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Milk signalling in the pathogenesis of type 2 diabetes

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ABSTRACT

The presented hypothesis identifies milk consumption as an environmental risk factor of Western diet promoting type 2 diabetes (T2D). Milk, commonly regarded as a valuable nutrient, exerts important endocrine functions as an insulinotropic, anabolic and mitogenic signalling system supporting neonatal growth and development. The presented hypothesis substantiates milk's physiological role as a signalling system for pancreatic β-cell proliferation by milk's ability to increase prolactin-, growth hormone and incretin-signalling. The proposed mechanism of milk-induced postnatal β-cell mass expansion mimics the adaptive prolactin-dependent proliferative changes observed in pregnancy. Milk signalling down-regulates the key transcription factor FoxO1 leading to up-regulation of insulin promoter factor-1 which stimulates β-cell proliferation, insulin secretion as well as coexpression of islet amyloid polypeptide (IAPP). The recent finding that adult rodent β-cells only proliferate by self-duplication is of crucial importance, because permanent milk consumption beyond the weaning period may continuously over-stimulate β-cell replication thereby accelerating the onset of replicative β-cell senescence. The long-term use of milk may thus increase endoplasmic reticulum (ER) stress and toxic IAPP oligomer formation by overloading the ER with cytotoxic IAPPs thereby promoting β-cell apoptosis. Both increased β-cell proliferation and β-cell apoptosis are hallmarks of T2D. This hypothesis gets support from clinical states of hyperprolactinaemia and progeria syndromes with early onset of cell senescence which are both associated with an increased incidence of T2D and share common features of milk signalling. Furthermore, the presented milk hypothesis of T2D is compatible with the concept of high ER stress in T2D and the toxic oligomer hypothesis of T2D and may explain the high association of T2D and Alzheimer disease.

Introduction

It is generally accepted that environmental and life style factors play a predominant role in the epidemic of type 2 diabetes (T2D). Degeneration of pancreatic islet β-cells is increasingly ranked as a key disease mechanism in T2D [1–3] but it is not entirely clear what the underlying molecular processes might be and how they impair insulin production and ultimately cause β-cell loss [4,5]. Quantitative measurements in postmortem pancreatic tissue from humans with T2D have reinforced early observations concerning the probable role of lowered β-cell numbers [6,7], and pointed to a linkage between β-cell disappearance and β-cell apoptosis [8,9]. Thus, most attention is recently focused on the mechanisms involved in β-cell apoptosis. However, pancreatic β-cell mass regulation is a matter of proliferation and apoptosis. Over lifetime, in T2D patients β-cells exhibit both an increased rate of proliferation and apoptosis when compared with non-diabetic subjects (Fig. 1) [10,11].

A remarkable burst of β-cell proliferation occurs during the early postnatal period, the time of exclusive milk exposure by breast feeding. In humans, only very limited information concerning the physiological role of milk for adequate postnatal β-cell proliferation and mass expansion is available.

For the required metabolic adaptations to pregnancy a significant rise in β-cell proliferation and mass expansion occurs. Prolactin receptor-mediated signalling has been recognised to play an important role in pregnancy-associated β-cell proliferation in rodents [12]. Several tyrosine kinase- and G-protein-coupled receptors expressed on β-cells are implicated in the regulation of β-cell proliferation, i.e., receptors for insulin, insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF) and betacellulin (BTC), prolactin (PRL), placental lactogen (PL), growth hormone (GH),

Abbreviations: AA, amino acids; BTC, betacellulin; CCK, cholecystokinin; ER, endoplasmic reticulum; GH, growth hormone; GI, glycaemic index; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; 5-HT, 5-hydroxytryptamine (serotonin); FoxO1, forkhead box transcription factor-1; IAPP, islet amyloid polypeptide; II, insulinaemic index; IGF-1, insulin-like growth factor-1; IPF-1, insulin promoter factor-1; α-LA, α-lactalbumin; LCT, long-chain triglycerides; MAPK, mitogen-activated protein kinase; Pdx-1, pancreatic duodenal homeobox factor-1; PI3K, phosphoinositol-3 kinase; PL, placental lactogen; PRL, prolactin; STAT5, signal transducer and activator of transcription factor-5; T2D, type 2 diabetes mellitus; Trp, tryptophan.

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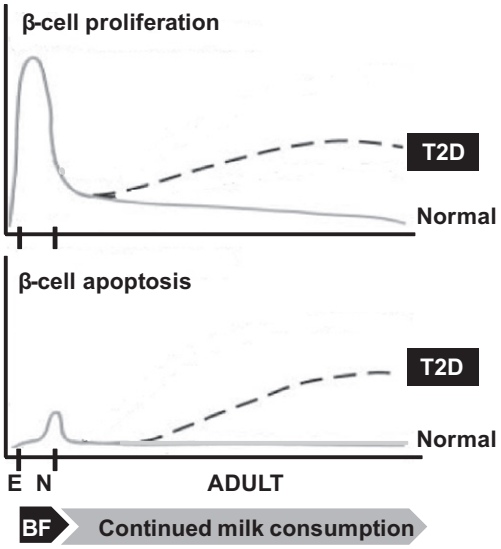

Fig. 1. Comparison of β-cell proliferation and apoptosis over lifetime in normal subjects and patients with type 2 diabetes (T2D) in relation to physiological breast feeding (BF) and continued milk consumption. E = late embryonic period; N = neonatal period; figure modified according to Rhodes [10] and Ackermann et al. [11].

glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1) and cholecystokinin (CCK) [13].

It is of crucial importance to regard mammalian milk not only as a complex nutrient for the newborn but as a most important *endocrine signalling system* regulating adequate β-cell proliferation and maturation for growth requirements. There is biochemical evidence that milk drives pituitary signalling pathways and involves the entero-insular axis by mediating incretin-signalling. To understand the development of T2D in industrialised countries, milk's sophisticated mitogenic signalling cascades have to be dissected in more detail. Milk's "secret" of efficient growth factor signalling resides in its excessive insulinotropic activity characterised by milk's high *insulinaemic index* [14–16]. Despite low *glycaemic indexes* (GI: 15–30) milk and dairy products produce three to six-fold higher insulinaemic indices (II: 90–98). A large and similar dissociation of the GI and II exists for both whole milk (GI: 42 ± 5; II: 148 ± 14) and skim milk (GI: 37 ± 9; II: 140 ± 13) [14–16]. Increased daily intake of milk but not meat significantly raised basal insulin serum and IGF-1 levels in 8-year old prepubertal Danish boys [17,18]. This is in accordance with the observation that skim milk is a potent insulin secretagogue in T2D patients [19]. It is therefore a common belief that milk and milk protein consumption have beneficial dietary effects in patients with developing or manifest T2D. Thus, no one challenges the health value of persistent milk consumption because milk promotes linear growth and displays most beneficial effects for neonatal growth and survival. However, when milk intake is continued by humans after the weaning period into adulthood, milk-derived signalling may exert long-term adverse signalling effects as those proposed here affecting pancreatic β-cell homeostasis and subsequent development of T2D.

Milk: a rich postnatal source of prolactin for β-cell proliferation

From studies of maternal β-cell adaptation in pregnancy we have learnt that PRL-signalling plays an important role in β-cell proliferation [12]. However, the strongest increase in β-cell proliferation, the *postnatal β-cell burst*, is observed during the breast feeding period (Fig. 1) [10,11]. In analogy with PRL-mediated β-cell proliferation of pregnancy, the neonatal β-cell burst appears to require PRL-signalling. In late gestation, fetal PRL plasma levels rise exponentially. After birth, colostrum, first milk and neonatal plasma contain exceptionally high concentrations of PRL [20–22]. During the first weeks of postnatal life when the intestinal barrier is still highly permeable, PRL appears to be absorbed in the intestine from mammalian milk [23,24]. After maturation of the intestinal permeability barrier, however, milk provides a second indirect mechanism to maintain PRL-signalling for continued β-cell proliferation and islet adaption to meet increasing insulin requirements of the growing neonate.

Milk: a neurotransmitter precursor for pituitary hormone signalling

The protein fraction of milk is composed of the casein proteins and the easily hydrolysed and fast absorbed whey proteins which contain the bulk of milk's growth factors like IGF-1, BTC, PRL, PL and others [25]. A most important multifunctional whey protein is α-lactalbumin (α-LA) which is involved in lactose synthesis and osmotic regulation of milk flow [26]. α-LA is unique among other proteins with regard to its four- to fivefold increased concentration of the essential amino acid tryptophan (Trp) [26]. Thus, milk is a transport system to provide sufficient amounts of Trp to the newborn. There is a straight relationship between the dietary supply of Trp and the brain's ability to synthesise the neurotransmitter serotonin (5-hydroxytryptamin) [27]. α-LA increases the plasma ratio of Trp to other large neutral amino acids which is important for the preferred Trp-uptake by the blood–brain barrier, the rate-limiting step for serotonin synthesis [27,28]. Pituitary synthesis and secretion of PRL and GH are stimulated by serotonergic signals [28–30]. In fact, milk and especially whey protein (α-LA) consumption increase plasma levels of PRL and GH [29–31]. Ingestion of hyperglycaemic carbohydrates further increases Trp-uptake by the brain because the other large neutral amino acids are preferentially taken up by peripheral tissues due to carbohydrate-mediated insulin signalling [28]. GH is a potent inducer of hepatic IGF-1 secretion and epidemiological studies confirmed that milk and dairy protein consumption significantly raise plasma IGF-1 levels [32–34]. Thus, mammalian milk has to be regarded as a neurotransmitter precursor for maintaining PRL- and GH/IGF-1-signalling which all stimulate β-cell proliferation [13] (Fig. 2).

Milk: an entero-insular incretin signalling system

Whey proteins, especially hydrolysed whey proteins, hydrolysed α-LA and their released amino acids evoke the synthesis and release of GIP by enteroendocrine K-cells, GLP-1 by L-cells and CCK by I-cells (Fig. 2) [35–39]. CCK secretion is also mediated by long-chain fatty acids of triglycerides, the predominant fatty acids of bovine milk. Whey protein/α-LA-mediated incretin-signalling thus appears to be the third most important signalling mechanism of milk to ensure adequate β-cell proliferation and maturation. Milk-signalling interacts with multiple tyrosine kinase receptors and G-protein-coupled receptors expressed on β-cells which finally activate signal transducer and activator of transcription-5 (STAT5), phosphoinositol-3-kinase (PI3K)/Akt and MAPK pathways, all known to activate β-cell proliferation [13]. A common target of all these pathways is the metabolic sensor and transcription factor *FoxO1* which is either down-regulated at the promoter level by STAT5 or inactivated by posttranslational modification due to PI3K/Akt-mediated phosphorylation and subsequent nuclear extrusion (Fig. 2) [40]. FoxO1 is an inhibitor of β-cell's master transcription factor *Pdx-1* in rodents (*IPF-1* = insulin promoter factor 1 in humans) [41]. Inhibition of FoxO1 by milk-derived growth factor- and incretin-signalling thus activates Pdx-1/IPF-1. The later controls