

# Acetaminophen: The Case for a Link to Neurodegenerative Diseases

Richard J. Sharpe, M.D.

May 27, 2008

Email: [rjsharmd@gmail.com](mailto:rjsharmd@gmail.com)

Abbreviations: CNS, Central Nervous System; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NSAIDS, non-steroidal anti-inflammatory drugs; U.S., United States; FDA, Food and Drug Administration

## Abstract

Acetaminophen is a centrally acting antipyretic and analgesic which has been used in humans since the 1970's. Its use has increased for a variety of reasons including its use for extended periods of time and for chronic pain. Acetaminophen either decreases or depletes the endogenous anti-oxidant glutathione in mammalian cells. Without the protective effects of glutathione, mammalian cell damage or cell death occurs.

Neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease and disorders of retinal cells, such as age associated macular degeneration, are due at least in part to cellular damage induced by free radicals and oxidative stress. By reducing or depleting neuronal and retinal glutathione, acetaminophen might trigger, accelerate or otherwise worsen these diseases. This hypothesis can best be tested in a large prospective cohort study of acetaminophen use and the risk of these diseases in humans. An acceptable alternative study design would be a population based retrospective cohort study. Although not necessarily predictive of human disease, acetaminophen can also be studied in animal models and with *in vitro* models of human neurodegenerative and oculodegenerative diseases.

## Background

Neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease as well as retinal degenerative diseases, such as age related macular degeneration are all associated with permanent neuronal damage and loss. The causes are for the most part unknown, although for certain diseases genetic factors [1] and advancing age [2, 3] play a role. A Parkinson's disease like loss of dopaminergic substantia nigra neurons can be triggered in primates by the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [4]. It has been postulated that environmental toxins may play a role in human neurodegenerative diseases, however to date no such link has been proven.

Since the 1970's, acetaminophen has become increasingly popular as an analgesic and antipyretic throughout the world. Some of this popularity has been driven by marketing although the gastric mucosa toxicity and anti-platelet function activity of aspirin and the classic non-steroidal anti-inflammatory drugs (NSAIDs) have also been a driver. Further, the discovery of the association between aspirin use and Reye's syndrome in infants and children has tipped the bias towards acetaminophen as a first line anti-pyretic [5]. Also, as the obesity epidemic worsens in the U.S. and other western societies [6], the increasing incidence of osteoarthritis may drive increased analgesic use, including the use of acetaminophen.

Acetaminophen, a relatively small lipophilic molecule, readily crosses the blood/brain barrier where it exerts its antipyretic and analgesic effects.

## Presentation of the Hypothesis

Although acetaminophen lacks the gastric toxicity and anti-platelet activity of aspirin and other classic NSAIDs, it is well known to have hepatotoxicity [7]. Chronic long term acetaminophen use increases the risk of liver failure and acute overdosage can cause fulminant liver necrosis and failure [7]. The mechanism by which acetaminophen causes liver toxicity is probably due to depletion of glutathione by this drug [7]. The hepatic cells are then unable to neutralize the toxic effects of peroxides, superoxide species and free radicals which are generated during the normal course of metabolism.

Neurons within the CNS are very metabolically active, moreover, there is evidence that the glutathione levels within CNS neurons fall with advancing age [8-10]. Others have postulated a role for oxidative stress in neurodegenerative diseases, including Parkinson's' disease and Alzheimer's disease [8, 9].

Given the ability of acetaminophen to cross the blood-brain barrier and its glutathione reducing activity, I postulate that the use of acetaminophen amplifies the toxic effects of oxidative stress on CNS neurons as well as retinal cells and their neuronal network.

Further, I hypothesize that the reduction of glutathione levels due to natural aging causes increased sensitivity to the toxic effects of acetaminophen in the elderly. Acetaminophen may thus be a direct cause of neurodegenerative and oculodegenerative diseases of the retina or may be a co-factor in the development and the acceleration of neuronal damage and loss in these diseases.

## Testing the Hypothesis

Animal models and *in vitro* models of neurodegenerative and retinal degenerative diseases exist [4]. Acetaminophen can be tested in these model systems.

However, *in vivo* and *in vitro* models do not directly mimic human disease. As such the most exact method to evaluate the hypothesis would be a long term prospective cohort trial in humans. Since retrospective questionnaire studies are less expensive and more time efficient such an approach might be more practical. Data mining of existing large databases as was recently done for statin use and neurodegenerative disease is another potential approach [11, 12].

## Implications of the Hypothesis

This paper raises the possibility that the widely used analgesic and anti-pyretic, acetaminophen, may be a trigger or co-factor in neurodegenerative and retinal degenerative diseases. Given the huge public health implications that such a link would have, proving (or disproving) this link should have a high priority. Indeed, the US Food and Drug Administration (FDA) is under pressure, primarily due to several recent high profile failures, to increase post-marketing surveillance [13,14].

With the aging of the population in the US and most developed countries, the prevalence and incidence of neurodegenerative and retinal degenerative diseases is at epidemic levels. Elimination of even a single negative co-factor in these disorders would do much to reduce the cost of healthcare as well as relieve much suffering.

## Competing Interests

The author declares that he has no competing interests.

## Acknowledgement

This paper is dedicated to the memory of Dr. Dan E. Pratt, a brilliant scientist and teacher.

## References

- [1] Silverman JM, Raiford K, Edland S, Fillenbaum G, Morris JC, Clark CM, Kukull W, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part VI. Family history assessment: a multicenter study of first-degree relatives of Alzheimer's disease probands and nondemented spouse controls. *Neurology*. 1994 Jul;44(7):1253-9.
- [2] Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA. Prevalence of parkinsonian signs and associated mortality in a community population of older people. *N Engl J Med*. 1996 Jan 11;334(2):71-6.
- [3] Lim A, Tsuang D, Kukull W, Nochlin D, Leverenz J, McCormick W, Bowen J, Teri L, Thompson J, Peskind ER, Raskind M, Larson EB. Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. *J Am Geriatr Soc*. 1999 May;47(5):564-9.
- [4] Dunnett SB, Björklund A. Prospects for new restorative and neuroprotective treatments in Parkinson's disease. *Nature*. 1999 Jun 24;399(6738 Suppl):A32-9.
- [5] Hurwitz ES, Barrett MJ, Bregman D, Gunn WJ, Schonberger LB, Fairweather WR, Drage JS, LaMontagne JR, Kaslow RA, Burlington DB, et al. Public Health Service study on Reye's syndrome and medications. Report of the pilot phase. *N Engl J Med*. 1985 Oct 3;313(14):849-57.

[6] Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002 Oct 9;288(14):1723-7.

[7] Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). *Gastroenterology*. 1995 Dec;109(6):1907-16.

[8] Smith MA, Perry G. Free radical damage, iron, and Alzheimer's disease. *J Neurol Sci*. 1995 Dec;134 Suppl:92-4.

[9] de la Asuncion JG, Millan A, Pla R, Bruseghini L, Esteras A, Pallardo FV, Sastre J, Viña J. Mitochondrial glutathione oxidation correlates with age-associated oxidative damage to mitochondrial DNA. *FASEB J*. 1996 Feb;10(2):333-8.

[10] Benzi G, Moretti A. Age- and peroxidative stress-related modifications of the cerebral enzymatic activities linked to mitochondria and the glutathione system. *Free Radic Biol Med*. 1995 Jul;19(1):77-101.

[11] Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med*. 2007 Jul 19;5:20-31.

[12] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992 Jun;45(6):613-9.

[13] Schultz WB. Bolstering the FDA's drug-safety authority. *N Engl J Med.* 2007 Nov 29;357(22):2217-9.

[14] Sharfstein JM, North M, Serwint JR. Over the counter but no longer under the radar-  
-pediatric cough and cold medications. *N Engl J Med.* 2007 Dec 6;357(23):2321-4.