Caffeine and Coffee Tolerance

To the Editor:

Corti et al.\(^1\) recently reported that habitual coffee drinkers display different degrees of caffeine tolerance, depending on the route of caffeine administration. Although the participants did not display elevated systolic blood pressure after consumption of caffeinated coffee, they did after intravenous caffeine administration. In both conditions, the amount of caffeine administered was selected to result in similar plasma levels of the drug. The authors concluded that “tolerance to coffee does not appear to be related to caffeine” (p. 2939).

We suggest that the difference in tolerance expression after oral and intravenous caffeine may be another demonstration of the situational specificity of tolerance. Results of research with a variety of species, including humans, indicate that drug tolerance is modulated not only by experience with the drug but also by experience with both exteroceptive and interoceptive drug-associated stimuli.\(^2\) That is, drug tolerance is more pronounced in the presence of the usual drug predictive cues than in the presence of alternative cues.

Habitual coffee drinkers have prior experience with salient exteroceptive cues, such as the taste and odor of the coffee, signaling the effects of caffeine; thus, it is not surprising that they are more tolerant to the drug administered in the presence of these cues (ie, in coffee) than in the absence of these cues (ie, intravenously). The finding is similar to an earlier report that tolerance to alcohol is more pronounced when the drug is consumed in a beverage previously associated with alcohol (beer) than when the same amount of alcohol is consumed in a novel beverage (blue and peppermint flavored).\(^3\)

Additionally, among the stimuli that comprise the drug predictive cues are those cues inherent within the administration procedure (eg, route of administration or early weak drug effects, experienced immediately after administration, that signal the later larger drug effect). When a drug-experienced, and drug-tolerant, organism experiences a drug via a new route of administration, the expected level of tolerance frequently is not observed. Thus, in humans, changing from oral to transdermal opioid administration may result in a loss of tolerance.\(^4,5\) Similarly, in rats, changing from intraperitoneal to intravenous morphine administration or from gradual intravenous morphine administrations to a rapid intravenous administration results in a disruption of the display of tolerance (research reviewed elsewhere).\(^2\) Coffee drinkers experience the effects of caffeine after interoceptive cues inherent to the oral route of administration. Evaluating tolerance after administration via a different route (intravenous) is tantamount to altering the usual predrug cues, which results in a disruption of tolerance.

Finally, caffeine administered in coffee is self-administered. In contrast, intravenous caffeine is administered by the experimenter—not the participant. If a drug is self-administered (rather than passively received), interoceptive response-initiating (or response-produced) cues are paired with the drug effect. Results of many experiments indicate that greater tolerance is displayed to a self-administered drug than to the same dose of a passively received drug. This effect of the self-administration contingency on tolerance has been demonstrated with a variety of drugs and species, including cocaine, nicotine, and alcohol in rats; phenylcyclidine in monkeys; and hydromorphone and alcohol in humans.\(^2\)

Situational specificity of tolerance has been implicated in tolerance to a variety of effects of many drugs, including opiates, alcohol, nicotine, pentobarbital, immunoneuohancing drugs, cholecystokinin, carisoprodol, haloperidol, and several benzodiazepines.\(^2\) Corti et al.\(^1\) may well be the first to demonstrate situational specificity of tolerance to caffeine.

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To the Editor:

Corti and colleagues\(^1\) tested cardiovascular activity and sympathetic nerve responses to caffeine versus placebo and caffeinated versus decaffeinated espresso. Bolus intravenous caffeine increased sympathetic nerve activity and systolic blood pressure and decreased heart rate but had no effect on diastolic pressure. Caffeinated espresso had similar effects but only in nonconsumers of caffeine, although it also increased diastolic blood pressure. The reported increase in sympathetic nerve traffic is new and interesting. The findings of cardiovascular effects largely replicate existing work\(^2\) and are consistent with other studies that show that tolerance develops to the effects of caffeine with daily intake.\(^3\)

The paper makes two claims that are unsubstantiated by the data. The first is that decaffeinated espresso elevates blood pressure, but only in nonconsumers of caffeine. The decaffeinated espresso was given to only 4 nonconsumers, who had a rise only in systolic blood pressure. This is contrary to a study comparing coffee with caffeine\(^4\) that shows caffeine to be the pressor agent in coffee and that caffeine is effective, even in regular users, after overnight abstinence.\(^2\) This work does not support the authors’ claims that “nonhabitual coffee drinkers . . . exhibited similar cardiovascular responses after decaffeinated [and caffeinated] coffee” or that “we here provide evidence that in nonhabitual coffee drinkers, the cardiovascular activation by coffee is independent of caffeine content.”\(^1\) In fact, the low statistical power of this test in 4 persons and the failure to include a regular-consumer contrast group make this finding uninterpretable.

Their second claim is that a cardiovascular response to intravenous caffeine, but not to oral espresso, in the habitual consumers shows that tolerance is due to the coffee but not to its caffeine. Comparing intravenous caffeine with an oral dose of coffee is inappropriate given the different routes of administra-
tion and rapid onset of a bolus dose. In fact, tolerance occurs in persons given either coffee or caffeine pills.\(^2\)\(^3\)\(^5\)

Related problems further limit conclusions. The study appears to be done single blind, not double blind. The observations do not come from a full crossover design in which subjects are their own controls across conditions. The groups are small and vary in composition. Given these shortcomings, one wishes that the authors had taken their own advice: “The impact of habitual versus nonhabitual coffee drinking is so important that appropriate stratification of patients seems essential in analyzing any data in this field.”

The paper remains an interesting new report of sympathetic nerve activity in response to caffeine.

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To the Editor:

We read with interest the article by Corti et al.\(^1\) on coffee and its effect on blood pressure independently of its caffeine content. It seems very interesting that decaffeinated and normal coffee increases blood pressure in nonhabitual coffee drinkers, whereas regular coffee in habitual coffee drinkers does not increase blood pressure. However, we have some critical remarks concerning the methodology and the conclusions of the trial.

It is reported that 15 healthy volunteers took part in the study, but the sum of subjects in the baseline table is 35, suggesting that some but not all participants received more than one treatment. This suggests possible interaction between the treatments. No information is given on how the patients were allocated to one or more of the treatment groups. In a study comparing two rather harmless therapy forms there are no ethical problems in performing a controlled randomized study. If the aim of the study was to show an effect of coffee on blood pressure regardless of its caffeine content, then why was no caffeine-free coffee administrated to the habitual coffee drinkers?

We disagree with the authors’ conclusion, that other ingredients than caffeine must be responsible for cardiovascular activation. This activation can also be explained by other factors, for example higher excitement in non–coffee drinkers when “forced” to drink any kind of coffee, a placebo effect, or a modification of the coffee due to the decaffeinating process. Although it is possible that other ingredients in the coffee are responsible, this conclusion cannot be drawn from the results presented in the article. The question whether decaffeinated coffee raises blood pressure cannot be answered by the study design presented in the paper, because of the lack of a control group. The clinical relevance of a future trial could also be increased by not excluding possible risk groups, such as offspring of hypertensive patients.

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To the Editor:

Contrary to the assertion of Corti et al.,\(^1\) the effect of caffeine on muscle sympathetic nerve activity (MSNA) has indeed been characterized. Data are available from both healthy and heart failure subjects, under resting conditions, and during exercise.\(^2\) Unlike Corti et al.,\(^1\) we documented a decrease in resting MSNA burst frequency in healthy volunteers after intravenous infusion of 4 mg/kg caffeine, a suppression that persisted over the 90-minute recording period. Because blood pressure rose and heart rate fell, the most likely mechanism for this effect was baroreflex-mediated sympathetic withdrawal.\(^2\) This increase in blood pressure can be attributed to blockade, by caffeine, of the tonic dilatory effects of adenosine on vasomotor tone and to adenal catecholamine release\(^3,4\) (mechanisms not considered by these authors when discussing their anomalous observations) rather than to sympathoneural activation. At the doses infused in both papers,\(^1,2\) caffeine acts as a nonspecific A1 and A2 receptor antagonist that attenuates or abolishes hemodynamic and MSNA responses to infused adenosine.\(^5\)\(^6\) After adrenalectomy, caffeine raises blood pressure and lowers plasma norepinephrine concentration.\(^7\)

The authors’ contention that “...most studies on the acute effect of caffeine or coffee reporting a pressor effect were performed on nonhabitual coffee drinkers or after a prolonged abstinence”\(^8\) ignores key studies performed previously by Smits et al.\(^1,4\) and others.\(^5\) Blood pressure responses to caffeine and adenosine are highly dependent on the preceding period of abstinence. Approximately 72 hours of withdrawal is necessary to eliminate the effects of adenosine receptor blockade\(^6\) and to detect a marked caffeine-induced increase in both sotolic and diastolic blood pressure in both heart failure and healthy subjects.\(^2\) Corti et al. studied subjects after only 16 hours of abstinence, when plasma caffeine was still at a concentration (5 μmol/L or 1 mg/L) that significantly reduces the hemodynamic and neurohumoral actions of both caffeine\(^4\) and adenosine.\(^5\) Persistent antagonism of adenosine receptors by caffeine can account for the lack of blood pressure increase in their habitual drinkers after ingestion of coffee.

The fact that coffee administration could not be blinded may explain why nonhabitual drinkers have similar hemodynamic and sympathetic responses to regular and decaffeinated coffee. Although the authors attributed this to an ingredient in coffee other than caffeine, equally plausible is that these could simply represent psychogenic responses to an alien or potentially repugnant substance.
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5. Rongen GA, Brooks SC, Ando S, et al. Caffeine abstinence augments the stimulatory effect of decaffeinated coffee seen in nonhabitual coffee drinkers, we think that substances other than caffeine may be in part responsible for the effect of coffee. The effect of coffee on cardiovascular regulation in normotensive and hypertensive subjects deserves further study as the complexity of the reactions may not be completely explained by looking at one compound (caffeine) only. This is reflected in the discrepancy between several reports—illustrating vasoactive properties of caffeine leading to hypertension—and recent epidemiological studies, which appear to exclude an association between coffee consumption and the risk of hypertension or cardiovascular morbidity and mortality.

Response
Several researchers have extensively evaluated the effect of caffeine on blood pressure (BP) in hypertensive and normotensive individuals. So far, these studies apply only partially to our results, as they mainly measured the effect of caffeine on BP or on sympathetic nerve activity (SNA)—the mechanism responsible for acute hemodynamic changes—without considering that coffee is a beverage that may contain several vasoactive substances.

Our results are not challenging previous results but simply demonstrate that we cannot reach definitive conclusions on the possible health hazards (hypertensive potential) of coffee by analyzing the cardiovascular effect of one component only, which has been the case for caffeine. In fact, the precise characterization of all potentially vasoactive substances contained in coffee has not yet been specified. The interaction between the different components could result in additive or inhibitory effects and may explain the different results between studies looking at the effect of caffeine and those looking at the effect of coffee.

Our results confirmed that caffeine infusion similarly increased SNA and BP in habitual and nonhabitual coffee drinkers. The effect of coffee appears more complex, and we were not able to give a definitive answer to our results. In fact, we noted a similar increase in SNA in habitual and nonhabitual coffee drinkers only, indicating that habitual coffee drinkers probably develop a tolerance to the effect of coffee.

The mechanisms of the cardiovascular effects of caffeine include the blocking of adenosine receptors and the inhibition of phosphodiesterases. An upregulation of adenosine receptor is the postulated biochemical mechanism of caffeine tolerance. In our study, in agreement with the previous reports of Drs Lovallo, Whitsett, and others, we did not find a tolerance to caffeine. Therefore, other mechanisms may be involved in blunting the cardiovascular effect of coffee in habitual drinkers.

Dr Siegel and colleagues propose a potential mechanism bound to the situational specificity of tolerance. We are not able to exclude that the effect of coffee may in part depend on the experience with both exteroceptive and interoceptive drug-associated stimuli. A placebo-controlled design is, however, not possible because of the inimitable taste, smell, odor, and color of coffee.

The second important finding in our study was that decaffeinated coffee increased SNA and BP in nonhabitual coffee drinkers, indicating that substances other than caffeine must be responsible for cardiovascular activation. As the effect of coffee drinking was blunted in habitual coffee drinkers, we tested the effect of decaffeinated coffee in nonhabitual coffee drinkers only. By removing caffeine, we were not expecting an additional stimulatory effect. The coffee brand and the preparation of the espresso were the same for caffeinated and decaffeinated coffee. Chemical analysis demonstrated that the only difference between the caffeinated and decaffeinated beans in the brand used in our study involved the caffeine content. Interestingly, nonhabitual coffee drinkers experienced the same trend over time in the stimulation of the SNA and BP increase after coffee and decaffeinated coffee. SNA progressively increased after coffee consumption over a period of 60 to 90 minutes, which is difficult to explain as a placebo effect. Because of the multitude of substances contained in coffee and the cardiovascular effect of decaffeinated coffee seen in nonhabitual coffee drinkers, we think that substances other than caffeine may be in part responsible for the effect of coffee. The effect of coffee on cardiovascular regulation in normotensive and hypertensive subjects deserves further study as the complexity of the reactions may not be completely explained by looking at one compound (caffeine) only. This is reflected in the discrepancy between several reports—illustrating vasoactive properties of caffeine leading to hypertension—and recent epidemiological studies, which appear to exclude an association between coffee consumption and the risk of hypertension or cardiovascular morbidity and mortality.

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