EFFECTS OF SPECIFIC COMPETITIVE INHIBITORS OF SWEET TASTE RESPONSE ON GLUCOSE-INDUCED INSULIN RELEASE

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ABSTRACT

The effects of specific competitive inhibitors of sweet taste response on insulin release and glucose oxidation were studied using isolated rat pancreatic islets. The α anomers of *p*-nitrophenyl-D-glucopyranoside (PNP-Glu) and *p*-nitrophenyl-D-mannopyranoside (PNP-Man) dose-dependently (~ 5 mM) inhibited insulin release induced by 10 mM D-glucose without affecting glucose oxidation in the islets, while the β anomers were ineffective, as reported in the gustatory cell. The inhibitory effect of the α anomers of these compounds, at 5 mM, were surmounted by increasing the concentration of D-glucose to 20 mM. Either anomer of *p*-nitrophenyl-D-galactopyranoside (PNP-Gal) had no effect on insulin release. Another series of specific competitive inhibitors of sweet taste response, the α anomers of methyl-4,6-dichloro-4,6-dideoxy-D-glucopyranoside (Met-Cl₂-Glu) and methyl-4,6-dichloro-4,6-dideoxy-D-galactopyranoside (Met-Cl₂-Gal) also dose-dependently (~ 20 mM) inhibited insulin release induced by 10 mM D-glucose; the effect of the former compound was significantly more potent than the latter, while both compounds inhibited glucose oxidation in the islets to the same extent. These findings suggest that the pancreatic B cell recognizes D-glucose as a signal for insulin release, at least in part, by a mechanism similar to the sugar recognizing mechanism of the gustatory cell and independent of glucose metabolism in pancreatic islets.

D-Glucose, an important fuel substance for most of cells, is known to act as a signal to initiate physiological responses in several cells. The pancreatic B cell and the sweet taste receptor cell have been most intensively studied in terms of the mechanism by which these cells recognize the sugar as a signal for insulin release or sweet taste sensation. The two types of cells share several features in common as far as a stimulant is D-glucose, though the spectrum of sugars recognized by the sweet taste receptor cell is much broader than that recognized by the pancreatic B cell (for reviews, see 20, 21). Different potencies of the α and β anomers in the glucose actions in the two types of cells have attracted a great deal of attention. The α anomer of D-glucose, as well as D-mannose, is more potent than the β anomer both in stimulating insulin release and in eliciting sweet taste response. Treatment with alloxan of the two types of cells was

reported to selectively inhibit their responses to D-glucose, and co-existence of D-glucose protected these cells from the alloxan toxicity, the α anomer being more effective than the β anomer in protecting the pancreatic B cell. However, the widely accepted hypotheses on the mechanisms by which these cells recognize D-glucose as physiological signals are different; in the pancreatic B cell, D-glucose is considered to be metabolized in the cell for signal production for insulin release (1, 12, 15), while the sugar is believed to bind a specific receptor on the cell membrane for producing sweet taste sensation in the gustatory cell (8, 9, 27). In the latter cell, a line of evidence to support the receptor hypothesis was obtained using specific competitive inhibitors of sweet taste response (8). We have previously reported the effect of one of such inhibitors, *p*-nitrophenyl-D-glucopyranoside (PNP-Glu), on insulin release (22). The α anomer, but not the β

anomer, of PNP-Glu dose-dependently inhibited glucose-induced insulin release without affecting glucose oxidation in the rat pancreatic islets. The findings suggest a similarity between the glucose recognizing mechanisms of the gustatory and pancreatic B cells. In the present study, we examined the effects of two series of specific competitive inhibitors of sweet taste response on glucose-induced insulin release, with the aim to further evaluate the physiological significance of the previous findings. One series of compounds used were *p*-nitrophenyl-D-mannopyranoside (PNP-Man) and *p*-nitrophenyl-D-galactopyranoside (PNP-Gal), and the other series of compounds were methyl-4,6-dichloro-4,6-dideoxy-D-glucopyranoside (Met-Cl₂-Glu) and methyl-4,6-dichloro-4,6-dideoxy-D-galactopyranoside (Met-Cl₂-Gal). In the gustatory cell, the α anomers of these inhibitors are known to be more potent than the β anomers (28, 29).

MATERIALS AND METHODS

Islets of Langerhans were isolated from the pancreases of fed male Wistar rats weighing 300–350 g by the collagenase digestion method (10). All incubations were performed at 37°C in gassed (95% O₂ and 5% CO₂) Krebs-Ringer bicarbonate solution (pH 7.4) containing 5 mg/ml bovine serum albumin (fraction V: Armour, Kankakee, IL) as a basic medium. Islets were preliminarily incubated for 60 min in the basic medium supplemented with 3 mM D-glucose.

Insulin release: Batches of 5 islets of comparable size were incubated for 60 min in 1 ml of the basic media containing the additions indicated. The insulin content of the media at the end of the incubation period was measured by solid phase radioimmunoassay (Insulin Riabead; Dainabot, Tokyo) using rat insulin as the standard (Novo, Bagsvaerd, Denmark). The inhibitors did not affect the assay at the concentrations used.

Glucose oxidation: Batches of 15 islets were incubated in 0.2 ml of the media containing 10 mM D-[U-¹⁴C]glucose (New England Nuclear, Boston, MA) (0.25 mCi/mmol) with or without the inhibitors as indicated for 60 min and the ¹⁴CO₂ formed was estimated as described previously (23).

The α and β anomers of PNP-Glu, PNP-Man and PNP-Gal were purchased from Sigma (St. Louis, MO) and the α anomers of Met-Cl₂-Glu and Met-Cl₂-Gal were kindly supplied by Professor W. Jakinovich, Jr. (Department of Biological Sciences, Lehman College, and the Graduate School, City

University of New York).

All results were expressed as mean $\pm$ SE, and statistical analysis was performed by the unpaired Student's *t*-test.

RESULTS

Fig. 1 shows the effects of the α anomers of *p*-nitrophenyl-D-hexopyranosides on glucose-induced insulin release from isolated rat pancreatic islets. Both the α anomers of PNP-Glu and PNP-Man dose-dependently ($\sim$ 5 mM) inhibited insulin release induced by 10 mM D-glucose. Difference between the inhibitory effects of the two compounds was not significant. On the other hand, the α anomer of PNP-Gal, at any concentration tested, had no effect on glucose-induced insulin release.

We have previously reported that the inhibitory action of α -PNP-Glu on glucose-induced insulin release was surmounted by a higher concentration of D-glucose (22). In the present study, the inhibitory action of 5 mM α -PNP-Man on glucose-induced insulin release was also eliminated when the glucose concentration was raised to 20 mM; the amounts of insulin released by 20 mM D-glucose

Fig. 1 The effects of the α anomers of *p*-nitrophenyl-D-hexopyranosides on insulin release induced by 10 mM D-glucose. Batches of 5 islets isolated from the rat pancreas were incubated for 60 min at 37°C in media containing 10 mM D-glucose and the α anomers of PNP-Glu (●—●), PNP-Man (○---○) or PNP-Gal (△---△) at concentrations indicated. Effects of the inhibitors are expressed in percentages of the control value found with 10 mM glucose alone (15.13 ± 0.94 ng/5 islets/60 min; $n=15$). Values are means $\pm$ SE shown by vertical lines ($n=6-7$). * $P < 0.01$ vs the value with D-glucose alone

Table 1 *Effects of the α and β Anomers of *p*-Nitrophenyl-D-Hexopyranosides, and Related Compounds on Insulin Release Induced by 10 mM D-Glucose*

Additions (5 mM)	Insulin release (ng/5 islets/60 min)
None	19.36 $\pm$ 0.70 (20)
<i>p</i> -Nitrophenyl- α -D-glucopyranoside	4.45 $\pm$ 0.67 (7)*
<i>p</i> -Nitrophenyl- β -D-glucopyranoside	19.15 $\pm$ 1.12 (6)
<i>p</i> -Nitrophenyl- α -D-mannopyranoside	4.06 $\pm$ 0.31 (7)*
<i>p</i> -Nitrophenyl- β -D-mannopyranoside	22.02 $\pm$ 1.68 (6)
<i>p</i> -Nitrophenyl- α -D-galactopyranoside	17.42 $\pm$ 1.08 (7)
<i>p</i> -Nitrophenyl- β -D-galactopyranoside	21.08 $\pm$ 1.57 (6)
Phenyl- α -D-glucopyranoside	20.90 $\pm$ 1.21 (7)
<i>p</i> -Nitrophenol	0.38 $\pm$ 0.06 (7)*

Batches of 5 islets isolated from the rat pancreas were incubated for 60 min at 37°C in media containing 10 mM D-glucose and the additions indicated. Values are means $\pm$ SE with the number of observations in parentheses.

* $P < 0.01$ vs the value with 10 mM D-glucose alone

Table 2 *Effects of the *p*-Nitrophenyl Derivatives which Inhibited Glucose-Induced Insulin Release on the Oxidation of 10 mM D-Glucose in the Islets*

Additions (5 mM)	Glucose metabolized to CO ₂ (pmol/islet/60 min)
None	13.52 $\pm$ 0.74 (20)
<i>p</i> -Nitrophenyl- α -D-glucopyranoside	13.04 $\pm$ 1.32 (9)
<i>p</i> -Nitrophenyl- α -D-mannopyranoside	13.09 $\pm$ 0.94 (6)
<i>p</i> -Nitrophenol	1.58 $\pm$ 0.30 (5)*

Batches of 15 islets were incubated for 60 min at 37°C in media containing 10 mM D-[U-¹⁴C]glucose (0.25 mCi/mmol) with or without the additions indicated. Rates of glucose oxidation were calculated from formation of ¹⁴CO₂. Values are means $\pm$ SE with the number of observations in parentheses. * $P < 0.01$ vs the value with 10 mM D-glucose alone

with and without 5 mM α -PNP-Man were not significantly different (27.65 $\pm$ 2.10 and 27.89 $\pm$ 2.07 ng/5 islets/60 min, $n = 7$).

Table 1 shows the effects of the α and β anomers of *p*-nitrophenyl-D-hexopyranosides, and related compounds on glucose-induced insulin release from the islets. Insulin release induced by 10 mM D-glucose was not inhibited by the β anomers of PNP-Glu and PNP-Man at a concentration of 5 mM, at which the α anomers of these compounds significantly inhibited insulin release. Neither the α nor the β anomer of PNP-Gal affected insulin release. When the *p*-nitrophenyl radical of α -PNP-Glu was replaced with a phenyl radical, the compound, phenyl- α -D-glucopyranoside, lost the inhibitory action on glucose-induced insulin release. On the other hand, *p*-nitrophenol molecule with-

out hexose moiety, at the same concentration, completely inhibited insulin release by 10 mM D-glucose.

Table 2 shows the effects of the compounds which inhibited glucose-induced insulin release on glucose oxidation in the pancreatic islets. The α anomers of PNP-Glu and PNP-Man did not inhibit the oxidation of 10 mM D-glucose at a concentration of 5 mM at which these compounds significantly inhibited insulin release induced by 10 mM D-glucose. *p*-Nitrophenol, at 5 mM, significantly inhibited glucose oxidation.

Fig. 2 shows the effects of the α anomers of chlorinated sugars on insulin release induced by 10 mM D-glucose. The α anomers of both Met-Cl₂-Glu and Met-Cl₂-Gal, at 5 mM, did not inhibit insulin release, but dose-dependently inhibited the release at

Fig. 2 The effects of the α anomers of chlorinated sugars on insulin release induced by 10 mM D-glucose. Batches of 5 islets were incubated in media containing 10 mM D-glucose and the α anomers of Met-Cl₂-Glu (●—●) or Met-Cl₂-Gal (○---○) at concentrations indicated. Effects of the inhibitors are expressed in percentages of the control value found with 10 mM glucose alone (20.68 ± 1.83 ng/5 islets/60 min; $n=10$). Values are means with SE shown by the vertical lines ($n=6-10$). ▲, $P<0.05$; ▲▲, $P<0.01$ vs value with D-glucose alone; △, $P<0.05$; △△, $P<0.01$ vs values with D-glucose and Met-Cl₂-Gal

higher concentrations; the inhibitory effect of the former compound being significantly greater than the latter. However, as shown in Table 3, both compounds at 20 mM inhibited the oxidation of 10 mM D-glucose to the same extent.

DISCUSSION

PNP-Glu, PNP-Man and PNP-Gal were reported to

inhibit sweet taste response in a competitive manner at the sweet taste receptor site of the gustatory cell (29). These inhibitors have no effect on the other taste qualities, such as salt, bitter or sour (29). The α anomers of the compounds are more potent than the β anomers in inhibiting sweet taste response (29). In the present study, we have observed that the α anomers of PNP-Glu and PNP-Man dose-dependently (~ 5 mM) inhibited insulin release induced by 10 mM D-glucose without affecting glucose oxidation, while the β anomers had no significant effect on the release at a concentration of 5 mM. As was observed using α -PNP-Glu (22), the inhibitory effect of α -PNP-Man on glucose-induced insulin release was surmounted by a higher concentration of D-glucose (20 mM). Phenyl- α -D-glucopyranoside, which does not inhibit sweet taste response (29), did not inhibit glucose-induced insulin release. These findings suggest a strong similarity between the inhibitory mechanisms of the compounds in the gustatory and the pancreatic B cells. However, at variance with sweet taste sensation, glucose-induced insulin release was not inhibited by either anomer of PNP-Gal. It is well known that D-glucose and D-mannose are potent insulin secretagogues and sweet substances, the α anomers being more potent than the β anomers, while D-galactose does not stimulate insulin release in spite of being a sweet substance (1, 8, 20). Thus, the actions of *p*-nitrophenyl-D-hexopyranosides in inhibiting insulin release are related to the actions of their hexose moieties in inducing insulin release. Therefore, the inhibitory effect of the compounds is considered not to result from non-specific toxicity but to involve the hexose recognizing mechanism of the pancreatic B cell. *p*-Nitrophenol itself, at a concentration of 5 mM, completely inhibited glucose-induced insulin release and glucose oxidation. It is assumed that

Table 3 Effects of the α Anomers of Chlorinated Sugars on the Oxidation of 10 mM D-Glucose

Additions (20 mM)	Glucose metabolized to CO ₂ (pmol/islets/60 min)
None	15.96 ± 0.88 (12)
Methyl-4,6-dichloro-4,6-dideoxy- α -D-glucopyranoside	10.18 ± 0.87 (12)*
Methyl-4,6-dichloro-4,6-dideoxy- α -D-galactopyranoside	10.82 ± 0.96 (12)*

For footnotes, see Table 2. Values are means $\pm$ SE with the number of observations in parentheses. * $P<0.01$ vs the value with 10 mM D-glucose alone

hexose moieties lead the compounds to a hexose recognition site(s) in the pancreatic B cell, and *p*-nitrophenyl moiety exerts its inhibitory effect at the site(s), the exact nature of which still remains to be elucidated.

It is now widely accepted that glucose metabolism in the pancreatic B cell is regulated by glucose transporter type 2 (GLUT 2) and/or glucokinase (ATP: D-glucose 6-phosphotransferase, EC 2.7.1.2), and a rise in cytosolic ATP concentration or ATP/ADP ratio is responsible for the closure of the ATP-sensitive K⁺-channel, leading to plasma membrane depolarization and gating of the voltage-sensitive Ca²⁺ channel (2, 3, 15). The significance of ATP-generating mitochondrial oxidative events in nutrient-induced insulin release has also been discussed (11). Although D-glucose, D-mannose and D-galactose are known to be transported through the plasma membrane of the pancreatic B cell (5), it is unlikely that the α anomers, but not the β anomers, of *p*-nitrophenyl-D-hexopyranosides inhibit glucose transport, since glucose uptake by pancreatic islets does not prefer the α anomer of D-glucose (17, 19). The findings from the studies on the islet metabolism of glucose anomers have not indicated the α -anomeric preference of glucose transport either (6, 7, 13, 14). No effect of the inhibitors on glucose oxidation in the islets also suggests that glucose transport was not grossly inhibited. Glucokinase discriminates the α and β anomers of D-glucose and D-mannose (15, 18), but does not take D-galactose as a substrate (25). Thus, it is conceivable that the α anomers of PNP-Glu and PNP-Man inhibit the enzyme activity while α -PNP-Gal does not, provided that these compounds are transported into the pancreatic B cell. However, the presumption does not agree with the present finding that glucose oxidation in the pancreatic islets was not inhibited by the α anomers of PNP-Glu and PNP-Man. It has been also proposed that mitochondrial oxidative events may play the essential role in the process of glucose-induced insulin release (11). It is unlikely that only the α anomers of PNP-Glu and PNP-Man inhibit the mitochondrial oxidative steps since the steps do not discriminate the two anomers of hexoses. No effect of the compounds on glucose oxidation in the islets is also incompatible with inhibition of mitochondrial oxidation. The possibility that PNP-Glu or PNP-Man acts as a mitochondrial uncoupler may be excluded since Tanigawa *et al.* (26) observed in a cell-attached patch clamp study that the α anomer of PNP-Glu (5 mM) did not affect the ATP-sensitive

K⁺-channel activity in the pancreatic B cell incubated with 10 mM D-glucose.

Another series of specific competitive inhibitors of sweet taste response, the α anomers of Met-Cl₂-Glu and Met-Cl₂-Gal, were reported to be less potent than the α anomer of PNP-Glu or PNP-Gal in inhibiting sweet taste response (29). Difference in the potencies of the two series of compounds was also observed in the pancreatic B cell. The α anomers of these chlorinated sugars at 5 mM did not inhibit insulin release induced by 10 mM D-glucose, but the compounds dose-dependently inhibited the release at higher concentrations; α -Met-Cl₂-Glu was significantly more potent than α -Met-Cl₂-Gal. However, both compounds at 20 mM inhibited glucose oxidation to the same extent, suggesting that the inhibitory effects of the compounds on glucose-induced insulin release are not solely attributable to their inhibition of glucose metabolism. Since D-galactose has no effect on insulin release, inhibition of insulin release by α -Met-Cl₂-Gal may result from a non-specific toxic effect of the compound on glucose metabolism in the islets, and the difference in the inhibitory effects between the two compounds on insulin release may reflect the specific inhibitory effect of α -Met-Cl₂-Glu on glucose-induced insulin release independent of glucose metabolism in the pancreatic B cell. In the gustatory cell, the α anomer of Met-Cl₂-Gal was reported to be more potent than the β anomer in suppressing sweet taste response (28). However, we could not compare the effects of the two anomers on insulin release, since the β anomers of these compounds were not available.

Although there is general consensus that stimulation of insulin release by D-glucose requires an increased metabolism of D-glucose in the pancreatic B cell, the biochemical nature of metabolic signals that link these two processes has yet to be established (16). The currently prevailing view that ATP is the coupling factor is still subject to be re-evaluated (4). Little attention has been paid to the alternative view that the pancreatic B cell directly recognizes D-glucose at a receptor site (16). On the other hand, an attempt to identify sugar-receptor molecule(s) in the gustatory cell has not yet succeeded (24). Thus, the sugar-recognizing mechanisms of these cells still remain to be elucidated. Our present findings suggest that the pancreatic B cell recognizes D-glucose as a signal for insulin release, at least in part, by a mechanism similar to, though not identical with, the mechanism of sugar recognition by the sweet taste receptor cell.

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