

Nicotine Decreases Blood Alcohol Concentrations in Adult Rats: A Phenomenon Potentially Related to Gastric Function

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Background: In spite of the fact that drinking and smoking often occur together, little is known about the pharmacokinetic interaction between alcohol and nicotine. Previous research in neonatal rats demonstrated that nicotine reduces blood alcohol concentrations (BACs) if alcohol and nicotine are administered simultaneously. However, it is unclear whether such a phenomenon can be observed in adult subjects, given the fact that there is an ontogenetic difference in alcohol metabolism.

Methods: A range of nicotine doses (0, 0.25, 0.5, 1, 2, 4, and 6 mg/kg) were administered individually with an alcohol dose (4 g/kg) via intragastric (IG) intubation to adult female rats, and the resultant BACs were measured at various time points following drug administration. Furthermore, the hypothesis that nicotine's role in reducing BACs is mediated through factors related to gastric function was examined by comparing the resultant BACs after an IG intubation or intraperitoneal (IP) injection of alcohol.

Results: The results from this study showed significant nicotine dose-related decreases in BACs with 0.5, 1, 2, 4, and 6 mg/kg doses of nicotine at the various time points assessed. This effect, however, occurred only when alcohol was administered via IG intubation, but not after an IP injection of alcohol.

Conclusions: These results suggest that the nicotine-induced decrease in BAC may be related to gastric function. One possible explanation was related to nicotine's action in delaying gastric emptying. The longer the alcohol was retained in the stomach, the more likely that the alcohol would be metabolized by gastric alcohol dehydrogenase before its absorption into the bloodstream by the small intestine (the major site of alcohol absorption).

Key Words: Cigarette Smoking, Ethanol, First-pass Metabolism, Gastric Emptying.

ALCOHOL AND NICOTINE are the 2 most commonly used drugs in our society (Anthony and Echeagaray-Wagner, 2000). The combined use of alcohol and nicotine (most often in the form of cigarette smoking) is especially prominent in alcoholic individuals and heavy smokers (Istvan and Matarazzo, 1984; NIAAA, 1998; Shiffman and Balabanis, 1995; Shiffman et al., 1994; Sobell et al., 1990). The reasons for this frequently observed co-use of alcohol and nicotine are not well understood, although recent research has suggested that dependence on these 2 drugs is probably genetically related (Madden and Heath, 2002; True et al., 1999). Neverthe-

less, both in vivo and in vitro studies suggest that "cross-tolerance" between alcohol and nicotine is a possible result of the action of nicotinic cholinergic receptors (Collins, 1996; Collins et al., 1988; Dohrman and Reiter, 2003; Lopez et al., 2001; Schaefer and Michael, 1992). A decrease in the sensitivity (reward) of either drug may facilitate the increased usage of the other drug to achieve the desired effects.

Regardless of the causes for the prevalence of the co-use of alcohol and nicotine, the fact remains that the concurrent use of these drugs represents a greater health concern than either individually. For example, the concurrent use of alcohol and cigarettes (nicotine) led to more severe gastric ulceration than either drug alone (Ko and Cho, 2000), and smoking worsened alcohol-mediated pancreatic inflammation (Hartwig et al., 2000). A more recent finding reported that cigarette smoking significantly increases the risk of pancreatic calcifications among alcoholic individuals (Maisonneuve et al., 2005). Furthermore, the combined use of alcohol and tobacco products increased the incidence of various cancers (Andre et al, 1995; Ebbert et al., 2005; Levi, 1999). According to the Alcohol Alert from NIAAA (1998), the pharmacokinetic interaction between alcohol and nicotine may be partially responsible

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for the co-use of these 2 drugs. For example, if the presence of nicotine increases alcohol metabolism, thereby decreasing the circulating alcohol in the physiological system, it could result in a decrease in the alcohol effect. The outcome of such a decrease in expected alcohol effect would be similar to the consequence of tolerance, a decrease in sensitivity (reward). Therefore, it is also important to understand whether the metabolism of either drug is affected by the presence of the other. Furthermore, recognizing the potential pharmacological interaction between drugs is important for assessing overall toxicity. For instance, the combined use of alcohol and cocaine leads to the formation of cocaethylene endogenously through hepatic carboxylesterase (Boyer and Petersen, 1992). Cocaethylene is a pharmacologically active compound and has been suggested to be responsible for enhanced euphoria and increased toxicity following the co-use of alcohol and cocaine (McCance et al., 1995; Pennings et al., 2002). Thus, without weighing the impact of cocaethylene, any measurement of the interactive effect of alcohol and cocaine could not be accurately interpreted. Similarly, understanding the basic pharmacological interaction between alcohol and nicotine may be crucial for the interpretation of the toxicity, teratogenicity, or addictive behavior resulting from their co-usage.

One interesting and unexpected discovery from our previous findings regarding the coexposure of alcohol and nicotine to neonatal rats is that the blood alcohol concentrations (BACs) were reduced in the presence of nicotine (Chen et al., 1998, 2001). The mechanism of nicotine's ability to lower BACs is not fully understood. Previously, it was hypothesized that, due to nicotine's ability to decrease the rate of gastric emptying (Nowak et al., 1987; Scott et al., 1993), alcohol is retained in the stomach longer and is therefore subjected to increased metabolism by gastric alcohol dehydrogenase (gADH). As the majority of alcohol is absorbed into the bloodstream through the small intestine rather than in the stomach (Holt, 1981; Johnson et al., 1991), this increased metabolism of alcohol by gADH would therefore result in a reduced amount of alcohol being absorbed into the bloodstream, thereby leading to a decrease in BAC.

It has been shown that there is an ontogenetic difference in alcohol metabolism (Silveri and Spear, 2000). Therefore, it is important to reevaluate whether the pharmacokinetic interaction between alcohol and nicotine that was previously observed in neonates is present in adult rats. In this study, various nicotine doses were tested to investigate whether there was a dose-related response in nicotine-induced decreases in BACs. More importantly, this study compared the route of alcohol administration [intragastric (IG) vs intraperitoneal (IP)] to confirm that the nicotine-induced decreases in BACs were associated with gastric-related mechanisms. Therefore, it was hypothesized that the BAC would not be affected by the presence of nicotine if alcohol was delivered via the IP route of

administration, bypassing alcohol metabolism by gADH in the stomach.

METHODS

This study consisted of 3 individual experiments: Experiment 1 evaluated the ability of relatively high doses of nicotine to lower BACs in adult rats. Experiment 2 was conducted independently and was similar to Experiment 1, except that lower doses of nicotine were used to evaluate the threshold dosage that would lead to nicotine-induced decreases in BACs. The reason for conducting Experiments 1 and 2 independently was that Experiment 2 was carried out following the data collection and analysis of Experiment 1, which showed no significant nicotine dose-related decreases in BAC. Experiment 3 was designed to determine whether the ability of nicotine to lower BACs is related to gastric function. This was achieved by comparing BACs after IG intubation and IP injection of alcohol.

Subjects

Eighty-one female adult Sprague-Dawley rats were used in this study. The rats were housed in pairs until the day of experimentation in a vivarium at Texas A&M Health Science Center with a 12:12-hour light/dark cycle. On the day of experimentation, the rats were weighed and singly housed throughout the entire period that blood samples were taken for BAC analysis. The experimental procedures used in this study were approved by the University Laboratory Animal Care Committee at Texas A&M University.

Alcohol and Nicotine Administration

Depending on the experiment assigned, animals were given alcohol via either an IG intubation (4 g/kg, 40% w/v alcohol solution in water) or an IP injection (2 g/kg, 20% w/v alcohol solution in sterile 0.9% saline). The rationale for a lower alcohol dose in the IP injection versus the IG intubation was to ensure that the resultant peak BACs would be similar between the 2 administration routes. It has been shown that similar doses of alcohol administered via an IP injection resulted in a higher peak BAC than if the alcohol was administered via an IG intubation (Livy et al., 2003).

Nicotine (nicotine-free base, Sigma Chemical Co., St. Louis, MO) was administered in doses of 0, 0.25, 0.5, 1, 2, 4, or 6 mg/kg (IG intubation) with alcohol. The nicotine was dissolved in either alcohol solution or water (in the case of the group receiving IP injections of alcohol).

Experiment 1: High-dose Nicotine Experiment

In Experiment 1, 25 adult female rats were intubated intragastrically with 4 g/kg alcohol, either with or without nicotine. The nicotine doses were 0, 2, 4, or 6 mg/kg [0 nicotine (NIC), 2 NIC, 4 NIC, and 6 NIC, respectively], which were identical to those used in a previous neonatal study (Chen et al., 2001). Twenty microliters of tail blood was taken from each rat at each sampling time point of 30, 60, 120, 180, 270, 360, and 450 minutes after the IG intubation procedure. The blood samples were collected and analyzed by headspace gas chromatography (Varian, Model 3400, Palo Alto, CA) as described previously (Chen et al., 2001). The BACs were reported as mg/dL.

Experiment 2: Low-dose Nicotine Experiment

Experiment 2 consisted of 26 adult female rats. The experimental procedures performed on these rats were identical to those described in Experiment 1, except that they received 0, 0.25, 0.5, or 1 mg/kg nicotine (0 NIC, 0.25 NIC, 0.5 NIC, and 1 NIC, respectively). Blood

samples (tail blood) were taken and analyzed in a similar manner as in Experiment 1, except for the addition of another time point at 90 minutes after the IG intubation.

Experiment 3: IG Versus IP Administration Experiment

This experiment compared nicotine's effects on BACs after either IG or IP administration of alcohol, and 30 rats were divided into 4 treatment groups in this experiment [IP ethanol (EtOH), IP EtOH/NIC, IG EtOH, and IG EtOH/NIC]. Nicotine (6 mg/kg) was administered IG simultaneously with either an IG (4 g/kg) or an IP (2 g/kg) dose of alcohol. The 6 mg/kg nicotine dose used in this experiment was based on the results of Experiment 1 and a previous study (Chen et al., 2001). The hypothesis was that nicotine given via the IG, but not IP, route of administration would increase the amount of alcohol metabolized by gADH (through the delay in gastric emptying) before alcohol absorption into the bloodstream in the small intestine. Twenty microliters of tail blood was taken as described previously at 30, 60, 90, 120, 180, 270, 360, and 450 minutes after drug administration, and the blood samples were analyzed by headspace gas chromatography as described previously.

Statistical Analyses

The BAC data (except peak BAC data) were analyzed using a mixed ANOVA, with drug treatment (with or without nicotine) as the between factor and time as the within factor. To analyze peak BACs among the different treatment groups, the peak BAC from each individual subject, regardless of time point, was used in the analyses. Although a mean peak BAC could be determined from the averaged BACs at all time points, not all subjects necessarily peaked at the same time. The peak BAC data from each experiment were analyzed using a 1-way ANOVA, with drug treatment as the only between factor. Post hoc analyses, if applicable, were conducted using Fisher's protected least significant difference (PLSD) test. All α levels were set at 0.05.

RESULTS

Experiment 1: High-dose Nicotine Experiment

The ANOVA showed main effects of drug treatment and time [$F(3, 21) = 34.15$ and $F(6, 126) = 95.78$, $ps < 0.0001$, respectively]. Fisher's PLSD post hoc comparisons revealed that the BACs in the 2, 4, and 6 NIC groups were significantly lower than those in the 0 NIC group across all time points and that there were no differences in BACs among the 3 nicotine-treated groups. As to the main effect of time, this finding was expected as alcohol would be metabolized and eliminated from the physiological system, resulting in a systematic decrease in BAC as a function of time. Furthermore, the analysis revealed a significant interaction between drug treatment and time [$F(18, 126) = 5.29$, $p < 0.0001$], suggesting that the magnitude of nicotine-mediated decreases in BACs was not uniform across all time points, with less robust mean BAC differences at the beginning and the end of the BAC curves (Fig. 1). In other words, nicotine not only lowered the BACs at all time points assessed but also changed the general shape of the BAC curves.

The one-way ANOVA performed on the peak BAC data showed a main effect of drug treatment [$F(3, 21) = 13.91$, $p < 0.0001$]. Further post hoc tests revealed that the mean

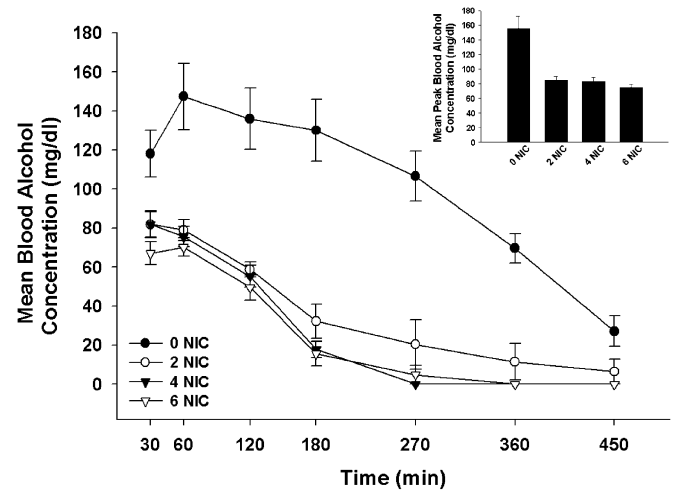


Fig. 1. Mean blood alcohol concentration (BAC) as a function of nicotine dose (0, 2, 4, and 6 mg/kg) and time in Experiment 1. The bar graph inset represents the mean peak BACs from all treatment groups (0 NIC, 2 NIC, 4 NIC, and 6 NIC). The vertical lines represent the standard errors of the mean (SEMs).

peak BAC in the 0 NIC group was significantly higher than those in the 2 NIC, 4 NIC, and 6 NIC groups (Fig. 1, inset). However, there were no differences among the 3 nicotine-treated groups.

Experiment 2: Low-dose Nicotine Experiment

The ANOVA for the BAC data from Experiment 2 revealed significant main effects of drug treatment and time [$F(3, 22) = 3.82$ and $F(7, 154) = 11.66$, $p < 0.05$, respectively]. There was no interaction between drug treatment and time factors. Further Fisher's PLSD post hoc comparisons revealed that the 0.5 NIC and 1 NIC groups were both significantly different from the 0 NIC and 0.25

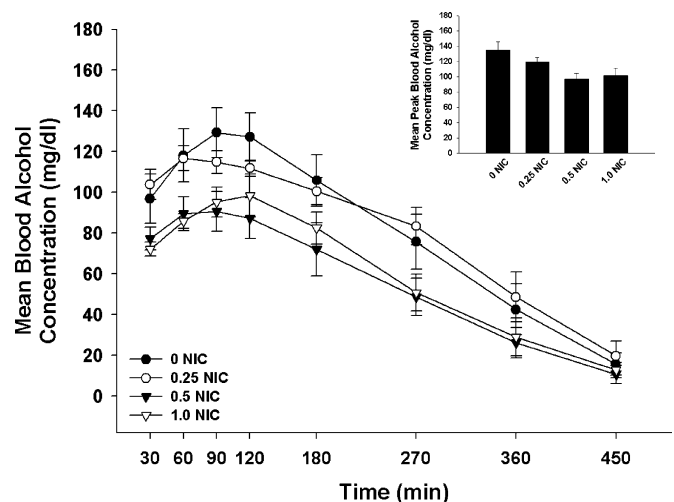


Fig. 2. Mean blood alcohol concentration (BAC) as a function of nicotine dose (0, 0.25, 0.5, and 1 mg/kg) and time in Experiment 2. The bar graph inset shows the mean peak BACs from all treatment groups (0 NIC, 0.25 NIC, 0.5 NIC, and 1 NIC). The vertical lines represent the standard errors of the mean (SEMs).

NIC groups (Fig. 2) and that there was no difference between the 0 NIC and 0.25 NIC groups or between the 0.5 NIC and 1 NIC groups.

For the peak BAC data, the ANOVA yielded a main effect of drug treatment [$F(3, 22) = 3.78, p < 0.05$]. The post hoc comparisons showed a significant difference in mean peak BACs between 0 NIC and either the 0.5 NIC or the 1 NIC group (Fig. 2, inset). However, the mean peak BAC in the 0.25 NIC group was not significantly different from that in the 0 NIC group.

Experiment 3: IG Versus IP Administration Experiment

The ANOVA conducted on the data from the IG treatment yielded main effects of drug treatment and time [$F(1, 12) = 20.36$ and $F(7, 84) = 17.25, p < 0.05$, respectively] and an interaction of treatment and time [$F(7, 84) = 10.77, p < 0.05$]. As illustrated in Fig. 1, the ability of nicotine to lower the BACs was dependent on the time assessed, with less significant differences at the beginning and the tail of the BAC curves between the IG EtOH and IG EtOH/NIC

groups (Fig. 3A). The second ANOVA performed on the data from the IP treatment revealed a main effect of time and an interaction between treatment and time [$F(7, 98) = 494.61$ and $F(7, 98) = 6.12, p < 0.05$, respectively], but not of drug treatment (Fig. 3B). Further pairwise tests showed that the BAC curves between the EtOH and EtOH/NIC groups diverged starting at the 120-minute time point ($p = 0.046$) and became significantly different at both 180 and 270-minute time points ($p < 0.01$), with the mean BACs in the EtOH/NIC groups being higher than those in the EtOH group. However, this transient effect of nicotine in inhibiting alcohol metabolism was diminished 360 minutes after the beginning of the drug treatment.

For the peak BAC analyses, 2 *t*-tests were used to reveal whether there was a difference in peak BACs between the IG EtOH and the IG EtOH/NIC groups or between the IP EtOH and the IP EtOH/NIC groups. The tests showed a significant difference in mean peak BAC between the IG EtOH and the IG EtOH/NIC groups ($t_{12} = 3.75, p < 0.01$), but not between the IP EtOH and IP EtOH/NIC groups, suggesting that nicotine did not alter the peak BAC if alcohol was administered via a route bypassing the gastric metabolism.

DISCUSSION

The findings from Experiments 1 and 2 demonstrated clearly that nicotine effectively lowers the peak BACs in adult rats. Furthermore, the capability of nicotine to lower the peak BACs appears to be dose related (Fig. 4), with 52 and 30% decreases in peak BAC following 6 and 0.5 mg/kg nicotine treatment, respectively. Among all nicotine doses tested in this study, the 0.25 mg/kg nicotine dose did not significantly lower the BACs across all time points examined. These findings indicated that there is a significant pharmacokinetic interaction between alcohol and nicotine following the experimental regimen used in this

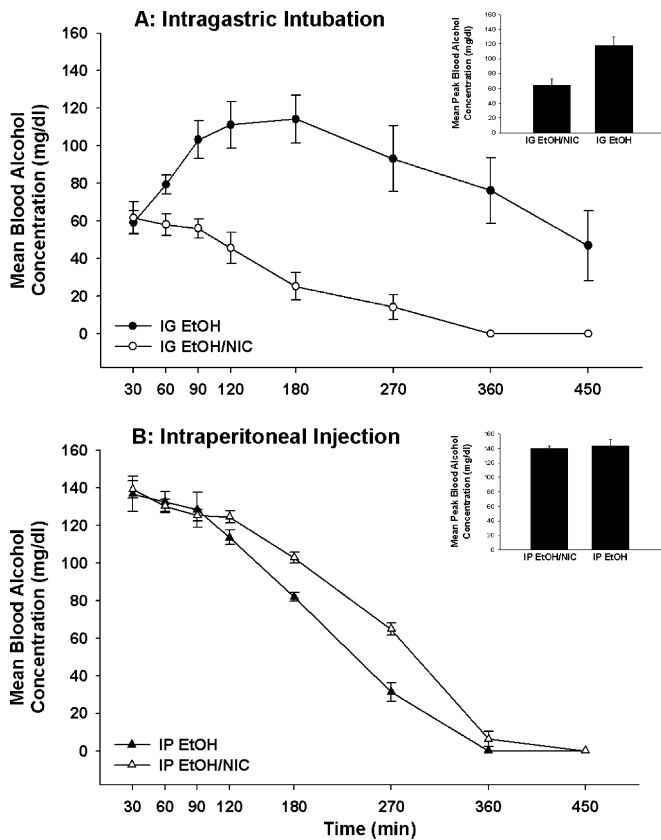


Fig. 3. (A) Mean blood alcohol concentration (BAC) following intragastric (IG) intubation of alcohol with nicotine (IG EtOH/NIC) or without nicotine (IG EtOH). (B) Mean BAC following intraperitoneal (IP) injection of alcohol with nicotine (IP EtOH/NIC) or without nicotine (IP EtOH). Note that nicotine was given via IG intubation in both IG EtOH/NIC and IP EtOH/NIC groups, even though the route of administration for alcohol was different between these 2 groups (IG vs IP). The bar graph insets represent the mean peak BACs. The vertical lines show the standard errors of the mean (SEMs). EtOH, ethanol; NIC, nicotine.

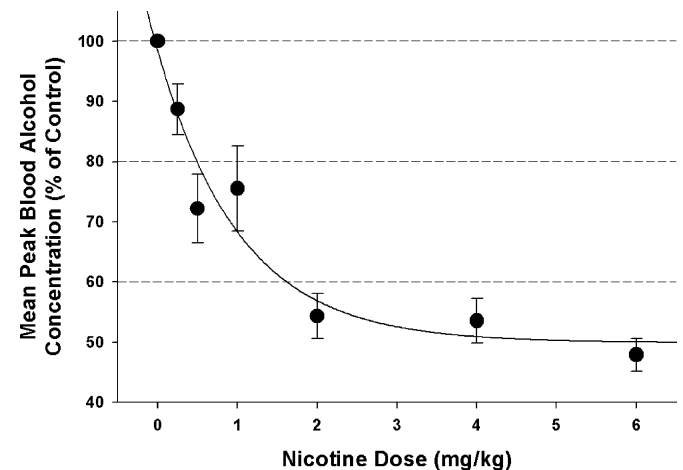


Fig. 4. Scatter plot of mean peak blood alcohol concentration (BAC) as a percent of controls and its corresponding nicotine dose. This figure indicates a nicotine dose-related decrease in peak BAC. The vertical lines represent the standard errors of the mean (SEMs).

study, even though the administration route of nicotine via IG intubation may result in decreases in nicotine bioavailability (Hukkanen et al., 2005). Clinically, there are limited studies specifically examining the pharmacokinetic interaction between alcohol and nicotine. There was, however, a clinical report documenting that cigarette smoking significantly reduced the peak BAC and the area under the BAC–time curve at 30 minutes after alcohol ingestion in humans (Johnson et al., 1991).

The results from Experiment 3 showed that nicotine lowered the BACs when alcohol was administered via IG intubation, but not following an IP injection. These findings support the hypothesis that a nicotine-mediated decrease in BACs is indeed related to gastric functions, possibly through nicotine's action on nicotinic acetylcholine receptors in the pylorus (Daniel, 1965; Ludtke et al., 1991; Mandrek and Kreis, 1992). The current experiments were not specifically designed to confirm that nicotine delayed gastric emptying in these subjects. Therefore, the proposed underlying mechanism that nicotine-induced reductions in BACs are a result of decreases in gastric emptying was not directly tested. However, this hypothesis agrees with the findings of Edelbroek et al. (1993), demonstrating that the administration of erythromycin, a drug capable of increasing gastric emptying, results in increased peak BACs in humans compared with subjects administered alcohol alone. Furthermore, Gritz et al. (1988) reported that the delay in gastric emptying is correlated with an increase in serum nicotine concentration. Taken together, these data support the working hypothesis that nicotine-induced decreases in BACs are due to nicotine's action in delaying gastric emptying, which increases the retention time for alcohol being held in the stomach, thereby increasing the likelihood of being metabolized via "first-pass metabolism" by gADH.

Reviewing the BAC data from the alcohol groups receiving no nicotine, the BAC curve from the IG administration in Experiment 3 differed slightly from those in Experiments 1 and 2, showing a lower peak BAC and a longer duration to reach the peak of the curve. This difference may be due, at least in part, to the added stress associated with the additional IP injections received by the subjects in Experiment 3. It has been demonstrated that stress has an inhibitory effect on gastric emptying (Mistiaen et al., 2002; Tsukada et al., 2003) similar to that of nicotine, but possibly through a different mechanism involving the sympathetic nervous system and/or corticotropin releasing factor (CRF) (Coskun et al., 1997; Lee and Sarna, 1997; Roland et al., 1990). Summarizing these findings, it suggests that the pharmacokinetic interaction between alcohol and nicotine is complex and as such may possibly be influenced by several unforeseen factors, such as stress.

If the lowering of BACs by nicotine occurs in humans, it may have several important clinical implications. The first consideration is the simultaneous use of alcohol and

nicotine by adults in a binge-drinking pattern. For example, if a person desires to drink to an effect (i.e., "get drunk") and smokes at the same time, the nicotine in cigarettes will then lower the BAC achieved. If this were to occur, this individual would have to drink more alcohol than usual to achieve the expected intoxication level. This would result in higher levels of alcohol metabolic products such as acetaldehyde, which has its own damaging effects on various physiological systems (Aberle et al., 2003; Holownia et al., 1999; Zhang et al., 2004). In light of this, combined with the negative effects of nicotine from smoking, the simultaneous use of alcohol and nicotine may prove to be more harmful than either drug alone, in spite of the fact that nicotine lowers BACs.

As reported in the NIAAA publication (Alcohol Alert), the relationship between the pharmacokinetic interaction of alcohol and nicotine and the contribution of this interaction to the likelihood of co-abuse of these 2 drugs remain to be determined. However, the present findings concerning nicotine's ability to lower BACs should be carefully considered in future investigations or interpretations aimed toward our understanding of the co-occurrence of alcohol drinking and cigarette smoking. This pharmacokinetic interaction between alcohol and nicotine in combination with psychological or physiological factors, such as reinforcement or tolerance, may serve as critical components of an ultimate behavioral modification—the co-abuse of alcohol and tobacco products.

In summary, the results from this study extended the previous findings from neonates that nicotine is capable of lowering BACs in adult rats and that the reduction in peak BACs is nicotine dose-related, with the lowest nicotine dose (0.25 mg/kg) in this study showing no significant effect on BAC produced by a 4 g/kg dose of alcohol. Furthermore, although there might be multiple mechanisms responsible for nicotine-mediated reduction in BACs, the current findings supported the notion that this phenomenon is at least partially related to gastric function rather than a direct action of nicotine on alcohol metabolism.

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