Título artículo / Títol article:	The Impact of Caffeine on the Behavioral Effects of Ethanol Related to Abuse and Addiction: A Review of Animal Studies
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Revista:	Journal of Caffeine Research, 2013, 3.1: 9-21.
Versión / Versió:	PDF Editorial
Cita bibliográfica / Cita bibliogràfica (ISO 690):	LÓPEZ-CRUZ, Laura; SALAMONE, John D.; CORREA, Mercè. The Impact of Caffeine on the Behavioral Effects of Ethanol Related to Abuse and Addiction: A Review of Animal Studies. Journal of Caffeine Research, 2013, 3.1: 9-21.
url Repositori UJI:	http://hdl.handle.net/10234/89432

JOURNAL OF CAFFEINE RESEARCH
Volume 3, Number 1, 2013

DOI: 10.1089/jcr.2013.0003

The Impact of Caffeine on the Behavioral Effects of Ethanol Related to Abuse and Addiction: A Review of Animal Studies

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The impact of caffeine on the behavioral effects of ethanol, including ethanol consumption and abuse, has become a topic of great interest due to the rise in popularity of the so-called energy drinks. Energy drinks high in caffeine are frequently taken in combination with ethanol under the popular belief that caffeine can offset some of the intoxicating effects of ethanol. However, scientific research has not universally supported the idea that caffeine can reduce the effects of ethanol in humans or in rodents, and the mechanisms mediating the caffeine–ethanol interactions are not well understood. Caffeine and ethanol have a common biological substrate; both act on neurochemical processes related to the neuromodulator adenosine. Caffeine acts as a nonselective adenosine A_1 and A_{2A} receptor antagonist, while ethanol has been demonstrated to increase the basal adenosinergic tone via multiple mechanisms. Since adenosine transmission modulates multiple behavioral processes, the interaction of both drugs can regulate a wide range of effects related to alcohol consumption and the development of ethanol addiction. In the present review, we discuss the relatively small number of animal studies that have assessed the interactions between caffeine and ethanol, as well as the interactions between ethanol and subtype-selective adenosine receptor antagonists, to understand the basic findings and determine the possible mechanisms of action underlying the caffeine–ethanol interactions.

Caffeine as a Modulator of Ethanol Abuse

Caffeine and ethanol are widely consumed recreational drugs.[1,2] Alcohol abuse is a worldwide health problem, with serious medical, economic, and social consequences.[3,4] On the other hand, caffeine intake, even in excess, appears to be relatively well accepted, because methylxanthines have activating and attention-preserving properties that can help productivity and enhance the performance. Interest in caffeine has grown ever since the introduction to the market of the so-called energy drinks, which contain caffeine and related substances in quite high concentrations. These drinks are being increasingly consumed, often in combination with substances that have abuse potential.[5] In addition, research with animals has demonstrated the ability of methylxanthines, and in particular caffeine, to modulate the psychopharmacological effects of drugs of abuse such as methamphetamine,[6] amphetamine,[7] nicotine,[8,9] cocaine,[10] and ethanol.[11] The reasons for combining caffeine with ethanol may stem from the popular belief that caffeine can antagonize the intoxicating effects of alcohol.[12] Some studies have supported this hypothesis, demonstrating that caffeine attenuates ethanol-induced changes in psychological parameters in humans such as information processing, memory, psychomotor performance, and others (for a review[13]).

Caffeine has been shown to indirectly modulate the activity of many neurotransmitters and neuromodulators, including dopamine, acetylcholine, or glutamate[14–17] in various brain areas. However, in terms of direct actions, caffeine is most widely described as an adenosine receptor antagonist that is nonselective for the A_1 and A_{2A} subtypes of adenosine receptors in the central nervous system.[1,17–19] Several articles have demonstrated that there are interactions between adenosine and ethanol. Ethanol can increase extracellular adenosine levels by increasing adenosine release,[20,21] and by decreasing adenosine uptake[22] that takes place via a facilitative nucleoside transporter.[23,24] Inhibition of this transporter in the presence of ethanol would lead to an increase in the extracellular adenosine and could thereby modulate some of the effects of ethanol.[21] Secondarily, ethanol increases the adenosine levels because acetate generated by ethanol metabolism promotes adenosine synthesis[25] (see Fig. 1).

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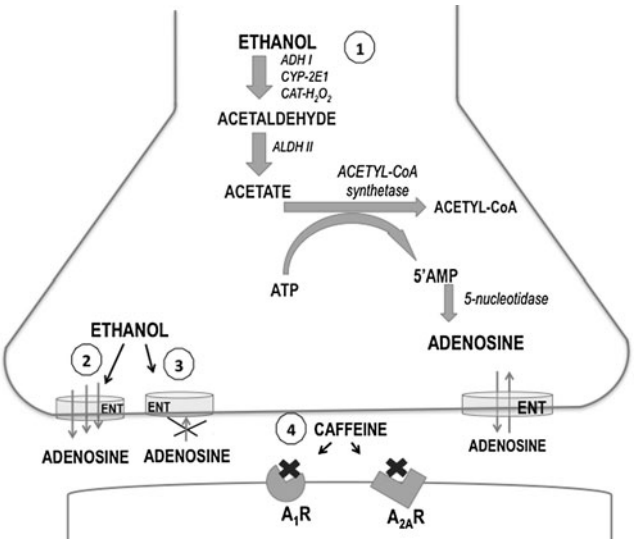

FIG. 1. Schematic showing ethanol regulation of adenosine production (1), release (2), and uptake (3), as well as caffeine blockade of adenosine receptors (4) in the central nervous system. A_1R and $A_{2A}R$, adenosine A_1 and A_{2A} receptors; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ATP, adenosine triphosphate; AMP, adenosine monophosphate; CAT-H_2O_2, catalase; CYP-2E1, cytochrome P4502E1; ENT, equilibrative nucleoside transporters.

In contrast to the studies showing that caffeine can blunt the effects of ethanol, there also is evidence that fails to support the idea of an antagonistic behavioral interaction between caffeine and ethanol, either in humans[26,27] (for review[13]) or in rodents.[28–30] A considerable number of studies employing experimental animal models have been performed to elucidate the impact of caffeine on the effects of ethanol and on ethanol consumption. In the present review, we have emphasized those studies addressing behaviors that can be relevant for the development of alcohol consumption, abuse, and addiction as a compulsive habit, as well as studies that evaluate signs of dependence after withdrawal, such as physical abstinence and craving, which are factors that can lead to relapse.

Drug addictions, including alcoholism, can be conceptualized as disorders of motivation characterized by an excessive control of the drug over behavior.[31–33] This disorder involves a reorganization of the preference structure of the person, dramatic changes in the allocation of behavioral resources toward the addictive substance,[34,35] and alterations in the elasticity of demand for the drug.[36] Typically, there is a heightened tendency to engage in drug-reinforced instrumental behavior and drug consumption, often at the expense of other behavioral activities. Addicts will go to great lengths to obtain the drug, overcoming numerous obstacles and constraints. In addition, the development of addiction is attributed to a profound sensitization in the neural processes that mediate the drug-seeking behavior, which can facilitate the incentive properties of drugs and drug-related stimuli as the addiction process proceeds.[37,38] Thus, as addiction progresses, the drug itself, as well as drug-associated stimuli, trigger an automatic seeking response that ultimately resolves in the consumption of the drug. This automatism has compulsive characteristics that are devoid of instrumental feedback, leading to the formation of drug-related habits.[39,40] Thus, addiction is a very complex set of behavioral and physiological processes that range all the way from drug consumption, to tolerance for some effects, sensitization of motor activity, establishment of implicit and explicit learning, initial sensitivity to reward and punishment, attention shifts, responsivity to Pavlovian cues, and other processes.

In the present review, studies addressing the impact of caffeine on some of those behaviors modulated by ethanol will be summarized. Because of the opposing actions of ethanol and caffeine on the adenosine system, studies focusing on the effects of selective adenosine receptor agonists and antagonists and their interaction with ethanol will be also presented in an attempt to shed light upon the potential receptor mechanisms involved.

Caffeine–Ethanol Interactions: Effects on Locomotion

The behavioral stimulant or suppressant actions of drugs are frequently evaluated by analyzing the locomotor activity of animals.[41,42] Although ethanol is generally classed as a sedative hypnotic and caffeine is considered to be a minor stimulant, both drugs are able to stimulate the locomotor activity in rodents at some dose,[43–48] typically with bell-shaped (or inverted-U) dose–response functions. Rodents (more in mice than rats) show a time- and dose-dependent locomotor response to acute ethanol administration, with low doses stimulating and high doses reducing locomotion.[46,49–52] Methylxanthines such as caffeine also can affect locomotor activity in a biphasic way.[53–56] However, few studies have evaluated the caffeine–ethanol interactions using locomotion as a measure.[51,53,57,58] Waldeck[51] evaluated the effect of ethanol (1, 3, or 4 g/kg, intraperitoneal [IP]) and caffeine (25, 50, or 100 mg/kg, IP) on locomotor activity in female mice, and observed that a moderate dose of caffeine (25 mg/kg) that stimulated locomotion also potentiated the stimulation induced by ethanol administered at the lowest dose (1 g/kg), although it abolished the stimulant effect of a higher dose of ethanol (3 g/kg). On the other hand, a motor-suppressant dose of caffeine (100 mg/kg) totally blocked the stimulant effect of ethanol (1 g/kg). Moreover, the motor-suppressant effect of the higher dose of ethanol (4 g/kg) was potentiated by all doses of caffeine employed.[51] These results with female mice are in close agreement with the observations obtained from cats reported by Pilcher[57]. This author concluded that "when small doses of caffeine and alcohol are combined, the result is generally a qualitative algebraic summation of both actions, that is, each drug produces, qualitatively, its ordinary effects. However, when large doses of the two drugs are combined, the effects of the stimulant drug tend to be reversed, resulting in a greater suppression than the suppressant drug alone."[57]

Oral administration of both drugs in mice could be a useful tool for studying the effects of the ethanol–caffeine interactions, since both drugs are consumed orally in humans. Indeed, as mentioned above, energy drinks contain high concentrations of caffeine, and their consumption in combination with alcoholic beverages is a common practice among young people. The popular belief suggests that, in humans, energy drinks could reduce the intensity of the motor-suppressant effects of ethanol.[26] However, only one study has explored the effects of ethanol on the stimulant effects of energy drinks in animal models.[59] In this study done in mice, oral

administration of energy drinks did not significantly alter the effects of moderate oral doses of ethanol (0.5, 1.0, or 1.5 g/kg), but was able to reduce the suppressant effects of a higher dose of ethanol (2.5 g/kg). It is possible that in this study, some effects could be attributed to other stimulant components of the energy drinks, such as taurine, which has been shown to interact with ethanol on locomotion.[60,61] However, acute oral coadministration of caffeine at a low dose (10 mg/kg) combined with ethanol (1.6, 2.4, and 3.2 g/kg) was demonstrated to increase locomotor activity compared with the effect observed after separate administration of each individual drug.[53]

It is also relevant to consider the effects of acute administration of caffeine or ethanol on the chronic actions of these substances.[58,62–64] Chronic caffeine intake reduces spontaneous locomotion in mice[62] and rats.[58] However, chronic caffeine consumption (0.1% during 30 days) increased sensitivity (relative to water consumption) to the activating effects of an acute dose of ethanol (1.5 g/kg, IP) in rats.[58] In contrast, in mice exposed to chronic caffeine (1 g/L during 7 days), acute doses of ethanol (1.5 and 2.5 g/kg, IP) significantly induced locomotion, but never to the level of animals in the water control group.[62–64] Further, acute caffeine administration (10–35 mg/kg) increased locomotion to a similar extent in mice chronically consuming ethanol (5%, v/v) and those in the water control group (in this case, ethanol did not affect spontaneous locomotion). Thus, chronic consumption of ethanol did not change the acute stimulant effects of caffeine.[62] The same pattern of results was found after acute administration of 5′-*N*-ethylcarboxamidoadenosine (NECA), an adenosine agonist with high affinity for both the A_1 and A_{2A} adenosine receptors. In this case, NECA suppressed locomotion in a similar manner in mice chronically consuming either water or ethanol.[62]

Adolescence is a vulnerable time for organisms exposed to drugs of abuse such as ethanol.[65] It is widely acknowledged that the human adolescent brain is not fully mature,[66,67] and there is evidence from animal studies that exposure to alcohol during adolescence can affect subsequent brain/behavior development.[68,69] Voluntary consumption of ethanol (at a concentration of 8.5 g/L that led to a dose of 1.0–1.5 g/kg), caffeine (at a concentration of 170 mg/L that led to a dose of 20–30 mg/kg), or an ethanol–caffeine combination during late adolescence in male and female rats had effects on the subsequent adult behavior that were dependent on the sex of the rats.[70] Males showed more ambulation after exposure to the alcohol–caffeine mixture, while females exposed to the mixture showed the opposite effects, that is, suppressed ambulation.[70] This pattern of results could be related to sex differences in the sensitivity to the neurotoxic effects of caffeine.[71] In hippocampal cultures pre-exposed to 5 mM ethanol for 10 days, caffeine (5 or 20 μM) produced greater neurotoxicity in cultures from female tissues than from male ones, specifically in the dentate gyrus and the CA1 region.[71] These results demonstrate the importance of including both sexes in investigations of this sort.

In summary, the interacting effects of caffeine and ethanol on locomotor activity are quite complex. It seems that at low doses, acute caffeine administration can increase the stimulant effects of acute doses of ethanol. However, when caffeine or ethanol doses are higher, a potentiation of the suppressant effects of both substances is most evident. On the other hand, chronic administration of either substance does not appear to change the acute doses at which locomotion can be stimulated.

Caffeine–Ethanol Interactions: Effects on Motor Coordination

At medium-to-high doses, a typical action of ethanol is to impair motor coordination.[72–76] This effect generally shows tolerance with repeated ethanol exposure.[77,78] The development of tolerance appears to be relevant for the emergence of ethanol abuse and dependence, because it can attenuate the performance impairing the effect of the drug, which promotes the use of escalating doses.[79] Several studies have investigated the ability of caffeine to modulate ethanol-induced motor incoordination and have explored the possible involvement of adenosine receptors.[28,29,76,80–82]

A single injection of a broad range of doses of caffeine (5–75 μg) administered in the brain ventricles intracerebroventricular (ICV) or peripherally (2.5–62.5 mg/kg, IP) did not alter motor coordination in mice evaluated in the rotarod test.[80,81] However, pretreatment with low doses of caffeine (2.5–25.0 μg ICV, or 2.5–5.0 mg/kg IP) was effective in decreasing the degree and duration of motor incoordination produced by a single dose of ethanol (2 g/kg, IP). The antagonism by caffeine of ethanol-induced motor incoordination was dose related, since higher doses of caffeine (75 μg ICV, or 62.5 mg/kg IP) enhanced ethanol-induced motor incoordination.[80,81] The methylxanthine (and caffeine metabolite) theophylline was less potent, but dose-dependently attenuated (100–150 μg, ICV, 50 mg/kg IP) the motor incoordinating effect of acute ethanol (1.5–2 g/kg, IP).[73,74] On the other hand, potentiation of ethanol-induced ataxia was also observed after pretreatment with another methylxanthine, 3-isobutyl-1-methylxanthine (IBMX).[81]

Chronic oral administration of caffeine for 10 days (45 and 90 mg/kg/day) and IBMX (30 and 60 mg/kg/day) potentiates acute ethanol-induced motor incoordination (1.5 g/kg, IP), an effect that was associated with increased adenosine A_1 receptor binding compared to tap water controls.[28] However, no interaction with ethanol-induced motor incoordination (1.5 g/kg, IP) was observed after chronic theophylline (75 and 150 mg/kg/day) consumption.[28] This lack of effect of chronic theophylline on motor incoordination induced by ethanol was paralleled with the lack of changes in the A_1 receptor density.[28]

More recently, it has been demonstrated that acute oral coadministration of caffeine (20 mg/kg) and ethanol (2.5 g/kg) attenuated the ethanol-induced motor impairment in rats evaluated in the accelerating rotarod.[29] This effect was also observed after acute IP administration of an A_1-selective receptor antagonist (8-cyclopentyl-1,3-dipropylxanthine; DPCPX) injected after oral ethanol administration, but not with an A_{2A} selective receptor antagonist 2-(2-Furanyl)-7-(2-phenylethyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidin-5-amine (SCH 58261), suggesting again that A_1 adenosine receptors are involved in motor incoordination induced by ethanol.[29] However, microinfusions of both the A_1 receptor-selective agonist cyclohexyladenosine (CHA) and the A_{2A}-selective agonist 5′-*N*-ethylcarboxamido-2-[2-(4-phenyl-(3-propanoic acid)] (CGS21680) into the rat motor cortex significantly accentuated motor incoordination induced by ethanol (1.5 g/kg IP) in a dose-related manner.[76] CHA was more potent than CGS21680 in producing this effect. However, the potentiation induced by the A_1 and A_{2A} agonists

was attenuated by the A_1-selective antagonist DPCPX, but not by the A_{2A} receptor-selective antagonist 8-(3-chlorostyryl)caffeine, further emphasizing the involvement of the adenosine A_1 receptor subtype in these effects.[76]

The involvement of different adenosine receptors in the development of rapid tolerance to ethanol-induced motor incoordination in mice has also been evaluated.[82] A single administration of caffeine (3, 10, or 30 mg/kg, IP) or selective antagonists of the A_1 or A_{2A} receptors did not change the performance of animals treated with ethanol (2.5 g/kg) on the first day of testing. However, caffeine administered on the first day was able to block the development of tolerance to ethanol that was manifested on the second day. Moreover, caffeine's blockade of the rapid tolerance to ethanol-induced incoordination appears to be mediated by the A_1 rather than A_{2A} receptors, because DPCPX, but not 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-*a*][1,3,5]triazin-5-ylamino]ethyl)phenol (ZM241385), also blocked rapid tolerance. These data are in agreement with previous studies,[29,76] and it is reasonable to suggest that this effect may be due to the high number of A_1 receptors in the areas controlling motor coordination, such as the cortex and cerebellum.[83]

To summarize, acute low doses of caffeine can reduce the incoordination effects of ethanol, but high doses of caffeine can potentiated them. Moreover, the adenosine A_1 receptors appear to be more important for these effects than the A_{2A} receptors. The ability of caffeine to attenuate the rapid tolerance to ethanol-induced incoordination effects also has been attributed more to the A_1 than A_{2A} receptors.

Caffeine–Ethanol Interactions: Sedation and Narcosis

Ethanol intoxication produces sedative and, at high doses, even hypnotic effects.[72,84–86] In contrast, caffeine enhances wakefulness and alertness, effects that are associated with its ability to block adenosine receptors.[87–91] Although the effects of ethanol or caffeine on sedation and alertness have been widely described, their interaction is much less well characterized, and only a few studies have explored the impact of caffeine on the narcosis or loss of the righting reflex (LORR) induced by ethanol in rodents.[28,92–95]

For example, it has been demonstrated in mice that when coffee (15 mg/mL) or caffeine (0.5 mg/mL) were orally administered before ethanol (75% v/v), the latency to the LORR increased.[92] However, this effect was not observed when caffeine was administered after ethanol. Moreover, this effect was not due to pharmacokinetic interference, since no decrease in plasma ethanol levels was detected in mice pretreated with coffee or caffeine.[92] In another study in mice, an intermediate dose of caffeine (25 mg/kg, IP) administered before an IP injection of narcotic doses of ethanol also blunted the effect of ethanol, in this case by reducing the duration of the LORR.[93] This effect was not seen with higher doses of caffeine (40–100 mg/kg).[81,93] Theophylline (50 mg/kg, IP) produced the same pattern of effects, prolonging the onset and shortening the duration of ethanol-induced LORR[81,73]; however, IBMX (12.5 mg/kg IP) did not alter the LORR induced by ethanol.[81]

Caffeine and theophylline have also been compared in long-sleep (LS) and short-sleep (SS) mice, which are selectively bred for differences in sensitivity to the LORR induced by ethanol, but also have differential sensitivity to purinergic agonists and antagonists.[94] LS and SS mice showed differences in sensitivity to the nonselective adenosine antagonists, theophylline and caffeine.[95] These drugs also produced a distinct pattern of effects in the two strains of mice; while theophylline reduced the duration of LORR induced by ethanol in both strains of animals (at a broader range of doses in LS mice), caffeine only did so in LS mice. Moreover, caffeine at doses of 10 and 20 mg/kg increased the LORR in SS mice. Theophylline did not change the blood or brain ethanol elimination rate, but the effects of caffeine on blood ethanol levels were affected.[95] The A_1 receptor-selective agonists CHA and l-phenyl isopropyl adenosine (PIA), as well as the nonselective A_1-A_{2A} agonists, 2-chloroadenosine and *N*-ethylcarboxamidoadenosine, increased the LORR in both LS and SS mice.[95] In general, LS mice were more affected than SS mice by purinergic drugs, suggesting that there may be differences in the adenosine systems of these lines of mice; this observation may aid in understanding how they differ in ethanol sensitivity as well.

As discussed above, adenosine is involved in mediating many of ethanol's intoxicating effects, such as ataxia[74,96,97] and sedation (for review[98,99]). However, in rodents, adenosine analogs seem to increase LORR only during interactions with hypnotic drugs, rather than causing a direct deep hypnotic effect or unconsciousness.[100] Thus, dipyrimadole (30–40 mg/kg IP), an inhibitor of adenosine uptake, increased the duration of LORR in mice only after the administration of hypnotic doses of ethanol (3.5–4.0 g/kg, IP).[73,93] In regard to the specific adenosine receptors implicated in the modulation of the hypnotic effects of alcohol, more recent studies using novel selective A_{2A} antagonists suggest that A_{2A} rather than A_1 receptors seem to mediate this effect. The A_{2A} antagonist SCH58261, but not the A_1 antagonist DPCPX, blocked LORR induced by ethanol.[93] In addition, female and male mice lacking the adenosine A_{2A} receptor (i.e., A_{2A} KO mice) showed a reduced duration of LORR compared to their wild-type (WT) siblings after ethanol administration.[93,101]

In summary, adenosine agonists seem to potentiate the duration of LORR, while adenosine antagonists reduce the LORR induced by high doses of ethanol. In general, nonselective adenosine receptor antagonists, as well as selective A_{2A} antagonism or genetic deletion, reduce ethanol induced LORR.

Caffeine–Ethanol Interactions: Effects on Learning and Memory

High doses of ethanol can also cause learning impairments, amnesia, or impaired retrieval of information, effects that can persist long after the drug wears off.[102–104] Complete or partial memory impairment occurs commonly from the episodes of binge drinking in both alcoholics and nonalcoholics.[105] This memory impairment may reflect a disruption of encoding, storage, consolidation, and/or retrieval capability.[106,107] Other studies have shown that moderate doses of ethanol delivered after learning generally enhance or have little effect on memory examined the next day,[108,109] and caffeine at moderate doses has been shown to facilitate memory acquisition and retention in animals assessed on various learning tasks.[110–113]

A few articles have focused on the interaction between caffeine and ethanol on the memory in rodents.[114,115] Ethanol and caffeine coadministration has demonstrated to be

neuroprotective in different models of ischemia.[114,116,117] Thus, an acute administration of caffeinol (combination of 10 mg/kg caffeine plus 0.65 g/kg alcohol, IP) 15 minutes after traumatic brain injury in rats, produced an improvement in working memory tasks in the Morris water maze, compared to the vehicle-treated animals.[114] This protection was not due to effects on motor performance.

Retrograde amnesic effects of ethanol, caffeine, or a combination of both agents have been evaluated in rats with an olfactory memory test that uses social odors.[115] A high dose of ethanol (3.0 g/kg, IP) administered after exposure to a novel odor produced memory recall or retrograde memory impairments the following day, and caffeine (5 mg/kg, IP), either 20 minutes before or 1 hour after exposure to the novel odor, prevented this ethanol disruption in recognition memory.[115]

In humans, ethanol and caffeine can also produce state-dependent memory effects.[118,119] State-dependent learning or memory is the term applied to the condition in which a behavior that is learned in a drug state is most readily recalled when the organism is in the same drug state.[120] In rodents, administration of ethanol before training can impair the retrieval of tasks learned in a state-dependent manner, which is reversible by readministering ethanol before the retrieval test.[121,122] This type of study also reflects the ability of ethanol to serve as an interoceptive cue that can aid learning and performance of a specific operant response.[123] Defined in this way, acute ethanol administration can exert state-dependent effects on conditioned avoidance responding.[124,125] However, caffeine (100 mg/kg, IP) does not change the performance of rats already trained to discriminate the interoceptive cue produced by ethanol administration (1.5 g/kg, IP) in an active avoidance task performed in a typical three-chamber apparatus.[126]

The interaction between caffeine and ethanol also has been evaluated using the acquisition of an avoidance task performed in a plus-maze discrimination apparatus.[127] This apparatus uses an elevated plus-maze consisting of two opposing open arms and two opposing enclosed arms. During training, animals are free to explore all four arms, but are conditioned to avoid one of the enclosed arms (the aversive arm) by the presentation of both light and white noise stimuli when they enter that arm. During the testing session (24 hours after the training session), animals are free to explore all four arms again, but no cues are presented. Time in the aversive arm was used as an index of memory. Ethanol alone (1.0 and 1.4 g/kg, IP) or in combination with caffeine (20 and 40 mg/kg, IP) administered before the training session produced a learning deficit manifested during the test session. Only the highest dose of caffeine alone (40 mg/kg) produced that effect. However, that was not due to a state-dependent effect, since the administration of this dose of caffeine before the test did not reverse the learning deficit.[127]

Caffeine also does not change the conditioned avoidance of a sweet solution produced by ethanol. This conditioned taste avoidance (CTA) is produced by administering an acute dose of ethanol after voluntary consumption of saccharine, and is observed as a reduction in saccharine consumption the following day.[30] Caffeine (2.5–10 mg/kg, IP) did not block the association between taste and ethanol effects (1.0–1.5 g/kg, IP); thus, saccharine consumption was not restored. However, caffeine by itself was able to produce CTA at a moderate dose (20 mg/kg, IP).[30]

Taken together, these studies indicate that caffeine appears to prevent explicit memory deficits induced by high doses of ethanol, but does not affect the perception of the interoceptive cue generated by ethanol, and it does not prevent the disruptive effects of ethanol on avoidance learning in discriminative procedures, suggesting a lack of effect of caffeine on implicit learning processes regulated by ethanol.

Caffeine–Ethanol Interactions: Effects on Anxiety and Stress

Considerable evidence indicates that ethanol is capable of reducing anxiety levels in humans and other animals,[128–130] and adenosine has been proposed as a mediator of this anxiolytic effect.[131–133] In this regard, adenosine itself, as well as adenosine receptor agonists, has anxiolytic effects as assessed by a number of ethological tests in rodent models.[134,135] On the other hand, methylxantines such as caffeine and theophylline have been demonstrated to increase anxiety in humans[136–139] and in rodents in different anxiety paradigms.[127,140–143]

Caffeine modulation of the effects of ethanol on anxiety has been explored in a handful of studies,[70,127,131] which also assessed the role of adenosine receptor subtypes in this interaction. Thus, caffeine, across a broad range of doses that extended into the anxiogenic range (10–40 mg/kg), was shown to reduce the anxiolytic-like effect of ethanol (1.0–1.4 g/kg, IP) in the elevated plus-maze in mice.[127,131] The effects of caffeine on acutely administered ethanol appeared to be mediated by the A_1 adenosine receptors, since the selective adenosine A_1 receptor antagonist DPCPX, but not the A_{2A} receptor antagonist ZM241385, significantly reduced the anxiolytic-like effect of ethanol (1.2 g/kg).[131] Moreover, an anxiolytic response was observed after coadministration of nonanxiolytic doses of the A_1 adenosine agonist 2-chloro-N6-cyclopentyladenosine (CCPA) and ethanol.[131]

A different pattern emerges when these substances are administered chronically. The anxiety-related effects of chronic oral consumption of alcohol (1.0–1.5 g/kg) combined with oral consumption of caffeine (20–30 mg/kg) during adolescence were evaluated in male and female rats when they reached mid-adulthood.[70] Males that had previously consumed alcohol plus caffeine showed anxiolysis in the light and dark box and in the open field. However, females exposed to the drug mixture showed an anxiogenic-like effect.[70] Thus, as described above, the results in females and males seem to be opposite.

Caffeine and ethanol not only regulate anxiety-like behavior but also regulate the stress responses involving activation of the hypothalamo–pituitary–adrenal (HPA) axis.[143–150] HPA axis activation ultimately leads to increases in the biosynthesis and systemic secretion of adrenocorticosteroids. The effects of alcohol and other drugs of abuse on this axis are relevant, because a link between the stress response and drug abuse and addiction has been observed. Stress is one of the main factors stimulating drug consumption and the relapse to drug taking in abstinent addicts.[151,152] Further, chronic drug exposure affects the brain stress response systems. Thus, drug abuse is often accompanied by enhanced brain stress responses, which in turn may contribute to the addiction process.[152]

In regard to ethanol and caffeine, moderate acute doses of ethanol[144–147] or caffeine[143,148–150] have been shown to

increase the plasma corticosterone levels in rodents and cortisol in humans. However, only one study so far has explored the interaction of caffeine and ethanol on corticosterone release.[153] In this study, a low dose of caffeine (5 mg/kg IP) delivered before a low dose of ethanol (0.8 g/kg IP) elevated plasma corticosterone levels. This increase was not observed after ethanol or caffeine was administered alone.[153]

In summary, more studies need to evaluate this complex interaction, but so far, the evidence suggests that caffeine and ethanol can counteract each other's effects on acute anxiety levels in rodents, and some of this evidence points to A_1 adenosine receptors as being responsible for the anxiolytic effects of ethanol as well as of the reversal of this effect by caffeine. It would be very important to have a clearer view of the interaction between these substances after chronic consumption, because tension reduction theories suggest that the anxiolytic effects of alcohol facilitate alcohol use by anxious individuals.[154,155] Moreover, a growing body of evidence shows that corticosterone may directly modulate alcohol drinking.[156–159]

Effect of Caffeine on Alcohol Self-Administration

Epidemiology studies have shown that a positive correlation may exist between the consumption of caffeine and that of ethanol.[160,161] Moreover, it has been demonstrated that people who use energy drinks consume alcohol more frequently than people who do not (for review[13]). Studies in rodents have shown a complex relationship between caffeine and ethanol intake.[11,162–164] Caffeine administered in the diet of malnourished female rats has been shown to facilitate voluntary ethanol drinking in a free access two-bottle paradigm,[162,163] and removal of caffeine from the diet restored alcohol consumption to baseline levels. This effect was not taste-related, because quinine did not produce the same pattern as caffeine.[163] However, slow-release caffeine pellets (200 mg/day during 21 days) failed to alter ethanol intake in an unlimited free-choice paradigm in female rats.[165] This lack of effect was specific to caffeine, since slow-release pellets containing other stimulants did increase ethanol consumption.[165] Caffeine administered acutely did not produce a consistent pattern of effects; a low dose of caffeine (5 mg/kg, IP) promoted ethanol drinking in male rats using a limited-access two-bottle choice paradigm.[11] However, a high acute dose of caffeine (50 mg/kg, IP) decreased ethanol as well as food intake in deprived male and female rats.[166] The lack of caffeine effects on ethanol intake has been also demonstrated in a recent study.[167] The presence of caffeine (1 g/L) in alcoholic solutions (10% v/v) did not increase the ethanol consumption of male rats exposed to a free-choice procedure during 50 days. Interestingly, it did prevent the alcohol deprivation effect (ADE), blocking an increase of ethanol intake after an abstinent period of 7 days.[167] Because ADE has been suggested as an animal model of human alcohol craving and relapse,[168] the effect of caffeine on such effect is a very relevant finding.

Research on the role of adenosine receptor subtypes in ethanol intake has mainly focused on the A_{2A} receptors. Ethanol intake and preference were increased in male and female KOA_{2A} mice compared to their WT counterparts in a free-choice task.[101] Results in the same direction have been observed in studies employing pharmacological manipulation of adenosine transmission. Both acute and subchronic (7 days) IP administration of the A_{2A} receptor antagonist 8-ethoxy-9-ethyl-9*H*-purin-6-amine (ANR94) increased the levels of ethanol intake in alcohol-preferring rats assessed in a free choice task.[169] Conversely, a reduction of ethanol intake was observed after acute IP administration of the A_{2A} receptor agonists CGS21680 and 5′-*N*-ethylcarboxamido-2-(2-phenethylthio) (VT7).[169]

The involvement of adenosine A_{2A} receptors in ethanol seeking and intake also has been evaluated in operant chambers in which animals have to exert various levels of effort to have access to ethanol (e.g., lever pressing on fixed ratio [FR] schedules ranging from FR1 to FR3).[169–172] In this case, the pattern of effects produced by different A_{2A} receptor antagonists was more complex. While SCH58261 reduced the number of ethanol-reinforced responses and ethanol consumption,[172] ANR94 increased responding.[169] Moreover, 3,7-dimethyl-1-propargylxanthine had a multiphasic effect on the number of lever presses and amount of ethanol consumed during operant self-administration.[170,171] The A_{2A} agonists CGS21680 and VT7 decreased lever pressing and alcohol consumption in alcohol-preferring rats tested on an FR1 schedule.[169] Using the same behavioral procedure, no effect was observed with an adenosine A_1 antagonist DPCPX.[170,172]

Taken together, it appears that the results so far are not conclusive (see summary in Table 1). The specific effects of adenosine antagonism on ethanol self-administration may depend on factors such as food restriction, sex, ethanol-intake or reinforcement paradigms, or other factors. For instance, it has been suggested that the suppressive effects of caffeine on ethanol intake seen in some studies could be due to the use of high toxic doses of caffeine.[165,166] However, the fact that chronic caffeine blocked the ADE effect[167] suggests that caffeine could be promising as a treatment for protective abstinence, although more studies should assess this point.

Effect of Caffeine on Ethanol Withdrawal

Withdrawal is a defining characteristic of drug dependence and is often characterized by an impaired physiological function and enhanced negative effect, symptoms strongly associated with relapse.[173] Symptoms of ethanol withdrawal appear between 12 and 24 hours after the time when ethanol levels in blood are no longer detectable. For instance, acute withdrawal appears several hours after a high dose of ethanol has been administered, and produces a mild set of symptoms (i.e., hangover) that, among other effects, can include increased anxiety.[132] Moreover, the withdrawal syndrome after chronic administration or chronic consumption of significant amounts of ethanol is also characterized by an increased anxiety response (for review[174]). Other common symptoms of this syndrome in rodents are marked hyperalgesia,[175] tremors, piloerection,[176,177] changes in cardiovascular[178] and gastrointestinal functions,[176] seizures, or convulsions,[179,180] which correspond to the withdrawal symptoms observed in humans (for review see[174,176]).

Although there are no animal studies focusing on the impact of caffeine on anxiety induced by ethanol withdrawal, other adenosine receptor modulators have been shown to regulate the signs of ethanol withdrawal. The administration of adenosine 18 hours after an acute ethanol injection in mice, which is at the onset of the peak of withdrawal as characterized by high levels of anxiety, reduced increases in anxiety

Table 1. Summary of the Effects of Pharmacological and Genetic Manipulations of Adenosine Receptors on Free Ethanol Intake and Operant Self-Administration

Free intake

Drug	*Mechanism of action*	*Sex/species*	*Ethanol concentration*	*Ethanol Intake*	*Refs.*
Caffeine	Non selective antagonist A_1/A_{2A}	Male and female rats	10% (v/v)	Increase	11, 163, 164
		Male and female rats	5% (w/v) 10% (v/v)	Decrease	166, 167
		Male rats	10% (v/v)	No effect	168
ANR94	A_{2A} antagonist	Male alcohol-preferring rats	10% (v/v)	Increase	170
	A_{2A} genetic deletion	Male and female mice	3%–20% (v/v)	Increase	101
CGS 21680	A_{2A} agonist	Male alcohol-preferring rats	10% (v/v)	Decrease	170
VT7	A_{2A} agonist	Male alcohol-preferring rats	10% (v/v)	Decrease	170

Operant self-administration

Drug	*Mechanism of action*	*Sex/species*	*Ethanol concentration/schedule*	*Ethanol intake*	*Refs.*
ANR94	A_{2A} antagonist	Male alcohol-preferring rats	10% (v/v), FR1	Increase	170
SCH58261	A_{2A} antagonist	Male alcohol-preferring rats	10% (v/v), FR3	Decrease	173
DMPX	A_{2A} antagonist	Male rats	10% (w/v) FR1	Decrease	172
		Male rats	10% (v/v), FR3	Bimodal effect	171
DPCPX	A_1 antagonist	Male alcohol-preferring rats	10% (v/v), FR3	No effect	171, 173
CGS21680	A_{2A} agonist	Male alcohol-preferring rats	10% (v/v), FR1	Decrease	170
VT7	A_{2A} agonist	Male alcohol-preferring rats	10% (v/v), FR1	Decrease	161

DMPX, 3,7-dimethyl-1-propargylxanthine.

observed in an elevated plus-maze.[132] This reversal effect was also observed after the administration of a selective adenosine A_1 receptor agonist CCPA, but not after a selective adenosine A_{2A} receptor agonist N^6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine.[132]Moreover, the anxiolytic effect of CCPA on ethanol withdrawal-induced anxiety was reversed by the selective adenosine A_1 antagonist DPCPX.[132] The results from studies involving chronic ethanol administration appear to be different from those observed after acute ethanol administration. In this case, the A_1 receptor antagonist 8-cyclopentyltheophylline reduced the anxiogenic effect produced by ethanol withdrawal in the elevated plus-maze and in the dark/light test in rats.[175]

Removal of a liquid diet containing ethanol (6.7%, v/v) after chronic exposure led to handling-induced hyperexcitability, a less-frequently used behavioral measure of withdrawal.[181] Administration of an adenosine A_1 receptor agonist R-PIA and the adenosine A_{2A} receptor agonist CGS21680 significantly reduced this withdrawal sign, suggesting the involvement of both the A_1 and A_{2A} receptors.[181] In this study, there were no changes in the adenosine A_1 and A_{2A} receptors or in adenosine transporter-binding sites in the frontal cortex and the cerebellum. However, a reduction in adenosine transporter-binding sites was observed in the striatum of ethanol-withdrawn mice.[181]

The administration of adenosine, adenosine analogs, or dipyridamole (an inhibitor of adenosine reuptake) has been shown to reduce the number of rats in which audiogenic convulsions appeared during ethanol withdrawal.[179] The adenosine A_1 receptor agonist CCPA also produced a dose-dependent reduction of the convulsions induced by an intense audiogenic stimulus, as well as tremors, which were apparent 24 hours after repeated high doses of oral ethanol administration (12–18 g/kg per day) in rats.[182] Moreover, administration of the adenosine A_1 antagonist DPCPX completely abolished the antagonistic effects of the adenosine A_1 agonist CCPA on both tremors and audiogenic seizures during ethanol withdrawal.[182] The A_{2A} adenosine receptor also has been implicated in withdrawal-induced convulsions.[183,184] In fact, these receptors are expressed in areas of the brain involved in epileptogenesis, including the striatum, neocortex, and hippocampus.[185] A_{2A}R KO mice are less susceptible to seizures caused by ethanol withdrawal that was induced by the cessation after 10 consecutive days of ethanol intake (up to 6.3% v/v). This effect has also been observed when the A_{2A} adenosine receptor antagonist ZM 241385 was administered during the last 5 of 10 days of ethanol intake.[180] Similarly, subchronic coadministration of theophylline (1 g/kg, IP; twice daily) during chronic ethanol intake (6.5% w/v) was demonstrated to decrease hyperalgesia and withdrawal scores in rats during ethanol withdrawal.[186] However, the protective effect of A_{2A} receptor antagonism or repeated theophylline administration was not observed after the acute administration of caffeine or theophylline (5–25 mg/kg, IP); in this case, there was no effect on the audiogenic seizures observed during ethanol withdrawal in rats.[179] However, caffeine and theophylline did antagonize the suppressive effects of adenosine analogs on these withdrawal symptoms.[179]

In summary, adenosine seems to play an important role in the regulation of ethanol withdrawal. Agonism of the adenosinergic system, especially via stimulation of A_1 adenosine receptors, reduces some of the withdrawal symptoms that occur after acute or chronic ethanol administration. More importantly, pharmacological antagonism or genetic deletion of the adenosine A_1 and/or A_{2A} receptors could have a role in prevention of withdrawal during ethanol intake.[180,186]

Nevertheless, most of these studies have employed manipulations affecting specific adenosine receptor subtypes rather than caffeine itself, and therefore have not directly assessed the popular belief that a cup of strong coffee can antagonize some of the symptoms of ethanol withdrawal, especially after an acute episode of alcohol consumption in nonalcoholic individuals.

Future Directions

After reviewing the literature on the caffeine–ethanol interactions, one can see that a significant body of work has been performed. However, a clear pattern of results does not easily emerge. Further experiments are needed to establish the specific range of doses, patterns of administration, sex differences, and other factors that could clarify some of the apparent contradictions in the results observed in many of the studies presented above.

More importantly, there is a dearth of studies about the interactions of both agents on processes that are particularly relevant for addiction, such as Pavlovian conditioning, habit formation, or motor sensitization, which seem to contribute to the acquisition and intensification of a compulsive drug-seeking behavior.[38,40] Although sensitization of locomotor activity by caffeine as well as cross-sensitization with other drugs such as amphetamine[187] and nicotine[188] has been observed, so far there are no studies of possible cross-sensitization between ethanol and caffeine. In fact, preliminary studies from our laboratory show that caffeine reduces locomotion in animals repeatedly exposed to a sensitizing dose of ethanol.[189] Further, the effects of the caffeine–ethanol interactions on learning processes are not well understood, in part due to the complexity of learning processes *per se*. Caffeine has been demonstrated to induce a conditioned place preference,[190–192] and also to modulate a conditioned place preference induced by methamphetamine or cocaine.[6] It also would be important to study the effects of caffeine on the acquisition of Pavlovian cues associated with ethanol in this paradigm.

In summary, despite the fact that this area of inquiry has grown increasingly important due to the potential dangers of combining high-caffeine energy drinks with ethanol, animal researchers have only scratched the surface of this complex and multifaceted field. Additional investigations will be required to identify how caffeine and ethanol interact to modulate the behavioral processes related to ethanol consumption, dependence, abuse, and addiction.

Acknowledgments

This research was supported by a grant from Plan Nacional de Drogas (2010/024) and from Ministerio de Educación, FPU (AP2010-3793), Spain.

Author Disclosure Statement

No competing financial interests exist.

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