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Can You Pill It? Demystifying Painkillers

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Introduction

One of my constant challenges as a high school chemistry teacher is designing lessons that make chemistry less inert and more alive and real to students. I want them to see that chemistry is more than memorizing terms and formulas and solving exercises. I want them to appreciate the relevance of chemistry in daily life and how it could help them make responsible and informed every day decisions and even participate in discussions over many public policy issues that affect them.

It is also important that the experience students get in my science classes will entice some of them to explore the possibility of a career in science, technology, engineering and math (STEM). But many of them still ask the question: why is this necessary?

As former secretary of education William J. Bennett pointed out, in the last forty years, the United States has led the way in terms of technological development and economic growth [1] . But we now live in a highly global competitive society. If the United States is to keep its place as the most competitive and innovative country in the world, it has to graduate students with strong STEM foundation. In fact, a report from the President''s Council of Advisors on Science and Technology released in February this year indicates that ""economic projections point to a need for approximately 1 million more STEM professionals than the U.S. will produce at the current rate over the next decade if the country is to retain its historical preeminence in science and technology. To meet this goal, the United States will need to increase the number of students who receive undergraduate STEM degrees by about 34% annually over current rates"" [2] .

A positive and engaging experience in high school science classes, such as chemistry, helps students consider STEM as a career. And one way this could be done is by helping students see the real world applications of what they are learning. Incorporating a unit on over–the–counter (OTC) pain relievers in the chemistry curriculum is one example of how the course can be made more relevant to students.

Why pain relievers? Millions of Americans use OTC pain relievers every day. Advil, Tylenol, Bayer aspirin, among others, have become ""wonder drugs"" that can make a headache from a hangover or discomfort from sore muscles disappear, allowing many to continue with their daily routine. OTC pain relievers have become a staple in the medicine cabinet of many American homes. Many people carry extra tablets in their purses or vehicles.

Students in my chemistry classes are no different. Almost every day, at least one student asks if I have Advil she could take for her headache (we are not allowed to give any form of medication to students). Every time a student hollers in class ""Who has Tylenol or Advil?"", there is always one student who will offer to ""share.""

The prevalent use of OTC pain relievers poses risks. Many people think that because they do not require prescription, OTC drugs offer no danger. But a study conducted by Northwestern University showed that many American consumers are unaware of what is in the OTC pain relievers they are taking [3] . The study revealed that only 41% of those surveyed admitted to reading drug labels. Moreover, only 31% of the participants knew that Tylenol contains acetaminophen, 75% knew Bayer has aspirin, 47% knew Motrin has ibuprofen, 19% knew Aleve has naproxen sodium and 19% knew Advil contains ibuprofen [4] .

This lack of awareness about the active ingredient in OTC pain relievers is alarming. For example, acetaminophen overdose has become the leading cause of acute liver failure in the country. In addition, aspirin, ibuprofen and naproxen belong to a group of medications called NSAID (non–steroidal anti–inflammatory drugs), which is one of the leading causes of stomach ulcers and have been associated with side effects ranging from stomach upset to stomach bleeding, which can be life threatening.

Rationale and Objectives

A curriculum unit on the chemistry of OTC pain relievers is timely and relevant. It will provide students an opportunity to understand how OTC pain relievers work, what they contain, and the possible risks involved in their use. The unit will focus only on OTC pain relievers that contain acetaminophen, aspirin, ibuprofen and naproxen. It will not include topical pain relievers such as Bengay.

The curriculum unit will be implemented in my college–prep chemistry classes at Terra Nova High School located in Pacifica, CA. The majority of the students in chemistry are sophomores while the rest are juniors and seniors. They have all successfully completed one year of college prep Biology and Algebra 1. For some of the juniors and seniors, chemistry is their third science course (after Earth Science and CP Biology). A few are taking chemistry and physics simultaneously.

The unit will be part of my module on Rates of Chemical Reactions. It will serve as the real world application of our lesson on the role of catalysts in chemical reactions. The 2–week unit will be divided into three parts.

Part 1 will focus on the basic chemical concepts linked to painkillers. We will talk about the collision theory and the four factors that affect the rate of a chemical reaction which include temperature, concentration, surface area, and use of a catalyst. Specific objectives in this part include the following:

1. Relate reaction rates to collisions between reacting particles
2. Describe the role of activation energy in a chemical reaction
3. Identify factors that affect reaction rate
4. Explain the role of a catalyst

In part 2, we will discuss what happens inside our bodies when we experience a painful sensation. Specific objectives for this part are as follows:

1. Define pain and describe how a stimulus is interpreted by the brain as painful
2. Explain how pain is classified
3. Describe the molecular and structural features of prostaglandins
4. Describe how prostaglandins are formed in the body and the role played by arachidonic acid and cyclooxygenase
5. Identify the functions of prostaglandins

Part 3 will be on the chemistry of OTC NSAID (aspirin, ibuprofen and naproxen) and acetaminophen and how these substances work as pain relievers. Specific objectives are as follows:

1. Describe how each of the following was discovered: aspirin, acetaminophen, ibuprofen and naproxen
2. Explain how aspirin, ibuprofen and naproxen work to relieve fever, pain, inflammation and other symptoms
3. Explain why acetaminophen relieves pain and fever but not inflammation
4. Identify possible side effects of each of the following: aspirin, ibuprofen, naproxen and acetaminophen
5. Describe health threats associated with misuse/abuse/overdose of OTC pain relievers

The unit addresses California Chemistry Standards 8b, 8c and 8d on reaction rates. It also provides students and opportunity to acquire and enhance eight scientific and engineering practices that they should engage in throughout their K–12 education as identified in A Framework for K–12 Science Education: Practices, Crosscutting Concepts and Core ideas [5] . The framework is the basis of the Next Generation of Science Education Standards which is being drafted by a team of experts and will be released in fall 2012. The practices include

1. Asking Questions and Defining Problems
2. Developing and Using Models
3. Planning and Carrying out Investigations
4. Analyzing and Interpreting Data
5. Using Mathematics, Information and Computer Technology, and Computational Thinking
6. Constructing Explanations and Designing Solutions
7. Engaging in Argument from Evidence
8. Obtaining, evaluating, and communicating information

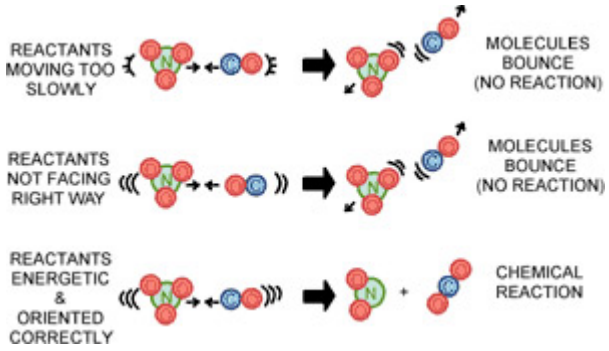
Background Information

Rates of Reaction

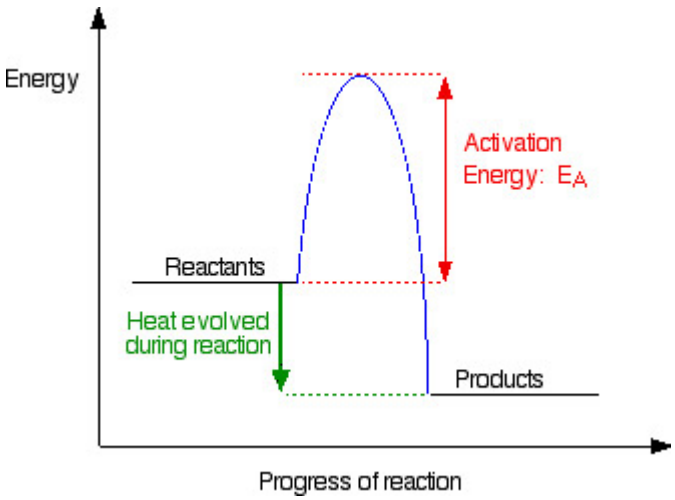
Collision Theory

The collision theory explains why chemical reactions take place. The theory is based on the assumption that for a chemical reaction to happen, reacting particles must collide. However, even if the particles collide, there is still a chance a reaction will not take place because the reacting particles must have a specific orientation when they collide. For example, consider the formation of NO_2 and CO_2 from NO_3 and CO. The two reactant molecules will react only if they have the proper orientation: that is, the N of NO_3 molecules must collide with

the C of CO molecules. This is shown in figure 1 [6] below.



Despite having the right orientation, reacting particles will not form products if they do not have the necessary minimum amount of energy needed for the reaction to happen. This minimum amount of energy is called activation energy. As Figure 2 shows, think of activation energy as the hill that the reactants must overcome in order to be changed into products. A higher hill means a higher activation energy.



In summary, the collision theory tells us that three conditions are needed for a reaction to occur. First, the reactants must collide. Second, the reactants must collide in a specific orientation. Finally, reactants must possess a certain minimum amount of energy called activation energy upon collision so that they will be changed into products.

Factors affecting Reaction Rate

Four factors that affect how fast a reaction will happen include concentration, temperature, surface area, and presence of a catalyst. How each factor speeds up or slows down a reaction can be explained in terms of the collision theory.

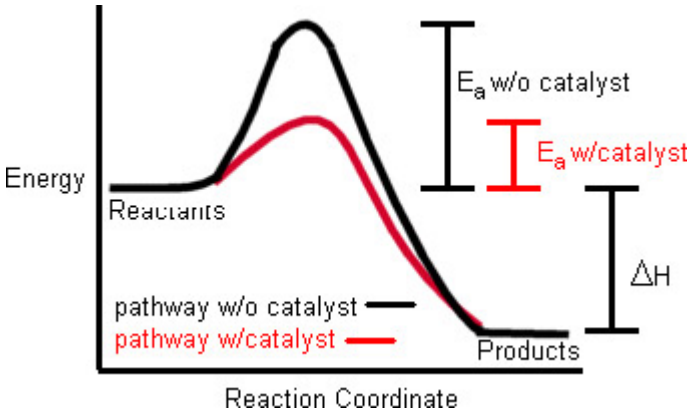
An increase in the concentration of the reactants speeds up the reaction. A higher concentration means there are more reacting particles per volume, which increases the frequency of collisions and, hence, the rate of reaction.

Increasing the temperature increases the kinetic energy of the reacting particles. This causes the particles to move faster and collide more frequently. At the same time, increasing the temperature also means more particles have the activation energy needed for the reaction to take place.

Smaller pieces of firewood burn faster than a big log of wood. The material available for burning is the material at the surface of the log: therefore, because smaller pieces of wood have a larger surface area per volume than a big piece of wood, they burn faster. Increasing surface area increases the number of reaction sites. Consequently, the frequency of effective collisions increases and the reaction happens faster.

Many reactions will occur faster with the use of catalysts. A catalyst is a substance that speeds up a reaction without itself being consumed in the reaction. For example, hydrogen peroxide decomposes slowly into water and oxygen. Adding potassium iodide speeds up the reaction. But potassium iodide is not used up in the course of the reaction, so it can be used over and over again.

A catalyst speeds up a reaction by lowering the activation energy as shown in Figure 3 below. Note how the initial and final energy of the system remain the same with or without a catalyst but the pathway of a catalyzed reaction shows a lower energy ""hill"", making it easier for the reactants to be converted into products. Think of the lower hill as a tunnel dug into a mountain. Instead of going up the hill to cross to the other side, cars can just pass through the tunnel and get to the other side faster.



Enzymes

Many chemical reactions taking place in the cells of living organisms require a catalyst. These biological catalysts are called enzymes. Enzymes are proteins that speed up almost all vital chemical reactions that would otherwise take place very slowly or not happen at all, thus compromising the organism''s survival. For example, the enzyme amylase is found in human saliva. Amylase speeds up the conversion of starch into sugar. Amylase is also found in the pancreas where it is used to break down carbohydrates.

Hydrogen peroxide bubbles when poured onto a cut or wound. The enzyme catalase is found in many cells throughout the body. Catalase breaks down hydrogen peroxide into water and oxygen. The bubbles observed are actually the oxygen produced. Hydrogen peroxide does not bubble when it comes into contact with unbroken skin because the catalase has not been released.

Enzymes are very specific when it comes to catalyzing biochemical reactions in organisms. The substrate or substance that will be converted into the product requires a particular enzyme. Only when the substrate fits the enzyme like a key in a lock can the biochemical reaction occur.

Like all other proteins, enzymes are polymers of hundreds (and even thousands) of amino acids. Each enzyme has a unique sequence of amino acids. No two enzymes have the same sequence of amino acids. A simple change in the sequence drastically alters the ability of an enzyme to catalyze a biochemical reaction.

The sequence of amino acids in enzymes forms coils and folds that result in a three–dimensional structure. Only a small part of this three–dimensional structure, called the active site, interacts with the substrate during the biochemical reaction. The active site complements the shape of the substrate that will be converted into another substance. If the shapes don''t fit, biochemical reactions will not take place.

Some substances prevent enzymes from interacting with the substrate. These substances are called enzyme inhibitors. Drugs and poisons often have their biological effects because they are enzyme inhibitors.

How We Sense Pain

The Pain Pathway

The most widely accepted definition of pain comes from the International Association for the Study of Pain which defines pain as ""an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage"" [7] . Pain as a subjective, psychological experience is a necessary element to our survival because it tells us to avoid potentially harmful events and to protect damaged tissue while it heals.

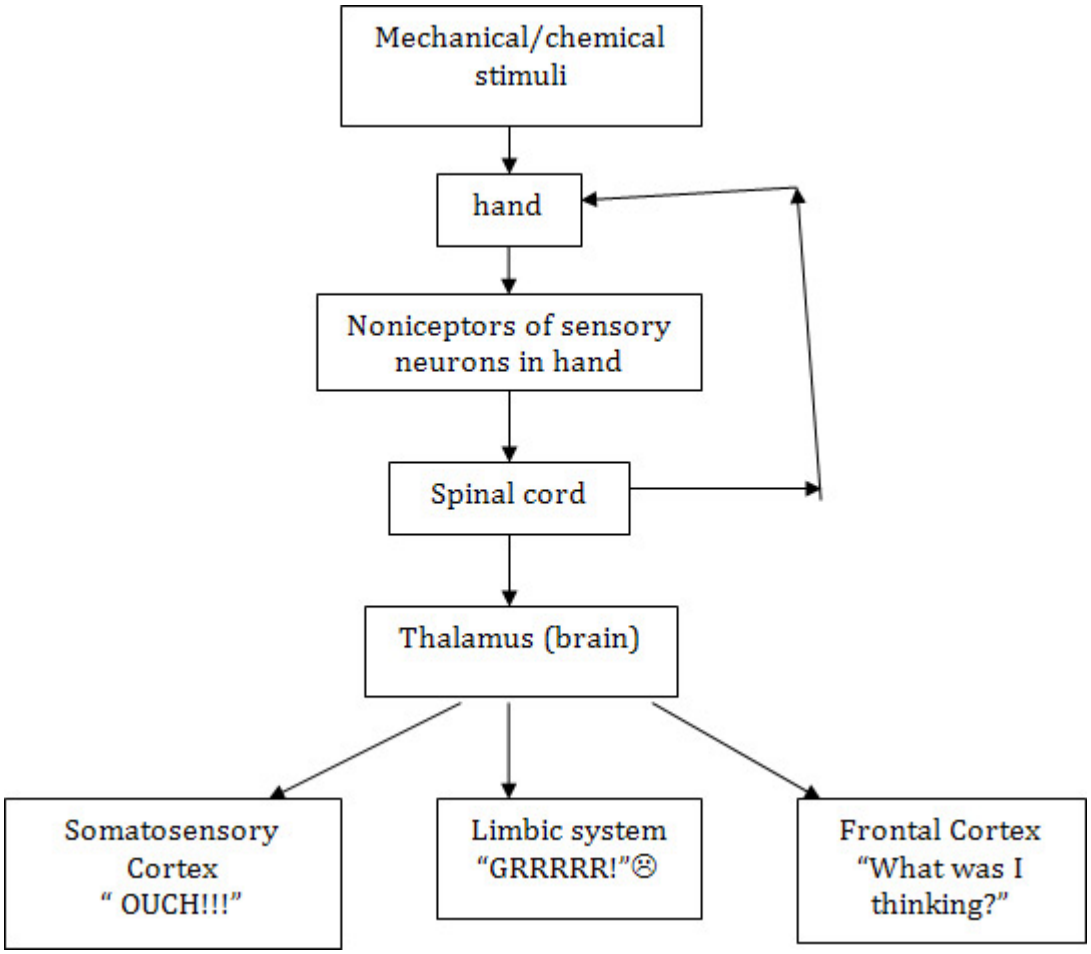
But how do we sense pain? The process by which a painful stimulus is transmitted to the central nervous system is called nociception. A simple description of this process involves the following steps [8] :

1. A mechanical or chemical stimulus that damages or could potentially damage tissue occurs. A mechanical stimulus can be pressure (like stubbing your toe), a puncture, or cut. A chemical stimulus includes burns.
2. Sensory neurons with specialized receptors or nerve endings sensitive to pain stimuli detect the stimulus. Neurons with these special pain receptors called nociceptors are found in the skin, internal organs, joints, muscles and tendons.
3. Nociceptors transmit the pain signal to the spinal cord and brain.
4. The brain receives the signal for processing and action.

For example, when you pick up the hot lid of a cooking pan with your bare hand, nociceptors in your fingers, detecting the heat, send an impulse through a sensory neuron to your spinal cord. Recall that the spinal cord relays all kinds of impulses to and from the brain. At the same time, the spinal cord also has the ability to make decisions on its own called reflexes. The impulse is received by an area of the spinal cord called the dorsal horn which does two things at the same time. The dorsal horn relays an immediate message—through a reflex arc that connects the sensory neuron to motor nerves that connect to muscles in the injured fingers—to pull away and you drop the hot object. This is an automatic, involuntary reflex, which the brain does not have to order.

At the same time , the dorsal horn relays the pain signal to an area of the brain called the thalamus. The thalamus acts like a sorting station that evaluates signals and sends them to appropriate areas of the brain for interpretation. The pain signal is sent to the somatosensory cortex (responsible for physical sensation), the frontal cortex (in charge of thinking), and the limbic system (linked to emotions) [9] . As a result, you feel the sensation of pain in your hand, you think picking up the hot lid without using a pot holder was a ""silly"" thing to do, and react emotionally by feeling annoyed at yourself for your lack of common sense. At the same time, the pain signal can also stimulate parts of the brain that control an increase in blood pressure, heart and breathing rate.

Figure 4 below shows a simple flowchart of the pain pathway.



Classifying Pain

There are different ways to classify pain. One form of classification divides pain into two main categories: nociceptive pain and non–nociceptive pain [10] . Nociceptive pain involves the stimulation of nociceptors that respond to heat, cold, pressure and chemical stimuli released by damaged cells. Non–nociceptive pain, on the other hand, results from a malfunction of the peripheral or central nervous system. No specific nociceptors are stimulated. A good analogy to consider in distinguishing between the two types of pain is a fire alarm. A fire alarm set of by smoke represents nociceptive pain while a fire alarm that goes off simply because it has malfunctioned is non–nociceptive pain.

Nociceptive pain may be further classified into two sub–types: somatic and visceral. Somatic pain involves the stimulation of nociceptors found in the tissues of skin, muscles, joints, bones, and ligaments. Heat, cold, vibration, stretch (muscles), inflammation (e.g. cuts and sprains which cause tissue disruption), and oxygen starvation (muscle cramps) are stimuli that activate these nociceptors. The pain is sharp and localized and touching or moving the damaged area reproduces the pain. Visceral pain results from the stimulation of nociceptors found in the internal organs of the three main cavities which include the heart and lungs in the thorax, liver, kidneys, spleen and bowels in the abdomen, and the bladder, womb, and ovaries in the pelvis. Pressure, inflammation and oxygen starvation are the stimuli that produce this type of pain which ""is poorly localized, and may feel like a vague deep ache, sometimes being cramping or colicky in nature"" [11] . It usually produces referred pain (pain felt at a site other than where the source is located) to the back, with pelvic pain

referring pain to the lower back, abdominal pain referring pain to the mid–back, and thoracic pain referring pain to the upper back"" [12] .

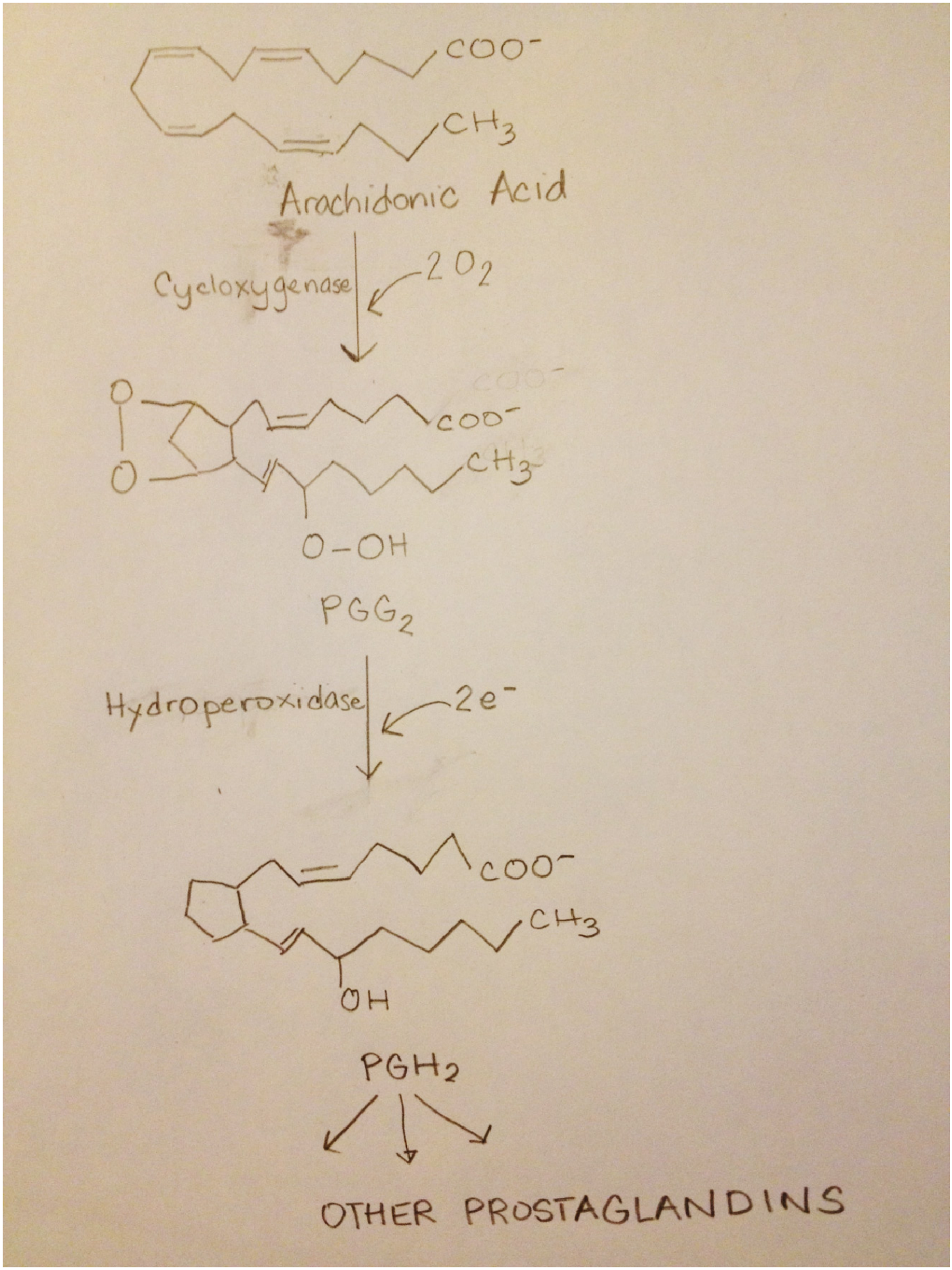
Non–nociceptive pain is either neuropathic or sympathetic. Neuropathic pain, also known as pinched or trapped nerve, stems from mechanical problems within the nervous system itself, either from the nerves between the tissues and the spinal cord (peripheral nervous system) or from the nerves between the spinal cord and the brain (central nervous system). The pain sensation arises from damage to the nerves due to degeneration such as in multiple sclerosis, pressure resulting in a trapped nerve, inflammation due to a slipped disc or a viral infection like shingles [13] . The damaged nerve fires off pain signals in a random and chaotic manner.

Sympathetic pain may be caused by over–activity of sympathetic nervous system, and central / peripheral nervous system mechanisms which could arise from fractures and soft tissue injuries of the arms and legs. This type of pain is associated with extreme hypersensitivity in the skin around the injury and also peripherally in the limb and even excessive sweating and increased temperature in the damaged area because blood flow, which is controlled by the sympathetic nervous system, is erratic [14] . The limb is usually so painful, that the patient refuses to use it, causing secondary problems after a period of time with muscle wasting, joint contractures, and osteoporosis of the bones [15] .

Biosynthesis of Prostaglandin By Arachidonic Acid Pathway

The synthesis of prostaglandin in the body starts when physical, chemical, and inflammatory stimuli including tissue damage activate an enzyme called phospholipase A2. This enzyme produces a fatty acid called arachidonic acid using membrane phospholipids as the substrate. Arachidonic acid is then metabolized to other substances, one of which is prostaglandin.

A complex enzyme called prostaglandin synthase catalyzes the conversion of arachidonic acid to the first prostaglandin PGG_2 . This enzyme is also known as cyclooxygenase or COX because it adds oxygen and forms a ring. A different active site of the enzyme COX is then used to change PGG_2 to another prostaglandin PGH_2 . Since the reaction involves the reduction of a hydroperoxyl in PGG_2 to a hydroxyl in PGH_2 , the enzyme in this step is called hydroperoxidase. The action of other enzymes then converts PGH_2 to various physiologically active prostaglandins. Figure 5 [16] shows this prostaglandin synthesis pathway.


COO⁻
CH3
Arachidonic Acid
Cycloxygenase
2 O2
COO⁻
CH3
O-OH
PGG2
Hydroperoxidase
2e⁻
COO⁻
CH3
OH
PGH2
OTHER PROSTAGLANDINS

Physiological Activity of Prostaglandin

Prostaglandins mediate a variety of physiological processes. Elevated concentrations of prostaglandin—which are produced by higher rates of synthesis due to the enzyme systems described above—trigger an inflammatory response which is the body''s way to counter the infection resulting from tissue damage. Inflammatory response includes fever, swelling and pain. Pain occurs because nociceptors are sensitive to changes in prostaglandin concentration. An increase in the synthesis of prostaglandin stimulates noniceptors and the pain pathway described above begins.

Prostaglandins are involved in more than the creation of local pain. Prostaglandins found in blood platelets can be converted to thromboxanes which are powerful blood clotting agents. Prostaglandins in the gastrointestinal tract are involved in lessening gastric acid and increasing mucus secretion. Certain prostaglandins are involved in many stages of reproduction including the normal implantation of the fertilized oocyte, induction and initiation of labor. For example, PGE_2 causes uterine contraction and hence menstrual cramps. It also has been used as a drug to induce labor.

Prostaglandins are involved in control of blood vessel constriction and dilation. Individuals with compromised kidneys because of one or more chronic organ diseases need prostaglandin in their kidneys to facilitate smooth renal flow. Other prostaglandins regulate blood pressure. Some prostaglandins promote the constriction of bronchi associated with asthma.

In the early 1990''s, several investigations showed that humans and other mammals have two genes for COX, the key enzyme in prostaglandin synthesis from arachidonic acid. These isoforms of the enzyme are called COX–1 and COX–2. Though they have very similar structures, they differ in terms of substrate, inhibitor selectivity and location within the cell. COX–1, found in most tissues, is called a housekeeper enzyme [17] . It helps maintain homeostasis in many organs. For example, the prostaglandins involved in blood clotting, gastric mucus secretion and smooth renal flow in compromised kidneys are synthesized by COX–1.

On the other hand, COX–2 is inducible by inflammation [18] . Prostaglandins resulting from the action of COX–2 are associated with inflammation, fever, pain, ovulation and the birth process. Both COX–1 and COX–2, though, have the same affinity for arachidonic acid so either isoform can catalyze the first two steps in the arachidonic acid pathway for prostaglandin synthesis.

Over-The-Counter Pain Relievers

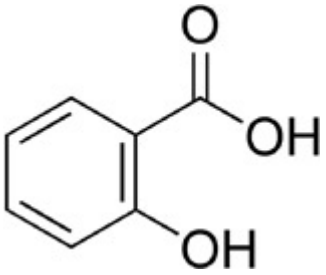
There are two kinds of over–the–counter (OTC) pain relievers, nonsteroidal, anti–inflammatory drugs (NSAIDs) and acetaminophen (also known as paracetamol). NSAIDs include aspirin, ibuprofen, and naproxen.

Aspirin

One of the most versatile drugs ever produced is aspirin or acetylsalicylic acid. It is an analgesic (i.e. it relieves pain), anti–pyretic (i.e. it reduces fever), and anti–inflammatory (i.e. it prevents swelling, redness and other symptoms associated with inflammation). It has also been prescribed for the prevention of stroke and heart attack.

Aspirin owes its origin to the ancient practice of using willow bark extract to ease pains and reduce fever. In fact, the father of modern medicine Hippocrates wrote about a bitter powder that could be extracted from willow bark and could be used as pain and fever remedy. By the early 1880''s, it was known that the active

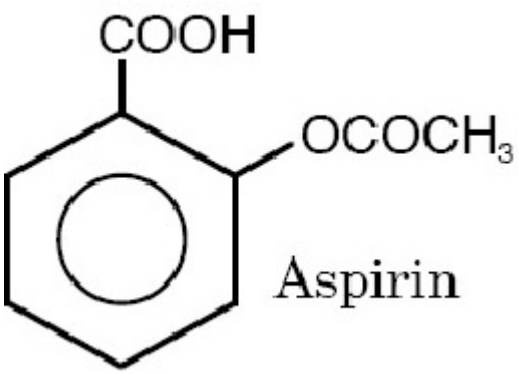
ingredient was salicin, which is transformed to salicylic acid once it is ingested. Figure 6 below is the structure of salicylic acid.



Salicylic acid was first synthesized from salicin by Italian chemist Raffaele Piria in 1838. In 1859, Adolph Kolbe working with other chemists at the Bayer Company in Germany, synthesized salicylic acid by heating phenol with carbon dioxide. But salicylic acid is such a stomach irritant that ""many patients preferred their aches and fever to the severe heartburn caused by the remedy."" [19]

In 1899, Felix Hoffman, a junior chemist at Bayer Company who was on the lookout for an alternative medication for his father suffering from severe arthritis, modified salicylic acid to make it more soluble in stomach acid and thus make it pass through the stomach faster. He reasoned that this chemical change would make the drug less irritating to the stomach. He came up with acetylsalicylic acid with a chemical formula of $C_9 H_8 O_2$. Bayer named the new drug aspirin: a from acetyl, and spirin from spirea or meadowsweet flower which is one of the natural plant sources of salicylic acid.

Acetylsalicylic acid is a weak acid that can go through the mucus lining of the stomach. The upper portions of the small intestine absorb most of the drug. It breaks down into acetic acid and salicylic acid once it enters the bloodstream. The structure of acetylsalicylic acid is shown in Figure 7.



Though aspirin is more soluble in stomach acids, it can still cause stomach irritation in a small percentage of people. For that reason, there is buffered aspirin which is made by combining the aspirin with an acid buffer thus reducing acidity. Still, stomach irritation is a major problem for people such as those suffering from arthritis who have to take aspirin daily. These people can take specially coated aspirin tablets that pass through the stomach without dissolving. Acids in the stomach are unable to dissolve the coating but the basic environment in the small intestine quickly disintegrates it.

How is aspirin able to accomplish a variety of functions? Aspirin works by inhibiting the COX enzyme, which sits at the start of the arachidonic acid pathway for the synthesis of prostaglandins, thus stopping the synthesis of prostaglandin. In 1994, a group of researchers from the University of Chicago figured out the

molecular structure of the enzyme. Using X–rays to probe the positions of the atoms in tiny crystals of the enzyme, they found out that the ""enzyme has a tunnel running into the middle of it. The substrate arachidonic acid must pass through this tunnel to reach the core of the enzyme, where it will be converted into prostaglandin"". [20]

In 1995, the same researchers reported that ""aspirin permanently attaches a portion of itself inside the tunnel, where it acts as a gate, blocking prostaglandin''s precursor from reaching the active site of the enzyme. They also showed that this gate can be in two positions, either fully or partially closed, and that the position of the gate may differ between the two forms of the enzyme, COX–1 and COX–2."" [21] Other investigations show that aspirin permanently inhibits the enzyme because it forms a strong covalent bond with the enzyme which cannot be broken. [22] This is an example of irreversible inhibition.

The ability of aspirin to bind with COX–2—which is responsible for the synthesis of prostaglandins associated with pain, fever and inflammation—explains why the drug is an analgesic, antipyretic, and anti–flammatory. Since it also inhibits COX–1 associated with the production of prostaglandins responsible for basic housekeeping duties such as increasing mucus secretion to protect the gastrointestinal tract, aspirin produces side effects such as stomach upset, gastric ulcers, and gastric bleeding.

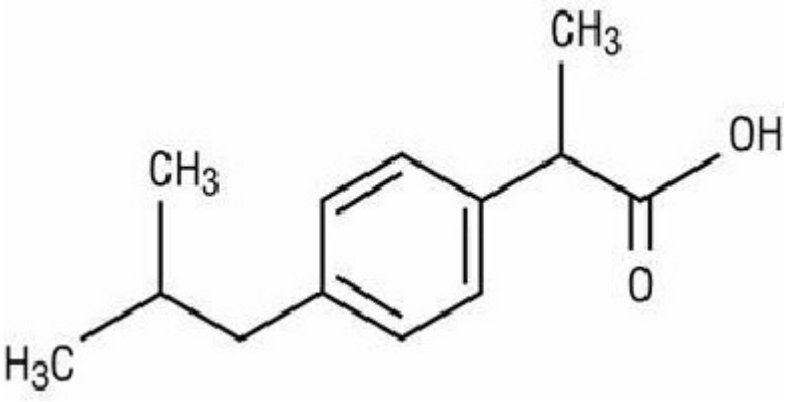
Furthermore, aspirin helps prevent stroke because inhibiting COX–2 limits the synthesis of prostaglandins that mediate platelet aggregation and blood clotting. A stroke could result from a blood clot blocking flow in smaller blood vessels in the brain, resulting in oxygen deficiencies. Some people refer to aspirin as a ""blood thinner."" This is not really an accurate description since what aspirin does is to stop the formation of prostaglandins that make platelets in the blood ""stick together"" and produce blood clot.

Ibuprofen

Ibuprofen is an NSAID drug marketed under various names including Advil and Motrin. It was developed and discovered by a team that was part of the research arm of the Boots company in the United Kingdom in the 1950s, patented in 1961, and first made available under prescription in 1969. [23] It became available in the United States in 1974 as a prescription drug and an OTC drug in 1984. [24]

Though it has antipyretic and anti–inflammatory properties, ibuprofen is widely marketed as an analgesic. It is particularly known for providing relief from arthritis and is widely used for the relief of headache including migraine and other pain conditions arising from various injuries especially those that involve inflammation, illnesses such as influenza and post–operative pain. It is also used to relieve the symptoms of primary dysmenorrhea.

The chemical name of ibuprofen is 2–(4–isobutylphenyl)propanoic acid. It has a molecular weight of 206.3. Its empirical formula is C_{13} H_{18} O_2 and its structural formula is shown by Figure 8.



Ibuprofen and aspirin have analogous functions but lower doses of ibuprofen produce less irritation of the gastrointestinal tract.

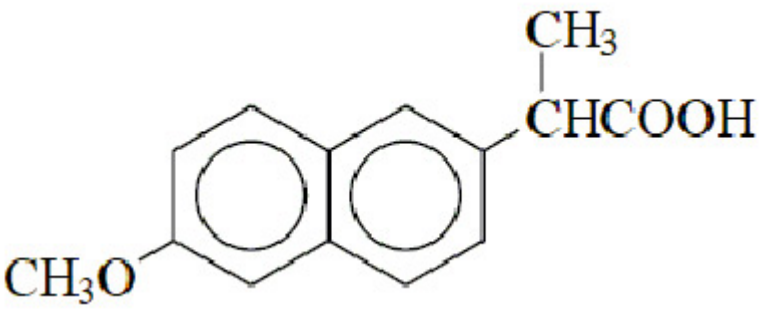
The mechanism of action of ibuprofen is similar to aspirin. It also inhibits COX at the beginning of the arachidonic acid pathway thus shutting down prostaglandin synthesis. Just like aspirin, it also inhibits both COX–1 and COX–2, but ibuprofen acts on the enzymes in a slightly different way. Ibuprofen forms a noncovalent bond with the enzyme. [25] This bond is not as strong as the bond formed by aspirin with COX. When the bond eventually breaks, the enzyme becomes active again. Ibuprofen is thus considered a reversible inhibitor.

Naproxen

Naproxen is the active ingredient of the OTC NSAID Aleve. It is the most recent of the four most popular OTC analgesics sold in the United States. [26] It is also available as a sodium salt, naproxen sodium, which is more rapidly absorbed from the gastrointestinal tract. [27] It is commonly used for the reduction of mild to moderate pain, fever, inflammation and stiffness caused by conditions such as arthritis, gout, menstrual cramps, tendinitis and primary dysmenorrhea. [28]

Naproxen was developed by the Syntex drug company in 1976. It was first sold as a prescription drug under the name Naprosyn. It quickly became the leading arthritis drug in the United States giving Syntex 80% gross profit margins. [29] Naproxen sodium was initially available as the prescription drug Anaprox in 1980. In 1994, the Food and Drug Administration approved naproxen sodium as an OTC drug.

Naproxen is an odorless, white to off–white crystalline substance with a molecular weight of 230.2628. [30] Its chemical name is (S)–6methoxy–αA–methyl–2–naphthaleneacetic acid and has an empirical formula of C_{14} H_{14} O_3 . Its structural formula is shown by Figure 10. [31]



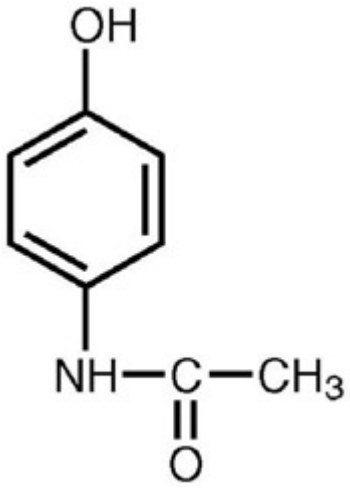
It is nonpolar, which means it is soluble in lipids but almost insoluble in water with a pH below 4 but becomes readily soluble at pH 6 or higher. [32]

Like aspirin and other NSAIDs, naproxen blocks the production of prostaglandins by inhibiting COX at the start of the arachidonic acid pathway, causing gastrointestinal tract irritation. Taking naproxen with food is one way to minimize this side effect.

Acetaminophen

Acetaminophen is found in several OTC medications such as Tylenol, Excedrin, Theraflu, and Nyquil as well as in prescription pain medicine like Vicodin which contains acetaminophen and another substance called hydrocodone. Though it was discovered by Harmon Northrop Morse in 1873, the medical use of acetaminophen began only in 1893. [33] It was approved for use by the U.S. Food and Drug Administration in 1950 [34] and went on sale as Tylenol in 1955.

The chemical formula of acetaminophen is C8H9NO2. Its chemical name is 4–hydroxyacetanilide. Figure 11 shows its chemical structure:



Like NSAIDs, acetaminophen is an analgesic and antipyretic. It has similar pain–relieving potency as aspirin and ibuprofen. But unlike NSAIDs, it does not possess anti–inflammatory properties. Thus, it cannot reduce the swelling of tissues resulting from a sprain or arthritis, for example.

Acetaminophen is an alternative for people who are allergic to aspirin. Because it does not stop mucus production, it causes less irritation to the gastro–intestinal tract and can be taken by those suffering from acid reflux and peptic ulcers. But unlike aspirin, it does not inhibit platelet aggregation therefore it does not provide reduced blood clotting protection for those who have heart problems.

Why does acetaminophen produce some similar effects as NSAIDs but also behaves differently? Just like NSAIDs, acetaminophen interferes with the synthesis of prostaglandins, hence, it relieves pain and reduces fever. But NSAIDs block prostaglandin synthesis at the beginning of the arachidonic acid pathway by binding with COX in the very first step, thus stopping the entire prostaglandin synthesis process. Consequently, all the physiological activities that involve prostaglandin are reduced including relay of pain signal, inflammation, fever, mucus production and blood clotting.

On the other hand, acetaminophen does not inhibit COX at the beginning of the pathway but another enzyme

located further downstream. [35] At that juncture of the pathway, the synthesis of prostaglandins responsible for inflammation, mucus secretion and blood clotting has been completed. Moreover, it is believed that acetaminophen is much more specific in terms of where it inhibits prostaglandin production. It blocks prostaglandin synthesis more specifically in the tissues of the central nervous system whereas NSAIDs act on a broader range of tissues. [36] Some scientists believe acetaminophen inhibits a third form of COX called COX–3 found in the central nervous system but this is still subject to debate. [37]

Acetaminophen is a safe and effective pain reliever as long as it is taken in its therapeutic dose of 500 mg every 4–6 hours. But it can severely damage the liver and even cause death when it is misused or abused. In fact, the improper use of acetaminophen has become the leading cause of acute liver failure in the United States. Enzymes in the liver break down acetaminophen into a very toxic compound called N–acetyl–p–benzoquinonimine. The body can easily detoxify and excrete small amounts of this compound. But when large amounts of the compound accumulate, the body''s detoxification system is overwhelmed and the compound starts killing liver tissues.

Strategies

The strategies that will be used to implement this unit have been selected to reflect the nature of science. Science is not just a body of knowledge. It is also a way of doing and a way of thinking. The unit will show that inquiry is an essential part of learning science. At the same time, a variety of strategies will be employed to ensure that the needs of students with various learning styles are addressed

Lecture–discussions will be supplemented by short videos/animations and slide presentations. There will be kinesthetic activities including simulations and model building. Literacy needs will be responded to through reading short articles, journaling and the use of graphic organizers. There will be cooperative learning activities such as Jigsaw and Think–Pair–Share not only to facilitate acquisition of content but also the development of group skills.

Demonstrations and experiments will serve to develop inquiry and science process skills. Technology through the use of the Internet, multi–media platforms, digital probes (e.g. Vernier pH probes) and graphing calculators will be used to engage the students who are all digital natives.

Classroom Activities

Activity 1 Elephant Toothpaste Demonstration

The unit opener is a dramatic demonstration called ""elephant toothpaste."" The purpose of the demonstration is to get students thinking about the role of a catalyst in speeding up chemical reactions. Because of the nature of this reaction, it is best to carry out the demonstration outside. If it is to be done in the classroom, the demonstration table must be cleared of other items. Putting the graduated cylinder on a big cafeteria–like tray will make cleaning up a lot easier. The teacher doing the demonstration must wear goggles and lab gown.

Materials

1000–mL graduated cylinder

30% hydrogen peroxide ($H_2 O_2$)

Potassium iodide (KI)

food coloring

liquid dishwashing detergent

big tray

Procedure

1. Carefully add 20 mL of hydrogen peroxide into a 1000–mL graduated cylinder.
2. Ask students if they have ever used hydrogen peroxide as an antiseptic. If they did, have them share what they observed when the liquid was added to an open wound. Why did it bubble? Draw out from the students that the hydrogen peroxide was decomposing into water and oxygen. Then ask students why they do not see the hydrogen peroxide in the graduated cylinder decomposing. (It is actually decomposing but at a very slow rate.) How can the reaction be made faster?
3. Put about 10 mL of liquid dishwashing detergent into the graduated cylinder then add a few drops of food coloring along the sides of the graduated cylinder. (This is just to create more bubbles, making the reaction more visible and dramatic.)
4. Use a spatula to add 1–2 grams of potassium iodide. The liquid will bubble immediately and colorful foam will come out of the graduated cylinder. To test that one of the products is oxygen, bring a glowing wooden splint very near the foam coming out of the cylinder. The glowing splint will burst into flame. (Oxygen supports combustion.)

Ask students what was the function of the potassium iodide. (It is a catalyst. It speeds up the decomposition of hydrogen peroxide into water and oxygen). Have them recall from their biology classes what term is used to refer to catalysts that speed up chemical reactions that occur in organisms. (They are called enzymes.)

This demonstration can also be performed using more readily available materials. 3% hydrogen peroxide available in drugstores can be used instead of the 30% hydrogen peroxide. Baking yeast or raw chicken, pork or beef liver can serve as the catalyst. To a 100–mL glass graduated cylinder, add 70 mL of the hydrogen peroxide. Then add half a teaspoon of yeast or a small piece (around 1 inch) of raw liver. Using food coloring and liquid detergent is optional.

Use the results of this demonstration to introduce the unit on kinetics or rates of reactions.

Activity 2 Write(Think)–Pair–Share on What is Pain

This activity begins the section on the pain pathway. Give students 2–3 minutes to write their answer to the question, ""What is pain?"" Then they will share their answer with a partner. They then decide what definition of pain they will share with the class. To ensure individual accountability, each student completes a Think–Pair–Share graphic organizer that will have the following elements.

1. What I think is the definition of pain
2. What my partner thinks is the definition of pain
3. What our pair''s agreed upon definition of pain

Activity 3 Dear Absent Classmate Letter

After a teacher–led PowerPoint presentation on the pain pathway, students will write a letter to an ""absent classmate"" explaining in their own words what the classmate missed about the lesson on how we sense pain. The letter must be no more than 3 paragraphs and must not exceed 2 pages. Students may use illustrations/drawings to make the letter not only easier to understand but also fun to read. Students must include their own example in tracing the pain pathway (e.g. aching feet after running a mile in PE). Encourage students to make their letter colorful.

Activity 4 Kinesthetic Activity on How Painkillers Work– Match Mine

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The purpose of this activity is to illustrate how NSAIDs serve as inhibitors and thus relieve pain. This is carried out once students have learned the various biological functions of prostaglandin and its synthesis through the arachidonic acid pathway.

Several identical sets of 2–piece jigsaw–like puzzles are prepared beforehand. Each two–piece puzzle is cut in such a way that one of the pieces is significantly smaller than the other piece. Each student gets one puzzle piece. Students are then instructed to find the puzzle piece that fits with their own puzzle piece. Once they have found their match, they go to the teacher who will give them a small piece of paper labeled prostaglandin.

Have students recall the first step of the arachidonic acid pathway for prostaglandin synthesis. Ask them which piece of the puzzle could be the enzyme that changes arachidonic acid to prostaglandin and which piece is the arachidonic acid. The class could agree that the bigger piece is the enzyme but it could also be the smaller piece. To facilitate faster discussion, guide the class to establish that the bigger piece is the enzyme.

Repeat the activity but this time, replace most of the smaller pieces with a different color (but the same shape and size as the smaller piece) of puzzle pieces. Students will see that fewer prostaglandins are synthesized. Have students hypothesize what the different color of puzzle pieces represent. Guide them to arrive at the conclusion that these puzzle pieces are NSAID molecules that attach to the enzyme, thus preventing the conversion of arachidonic acid to prostaglandin.

Activity 5 Jigsaw Cooperative Learning on the 4 OTC Pain Relievers

Students will learn about the 4 OTC pain relievers through a cooperative learning strategy called Jigsaw.

The class will be divided into groups of 4. This will be the home group. In each home group, students 1, 2, 3 and 4 will be assigned to find information about aspirin, ibuprofen, naproxen, and acetaminophen. The following guide questions are given to students to help them focus their research.

1. How was the drug discovered? When did it become available as an OTC drug?
2. What is the chemical formula of the drug? Describe some of its physical and chemical properties. Give examples of popular trade names of the drug.
3. How does the drug work?
4. What are the side effects associated with the use of the drug? What are some possible health threats that could arise from the misuse and abuse of the drug?

Depending on the resources available, students can go online to find the needed information or they can use teacher–prepared hand–outs and other reading materials.

Students organize their findings using a graphic organizer shown in the appendix.

Before students go back to their group to share their information, they will meet with students from other groups working on the same topic. These are the expert groups. Students in the expert groups share and verify the information they have gathered. At this point, they may have to modify their graphic organizer to ensure the information they will bring to their group is accurate and complete.

The home groups then reconvene. Each member shares what he has learned about the drug assigned to him. The home group will then prepare a summary chart that contains information about all four drugs. Challenge each home group to be creative in designing their own summary chart. Also, reiterate that it is the responsibility of each home group member to learn from each other.

Activity 6 Lab on Effect of Acidic and Basic Environment on Aspirin

In this lab, students will compare the behavior of regular, buffered and coated aspirin in acidic and basic environments. The acidic environment will simulate the stomach while the basic environment will simulate the small intestine.

Materials

Three 150–mL beakers

Three stopwatches

Two tablets each of regular aspirin, buffered aspirin, and coated aspirin

Vinegar

Baking powder

Distilled water

Graduated cylinder

Stirring rod

pH paper or pH meter

Acidic Environment

1. Measure the pH of the vinegar using pH paper or a pH meter
2. Add 50 mL of vinegar to each of three 150–ml beakers.
3. Simultaneously add one tablet of regular aspirin to the first beaker, buffered aspirin to the second beaker, and coated aspirin to the third beaker.
4. Observe and record what happens to the aspirin in each beaker every minute until the tablets have completely dissolved. Record the time it takes for each tablet to dissolve completely.
5. Rinse and dry the beakers and graduated cylinder.

Basic Environment

1. Add 100 mL of distilled water to each of three 150–mL beakers.
2. Add a teaspoon of baking powder to each of the beakers. Dissolve the baking powder using a stirring rod.
3. Measure the pH of the baking powder solution using pH paper or a pH meter.
4. Simultaneously add a tablet of regular aspirin, buffered aspirin, and coated aspirin to beakers one, two and three, respectively.
5. Observe and record what happens to each tablet every three minutes for 30 minutes or until the tablet has dissolved completely. Record the time it takes for each tablet to dissolve completely.

Questions

1. How do you know that the aspirin tablets are ""reacting"" in an acidic environment in the first part of the lab?
2. Which aspirin dissolved the fastest in an acidic medium? the slowest?
3. Explain any differences observed in the rate of dissolving of the three tablets in an acidic medium.
4. How do you know that the aspirin tablets are ""reacting"" in a basic environment in the second part of the lab?
5. Which aspirin dissolved the fastest in a basic medium? the slowest?
6. Explain any difference observed in the rate of dissolving of the three tablets in a basic medium.
7. Compare the behavior of each type of aspirin in an acidic and basic medium.
8. What does buffered aspirin mean? What does coated aspirin mean?
9. Based on your observations, what conditions would make it more advantageous to use buffered aspirin? coated aspirin?

If pH digital probes are available, the pH of each of the six tablets can be monitored every minute until the tablets have completely dissolved. A graph of pH as a function of time can then be created manually or by using a computer software or a graphing calculator.

Activity 7 Multimedia Project on Deciphering OTC Pain Relievers

For their culminating project, students working in groups of 3 or 4 will select one of the four OTC pain relievers discussed in the unit. They will then visit a local drug store and examine choices available for the pain reliever they have picked. They will write down and compare actual ingredients of each brand and analyze how ""different"" the various brands and variants are from each other. As they read the labels, they should take note of the following questions.

1. How is the product being marketed? What ""catchy phrases"" are printed on the label to entice consumers to pick the product?
2. What is the cost per dosage? Is the difference in cost per dosage justified?
3. Based on the package label and what they have learned from the unit, does it make any difference if they purchase the generic or store brand rather than the name or popular brand?

Groups will present their findings in the form of any of the following: PowerPoint or Prize presentation, podcast or a short video.

Appendix

California Content Standards: Chemistry

Reaction Rates

8. Chemical reaction rates depend on factors that influence the frequency of collision of reactant molecules. As a basis for understanding this concept:

b. Students know how reaction rates depend on such factors as concentration, temperature and pressure.

c. Students know the role a catalyst plays in increasing the reaction rate.

d. Students know the definition and role of activation energy in a chemical reaction.

Graphic Organizer for the Jigsaw Strategy

Name of OTC drug: _____

table 12.05.02.01 is available in print form

End Notes

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1. Bennett, William J. . "U.S lag in science, math a disaster in the making – CNN.com." CNN.com – Breaking News, U.S., World, Weather, Entertainment & Video News. http://www.cnn.com/2012/02/09/opinion/bennett–stem–education/index.html (accessed June 30, 2012).

2. Ibid.
3. Paul, Marla. "Public Confused About Ingredients in Pain Relievers : Northwestern University Newscenter." Home : Northwestern University. http://www.northwestern.edu/newscenter/stories/2011/05/public–confused–about–pain–relievers.html (accessed June 30, 2012).
4. Ibid.
5. Committee on Conceptual Framework for the New K–12 Science Education Standards. *A framework for K–12 science education: practices, crosscutting concepts, and core ideas*. Washington, D.C.: The National Academies Press, 2012.
6. "Concepts in Biochemistry – Concept Reviews." Wiley: Home . http://www.wiley.com/college/boyer/0470003790/reviews/kinetics/kinetics_effectors.htm (accessed August 1, 2012).
7. Merskey, H., and N. Bogduk. "International Association for the Study of Pain | IASP Taxonomy." International Association for the Study of Pain | Welcome to IASP. http://www.iasp–pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm (accessed July 10, 2012).
8. Freudenrich, Craig. "HowStuffWorks "Introduction to How Pain Works"." HowStuffWorks "Science". http://science.howstuffworks.com/environmental/life/human–biology/pain.htm (accessed July 10, 2012).
9. Ibid.
10. "Pain Types – About Pain – Pain Clinic – Somatic, Visceral, Neuropathic, Sympathetic." The Pain Clinic – Information, help, and advice for pain sufferers on the diagnosis and treatment of acute and chronic pain complaints. http://www.painclinic.org/aboutpain–paintypes.htm (accessed July 10, 2012).
11. Ibid.
12. Ibid.
13. Ibid.
14. Ibid.
15. Ibid.
16. Kimbrough, Doris. "Aspirin: Pain Relief and More." *ChemMatters*, February 2004.
17. "COX 1 and 2 ." The Arthritis Pages of drdoc on–line. http://www.arthritis.co.za/cox.html (accessed July 11, 2012).
18. Ibid.
19. Marsella, Gail. "Aspirin." *ChemMatters*, February 1993.
20. "How aspirin works." University of Chicago Chronicle: June 11, 2009. http://chronicle.uchicago.edu/950817/aspirin.shtml (accessed July 16, 2012).
21. Ibid.
22. "Ibuprofen – Chemistry Encyclopedia – structure, name." Chemistry: Foundations and Applications. http://www.chemistryexplained.com/Hy–Kr/Ibuprofen.html (accessed July 12, 2012).
23. Ibid.
24. Ibid.
25. Ibid.
26. American Chemical Society. "The Aspirin Effect: Pain Relief and More." *ChemMatters Teachers Guide*, February 2004.
27. Ibid.
28. Ibid.
29. Ibid.
30. Ibid.
31. Ibid.
32. Ibid.
33. Kimbrough, Doris. "Aspirin: Pain Relief and More." *ChemMatters*, February 2004.
34. "Acetaminophen – Chemistry Encyclopedia – structure, name." Chemistry: Foundations and Applications. http://www.chemistryexplained.com/A–Ar/Acetaminophen.html (accessed July 16, 2012).

35. Kimbrough, Doris. "Aspirin: Pain Relief and More." *ChemMatters*, February 2004
36. Ibid.
37. McNichol, Ewan . "How does acetaminophen relieve pain?." Tufts Journal. http://tuftsjournal.tufts.edu/2008/04/professor/01/ (accessed May 5, 2012).

Bibliography

"Chemistry in your cupboard | Nurofen ."Chemistry in your cupboard | Home http://www.chemistryinyourcupboard.org/nurofen (accessed July 13, 2012).

"Acetaminophen – Chemistry Encyclopedia – structure, name." Chemistry: Foundations and Applications. http://www.chemistryexplained.com/A–Ar/Acetaminophen.html (accessed July 16, 2012).

"Acetylsalicylic Acid – Chemistry Encyclopedia – structure, name." Chemistry: Foundations and Applications. http://www.chemistryexplained.com/A–Ar/Acetylsalicylic–Acid.html (accessed July 13, 2012).

Aldridge, Susan. *Magic molecules: how drugs work*. Cambridge, UK: Cambridge University Press, 1998.

American Chemical Society. "The Aspirin Effect: Pain Relief and More." *ChemMatters Teachers Guide*, February 2004.

Bennett, William J. . "U.S lag in science, math a disaster in the making – CNN.com." CNN.com – Breaking News, U.S., World, Weather, Entertainment & Video News. http://www.cnn.com/2012/02/09/opinion/bennett–stem–education/index.html (accessed June 30, 2012).

"COX 1 and 2 ." The Arthritis Pages of drdoc on–line. http://www.arthritis.co.za/cox.html (accessed July 11, 2012).

"Concepts in Biochemistry – Concept Reviews." Wiley: Home . http://www.wiley.com/college/boyer/0470003790/reviews/kinetics/kinetics_effectors.htm (accessed August 3, 2012).

John Wiley & Sons Publishers Inc. "Concepts in Biochemistry – Cutting Edge: Aspirin." Interactive Concepts in Biochemistry. http://www.wiley.com/legacy/college/boyer/0471661791/cutting_edge/aspirin/aspirin.htm (accessed May 5, 2012).

Dingrando, Laurel, Kathleen (Gregg) Tallman, Nicholas Hainen, and Cheryl Wistrom. *Chemistry: matter and change*. Teacher Wraparound Edition ed. New York, N.Y.: Glencoe/McGraw–Hill, 2005.

Freudenrich, Craig. "HowStuffWorks "Introduction to How Pain Works"." HowStuffWorks "Science". http://science.howstuffworks.com/environmental/life/human–biology/pain.htm (accessed July 10, 2012).

"How aspirin works." University of Chicago Chronicle: June 11, 2009. http://chronicle.uchicago.edu/950817/aspirin.shtml (accessed July 16, 2012).

"Ibuprofen – Chemistry Encyclopedia – structure, name." Chemistry: Foundations and Applications. http://www.chemistryexplained.com/Hy–Kr/Ibuprofen.html (accessed July 12, 2012).

J. Chem. Educ Staff. "Medicinal Chemistry of Aspirin and Related Drugs." Journal of *Chemical Education* 56, no. 5 (1979): 331–333.

Kimbrough, Doris. "Aspirin: Pain Relief and More." *ChemMatters*, February 2004.

Marsella, Gail. "Aspirin." ChemMatters, February 1993.

McNichol, Ewan . "How does acetaminophen relieve pain?." Tufts Journal. http://tuftsjournal.tufts.edu/2008/04/professor/01/ (accessed May 5, 2012).

Merskey, H., and N. Bogduk. "International Association for the Study of Pain | IASP Taxonomy." International Association for the Study of Pain | Welcome to IASP. http://www.iasp–pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm (accessed July 10, 2012).

National Research Council, Committee on Conceptual Framework for the New K–12 Science Education Standards. *A framework for K–12 science education: practices, crosscutting concepts, and core ideas*. Washington, D.C.: The National Academies Press, 2012.

"Pain Types – About Pain – Pain Clinic – Somatic, Visceral, Neuropathic, Sympathetic." The Pain Clinic – Information, help, and advice for pain sufferers on the diagnosis and treatment of acute and chronic pain complaints. http://www.painclinic.org/aboutpain–paintypes.htm (accessed July 10, 2012).

Paul, Marla. "Public Confused About Ingredients in Pain Relievers : Northwestern University Newscenter." Home : Northwestern University. http://www.northwestern.edu/newscenter/stories/2011/05/public–confused–about–pain–relievers.html (accessed June 30, 2012).

Postlethwait, John H., and Janet L. Hopson. *Modern biology*. California Teacher's ed. Orlando: Holt, Rinehart and Winston, 2007.

"Prostaglandins and Biologically Active Substances | Steps of the Scientific Method, Research and Experiments| Experiment–Resources.com." Steps of the Scientific Method, Research and Experiments | Experiment–Resources.com. http://www.experiment–resources.com/prostaglandins.html (accessed July 11, 2012).

Simmons, Daniel , Regina M. Botting, and Timothy HIa. "Cyclooxygenase Isozymes: The Biology of Prostaglandin Synthesis and Inhibition ." *Pharmacological review* 56 (2004): 387–437.

Sohn, Emily . "How Over–The–Counter Painkillers Work." *Los Angeles Times*, February 11, 2011, sec. Health. http://articles.latimes.com/2011/feb/11/health/la–he–0214–painkillers–biology–20110211 (accessed May 5, 2012).

"The Science of Pain UCTV – University of California Television." UCTV – University of California Television. http://www.uctv.tv/search–details.aspx?showID=23157 (accessed June 29, 2012).

"The Science of Pain | KQED QUEST." Science | KQED Public Media for Northern CA. http://science.kqed.org/quest/2011/06/03/the–science–of–pain/ (accessed May 5, 2012).

Vane, J.R., Y.S. Backle, and R.M. Botting. "Cyclooxegenases1 and 2." *Annu.Rev.Pharmacol.Toxicol.* 38 (1998): 97–120.

"What Is Ibuprofen? What Is Ibuprofen Used For?." Medical News Today: Health News. http://www.medicalnewstoday.com/articles/161071.php (accessed May 5, 2012).

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