Acute caffeine ingestion does not impair glucose tolerance in persons with tetraplegia

D. S. Battram,1 J. Bugaresti,2 J. Gusba,1 and T. E. Graham1

1Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario; and 2Hamilton Health Sciences, Chedoke Site, Hamilton, Ontario, Canada

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Battram DS, Bugaresti J, Gusba J, Graham TE. Acute caffeine ingestion does not impair glucose tolerance in persons with tetraplegia. J Appl Physiol 102: 374–381, 2007. First published October 26, 2006; doi:10.1152/japplphysiol.00901.2006.—Acute caffeine (Caf) ingestion impairs glucose tolerance in able-bodied humans during an oral glucose tolerance test (OGTT). The mechanism responsible for this effect remains unclear, however, it is suggested to be due to the accompanying increase in epinephrine concentration. We examined whether or not Caf would elicit a glucose intolerance in persons with tetraplegia (TP) who do not exhibit an increased epinephrine response following Caf ingestion. All TP [n = 14; 9 incomplete (Inc) lesion, 5 complete (Com) lesion] completed two OGTT 1 h after consuming either gelatin (Pl) or Caf capsules (dose = 4 mg/kg). Blood samples were collected at baseline (time = 0 min), 1 h after capsule ingestion (time = 60 min), and every 30 min during the OGTT (time = 90–180 min). Glucose, insulin, proinsulin, and C-peptide responses were similar (P > 0.05) between treatments, demonstrating no effect of Caf on glucose tolerance. This lack of a Caf effect may be due to the low epinephrine concentration that remained unchanged (P > 0.05) throughout all experiments. Interestingly, the Com exhibited a 50% higher glucose response (P ≤ 0.05) and a 46% (P > 0.05) lower insulin response (vs. Inc), suggesting a more pronounced glucose intolerance within this subgroup. Furthermore, nine TP (5 Com, 4 Inc) had glucose levels of ≥ 7.8 mM at the end of the OGTT (time = 180 min), classifying them as glucose intolerant. In summary, acute Caf ingestion does not increase epinephrine concentration or impair glucose tolerance in TP.

Adenosine receptor antagonist; Type 2 diabetes; spinal cord injury; insulin resistance

ACUTE CAFFEINE INGESTION RESULTS in a transient impairment of glucose tolerance in able-bodied humans (13, 29, 30, 35). During an oral glucose tolerance test (OGTT), caffeine ingestion results in elevated insulin and C-peptide responses without a subsequent lowering of the glucose response (13, 35) suggesting a caffeine-induced impediment to the actions of insulin. This impediment in insulin action is further demonstrated by studies employing the euglycemic-hyperinsulinemic clamp technique that report a 15–25% decrease in whole body insulin-mediated glucose disposal following caffeine ingestion (16, 22, 34). Furthermore, Thong et al. (34) demonstrated a 50% decrease in skeletal muscle (leg) glucose uptake, which is the predominant tissue responsible for whole body glucose disposal in humans.

The mechanism by which caffeine decreases glucose tolerance and/or glucose disposal remains undetermined. Although caffeine is a known adenosine receptor antagonist (6, 31), it remains unclear as to whether or not adenosine contributes significantly to insulin-mediated glucose uptake within skeletal muscle. Within adipose tissue, adenosine has been consistently reported to enhance insulin-mediated glucose uptake (8, 9, 18); however, the results obtained for skeletal muscle have been conflicting. Studies conducted on rodent muscle have demonstrated increases (10, 26), decreases (17), and no change (38) in insulin-mediated glucose uptake following the administration of an adenosine receptor antagonist. In humans, the infusion of the adenosine reuptake inhibitor dipyridamole failed to show an enhancement of whole body insulin-mediated glucose disposal during a euglycemic-hyperinsulinemic clamp, suggesting that adenosine may not contribute significantly to insulin action in humans (22).

Another potential mechanism by which caffeine could impede insulin-mediated glucose disposal is by increasing plasma epinephrine concentrations. Epinephrine is a potent antagonist of many of insulin’s actions, including glucose disposal (23, 24). It has been proposed (20, 33) that the small, albeit significant elevation in epinephrine concentration from 0.3 to 0.6 nM is solely responsible for the caffeine-induced impairment in glucose tolerance. This concept was based partly on the finding that simultaneous administration of caffeine and propranolol, a β-adrenergic receptor antagonist, abolished the caffeine effect on glucose tolerance (35). In contrast the infusion of epinephrine in humans to levels similar to that observed following caffeine ingestion (0.6 nM) was unable to decrease insulin-mediated glucose disposal during an euglycemic-hyperinsulinemic clamp (4). This suggests that whereas epinephrine may be a potent antagonist of insulin, the level at which caffeine elevates it is not sufficient to account for the entire caffeine effect and another mechanism(s) must be involved.

Therefore, the purpose of the present study was to reexamine the effect of caffeine on glucose tolerance when caffeine does not elicit an epinephrine response. To achieve this, instead of antagonizing the actions of epinephrine with a β-adrenergic receptor antagonist, we studied persons with tetraplegia (TP) who not only have low basal concentrations of epinephrine (~0.1 nM) but also on ingestion of caffeine do not demonstrate the characteristic elevation in epinephrine concentration (36). We hypothesized that caffeine ingestion would not result in an impairment in glucose tolerance because of the fact that epinephrine concentrations will remain unchanged (i.e., similar to baseline levels) throughout the experiment.

METHODS

Subjects. This study was approved by both the University of Guelph’s Human Ethics Committee and the Hamilton Health Sciences...
Subject recruitment efforts yielded a total of 38 potential participants. Of those contacted, 14 declined to participate because of lack of interest, 4 did not meet the level of injury inclusion criterion, and 1 was excluded based on an inability to access the antecubital vein. Of the remaining 19 participants who met the inclusion criteria and agreed to participate in the study, 5 withdrew from the study stating reasons of transportation limitations and potential discomfort of the venipuncture procedure, leaving 14 persons with TP who completed the study. These 14 TP were further divided into two subgroups: incomplete (Inc; ASIA B and C; n = 9) and complete (Com; ASIA A; n = 5) lesion for additional comparison. Subject characteristics are provided in Table 1.

**Experimental design and procedures.** Before each experiment, participants were required to maintain their regular dietary and activity patterns (if any) and to maintain their individual medication regimes. In addition, 2 days before each experiment, participants were required to refrain from consuming any caffeine-containing beverages and/or substances and alcohol.

All participants completed two trials in a randomized, single-blinded manner, and each trial was separated by at least 7 days. Participants entered the laboratory ~4 h after consuming a light breakfast. The composition of this breakfast was recorded on the first trial day, and subjects were instructed to consume the identical breakfast before the second trial. Participants were weighed and asked to complete a screening questionnaire, verbally administered by the study coordinator. On completion of the screening questionnaire, participants gave their written and oral consent to continue with the experiment. Once consent was obtained a baseline blood pressure and pulse were measured. A catheter was then inserted into the antecubital vein for venous blood sampling and a baseline blood sample was taken (time = 0 min). Immediately following this sample, participants consumed a standard 75-g glucose solution (TRUTOL 75, Nerl Diagnostics, East Providence, RI) at which time the oral glucose tolerance test (OGTT) was initiated. Throughout the next 2 h, blood pressure and pulse measurements were taken (Dinamap Plus Vital Signs Monitor-model 9720, Johnson & Johnson Medical, Tampa, FL), and blood samples were collected at 30-min intervals. All blood samples were analyzed for glucose, insulin, C-peptide, free fatty acid (FFA), glycerol, lactate and glucagon-like peptide-1 (GLP-1) concentrations. Because of technical limitations, the latter analysis was performed on 10 subjects (i.e., 5 Inc and 5 Com), and hence they are only considered preliminary findings. Baseline blood samples were further analyzed for interleukin-6 (IL-6) concentrations, and the 60- and 90-min samples were analyzed for proinsulin concentrations as an estimate of β-cell function (11). In addition, as a precaution throughout the trial, blood glucose concentrations were monitored at all time points using a glucometer (Medisense Products; Abbott Laboratories, Bedford, MA).

**Analyses.** Blood samples were collected in both heparinized and nontreated tubes. Approximately 8 ml of blood were added to a 10-ml heparinized tube. A 1.5-ml aliquot of heparinized blood was transferred to a 1.5-ml Eppendorf tube and immediately centrifuged. The supernatant (plasma) was then collected and stored on ice until the end of the experiment, at which time plasma glucose and lactate was measured by an automated analyzer (YSI 2300, YSI, Yellow Springs, OH). Once glucose and lactate concentrations were measured, the remaining plasma was stored at ~20°C for determination of plasma methylxanthines by HPLC as previously described (2). To the remaining heparinized blood (6.5 ml), 120 μl of EGT-A-GSH was added, and the blood was stored on ice for 5 min. The tube was then centrifuged for 10 min, and the plasma was collected and stored at ~80°C for later determination of plasma epinephrine (Adrenaline RIA kit, Labor Diagnostika Nord, Nordhorn, Germany). Approximately 10 ml of blood were collected in the nontreated tube. This was kept at room temperature for 30 min to allow the blood to clot. The tube was then centrifuged for 10 min, and the supernatant (serum) was collected and stored at ~20°C for later determination of plasma epinephrine (Adrenaline RIA kit, Diagnostic Products, Los Angeles, CA), C peptide (Human C-peptide RIA kit, Linco Research, St. Charles, MO), proinsulin (Human Proinsulin RIA kit, Linco Research), IL-6 (Human IL-6 HS ELISA kit, Quantikine, R&D Systems, Minneapolis, MN), FFA (NEFA kit, Wako Bioproducts, Richmond, VA), glycerol (27), and GLP-1 (Human GLP-1 RIA kit, Linco Research).

**Calculations and statistics.** During the 120-min OGTT, area under the curve (AUC) for blood glucose, serum insulin, C peptide, and GLP-1 was estimated using the trapezoid method, with the concentration at time 60 min taken as the baseline value. The insulin sensitivity index (ISI) was calculated using the equation developed by Matsuda and DeFronzo (28) to estimate whole body insulin sensitivity. The proinsulin to insulin (PI/I) ratio was calculated during the initial 30 min of the OGTT (time points 60 and 90 min) as an estimate of β-cell function (11). Mean arterial pressure (MAP) was calculated using the following equation: DBP + 1/3 (SBP − DBP), where DBP and SBP are the diastolic and systolic blood pressures, respectively. Glucose tolerance was determined based on both fasting (>6.1 mM) and 2 h OGTT (>7.8 mM) glucose blood concentrations according to the World Health Organization (WHO) classification system. While caffeine was used to ascertain time and treatment effects within the whole group (TP; n = 14), they were also used to determine whether any differences existed between complete (Com; n = 5) and incomplete (Inc; n = 9) lesion subgroups. A two-way ANOVA for repeated measures was used to ascertain time and treatment effects within the TP and the Inc and Com subgroups for glucose, insulin, C peptide, proinsulin, proinsulin-to-insulin (PI/I) ratio, glycerol, FFA, epinephrine, GLP-1, pulse pressure, and blood pressure, and when differences were found a Tukey’s test was used for post hoc analysis. To elucidate differences in AUC for glucose, insulin, C peptide, and GLP-1 and for

![Table 1. Subject characteristics for TP and Com and Inc subgroups](http://jap.physiology.org/Downloadedfrom/)
baseline IL-6 within the TP and the Inc and Com subgroups, a paired t-test was used. To determine whether differences existed between the Com and Inc lesion subgroups, AUC for glucose, insulin, C peptide, and GLP-1, as well as for the PI/I ratio, and ISI, a two-way ANOVA was used, and when differences were found a Tukey’s test was used for post hoc analysis. To elucidate differences in FFA and glycerol concentrations, a paired t-test was used to compare the change in FFA and glycerol concentrations during the initial 60 min after treatment ingestion (change from 0 to 60 min). To ascertain differences in epinephrine concentrations between these subgroups, the average concentration during the OGTT (time 60 to 180 min) was compared using a two-way ANOVA. To ascertain time effects within the Caf trial, a one-way ANOVA was used, and when differences were found a Tukey’s post hoc test was used. Differences were considered significant at $P \leq 0.05$.

RESULTS

At baseline, glucose concentrations were similar between Pl and Caf treatments ($P > 0.05$; Fig. 1). Following capsule ingestion, glucose concentrations remained unchanged from baseline, indicating that capsule ingestion alone had no effect on the blood glucose response. As expected, on initiation of the OGTT, blood glucose concentrations increased ($P \leq 0.05$). It is noteworthy that in all trials, glucose concentrations remained elevated at the end of the OGTT compared with resting concentrations, suggesting that the insulin response (see below) was insufficient to clear the ingested glucose during this time period. Using the WHO classification guidelines for glucose tolerance, we observed that despite normal baseline values, five Com and four Inc were at least impaired glucose tolerant based on the blood glucose concentrations at the end of the OGTT ($time = 180 \text{ min}$). AUC analysis within the TP and the Com and Inc subgroups confirmed no effect of Caf on the glucose response during the OGTT ($P > 0.05$) compared with Pl (Table 2). Interestingly, a comparison between the Com and Inc subgroups revealed a 50% greater ($P \leq 0.05$) glucose AUC for the Com subgroup compared with the Inc subgroup.

Insulin concentrations were similar ($P > 0.05$) between treatments both at baseline and 60 min posttreatment ingestion. As observed for glucose, insulin concentrations increased ($P > 0.05$) throughout the OGTT (Fig. 2). AUC analysis for insulin revealed no treatment effects within or between subgroups (Table 2). It is noteworthy, however, that although not significant ($P = 0.12$) the Com demonstrated a 46% lower AUC compared with the Inc. Interestingly, despite this and the 50% higher glucose AUC within the Com compared with the Inc, there were no differences in the ISI ($7.3 \pm 2.1$ and $6.0 \pm 1.3$ for Com and Inc, respectively; data not shown) between these subgroups. High resting IL-6 ($3.5 \pm 1.7$ and $3.2 \pm 1.0$ pg/ml for Com and Inc respectively) concentrations were also observed (data not shown), which suggests an impairment in glucose tolerance ($7$).

Because of the fact that C peptide is secreted in equimolar concentrations to insulin and can therefore be used as an indication of insulin secretion, it is not surprising that all C-peptide results parallel those of insulin (Fig. 3, Table 2), with one exception. Within the Com subgroup, C-peptide concentrations continued to increase throughout the OGTT, such that the concentration at the end of OGTT ($time = 180 \text{ min}$) was higher than at all other time points. This is in contrast to the Inc group, whose concentrations remained elevated but unchanged during the last 60 min of the OGTT.

To assess B-cell function, proinsulin concentrations were measured during the first 30 min after the initiation of the OGTT. As anticipated, because of the stimulation of insulin secretion, the proinsulin levels increased from 60 min (just before glucose ingestion) to 90 min ($+17.3 \pm 1.5$ pM). In

<table>
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<th>Parameter</th>
<th>Group</th>
<th>TP ($n = 14$)</th>
<th>Com ($n = 5$)</th>
<th>Inc ($n = 9$)</th>
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<td></td>
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<tr>
<td>Pl</td>
<td>428.9 ± 34.9</td>
<td>530.2 ± 25.4*</td>
<td>372.6 ± 42.3*</td>
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<td>Caf</td>
<td>419.8 ± 42.3</td>
<td>548.8 ± 70.7*</td>
<td>348.1 ± 36.5*</td>
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<td></td>
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<tr>
<td>Pl</td>
<td>66,006.1 ± 16,220.6</td>
<td>46,416.8 ± 6,749.6</td>
<td>76,889.1 ± 24,717.7</td>
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<td>Caf</td>
<td>58,214.8 ± 13,105.5</td>
<td>34,157.9 ± 3,014.0</td>
<td>71,579.7 ± 19,212.4</td>
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<tr>
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<td>2,799.7 ± 289.2</td>
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<tr>
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<td>2,277.8 ± 162.5</td>
<td>2,952.2 ± 423.2</td>
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</table>

Values are means ± SE; $n$, no. of subjects. Pl, placebo trial; Caf, caffeine trial. *Differences ($P \leq 0.05$) in the area under the curve for a given metabolite between Com and Inc subgroups.
agreement with the differences observed in the subgroups’ insulin responses, the increase observed in the Com was ~40% lower (+11.2 ± 1.1 pM; P ≤ 0.05) than that observed with the Inc (+20.7 ± 1.9 pM) subgroup. Analysis of the PI/I ratio revealed a significant decline from 60 to 90 min (0.22 to 0.06), with no differences observed between groups (P > 0.05). In all cases, Caf ingestion had no effect (P > 0.05) on either absolute proinsulin concentrations or the PI/I ratios (data not shown).

GLP-1 concentrations were similar (10.8 ± 2.1 and 9.7 ± 1.6 pM for Pl and Caf, respectively; P > 0.05) between treatments at baseline and remained unchanged during the 60 min posttreatment ingestion period for both groups (n = 10, 5 Inc and 5 Com). Following the initiation of the OGTT, GLP-1 levels increased, reaching a peak concentration at 90 min (~32 pM) and then gradually declining to baseline levels by 120 and 180 min. AUC analysis revealed no differences (P > 0.05) between treatments (1,192 ± 649 and 1,284 ± 400 pM/h for Pl and Caf treatments, respectively) within a group or between Com and Inc subgroups, suggesting that glucose absorption was similar during all experiments (data not shown). It is noteworthy that this analysis was conducted on a subset of subjects (n = 5 per subgroup), and therefore these results should be considered preliminary and should be interpreted with caution.

At baseline, caffeine concentrations were often undetectable or were very low (Table 3), indicating good adherence to preexperimental guidelines. Within the Pl trial, concentrations remained unchanged (P > 0.05) and similar to baseline. Following capsule ingestion during the Caf trial, caffeine concentrations increased, reaching a peak concentration at 60 min. These concentrations remained elevated from baseline, but they gradually declined throughout the rest of the experiment. A comparison between Inc and Com subgroups revealed no differences (P > 0.05) in caffeine concentration either prior to or during the OGTT (data not shown). As expected, caffeine metabolite (paraxanthine, theophylline and theobromine) concentrations gradually increased throughout the Caf experiments (data not shown).

Epinephrine concentrations were similar (P > 0.05) before capsule ingestion in both trials (Fig. 4). Following the ingestion of Pl and Caf capsules, epinephrine concentrations remained unchanged (P > 0.05) from those observed at baseline and remained at these levels throughout the rest of the experiment. A comparison of the average epinephrine concentrations during the OGTT between Inc and Com subgroups revealed no significant differences (P > 0.05).

Overall, Caf ingestion resulted in a higher FFA response at 0, 60, and 90 min compared with Pl (Fig. 5). Because of the fact that baseline FFA concentrations were higher in the Caf trial, analysis was conducted on the change in FFA concentrations during the initial 60 min following capsule ingestion (i.e., change between 0 and 60 min). Although Caf ingestion resulted in a 288 ± 54 μM increase in FFA concentrations, only a trend (P > 0.07) toward significance was observed compared with Pl. Interestingly, whereas the Inc subgroup demonstrated a similar trend (P = 0.07) toward a Caf-induced increase in lipolysis (+360 ± 67 μM), the Com group did not (+158 ± 62) (data not shown). Baseline glycerol concentrations were not different (P > 0.05) between treatments in all subjects (Table 3). In parallel to the FFA response, Caf ingestion did result in a higher overall glycerol response (P < 0.05). The change in glycerol concentration during the first 60 min following capsule ingestion (i.e., the delta between 0 and 60 min) were not different between treatments; however, a comparison between Com and Inc subgroups did demonstrate an overall larger increase in glycerol concentrations (P ≤ 0.05) within the Inc subgroup (−2 ± 10 vs. +32 ± 6 μM for Com and Inc respectively) (data not shown).

As anticipated, all subjects had very low MAP at baseline. There were no differences in MAP (P > 0.05) at baseline between Pl and Caf treatments within any group (Table 3). There was an overall treatment effect (P ≤ 0.05) with Caf ingestion resulting in a higher blood pressure at 60, 90, and 150 min compared with Pl. Pulse rate was not different at baseline between treatments, and unlike MAP, Caf ingestion did not
result in a higher pulse rate compared with Pl (Table 3). Although no differences were observed \( (P > 0.05) \) between the Com and Inc subgroups with respect to absolute MAP or pulse rate values, within the Inc subgroup Caf resulted in an increased MAP \( (P \leq 0.05) \), an effect not observed within the Com subgroup.

**DISCUSSION**

Whereas previous investigations have demonstrated that acute caffeine ingestion results in a transient glucose intolerance within a wide range of subjects (i.e., lean, obese, and with Type 2 diabetes) (13, 29, 30), the present findings confirm our hypothesis that caffeine ingestion does not impair glucose tolerance in persons with TP. This lack of caffeine effect was observed despite the fact that Caf resulted in a trend \( (P = 0.07) \) toward an elevation in caffeine concentration, an increase in glycerol concentration \( (P \leq 0.05) \), and a marked increase \( (P \leq 0.05) \) in MAP. Furthermore, as previously demonstrated (36), Caf ingestion did not change epinephrine concentrations \( (P > 0.05) \) throughout the experiments. These data suggest that not only does caffeine elicit epinephrine-independent effects on adipose tissue lipolysis and blood pressure but also that these effects are either not responsible for or do not exert enough of an effect to alter glucose metabolism. Furthermore, a comparison of Inc and Com subgroups demonstrated a more pronounced glucose intolerance, indications of less insulin secretion and no effect \( (P > 0.05) \) of Caf on FFA concentrations and MAP within the latter subgroup. Despite these hemodynamic and metabolic differences, the effect of caffeine on glucose tolerance and epinephrine levels were similar between these subgroups, again providing additional evidence of a role for epinephrine in the mechanism by which caffeine impairs glucose tolerance.

Whereas Caf ingestion resulted in similar glucose, insulin, C-peptide, proinsulin, GLP-1, and epinephrine responses throughout all trials, we did observe a trend for an increase \( (P = 0.07) \) in FFA concentrations, an increase in glycerol concentrations \( (P \leq 0.05) \), and marked increases in MAP \( (P \leq 0.05) \). The latter results demonstrate that TP respond both metabolically and hemodynamically to caffeine. The mobili-
zation of FFA by an epinephrine-independent mechanism has been reported previously in this population following caffeine ingestion (36) and suggests that caffeine may have a direct effect on adipose tissue lipolysis. In addition, Smits et al. (32) previously reported no impairment of caffeine’s ability to increase blood pressure by either propranolol and metoprolol, suggesting that epinephrine is not required for these effects and that another mechanism is responsible. Whereas both these effects of caffeine have been suggested to occur via the antagonism of adenosine receptors (33, 36), we cannot ascertain this from the present study. However, it is possible that norepinephrine elicited these effects because caffeine increases norepinephrine spillover during exercise in humans (12). Van Soeren et al. (36) observed no increase in norepinephrine concentrations following caffeine ingestion by persons with TP at rest; however, changes in norepinephrine concentrations with the present dose of caffeine are difficult to detect with mixed venous sampling. Because of the fact that norepinephrine was not measured in the present study, we cannot exclude the possibility that the increase in blood pressure was via norepinephrine, especially because this population is known to exhibit an enhanced response to small changes in this hormone (3).

Because of the fact that caffeine exerted some epinephrine-independent actions without altering glucose tolerance, it may be that the low and unchanging levels of epinephrine throughout the CAf and PI trials is at least partly responsible for the lack of a caffeine effect on glucose tolerance. Previous work in our laboratory by Thong and Graham (35) demonstrated, under similar experimental conditions, a lack of a caffeine effect on glucose tolerance when the nonselective β-adrenergic antagonist, propranolol, was administered simultaneously with caffeine. Taken together with the present findings, these studies suggest that epinephrine plays a dominant role in the caffeine-induced impairment in glucose tolerance in humans. In direct contrast, however, an epinephrine infusion to similar concentrations obtained following caffeine ingestion (0.7 nM) does not attenuate whole body insulin-mediated glucose disposal during a isoglycemic-hyperinsulinemic clamp (4). Therefore, it is more likely that the level at which caffeine increases epinephrine concentrations is insufficient to account for the entire caffeine-induced glucose intolerance, and yet the removal of epinephrine or the blocking of its actions abolishes the caffeine effect.

The reason for these conflicting findings is not obvious. It is possible that it is the additive or synergistic effect of multiple mechanisms that is responsible for the significant decline in glucose tolerance following caffeine ingestion. Within isolated adipocytes, lipolytic agents, such as isoproterenol, are more effective when endogenous inhibitors of lipolysis (i.e., adenosine) are removed (21). Furthermore, the impairment of insulin-mediated glucose uptake by isoproterenol within adipose tissue occurs only when adenosine is removed by adenosine deaminase (14, 37). Whether or not this occurs within skeletal muscle is unknown. Caffeine is an adenosine receptor antagonist (6, 31), but adenosine’s role in insulin-mediated glucose uptake within this tissue remains controversial. Studies employing both the isolated soleus strip (10, 17, 26) and hindlimb perfusion (38) models have yielded conflicting findings. Although the present study does not allow for a direct conclusion to be made, it is possible that while the effects of epinephrine were minimal, caffeine may have exerted other effects via another mechanism (i.e., the antagonism of adenosine receptors). Assuming that the effect of epinephrine is minimal, this additional action of caffeine alone may have been sufficient to alter blood pressure and mobilize FFAs but unable to elicit enough of an effect to detect changes in glucose tolerance.

Persons with TP provide an appropriate model to study the effects of caffeine on glucose tolerance without the confounding effects of epinephrine. However, it is possible that the tetraplegic condition itself may have introduced other factors that may have altered the response to caffeine. The majority of this population exhibits glucose intolerance (see discussion below). Studies with rodents have reported a reduced number of adenosine receptors within adipose tissue in insulin-resistant conditions (15). Therefore, it is possible that TP results in a reduced number of adenosine receptors, and, therefore, if caffeine decreases glucose tolerance via antagonism of adenosine receptors, an effect may not be observed. Although the caffeine-induced increase in FFA and glycerol concentrations within the Inc subgroup reflect a mobilization of FFAs, the lack thereof in the Com subgroup may provide some evidence to this downregulation of receptors. It is unlikely, however, that this contributed significantly to the lack of caffeine effect because both groups demonstrated similar glucose, insulin, C-peptide, proinsulin, and GLP-1 responses to caffeine. Furthermore, previous studies in subjects who were obese and had Type 2 diabetes, both of whom demonstrate varying degrees of glucose intolerance, report the caffeine-induced decline in glucose tolerance both during an OGTT (29, 30) and during an euglycemic-hyperinsulinemic clamp (25).

As mentioned above, persons with TP tend to exhibit varying degrees of glucose intolerance. Previous studies within this population have attempted to ascertain the mechanisms responsible for this impairment and have demonstrated altered function of enzymes involved in glucose metabolism (19), a decrease in muscle mass (1), and/or a change in muscle fiber type to less oxidative fibers (type 1 to type 2b) (1). Regardless, using the WHO classification system, we observed that 100% of our Com and 44% of Inc patients would be classified as at least impaired glucose tolerant but only when based on the 2-h OGTT value. In addition, we observed higher resting IL-6 concentrations within both subgroups, which have been correlated with insulin-resistant conditions (7). Although the observation of glucose intolerance within this population has been reported previously (5), our study provides some further characterization of this intolerance. Proinsulin levels were within an appropriate range considering the amount of insulin present during the same time period, indicating that the pancreas appears to respond with a sufficient amount of “functional” insulin when faced with a glucose load. Furthermore, preliminary GLP-1 concentrations were not only similar between subgroups but also comparable to values in able-bodied individuals (20), indicating indirectly that glucose absorption remained unaltered. However, within the Com subgroup, we have demonstrated that although the pancreas is able to respond to a glucose load, the response is somewhat compromised. This is supported by the 46% less (vs. the Inc subgroup) insulin response and gradual rise in C-peptide concentrations during the OGTT, with a simultaneous 50% increase in the glucose response. Taken together, it appears that although Com respond similarly to a glucose load in terms of functional insulin, the amount of hormone secreted for a given amount of
glucose is blunted and hence results in a more pronounced glucose intolerance. It is noteworthy that both our pre- and post-OGTT C-peptide values were uncharacteristically high (i.e., a normal resting value = 0.5 nM vs. our 11 nM). Because of the fact that a light breakfast was permitted 4 h before the commencement of the experiment, it is possible that these abnormally high values could be a result of this meal. Aksnes et al. (1) reported a reduced insulin clearance within this population, so it may be possible that C-peptide clearance is reduced as well. The fact that glucose levels remained elevated during both the Pl and Caf trials simultaneously with C-peptide levels not only provides evidence of an impairment in clearance but also provides reassurance that these high levels did not alter the results of the study.

In summary, caffeine ingestion does not impair glucose tolerance within persons with TP as demonstrated by the similar glucose, insulin, C-peptide, proinsulin, and GLP-1 responses during both the Pl and Caf trials. Although we cannot exclude the possibility that other mechanisms may be involved, this lack of caffeine effect may be partially attributed to the low and unchanging plasma epinephrine concentrations observed throughout the experiment. Furthermore, although the glucose intolerance observed within this population was unlikely to confound the present study’s results, we have demonstrated that the use of fasting glucose values in the classification of glucose tolerance within this population is inadequate from a clinical perspective, the management of postprandial glucose metabolism should be of primary importance.

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