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Neuro-Insular Complexes in the Human Pancreas

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Abstract

It is well known that pancreatic islets are complex structures composed of endodermally derived endocrine cells, integrated with endothelial cells and other cells, originating from the mesoderm, and innervated by nerve fibers that have a neuroectodermal origin. In our studies, we focused on the interactions between the structures of the nervous system and endocrine cells, the so-called neuro-insular complexes, in the human pancreas. In this chapter, we present our results and literature data concerning the morphological organization of neuro-insular complexes in humans and other mammals. We also discuss the possible functional role of neuro-insular complexes, such as the involvement of the nervous system in the regulation and synchronization of islet hormone secretion and the morphogenetic plasticity of the endocrine pancreas in adults, as well as in the regulation of endocrine cell proliferation and maturation during prenatal development of the pancreas.

Keywords: pancreas, islets of Langerhans, neuro-insular complex, human development

1. Introduction

Pancreatic innervation is of interest due its role in the pathogenesis of some diseases, including chronic pancreatitis [1], pancreatic cancer [2] and type 1 diabetes [3–5]. The pancreas is well innervated by the autonomic nervous system [6–10]. In histological studies on the mammalian pancreas, the abundant innervation of the blood vessels, exocrine and endocrine part of the gland has been identified [11, 12]. Later, nerve endings were found around blood vessels, as well as pancreatic acinar, ductal and endocrine cells using immunohistochemistry and electron microscopy [13, 14]. Four types of plexuses (perivascular, periductal, periacinar and peri-insular)

have been identified in the mouse pancreas [14]. Similar data were obtained in studies on the pancreas of the rat [15] and nutria [16].

Since the classical study by Claude Bernard, which showed that an injury to the floor of the fourth cerebral ventricle caused hyperglycemia, the involvement of the nervous system in the regulation of pancreatic endocrine function and metabolic control has been shown in many studies [17–19]. At the same time, the precise innervation patterns of islets were unknown, particularly in humans [9]. Single nerve cells and nerve ganglia, as myelinated and demyelinated nerve fibers, have been identified in the human pancreas [1, 20–22]. However, the literature data indicate poor innervation of adult human pancreatic islets in comparison with rodents [1, 9, 20, 23].

One of the most interesting features of the mammalian pancreas is that endocrine cells may form highly organized complexes with structures of the nervous system, so-called neuroinsular complexes (NIC). The structure of NIC in the human pancreas has not been studied in detail since their first description by Van Campenhout [24] and Simard [25].

In this chapter, we summarize the literature data and our previous results concerning the morphological organization of NIC in the human fetal and adult pancreas. We also discuss the possible role of the close integration between the nervous system and endocrine cells in the development of the endocrine pancreas.

2. Morphological organization of NIC in the mammalian pancreas

These structures consist of autonomic nerve cells, islet cells and nerve fibers in juxtaposition with each other, as described for the first time by Van Campenhout in studies on the histogenesis of islets in human, sheep and dog [24]. Later, Simard [25] confirmed the presence of such complexes in the human pancreas at different ages and termed these structures the neuroinsular complex (NIC) (cited from [26]).

In 1959, Fujita described two types of NIC, which he observed in the fetal and adult pancreas of the dog, cat and rabbit [26]. Some of the ganglia enclosed by the perineural sheath contained islet cells (β - or α -cells) forming NIC type I (NIC I). In NIC I, islet cells contact directly with nerve cells and no intercellular element can be recognized between these two cell types. In NIC type II (NIC II), islet cells lie on the surface of, or even in the midst of, the nerve bundle. However, the distinction between these two types of complexes is conditional because there is an intermediate type of complex in which a mass of islet cells associates with nerve cells in one part of the complex and with nerve fibers in another. Moreover, the ratio between nervous and endocrine elements in different complexes varies greatly [26]. As a variation of NIC I, complexes in which a single or a few nerve cells lying in a corner of a pancreatic islet were observed in the pancreas of the rabbit [26].

Consequently, the structure of the NIC has been intensively studied using histochemical, immunohistochemical methods and electron microscopy [13, 14, 27–31]. Analysis of the thin structure of NIC I and NIC II has shown that endocrine cells contact either directly with axons

or with the processes of glial cells (Schwann cells or satellite cells) [27–29]. The gap between the plasmalemma of endocrine cells and glial cells is about 30 nm [28, 29]. Desmosome-like contacts and synaptic contacts between endocrine cells and glial cells or axons have occasionally been found by some authors [28]. As in histological studies, various morphological forms of the NIC were detected using electron microscopy. In many mammals, pancreatic islets are richly innervated by thin nerve fibers, which are located at the periphery of islets, forming peri-insular nerve plexuses; they occasionally pass through islets separately or along capillaries [14, 16, 27, 29, 32, 33]. The density of the peri-insular neural network varies between species [27]. It has also been shown that various transitional forms between the classical NIC II in which endocrine cells are located inside nerve bundles and innervated islets are present in the pancreas of the dog [27]. Similarly, various NIC I representing all transitional forms between pure islets with a single neuron and pure ganglia containing only a few endocrine cells have been detected in the pancreas of the cat [28]. Based on these findings, Böck [28] in 1986 introduced the classification of NIC reflecting a gradual transformation between pure neural and pure endocrine structures: 1. An autonomic ganglion with no endocrine cells; 2. NIC I: a) a few endocrine cells in the ganglion; b) a few ganglion cells in the islet; 3. NIC II: a) a single or few endocrine cells integrated with a bundle of nerve fibers; b) heavily innervated islet tissue; 4. A classical islet of Langerhans, either a) innervated or b) not innervated.

In addition to neurons and nerve fibers, glial cells immunopositive for S100 protein and glial fibrillary acidic protein (GFAP) have been detected at the periphery of islets in many mammals [3, 13, 14, 32, 34]. These cells have a triangular or spindle-like shape and possess long, thin leaf-like processes which cover endocrine cells, separating them from the connective tissue and from the acini.

Thus, the NIC are highly organized structures composed of endocrine cells, neurons, nerve fibers and glial cells (Schwann cells or satellite cells). The morphological organization of NIC varies considerably depending on the types of cells forming the complex and their ratios.

3. Structure of NIC in human pancreas

According to the literature, few nerve fibers are found in pancreatic islets in adult humans [1, 9, 20, 23]. However, the human pancreas receives extensive innervation, with peculiar growth dynamics during prenatal development [21]. In our previous study, rich innervation of human fetal islets was reported, and both NIC I and NIC II were detected [22].

As mentioned above, the structure of NIC in the human pancreas has not been studied in detail since their first description by Van Campenhout [24] and Simard [25]. In our studies, we investigated the structure of NIC in the human pancreas using immunohistochemistry [22, 35]. We analyzed pancreatic autopsies from 46 fetuses (from the 10th to 40th gestational week (g.w.)), 2 children (3 months old and 3 years old) and 15 adults (24–91 years old). The gestational age of fetuses was determined as the time since the last menstrual period on the basis of the measured crown-rump length and biparietal diameter by ultrasonography. Fetal pancreatic autopsies were divided into four groups, according to the classification of the fetal period [36]:

pre-fetal period (10–12 g.w.), early fetal period (13–20 g.w.), middle fetal period (21–28 g.w.) and late fetal period (29–40 g.w.).

To identify structures of the nervous system, we used various neural markers, such as neural cell adhesion molecule (NCAM), peripherin, neuron-specific class III β -tubulin, synaptosomal-associated protein of 25 kDa (SNAP-25), S100 protein and neuron-specific enolase (NSE) [22, 35]. Both types of NIC representing groups of islet cells integrated with ganglionic neurons (NIC I) or with nerve bundles (NIC II) were detected in the fetal pancreas from 14th g.w. onwards [22, 35]. In the pre-fetal period (10–13 g.w.), only contacts between single endocrine cells or small groups and thin nerve fibers were detected [35], and classical NIC I and NIC II were not found.

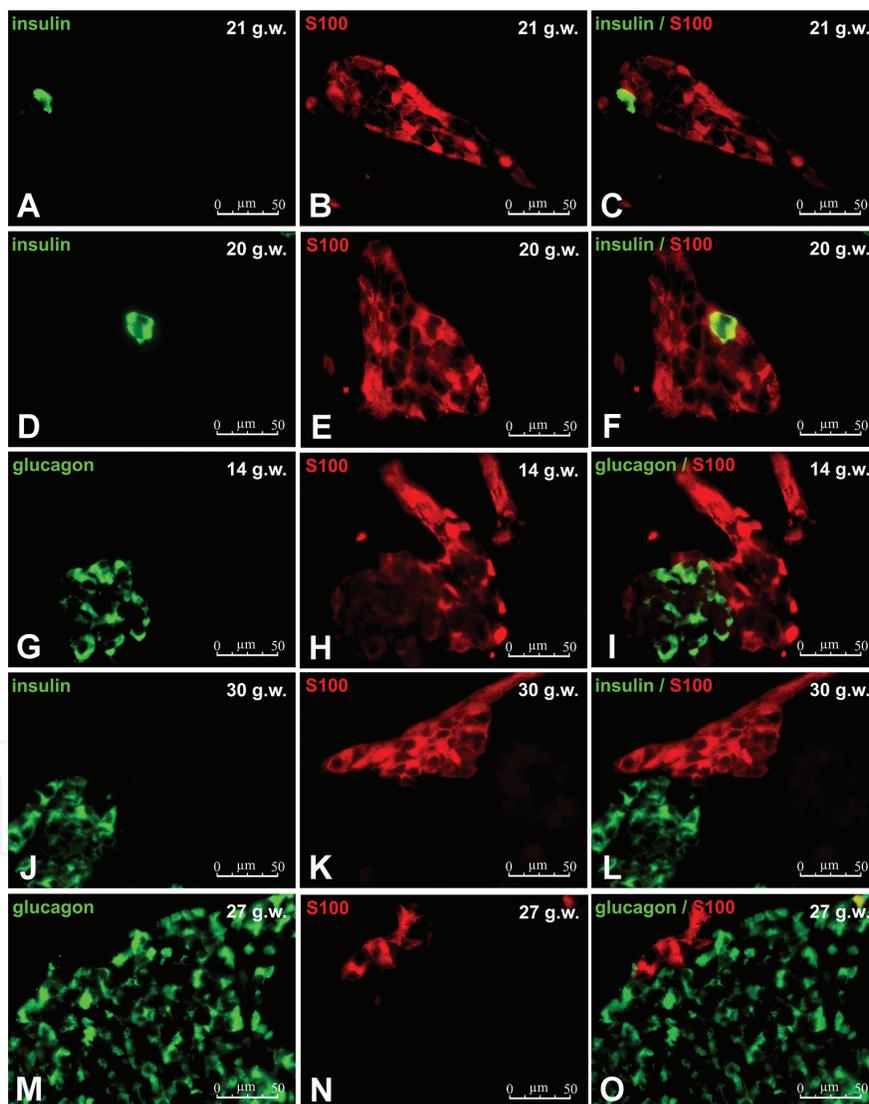


Figure 1. Various forms of NIC I in the human fetal pancreas: single (A–C) or few (D–F) β -cells in the ganglion; pancreatic islets associated with the ganglia (G–L) and few S100-positive cells in the large islet (M–O). Immunofluorescent labeling with antibodies to insulin or glucagon (green) and S100 protein (red).

To identify various subtypes of NIC in the human pancreas we used double immunohistochemical labeling with antibodies to neural makers (S100 protein or NSE) and endocrine hormones (insulin or glucagon) [35]. During prenatal development, i.e. from the 14th to 40th g.w., NIC I was present in the following forms: single (**Figure 1 A–C**) or few (**Figure 1 D–F**) endocrine cells located among ganglionic cells, pancreatic ganglia associated with islets (**Figure 1 G–L**) and few ganglionic cells located at the periphery of islets (**Figure 1 M–O**). We also detected various forms of NIC II: single or few endocrine cells in nerve bundles (**Figure 2 A–C**), pancreatic islets associated with nerve bundles (**Figure 2 D–F**), thin nerve fibers in close proximity to single endocrine cells or small groups and to islets (**Figure 2 G–L**).

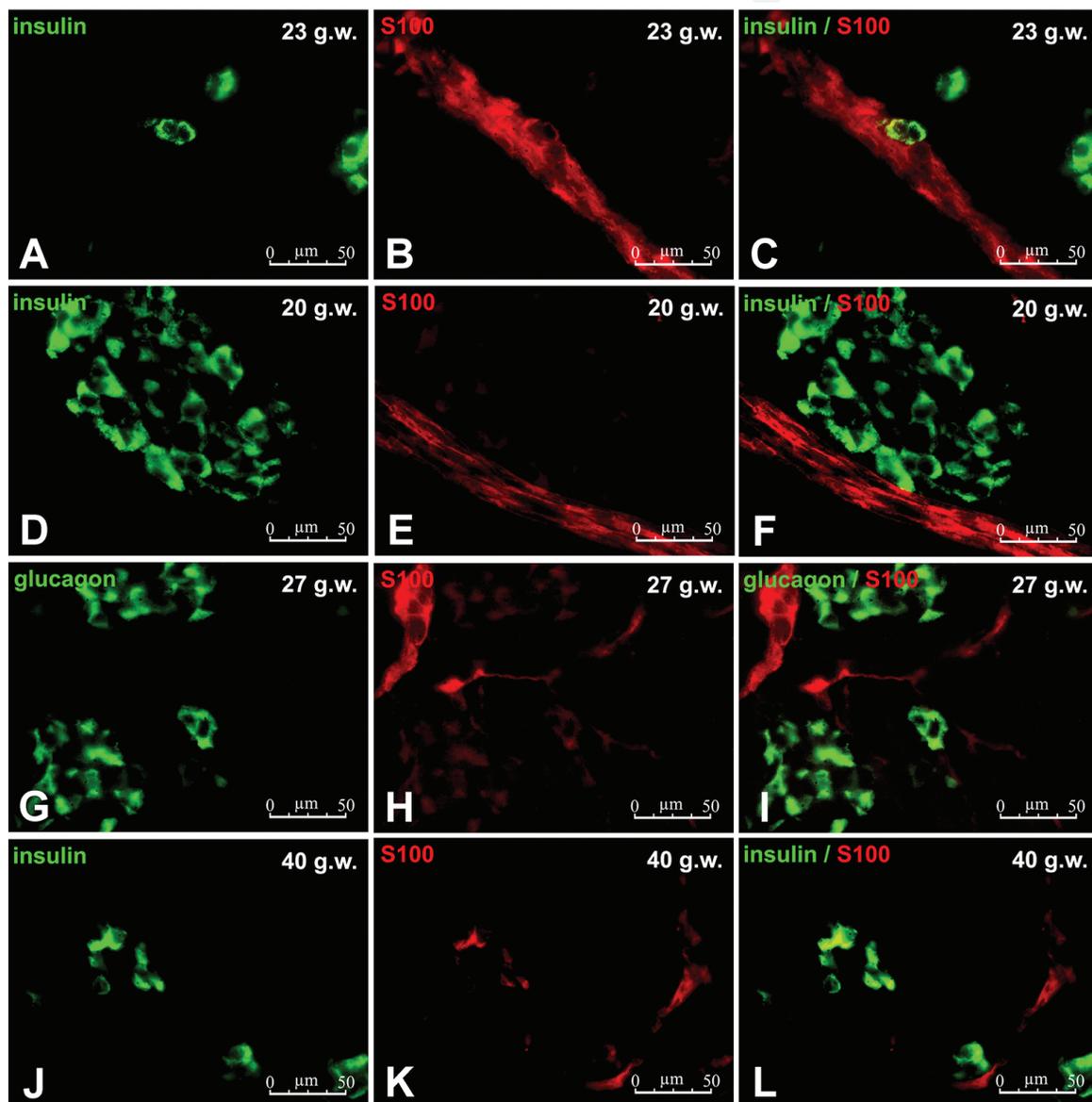


Figure 2. Various forms of NIC II in the human fetal pancreas: two β -cells in the nerve bundle (A–C); pancreatic islet associated with the nerve bundle (D–F) and thin nerve fibers in close proximity to the islets and single endocrine cells (G–L). Immunofluorescent labeling with antibodies to insulin or glucagon (green) and S100 protein (red).

Thus, the various forms of NIC that we observed in the human fetal pancreas are similar in their morphological organization to the NIC, which were found in the fetal and adult pancreas of other mammals [26–29].

The amount of NIC gradually decreases at birth. In the pancreas of children and adults, NIC are less abundant than in the fetal pancreas [22]. Our quantitative data indicate that the largest number of NIC I was observed in the early and middle fetal periods, during the active morphogenesis of pancreatic islets, whereas at birth (in the late fetal period) and in the adult, NIC II became more prevalent [35]. It should also be noted that NIC I and NIC II in which a single or few endocrine cells were located inside ganglia or in nerve bundles were found only in the fetal pancreas. We did not find these types of NIC in the adult pancreas, probably due to an insufficient number of fields of observation. Therefore, we could not exclude that these types of NIC can be present in the adult pancreas, but they are rare. NIC I in which pancreatic islets were associated with ganglia were more numerous in the fetal pancreas and were occasionally found in the pancreas of children [22] and adults [35]. Among the NIC II, at all investigated stages of development, as well as in children and adults, interactions between thin nerve fibers and endocrine cells located separately or inside the islets prevailed [35].

To identify whether glial (Schwann) cells cover the periphery of islets in humans, as in other mammals, we used immunohistochemical labeling with antibodies against S100 protein and GFAP as well as electron microscopy. We found small S100-positive cells with thin processes at the periphery of some islets in humans [37, 38]. The same small oval, triangular or elongated cells with long thin processes were observed in the fetal pancreas using electron microscopy [38]. The processes of these cells were often cover or surround nerve fibers passing into islets [38]. In contrast to mice and rats [3, 13], these cells were immunonegative to GFAP. However, according to their ultrastructural characteristics and integration with nerve fibers, these small S100-positive cells with thin processes that we detected in the human pancreas correspond to the glial (Schwann) cells observed at the periphery of islets in other mammals [3, 13, 14, 34]. It should be noted that, in humans, S100-positive glial cells are present only in some islets in small numbers and their processes do not cover endocrine cells, as has been described in other mammals [3, 13, 14, 32, 34].

Taken together, our findings indicate that, in the human pancreas, NIC are more abundant and variable in their morphological organization in the prenatal period, i.e. during the active morphogenesis of pancreatic islets. Based on these findings, we suggest that the nervous system may be involved in the development of the human endocrine pancreas. In the next part of this chapter, we discuss the existing points of view on the possible functional role of NIC.

4. Functional role of NIC

Since the description of NIC, researchers have been interested in questions about the functional role of NIC and the mechanisms of their formation. These two interrelated problems remain unresolved today. The idea of a regulatory role of the nervous system in endocrine secretion is commonly accepted now [8]. The pancreas is innervated by sympathetic and parasympa-

thetic nerve fibers [8, 39]. Moreover, in the pancreatic islets of humans and rodents, there are the afferent (sensory) nerve fibers [7, 40, 41]. Many studies have demonstrated a role for the nervous system in the regulation and synchronization of hormone secretion from endocrine cells [7, 8, 17–19, 42, 43]. Stimulation of sympathetic nerves increases the release of glucagon and reduces the release of insulin and somatostatin [10, 41, 44]. Parasympathetic stimulation increases the release of insulin, glucagon, somatostatin and pancreatic polypeptides in various species [7, 8, 10, 44, 45]. Sensory nerves are also involved in the regulation of hormone secretion by pancreatic endocrine cells. The chemical destruction of sensory nerves (capsaicin treatment) in mice increases insulin secretion in response to glucose, compared to control. Consequently, sensory fibers may exert an inhibitory effect on insulin secretion [46].

Both the parasympathetic and sympathetic nervous systems impact the postnatal development of the endocrine pancreas and pancreatic plasticity in adult animals [17, 43]. For example, a decrease in the proliferation of β -cells has been detected in mice and rats after vagotomy [47, 48].

However, the concept of the regulatory role of the nervous system in the control of hormone secretion and endocrine cell proliferation does not explain the presence of endocrine cells inside ganglia or in nerve bundles. Simard [25] proposed that these endocrine cells may secrete hormones directly into nervous tissue. However, histological and cytological analysis performed by Fujita [26] has shown that endocrine cells in the NIC are similar in their mode of secretion to endocrine cells located in pancreatic islets, because their secretory granules accumulate on the side of the cell facing the capillaries.

In the second half of the twentieth century, there were two widespread concepts: APUD (amine precursor uptake and decarboxylation) [49, 50] and “paraneuron” [51]. It is well known that endocrine cells of the pancreas and neural cells express many common proteins, such as S100, glutamic acid decarboxylase (GAD), NSE, NPY and so on [3, 52–54], and have similarities in their developmental control mechanisms (for review, see [55, 56]). Similarities between endocrine cells and neurons are also confirmed by phylogenetic data. Endocrine cells (insulin-, glucagon-, somatostatin- and PP-secreting) were found in the brain in some invertebrates and lower vertebrates [57]. In the “APUD” and “paraneuron” concepts, these similarities were explained by the common embryonic origin of pancreatic endocrine cells and neurons from the neuroectoderm [49–51]. It has also been proposed that pancreatic islets can be regarded as modified ganglia because of the gradation between pure ganglia, mixed forms representing NIC, and pure islets [29]. This hypothesis was disproved in a series of classic experiments with quail-chick chimeras and in cell culture studies in which the endodermal origin of endocrine cells was established [58–60].

Today, it is well known that pancreatic endocrine cells differentiate from epithelial progenitors. In human fetal pancreas, epithelial ductal cells express numerous transcriptional factors that regulate endocrine cell differentiation [61–63], and differentiating endocrine cells transiently retain epithelial markers and are often associated with the ductal epithelium [61, 62]. The structures of the nervous system originate from the neuroectoderm [64]. The data concerning the mechanisms of the formation of NIC are very limited. Studies on rodents (mice and rats) have demonstrated that the innervation of islets develops in the early postnatal period [31,

65]. In other mammals (cats, dogs and rabbits) [26] including humans, NIC have been detected in the pancreas during prenatal development. The morphogenetic mechanisms underlying the integration between structures of the nervous system and endocrine cells remain unclear.

In his work, Van Campenhout [24] found that all primary islets (Laguesse islets) form NIC; he first suggested that the nervous system may be involved in the development of the endocrine pancreas. He proposed that NIC form through the budding of islet cells from the primitive ducts followed by their migration into adjacent neural tissue and that the differentiation of islet cells may occur under the influence of nervous components of these complexes (cited from [26]). Consequently, it was shown that both NIC and non-innervated islets can be detected in the fetal pancreas. In our studies, we also found NIC and non-innervated islets in the human fetal and adult pancreas [22, 35].

Nonetheless, genetic studies on mice have confirmed that the nervous system may regulate the differentiation of endocrine cells. In mice deficient for *Phox2b* or *Foxd3* gene expression (*Phox2b*^{-/-} or *Foxd3*^{-/-}), neural crest cells and their derivatives are absent in the pancreas. It was shown that, in such mutant embryos, the total β -cell mass and β -cell proliferation had increased [66]. Furthermore, β -cells in the mutant embryos were immature, since the expression levels of *MafA* and *Pdx1* mRNA in β -cells were decreased, and insulin granules had abnormal morphology and were decreased in number [67]. Taken together, these data demonstrate that signals from the neural crest negatively regulate β -cell proliferation and positively regulate β -cell maturation [66, 67]. Moreover, in the developing mouse pancreas, neural crest cells and their derivatives are located in close proximity to endocrine β - and α -cells, suggesting that the regulation of β -cell mass and their maturation may occur through juxtacrine and paracrine signals from the nervous system [67, 68]. Similar results, demonstrating that co-culturing pancreatic islets with neural crest stem cells promotes the regeneration of functional β -cells, were observed *in vitro* [69].

A recent study has also shown an important role of sympathetic innervation in the establishment of pancreatic islet architecture and functional maturation during development. The absence of sympathetic innervation during development resulted in altered islet architecture, reduced insulin secretion and impaired glucose tolerance in adult mice [70].

Several studies have demonstrated that the structures of the nervous system interact with endocrine cells through the homophilic binding of cell adhesion molecules (NCAM and SynCAM), which are expressed on the surface of pancreatic endocrine cells and neural crest-derived cells in both rodents [68, 71] and humans [72]. Contacts between forming islets and NCAM-positive nerve fibers have been observed in the human fetal pancreas [72]. Therefore, it has been proposed that autonomic nerves may facilitate the outpouching of endocrine cell clusters to form islets through the homophilic binding of CD56 (NCAM) molecules on both of these tissues [72].

In our studies, we have demonstrated close integration between the structures of the nervous system and endocrine cells in the human pancreas, which was more frequently observed during prenatal development. We suggest that such integration may be necessary for the development of the endocrine pancreas in humans [22, 35]. It is possible that the nervous

system may regulate endocrine cell mass and their maturation, as has been shown in mice. It is also possible that the contacts with structures of the nervous system may be necessary for the migration of epithelial progenitors into forming islets. In this case, different types of NIC may represent various stages of pancreatic islet morphogenesis.

5. Conclusions

In the pancreas of many mammals, including humans, endocrine islet cells are closely integrated with the structures of the nervous system into NIC. The morphological organization of such complexes varies considerably depending on the type of cells forming the complex and their ratios. According to the most current data, the nervous system is involved in the regulation and synchronization of islet hormone secretion and the morphogenetic plasticity of the endocrine pancreas in adults. During the prenatal development of the pancreas, the nervous system regulates endocrine cell proliferation and maturation and is involved in the establishment of islet architecture. In humans, NIC are more abundant and variable in their structure during prenatal development. This fact may serve as morphological evidence of the involvement of the nervous system in the morphogenesis of the human endocrine pancreas.

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