Cocoa beans, the fermented ground seeds from the fruit of *Theobroma cacao*, the chocolate tree, have been employed as an ingredient in comestibles for the last 3.4 millennia. Ancient urns containing traces of the signature molecule, theobromine, from archeological digs in the Ulua Valley, now Honduras, suggest that cacao has been part of the human diet for at least 113 generations [1]. Yet, despite a history transcending Olmec, Mayan, and Aztec civilizations and more than 150 yr of contemporary chocolate-making, a certain mystique still surrounds the effects of chocolate on the mind and body. Indeed, the history of chocolate is filled with fanciful descriptions of its potency, from the hedonistic and superhuman connotations reported from the court of Aztec royalty to modern-day associations of fine dark chocolate with health benefits, a feeling of well-being, and aphrodisia.

What are the origins of these enthralling descriptions of potency and what light can be shed on this matter with modern technology?

First, consider that there has been an almost unfathomable amount of change in the consumers of cocoa and the comestible itself over the ages. Cacao was probably originally consumed as a frothy, tart-tasting, and mildly alcoholic beverage among the Olmec and Maya. Given the propensity of plant material to spontaneously ferment in the tropical heat and humidity, it likely made for some very interesting and variable brews! Depending on how much ground cacao was consumed, the beverage would also have had significant calorific value; thus, cacao likely represented a critical source of energy and vigor. We do know that cakes made of cacao were a part of standard Aztec military rations and that these, along with toasted maize, were considered enough to sustain a soldier on the march [2]. Thus, without invoking any medicinal qualities, it is likely that cacao, at approximately 170 cal/oz, had remarkable energetic properties in a calorie-constrained society.

In stark contrast, modern-day chocolate, a miracle of the industrial revolution, has been promoted as a luxury food-stuff at a time when calories need to be rationed, not sought. Furthermore, chocolate underwent a gradual devolution in the 20th century as it was diluted and adulterated to meet market demand for low-cost candy. Thus, cacao went from a critical ingredient in a potion-like beverage to eventually being relegated to a sweet, brown, mass-marketed commodity detached from its antiquity and original potency.

Similar to coffee, the cultural interest in fine dark chocolate and cacao has been subject to a renaissance in recent years. Even with the caveats regarding changes in dietary habits and the exceedingly wide variation of cacao comestibles, there are plenty of data to indicate that certain forms of cocoa and chocolate have palpable and measurable effects on human physiology.

Polyphenolic antioxidants in chocolate have received the most attention in the medical literature (Fig. 1) and to a large degree are associated with the popular resurgent interest in dark chocolate, reviewed by McShea et al. [3]. The most interesting molecule in this family seems to be the flavonol epicatechin, which is absorbed into the bloodstream soon after consuming cacao or chocolate [4]. A relatively modest 6-g portion of dark chocolate, a negligible 30 cal, produces measurable reductions in blood pressure [5]. Mechanistically, the flavonol epicatechin acts as a vasodilator, widening the blood vessels throughout the body, increasing blood flow to the extremities and the brain, and lowering blood pressure.

In addition, there is significant evidence that polyphenol antioxidants in chocolate and cacao act as systemic inflammatory mediators, reducing platelet and endothelial cell...
activation and the expression of inflammatory mediators, i.e., significant physiologic effects that are associated with positive health benefits, as reviewed by Corti et al. [6]. There is even compelling microbiological evidence to suggest that chocolate, rather antithetically, can inhibit oral caries, or progressive tooth decay [7]. Significantly, certain polyphenols also cross the blood–brain barrier and clinical studies have indicated that cerebral blood flow increases in humans after consumption of cocoa [8].

Cacao and chocolate also contain significant concentrations of theobromine, a central nervous system stimulant that contributes to the bitter flavor of chocolate. Theobromine is a close relative and metabolite of caffeine that differs by the presence of a methyl group. Although its effects on the central nervous system last longer than those mediated by caffeine, they are also quite distinct from the latter, and less acute.

Finally, there is a suspicion that chocolate and cocoa contain additional psychoactive factors. A number of candidates have been suggested, including bioactive amines such as phenylethylamine and anandamide [9], but conclusive causal relations between these candidate molecules and biological effect remain to be proven. In part, the difficulty stems from identifying which of the myriad compounds in specific chocolate formulations actually are bioavailable, with the potential to act on the central nervous system.

But perhaps the larger issue is that no one can really agree on what measurable effects chocolate actually has on humans! Does chocolate truly have addictive properties? What is the nature of the feeling of well-being that we experience after consuming chocolate—is it simply satiation, or are certain individuals really “moved” by consuming specific types of chocolate?

So what is the take home message? Is chocolate a “new coffee” with stimulatory and anti-inflammatory properties, or does it represent something “mind-alteringly” unique?

To some degree the answer lies in the details behind what constitutes “true” chocolate, the form in which it is consumed, and the state of mind (and body) of the consumer. The experience of a calorically constrained Aztec warrior when consuming a strong, thick beverage made from ground cacao is likely to be very different from the modern chocolate experience: a guilty pleasure associated with consuming sugar-laden confectionary while reflecting on one’s weight ....

It does, however, seem likely that certain types of chocolate have real and measurable effects on the mind, even without invoking a “psychotropic X-factor.” Certainly the polyphenols and theobromine in chocolate are to blame, but it is also possible that other bioactive moieties play a significant role. Unraveling the components of a lipid-rich, small molecule–laden foodstuff that varies by genetics, fermentation method, and the chocolate-making process is a tall order. So, perhaps the answer lies in understanding the pharmacology of specific chocolate formulations rather than taking a one-size-fits-all approach to this age-old problem. Or maybe chocolate remains more interesting as an enigmatic mystery?

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