PEPTIDES 27 (2006) 2031–2036

available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevier.com/locate/peptides

Review

CART is a novel islet regulatory peptide

Nils Wierup *, *Frank Sundler*

Department of Experimental Medical Science, Division of Diabetes, Metabolism, and Endocrinology, Lund University, Lund, Sweden

ARTICLE INFO

Article history:
Received 16 September 2005
Accepted 7 February 2006

Keywords:
CART
Cocaine and amphetamine regulated transcript
Islet peptides
Insulin secretion
Type 2 diabetes
Neuropeptides
Islet development

ABSTRACT

CART peptides have emerged as important islet regulators. CART is expressed both in islet endocrine cells and in parasympathetic and sensory nerves innervating the islets. In adult rats the intra-islet expression of CART is limited to the somatostatin producing δ-cells, while in adult mice CART is mainly expressed in nerve fibers. During development islet CART is upregulated; in rats in almost all types of islet endocrine cells, including the insulin-producing β-cells, and in mice mainly in the α-cells. This pattern of expression peaks around birth. CART is also expressed in human pancreatic nerves and in islet tumours where the expression level of CART may be related to the degree of differentiation of the tumour. Interestingly, in several rat models of type 2 diabetes CART expression is robustly upregulated in the β-cells, and is prominent during the phase of beta cell proliferation and hypertrophy. While CART inhibits glucose stimulated insulin secretion from rat islets it augments insulin secretion amplified by cAMP. Mice lacking CART, on the other hand, have islet dysfunction, and humans with a missense mutation in the *cart* gene are prone to develop type 2 diabetes. These data favor a role of CART in normal islet function and in the pathophysiology of type 2 diabetes.

Contents

* *Corresponding author at*: Lund University, Department of Experimental Medical Science, Division of Diabetes, Metabolism, and Endocrinology, Unit of Neuroendocrine Cell Biology, BMC B11, 22 184, Lund, Sweden. Tel.: +46 46 222 36 30; fax: +46 46 222 45 46.
E-mail address: nils.wierup@med.lu.se (N. Wierup).
0196-9781/$ – see front matter
doi:10.1016/j.peptides.2006.02.011

1. Introduction

The pancreatic islets contain four main cell types; insulin-producing β-cells, glucagon-producing α-cells, somatostatin-producing δ-cells and pancreatic polypeptide (PP) producing PP-cells. Recently, a fifth islet cell type, the ghrelin cell, was identified in human and rodent islets [34,36]. Further, gastrin producing cells are present in the developing rat islets [22]. In addition to the peptides expressed in "own" cell types a great number of regulatory peptides are more promiscuously expressed in the developing islets and coexist with the established hormones, some of them transiently during development and/or when the islets are challenged, e.g., in type-2 diabetes. Such co-expressed peptides in islet cells include neuropeptide Y (NPY), peptide YY (PYY), islet amyloid polypeptide (IAPP), and calcitonin gene-related peptide (CGRP) which have been reviewed elsewhere [25]. Many of these peptides are also present in nerves innervating the pancreas [reviewed in 1].

Expression of CART in endocrine cells has been reported in other organs, including pituitary [7,9], adrenal medulla [7,11,20], and in the antral gastrin producing G-cells in the stomach [12]. Here, we review the distribution of CART in the pancreas and functional islet related data obtained so far. Special attention has been given to the distribution pattern of CART in the islets and to the role of CART in islet function.

2. CART distribution and expression in the pancreas

2.1. *Fetal, neonatal and adult rodent islet cells*

In normal adult rats CART is mainly expressed in the somatostatin producing δ-cells and in pancreatic neurons [18,35]. However, during development CART is highly expressed also in β-cells (Fig. 1), α-cells, PP-cells, but somewhat surprisingly, not in the ghrelin cells [35]. In the rat, islet ghrelin cells deviate from the other islet cells in that they are only present during fetal and neonatal development and virtually disappear a few weeks after birth [36]. A similar developmental pattern holds also for the gastrin producing islet cells, but in contrast to the ghrelin cells a great proportion of the gastrin producing cells express CART [22,35]. The expression of CART in the islet gastrin cells is reminiscent of the CART expression in the gastric G-cells of adult rats [12]. In adult mouse islets only very few δ-cells are weakly CART IR [38]. However, in developing mouse islets CART is upregulated in the α-cells (Fig. 2C). In contrast to the developing rat islets, virtually no CART immunoreactive (IR) β-cells (Fig. 2A and B), and no CART IR δ-cells (Fig. 2B and D) were detected. In addition, a small subpopulation of the PP-cells and the ghrelin cells were CART IR.

2.2. *Islets of rodent models of type-2 diabetes*

CART is markedly upregulated in the β-cells of several type-2 diabetes models of rats and mice. One such model is dexamethasone (DEX) induced diabetes [30]. Rats treated with DEX in a high dose for 12 days display ten-fold higher relative number of CART IR β-cells (Fig. 3) and ten-fold higher CART mRNA expression compared to control rats [39]. The GK rat, a polygenic model of inherited type-2 diabetes [14], displays thirty-fold higher relative number of CART IR β-cells paralleled by a robust increase in CART mRNA expression compared to the Wistar control rats [39]. CART is robustly upregulated also in the β-cells of ob/ob mice, and Zucker diabetic fatty (ZDF) rats [37]. Altogether, CART is upregulated in the β-cells of four, mechanistically different, models of typ-2 diabetes in two different species. Interestingly, in the CNS CART is positively regulated by leptin, and leptin deficient animals have decreased expression of CART in the CNS [13,21]. Our finding of increased expression of β-cell CART in ZDF rats and ob/ob mice, which have disrupted leptin signaling, is therefore somewhat surprising and quite opposite of the central effect. To our knowledge this is the first finding of upregulated CART in animals with deficient leptin signaling.

Investigation of the subcellular localization of CART using TEM and immunogold labeling on ultrathin sections revealed that anti-CART labeling in DEX rats localized to the secretory granules of both β-cells and δ-cells [39]. This is a strong indication that CART is secreted from both β-cells and δ-cells, and, in addition, it provides a morphological substrate for co-secretion of CART and insulin as well as CART and somatostatin.

2.3. *Neurons*

In addition to endocrine cells, CART is widely expressed in both nerve fibers and in nerve cell bodies in pancreatic ganglia, sometimes forming neuroislet complexes. The CART expressing neurons are particularly prominent in the mouse pancreas during development (Fig. 2A). In both rat and mouse

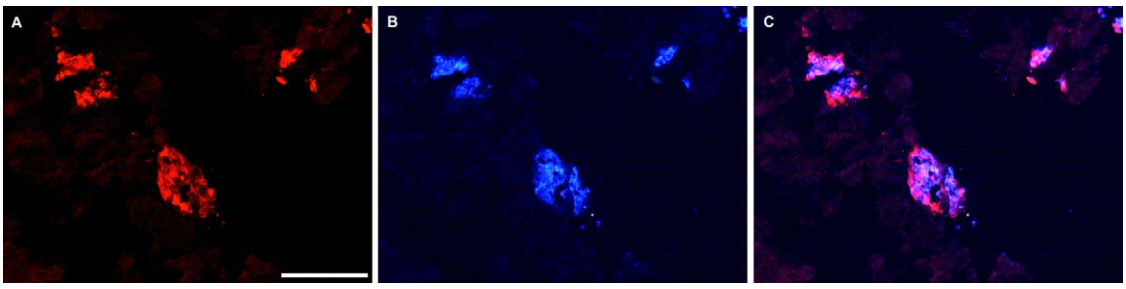

Fig. 1 – Low magnification immunofluorescence photomicrographs of fetal rat pancreas (E20) double immunostained for CART (A) and insulin (B), merged in (C). Scale bar = 100 μm. CART is expressed in all islets, predominantly in the insulin-producing β-cells.