Nicotine actions on beta cell function in health and disease

Rendicontazione

Informazioni relative al progetto

NACHO

ID dell'accordo di sovvenzione: 795912

Sito web del progetto

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Progetto chiuso

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Periodic Reporting for period 1 - NACHO (Nicotine actions on beta cell function in health and disease)

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Sintesi del contesto e degli obiettivi generali del progetto

Tobacco abuse elevates the risk of developing type 2 diabetes. This effect has been recently attributed to nicotine, which is the major addictive compound in both cigarette smoke and chewing tobacco. Nicotine acutely activates its receptors while extended exposure results in receptors

desensitization. Accumulating evidence suggests that long-term exposure to nicotine impairs pancreatic beta cell function. We have recently demonstrated that nicotine acutely modulates insulin secretion from pancreatic beta cells and that reduced expression of nicotinic receptors in beta cells results in an increased risk for developing type 2 diabetes. This suggests that activation of nicotinic receptors is critical for β-cell function. However, the precise mechanisms used by these receptors to modulate beta cell function upon long-term exposure to nicotine in healthy and metabolically compromised conditions have not been determined yet. Here we propose to investigate the effects of nicotine on insulin secretion using animal models and human islets. We will study the mechanisms by which nicotine affect insulin secretion in beta cells. Furthermore, we will assess the effects of long-term nicotine exposure on beta cell function in obese animals and the impact on insulin release in humans. Understanding how nicotine influences beta cell function in diabetes development is of considerable clinical interest since tobacco abuse is still common and nicotine treatment is widely used as smoking cessation therapy.

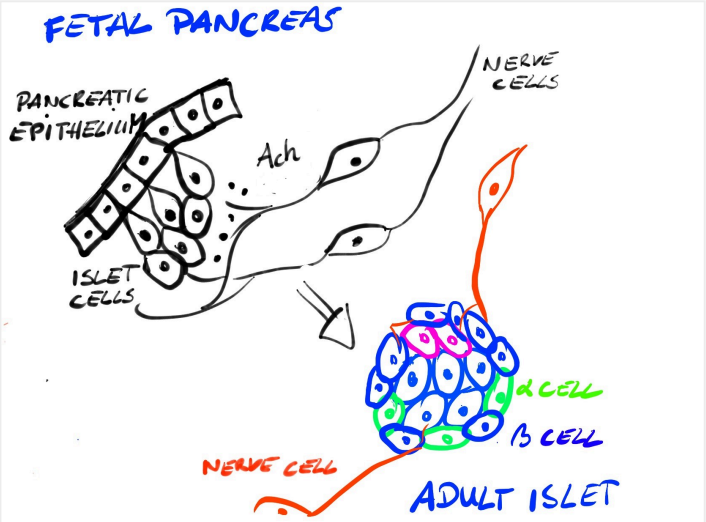
Lavoro eseguito dall'inizio del progetto fino alla fine del periodo coperto dalla relazione e principali risultati finora ottenuti

The general aim of the NACHO project was to determine how nicotinic signaling is participating in β-cell function in healthy and metabolically compromised conditions. We have performed a thorough analysis of nicotine's effect on beta cell function in response to parasympathetic acetylcholine stimulation using cell lines, animal models and mouse and human tissue.
During these 2-year project we have done in vitro and in vivo experiments using mouse MIN6 beta cells and pancreatic islets from mice lacking nicotinic receptors and human donors. We performed pharmacological treatments with agonists of muscarinic (oxotremorine) or nicotinic (nicotine, varenicline (selective for β2/β4)) receptors or antagonists (mecamylamine) of nicotinic receptors and evaluated how they affected the acetylcholine-promoted glucose-stimulated insulin secretion (stimulation with glucose w/wo acetylcholine). We also evaluated whether these treatments affected mitochondrial activity (oxygen consumption rate, OCR) and calcium influx, being both critical molecular events during glucose-mediated insulin secretion.
In an in vivo study, we fed mice with a high fat diet and treated them with nicotine in drinking water for one month. After treatment, the lean and obese mice (w/wo nicotine) were subjected to 2DG-intraperitoneal glucose tolerance test (mimicking parasympathetic stimulation of insulin secretion) and analyzed the insulin secretion response in vivo. As expected, MafA mutant animals and islets (mouse model for beta cell dysfunction lacking nicotinic receptor expression) did not respond to acetylcholine and 2DG stimulation. Interestingly, we observed that long-term treatment of mice with nicotine reduced parasympathetic-promoted insulin secretion in lean but not obese mice. However, we observed no significant changes in the acetylcholine -promoted glucose-stimulated insulin secretion after short-term treatment with nicotine or nicotinic receptors agonist/inhibitors of MIN6 cells, mouse or human islets. Consistently, we did not observed changes in the acetylcholine-promoted glucose-stimulated mitochondrial oxygene consumption rate and cytosolic Ca2+ transients when MIN6 cells were treated with nicotinic receptors-directed drugs.
These results show that nicotine is affecting beta cell function after long-term in vivo treatment (similarily to smoking), most likely by impairing communication between nerve and beta cells. A

hypothesis further supported by our related finding that blocking nicotinic signaling during beta cell development is impairing the formation of beta cell clusters and connection to nerve cells (see figure). Dissemination of results: Two publications are planned during 2020 in open access journals.

Progressi oltre lo stato dell'arte e potenziale impatto previsto (incluso l'impatto socioeconomico e le implicazioni sociali più ampie del progetto fino ad ora)

Diabetes affected over 387 million people and contributed to 4.9 million deaths worldwide in 2014. Environmental factors like smoking cigarette/tobacco significantly elevate the risk for type 2 diabetes onset. The increased risk of smokers to develop type 2 diabetes has been previously attributed to nicotine's adverse effect on insulin sensitivity, but additional evidence points towards effects of prolonged nicotine exposure on β-cell function.
In this project, we aimed to determine if nicotine and nicotinic signaling directly affect beta cell function in response to parasympathetic stimulation, which is a critical component of physiological insulin secretion. Previous studies have focused on determining if nicotine affected insulin secretion in response to glucose, but not in response to parasympathetic stimulation. Our results demonstrate that long-term in vivo exposure to nicotine affects parasympathetic-stimulated insulin secretion, while we did not see an effect after short-term nicotine treatment in vitro. These findings suggest that nicotine affects the communication between the nervous system and beta cells only after long-term treatment. Loss of parasympathetic stimulation has been reported as a risk factor for type 2 diabetes development and our findings suggest that nicotine exposure (smoking) which is also a risk factor for type 2 diabetes impairs this mechanism. Moreover, we have results demonstrating that nicotinic signaling is required for islet formation during development, suggesting that nicotine exposure during pregnancy may affect adult beta cell function, further elevating the risk for developing type 2 diabetes. Our results demonstrate the critical impact of nicotine on type 2 diabetes development and provides mechanistic insight in how nicotinic signaling is required for beta cell development and islet formation. Further emphasizing the importance of public health smoking prevention programs, especially for women in childbearing age.



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