

Newsletter



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HIDDEN ADVANTAGES OF NSAIDS

We have all seen the effects of inflammation - the hot, painful swelling that follows an injury or surrounds an arthritic joint are obvious examples. But inflammation could also have hidden effects that may contribute to some of the most important diseases affecting us today. Heart attacks, cancer, Alzheimer's disease and diabetes are among the biggest causes of illness and premature death in our society and scientists now believe that inflammation could play a far-reaching role in each of them. Recognising this will help us to develop new ways of preventing and treating serious long-term illnesses and, by re-deploying the drugs we already use to reduce inflammation, we should be able to provide accessible and inexpensive treatments for the future.

What is it about inflammation that makes it a long-term killer? It is, after all, a mechanism that evolved to protect us against infection or injury. It starts kindly enough, as part of the body's immediate response to an invasion of disease-causing microbes or to damaged tissues. Microbes are recognised as a potential threat by specialised cells, known as mast cells, that are found in connective tissue throughout the body. The mast cells then trigger the massive cascade of events that make up the body's immune reaction by releasing a chemical known as histamine. This acts on the surrounding blood vessels, making them dilate (causing redness) and allowing plasma to leak from them (increasing the volume of fluid in the immediate vicinity, causing swelling).

Other defensive cells become activated and now join in: macrophages attack and digest the invading microbes and release large numbers of signalling chemicals, known as cytokines. These attract even more specialised cells to the battlefield to help destroy the microbes, and to break down and remove the debris of dead organisms and damaged tissue. The

body's defence cells also produce substances such as the prostaglandins that help to keep the cycle of events going, and these affect the adjacent nerves and cause pain.

These three signs - swelling, redness and pain - are what we recognise as inflammation. It continues as long as there are microbes to be killed because their presence is the trigger to the entire process. Once they and the debris of battle have been removed, the inflammation dies down over a period of days.

Injury causes a similar train of events, except the trigger that mast cells recognise is not an invading microbe but the presence of proteins and substances released from damaged tissue.

So far so good: inflammation plays a key role as a short-term mechanism for defence and repair but why do scientists think it is important in long-term conditions such as cancer and Alzheimer's disease? The first clues came from *observational* studies, in which large groups of people are monitored for many years; these allow scientists to investigate how any of a number of possible causes (such as medicine use, exercise or diet) might over time correspond to the development of long-term disorders. There are many such studies and some of the biggest have produced startling results. They show that people who regularly take drugs that reduce inflammation (non-steroidal anti-inflammatory drugs, or NSAIDs) have a lower risk of developing certain serious illnesses.

In Ohio, USA, for example, the Women's Health Initiative study showed that women who regularly took the NSAID ibuprofen for 5 - 9 years had only half the risk of developing breast cancer compared with women who did not take an NSAID. Similar studies have linked regular NSAID use with lower risks of colorectal cancer, lung cancer and oesophageal cancer. Three possible mechanisms for the effects of NSAIDs on

cancer risk have been suggested. They may slow the formation of new blood vessels on which some cancers depend, or they could switch cancer cells back into a normal life cycle. But it has also been found that some cancers are linked with over-activity of an enzyme known as cyclo-oxygenase 2 (COX-2). This enzyme is normally switched off but, in response to a stimulus such as an injury, it switches on and greatly increases the formation of prostaglandins. As we have seen, these substances promote inflammation. Why COX-2 is switched on in some cancers is unknown but what is clear is that NSAIDs inhibit COX-2 and reduce the formation of prostaglandins.

Since the late 1990s, several studies have looked at how frequently Alzheimer's disease develops in people who took NSAIDs. They have found that the longer an NSAID is taken, the lower is the risk of developing Alzheimer's. When the data from these studies were pooled and analysed they showed that, after taking an NSAID for 2 or more years, the risk of Alzheimer's was reduced by 73 percent compared with that in people who did not take an NSAID.

The characteristic feature of Alzheimer's disease is deposits in the brain of a protein known as amyloid beta. The brain is protected by specialised cells known as microglial cells, which react to the amyloid deposits by triggering inflammation. It seems likely that this process, which should promote healing, is the reason why neurones in the brain die and it could explain why NSAIDs may lower the risk of developing Alzheimer's disease in the long term. However, other mechanisms may also be important. Scientists in California recently showed that ibuprofen reduces the formation of amyloid by mouse brain cells, and a second group showed that, in the laboratory at least, ibuprofen promotes the break-up of amyloid deposits.

The role of inflammation in heart attacks is well established. One of the most important causes of heart disease is atherosclerosis, a long-term condition in which blood vessels become hardened and narrowed due to deposits of cholesterol and fatty substances known as plaques. Some plaques cause inflammation in the wall of the blood vessel, and this makes the plaque unstable and prone to rupture. A healing process then begins, the first part being the formation of a blood clot over the raw surface of the vessel wall. However, this clot

can break off and lodge in the narrowed artery; this cuts off the blood supply and starves an area of heart muscle of oxygen, causing a heart attack.

It is difficult to study the anti-inflammatory effects of NSAIDs in this setting because they reduce the risk of heart attacks by inhibiting clotting. Instead, the 'Eureka moment' came from clinical trials of the statins, a group of drugs that lower cholesterol. Analysts found that the statins reduced the risk of heart disease by more than could be explained by their effects on cholesterol levels. Laboratory studies have since revealed that statins also have anti-inflammatory properties that probably help to reduce plaque instability.

The newest evidence implicating inflammation as a cause of serious long-term disease comes from studies in people with diabetes. These have shown that blood levels of substances linked with inflammation are raised in people who have diabetes or who are resistant to the actions of insulin. These substances, key components of the inflammation cascade such as C-reactive protein and the cytokines tumour necrosis factor and interleukin-6, are also elevated in people who don't have diabetes to start with but later develop it, and in people with obesity (who are at increased risk of developing diabetes). It is also possible that long-term, low-level inflammation in people with diabetes may contribute to their greatly increased risk of heart disease. The cause of inflammation in people with diabetes is still unknown but possible factors include a reduction in the protection afforded by insulin and the metabolic effects of increased food consumption associated with obesity.

What are the implications of these findings? The investigators who are seeking new treatments for the long-term diseases that cause so much illness and consume a large proportion of health care resources now have a new - but familiar - target to aim for. If new treatments can now be developed to tackle inflammation, they may slow or even stop the progression of these diseases. Ultimately, we may be able to prevent many cases. We already have many treatments with anti-inflammatory properties, notably NSAIDs such as ibuprofen, and these are now being evaluated for their effects on conditions like Alzheimer's disease. They may not provide a single solution to the problem, but they could offer an inexpensive addition to more specific treatments.