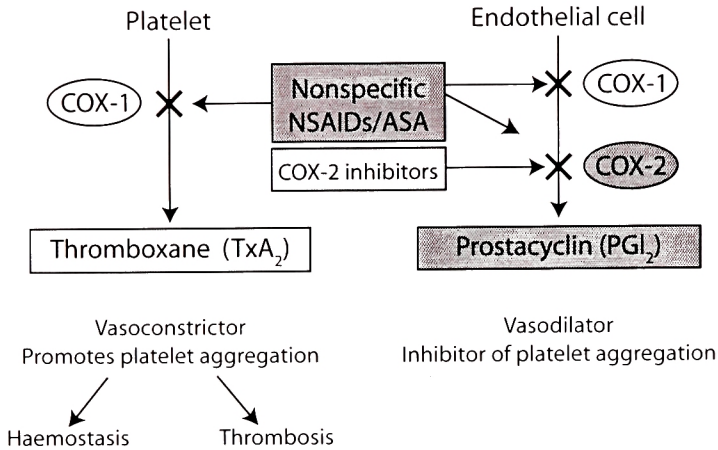

Figure 3: Traditional Non-specific NSAIDs and aspirin inhibit both COX-1 and COX-2 activity, preventing the production of both Thromboxane A_2 and Prostacyclin (PGI_2); therefore, the effects on haemostasis (blood clotting) are balanced. COX-2 specific inhibitors inhibit only Prostacyclin (PGI_2) production causing a shift towards increase vasoconstriction and blood clotting. (Clark, 2004)

Adverse Cardiovascular Effects Of COX-2 Inhibitors

Aside from inflammation, one fundamental physiological function of prostaglandins is haemostasis, maintaining a balance between liquid and solid (clotting) blood. In particular, it is thromboxane A_2 (TXA_2) which initiates platelet aggregation and clot formation, and prostacyclin (PGI_2) which serves as an anti-aggregatory blood thinner (Clark, 2004). TXA_2 production in platelets is mediated by COX-1, while PGI_2 production in vascular endothelial cells is mediated by COX-2. Traditional non-selective NSAIDs inhibit both COX-1 and COX-2 and therefore the effects on haemostasis are counterbalanced. However, COX-2 specific NSAIDs inhibit PGI_2 production only; this shifts the haemostatic balance towards increased platelet aggregation and vasoconstriction of blood vessels (Clark, 2004). These two conditions lead to the increased cardiovascular complications found in patients using Vioxx.

The results of the VIGOR (VIOXX Gastrointestinal Outcomes Research) in 2000 revealed that while Vioxx demonstrated less gastrointestinal toxicity than the comparative non-selective NSAID, it also led to a marked increase in adverse cardiovascular events (Bombardier et al. 2000). However, it was not until four years later when the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial confirmed these cardiotoxicity findings that Vioxx was recalled.

Drugs, Tea and Curry: The Means to Finding a Cure for Alzheimer's Disease?

Danny Ricci

There is no known cure for Alzheimer's disease, but certain substances and drugs have shown promising results in treating this neural degenerative disorder.

Alzheimer's disease is a neural degenerative disorder that affects 11% of the population over the age of 65 (Tortora & Grabowski, 2003). A German physicist, Alois Alzheimer, discovered Alzheimer's disease in 1906, after his study of a 51-year old woman who had various abnormalities in the brain, particularly the cerebral cortex (Kolb & Whishaw, 2001). Individuals with Alzheimer's disease become forgetful, confused, disoriented and may experience paranoia and delirium. As the brain deteriorates, they lose the ability to read, speak, eat, walk and write. Alzheimer's disease leads to dementia, the permanent or progressive loss of intellectual abilities, including the impairment of judgment, abstract thinking and memory. The causes of Alzheimer's disease are still unknown, though evidence suggests that the disease results from a combination of genetic and environmental factors, as well as the aging process (Tortora & Grabowski, 2003). Researchers have been studying the neuronal abnormalities that occur during Alzheimer's disease and also new methods to treat the disease.

Plaque Deposits In The Cerebral Cortex

One of the changes that occurs in the brain during Alzheimer's disease is the development of plaques in the cerebral cortex (Kolb & Whishaw, 2001). The plaques are

composed of protein material called amyloid, which is produced through the division of a large molecule, known as the amyloid precursor protein. Three types of enzymes, known as alpha, beta and gamma secretases, divide the amyloid precursor protein into smaller fragments (Pedrini et al., 2005). The division of the amyloid precursor protein can produce soluble, harmless fragments (such as amyloid-beta38) if alpha-secretase divides the protein. However, if the division of the amyloid precursor protein involves the beta-secretase, then insoluble fragments called amyloid-beta42 are formed (Pedrini et al., 2005). The amyloid-beta42 fragments combine together to produce plaques deposited outside of neural cells (Tortora & Grabowski, 2003).

Although amyloid-beta42 plaques are one of the common signs of Alzheimer's disease, researchers are studying why the amount of insoluble amyloid-beta42 plaques deposited in the brains of Alzheimer's patients may not be related to the severity of their symptoms. Studies performed at the National Institutes of Health suggest that there are two types of amyloid-beta fibrils (the main fibrils in the plaque deposits located in the cerebral cortex). These two different types of fibrils have different molecular structures and are not equally hazardous (Petkova et al., 2005). The researchers also found that the basic building blocks of amyloid-beta fibrils, the protofilaments, possess two different three-dimensional structures. During an *in vitro* study, the researchers concluded that the structure of the protofilaments is determined by variations in the growth conditions under which amyloid-beta is allowed to accumulate (Petkova et al., 2005). In addition, the structure of the protofilaments determines whether the fibrils are twisted or parallel to each other. Furthermore, it was found that the two types of fibrils express different toxicities in neuronal cell cultures. The researchers believe that the difference is due to the nature of the amino acids exposed on the fibril surfaces (Petkova et al., 2005).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The amyloid-beta fibrils that make up the plaque deposits may have different forms, but when using non-steroidal anti-inflammatory drugs (NSAIDs) to treat Alzheimer's disease, the different forms of fibrils make no difference. NSAIDs, including the drugs ibuprofen (such as Advil and Motrin), naproxen, flurbiprofen, and aspirin, treat various inflammatory disorders, such as tennis elbow and rheumatoid arthritis (Tortora & Grabowski, 2003). Researchers speculate that NSAIDs produce a beneficial effect against Alzheimer's by influencing the division of amyloid precursor protein (Lleo et al., 2004).

Oasis Herbs and Spices. www.oasisherbsandspices.com

Researchers at the Massachusetts General Hospital studied the effect of NSAIDs on the interaction between one of the enzymes that divides amyloid precursor protein, gamma-secretase, and the actual amyloid precursor protein *in vitro*. The researchers concluded that NSAIDs reduce the production of amyloid-beta42 relative to non-toxic amyloid-beta molecules but do not reduce the total quantity of amyloid-beta molecules (Lleo et al., 2004).

Presenilin 1, which is a section of the gamma-secretase enzyme, is believed to be the division site for amyloid precursor protein. As a result, the researchers at the Massachusetts General Hospital also conducted a study using a technique known as fluorescence resonance energy transfer (Lleo et al., 2004). Using this technique, the researchers demonstrated that NSAIDs open the presenilin 1 site and alter the relative positions of amyloid precursor protein and presenilin 1. Even though ibuprofen affects amyloid precursor protein and presenilin, other NSAIDs, such as naproxen and aspirin, have no effect on the amount of amyloid-beta42 in the brain as they do not change the positions of amyloid precursor protein or presenilin 1 (Lleo et al., 2004).

Researchers studying the effects of NSAIDs on Alzheimer's disease are trying to scientifically explain why certain NSAIDs increase the probability that the amyloid precursor protein is divided to produce the soluble amyloid-beta38 instead of the insoluble amyloid-beta42. One explanation is that these drugs reshape the site of the amyloid precursor protein where division occurs (Lleo et al., 2004).

NSAIDs are not the only types of drugs that influence the division of the amyloid precursor protein. Statin drugs, such as Lipitor (atorvastatin) and Zocor (simvastatin), are used to lower cholesterol, but researchers are suggesting that they can also be used to treat Alzheimer's disease. These types of drugs can treat Alzheimer's disease by

performing the same function as NSAIDs: affect the division of the amyloid precursor protein (Pedrini et al., 2005).

Statins

Statins and the amyloid precursor protein are potentially related due to a type of protein known as Rho, which is a part of a family of molecules called small G-proteins. These proteins are involved in various cellular functions, such as cytoskeletal reorganization and gene expression (Pedrini et al., 2005). Researchers at Thomas Jefferson University in Philadelphia have explored the effect of statins on amyloid precursor processing and the Rho pathway in neural cultured cells. The researchers were particularly interested in a protein called ROCK1, which is activated by Rho. Once ROCK1 is activated, it phosphorylates a number of other proteins (Pedrini et al., 2005).

The researchers at Thomas Jefferson University concluded that the activation of ROCK1 promoted the type of amyloid precursor protein division that formed amyloid-beta42. The researchers determined that the statin drugs Lipitor and Zocor inhibited ROCK1 activity and promoted the formation of the soluble amyloid-beta38 (Pedrini et al., 2005).

The researchers believe that ROCK1 affects the division of the amyloid precursor protein through alpha-secretase. This interaction may be indirect, with an accessory molecule being phosphorylated by ROCK1. This accessory molecule then interacts with the alpha-secretase enzyme (Pedrini et al., 2005). However, Cordle and Landreth (2005) at Case Western Reserve University prefer to explain the effects of statins on Alzheimer's disease in a different way. They suggest that amyloid-beta42 produces an inflammatory response in the brain and promote white blood cells, such as microglia and monocytes, to release molecules (for example, interleukin-1-beta and tumor necrosis factor alpha) to encourage inflammation (Cordle & Landreth, 2005). Later, neurons die due to the exposure to these inflammatory molecules. However, when monocytes and microglial cells are exposed to statins, the expression of the monocytes and microglia was inhibited due to the presence of amyloid-beta42. Therefore, in addition to its cholesterol-lowering effects, statins may also have anti-inflammatory properties, according to the studies done by Cordle and Landreth (Cordle & Landreth, 2005).

How is cholesterol involved with decreasing amyloid-beta42 deposition in the brain? Researchers are trying to better understand the relationship between cholesterol and amyloid-beta42 deposits by studying another type of drug that affects cholesterol levels: Acyl-coenzyme A/cholesterol acyltransferase (ACAT) inhibitors. This type of drug blocks acyl-coenzyme A/cholesterol acyltransferase ACAT, an enzyme that converts cholesterol in cell membranes into droplet form to be stored in cells for later use (Hutter-Paier et al., 2004). Therefore, when the active site of ACAT is blocked, cholesterol cannot be stored.

Researchers at Harvard Medical School demonstrated that inhibiting ACAT with an inhibitor, CP-113,818, eliminated nearly all of the amyloid-beta42 deposits in a mouse model of Alzheimer's disease. After analyzing the brain tissue from the mice used in the study, the researchers believed that the ACAT inhibitor lowers production of amyloid-beta42 instead of reducing its deposition (Hutter-Paier et al., 2004).

The apparent connection between cholesterol and Alzheimer's disease is supported by findings related to apolipoprotein E, a molecule that aids in the transportation and metabolism of cholesterol and triglycerides. The genes that code for apolipoprotein E influence the risk of people getting Alzheimer's disease (Dodart et al., 2005). Most individuals carry the E3 version of the apolipoprotein E gene (Rovner, 2005). However, there are some individuals who possess the E2 version and are less likely than the E3 carriers to develop Alzheimer's disease. The individuals having the E4 version are more likely than the individuals with the E3 version to develop Alzheimer's since the E4 version facilitates the accumulation of amyloid-beta42 in the brain (Dodart et al., 2005).

Researchers at the Salk Institute in La Jolla, California suggested that inserting copies of the E2 version of the apolipoprotein E gene into an organism's DNA would enhance the production of the protective form of apolipoprotein E. To test their hypothesis, the researchers injected viruses carrying several apolipoprotein E versions into the brains of numerous mice (Dodart et al., 2005). Once the DNA of the mice took up the new genes, the mice began producing the apolipoprotein E version programmed by the particular version they had received. The researchers found that expression of the E4 version promoted fibril formation and deposition of amyloid-beta42. However, the expression of the E2 version resulted in a reduction of amyloid-beta42 in the brain (Dodart et al., 2005).

Tea And Curry

One research team found that green and black tea inhibit the activity of acetylcholinesterase in vitro (Okello et al., 2004). Alzheimer's disease is characterized by the decrease in the neurotransmitter acetylcholine, involved in memory. Tea also inhibits the enzyme butyrylcholinesterase, which also breaks down acetylcholine. Furthermore, green tea inhibits the activity of beta-secretase, one of the enzymes that divide the amyloid precursor protein into amyloid-

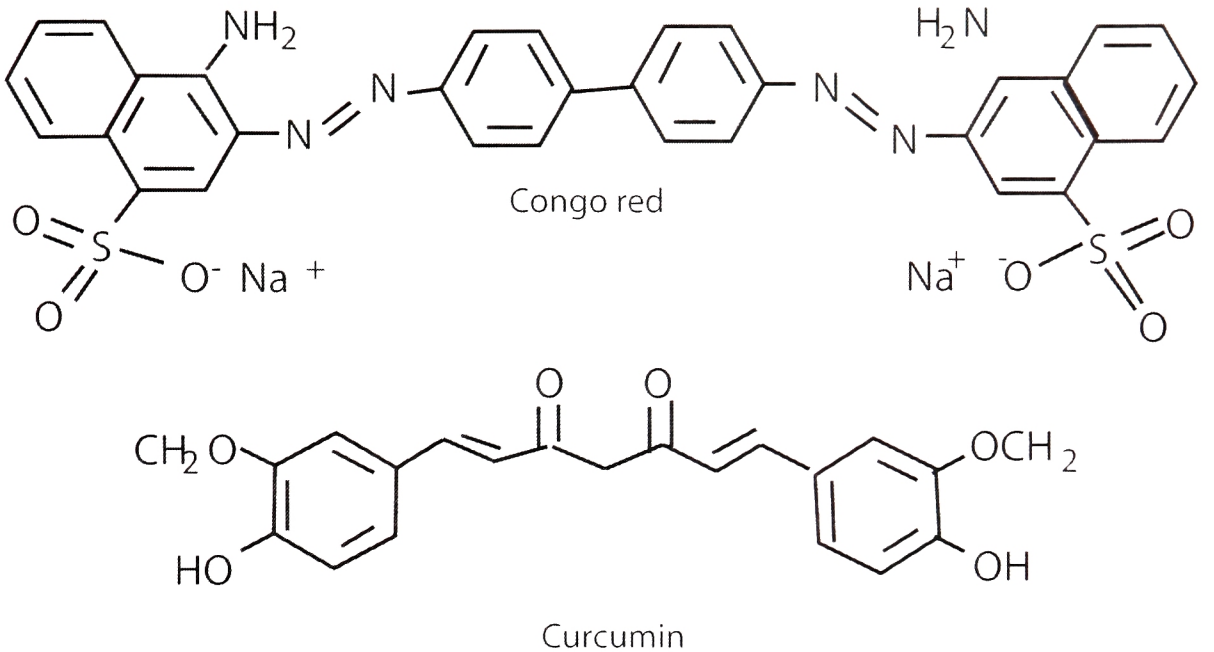

Figure 1: The chemical structures of Congo red and curcumin, the yellow pigment found in curry. Both Congo red and curcumin have two polar groups separated by a hydrophobic bridge (Rovner, S.L., 2005).

beta fragments. The researchers have yet to isolate the active ingredients in tea, but they have already ruled out the possibilities of theophylline, theobromine and caffeine (Okello et al., 2004).

In addition to tea, the yellow pigment in curry, curcumin, has been shown to aid in fighting Alzheimer's disease. Research conducted at the University of California focused on how curcumin functions in the body (Yang et al., 2005). The researchers state that the structure of curcumin is similar to the structure of Congo red, a dye known to bind to amyloid-beta42 fibrils in cultured cells. Congo red, however, is both toxic and unable to cross the blood-brain barrier (because it is negatively-charged) to reach amyloid-beta42 plaques (Yang et al., 2005).

The researchers at the University of California think that because curcumin has a hydrophobic nature, instead of being negatively charged like Congo red, curcumin can be allowed to enter the brain. Also, curcumin has been used as an antioxidant food preservative and as an anti-inflammatory extract in traditional Indian medicine. As a result, the researchers believe that curcumin may combat both the oxidative damage and inflammation associated with Alzheimer's disease (Yang et al., 2005).

Through *in vitro* tests, the researchers at the University of California have shown that curcumin inhibits the formation of amyloid-beta fibrils. In addition, researchers have found that when curcumin is injected into the bloodstream or fed to a mouse, the curcumin crosses over into the mouse's brain and binds to amyloid-beta42 (Yang et al., 2005). Moreover, when curcumin was added to the diet of an aged mouse, the amyloid-beta42 plaques in the mouse's brain appeared to break apart. These properties would be invaluable because the outward symptoms of Alzheimer's disease do not become apparent until decades after amyloid begins to accumulate in the brain (Yang et al., 2005).

What's Next?

Alzheimer's disease continues to take millions of lives every year. Therefore, it is imperative that researchers from all parts of the world do as much as possible to uncover a treatment that will dramatically reduce the effects of this disease. Based on the studies being done at the present time, a beneficial treatment for Alzheimer's disease is not going to be a "magic" potion or an outrageously ingenious therapy. Instead, common medications, such as Advil and Lipitor, or a simple cup of tea could be the "miracle cure" which scientists and researchers dealing with Alzheimer's disease have been searching for. The medication you take to reduce inflammation and lower your cholesterol, the cup of tea you drink at the local coffee shop, and even the chicken curry that you eat for supper could be the answer to the prayers of so many individuals affected by Alzheimer's disease around the world. M