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Review Article

The adenosine, adrenergic and opioid pathways in the regulation of insulin secretion, beta cell proliferation and regeneration

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ABSTRACT

Insulin, a key hormone produced by pancreatic beta cells precisely regulates glucose metabolism in vertebrates. In type 1 diabetes, the beta cell mass is destroyed, a process triggered by a combination of environmental and genetic factors. This ultimately results in absolute insulin deficiency and dysregulated glucose metabolism resulting in a number of detrimental pathophysiological effects. The traditional focus of treating type 1 diabetes has been to control blood sugar levels through the administration of exogenous insulin. Newer approaches aim to replace the beta cell mass through pancreatic or islet transplantation. Type 2 diabetes results from a relative insulin deficiency for the prevailing insulin resistance. Treatments are generally aimed at reducing insulin resistance and/or augmenting insulin secretion and the use of insulin itself is often required. It is increasingly being recognized that the beta cell mass is dynamic and increases insulin secretion in response to beta cell mitogens and stress signals to maintain glycemia within a very narrow physiological range. This review critically discusses the role of adrenergic, adenosine and opioid pathways and their interrelationship in insulin secretion, beta cell proliferation and regeneration.

1. Introduction

The peptide hormone, insulin, secreted by the pancreatic beta cells, precisely regulates glycemic control in vertebrates. Blood glucose levels may increase with ageing, obesity, genetics, and viral diseases suggesting beta cell dysfunction and a vulnerability of the beta cell when exposed to such physiological and pathological stressors. Animal studies indicate that the beta cells continuously adapt to these changing demands through hyperplasia, hypertrophy and facultative beta cell mass proliferation, and respond by increasing insulin synthesis and secretion to maintain normoglycemia [1]. In humans, reduced insulin requirement often observed shortly after the diagnosis of type 1 diabetes is a result of the transient improvement of beta cell function, and normal or near normal glycaemia can be achieved by administration of only minimal amounts of insulin [2]. The so called “honeymoon phase” indicates that the human beta cells have a degree of plasticity. Evidence about the remission following the honeymoon phase is limited and can have a varying efficacy and length [3–5]. When this adaptive response is impaired or defective, hyperglycemia ensues. Prolonged hyperglycemia is toxic and impairs the function of various organs including the pancreatic beta cells themselves.

Multiple studies utilising small animal models like rodents and zebrafish indicate that the beta cells have an intrinsic capability to proliferate [6–8]. Beta cell proliferative capacity in humans in less clear [9]. It is postulated that beta cell proliferation in humans occurs following differentiation from beta cell precursors [10]. A compensatory increase in the beta cell population also occurs during periods of metabolic stress such as pregnancy [11] and obesity [12]. Under such conditions insulin secretion and beta cell mass are influenced by nutrients, hormones and the nervous system [13–15]. The major pathways include the adrenergic, adenosine and the opioid pathways [16–21]. These systems work cooperatively; modulating various systemic functions, and are influenced by beta cell mitogens. The purpose of this review is twofold; i) provide an overview of the beta cell mass regulation ii) provide a hypothesis for the cross talk of the adrenergic, adenosine and opioid pathways in insulin secretion and beta cell mass

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Abbreviations

ADK-I	Adenosine kinase inhibitor
cAMP	Cyclic adenosine monophosphate
CTOP	D-Phe-Cys-Tyr-d-Trp-Orn-Thr-Phe-Thr-NH2
DAMGO	[D-Ala2 NeMe-Phe4 Gly5-ol]-enkephalin
DPDPE	[D-Pen2,5]-enkephalin
EPI	Epinephrine
NE	Nor-epinephrine
NECA	5′eN-ethylcarboxamidoadenosine
UK 14,304	Brimonidine
α2a-AR	Alpha 2a adrenergic receptor
α2-AR	Alpha 2 adrenergic receptor
β-AR	Beta-adrenergic receptor
β-ARs	Beta-adrenergic receptors

regulation from the available literature.

2. Regulation of beta cell mass

Maintenance of the beta cell mass relies on a delicate balance between beta cell growth and apoptosis during neonatal development [22]. Although recent advancements have allowed the use of human pluripotent stem cells to develop pancreatic beta cells both *in-vivo* and *in-vitro*, information about early human pancreatic development is typically constrained by limited access to tissue [23–25]. Despite noticeable differences between animal models and humans with respect to pancreatic development, our understanding of early pancreatic development is derived from animal models such as mice [26,27], rat [28,29] and zebrafish [30,31]. From these studies it is evident that a variety of transcription factors are expressed at different stages of beta cell development, which drive the differentiation of endodermal cells to the insulin-secreting pancreatic beta cells [32] (see Table 1). Gastrointestinal hormones like glucagon-like peptide 1 [33–35], glucose-dependent insulinotropic polypeptide [33,36–38], cholecystokinin [39] and gastrin [40] secreted in response to nutrients regulate insulin secretion and beta cell mass expansion during post-natal growth. Finally, multiple signalling pathways and numerous exogenous and endogenous substances appear to stimulate the entry of the beta cells into the cell cycle (see Table 2).

Beta cell proliferation occurs at various stages of life. During the prenatal period, beta cells first appear in the human pancreas at around 7.5 weeks of gestation [41]. The majority of the beta cell mass growth and expansion occurs from ~20 weeks of gestation as a result of the differentiation from non-endocrine progenitor cells, whereas duplication from the pre-existing endocrine cells is generally low [32,42]. It is also speculated that cells coexpressing insulin and duct-type cytokeratin transdifferentiate into beta cells during early neonatal life [43]. It is during this stage, that a sufficient number of beta cells are formed that support metabolism throughout the human lifespan.

In humans, the post-natal growth and proliferation of the beta cell mass is age-dependant and occurs mainly through beta cell replication [22,32,44]. Islet precursor cells, which establish a functional beta cell mass during prenatal life, disappear in the first week after the birth, and further growth of the beta cell mass occurs through self-replication [32]. The beta cell mass grows rapidly during the first 3 years of life and adolescence, and gradually declines in adulthood [44].

Other have shown that the transdifferentiation of alpha and delta cells to beta cells can occur. Transdifferentiation of pancreatic acinar cells [45,46], self-duplication of adult beta cells [47] and the generation of beta cells formed from stem cells [48–50] (see Fig. 1) also contribute to increased beta cell mass post birth. It has also been reported that an age-dependent plasticity of pancreatic cells to transdifferentiate into insulin-producing cells occurs after near-total beta cell loss. Transgenic mice bearing an insulin promotor and diphtheria toxin receptor coding sequence (RIP-DTR) showed a 45-fold increase in beta cell number 4 months following diphtheria toxin-induced near-total beta cell ablation (99%) at 2 weeks of age. Lineage tracing confirmed that in pre-pubescent mice, delta cells were the predominant source of beta cells while alpha to beta cell transdifferentiation was the major mechanism of insulin production in adult and aged RIP-DTR mice [51]. Whether such a process occurs in humans after extreme beta cell loss in diabetes is unknown [49]. To summarise, evidence from existing animal studies indicates that the beta cell mass is capable of proliferating through various mechanisms.

3. Adrenergic, adenosine and opioid pathways in insulin secretion, beta cell proliferation and regeneration

3.1. Adrenergic signalling

The autonomic nervous system mediates the ‘fight-or-flight’ response in humans by the neurotransmitters-epinephrine (EPI) and nor-epinephrine (NE). EPI and NE influence responses such as pupil dilation, increased heart rate, increased blood flow to the skeletal muscles from the non-essential organs and stimulate insulin secretion [52–54]. The pancreas is innervated by the splanchnic nerves, and release of neurotransmitters like EPI and

Table 1
Transcription factors expressed during pancreatic organogenesis in various organisms.

Gene name	Mouse	Zebrafish	Human
Hlxb9	E8-E9 [112]	14 hpf [113]	7 wk, expression reduced by 14–16 wk [114]
Hnf6	~E9 onwards [112]	72 hpf [113,115]	7–21 wk, consistently expressed [114]
Ipf1/Pdx1	E8-E10 [112]	14 hpf [113]	4 wk [114]
Isl1	E9 [112]	15 hpf [113]	8–10 wk [114]
Neurod	E9.5 [112]	16 hpf [113]	15 wk [114]
Ngn3	E9 [112]	Not yet described in zebrafish pancreatic anlage [116]	8 wk, expression elevated around 11 wk and then reduced to low levels at 19 wk [114]
Nkx2.2	E8-E9 [112]	14 hpf [113]	8–11 wk [114]
Pax4	E9.0-E9.5 [112]	16 hpf [117]	9 wk [114]
Pax6	E9.0-E9.5 [112]	15-24 hpf, only *pax6b* expressed in zebrafish pancreas [118]	14–16 wk, maintained in adult islet cells [114]

Note: E, Embryonic Day; hpf: Hours post fertilization; wk, week.

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