Oxidation of [1,12-^{14}C]dodecanedioic acid by rat pancreatic islets

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Abstract. Several aliphatic dioic acids were recently reported to stimulate insulin release in isolated rat pancreatic islets incubated at close-to-physiological D-glucose concentrations. In order to gain insight into the mode of action of these acids in pancreatic islet B-cells, the oxidation of [1,12-^{14}C]dodecanedioic acid (5.0 mM) was now measured in rat islets. Expressed as pmol of [1,12-^{14}C]dodecanedioic acid equivalent, the production of $^{14}CO_2$ was close to 1.0 pmol/islet per 120 min, representing about 8% of that attributable to the oxidation of D-[U-^{14}C]-glucose (8.3 mM). The dioic acid and the hexose failed to exert any significant reciprocal effect upon their respective oxidation rate. These findings support the view that the insulinotropic action of dodecanedioic acid, and presumably other aliphatic dioic acids, is causally linked to their capacity to act as nutrients in pancreatic islet cells.

Introduction

Medium chain dicarboxylic acids are currently under investigation as alternate fuel substrates both in normal and pathological conditions in man (1-5). They were recently reported to stimulate insulin secretion from rat pancreatic islets incubated at close-to-physiological concentrations of D-glucose (6). The latter finding was considered to provide further support to the contention that medium-chain dicarboxylic acids may be regarded as useful energy substrates. However, no information was so far available on the metabolic fate of such dioic acids in isolated pancreatic islets.

The main aims of the present study are to measure the oxidation of [1,12-^{14}C]dodecanedioic acid in isolated rat pancreatic islets, to compare it to that of D-[U-^{14}C]glucose, and to investigate possible reciprocal effects of these two nutrients upon their respective oxidation rate.

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Materials and methods

[1,12-^{14}C]dodecanedioic acid (99 mCi/mmol) and D-[U-^{14}C]-glucose (310 mCi/mmol) were purchased from NEN™ Life Science Products (Boston, MA, USA).

The method used to measure the oxidation of either [1,12-^{14}C]dodecanedioic acid or D-[U-^{14}C]glucose by isolated rat pancreatic islet was identical to that previously described elsewhere (7). Briefly, groups of 20 islets each, prepared by the collagenase procedure from the pancreas of fed female Wistar rats, were incubated for 120 min at 3°C in 50 µl of a bicarbonate-and HEPES-buffered medium containing 5 mg/ml bovine serum albumin and equilibrated against a mixture of O_2/CO_2 (95/5, v/v). The recovery of $^{14}CO_2$ was then achieved over 60 min incubation at 37°C after addition of metabolic poisons to the incubation medium.

All results are presented as mean values (± SEM), together with the number of individual observations (n). The statistical significance of differences between mean values was assessed by use of Student's t-test.

Results

As documented in Table I, over 120 min incubation at 3°C, the oxidation of D-[U-^{14}C]glucose (8.3 mM) by isolated rat islets was not affected significantly by the presence of dodecanedioic acid (5.0 mM) in the incubation medium. Likewise, D-glucose (8.3 mM) failed to affect significantly the oxidation of [1,12-^{14}C]dodecanoic acid (5.0 mM).

Discussion

The present findings reveal that [1,12-^{14}C]dodecanoic acid is converted to $^{14}CO_2$ by rat pancreatic islets. D-glucose (8.3 mM) and dodecanoic acid (5.0 mM) failed to exert any significant reciprocal effect upon their respective rate of oxidation by the islets.

Assuming full oxidation of the latter acid, the generation of CO_2, relative to the concentration of the exogenous nutrient was about 7-8 times lower than that of the hexose. On the basis of the same assumption, the production of CO_2 from dodecanedioic acid (5.0 mM) represented about 7.7% of that of D-glucose (8.3 mM), in fair agreement with prior findings indicating that, under comparable experimental conditions, the increment in insulin output evoked by dodecanedioic acid represents about 12.5% (d.f.=184; $p<0.05$) of the control

Table I. Oxidation of [1,12-^{14}C]dodecanedioic acid and D-[U-^{14}C]glucose by rat islets.

Dodecanedioic acid (mM)	D-glucose (mM)	Oxidation rate (pmol/islet per 120 min)[a]
Nil	D-[U-^{14}C]glucose (8.3)	26.20±2.97 (15)
Unlabelled dodecanedioic acid (5.0)	D-[U-^{14}C]glucose (8.3)	25.98±2.87 (16)
[1,12-^{14}C]dodecanedioic acid (5.0)	Nil	1.00±0.10 (12)
[1,12-^{14}C]dodecanedioic acid (5.0)	Unlabelled D-glucose (8.3)	1.02±0.16 (13)

[a]Results expressed as ^{14}C-labelled nutrient equivalent.

secretory rate recorded in the sole presence of D-glucose (6). In considering such a comparison, it should be kept in mind that the oxidation of exogenous nutrients needs to exceed a threshold value in order to augment insulin output above its basal value (8).

In conclusion, therefore, the present work suggests that the insulinotropic action of dodecanedioic acid, and presumably other aliphatic dioic acids (6), may be causally linked to their capacity to act as nutrients in islet cells, in good agreement with the fuel concept for nutrient-stimulated insulin secretion (9,10).

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