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Effects of Caffeine on Alcohol Consumption and Nicotine Self-Administration in Rats

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Abstract

Background—Caffeine, alcohol and nicotine are three of the most widespread self-administered psychoactive substances, which are known to be extensively co-administered. However, little is known about the degree to which they may mutually potentiate each other's consumption.

Methods—In the current set of studies, we examined in rats the effect of caffeine administration on alcohol drinking and intravenous (i.v.) self-administration of nicotine. In male alcohol-preferring P rats, caffeine (5, 10 and 20 mg/kg) or the saline vehicle was administered acutely either by subcutaneous (S.C.) injection or orally (PO) by gavage. In a chronic study, the effect of oral caffeine (5 and 20 mg/kg) on alcohol intake over a 10-day period was tested. In another experiment, the effect of acute oral administration of caffeine (20 mg/kg) or saline on saccharin intake (0.2% solution) was determined in P rats. Effects of 20 mg/kg caffeine on motor activity were also determined in P rats. Finally, the effects of acute oral caffeine administration on nicotine self-administration in Sprague-Dawley rats were also determined.

Results—Both routes of administration of caffeine, S.C. and PO, caused a significant dose-related decrease in alcohol intake and preference during free access to alcohol and after 4-day deprivation of alcohol. However, the low dose of 5 mg/kg caffeine increased alcohol intake. Acute oral caffeine also reduced saccharin intake. Acute systemic administration of 20 mg/kg caffeine did not exert a significant effect on motor activity. In Sprague-Dawley rats trained to self-administer i.v. nicotine, acute oral administration of caffeine significantly increased self-administration of nicotine in a dose-related manner.

Conclusions—These results suggest that adenosine receptor systems may play a role in both alcohol and nicotine intake and deserve further study regarding these addictions.

Keywords

Adenosine; Saccharin; Self-administration; Alcohol preferring rats; Alcohol drinking; Addiction; Locomotor activity

CAFFEINE, ALCOHOL AND NICOTINE are three of the most widely used psychoactive drugs in the world. Although these drugs are often used together, the influence of caffeine on consumption of alcohol and nicotine is not fully explored. The aim of the current study was to investigate the effect of caffeine on alcohol consumption in selectively-bred alcohol preferring rats and on intravenous (i.v.) nicotine self-administration in Sprague-Dawley rats.

There is considerable evidence indicating an interaction between alcohol and the adenosine system in the brain. Alcohol blocks re-uptake of adenosine resulting in an increase in extracellular adenosine (Nagy et al., 1990) which leads to the activation of adenosine receptors (Yao et al., 2002). Activation of adenosine A2A receptors inhibits dopamine transmission and blockade of these receptors by adenosine receptor antagonists such as caffeine enhances dopamine release (Shook and Jackson, 2011). Thus, adenosine can play a significant role in the reinforcing effects of alcohol and other drugs of abuse by modulating dopamine which has been implicated in drug seeking behavior (Dohrman et al., 1997; Koob, 2003; Mailliar and Diamond, 2004; Ruby et al., 2010). Adenosine has also been shown to be involved in alcohol-induced ataxia (Dar, 2001).

The caffeine molecule is structurally similar to adenosine and acts as competitive non-selective antagonist for adenosine receptors including adenosine A1 and A2A receptors which suppress several neurotransmitters including monoaminergic transmitters and acetylcholine (Basheer et al., 2004; Fisone et al., 2004; Fredholm et al., 1999; Shook and Jackson, 2011; Tanda and Goldberg, 2000). Caffeine by blocking adenosine receptors enhances dopamine transmission in the dopaminergic terminals (Ferre et al., 2008; Shook and Jackson, 2011). Thus, considering the role of the dopaminergic systems in both alcohol and nicotine self-administration (Di Chiara, 2000; Koob, 2003; McBride et al., 2003) it is expected to see a change in alcohol and nicotine intake as a result of caffeine or other adenosine receptor antagonists administration.

It has been shown that administration of adenosine A2 receptor antagonist 3,7-dimethyl-propargylxanthine significantly decreases lever pressing for alcohol in a dose-dependent manner in Wistar rats (Thorsell et al., 2007). It has also been demonstrated that the administration of the selective adenosine A2A receptor antagonist, SCH 58261 or the selective A1 receptor antagonist DPCPX, reduces fixed ratio responding for alcohol in inbred alcohol preferring iP rats (Adams et al., 2008) and systemic administration of adenosine A2 receptor antagonist, DMPX, significantly reduces alcohol intake in Long Evans rats (Arolfo et al., 2004) suggesting an important role for adenosine A2 receptors in the regulation of alcohol intake.

However, adenosine receptor antagonist 8-cyclopentyl-1,3-dimethylxanthine (CPT) was not found to have a significant effect on alcohol intake in male Long-Evans rats (Gatch et al., 1999) and pretreatment with an A2A receptor antagonist (ANR 94) increased alcohol intake while A2A agonists (VT 7 and CGS 21680) reduced alcohol intake using a limited access paradigm in a selectively-bred alcohol preferring rats (msP) (Micioni Di Bonaventura et al., 2012). Acute systemic IP administration of caffeine at a dose of 5 mg/kg has been shown to increase alcohol intake, while doses of 2.5 and 10 mg/kg showed no effects on alcohol intake in outbred Wistar rats using a limited 1-hr access paradigm (Kunin et al., 2000). Thus, it seems that there is an inconsistency in the literature regarding the effects of adenosine agonist and antagonist on alcohol intake. There are several reasons for this inconsistency. In all of these experiments a limited (1-2 hr) access to alcohol was provided and the animals did not drink long enough to become dependent on alcohol. The other reason might be related to the dose of the drug used. In one study only one dose was used (Gatch et al., 1999). Another reason might be related to the genetic background of these animals. Furthermore, in these studies the effects of these drugs on alcohol intake at different time points after the drug administration were not measured. Considering these issues, we systematically investigated the effect of different doses of caffeine given both acutely and chronically in chronically drinking alcohol preferring (P) rats. Furthermore, we studied the effects of caffeine on alcohol intake following a period of alcohol deprivation in P rats.

Interaction of caffeine and nicotine has been also reported (Tanda and Goldberg, 2000). It has been shown that pretreatment with caffeine markedly potentiates the discriminative-stimulus effects of nicotine in rats without affecting the pharmacokinetics of nicotine (Gasior et al., 2002). Furthermore, chronic oral exposure to caffeine has been shown to facilitate acquisition of self-administration and discrimination of nicotine in rats (Gasior et al., 1999; Shoaib et al., 1999). These findings support previous results from other laboratories that showed chronic caffeine exposure potentiates the reinforcing properties of nicotine in non-human primates (Yaser et al., 1997). Altogether, these findings suggest that caffeine can significantly potentiate the reinforcing properties of nicotine. This may explain the positive correlation that has been reported in several studies between coffee drinking and smoking in humans. Both anecdotal and clinical reports suggest that heavy smokers tend to drink more coffee than non-smokers and smokers smoke more while drinking coffee (Brown and Benowitz, 1989; Emurian et al., 1982; Istvan and Matarazzo, 1984; Tanda and Goldberg, 2000). However, it should be noted that there are some epidemiological and clinical data suggesting no causal correlation between smoking and coffee drinking (Bundey et al., 1993; Istvan and Matarazzo, 1984; Swanson et al., 1994).

Since caffeine is so widely consumed, it is important to know the effect of caffeine on consumption of other potentially addictive drugs such as alcohol and nicotine. Given the fact that these three drugs are often used together, the present study was designed to determine whether caffeine would alter consumption of alcohol or nicotine. It was hypothesized that caffeine administration would reduce alcohol intake, but would increase nicotine self-administration.

MATERIALS AND METHODS

Subjects

Adult male selectively-bred alcohol preferring (P) rats (n=18) supplied by the University of Indiana were used for alcohol and saccharin studies and adult male Sprague-Dawley rats (n=9) were used for the nicotine study. A separate group of female P rats (n=12) were used for the locomotion study. Rats were maintained in a standard laboratory with controlled temperature of 21 ± 2 °C and humidity of 50 ± 10 and reversed light cycle (lights off: 0700-2200). P rats were housed individually in specialized cages that were fitted with two 100-ml graduated Richter tubes for the recording of water and alcohol (10%, v/v) or water and saccharin intake. The P rats were initially exposed to a solution of 10% alcohol for three consecutive days, and then had a free choice between water and alcohol for the remainder of the study (Rezvani et al., 2009; 2010).

Drug Preparation

Caffeine (1,3,7, trimethylxanthine) was dissolved in saline solution and administered S.C. (1 ml/kg) or orally by gavage (4 ml/kg) at doses of 5, 10 and 20 mg/kg. Saccharin was dissolved in tap water at a concentration of 0.2%. Nicotine tartrate was dissolved in saline solution at the concentration of 0.03 mg/kg/infusion and its pH was adjusted to 7.0 with NaOH. The nicotine dose was calculated as base. All drug compounds were purchased from Sigma, St. Louis, MO, USA.

Experimental Protocol

The following experiments were carried out to study the effects of caffeine on alcohol intake and preference and motor activity in P rats and on nicotine self-administration in Sprague Dawley rats.

1. Effects of Caffeine on Alcohol Intake

Acute Study—After the rats exhibited a stable and reliable baseline for alcohol and water intake for several weeks, they were given 5, 10, and 20 mg/kg caffeine or an equal volume of saline subcutaneously following a counterbalanced order 15 min before exposure to alcohol. In another experiment, the effects of oral administration of the same doses of caffeine were determined. Both alcohol and water consumption as well as alcohol preference were recorded at 2, 4, 6 and 24 hr after caffeine administration.

Chronic Study—Based on the outcome of the acute dose-response study, doses of 5 and 20 mg/kg caffeine, with an administration volume of 4 ml/kg, were selected for the chronic study to be administered orally for 10 consecutive days. Upon the completion of the acute study and after re-establishment of a stable baseline for alcohol and water intake, animals were given an oral dose of 5 mg/kg, 20 mg/kg caffeine or saline by gavage. All animals received all treatments following a counter-balanced design. Alcohol and water intakes were recorded at 2, 4, 6 and 24 hr. after each treatment.

Post-deprivation Study—Studies with P rats have shown that a significant increases in alcohol intake following a period of alcohol deprivation (Rodd-Henricks et al., 2000). This post-deprivation paradigm has been used to gauge the potency of anti-craving compound on suppressing the enhanced craving seen after alcohol deprivation (Rezvani et al., 2009; 2012). We utilized this paradigm to test the efficacy of caffeine on alcohol intake. After 4 days of alcohol deprivation and 15 min before the re-exposure to alcohol, rats were injected S.C. with 20 mg/kg caffeine or the vehicle. Alcohol and water intake were measured at 2, 4, 6 and 24 hr after alcohol re-exposure. All rats went through alcohol deprivation 2 times with treatments in a counter-balanced order. All P rats (n=18) received all treatments following a counter-balanced design.

Saccharin Study—To determine the selectivity of caffeine effects on alcohol intake, the effects of a high dose of caffeine on saccharin preference was also assessed. P rats were withdrawn from alcohol and were put on two-bottle choice of water and a solution of 0.2% (w/v) saccharin for 4 consecutive days. After the establishment of stable baseline for saccharin intake, rats were orally administered with saline or 20 mg/kg caffeine in a volume of 4 ml/kg and saccharin and water intake were recorded at 2, 4, 6 and 24 hr after the treatment. The interval between treatments was 2 days.

2. Effects of Caffeine on Nicotine Self-administration

Before beginning nicotine self-administration, the Sprague Dawley rats (n=9) were trained for three sessions on lever pressing in an operant box for food reinforcement. Then rats, under anesthesia, were fitted with an i.v. catheter for self-administering nicotine (0.03 mg/kg/infusion) on an FR1 schedule for five consecutive sessions. After training for nicotine self-administration, the effects of an acute oral dose of caffeine (5, 10 and 20 mg/kg) or saline on nicotine self-administration was determined following a repeated measures counter-balanced design. The number of i.v. nicotine infusions per session (45 minutes) was recorded as a measure of nicotine self-administration (Levin et al., 2010; Rezvani et al., 2010).

3. Effect of Caffeine on Locomotor Activity

In this experiment the effect of caffeine on locomotor activity was assessed. P rats were injected S.C. either with saline or 20 mg/kg caffeine about 15 min before testing. A computerized Figure-8 apparatus was used to measure the locomotor activity. The movement of rats was indexed by breaking the photobeams. The number of photobeam

breaks in each five-minute block in a one-hour session was tallied by a microcomputer. The average activity counts across the 1-hour session was served as a measure of activity.

Statistical Analysis—The drug self-administration data were evaluated by analysis of variance for repeated measures, with factors of caffeine dose, time after caffeine administration and day of chronic administration. Planned pair-wise comparisons were made between the control condition and each caffeine dose. The cut-off for significance was $p < 0.05$, two-tailed.

RESULTS

Acute Effects of Caffeine on Alcohol Intake

Subcutaneous administration—The main effect of S.C. administration of caffeine in reducing alcohol intake was significant ($F(2, 51)=134.96$, $p < 0.0005$). Compared with saline, subcutaneous administration of caffeine at 20 mg/kg significantly ($p < 0.0005$) reduced alcohol intake at 6 and 24 hrs. 10 mg/kg caffeine reduced alcohol intake significantly ($p < 0.001$) only at 24 hr. Subcutaneous administration of 5 mg/kg caffeine did not exert significant effects on alcohol intake at any time point (Fig. 1A). Caffeine (S.C.) produced a significant ($F(3,51)=15.75$, $p < 0.0005$) main effect with the 20 mg/kg caffeine dose significantly ($p < 0.0005$) reducing average alcohol preference and the two lower doses not having significant effects on average preference. There was also a significant interaction of caffeine x time ($F(9,153)=3.11$, $p < 0.005$). Tests of the caffeine doses at each time point showed that 20 mg/kg significantly reduced alcohol preference at 2 hr ($p < 0.05$), 4 hr ($p < 0.0005$), 6 hr ($p < 0.0005$) and 24 hr ($p < 0.0005$). The 10 mg/kg caffeine dose significantly reduced alcohol preference at 4 hr ($p < 0.0005$) and 24 hr ($p < 0.05$). The 5 mg/kg caffeine dose did not affect alcohol preference at any time point (Fig. 1B).

Oral administration—The main effect of the oral administration of caffeine on alcohol consumption was significant ($F(3,51)=19.24$, $p < 0.0005$). There was a significant caffeine x time interaction ($F(9,153)=16.21$, $p < 0.0005$). Alcohol consumption was significantly ($p < 0.005$) increased by the oral administration of 5 mg/kg caffeine at 2 ($p < 0.05$), 4 ($p < 0.05$), 6 ($p < 0.005$) and 24 hr ($p < 0.0005$). PO administration of 10 mg caffeine significantly decreased alcohol self-administration at 6 ($p < 0.05$) and 24 hr ($p < 0.0005$). 20 mg/kg of caffeine significantly reduced alcohol consumption at 4, ($p < 0.0005$) 6 ($p < 0.0005$) and 24 hr ($p < 0.0005$). With regard to percent preference for alcohol, caffeine caused a significant ($F(3,51)=17.45$, $p < 0.0005$) main effect, with the 20 mg/kg dose significantly ($p < 0.0005$) reducing alcohol preference averaged over all time points. There was also a significant caffeine x time interaction ($F(9,153)=2.26$, $p < 0.025$). Simple main effects comparisons of caffeine dose effects at each time point showed that the high 20 mg/kg dose significantly reduced alcohol preference at 2 hr ($p < 0.005$), 4 hr ($p < 0.0005$), 6 hr ($p < 0.0005$) and 24 hr ($p < 0.0005$). The intermediate 10 mg/kg dose caused a significant reduction in alcohol preference at 4 hr ($p < 0.005$) and 6 hr ($p < 0.0005$). The low 5 mg/kg caffeine dose caused a significant increase in alcohol preference at 2 hr ($p < 0.005$) (Fig. 2B).

Chronic Effects of Caffeine on Alcohol Intake

Chronic oral caffeine caused a significant ($F(2,34)=11.75$, $p < 0.0005$) main effect on alcohol intake (Fig. 3A). The higher dose of 20 mg/kg caused a significant ($p < 0.0005$) decrease in alcohol intake over the ten day study whereas the lower 5 mg/kg dose did not have a significant effect relative to control. There was no significant caffeine x day interaction. Percent preference was also significantly ($F(2,34)=15.47$, $p < 0.0005$) reduced by caffeine (Fig. 3B). The higher dose of 20 mg/kg caused a significant ($p < 0.0005$) decrease in alcohol preference averaged over the ten day study whereas the lower 5 mg/kg dose did not have a

significant effect relative to control. There was also a significant interaction of caffeine and day ($F(18,306)=2.48$, $p<0.005$). Comparisons of each caffeine dose vs. control for each day showed that the higher 20 mg/kg dose significantly decreased alcohol preference on days 1 ($p<0.0005$), 2 ($p<0.05$), 3 ($p<0.005$), 4 ($p<0.0005$), 5 ($p<0.0005$), 6 ($p<0.0005$), 7 ($p<0.0005$) and 8 ($p<0.0005$). The 20 mg/kg caffeine dose did not significantly affect alcohol preference on days 9 and 10. The lower 5 mg/kg caffeine dose did not significantly affect alcohol preference on any day.

Alcohol Deprivation Study

Compared with control vehicle, pretreatment with 20 mg/kg caffeine after 4-day alcohol deprivation dramatically ($F(1,17) = 26.70$, $p<0.0005$) reduced alcohol intake. The caffeine x hour interaction was significant ($F(3,51)=40.72$, $p<0.0005$). Caffeine significantly (2 hr $p<0.05$, 4 hr $p<0.0005$, 6 hr $p<0.0005$, 24 hr $p<0.0005$) reduced alcohol intake at all time points (Fig. 4A). Caffeine also reduced average alcohol preference. The main effect of caffeine on alcohol preference was significant ($F(1,17)= 17.88$, $p<0.001$). However, the caffeine x hour interaction was not significant (Fig. 4B).

Acute Effects of Oral Caffeine on Saccharin Intake

Saccharin intake (mg/kg) was significantly ($F(1,17)=5.20$, $p<0.05$) decreased by acute oral administration of 20 mg/kg caffeine compared with vehicle control. There was also a significant caffeine x time interaction ($F(3,51)=10.79$, $p<0.0005$). As shown in Fig. 5A, compared with the control vehicle, 20 mg/kg caffeine given orally significantly ($p<0.0002$) reduced saccharin intake at 6 and 24 hr, but not at the earlier time points. Percent preference for saccharin vs. plain water was also affected by caffeine. The main effect was not significant with this measure, but the caffeine x time interaction was significant ($F(3,51)=3.08$, $p<0.05$). Tests of the caffeine effects at each time point showed that caffeine significantly reduced preference for saccharin at 4 hr ($p<0.05$), 6 hr ($p<0.005$) and 24 hr ($p<0.05$) but not 2 hr (Fig. 5B).

Acute Effects of Caffeine on Nicotine Self-administration

There was a significant ($F(3,48)=2.85$, $p<0.05$) main effect of caffeine on nicotine self-administration. Compared with saline, oral administration of caffeine at 10 ($p<0.05$) and 20 mg/kg ($p<0.025$) significantly increased nicotine self-administration in Sprague Dawley rats. The 10 mg/kg dose increased nicotine self-administration from 8.22 ± 1.88 infusions per session with saline to 10.78 ± 2.07 with caffeine and 20 mg/kg caffeine raised nicotine self-administration to 11.33 ± 1.66 infusions per session for a 31% and 39% increase, respectively (Fig. 6).

Effect of Caffeine on Locomotor Activity

Compared with the control vehicle, systemic administration of 20 mg/kg caffeine 15 min. before testing did not significantly affect locomotor activity of P rats. The mean activity for caffeine-treated group ($n=6$) was 35.4 photobeam breaks per 5-min block which was not significantly different ($p=0.424$) from 39.2 for the control group ($n=6$).

DISCUSSION

Alcohol, nicotine and caffeine are the three most widely used psychoactive drugs in the world. However, caffeine interaction with alcohol and nicotine intake has not been very much investigated. The present study provides direct causal experimental evidence that caffeine significantly alters alcohol and nicotine intake in rats. Caffeine interactions with alcohol and nicotine intake are quite different in nature. Caffeine has a biphasic dose-effect

on alcohol intake with a low dose of 5 mg/kg significantly increasing alcohol intake and higher doses of 10 and 20 mg/kg causing decreases in alcohol intake. In contrast, the same dose range caused a monotonic increase in nicotine self-administration with the 10 and 20 mg/kg doses significantly increasing self-administration of nicotine. Caffeine administration also reduced alcohol intake and alcohol preference after 4-day of alcohol deprivation. Furthermore, chronic oral administration of caffeine significantly reduced alcohol intake and alcohol preference; however, there were indications of diminished effectiveness of caffeine by the end of the ten-day treatment. When tested on another rewarding compound such as non-caloric saccharin solution, it was shown that acute oral administration of caffeine also significantly reduced saccharin intake in P rats. The reduction in saccharin intake by caffeine may be related to the interaction of caffeine with dopaminergic transmission in the nucleus accumbens, an area that has been implicated in the rewarding effects of saccharin (Mark et al., 1994; Sclafani et al., 2011). While these results suggest a potential promise for using adenosine receptor antagonist therapy to reduce alcohol consumption, they also raise a caution for a potential increased risk of nicotine use.

Our findings regarding the effect of caffeine on alcohol intake confirm some of the previous findings demonstrating that adenosine receptor antagonists also reduced alcohol intake in rats (Adams et al., 2008; Arolfo et al., 2004). Although the exact mechanism of interaction between caffeine and alcohol intake is not fully understood, based on the existing scientific literature one can speculate that the interaction between the adenosinergic systems and the dopaminergic systems in the brain may explain our findings on alcohol consumption. Along with other neurotransmitters, dopaminergic systems in the ventral tegmental area (VTA) and the nucleus accumbens have been shown to be involved in excessive drinking in alcohol preferring rats (McBride et al., 1993), as alcohol facilitates dopamine release (Wisse et al., 1993). The adenosine A2A receptors are largely co-localized with dopaminergic D2 receptors in striatum and mesolimbic areas, including core and shell regions of the nucleus accumbens and the tuberculum olfactorium (Fink et al., 1992; Svenningsson et al., 1997) in which the actions of adenosine and dopaminergic receptors mutually antagonized (Vidi et al., 2008). Stimulation of adenosine A2A receptors inhibits dopamine transmission and blockade of adenosine A2A receptors by an adenosine receptor antagonist, such as caffeine, increases dopamine release. Caffeine modulates dopamine signaling in part by its antagonistic effect on adenosine A2A (Ferre et al., 2008) and A1 receptors (Vanattou-Saifoudine et al., 2011). Thus, caffeine by acting at adenosine receptors can diminish or remove the inhibitory tone of adenosine on dopaminergic receptors and consequently enhance dopamine release in dopaminergic terminals (Shook and Jackson, 2011).

Caffeine at doses of 10 and 30 mg/kg given systemically has been shown to increase dialysate dopamine in the shell of nucleus accumbens in rodents (Solinas et al., 2002). It has also been demonstrated that caffeine and A2A antagonists elicit an increase in dialysate dopamine in the medial prefrontal cortex in rats (Acquas et al., 2002). More recent findings from the same laboratory have failed to show an increase in dopamine release in the nucleus accumbens shell due to caffeine administration; however, an increase in dopamine release in prefrontal cortex of rats was confirmed (De Luca et al., 2007). Interestingly, in healthy human subjects it has been shown that caffeine leads to an increase in D2/D3 receptors availability in the ventral striatum measured with PET and [¹¹C]raclopride (Kaasinen et al., 2004). Altogether, it is likely that caffeine administration, by stimulating dopamine release within the reward system in the brain, partially satisfies the need for dopamine in selectively-bred alcohol preferring P rats which have innate reduced dopamine D2 receptors in specific brain regions (McBride et al., 1993). It is possible that caffeine action on the dopamine neurotransmission substitutes for the alcohol's effect on dopamine, as both alcohol and caffeine stimulate dopamine release.

Our findings show that contrary to 10 and 20 mg/kg, the lower dose of 5 mg/kg caffeine increased alcohol intake in P rats. Although the reason for this increase in alcohol intake is not immediately obvious, it might be due to the priming effect of a low dose of caffeine. Indeed, it has been shown that caffeine at low doses exerts a cue-like effect resembling a weak dopaminergic stimulus (Fredholm et al., 1999). A previous study found that, similar to caffeine, systemic administration of an adenosine A2 receptor antagonist DMPX, produced bimodal effects on alcohol intake. A low dose of DMPX increased, while a high dose significantly and dose-dependently decreased alcohol intake in Long-Evans rats (Arolfo et al., 2004). Interestingly, the bimodal effects were not observed in Wistar rats, a strain that has a higher baseline alcohol intake than Long Evans rats (Thorsell et al., 2007). It has been suggested that this bimodal effect may be due to the non-selective nature of the antagonist on A2 receptors (Ruby et al., 2010). It would be of interest to see if this dose or lower doses of caffeine will increase alcohol intake in rats that normally have a low preference for alcohol. As mentioned earlier in the introduction, adenosine A1 receptors have also been shown to play a role in the regulation of alcohol intake (Adams et al., 2008). Thus, the possible role of adenosine A1 receptors should not be underestimated as it has been shown that caffeine regulates dopamine release in striatal tissue slices, via inhibition of adenosine A1 receptors, an effect that can be blocked with 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), a specific adenosine A1 receptor antagonist (Vanattou-Saifoudine et al., 2011).

Chronic administration of 20 mg/kg caffeine produced significant reductions in both alcohol intake and alcohol preference. However, there were indications of reduced efficacy of caffeine towards the end of the treatment. A similar finding has been reported for the effect of naloxone, an opiate antagonist, on alcohol intake in rats (Overstreet et al., 1999). The reduced efficacy of caffeine may have a pharmacokinetics or a pharmacodynamics nature that can be overcome by escalating dosing or imposing a drug-holiday for few days. It is also possible that this phenomenon may not occur in human as the rate of metabolism in human is several folds lower than that in rats.

Caffeine at high doses has potent behaviorally stimulating properties and one may suggest that at 20 mg/kg it was behaviorally stimulating enough to be distracting and aversive. However, our findings on the effects of caffeine on motor activity do not support this notion. Our findings showed no significant differences between the motor activity of saline-treated and caffeine-treated rats. Thus, the reduction in the alcohol intake cannot be attributed to the overstimulation and distracting effects of caffeine. Although at this point we do not know if the effects of caffeine on alcohol intake or motor activity in P rats are sex-dependent, it has been shown that the effects of two other stimulants, cocaine and nicotine, on motor activity are not sex-dependent in P rats (Zachary A. Rodd, personal communication).

The dose range selected for this study was relatively comparable with the amount of caffeine used by humans. According to Bunker and McWilliams (1979), a 7 oz. cup of coffee contains 115-175 mg coffee. If a 70 kg individual consumes 3 cups of coffee a day, this would translate into 4.8-7.5 mg/kg. Considering much higher rate of metabolism in rats (about 5 times higher than humans), the doses were used in the current study are comparable with human doses.

Regarding the interaction of caffeine and nicotine, our data are in agreement with previous findings in other laboratories (Gasior et al., 2002; Shoaib et al., 1999) showing that pre-treatment with caffeine potentiates nicotine self-administration in a dose-dependent manner. It is also known that smokers are more liable to smoke when drinking coffee (Fredholm et al., 1999). Lane has shown that the rate of smoking is higher during the period that caffeine-containing beverages are consumed (Lane, 1996). In this regard, nicotine is similar to alcohol and has been shown to increase dopamine in the nucleus accumbens in rats (Di

Chiara, 2000; Pontieri et al., 1996; Tanda and Goldberg, 2000). Caffeine also has been shown to increase dopamine release by blocking the endogenous inhibitory action of adenosine on dopaminergic terminals (Solinas et al., 2001). One possible mechanism is that inducing dopamine release by pre-treatment with caffeine may make nicotine more reinforcing in which results in more nicotine infusion in Sprague Dawley rats. Nicotine compared to alcohol intake may differ in response to 10 and 20 mg/kg of caffeine because of the substantially lower reinforcing efficacy of nicotine may leave way for enhancing effects of added dopamine effects.

It has been shown that caffeine at low dose markedly enhances responding to low dose of cocaine, even though it reduces cocaine-induced responding at high doses (Harland et al., 1989). Caffeine, considered a mild stimulant, has been shown to facilitate cocaine-induced conditioned place preference (Tuazon et al., 1992) and increase the rate of cocaine self-administration in rats (Horger et al., 1991) presumably by sensitizing rats to the reinforcing effects of cocaine (Fredholm et al., 1999). Thus, considering the fact that nicotine is also a mild stimulant, it is possible that caffeine exerted the same priming effects when it was given prior to nicotine-self-administration, leading to an increase in nicotine intake.

One other explanation for observing opposite effects of caffeine on alcohol intake and nicotine self-administration may relate to the fact that we used two different rat lines for these particular experiments. P rats are genetically different from Sprague Dawley rats. It has been shown that densities of dopamine D2 receptors are reduced in specific brain regions of P rats (McBride et al., 1993). It is possible that this and other reported innate deficiencies in P rats may contribute to these opposite effects seen with alcohol and nicotine intake. Furthermore, these two lines of rats had different history as P rats were consuming alcohol for several weeks before being treated with caffeine while Sprague Dawley rats did not have any exposure to alcohol. This difference in these two lines of rats may have contributed to the differential effects of caffeine on alcohol and nicotine intake. One other important issue to be considered is the differential effects of alcohol and nicotine on nicotinic receptors. Nicotine administration desensitizes nicotinic receptors which may directly or indirectly influence the effects of caffeine.

The other possible explanation is the pharmacokinetic interaction between caffeine and nicotine. However, the observed effect of caffeine on nicotine self-administration is unlikely to be of pharmacokinetic nature because acute and chronic administration of caffeine with the threshold dose of nicotine (0.05 mg/kg) has been shown to have no significant effect on plasma levels of nicotine or its metabolite cotinine in rats (Gasior et al., 2002), suggesting a central interaction between these drugs.

Caffeine has widespread effects on the activity of the nervous system and neurotransmitters. It has been shown that caffeine, in addition to dopamine, also increases the turnover of other monoaminergic neurotransmitters such as serotonin and noradrenalin (Fredholm et al., 1999) which may play different roles in alcohol and nicotine addiction. Also, effects of caffeine on cerebral glucose utilization (Nehlig, 1986), its central vasoconstrictive effect (Nehlig, 1994) and its other, as yet unknown, actions may contribute to its effect on alcohol and nicotine intake. In conclusion, these preclinical studies with caffeine suggest that adenosine receptor systems in the brain may play an important role in both alcohol and nicotine intake and deserve further preclinical and clinical studies regarding these and other addictions.

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Figure 1.

Acute effects of subcutaneous injection of caffeine on alcohol consumption (g/kg) (panel A) and alcohol percent preference vs. water (panel B) (mean±sem), N=18.

Figure 2.

Acute effects of oral administration of caffeine on alcohol consumption (g/kg) (panel A) and alcohol percent preference vs. water (panel B) (mean±sem), N=18.

Figure 3. Chronic effects of oral administration of caffeine on alcohol consumption (g/kg) (panel A) and alcohol percent preference vs. water (panel B) (mean±sem), N=18.

Figure 4.

Acute effects of subcutaneous administration of caffeine on alcohol intake (g/kg) (panel A) and alcohol preference (panel B) after 4-day of alcohol deprivation (mean±sem), N=18.

Figure 5. Acute effects of subcutaneous injection of caffeine on saccharin intake (ml/kg) (panel A) and saccharin preference (panel B) (mean±sem), N=18.

Acute Caffeine Effects on IV Nicotine Self-Administration

Figure 6.

Acute effects of oral administration of caffeine on nicotine self-administration (number of infusions per session; each infusion contains 0.03 mg nicotine base/kg) (mean±sem), N=9.