



# Brewing controversies: Darwinian perspective on the adaptive and maladaptive effects of caffeine and ethanol as dietary autonomic modulators

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**Summary** Ethanol and caffeine are two of the oldest human drugs. Their pervasive integration into the modern human diet may reflect behavioral attempts to correct maladaptations induced by evolutionary displacement of the autonomic system. The dietary adoption of caffeine may parallel the emergence of cognition as an independent basis of competition. Enhancement of the cognitive ability to gather and process information likely evolved as a valuable adjunct to physical behavior in prehistoric fight-or-flight encounters. Caffeine effectively exploits this pre-existing association between adrenergic activity and cognitive readiness, leading to its use in the modern environment where success in competition increasingly depends on cognitive, rather than physical, prowess. Ethanol may have emerged as a dietary means to buffer the maladaptive chronic sympathetic activation and fear response associated with stressful lifestyles and the social phobias associated with the dissolution of kin networks. We explore the health implications of ethanol and caffeine use, with particular attention to their acute and chronic effects on the autonomic axis. The putative protective effects of ethanol in surviving major trauma or reducing inflammation and heart disease may relate to tempering the behavioral and cardiovascular consequences of catastrophic or chronic sympathetic activation. Acute or chronic abuse of ethanol manifests paradoxical pro-adrenergic effects such as tremors and insomnia that may partly represent compensatory responses. Compensatory remodeling may also explain why confirmation of detrimental effects related to caffeine-induced sympathetic activation has proven elusive; indeed, paradoxical pro-vagal benefits may eventually be recognized. Ethanol and caffeine are potential agents that may beneficially expand the dynamic range of the autonomic system. In an environment where the Darwinian value of knowledge has increasingly supplanted that of physical traits, the consumption of caffeine and alcohol may represent both a cause and an effect of modern human evolution.

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## Darwinian perspective

Ethanol and caffeine are two of the oldest human drugs. As early as 700,000 BC, humans may have

chewed the seeds, bark, or roots of plants that yield caffeine. In 2737 BC Shen Nung, the mythical first Emperor of China, detailed the medicinal uses of tea in his compilation of medical records entitled *Pen ts'ao*, including references to the antibacterial, mood-enhancing, bronchodilatory, and diuretic effects of tea. With respect to alcohol, in ancient China, Mesopotamia, and Egypt, herbal

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medications were typically dissolved in fermented beverages.

The pervasive integration of caffeine and ethanol into the modern human diet may reflect behavioral attempts to correct maladaptations induced by evolutionary displacement of the autonomic system. The dietary adoption of caffeine may parallel the emergence of cognition as an independent basis of competition. Enhancement of the cognitive ability to gather and process information likely evolved as a valuable adjunct to physical behavior in pre-historic fight-or-flight encounters. Caffeine effectively exploits this pre-existing association between adrenergic activity and cognitive readiness, leading to its use in the modern environment where the basis of competition is increasingly tilting towards cognitive, rather than physical, prowess. Ethanol may have emerged as a dietary means to buffer the maladaptive chronic sympathetic activation and fear response associated with increasingly stressful lifestyles and the social phobias associated with the dissolution of kin networks. We explore the health implications of ethanol and caffeine use, with particular attention to their acute and chronic effects on the autonomic axis.

## Caffeine

Caffeine is a xanthine alkaloid that undergoes rapid absorption with extremely high bioavailability [1]. Acute sympathomimetic effects associated with caffeine such as vasoconstriction and tachycardia initially led to the recommendation of caffeine avoidance in patients with hypertension and coronary artery disease [2–4]. Concern over potential arrhythmogenicity also initially produced warnings against caffeine use in the setting of underlying structural and electrophysiologic heart disease [5]. Nonetheless, empirical data to evaluate these purported risks has proven mixed. Epidemiologic studies on caffeine and blood pressure encompass a spectrum of seemingly contradictory findings ranging from promotion to attenuation [6]. Prospective cohort studies involving thousands of subjects have concluded that caffeine intake exerts no detrimental effect on coronary artery disease, stroke [7,8] or electrophysiologic events [9]. Numerous factors hamper caffeine studies, including a paucity of long-term follow-up, a shortage of statistical power, dosing heterogeneity, recall bias, and confounding behavioral variables. Wide variation in dosing regimens, dosing chronicity, dosing vehicle and measurement time after dosing have added to the confusion. For instance, given that the mean half-life of caffeine in plasma is

about 5 h, one might expect different results between near-continuous consumers of caffeine versus intermittent consumers. Indeed, acute intake of caffeinated beverages increases blood pressure in non-habitual coffee drinkers, but not in chronic users [10–14].

Numerous studies suggest that caffeine may confer benefit in cardiovascular disease. Prospective administration of coffee extract to subjects in a once-daily pulsed fashion improved a vascular reactivity profile after one month of use [15]. Modest caffeine intake may also restore heart rate variability in type 1 diabetics [16]. Some studies suggest that chronic caffeine consumption may lower blood pressure [17]. These benefits may arise from several mechanisms of action. Caffeine blocks the activity of cellular phosphodiesterase, in turn raising cyclic AMP and increasing myocardial inotropy. Antagonistic effects on the cardiac adenosine receptor may also enhance inotropy. Caffeine purportedly possesses anti-platelet activity [18], a feature that should afford a degree of cardioprotection. Additional cardioprotective properties of coffee and tea appear to include decreased insulin resistance, diuretic activity, antioxidant properties, and increased fat metabolism [19–22].

We assert that chronic but moderate caffeine consumption may confer health benefits by paradoxically reducing background sympathovagal ratio as the body compensates for the chronic adrenergic challenge, not unlike those effects seen with exercise. Chronic administration of medication can lead to development of compensatory response through counter-regulatory activity, necessitating escalating doses of medication and producing rebound effects upon its withdrawal. Compensatory response to caffeine is well known to anyone who has experienced a decline in baseline alertness after repeated exposures, provoking further consumption. The induction of paradoxical compensation by repeat caffeine exposure may translate into systemic reduction of sympathovagal ratio to produce beneficial effects.

## Ethanol

Although inebriation increases the risk of accident-related major trauma [23,24], considerable debate remains as to the relative outcome of inebriated versus sober patients in the trauma setting. Various retrospective studies have suggested that alcohol ingestion has either negative [25–27] or no [28–30] impact on outcome in trauma patients. However, a prospective study found that patients who had blood alcohol concentration (BAC) greater than

22 mmol/L manifested trends towards lower death rates at the scene of accident, within 24 h of hospitalization, and after 24 h of hospitalization, as compared to patients whose BAC was below 22 mmol/L (adjusted for age, injury severity, and type of injury) [31]. The former group also showed trends towards fewer infections, respiratory failure, ICU admission, surgery, requirement for pressors, and all complications except for pneumonia [30]. Significantly fewer intoxicated patients required more than a single week of hospitalization [30]. Furthermore, prior ethanol consumption appears to significantly reduce mortality rates at equivalent degrees of injury [29]. Mechanistic explanation behind these observations is unknown. A common belief, though unsupported by data, holds that musculoskeletal laxity associated with alcohol may offer protection during major trauma under the presumption that the laxity might cushion the body from deceleration forces.

We propose instead that ethanol may produce unexpected benefits in the setting of trauma by buffering against autonomic collapse. Sympathetic activity represents a normal, adaptive component of the trauma response, but the response can become counterproductive during severe trauma if excessive invocation occurs. In such cases, the trauma victim may be at higher risk of developing arrhythmias, frank cardiovascular collapse, or shock following depletion of adrenergic reserves. Alcohol consumption acutely blunts sympathetic tone and mitigates behavioral and physiologic dimensions of stress. Whereas consumption of caffeine generally occurs during work hours, consumption of alcohol corresponds to times where induction of parasympathetic bias may provide benefits, such as during periods of relaxation and ingestion. A recent randomized crossover study of young volunteers who received one week of low dose alcohol showed alterations in heart rate variability consistent with a decreased ratio of sympathetic to parasympathetic activity [32]. Though the mechanism by which alcohol consumption acutely suppresses sympathetic activity remains unknown, alcohol produces well-known physiologic effects that are consistent with parasympathetic activity: decreased respiratory drive [33,34], decreased tachycardic response to stress [35], increased airway resistance [36], central nervous system depression [37], somnolence [38], diuresis [39], hypothermia, and peripheral vasodilatation [40]. Interestingly, the lore of military medicine has long touted the potential therapeutic benefit of alcohol in reducing pain and shock among the wounded [41]. The reduction of sympathovagal ratio and the associated reduction in inflammation may ac-

count for the putative protective effects of modest ethanol consumption on heart disease [42].

Some studies link alcohol to a hyperadrenergic response [43,44]. As with the data set for caffeine, inconsistent conclusions may arise across alcohol studies due to methodological differences relating to dose amount, dosing chronicity, dosing vehicle, time lags following consumption, duration of follow-up, statistical analysis, and confounding behavioral variables. It is also important to segregate the acute primary effects of alcohol, which we believe to be pro-parasympathetic, with the secondary compensatory effects mounted by the body, which we believe to be pro-adrenergic. The compensatory effect following alcohol ingestion is corroborated by the hang-over effect from acute ethanol intoxication, which produces symptoms that mimic sympathetic excess [45]. Alcohol withdrawal or chronic alcohol consumption produces symptoms such as tremor that may develop from paradoxical pro-adrenergic effects and compensatory activation of the stress axis [41,46]. Whereas somnolence accompanies acute alcohol use, insomnia emerges in chronic alcoholics and patients withdrawing from alcohol [47,48]. Diuresis following ethanol use may involve suppression of vasopressin, a primitive hormone that constitutes part of the acute adrenergic trauma response [49]. Conversely, patients experiencing ethanol withdrawal show activation of vasopressin [40]. Chronic heavy drinkers manifest osteoporosis [50], which is partially mediated by Th2 inflammation that is associated with sympathetic bias [51].

## Darwinian perspective

Integration of caffeine and ethanol into the human diet may have driven many aspects of human cultural evolution. Caffeine consumption has been recognized as a contributing force in many stages of human evolution from the emergence of civilization to the industrial revolution. In turn, as success in competition increasingly depends on cognitive rather than physical prowess, human cultural evolution drives ever-greater global caffeine consumption. As each successive stage of modern human evolution has required an increasing level of participative perspicacity for an increasing fraction of our daily existence, we have ultimately become required to pay attention around the clock [52], with caffeine consumption playing a conspicuous role. This feed-forward cycle is magnified by the psychological and physiological dependency on caffeine due to tachyphylaxis.

While progressive caffeination of society has increased our susceptibility to information, recent technical innovations have dramatically enhanced information liquidity. While the benefits of these synergistic trends may seem apparent, the potential perils of the information culture – information oversupply and illegitimate signaling – also warrant consideration. We have previously described how the overconsumption of information may account for a host of unforeseen health problems, including sleep disorders, obesity, inflammatory disorders, physiologic stress and behavioral dysfunction [53].

Furthermore, information liquidity does not necessarily connote information efficiency. Our factory settings for assimilating information and acquiring traits through envy and communication were shaped during prehistoric tribal settings governed by kin altruism. Without genetic alignment of interests prevalent in prehistoric tribal structures, modern mobile individuals have increasing incentives to extract fitness from counterparties by exploiting the prehistoric fear response and the gullibility of others using illegitimate signals. Indeed, much of what passes as information today actually constitutes noise or illegitimate signals masquerading as useful knowledge. Many of these distortions serve to instill fear, whether as a threat or a sense of inadequacy, which contributes to behavioral dysfunctions such as distrust, hyper-consumerism, isolation, and chronic stress.

The barrage of information distortion and perpetual dissatisfaction represents important elements of the behavioral dysfunctions of modern life, compounded by clock-controlled work schedules, high-density habitats comprised of strangers, social isolation, and unmitigated ambition accompanying increasing opportunities. These trends of the modern information environment, especially the mass distribution of fear, have come to play an increasing role in the emergence of behavioral and health dysfunctions related to chronic stress. In this setting, ethanol may have emerged as an accessible, if imperfect, chemical crutch – a ready instrument to remodel the autonomic axis so as to cope with the maladaptive chronic fears associated with modern life, including vocational anxiety, family conflicts, economic angst, and social isolation.

Caffeine and alcohol are both byproducts of an information culture. One can be used to enable the pursuit of success, while the other can be deployed to manage a sequela of this striving, namely fear. Ultimately, caffeine and ethanol both participate in the filtering of information. From a medical perspective, the possibility of harnessing the paradoxical compensatory effects associated with

intermittent caffeine or alcohol exposures to treat behavioral and physiologic ailments associated with autonomic maladaptations remains largely unexplored. We have previously illustrated the principle of using controlled, timed pro-adrenergic agents to treat ailments resulting from chronic sympathetic bias [54]. In addition to exercise, growing evidence suggests that remodeling occurs to compensate for ongoing challenge to the autonomic nervous system. Examples include ischemic reconditioning, beta-blocker holidays in the treatment of ocular hypertension, and tachyphylaxis to beta-agonists in reactive airway disease [54]. Ethanol and caffeine are agents whose effects may potentially serve to beneficially expand the dynamic range of the autonomic system. In an environment where the Darwinian value of knowledge has increasingly supplanted that of physical traits, the consumption of caffeine and alcohol may represent both a cause and an effect of modern human evolution.

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## References

- [1] Rall TW. The methylxanthines. In: Hardman J, editor. Goodman and Gilman's pharmacological basis of therapeutics. New York: McGraw-Hill; 1993. p. 1663.
- [2] Paul O, Leper MH, Phelan WH. A longitudinal study of coronary heart disease. *Circulation* 1963;28:20–31.
- [3] Nichols AB. Coffee drinking and acute myocardial infarction. *Lancet* 1973;1:480–1.
- [4] Lacroix AZ, Mead LA, Liang Ky, Thomas CB, Pearson TA. Coffee consumption and the incidence of coronary heart disease. *N Engl J Med* 1986;315:977–82.
- [5] Hebbbar AK, Hueston WJ. Management of common arrhythmias: part 1. supraventricular arrhythmias. *Am Fam Physician* 2002;65:2479–90.
- [6] Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. *Eur J Clin Nutr* 1999;53(11):831–9.
- [7] Kleemola P, Jousilahti P, Pietinen P, et al. Coffee consumption and the risk of coronary heart disease and death. *Arch Intern Med* 2000;160:3393.
- [8] Grobbee DE, Rimm EB, Giovannucci E, et al. Coffee, caffeine, and cardiovascular disease in men. *N Engl J Med* 1990;323:1026.
- [9] Graboyes TB, Blatt CM, Lown B. The effect of caffeine on ventricular ectopic activity in patients with malignant ventricular arrhythmia. *Arch Intern Med* 1989;149:637.
- [10] Sudano I, Binggeli C, Spieker L, Lüscher TF, Ruschitzka F, Noll G, et al. Cardiovascular effects of coffee: is it a risk factor? *Prog Cardiovasc Nurs* 2005;20(2):65–9.

- [11] Corti R, Binggeli C, Sudano I, Spieker L, Hanseler E, Ruschitzka F, et al. Coffee acutely increases sympathetic nerve activity and blood pressure independently of caffeine content: role of habitual versus nonhabitual drinking. *Circulation* 2002;106:2935.
- [12] Sharp DS, Benowitz NL. Pharmacoepidemiology of the effect of caffeine on blood pressure. *Clin Pharmacol Ther* 1990;47:57.
- [13] Curatolo PW, Robertson D. The health consequences of caffeine. *Ann Intern Med* 1983;98:641.
- [14] Noordzij M, Uiterwaal CS, Arends LR, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. *J Hypertens* 2005;23(5):921–8.
- [15] Ochiai R, Jokura H, Suzuki A, Tokimitsu I, Ohishi M, Komai N, et al. Green coffee bean extract improves human vasoreactivity. *Hypertens Res* 2004;27(10):731–7.
- [16] Richardson T, Rozkovec A, Thomas P, Ryder J, Meckes C, Kerr D. Influence of caffeine on heart rate variability in patients with long-standing type 1 diabetes. *Diabetes Care* 2004;27(5):1127–31.
- [17] Winkelmayr WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA* 2005;294(18):2330–5.
- [18] Varani K, Portaluppi F, Gessi S, et al. Dose and time effects of caffeine intake on human platelet adenosine A(2A) receptors: functional and biochemical aspects. *Circulation* 2000;102:285.
- [19] Acheson KJ, Zahorska-Markiewicz B, Pittet P, Anantharaman K, Jequier E. Caffeine and coffee: their influence on metabolic rate and substrate utilization in normal weight and obese individuals. *Am J Clin Nutr* 1980;33(5):989–97.
- [20] Dorfman LJ, Jarvik ME. Comparative stimulant and diuretic actions of caffeine and theobromine in man. *Clin Pharmacol Ther* 1970;11(6):869–72.
- [21] Wu LY, Juan CC, Hwang LS, Hsu YP, Ho PH, Ho LT. Green tea supplementation ameliorates insulin resistance and increases glucose transporter IV content in a fructose-fed rat model. *Eur J Nutr* 2004;43(2):116–24.
- [22] Scalbert A, Manach C, Morand C, Remesy C, Jimenez L. Dietary polyphenols and the prevention of diseases. *Crit Rev Food Sci Nutr* 2005;45(4):287–306.
- [23] Council on Scientific Affairs. Alcohol and the driver. *JAMA* 1986;255(4):522–7.
- [24] Vinson DC, Mabe N, Leonard LL, Alexander J, Becker J, Boyer J, et al. Alcohol and injury: a case crossover study. *Arch Fam Med* 1995;4(6):505–11.
- [25] Luna G, Maier R, Sowder L, Copass MK, Oreskovich MR. The influence of ethanol intoxication on outcome of injured motorcyclists. *J Trauma* 1984;24:695–700.
- [26] Pories SE, Gamelli RL, Vacek P, Goodwin G, Shinozaki T, Harris F. Intoxication and injury. *J Trauma* 1992;32:60–5.
- [27] Waller PF, Stewart JR, Hansen AR, Stutts JC, Popkin CL, Rodgman EA. The potentiating effects of alcohol on driver injury. *JAMA* 1986;256:1461–6.
- [28] Huth J, Maier R, Simonowitz D, Herman C. Effect of acute ethanolism on the hospital course and outcome of injured automobile drivers. *J Trauma* 1983;23:494–9.
- [29] Thal ER, Bost RO, Anderson RJ. Effects of alcohol and other drugs on traumatized patients. *Arch Surg* 1985;120:708–12.
- [30] Ward RE, Flynn TC, Miller PW, Blaisdell WF. Effects of ethanol ingestion on the severity and outcome of trauma. *Am J Surg* 1982;144(1):153–7.
- [31] Jurkovich GJ, Rivara FP, Gurney JG, Fligner C, Ries R, Mueller BA, et al. The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. *JAMA* 1993;270(1):51–6.
- [32] Flanagan DE, Pratt E, Murphy J, Vaile JC, Petley GW, Godsland IF, et al. Alcohol consumption alters insulin secretion and cardiac autonomic activity. *Eur J Clin Invest* 2002;32(3):187–92.
- [33] Bailey PL, Fung MC, Price RL, East KA, Pace NL, Goldman MD. Is there central respiratory depression after intravenous administration of propranolol? *Respiration* 1990;57(2):65–9.
- [34] Zink BJ, Feustel PJ. Effects of ethanol on respiratory function in traumatic brain injury. *J Neurosurg* 1995;82(5):822–8.
- [35] Varga K, Lovas G, Palkovits M, Kunos G. Ethanol inhibition of stress-related tachycardia involves medullary NMDA receptors. *Eur J Pharmacol* 1996;310(2–3):145–53.
- [36] Dawson A, Bigby BG, Poceta JS, Mitler MM. Effect of bedtime alcohol on inspiratory resistance and respiratory drive in snoring and non-snoring men. *Alcohol Clin Exp* 1997;21(2):183–90.
- [37] White AM, Matthews DB, Best PJ. Ethanol, memory and hippocampal function: a review of recent findings. *Hippocampus* 2000;10(1):88–93.
- [38] Roehrs T, Roth T. Sleep, sleepiness, and alcohol use. *Alcohol Res Health* 2001;25(2):101–9.
- [39] Taivainen H, Laitinen K, Tahtela R, Kilanmaa K, Valimaki MJ. Role of plasma vasopressin in changes of water balance accompanying acute alcohol intoxication. *Alcohol Clin Exp Res* 1995;19(3):759–62.
- [40] Johnson RH, Eisenhofer G, Lambie DG. The effects of acute and chronic ingestion of ethanol on the autonomic nervous system. *Drug Alcohol Depend* 1986;18(4):319–28.
- [41] Adams GW. *Doctors in blue: the medical history of the union army in the civil war*. Baton Rouge (LA): Louisiana State University Press; 1996.
- [42] Lee PY, Yun AJ, Bazar KA. Acute coronary syndromes and heart failure may reflect maladaptations of trauma physiology that was shaped during pre-modern evolution. *Med Hypotheses* 2004;62(6):861–7.
- [43] Reed SF, Porges SW, Newlin DB. Effect of alcohol on vagal regulations of cardiovascular function: contributions of polyvagal theory to the psychophysiology of alcohol. *Exp Clin Psychopharmacol* 1999;7(4):484–92.
- [44] Koskinen P, Vriolainen J, Kupari M. Acute alcohol intake decreases short-term heart rate variability in healthy subjects. *Clin Sci (Lond)* 1994;87(2):225–30.
- [45] Bogin RM, Nostrant TT, Young MJ. Propranolol for the treatment of the alcoholic hangover. *Am J Drug Alcohol Abuse* 1987;13(1–2):175–80.
- [46] Wilkins JN, Gorelick DA. Clinical neuroendocrinology and neuropharmacology of alcohol withdrawal. *Recent Dev Alcohol* 1986;4:241–63.
- [47] Alling C, Balldin J, Bokstrom K, Gottfries CG, Karlsson L, Langstrom G. Studies on duration of a late recovery period after chronic abuse of ethanol. A cross-sectional study of biochemical and psychiatric indicators. *Acta Psychiatr Scand* 1982;66(5):384–97.
- [48] Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. *Am J Psychiatr* 2001;158(3):399–404.
- [49] Barton RN. The neuroendocrinology of physical injury. *Baillieres Clin Endocrinol Metab* 1987;1(2):355–74.
- [50] Chakkalakal DA, Novak JR, Fritz ED, Mollner TJ, McVicker DL, Garvin KL, et al. Inhibition of bone repair in a rat model for chronic and excessive alcohol consumption. *Alcohol* 2005;36(3):201–14.
- [51] Yun AJ, Lee PY. Maladaptation of the link between inflammation and bone turnover may be a key determinant of osteoporosis. *Med Hypotheses* 2004;63(3):532–7.

- [52] Reid TR. Caffeine: it's the world's most popular psychoactive drug. *Natl Geogr* 2005;3–33.
- [53] Bazar KA, Yun AJ, Lee PY, Daniel SM, Doux JD. Obesity and ADHD may represent different manifestations of a common environmental oversampling syndrome: a model for revealing mechanistic overlap among cognitive, metabolic, and inflammatory disorders. *Med Hypotheses* 2006;66(2):263–9.
- [54] Yun AJ, Lee PY, Bazar KA. Paradoxical strategy for treating chronic diseases where the therapeutic effect is derived from compensatory response rather than drug effect. *Med Hypotheses* 2005;64(5):1050–9.

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