A synergistic effect of Cremophor and beta glucosylceramide to exert liver and sugar protection

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Abstract Many commonly used drugs carry the potential to induce hepatotoxicity, and a large number of foods and beverages induce an increase in blood sugar levels. A change in lifestyle by omitting these compounds is not applicable in many circumstances. β -Glucosylceramide (GC) is a naturally occurring glycosphingolipid that exerts an effect on the immune system. Cremophor EL (CrEL) is a synthetic, nonionic surfactant that is used as a vehicle for the administration of water-insoluble compounds. The aim of the present study was to determine the synergistic effect of oral administration of the combination of GC and CrEL (GCC) when added to potential toxic substrates or to sugar-enriched compounds. Four groups of mice, treated with PBS, GC, CrEL, or GCC were studied in the concanavalin A immune-mediated hepatitis model, in the acetaminophen (APAP) toxicity model, and as additives to two types of sugar-enriched soda drinks. Both GC and CrEL exerted hepatoprotective effects in the ConA hepatitis and APAP toxicity models. Moreover, in both models, GCC exerted a synergistic effect in ameliorating liver damage as manifested by a significant decrease in the ALT serum levels. When added to two types of sugar-enriched sodas, GCC exerted a synergistic effect in ameliorating the increase in blood sugar levels. GCC exerts synergistic hepatoprotective and glucose-protective effects in models of liver damage and increased serum glucose. GCC can provide liver and sugar protection when co-administered with hepatotoxic drugs or sugar-enriched drinks.

Keywords β -Glucosylceramide · Cremophor EL · ConA hepatitis · Acetaminophen · Soda drinks

Abbreviations

GC	β -Glucosylceramide
CrEL	Cremophor EL
GCC	β -Glucosylceramide with Cremophor E
ConA	Concanavalin A
APAP	Acetaminophen
AUC	Area under the curve

Introduction

Many compounds used in everyday life, including commonly used drugs, carry the potential to induce hepatotoxicity (Rusmann et al. 2010; Garcia-Cortes et al. 2011; Stickel et al. 2005; Larrey 2000). Similarly, a large number of foods and beverages, enriched in sugars, induce an increase in blood sugar levels or are associated with augmenting an insulin resistance state (Bundrick et al. 2014; Brown et al. 2012; Brown and Rother 2012; Nettleton et al. 2009). Protection of the liver from hepatotoxic substrates and the prevention of an increase in blood sugar following the administration of sugar-enriched compounds are major public health unmet needs. Lifestyle modification by omitting the use of these compounds is the best way to prevent these complications, but is not applicable in many cases (Whitehead and Russell 2004). Therefore, adding a hepato- or sugar-protective substrate into foods or drugs is a more practical, realistic, and convenient way to prevent and/or ameliorate the health burden related with their use.

β -Glucosylceramide (GC) is a naturally occurring intermediate in the metabolic pathways of complex

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glycosphingolipids and has been suggested to exert an immune-modulatory effect (Margalit et al. 2005; Zigmond et al. 2007). Previous studies have suggested that GC exerts a beneficial effect in animal models of type 2 diabetes and fatty liver disease (Margalit et al. 2006; Zigmond et al. 2009). A phase I clinical trial has shown that the oral administration of GC is safe in humans and may exert a beneficial effect on insulin resistance and fatty liver disease (Zigmond et al. 2006).

Cremophor is a version of polyethoxylated castor oil prepared from the reaction of ethylene oxide with castor oil. Cremophor EL (CrEL) is a synthetic, nonionic surfactant. Its usefulness comes from its ability to stabilize emulsions of nonpolar materials in aqueous systems. CrEL is used as a vehicle for both the oral and intravenous administration of water-insoluble compounds in humans. It is an excipient or additive in several drugs, including the anticancer agent paclitaxel (Taxol) (Adams et al. 1993; van Zuylen et al. 2001). In contrast to earlier reports, CrEL is not an inert vehicle but exerts a range of biological effects, some of which may have clinical implications (Gelderblom et al. 2001). CrEL can form micelles in aqueous solutions, affecting the disposition of various drugs by changing the unbound drug concentration through micellar encapsulation (van Zuylen et al. 2001). Its use has been associated with the modulation of P-glycoprotein activity (van Zuylen et al. 2001), and with the alteration of lipoprotein patterns (Gelderblom et al. 2001). It was also associated with severe anaphylactic hypersensitivity reactions, hyperlipidemia, aggregation of erythrocytes, and peripheral neuropathy (Gelderblom et al. 2001). CrEL has also shown anti-cancer effects, including reversing the multidrug resistance (MDR) phenotype (Woodcock et al. 1990).

The aim of the present study was to determine the synergistic effect of the oral administration of beta glucosylceramide with Cremophor when added to potential hepatotoxic substrates or to sugar-enriched compounds. The data suggest a synergistic effect between the two to provide liver and sugar protection.

Materials and methods

Animal Trials

C57BL/6 (B6) male mice, aged 10–11 weeks, were purchased from Harlan Laboratories. All of the mice were maintained at the Animal Core of the Hadassah-Hebrew University Medical School. Mice were given standard laboratory chow and water ad libitum and were maintained in a 12-h light/dark cycle. All of the animal experiments were carried out in accordance with the guidelines of the Hebrew University-Hadassah Institutional Committee for

the Care and Use of Laboratory Animals and with the committee's approval.

Oral administration of GC and CrEL

β -Glucosylceramide (GC) was purchased from Avanti Polar Lipids (Alabaster, AL, USA), dissolved in ethanol, and emulsified in Cremophor EL (CrEL) purchased from Sigma with a final 1:1 ratio of CrEL and ethanol (CE).

Effect of GC and CrEL in the ConA hepatitis model

Induction of ConA hepatitis

ConA (MP Biomedicals, USA) was dissolved in 50 mM Tris pH 7, 150 mM NaCl, 4 mM CaCl_2 and was injected into the tail vein at a dose of 500 $\mu\text{g}/\text{mouse}$ (15 mg/kg). Experimental groups: Four groups of mice (25 g) were studied ($n = 5/\text{group}$). All were injected with ConA (500 $\mu\text{g}/\text{mouse}$) and were sacrificed 16 h later. Mice in control group A were treated with PBS; mice in group B were fed 3 mg of GC and 30 μl of CrEL; mice in group C were fed 3 mg of GC; and mice in group D with were fed 30 μl of CrEL. All of the treatments were administered 2 h before ConA injection. Liver damage was determined by the ALT and AST serum levels, and liver histology.

Effect of GC and CrEL in the APAP-induced hepatotoxicity model

Induction of APAP-mediated hepatotoxicity

APAP-mediated hepatotoxicity was induced in mice by the oral administration of 4 mg of APAP. Liver toxicity was determined by the ALT and AST serum levels, and liver histology.

Experimental and control groups

Mice (25 g) were orally treated using a combination of APAP and 3 mg of GC, and 30 μl of CrEL.

Assessment of the effect of the new formulation on APAP absorption and biological activity

To determine that these combinations do not prevent the anti-inflammatory effect of APAP, mice (25 g) were tested for the serum levels of $\text{TNF}\alpha$. In addition the effect of the treatment on $\text{TNF}\alpha$ secretion from ConA-activated splenocytes harvested from mice in all groups was performed. A total of 10^6 splenocytes were incubated for 24 h with 5 $\mu\text{g}/\text{ml}$ ConA in vitro followed by $\text{TNF}\alpha$ measurement in the media. Triplicates were prepared from each

mouse for each of the groups. ELISA assay was used for TNF α measurements using the TNF α Quantikine kit (R&D systems).

Effect of GC and CrEL in alleviating the increase in blood sugar following the administration of sugar-enriched sodas

Increase in blood sugar levels following the oral administration of sugar-enriched sodas

An increase in blood sugar was induced in mice by the oral administration of two commonly used sugar-containing sodas marked soda 1 and soda 2, 400 μ l, once per mouse, following an overnight fast.

Experimental and control groups

Four groups of mice (25 g) were studied. All were orally administered by gavage with 400 μ l of one of the two soda drinks marked 1 and 2. Mice in the control group A were treated with PBS; mice in group B were fed 3 mg of GC and 30 μ l of CrEL; mice in group C were fed 3 mg of GC; and mice in group D with 30 μ l of CrEL. Glucose and insulin levels were measured at the time points 0, 15, 30, 60, 90, 120 and 180 min after soda drink administration.

Results

Synergistic effect of GC and CrEL in the ConA hepatitis model

Figure 1 shows the synergistic effect of GC and CrEL in the amelioration of the immune-mediated liver damage in the ConA hepatitis model. Four groups of mice were studied. Mice in the control group were treated with PBS; mice fed with GC or CrEL showed significant reduction in both ALT and AST serum levels. Mice treated with the combination of both had a significantly more profound amelioration of the liver damage (ALT levels were 8887 ± 4484 ; 872 ± 996 ; 1875 ± 1840 ; and 1472 ± 905 IU; for controls, GCC, GC and CE treated mice, respectively; $p < 0.005$ for both treated group versus controls; $p = 0.045$ between the GCC- and CE-treated groups).

Synergistic effect of GC and CrEL in the APAP-induced hepatotoxicity model

Figure 2a shows the synergistic effect of GC and CrEL in preventing the APAP-induced liver damage. Both GC and CrEL exerted a beneficial effect on amelioration of

Fig. 1 Four groups of mice were studied in the ConA hepatitis model. Mice were treated with PBS, GC, CrEL, or GCC. Mice were followed for ALT and AST serum levels. Mice treated with GCC showed a synergistic effect of GC and CrEL ($p = 0.045$ between the GCC- and CE-treated groups)

the liver damage; however, a more profound effect was noted in GCC-treated mice (ALT levels were $15,612 \pm 6396$; 7996 ± 3774 ; 9290 ± 2618 ; and $10,085 \pm 1830$ IU; for controls, GCC, GC and CE treated mice, respectively).

To determine that the protective combination does not jeopardize the anti-inflammatory effect of APAP, mice in all groups were tested for serum TNF α levels and for TNF α secretion from ConA-activated splenocytes. No significant differences in the serum TNF α levels were noted between the GC, CrEL, and GCC versus APAP groups (data not shown). Figure 2b shows a lack of significant changes in TNF α secretion from ConA-activated splenocytes harvested from all groups compared with APAP controls (TNF α levels were 64 ± 13 ; 88 ± 2 ; 87 ± 35 ; and 77 ± 14 pg/ml; for controls, GCC, GC and CE treated mice, respectively; $p = \text{NS}$ between APAP and all other groups).

Synergistic effect of GC and CrEL in alleviating the increase in blood sugar following the administration of sugar-enriched sodas

A synergistic effect of GC with CrEL, when added to two types of soda drinks, was documented in the amelioration of the increase in sugar blood levels. Figure 3a shows the increase in blood sugar levels in all groups of mice following the oral administration of soda 1. Mice receiving

Fig. 2 Four groups of mice were studied in the APAP-induced liver damage model. Mice were treated with PBS, GC, CrEL, or GCC, and followed for ALT serum levels. **a** Both GC and CrEL exerted a beneficial effect on the amelioration of the liver damage; however, a more profound effect was noted in the GCC-treated group ($p < 0.05$). **b** In vitro TNF α secretion was measured from ConA-activated splenocytes harvested from all groups using ELISA ($p = \text{NS}$ between APAP and all other groups)

soda 1 with GCC had a profound decrease in the blood sugar levels compared with all of the other groups. Figure 3b shows the area under the curve (AUC) in 30 min following the oral administration of soda 1. A significant synergistic effect was documented for GCC in ameliorating the increase in blood sugar levels compared with GC or CrEL alone ($p = 0.001$ for GCC vs. GC or CrEL). Figure 3c displays the AUC in 60 min showing a synergistic effect of GCC (AUC of $10,010 \pm 1219$; 7826 ± 593 ; 9056 ± 468 ; and 8678 ± 643 , for controls, GCC, GC and CE treated mice, respectively; $p < 0.05$ for GCC vs. GC and CrEL).

The experiment also tested an additional commonly used glucose-enriched soda, marked soda 2. Figure 3d

shows that mice receiving soda 2 with GCC had a profound decrease in the blood sugar levels compared with all of the other groups following the oral administration of soda 2. Figure 3e shows the AUC in 30 min following the oral administration of soda 2. A significant synergistic effect was documented for GCC in ameliorating the increase in blood sugar levels compared with GC or CrEL alone (AUC of 3467 ± 254 ; 3010 ± 200 ; 3606 ± 576 ; and 3438 ± 392 , for controls, GCC, GC and CE treated mice, respectively; $p < 0.05$ for GCC vs. GC or CrEL).

Discussion

The results of the present study showed that GCC, a combination of GC with CrEL, is synergistic in exerting a hepatoprotective effect and sugar-protecting effect in animal models.

Preventive medicine is one of the best options for improving health. It can be achieved by lifestyle modification, which is difficult to sustain (Bazzano et al. 2005; Shrestha and Ghimire 2012; Butryn et al. 2011). Omitting the use of potentially toxic or hazardous compounds, or glucose-enriched foods, is an alternative for the prevention of the development of disease and improving health. However, many of the drugs or foods that carry potential health hazards are either difficult to replace or involve major changes in lifestyle. Both are challenging to apply and maintain for long periods of time. A somewhat more practical way for overcoming these obstacles is via the co-administration of protective substrates.

GC is a soy-derived compound, and Cremophor is a polyethoxylated castor oil prepared from the reaction of ethylene oxide with castor oil. Our data show that a combination of GC and CrEL (GCC) exerted a synergistic hepatoprotective effect, improving glucose metabolism when added to potentially toxic compounds.

GCC exerted a hepatoprotective effect in the ConA hepatitis model, supporting a beneficial anti-inflammatory effect when it is being administered under a pro-inflammatory environment. The data supported their potential use as anti-inflammatory and immune-modulatory compounds. A synergistic effect of GC and CrEL was demonstrated in the APAP-induced hepatotoxicity model, suggesting that combining these compounds with potentially hepatotoxic drugs can prevent liver damage without jeopardizing their beneficial clinical effect. Drug-induced liver injury (DILI) affects 20 new cases per 100,000 persons each year (Leise et al. 2014). Idiosyncratic DILI accounts for 11% of the cases of acute liver failure in the United States. APAP, amoxicillin/clavulanate isoniazid, and non-steroidal anti-inflammatory drugs, commonly used medications, are among the most common causes of DILI (Leise et al. 2014;

Fig. 3 PBS, GC, CrEL, or GCC was added to two types of sugar-enriched soda drinks. **a** The increase in the serum glucose levels following the oral administration of soda 1. Mice receiving soda 1 with GCC manifested a profound decrease in blood sugar levels compared with all other groups. **b** AUC in 30 min following the oral administration of soda 1. A significant synergistic effect was documented for GCC in ameliorating the increase in blood sugar levels compared with GC or CrEL alone ($p = 0.001$ for GCC vs. GC or CrEL). **c** AUC in 60 min following the oral administration of soda

1. A synergistic effect of GCC is noted on the decrease in blood sugar levels ($p < 0.05$ for GCC vs. GC or CrEL). **d** The increase in serum glucose levels following the oral administration of soda 2. Mice receiving soda 2 with GCC manifested a profound decrease in blood sugar levels compared with all other groups. **e** AUC in 30 min following the oral administration of soda 2. A significant synergistic effect was documented for GCC in ameliorating the increase in blood sugar levels compared with GC or CrEL alone ($p < 0.05$ for GCC vs. GC or CrEL)

Stine and Lewis 2011). APAP remains one of the more common drugs taken in overdose with potentially fatal consequences (Hodgman and Garrard 2012). Equally common to acute overdose is the repeated use of excessive

amounts of acetaminophen, as well as the simultaneous use of acetaminophen-containing products (Hodgman and Garrard 2012). The sterile inflammatory response occurring during APAP hepatotoxicity may be beneficial by

limiting the formation and impact of pro-inflammatory mediators, thus promoting tissue repair (Jaeschke et al. 2012). Pro- and anti-inflammatory cytokines and chemokines can directly promote intracellular injury mechanisms by inducing nitric oxide synthase, inhibiting cell death mechanisms by the expression of acute-phase proteins (HSPs, heme oxygenase-1), or by promoting hepatocyte proliferation (Jaeschke et al. 2012). The data of the present study suggest that combining GCC with potentially hepatotoxic agents may exert hepato-protection without jeopardizing their beneficial clinical effects.

Several liver protectors such as *Silybum marianum* (Milk thistle), *Phyllanthus niruri*, and *Panus giganteus* (Berk), were shown to improve liver damage (Vargas-Mendoza et al. 2014). Silymarin contains at least seven flavoligands and the flavonoid taxifolin. The hepatoprotective and antioxidant activity of silymarin is caused by its ability to inhibit the free radicals that are produced from the metabolism of toxic substances such as ethanol, acetaminophen and carbon tetrachloride (Vargas-Mendoza et al. 2014). However, none of these was shown to prevent either APAP-mediated hepatotoxicity or DILI.

The present data show that GCC, a combination of GC and CrEL, exerted a synergistic effect in alleviating the increase in blood sugars following the administration of sugar-enriched sodas.

Previous studies showed that GC as well as soy-derived products exert a beneficial immunomodulatory effect in an NKT and T cells-dependent way (Khouri et al. 2015; Ilan 2016). Inflammation is a major contributing factor for the pathogenesis of target organ damage in the metabolic syndrome, contributing to both liver damage and insulin resistance (Sundara Rajan and Longhi 2016; Hotamisligil 2006). A systemic immunomodulatory effect may underlines the beneficial sugar and liver protective effect noted in the present study (Ilan 2016a, b, c).

Dietary habits have been associated with the prevalence of metabolic syndrome (Amini et al. 2010; Nettleton et al. 2008). The association between soda drinking and risk of metabolic syndrome has been described in several trials. Soda consumption is a marker for excess energy consumption and is associated with weight gain (Bundrick et al. 2014). Frequent soda consumption is positively associated with visceral obesity (Mollard et al. 2014). Soft drink consumption is significantly linked to overweight, obesity, and diabetes worldwide, including in low- and middle-income countries (Basu et al. 2013). In subjects without diabetes, the energy consumed from soda is negatively related to choosing low-fat foods, and positively associated with choosing solid foods high in simple sugars, and with overall average daily energy intake.

Consumption of a diet rich in sugar-sweetened soda may promote insulin-resistant phenotypes, while consumption

of a diet rich in fruits, vegetables, whole grains and reduced-fat dairy, protects against these phenotypes (Liu et al. 2009). The ‘Soda’ diet pattern had a significantly higher mean fasting insulin concentration (Liu et al. 2009). An association between the increased incidence of type 2 diabetes and high consumption of sugar-sweetened soft drinks was reported in European adults (InterAct Consortium 2013). Soft drink consumption was associated with an increased risk of type 2 diabetes in Japanese women (Eshak et al. 2013). High intake of sugar-sweetened beverages in childhood is linked to an increased risk of obesity and type II diabetes later in life (Lasater et al. 2011).

Consumption of non-nutritive sweeteners can elicit the secretion of gut hormones such as glucagon-like peptide 1 and glucose-dependent insulintropic peptide in enteroendocrine or islet cells (Brown and Rother 2012). Four weeks of sugar-sweetened beverage supplementation in healthy individuals shifted the substrate metabolism toward carbohydrates, increasing glycolytic and lipogenic gene expression and reducing mitochondrial markers (Sartor et al. 2013).

The consumption of “diet sodas”, at least daily, is associated with significantly greater risks of select incident metabolic syndrome components and type 2 diabetes (Nettleton et al. 2009). The associations between diet soda consumption and type 2 diabetes were independent of baseline measures of adiposity or changes in these measures. The data support the notion that, while using non-nutritive sweeteners may be associated with reduced caloric intake, it does not omit the risk of type 2 diabetes. Non-nutritive sweeteners can bind to sweet-taste receptors present in the oral cavity and on enteroendocrine and pancreatic islet cells (Bundrick et al. 2014). Thus, these sweeteners may have biological activity by eliciting or inhibiting hormone secretion. In humans, few studies have examined the hormonal effects of non-nutritive sweeteners, and inconsistent results have been reported. In one study, the ingestion of diet soda before a glucose load augmented glucagon-like peptide 1 (GLP-1) secretion in type 1 diabetics and control subjects but not in type 2 diabetic subjects (Brown et al. 2012). The strategy described in the present study, of using a sugar protector additive, may thus alleviate some of these risks associated with sugar-sweetened soda and with non-nutritive sweeteners. In parallel with attempts to alter life style, it may offer a relatively healthier soda, which may decrease the relevant unwanted effects of these drinks.

In summary, the results of the present study support the notion of using the synergistic combination of GC and CrEL, GCC, as an additive to hepatotoxic drugs or sugar-containing beverages or foods, may alleviate some of the damage associated with their consumption. GCC is an immune-modulatory combination that can also be used for

the treatment of acute and chronic inflammatory states. GCC can serve as a protective adjuvant for the prevention of drugs, drinks, and food-related complications. This strategy may be complimentary to educational and other measures being taken to prevent the liver and metabolic damage associated with regular or overconsumption of these products. Further studies are required to determine the long-term effects of their use in humans.

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