Targeting bioelectronically the carotid sinus nerve in Type 2 diabetes: strengths, drawbacks and challenges for the future

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“We hypothesize that different CSN fibers are coupled with responses to different stimulus and so, the characterization and discrimination of fiber–stimulus associations will allow selective modulation of the fibers at the CSN. If proven right, this hypothesis leads the way to intervene in CSN-mediated metabolic diseases without affecting O₂ and CO₂ chemosensitivity.”

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Why is the carotid sinus nerve a therapeutic target for bioelectronic modulation in metabolic diseases?

In recent years, the carotid bodies (CB), classically defined as peripheral sensors for O₂, CO₂ and pH, have gained increasing attention due to their function as metabolic sensors implicated in the control of energy homeostasis [1–4]. These tiny organs, located at a privileged anatomic location to signal threats to the central nervous system, are overactivated in insulin resistant, glucose intolerant and hypertensive animal models [5–7] causing an increased adrenergic tone [5,6]. Our research group has shown that disturbed CB activity observed in metabolic syndrome and prediabetes [5,8] may be surgically circumvented through resection of the carotid sinus nerve (CSN), which both prevents and restores insulin resistance, glucose intolerance and hypertension in animal models of metabolic syndrome and Type 2 diabetes [5–7]. These positive effects of CSN resection in whole body metabolic homeostasis are mediated by increased glucose uptake and insulin signaling in the liver and in the visceral adipose tissue [6] and by a significant decrease in the heightened sympathetic tone that portrays metabolic diseases [5,6]. Supporting the above-mentioned preclinical data, our lab has also shown that intermittent hyperbaric oxygen therapy, frequently used to promote wound healing in diabetic foot ulcers, improves glucose homeostasis in Type 2 diabetes patients [9], an effect that may be attributed to a CB-mediated mechanism, as hyperoxia dramatically reduces peripheral chemoreceptor activity [10]. Therefore, there is currently very strong evidence that CSN neuromodulation may be an appealing alternate approach for patients suffering from metabolic syndrome and early Type 2 diabetes. The attempted therapeutic approaches for CSN neuromodulation, surgery and oxygen therapy, despite being very effective in the disease phenotype, may cause numerous side effects and complications, with varying degrees of seriousness. It has been described that hyperbaric oxygen therapy can frequently produce fatigue and lightheadedness and, more rarely, can cause more severe side effects derived from O₂ toxicity as lung damage, rupture of the middle ear, sinus damage and permanent blurred vision [11]. On the other hand, surgical resection of the CSN, apart from being an invasive approach, can lead to side effects related with loss of the peripheral hypoxic response, with decreased sensitivity to CO₂ [12,13], impaired response to exercise [14–16] and fluctuations in blood pressure [17]. An alternate approach would be to use a medical device implanted in the CSN, a bioelectronic medicine, with the ability to selectively target disease, by correcting defective action potential patterns without disturbing normal physiological functions.

Continuous kilohertz frequency alternative current neuromodulation of the carotid sinus nerve

We recently tested the use of chronic continuous kilohertz frequency alternate current to block CSN transmission and assessed its effects on insulin resistance and glucose intolerance in an early Type 2 diabetes animal model [7]. We demonstrated that bilateral high frequency conduction modulation of the CSN mimics the positive metabolic effects in insulin-resistant, glucose-intolerant animals, previously observed upon CSN bilateral surgical resection, with the advantages of being tunable, nonablative and reversible [7]. The results showed that electrical neuromodulation of the CSN has significant therapeutic potential as a means of controlling CSN activity in metabolic diseases. However, the CSN conveys not only the information that comes from the CB, but also the baroreceptor information that emerges from the carotid sinus and that is involved in the acute adjustment of blood pressure [18]. Despite this, we did not observe significant side effects related to increased blood pressure variability in our experimental setting, the hypothesis that continuous electrical neuromodulation of whole CSN nerve may cause side effects related with blood pressure fine tuning in humans is likely [17,18].

Also, as the CB is involved in adaptation to hypoxic environments and response to acidosis, adverse effects related with continuous electrical modulation may include exercise intolerance and unsafe hypoxic acclimatization [14–16,19].

Will electrical neuromodulation of carotid sinus nerve be a suitable therapeutic for all Type 2 diabetes phenotypes?

Although it is widely accepted that metabolic diseases are characterized by increased sympathetic activation, the role of CB activation as an etiological factor in the different disease phenotypes has yet to be assessed.

Thus, CB functional diagnosis may have predictive value regarding the efficacy of a therapeutic bioelectronic approach directed toward corrective neuromodulation of disturbed CSN discharges. Currently, there is no medical device that synchronizes CB function diagnosis with neuroendocrine homeostasis variables nor clinical guidelines focused on assessing CB function associated with glucose and lipid homeostasis.

The peripheral chemoreceptors, located at the CBs, are intimately involved in cardiorespiratory control, and the assessment of hemodynamic and respiratory variables is the classical way to look at CB function.

In 1962, Dejours described a way of assessing the ‘Respiratory Chemoreflex’ measuring the latency of the ventilatory responses after an acute hyperoxic challenge [20]. The Dejours test, as it is still known, was a dynamic respiratory functional test in which baseline respiration was recorded while volunteers breathed 21% O₂ for 45 s, followed by 100% O₂ for 20 s. Respiratory variables were analyzed for 20 s during 21% O₂ and during the last 15 s of hyperoxia, to evaluate the sensitivity of the CBs. The amount of the decrement in ventilatory responses, consequent to oxygen breathing, was considered to represent the component of the ventilatory drive attributed to the peripheral chemoreceptors [20]. Although described since 1962, and often used in experimental settings, the Dejours test did not gain clinical relevance due to the scarce knowledge on the pathophysiological involvement of CB function in clinically relevant diseases. With the new finding that the peripheral chemoreceptors located in the CBs are involved in the genesis and progression of pandemic nontransmittable diseases, like Type 2 diabetes, the evaluation of the CBs function, as a means to evaluate disease risk, to diagnose subclinical pathologies and to stratify patients for CB modulatory interventions grows in clinical importance. Additionally, due to the finding that the CBs also control glucose metabolism and homeostasis, the evaluation of its function must be performed, not only at the cardiorespiratory level, but also in terms of metabolic parameters creating a novel clinical parameter designated as the ‘metabolic chemoreflex’ that will consist in measuring the latency of the ventilatory responses after an acute mixed meal challenge. The development of a ‘CBmeter’ that assesses these variables would serve to diagnose patients with altered respiratory and metabolic chemoreflexes, and could be used as a screening tool to detect people with high risk for metabolic diseases and eligible for carotid sinus nerve bioelectronic interventions.

Overcoming the side effects of continuous kilohertz neuromodulation of the carotid sinus nerve

As the concept of bioelectronic devices targeting the CSN to restore metabolic function is gaining attention and adepts, we have been working in minimizing the off-target effects of neuromodulation of the CSN. Within several specific aims, the one related to identification and characterization of neuronal circuits and signatures that are overactivated within the CSN in metabolic diseases has been the one we have been most dedicated to. We hypothesize that different CSN fibers are coupled with responses to different stimulus and so, the characterization and discrimination of fiber–stimulus associations will allow selective modulation of the fibers at the CSN. If proven

right, this hypothesis leads the way to intervene in CSN-mediated metabolic diseases without affecting O₂ and CO₂ chemosensitivity. Additionally, other therapeutic alternatives to continuous high frequency block of the CSN would be to resynchronize action potential firing disease patterns in specific fibers or, in a less targeted approach, to assess the efficacy of intermittent block of the CSN, as an alternative to continuous block, in metabolic homeostasis control.

In conclusion, evidence points toward bioelectronic modulation of the carotid sinus nerve as a robust therapeutic alternative in metabolic syndrome and Type 2 diabetes. The challenges for the future are mainly related to finding an appealing alternative to continuous high frequency alternate current to achieve selective modulation of metabolic responsive CSN fibers with minimal off-target effects.

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