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Cinnamon water extracts increase glucose uptake but inhibit adiponectin secretion in 3T3-L1 adipose cells

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The effects of three concentrations (0.2, 0.3, and 0.4 mg/mL) of a cinnamon extract (CE) (*Cinnamomum zeylanicum*) on glucose uptake and adiponectin secretion in 3T3-L1 adipocytes were examined in the presence and absence of 0.5 nM and 50 nM insulin. In the absence of insulin, adipocytes exposed to 0.2 mg/mL CE showed an approximate two-fold increase in glucose uptake relative to controls although glucose uptake was unaffected by the two higher concentrations of CE. No effect of CE on glucose uptake was noted in the presence of 0.5 nM insulin whereas the two highest concentrations (0.3 and 0.4 mg/mL) of CE showed a significant dose-dependent decrease in glucose uptake in the presence of 50 nM insulin. Treatment of the adipocytes with 50 nM wortmannin, an irreversible inhibitor of the p110 isoform of phosphoinositide 3′-kinase, was associated with complete inhibition of the stimulated glucose uptake induced by 0.2 mg/mL CE. Treatment of the adipocytes with 0.2 mg/mL CE was associated with an inhibition of adiponectin secretion to levels that were nondetectable. The present study indicates that although 0.2 mg/mL CE has insulin–mimetic action in 3T3-adipocytes in terms of glucose uptake, secretion of the antidiabetic hormone adiponectin is adversely affected.

Keywords: Adiponectin / 3T3-L1 adipose cells / Cinnamon / Glucose / Uptake

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1 Introduction

In the year 2002, 151 million people worldwide were suffering with diabetes and this number is expected to rise to 221 million people by the year 2010 [1]. More than 90% of these cases are type 2 diabetics suffering from severe insulin resistance. Research has begun to focus on adipose tissue as a possible central mediator of whole-body insulin resistance. Evidence for this central role comes not only from the link between obesity and type 2 diabetes [2], but also from the role of adipose tissue in regulating serum lipid concentrations [3] and, more recently, from the emerging role of adipose tissue as an endocrine organ [4].

The specific and/or limited effects of current drug treatments for diabetes, combined with the dangerous side effects that most of them induce, have fueled the search for alternative medicines. Cinnamon (*Cinnamomum zeylanicum* and related species) is the dried inner bark of various trees in the *Lauraceae* family that is native to Sri Lanka and India but is cultivated extensively in the tropical regions of the world [5]. Water and ammonium hydroxide extracts of cinnamon have been shown to increase glucose uptake by 5- to 32-fold in isolated rat fat cells [6, 7]. This cinnamon extract (CE) also increased insulin receptor (IR) kinase autophosphorylation and decreased protein tyrosine phosphate (PTP)-1 activity [8]. It is thought that the active component of cinnamon is a methylhydroxychalcone polymer (MHCP) that was isolated and found to potentiate the activity of insulin by two-fold for glucose uptake and four-fold for glycogen synthesis in 3T3-L1 adipocytes, but only had a slight effect without the presence of insulin [9]. Confirming the *in vitro* results, rats fed on a hot water extract of cinnamon daily for 3 wk showed an almost 150% increase in the

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Abbreviations: CE, cinnamon extract; **FBS,** fetal bovine serum; **IBMX,** 1-isobutyl-3-methylxanthine; **KRH,** Krebs-Ringer-HEPES; **MHCP,** methylhydroxychalcone polymer; **MTT,** (3,4,5 dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium; **PI3-kinase,** phosphoinositide 3′-kinase; **PPAR,** peroxisome proliferator-activated receptor; **PTP,** protein tyrosine phosphate

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glucose infusion rate during euglycemic clamp testing [10]. In a clinical trial, administration of 1, 3, or 6 g of cinnamon daily for 40 days led to a 18–29% decrease in fasting serum glucose levels as well as a similar degree of improvement in blood lipid parameters [11].

Previous studies have not examined the role that hormone and cytokine secretion from adipose tissue may have in mediating whole-body insulin resistance following cinnamon treatment. Adiponectin is an adipocytokine secreted solely by adipose tissue and has been shown to have both antidiabetic and antiatherogenic properties [12]. In the present study, a water extract of cinnamon was used in combination with insulin as treatments on 3T3-L1 adipocytes to study their effects on glucose uptake and adiponectin secretion.

2 Materials and methods

2.1 Materials

3T3-L1 fibroblast cells were purchased from American Type Culture Collection (Manassas, VA) with a range of 1–5 passages used in the experiments. 1-Isobutyl-3-methylxanthine (IBMX), dexamethasone, 0.25% Trypsin-EDTA, 2-deoxy-D-[1,2-^{3}H]glucose, (3,4-5 dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium (MTT), and wortmannin were purchased from Sigma-Aldrich Chemical (St. Louis, MO). DMEM, fetal bovine serum (FBS), penicillin-streptomycin, and human insulin were purchased from Life Technologies (Burlington, ON). General chemicals and lab equipment were purchased from either Sigma-Aldrich Chemical, Fisher Scientific (Nepean, ON), or Ultident Scientific (St. Laurent, QC).

2.2 CE preparation

Cinnamon sticks were purchased in stick form from the grocery store. Previous work has shown no significant differences in effects on glucose uptake when seven different sources and four different species of cinnamon were tested [13]. Cinnamon sticks were grinded with a plant tissue grinder. The powder (98.5 g) was extracted in double distilled water (5:1) overnight for 14 h with continuous stirring. The resulting extract was centrifuged at $400 \times g$ for 30 min to remove particulates and fiber. The supernatant was then filtered through Whatman #1 paper. The filtrate was freeze-dried (2.9 g) and stored at -80°C until use. The cinnamon freeze-dried extract was dissolved in water at a concentration of 25 mg/mL by heating the mixture to 37°C and vortexing every 10 min for approximately 1 h. The subsequent dilutions of the extract used in the cell culture experiments were completely soluble.

2.3 Cell culture

3T3-L1 cells were maintained in high-glucose DMEM containing 10% FBS and 1% penicillin-streptomycin at 37°C in a humidified atmosphere of 5% CO_2. Cells were subcultured every 3 to 4 days at approximately 90% confluence. Cells were grown in the plates to reach confluence in 3 days. At this point (day 0), cells were switched to differentiation medium (DMEM, 10% FBS, 0.25 µM dexamethasone, 0.25 mM IBMX, and 1 µg/mL insulin) for 3 days, with one medium change in between. On day 3, the dexamethasone and IBMX were removed leaving insulin on the cells for an additional 4 days, changing the medium every 2 days. Thereafter, the cells were maintained in the original propagation DMEM, changing medium every 2–3 days until use. Plates where cells were >90% differentiated were used for experiments between days 9 and 12 postinduction. Percentage differentiation was used by a visual method. On the day of the experiment, each well was examined under the microscope to identify the percentage of cells that had not yet become adipocytes, which are round and full of easily distinguishable fat globules. Wells that were used for experimentation contained little to no preadipocyte cells and were easily distinguishable as >90% differentiated overall.

2.4 Glucose uptake

Glucose-uptake activity was determined using 12-well plates as described previously [14]. The Krebs-Ringer-HEPES (KRH) buffer was composed of 128 mM NaCl, 4.7 mM KCl, 1.25 mM $CaCl_2$, 1.25 mM $MgSO_4$, 10.0 mM Na_2HPO_4, and 20 mM HEPES. Treatment with insulin (0.5 or 50 nM) occurred in the presence and absence of CE dissolved in KRH buffer, which was allowed to proceed for 30 min. For measurement of glucose transport, 2-deoxyglucose was used together with the radiolabeled tracer, 2-deoxy-D-[1,2-^{3}H]-glucose, to give a concentration of 0.2 mM (0.5 mCi/mmol) yielding an activity of 0.1 µCi/mL. After 60 min at 37°C, glucose uptake was terminated by first placing the plates on a bed of ice while the medium was collected to vials, and frozen at -20°C for later adiponectin analysis. The plates were washed with 3 mL/well ice-cold PBS and the cells were digested with 0.7 mL 1% Triton X-100 for 40 min at 37°C. Scintiverse BD (Sigma-Aldrich Chemical) was added and tritium counts were obtained using a 1209 Rackbeta liquid scintillation analyzer (LKB-Wallac, Finland). Measurements were made in duplicate and corrected for specific activity.

2.5 MTT viability assay

Cell viability was assessed using an MTT assay as described previously [15]. This assay is based on the reduction of

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MTT into purple formazan pigment by the succinate–tetrazolium reductase system in the respiratory chain of the mitochondria [16, 17]. The absorbance reading correlates with viable cell number and metabolic activity of the cells. The cells were seeded in 24-well plates. Cells were pretreated with serum-free DMEM and KRH buffer as described above in the methods used for glucose uptake. Treatment with CE dissolved in KRH buffer was allowed to proceed for 90 min at 37°C (in order to mimic the half hour pretreatment and 1 h glucose uptake period used for glucose-uptake experiments). At the end of the 90 min treatment time, all wells were aspirated and refilled with MTT solution (0.5 mg/mL MTT in glucose-free, phenol-red-free DMEM). The cells were incubated in this solution for 3 h at 37°C in an incubator. After 3 h, the wells were aspirated and refilled with a 0.04 N HCl in isopropanol solution. The wells were left to incubate for 5 min with gentle shaking until all the dark MTT color had been converted to a yellow color. An aliquot of 100 µL was collected from each well and transferred to a 96-well microplate. The absorbance for each well was read at 540 nm using a series 750 scanning spectrophotometer microplate reader (Cambridge Technology, Cambridge, MA, USA). Viability was expressed in terms of cell viability, as a ratio of the treatments to the KRH buffer control population.

2.6 Wortmannin inhibition of glucose uptake

This assay was performed in exactly the same way as the glucose-uptake assay but with the addition of 50 nM wortmannin 30 min prior and concurrently with the CE or insulin additions. Based on preliminary tests where 50 nM wortmannin showed complete inhibition of insulin-dependent glucose uptake, this concentration of wortmannin was used in combination with 50 nM insulin, and 0.2 mg/mL CE for this experiment. This concentration of CE was shown to be the most effective treatment at increasing glucose uptake.

2.7 Adiponectin secretion

Adiponectin secretion by the treated 3T3-L1 adipocytes was measured using a Quantikine ELISA Mouse Adiponectin Immunoassay (R&D Systems, MN), using the medium collected after the 60 min glucose-uptake period.

2.8 Statistical analysis

All data are expressed as mean ± SD and each value represents a minimum of three (n = 3–4) replicate experiments, and all assays were performed in triplicate. Data were analyzed using SAS version 8e (SAS Institute, 1994). One-way ANOVA was employed to determine main treatment effects. When a significant ANOVA result was obtained, Tukey's post-hoc test was used to determine differences among treatments (p <0.05). A paired, two-tailed t-test was used to determine significant differences (p <0.05) in glucose uptake between treatments with and without wortmannin.

3 Results

3.1 Glucose uptake

Preliminary tests allowing a 10 min glucose-uptake period were sufficient to show insulin-mediated uptake but the CE showed no effect. After the 1 h period of glucose uptake, significant insulin activation of 2-deoxy-glucose uptake was observed at both concentrations of insulin with the maximum stimulation detected at 50 nM insulin (Fig. 1). The uptake of 2-deoxy-glucose ranged between two- to five-fold for 0.5 nM (4339 ± 1760 dpm) and 50 nM insulin (13 945 ± 2213 dpm), respectively, as compared to that of basal uptake (2645 ± 1248 dpm).

Adipocytes exposed to 0.2 mg/mL CE without the presence of insulin showed a significant increase (approximately two-fold) in glucose uptake over the KRH buffer control (p <0.01) (Fig. 1). Any glucose uptake induced by the two higher concentrations (0.3 and 0.4 mg/mL) of CE in this treatment group was not significant and returned to near basal levels of glucose uptake at the highest concentration of 0.4 mg/mL. In combination with 0.5 nM insulin, CE did not show any significant changes to glucose uptake from the 0.5 nM insulin control but the uptake did show a trend to decrease with increasing CE concentration (Fig. 1). In combination with 50 nM insulin, the two highest concentrations (0.3 and 0.4 mg/mL) of CE significantly decreased glucose uptake (p <0.01) compared to the uptake with 50 nM insulin alone (Fig. 1).

3.2 MTT assay

The CE treatments (0.2 and 0.3 mg/mL) significantly increased cell viability over the KRH control. The KRH control cells experienced a significant decrease in absorbance measurement in comparison to the cells left in DMEM (Fig. 2). Treatment with the two lower concentrations of CE (0.2 and 0.3 mg/mL) increased the absorbance to the same level as the cells left in DMEM and were significantly higher than the KRH control. The highest concentration of CE also increased absorbance to the same degree as the cells left in DMEM but did not show significant difference from the KRH control.

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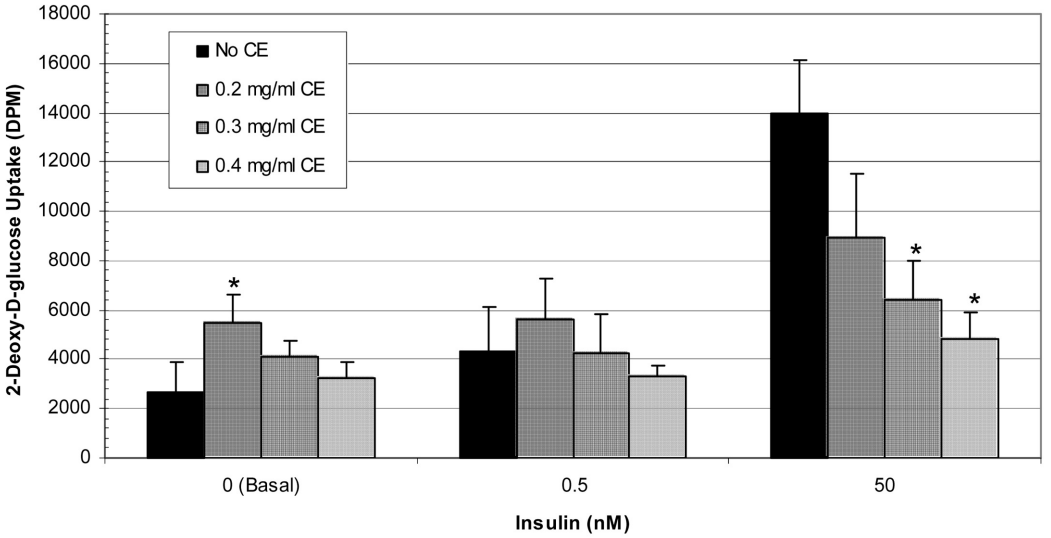

Figure 1. CE effect on glucose uptake in 3T3-L1 adipocytes with or without the presence of 0.5 or 50 nM insulin. After a 30 min pretreatment of the cells with CE and/or insulin, glucose uptake was allowed to proceed for 60 min in the presence of CE extracts and/or insulin. Data are mean uptakes ± SD from three or more independent experiments performed in triplicate, expressed as disintegrations *per* min (DPM). Significant difference between untreated cells (solid black bar) and the CE-treated cells was tested within groups based on insulin concentration. * $p < 0.05$ (using Tukey's post-hoc test).

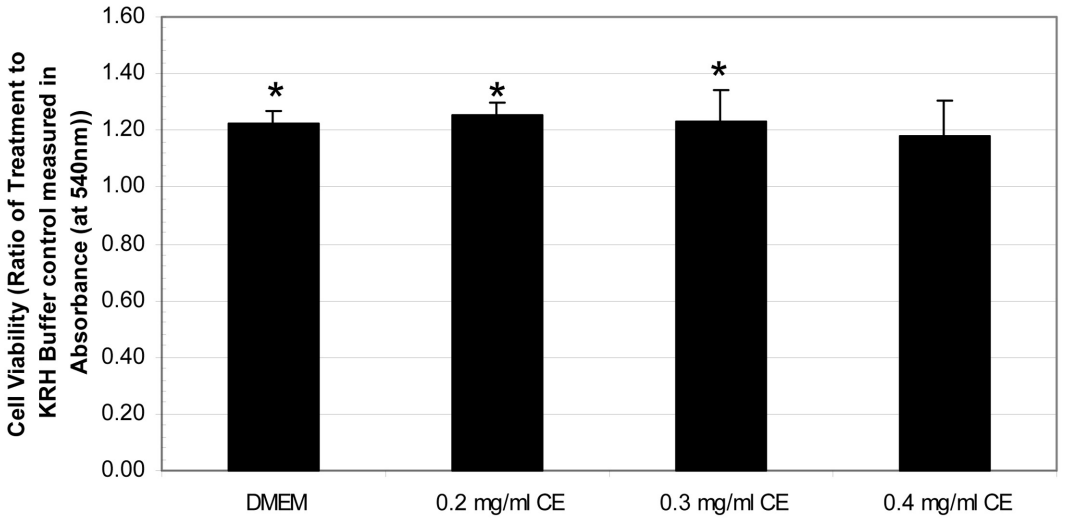

Figure 2. The effect of CE extract concentration on cell viability using the MTT assay. Cells were exposed to the CE treatment for 90 min in order to mimic the half hour pretreatment and 1 h glucose uptake used in the glucose-uptake experiments. The DMEM treatment cells were left in the DMEM medium with changes to fresh DMEM each time the treated and KRH control cells underwent a medium change. Data are mean ± SD of three replicate experiments and expressed as population growth, absorbance measured for the treatment divided by the absorbance measured for the KRH buffer control population (absorbance = 0.151 ± 0.01 at 540 nm). Significant difference was tested between the treatments shown and the KRH buffer control (ratio = 1). * $p < 0.05$ (using Tukey's post-hoc test).

3.3 Effect of wortmannin on CE-stimulated glucose uptake

The effect of wortmannin on 2-deoxyglucose uptake in the presence of 50 nM insulin or 0.2 mg/mL CE is shown in Fig. 3. In the absence of pre- and concurrent incubation with wortmannin, 50 nM insulin caused a 7.5-fold stimulation of 2-deoxy-D-glucose uptake. The 0.2 mg/mL CE treatment caused an almost three-fold stimulation of 2-deoxyglucose uptake in the absence of pre- and concurrent incubation with wortmannin. Treatment of the adipocytes with 50 nM wortmannin was associated with a significant ($p < 0.05$) inhibition of the stimulated uptake of glucose by the 0.2 mg/mL CE dose. Similarly, glucose uptake asso-

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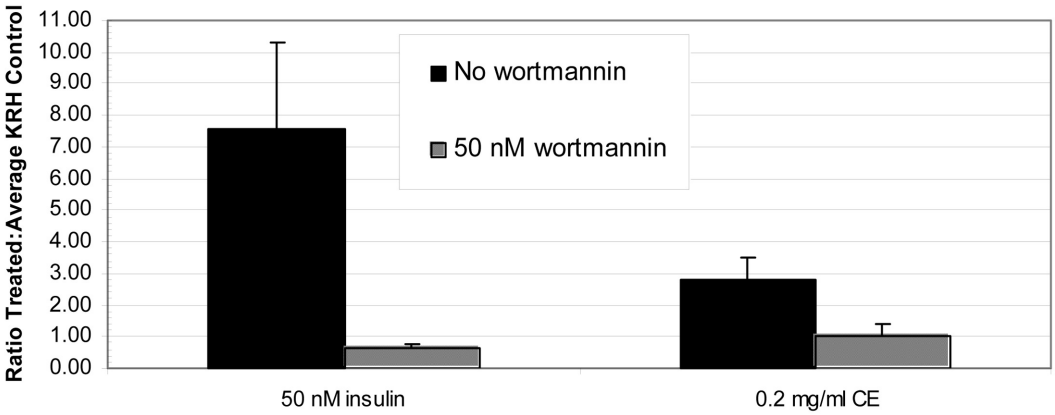

Figure 3. The effect of 50 nM wortmannin on 3T3-L1 adipocyte glucose uptake when treated with 50 nM insulin alone or with 0.2 mg/mL CE alone. Cells were exposed to wortmannin from the beginning of the 30 min KRH buffer pretreatment until the end of the 60 min glucose-uptake period. Data are expressed as the DPM obtained in the treatment divided by the DPM from the KRH buffer control (basal glucose uptake). Significant differences (p <0.05) were determined using paired, two-tailed t-tests to test for glucose uptake with and without 50 nM wortmannin in the 50 nM insulin treatment and the 0.2 mg/mL CE treatment. Data were derived from three independent experiments performed in triplicate, and expressed as means ± SD.

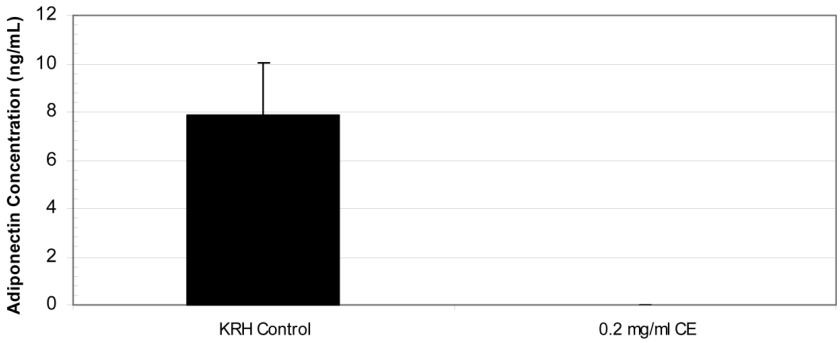

Figure 4. Effect of CE on adiponectin secretion into the medium. The medium was collected from the 12-well plates used in the glucose-uptake experiments after the 60 min exposure to ^{3}H-deoxy-D-glucose with or without 0.2 mg/mL CE. The bars represent the mean ± SD of at least three repetitions (n = 3–4) from different experiments.

ciated with the 50 nM insulin treatment was significantly (p <0.05) inhibited to slightly below basal glucose levels.

3.4 Adiponectin secretion

These adiponectin concentrations were measured in the medium collected after the 1 h period of glucose uptake during the glucose uptake experiments. Since the 0.2 mg/mL CE treatment significantly increased glucose uptake in the adipocytes, adiponectin concentration was measured in this treatment medium. Compared to the KRH control medium that had an adiponectin concentration of 7.9 ng/mL, adiponectin secretion by 3T3-L1 adipocytes was significantly and dramatically decreased by the CE treatment to nondetectable levels of adiponectin (Fig. 4).

4 Discussion

The present study shows that a water extract from cinnamon can increase glucose uptake in 3T3-L1 adipocytes without the presence of insulin. At a concentration of 0.2 mg/mL, CE increased glucose uptake by 3T3-L1 adipocytes by two-fold over basal uptake levels (Fig. 1). At concentrations above 0.2 mg/mL, however, glucose uptake stimulation was reduced and reached the basal level at the 0.4 mg/mL dose of CE. Despite the positive outcome of glucose-uptake stimulation with the CE dose of 0.2 mg/mL, the present findings indicate that CE was associated with a dose-dependent inhibition of the insulin-mediated glucose uptake (Fig. 1). The results of the MTT assay indicate that the changes to glucose uptake associated with the CE treatment cannot be explained by differences in the number of viable cells among the treatments. The concentrations of CE used in the

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experiment appear to increase the number of viable cells or at least the metabolic activity of the cells over the KRH control (Fig. 2). The increase in cell viability, however, was minimal and would not support the two-fold increase in glucose uptake by 0.2 mg/mL CE or the dose-dependent decrease in glucose uptake observed with CE in the presence of insulin.

Similar results have recently been reported in a rat epididymal fat pad assay where the lower concentrations of CE used (0.54–0.014 mg/mL) reduced insulin-mediated glucose uptake [13]. Some other plant extracts have also been shown to increase glucose uptake on their own but negatively impact the effects of insulin [13, 18]. A water extract of *Lagerstroemia speciosa* that showed similar results to the present findings on glucose uptake in 3T3-L1 adipocytes was shown to decrease blood glucose levels in type 2 diabetics by 30% over 2 wk [19].

Water extracts of cinnamon have been shown to increase IR phosphorylation and decrease PTP-1 activity in *in vitro* adipose cells [8]. CEs also increase 1-insulin receptor substrate-1 (IRS-1) phosphorylation and IRS-1/PI3-kinase association in the skeletal muscle of rats [10], indicating that cinnamon acts upstream of PI3–kinase near the surface of the cell. The results of the present study indicate that CE may be competing with insulin at some point along the insulin signaling pathway because at each concentration of CE used, glucose uptake occurred to a similar extent between the CE treatments either in the presence or absence of 0.5 nM insulin (Fig. 1). At 50 nM insulin, however, CE treatment was associated with a dose-dependent decrease in glucose uptake although glucose uptake was never diminished to the degree observed with CE treatment alone (Fig. 1). Taken together, the above results indicate that CE, especially at the higher doses, predominates over insulin in the control of glucose uptake by the 3T3–L1 adipocytes. The CE does not appear to act directly on the cell surface as, unlike insulin, 1 h of concurrent CE and glucose exposure was required to show any changes in CE-mediated glucose uptake. As theorized previously with the MHCP component of cinnamon [9], the CE active component(s) may require additional time to pass through cell membranes to reach the intracellular locations where they can exert their effect.

In contrast to the present findings, when the MHCP isolate from cinnamon was tested on 3T3-L1 cells, it exhibited an insulin-sensitizing effect [9]. The concentration of MHCP in the CE was not measured; however, less specific CEs (using water and NH_4OH) have been used in isolated fat cell experiments and shown positive results on glucose uptake [7, 13]. Significantly, water extracts of cinnamon or simply ground cinnamon have shown positive results on glucose levels with *in vivo* experiments on rats and humans [10, 11]. The extract used in our study would have a similar composition to the extracts used in the aforementioned studies as all these extracts would include all the water-soluble components of cinnamon. Other studies have used more intensive extraction procedures and found multiple active fractions [8, 9, 13]. Although MHCP has been identified and further tested as an active component, other isolated fractions of CE have been shown to potentiate insulin action [13]. It would seem that different components of cinnamon may affect glucose uptake in various ways. In the present study, some CE components could be repressing the activity of insulin-sensitizing components such as MHCP, or the insulin-sensitizing component was not extracted in CE.

In the present study, wortmannin treatment was associated with a complete inhibition of the increase in glucose uptake caused by the 0.2 mg/mL CE dose (Fig. 3), which demonstrates that, similar to insulin, CE relies on a wortmannin-sensitive protein to increase glucose uptake. This effect of wortmannin on CE-induced glucose uptake also confirms that the increase in glucose uptake seen with CE is not simply a result of a difference in viable cell number or cell metabolic activity. Wortmannin is a potent and irreversible inhibitor of the p110 isoform of PI3-kinase, thereby preventing insulin-stimulated GLUT4 and GLUT1 translocation and inhibiting glucose uptake with nanomolar efficiency [20]. For this reason, wortmannin is often used in cell culture to test the reliance of glucose uptake potentiating substances or extracts on this protein [8, 9]. More recent evidence shows that wortmannin has a second higher affinity, reversible target that may or may not be a PI3-kinase but is involved in the p38 MAPK pathway activation of cell surface GLUT4 [21]. Further research is needed to identify the high affinity target of wortmannin and to determine whether the glucose uptake activity of CE relies on one or both of these wortmannin targets.

The most striking finding of the present study is that the effective CE dose of 0.2 mg/mL that was associated with an increased glucose uptake, also appeared to concurrently inhibit all detectable adiponectin secretion from the 3T3-L1 adipocytes (Fig. 4). Given that insulin has been shown to stimulate adiponectin secretion from 3T3-L1 adipocytes by increasing the release of adiponectin from a distinct, secretory compartment within the cell [22], this form of CE treatment cannot be considered a complete insulin–mimetic. Also, given the mounting research to show adiponectin as insulin-sensitizing and antiatherogenic adipocytokine, the present results cast doubt regarding the role of CE as an antidiabetic in this regard. The inhibition of CE on adiponectin secretion may be mediated by the same pathway that insulin uses to regulate the compartmental release of adiponectin or by acting on peroxisome proliferator-activated receptor (PPAR)-γ. PPAR-γ is a transcriptional factor that affects insulin sensitivity and glucose metabolism in part by

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regulating the expression and secretion of adipocytokines, including adiponectin. Thiazolidinediones (TZDs) are a class of antidiabetic drugs that act specifically as PPAR-γ ligands and have been shown to increase both glucose uptake and adiponectin secretion in 3T3-L1 adipocytes [23]. Clearly, CE has the opposite effect of these well known antidiabetic drugs in terms of adiponectin secretion, but it remains to be determined which component(s) of CE are inhibiting the secretion and how this inhibition is occurring.

In summary, at a concentration of 0.2 mg/mL, the water extract of cinnamon was able to act as an insulin–mimetic in terms of its ability to increase glucose uptake by two-fold in 3T3-L1 adipocytes. Concurrent with the increased glucose uptake, however, CE showed an opposite effect to insulin by inhibiting adiponectin secretion to nondetectable levels from the cells. Moreover, in combination with insulin, CE showed a dose-dependent inhibition of insulin-stimulated glucose uptake. Although these results indicate both pro- and antidiabetic effects of CE, pure cinnamon powder has been shown to improve blood glucose and lipid parameters in type 2 diabetics [11] and it may be that some components in CE involved in the antidiabetic action become altered or remain unabsorbed during digestion. Given the potency of adiponectin to mediate whole-body insulin resistance and atherogenesis, however, the results of the present study indicate that further research is needed regarding the effects of cinnamon on the secretion of adiponectin and other hormones and cytokines that regulate insulin sensitivity. Such studies will help determine the overall and long-term effects of cinnamon consumption on diabetes and its complications.

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