Caffeine is arguably the most widely consumed drug in Western society. The annual world consumption of coffee exceeds 4 million tons. Caffeine constitutes 1–2% of roasted coffee beans and is present in many over-the-counter preparations for the treatment of cold and allergies, headaches, diuretics, and stimulants. In general, one cup of coffee is assumed to contain 100 mg of caffeine, and soft drinks contain ~10–50 mg of caffeine per 12-oz serving. The per capita consumption of caffeine averages ~200 mg/day, but in some countries, it can exceed 400 mg/day (1). There has been great interest, therefore, in defining the mechanism of action of caffeine and determining the health consequences of its consumption. Progress has been made on both accounts, but not without controversy.

It is now evident that caffeine acts as an antagonist of adenosine receptors (1,2). Only concentrations reaching toxic effects are effective in increasing intracellular calcium or inhibiting cyclic nucleotide phosphodiesterases (1), the alternative mechanisms of action. Caffeine (1,3,7-trimethylxanthine) and the closely related theophylline (1,3-dimethylxanthine) are relatively poor adenosine receptor antagonists, with EC50 values in the low μmol/l range. These concentrations, however, are readily achieved during habitual caffeine consumption. In experimental studies in humans, an oral dose of caffeine at 250 mg t.i.d. (~5–7 cups of coffee/day), which is well tolerated, produced plasma caffeine concentrations in excess of 40 μmol/l (2), and plasma concentrations of paraxanthine (1,7-dimethylxanthine), the principal metabolite of caffeine, of ~20 μmol/l. Paraxanthine is as potent as caffeine in blocking adenosine receptors (2) and produces similar cardiovascular effects in humans (3). Caffeine is a nonselective adenosine receptor antagonist, although it is more potent at A2A receptors (K0.5 2.4 μmol/l) and less potent at A3 receptors (80 μmol/l) compared with A1 (12 μmol/l) and A2B (13 μmol/l) receptors (1).

Once ingested, caffeine is distributed widely throughout the body. Levels found in the brain are comparable with those in plasma (4), and caffeine readily crosses the placenta and is also found in breast milk (5). There have been concerns about the cardiovascular effects of caffeine consumption (6,7), its potential for dependence (1,8), and its association with osteoporosis (9) and adverse pregnancy outcomes and developmental problems (5,10,11), among others. A critical review of the evidence for and against a deleterious effect of caffeine is beyond the scope of this editorial, but it is fair to say that in most cases, a clear smoking gun is not found.

The article by Keijzers et al. (12) in this issue of Diabetes Care adds another item to the list of potential deleterious effects of caffeine. They report that intravenous caffeine, at doses that produce plasma levels of ~30 μmol/l, decreases insulin sensitivity in humans by ~15%, from 0.46 to 0.39 μmol/kg per min/mU/l. This reduction is relatively small compared with the ~40% increase in insulin seen in obesity. Although it is difficult to extrapolate these findings to physiological releases of insulin, this reduction in insulin sensitivity could be of potential importance, given the widespread use of caffeine.

Before we recommend giving up coffee, however, it is important to discuss the reasons why it is often difficult to assign a deleterious effect to caffeine consumption. Some of these caveats also apply to this study. First, adenosine receptors are widespread, and their activation produces a myriad of sometimes-contradictory effects. Adenosine receptors are present in fat, skeletal muscle, and liver cells and modulate metabolism in many ways, as described by Keijzers et al. The authors propose, however, that the decrease in insulin sensitivity produced by caffeine is not a direct effect on these cells but is mediated indirectly by increasing circulating levels of epinephrine, most likely caused by its central stimulatory effects (of interest, cortisol was not increased). This is a hypothesis that could be tested by repeating these studies in the presence of β-blockade. It should be noted that the plasma concentrations of epinephrine produced by caffeine (~0.75 nmol/l or 140 pg/ml) are relatively low. It would be important to determine whether an infusion of epinephrine, treated to achieve comparable plasma concentrations, would produce a similar reduction in insulin sensitivity. The authors exclude a change in glucose delivery as contributing to the decrease in insulin sensitivity because “blood flow” was increased. However, only forearm blood flow was measured. Given that blood pressure increased, it is likely that vasocostriction occurred in other vascular beds. In this regard, it is important to note that oral caffeine produces a 19% reduction in liver plasma flow (13). Similarly, the greater levels of free fatty acids produced by caffeine may have contributed to the reduction in insulin sensitivity.

Second, adenosine is considered a retaliatory hormone. The importance of adenosine as a regulatory autacoid is greatest when its interstitial concentrations are increased, e.g., during ischemia or stress, and are of lesser importance during resting conditions. It is therefore possible that the effects reported by Keijzers et al. may be quantitatively (or even qualitatively) different during exercise or hypoglycemia, when the tonic effects of adenosine may be magnified. Also, it will be of interest to determine whether this phenomenon is observed in obese individuals or patients with type 2 diabetes.

Third, there is tolerance to the cardiovascular effects of chronic caffeine consumption (14), probably explained by upregulation of adenosine receptors (2,15). It would be important to determine to what degree tolerance occurs to the metabolic effects of caffeine and whether this tolerance will dampen the decrease in insulin resistance produced by acute caffeine administration.

This group of investigators has previously made important contributions to our understanding of the clinical pharmacology of caffeine, and this study adds a new facet to the potential actions of this compound. It is, however, not without limitations. Notably, insulin sensitivity was not reduced in the caffeine group as much as it was increased in the placebo group (Fig. 2 from Keijzers et al.), so that differences between groups were apparent only in the last 20 min of a 2-h hyperinsulinemic-euglycemic clamp. How this translates to physiological release of insulin is unclear. Also, the plasma concentra-
tions of insulin induced in this study are relatively high. It is uncertain that the reduction in insulin sensitivity produced by caffeine would be of similar magnitude at lowered, arguably more physiological, insulin levels or in patients with insulin resistance, who already start at a lower insulin sensitivity.

As with most innovative research, this study raises more questions than answers. We have tried to enumerate some of these questions in the hope of encouraging research in this field.

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