meetings in Washington DC in mid-November once again promise to be both large and exciting. At times, the meeting seems to be overwhelmingly large, but the great feature of that size is that no matter what area of neuroscience one is interested in, it is sure to be represented. Be sure to stop by the David Kopf Instrument booth (booth 1625) to visit with one of the Kopf representatives, look at the equipment on display and get updated catalogues sent to you. As always, the booth will feature the major Kopf products from the most complete and reliable line of stereotaxic and related instruments in the world.

Once again this year, David Kopf Instruments is proud to sponsor the David Kopf Lecture on Neuroethics in memory of David Kopf. The lecturer this year is Svante Paabo, Ph.D. from the Max Planck Institute for Evolutionary Anthropology. The title of his talk is "A Neanderthal Perspective on Human Origins". The lecture will be delivered on Monday, November 14 at 11:10 am. We hope to see you there.

This issue of the *Carrier* features a very nice review article on Alzheimer's dementia and its possible treatment by resveratrol. The article was written by Joerg R. Leheste and colleagues at the New York Institute of Technology. Dr. Leheste and two of the other authors, Brian Hallas, Ph.D. and German Torres, Ph.D. have contributed several articles to the *Carrier* and as usual, this one is both interesting and informative. We thank them for their work.

It is the height of hurricane season in Florida, where we live. This year, we have been fortunate so far in that only two hurricanes have made landfall in the US. Don brought a lot of rain to south Texas, but did little damage. Irene brought a lot of rain and did extensive damage to the upper east coast, including New York. She was a rather rare hurricane in that she struck so far north. However, the season has a ways to go, lasting until the end of November. We have been living in our home-away-from-home condo in Dublin, Ohio for a couple months so have our Florida house all secured with hurricane shutters for now. We hope that the last two months of the hurricane season are quiet ones for the US and especially for Florida. We will be going back there in mid-October.

We hope to see you at the Neuroscience meetings in Washington. Please stop by the Kopf booth to say hello and chat. If you want to write an article for the *Carrier*, please see me there or send me an email. I can send you author instructions and answer any questions you may have.

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