

Editorial

PANCREATIC β CELL CLOCK AND TELOCYTES

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Circadian clocks are cell-autonomous molecular oscillators that drive daily rhythms of physiology and behavior [1,2]. Apart the well known fundamental processes like sleep/wake cycle, physical activity and metabolism, highly integrated into the 24 hour (circadian) periodicity [1, 3], there are some infradian or ultradian tissue clocks, whose significance and mechanisms are not yet well known [2].

Pancreatic β cells show at least three types of insulin secretory pulsations which seems to be related to the metabolic activity regulation in various peripheral tissues/organs, involved in maintaining the energy homeostasis of human body [4]. The rapid insulin pulsation with a periodicity of 6-10 min., slows ultradian (~ 140 min) and circadian (~24 hr) oscillatory pattern of insulin secretion [4, 5] were detected during *in vivo* studies by the mean of frequent insulin measurements during an appropriate stimulation. It is worthy of note that the ultradian oscillation which occurs several times per day are particularly associated with meals [6, 7].

Such secretory pulsation can be secondary to small oscillation in blood glucose levels induced by the decrease (by utilization) or an increase (by hepatic release) of blood glucose levels. In such case, the pulsation of insulin secretion will follow the oscillation in blood glucose level. Such *entrainment* can be reproduced by inducing small increase of

blood glucose level by a controllable infusion of glucose [8, 9]. Failure on *entrainment* has been detected in early stages of the natural history of diabetes [7,9].

The decrease or the disappearance of both rapid and slow ultradian insulin pulsations [4] can precede the detection of the alteration in biphasic insulin secretion (the early phase at 3-7 min and the late phase at ~ 45 min), or by the increase in the proinsulin levels or the proinsulin/insulin ratio [10, 11].

The circadian periodicity in several fundamentally processes have in their core clock machinery, the central pacemaker neurons of the supra-chiasmatic nucleus of the hypothalamus [1, 3]. A number of genes and molecules (*Clock*, *Period*, *Cryptochrome*) are the major clock regulators which function not only in hypothalamus but also in the peripheral metabolic tissues, such as the liver, white adipose and muscles where control various branches of the biochemical network regulating the energy homeostasis of the human body.

Recently, using the generation of several types of knockout mice for some of these “clock” like molecules resident in the pancreatic β cells [3, 12] has showed that their involvement in insulin signaling, glucose uptake and metabolism, pancreatic β -cell growth and development. An important role of core clock molecular components, both in insulin secretion and in pancreatic β cell

survival, has been suggested [12]. The persistence of clock expression gene in the explants of pancreas or even in isolated islets [3] suggests that their activation can be regulated by some intrinsic mechanisms. They confirm the classic data showing that the denervation of the pancreas is not associated with an evident alteration in blood glucose regulation. In fact, the mechanistic explication of the physiologic insulin pulsation is not clear.

Several years ago, when the team leaded by Popescu [13-18] described the presence of the interstitial Cajal-like-cells (ICLC), initially in pancreas and than in almost all organs of the human body, I was wondering if this type of cells can not be related with the well known oscillation in insulin secretion.

In the last years, it have been realized that ICLC are in fact, a new type of cells, different from fibroblasts, which recently have been called *telocytes* [19-21]. This is a new term for

a new type of cells which are characterized by a small body, but with very long (several hundred μm) prolongation. These prolongations are very thin (0.1-0.2 μm), posses caveoles and have a moniliform aspect, visible only in electronic microscopy. The unusual long prolongations of these cells can make the links with various structures inside the organs via *exosomes*, a kind of “secretory vesicles”, but with a known product. The specific function of telocytes is not well known, but seems to be involved in cell maintenance and repair, functioning in tandem with stem cells. Although they had studied more for repairing the myocardium after an infarction, their carefully study in pancreas might open a new area of understanding the substrate of various types of insulin pulsation whose disappearance is associated with the onset on diabetes. Could have telocytes a role in pathogenesis of type 2 diabetes? And in future for their repair?

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