



HUMANS AND CAFFEINE—A VERY LONG RELATIONSHIP

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JESUS
13 YEARS OLD



XIMENA
8 YEARS OLD



GERARDO
12 YEARS OLD

Why do humans take every day beverages prepared by mixing hot water and tea leaves or coffee beans? We do not need hot beverages to play baseball better or to get higher scores at school. However, as soon as humans started to drink hot beverages thousands of years ago, they noticed benefits that are similar than those we feel today. Caffeine is the most known of the components in coffee that provide benefits for our living style and for our health. As you know perfectly well, the taste of coffee or tea is not pleasant. The reason we stick to drinking these beverages is the content of caffeine (or similar substances) plus the addition of sugar or sweeteners, which by the way, can be found in cola drinks. Remarkably all beverages, selected by humans in different ages and countries, contain caffeine or a similar substance. Humans discovered fire and learned to prepare hot drinks to become the most successful species on Earth.

Charles Darwin in the eighteenth century studied how simple animals could evolve to be *Homo sapiens*, i.e., humans. Is there any substance in nature that has helped us to become the most successful animals in nature? Indeed, caffeine has helped humans in their evolutionary journey.

Back in time, humans and any other animal on Earth needed to eat. Food consisted of fruits and cereals, which are rich in carbohydrates. Carbohydrates are our main nutrients still today. As its name says, they are formed basically of Carbon atoms bounded to Hydrogen and also to Oxygen atoms. Glucose is one of the simplest carbohydrate known and has 6 atoms of Carbon, 12 of Hydrogen, and 6 of Oxygen. Many carbohydrates (glucose, sucrose, lactose, etc.) are sweet, and for this reason they are also known as sugars. The second most important nutrient for early humans was probably protein, and hunting/fishing wild animals was the best way to get protein. Lipids, vitamins and minerals, and other nutrients needed to keep early humans alive were obtained from the vegetable/fruit and animal foods. But there is one thing missing—actually the most important one—water. A relevant point for this article is the way *Homo* drank water before and after fire discovery. Before fire was discovered, humans obviously had to drink water that was at “room” temperature, but after they discovered fire, humans were able to prepare hot drinks.

The ability to heat water probably made eating more enjoyable for early humans. Many foods taste better when they are heated or cooked. Cooking food at high temperatures using water or vegetable oils was an early achievement of early humans that is still around today. But hot water led to something else; it led to the possibility to drink water containing products from leaves without eating the leaf itself. Interestingly, all cultures and all races have ended up with some things in common in the way they live their lives, and one of these is making drinks from the process of boiling plants in water, called infusions (Figure 1).

FIGURE 1

Drinks, such as coffee, that contain methylxanthines, have been a part of human social gatherings for almost as long as humans have been on Earth, and these drinks have helped different cultures to interact with each other.



FIGURE 1

METHYLXANTHINES

Human cells may produce xanthine whereas xanthines with methyl (CH₃) groups, methylxanthines, are made by plants. The best-known are: Caffeine in coffee, theobromine in tea, and theophylline in cacao.

HORMONE

Biochemical compound generated in an organ that travels throughout the blood to reach its specific receptor to produce a biological/physiological effect. Examples are: adrenaline/epinephrine, cortisol, and insulin.

FIGURE 2

Examples of modern beverages and foods containing methylxanthines.

From a historical point of view, it is very likely that the first infusions prepared with leaves in hot water were used for ceremonies, and not specifically used just to get nutrients. They probably did not taste very good, since many drinks made this way taste bitter, and bitterness was often a signal to early humans that something was poisonous. So, what were the benefits of those drinks? We believe that the short answer is that many of those drinks contained substances called **methylxanthines**.

Caffeine and substances that are similar—we may call them “sister compounds”—are methylxanthines because they contain two rings, one with six atoms and the other one with five. Of all these atoms, at least four have to be Nitrogen atoms (this is what chemists call Xanthine structure), whereas another one has to be a Carbon atom surrounded of three Hydrogen atoms (Methyl group). Then, each methylxanthine has its own modifications and chemical groups that make them different to each other. The most consumed in the World is caffeine, found in coffee and in cola drinks. Theophylline, which is extracted from tea leaves and the methylxanthine found in chocolate, theobromine, are also highly consumed by humans of all countries, cultures, and races (Figure 2). As everybody knows, coffee/cola drinks, tea, and chocolate are part of human’s diet all over the world! Is the presence of methylxanthine in coffee, tea, or chocolate the reason why so many cultures love these drinks and they had been consumed up to the present day (Figure 3)? We will try to answer this question.

HOW METHYLXANTHINES ACT

While many people drink beverages with caffeine (or theophylline) in them, not many people know how these substances work. Their mode of action is blocking the adenosine receptors.

A receptor is a protein of our cells that specifically binds a substance/**hormone** and when it does so, the cell responds. The energy that an organism

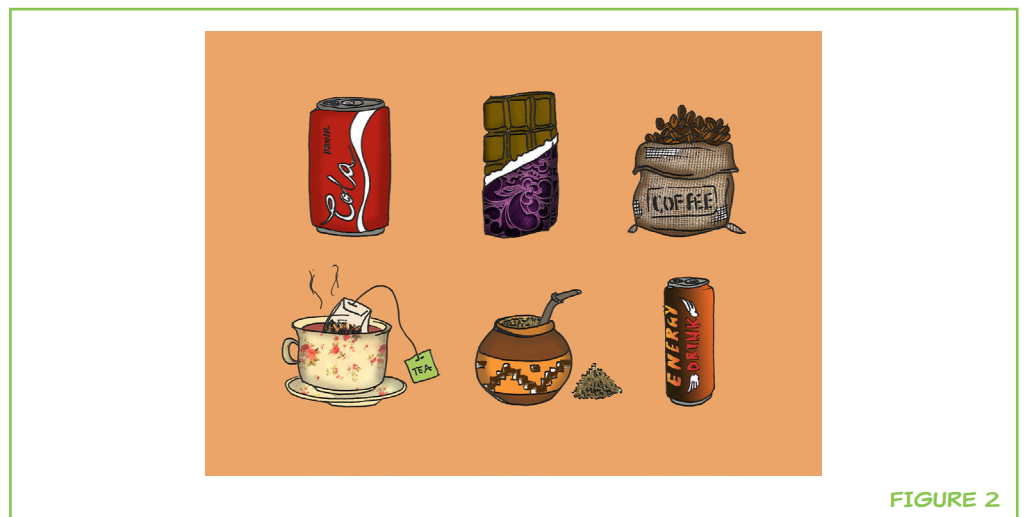
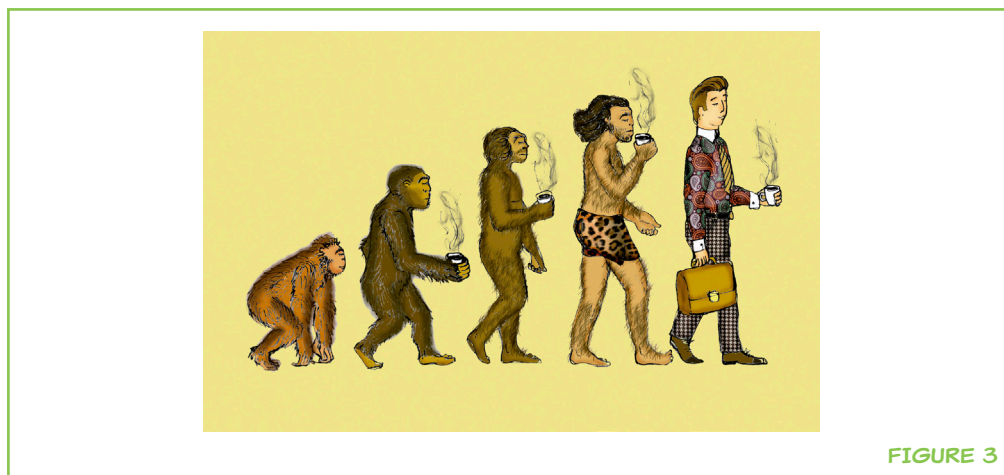


FIGURE 2

FIGURE 3

Methylxanthine-containing drinks have been around since shortly after humans evolved from monkeys/primates.

**FIGURE 3****ATP**

Acronym of Adenosine TriPhosphate. Chemical compound that is the cell's provider of energy for costly processes such as synthesis of nucleic acids.

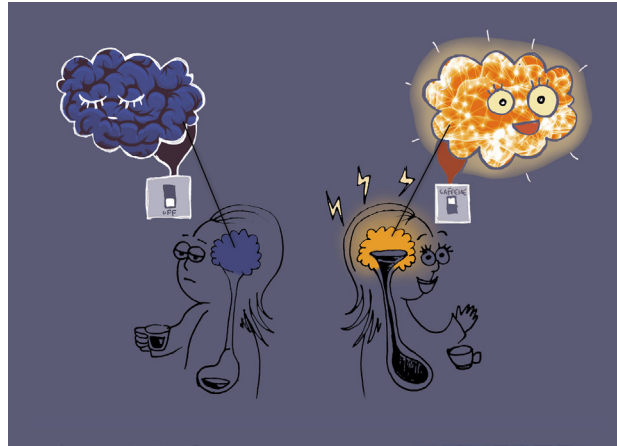
needs to maintain life or a cell to do chemical reactions is provided by **ATP** (Adenosine TriPhosphate). When ATP is used, cells generate adenosine plus phosphate. Therefore, if we have a lot of adenosine within our cells, it would mean that we do not have much ATP. Cells notice in every moment the balance between ATP and adenosine. Any increase of adenosine is a sign that cells have to slow down activities and restore ATP levels to maintain their energy levels and strength. This action is performed by adenosine receptors that appeared around a 100 million years before humans discovered fire (see Ref. [1] and references therein).

What happens if we drink coffee, tea, or chocolate? Caffeine, theophylline, or theobromine do not have relevant effects in our organisms except when they arrive in the brain. The impact of these substances in the brain has helped humans evolve. Once bound to adenosine receptors, methylxanthines modulate their action in the brain. Following what we have explained above, if adenosine receptors are active, the neurons try to slow down and recover some energy. When caffeine (or theophylline and theobromine) block their action, neurons could be active again, helping us to wake up in the morning, stay awake in class or during long meetings, making us work harder, or even clearing our mind and helping us to have a better mood (Figure 4). Almost all of these effects happen because caffeine blocks adenosine receptors. In summary, from the early humans to us, people had been taking potions, infusions or foods containing methylxanthines because they made us be more active even when we were tired, more focused even after many hours of working and also more clear-minded even in troubled situations. All these have led us to solve more problems and together with so many other things, improve and evolve more than other species of animals.

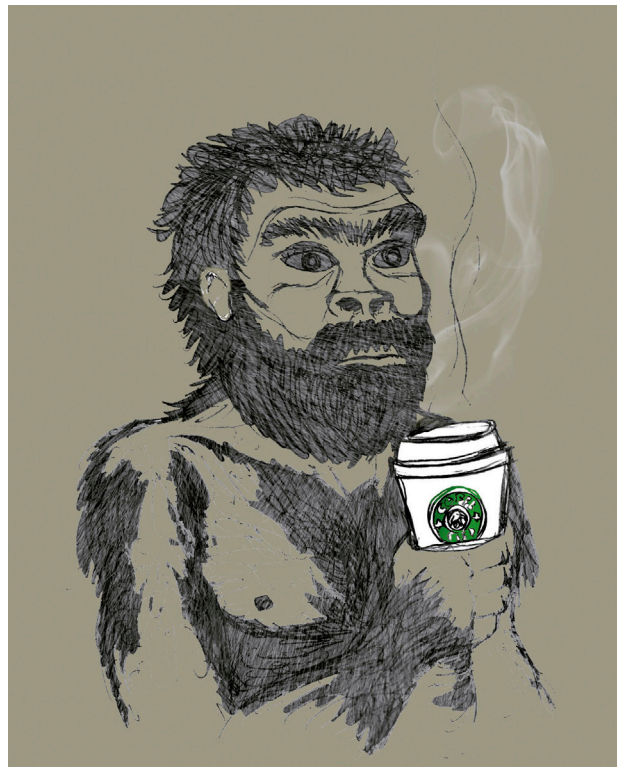
Are methylxanthines still useful for humans? A literature (<https://www.ncbi.nlm.nih.gov/pubmed>) search reveals more than 29,000 scientific articles about caffeine, and a third of them have “caffeine” in the title. A recent research paper says that “*daily coffee and caffeine intake can be part of a healthy balanced diet*;

FIGURE 4

Coffee can make you feel more awake and put you in a better mood by blocking the adenosine receptors in the brain. Caffeine mainly binds to (and blocks) adenosine receptors, which normally (when not blocked by caffeine) help the brain to relax.

**FIGURE 4****FIGURE 5**

Homo Starbucks. We, first inventors of caffeine-containing drinks, have evolved with coffee as fellow traveler.

**FIGURE 5**

its consumption does not need to be stopped in elderly people” [2]. We know that methylxanthines have been included in the human diet for a long time and probably helped humans to interact with each other and evolve (Figure 5). People have only recently started asking if they are healthy for us or not, but it seems that these substances are finally being accepted as important for health-maintenance in human daily life (Box 1). The positive effects of methylxanthines have brought them to be useful for the prevention or treatment of some pathologies of the central nervous system or the respiratory tract [3].

PARKINSON'S DISEASE

Neurodegeneration in the brain of patients displaying tremors/muscle rigidity and having difficulties in undertaking certain type of movements (walking, pressing a car brake, etc.).

ABSTINENCE SYNDROME

State that suffers people who are addicted to alcohol, cocaine, or other drugs when are withdrawn of those substances. It is characterized by sleeplessness, shakiness, irritability, and sweating.

Moreover, in 2013, a pharmaceutical company created a new methylxanthine acting on adenosine receptors that is being used in therapy of a disease of the motor/movement control system called **Parkinson's disease** (Nouria[®]). In addition, other methylxanthines are being investigated to see if they could help blood cells to fight against cancer [4].

The fact that methylxanthines are consumed all over the World and by all human cultures and in very different types of beverages (Figure 1) tells us how important they are. Coffee was not invented by European or American people. The origin of coffee drinking is not certain, but legends say it started in Africa (Ethiopia) or in the Middle East. It is likely that people started drinking tea soon after fire discovery. It is assumed that tea drinking started in China about 4,000 years ago. A bunch of other plants, such as *Paulliania cupana* (guaraná) and *Camellia ptilophylla* (cocoa tea), also have a high content of methylxanthines. The content of theophylline in yerba mate, known as *Ilex paraguariensis* mate tea, is even higher than in black tea. It is unlikely that cultures discovering tea drinking existed in the same place and in the same time than cultures discovering yerba mate drinking. It is also unlikely that taste was the main reason for drinking either yerba mate, or coffee, or even tea. The first version of these drinks probably did not taste good, and only after many years did humans learn how to make these drinks taste better (by adding sugar or honey or mixing them with aromatic flowers, etc.). But, it is a

BOX 1 | IS CAFFEINE ADDICTIVE?

Unlike some other natural substances from plants that have effects on the nervous system, methylxanthines are not addictive. The difference between drugs that are addictive and can end up being abused (such as nicotine, cocaine, heroin, or amphetamine) and drugs that are not addictive is sometimes difficult to determine. Different cultures have varying opinions and laws about certain kinds of drugs. For instance, alcohol is acceptable with a few restrictions in the USA and other Western societies, but it is forbidden in Islamic societies. Cocaine is forbidden in almost every country, and coffee and tea are accepted in almost every country. Quite interestingly, tobacco smoking is legal in some nations despite the fact that everyone knows that nicotine, in tobacco, is addictive. Although in the recent past, caffeine consumption was considered dangerous for people with certain diseases or disorders, and coffee and cola drinks were restricted for many patients, the current view is that caffeine is safe except for people that are nervous/stressed/anxious or have some specific heart disorders. Also, caffeine is not *officially* considered to be a drug that improves sports or athletic performance.

The serious bad feelings after abrupt deprivation of a substance producing dependence in humans, i.e., the "**abstinence syndrome**," has been reported for heavy caffeine drinkers or shown on TV shows in "experiments" with volunteers who drink large quantities of caffeine. However, these individuals do not require specific medications required to stop taking other addictive drugs, such as cocaine. Neither carbohydrates, nor proteins in food, nor caffeine/theophylline/theobromine are drugs of abuse. Drugs of abuse alter our perception of reality, whereas caffeine helps us to get better information from our senses and to appropriately process it. Indeed, neither foods, nor the main ingredients in them (carbohydrates, lipids, and amino acids), nor coffee, nor tea, nor caffeine make us experiment another reality. In summary, caffeine helps us to better sense our real world and drinking coffee is, for instance, the best way to prevent road accidents in professional drivers! Caffeine-containing drinks may reduce the risk of road accidents by up to 40% [5]!

proven fact that different races and/or different cultures selected drinks with a high content of methylxanthines. Many of those drinks consumed by early humans are essentially the same to those we drink today.

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SUBMITTED: 25 May 2016; **ACCEPTED:** 31 May 2017;

PUBLISHED ONLINE: 20 June 2017.

EDITED BY: Vaughan G. Macefield, Mohammed Bin Rashid University of Medicine and Health Sciences, United Arab Emirates

CITATION: Angelats E, Martínez-Pinilla E, Oñatibia-Astibia A, Franco N, Navarro G and Franco R (2017) Humans and Caffeine—A Very Long Relationship. *Front. Young Minds* 5:27. doi:10.3389/frym.2017.00027

CONFLICT OF INTEREST STATEMENT: For about 5 years (2008–2013 period) RF was consulting for CICAS (Centro de Información Café y Salud, www.cicas.es). The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEWED BY



JESUS, 13 YEARS OLD

Hi, My name is Jesus, I am 13 years old, and I live in Mexico. I am good in math, and I like to play strategy games. I also like programming, astronomy and physics, specifically quantum physics.



XIMENA, 8 YEARS OLD

Hello, my name is Ximena. I am 8 years old, and I like to play with my friends and watch TV movies during the weekends. I am in third grade, and I have three brothers.



GERARDO, 12 YEARS OLD

Hi, my name is Gerardo, and I am 12 years old. I live in Mexico. I like to play games with my friends at school and when I go home I usually play videogames or watch videos and documentaries. Also, I like reading books.

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After his Bachelor in Biomedical Science and a Master degree in Neuroscience, Edgar Angelats is developing a Ph.D. in the Molecular Neurobiology laboratory of the School of Biology of the University of Barcelona. His work relates to identifying differential characteristics of adenosine receptors in microglia, a particular cell type in the central nervous system. He is active in a variety of sports and he left the professional water polo-player activity to devote his career to look for novel therapeutic approaches in neurodegenerative diseases.



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