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The evolving obesity challenge: targeting the vagus nerve and the inflammatory reflex in the response

Valentin A. Pavlov ^{a,b,*}

^a Institute of Bioelectronic Medicine, The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY 11030, USA

^b Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY 11549, USA



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ABSTRACT

Obesity and the metabolic syndrome (MetS), which have reached pandemic proportions significantly increase the risk for type 2 diabetes, cardiovascular disease, and other serious conditions. Recent data with COVID-19 patients indicate that obesity also is a significant risk factor for this novel viral disease and poor outcome of associated critical illness. These findings considerably change the view of obesity as a driver of serious, but slowly-progressing chronic diseases, and emphasize the urgency to explore new therapeutic approaches. Inflammation is a recognized driver of metabolic derangements in obesity and MetS, and a core feature of COVID-19 pathobiology. Recent advances in our understanding of inflammatory regulation have highlighted the role of the nervous system and the vagus nerve-based *inflammatory reflex*. Current bioelectronic and pharmacological therapeutic explorations centered on the inflammatory reflex offer new approaches for conditions characterized by immune and metabolic dysregulation and for ameliorating the escalating burden of obesity, MetS, and COVID-19.

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Abbreviations: ARDS, acute respiratory distress syndrome; ACh, acetylcholine; AChE, acetylcholinesterase; $\alpha 7$ nAChR, alpha 7 nicotinic acetylcholine receptor; BMI, body mass index; DMN, dorsal motor nucleus of the vagus; COVID-19, coronavirus disease 2019; ChAT, choline acetyltransferase; GI, gastrointestinal; HDL-C, high density lipoprotein-cholesterol; IBD, inflammatory bowel disease; ICU, intensive care unit; IL, interleukin; JAK2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3; LPS, lipopolysaccharide; HRV, heart rate variability; MERS-CoV, Middle East respiratory syndrome corona virus; MetS, metabolic syndrome; mAChR, muscarinic acetylcholine receptor; NA, nucleus ambiguus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF- κ B, nuclear factor kappa B; NLRP3, NLRs nucleotide-binding oligomerization domain (NOD)-like receptors nucleotide-binding oligomerization domain-like receptor family pyrin domain containing-3; NTS, nucleus tractus solitarius; SARS-CoV, severe acute respiratory syndrome CoV; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TLR, toll-like receptors; TNF, tumor necrosis factor; VNS, vagus nerve stimulation.

* Corresponding author at: The Feinstein Institutes for Medical Research, Northwell Health 350 Community Dr, Manhasset, NY 11030, USA.

E-mail address: vpavlov@northwell.edu.

1. Introduction

Obesity and the metabolic syndrome (MetS) continue to fuel type 2 diabetes, cardiovascular disease, non-alcoholic steatohepatitis (NASH), cancer, and many other debilitating and lethal diseases (Eckel, Grundy, & Zimmet, 2005; Grundy, 2008). Despite decades of active research and therapeutic development, progress in finding adequate solutions for these pandemic disorders remains limited. The recent outbreak of coronavirus disease 2019 (COVID-19), caused by a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), resulted in a new pandemic challenging the preparedness of healthcare and medicine to deal with such an unprecedented event. As of December 1, 2020, COVID-19 has been confirmed in more than 63 million people globally and in more than 13 million people in the United States with mortality of 1,474,213 and 268,880 respectively (<https://coronavirus.jhu.edu/map.html>). Of note, obesity and hypertension - key features of MetS (Alberti et al., 2009; Grundy, 2004) were identified as major comorbidities in a study with 5,700 COVID-19 patients in the New York City area, admitted to hospitals in Northwell Health - the largest academic health system in New York (Richardson et al., 2020). Obesity has been associated with significantly worsened progression of COVID-19, increased hospital and intensive care unit (ICU) admissions, and increased death rates (Gao et al., 2020; Goyal et al., 2020; Hamer, Gale, Kivimäki, & Batty, 2020; Tartof et al., 2020; Richardson et al., 2020; Simonnet et al., 2020; Yang et al., 2020). This newly identified relationship between obesity and COVID-19 stresses the need for new treatments to alleviate the long-standing obesity and MetS health crisis.

Active research generating novel insights into the regulatory functions of the nervous system has recently resulted in clinical translation of conceptually new treatments for various diseases based on neuromodulation, defining the new field of *Bioelectronic Medicine* (Levine et al., 2019; Olofsson & Tracey, 2017; Pavlov, Chavan, & Tracey, 2019; Pavlov et al., 2019; Pavlov, Chavan, & Tracey, 2018). The nervous system controls inflammation and recent discoveries have identified the role of a major vagus nerve-mediated physiological mechanism - *the inflammatory reflex* in this regulation (Hoover, 2017; Pavlov et al., 2018; Tracey, 2002, 2009). Studies on the inflammatory reflex within the scope of bioelectronic medicine have resulted in new treatments, for diseases characterized by immune and metabolic derangement (Koopman et al., 2016; Bonaz et al., 2016; Pavlov et al., 2019). Aberrant inflammation is a key underlying mechanism of pathogenesis and a therapeutic target in obesity, MetS and COVID-19. Bioelectronic vagus nerve stimulation (VNS) and cholinergic drugs, targeting the inflammatory reflex, including the acetylcholinesterase (AChE) inhibitor galantamine have been increasingly explored in treating obesity-associated inflammation and metabolic complications (Consolim-Colombo et al., 2017; Chang, Chavan, & Pavlov, 2019; Pavlov & Tracey, 2012). VNS and pharmacological cholinergic stimulation are currently being explored in treating patients with COVID-19. A timely overview of this new line of research and its growing clinical translatability is presented here.

2. Obesity and MetS: global health threats with limited treatment options

Obesity is a chronic disorder, associated with a variety of health risks and decreased life expectancy (Ebbeling, Pawlak, & Ludwig, 2002; Heysfield & Wadden, 2017). Obesity is recognized as a disease by the American Medical Association and a growing number of other professional medical and health organizations (Bray, Kim, Wilding, & Federation, o. b. o. t. W. O., 2017; Jastreboff, Kotz, Kahan, Kelly, & Heysfield, 2019). The rates of obesity have been persistently increasing for the last few decades. As recently reported for the United States, the age-adjusted prevalence of obesity in adults in 2017–2018 was 42.4%, with no significant differences between men and women for all

adults or by age category, including younger adults (aged 20–39), middle-aged adults (aged 40–59), and older adults (aged 60 and over) (Hales et al., 2020). The prevalence of both obesity and severe obesity has increased among adults from 1999–2000 through 2017–2018 (Hales et al., 2020). Obesity is closely related to MetS - clustering of central (abdominal) obesity, increased triglycerides (hypertriglyceridemia), reduced high-density lipoprotein cholesterol (HDL-C), hypertension, and hyperglycemia (Alberti et al., 2009) (Fig. 1). Three abnormal findings out of these five components (risk factors) would qualify a person for MetS (Alberti et al., 2009). MetS is linked to a 5-fold increased risk of type 2 diabetes, a two-fold higher risk of cardiovascular disease, and increased risks of NASH, cancer, and many other diseases, compared with the risks presented by MetS individual components (Alberti et al., 2009; Eckel et al., 2005; Grundy, 2008; James, Rigby, & Leach, 2004) (Fig. 1). A large follow-up study of 3,323 middle-aged adults for over an 8 year period has identified MetS as an essential precursor for development of cardiovascular disease and type 2 diabetes in both men and women (Wilson, D'Agostino, Parise, Sullivan, & Meigs, 2005). Cardiovascular disease is the leading cause of illness and death in the United States (Nabel, 2003). As reported in 2017, type 2 diabetes affects 415 million people worldwide, and an estimated 193 million people have undiagnosed type 2 diabetes (Chatterjee, Khunti, & Davies, 2017). An early event in type 2 diabetes pathogenesis is the obesity- and MetS-related insulin resistance, which is followed by progressive pancreas β -cell dysfunction and loss prior to the onset of clinical hyperglycemia (Stumvoll, Goldstein, & van Haeften, 2005). Non-alcoholic fatty liver disease (NAFLD) associated with ectopic fat accumulation in the liver (steatosis) is considered the hepatic manifestation of MetS (Dietrich & Hellerbrand, 2014). In the United States and globally, NAFLD is the leading cause of chronic liver disease in adults and children (Dietrich & Hellerbrand, 2014). Within the spectrum of

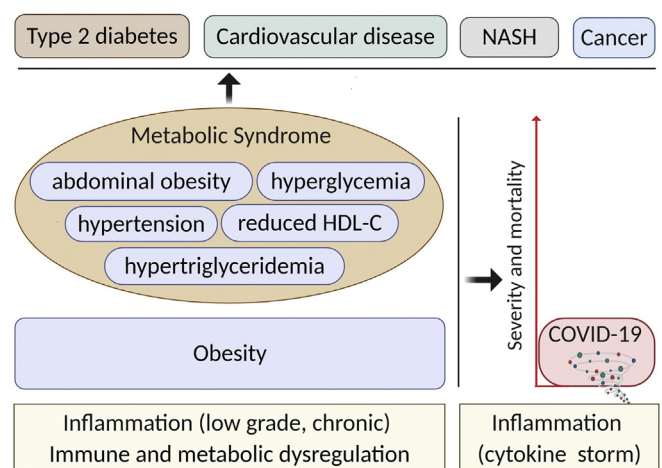


Fig. 1. Obesity, metabolic syndrome and COVID-19: a role of inflammation as a driver of pathogenesis. Obesity by itself is associated with significant health risks, but when abdominal obesity clusters with hyperglycemia, hypertension, reduced HDL-C, and hypertriglyceridemia in the MetS, the risks for type 2 diabetes, cardiovascular disease, NASH, cancer, and other chronic diseases are significantly higher. Recent findings identify a correlation between obesity and MetS and significantly higher severity and mortality of acute COVID-19, thus changing the chronic disease-centered obesity paradigm. Low-grade chronic inflammation driven by metabolic and immune dysregulation and manifested by increased levels of TNF, IL-6, leptin and resistin and decreased IL-10, and adiponectin is an important driver of insulin resistance and other metabolic derangements in obesity and MetS, and progression into serious chronic diseases. Increased levels of pro-inflammatory cytokines, e.g. IL-6 and TNF mediate acute inflammatory responses and the *cytokine storm* in COVID-19 pathogenesis. The mechanisms linking obesity and MetS to increased COVID-19 severity remain elusive, but inflammation might be a predisposing factor. COVID-19, coronavirus disease 2019; HDL-C, high-density lipoprotein cholesterol; IL, interleukin; MetS, metabolic syndrome; NASH, non-alcoholic steatohepatitis; TNF, tumor necrosis factor. See text for details. (Figure created using Biorender)

NAFLD, hepatic steatosis progresses into the more severe form - NASH, characterized by liver inflammation with or without fibrosis and increased risks of cirrhosis and liver cancer (Byrne & Targher, 2015; Dietrich & Hellerbrand, 2014). NAFLD is considered a multisystem disease and perhaps not surprisingly, because of its close relationship with MetS, is also linked to significantly increased risks of cardiovascular disease and type-2 diabetes (Anstee, Targher, & Day, 2013; Byrne & Targher, 2015; Targher, Day, & Bonora, 2010). There is some evidence for racial and ethnic heterogeneity in the prevalence of obesity, hypertension, type 2 diabetes and cardiovascular disease. A prominent example is that African Americans are more severely affected by these conditions compared with white (non-Hispanic) individuals (Cossrow & Falkner, 2004; Marinos et al., 2017; Mensah, Mokdad, Ford, Greenlund, & Croft, 2005; Roger et al., 2011; Safford et al., 2012).

In the obesity and MetS management, dieting and increased physical activity have been and will certainly continue to be first choices for achieving a weight loss and reducing abdominal fat deposition (Paley & Johnson, 2018). However, for many these lifestyle modifications are challenging to implement and maintain, and the desirable effects are difficult to sustain because they may trigger biological mechanisms that promote weight regain (Heymsfield & Wadden, 2017; Paley & Johnson, 2018). Dieting and exercising are even more challenging and may become even impossible to implement as age advances. Therefore, there is a critical need for efficacious therapeutic approaches for obesity. Active research continues to improve our understanding of mechanisms of energy balance, appetite, satiety, eating behavior, genetics, and environmental, and psychological aspects of obesity (Ahima & Antwi, 2008; Arora & Anubhuti, 2006; Friedman, 2004; Goodarzi, 2018; Kim et al., 2019; Maes, Neale, & Eaves, 1997; Pavlov & Tracey, 2012; Romieu, et al., 2017; Roth et al., 2016; Verdich et al., 2001). This research resulted in generating several anti-obesity drugs, including pancreatic lipase inhibitors, gamma-aminobutyric acid receptor agonists, a serotonin 2C receptor agonist, opioid antagonist, dopamine-norepinephrine reuptake inhibitor, and glucagon-like peptide-1 receptor agonists (Bessesen & Van Gaal, 2018). However, the use of these currently available therapeutics remains limited, which is at least partially related to limited efficacy and patients' concerns about side effects (Bessesen & Van Gaal, 2018). Treating MetS is very complex and usually several medications treating its individual components are required (Cornier et al., 2008; Eckel et al., 2005).

3. Inflammation in obesity and MetS

Inflammation is a vital protective biological response to tissue injury and infection, which is localized, balanced, and typically resolved in a timely manner (Medzhitov, 2008). It is triggered by the interaction of pathogen-associated molecular patterns or damage-associated molecular patterns with pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (cytosolic) on macrophages and other immune and non-immune cells (Akira, Uematsu, & Takeuchi, 2006; Kawai & Akira, 2009). These innate immune responses are mediated through intracellular signaling, involving nuclear factor-kappa B (NF- κ B), other transcription factors, and inflammasomes, and lead to increased production of TNF, IL-6, IL-1 β , and other cytokines, chemokines and other inflammatory mediators (Akira et al., 2006; Medzhitov, 2008). Pathogens can also interact with neurons to cause the release of neuropeptides that regulate inflammation (Chiu et al., 2013; Talbot, Foster, & Woolf, 2016).

Sometimes however, the normal protective course of inflammation is disrupted and inflammation becomes excessive and systemic, non-resolved, and chronic. These forms of inflammation drive the pathogenesis of numerous diseases (Chavan, Pavlov, & Tracey, 2017; Olofsson, Metz, & Pavlov, 2017). Low-grade chronic inflammation with systemic manifestations is an important underlying event in obesity and MetS

pathobiology (Lumeng & Saltiel, 2011; Sutherland et al., 2004) (Fig. 1). Inflammation in obesity and MetS is somewhat "unorthodox", because of the lack of obvious infection or tissue injury. This characteristic chronic inflammatory state is driven by immune and metabolic dysregulation (Lumeng & Saltiel, 2011; Saltiel & Olefsky, 2017; Shoelson, Herrero, & Naaz, 2007). A recognized source of obesity-associated inflammation is the expanded abdominal white adipose tissue infiltrated with immune cells, including macrophages and neutrophils (Lumeng & Saltiel, 2011; Saltiel & Olefsky, 2017). The crosstalk between enlarged adipocytes with altered metabolic activity and immune cells results in the increased production and release of pro-inflammatory cytokines and adipokines, including TNF, IL-1 β , IL-6, leptin and resistin, and decreased release of anti-inflammatory molecules such as IL-10 and adiponectin (Saltiel & Olefsky, 2017; Shoelson et al., 2007). The increased levels of free fatty acids is another inflammatory driver in obesity and MetS (S. M. Grundy, 2008; Shi et al., 2006). Free fatty acids cause activation of TLR4-mediated intracellular inflammatory signaling in adipocytes, macrophages, and hepatocytes, which results in NF- κ B activation, and increased TNF and other pro-inflammatory cytokine production (Lumeng & Saltiel, 2011; Shi et al., 2006). *Metabolic endotoxemia*, linked to increased gut lipopolysaccharide (LPS)-containing microbiota in obesity, and subsequently increased intestinal permeability is another source of inflammation in this context (Cani et al., 2007; Cani & Delzenne, 2009). Increased systemic LPS levels are associated with enhanced production of TNF and other pro-inflammatory cytokines in adipose tissue, skeletal muscle and liver (Meli, Mattace Raso, & Calignano, 2014; Neves, Coelho, Couto, Leite-Moreira, & Roncon-Albuquerque, 2013). Low-grade chronic inflammation in obesity and MetS drives insulin resistance and other metabolic derangements, and progression towards type 2 diabetes, cardiovascular disease and NASH (Chang, Chavan, & Pavlov, 2019; Donath & Shoelson, 2011; Esser, Legrand-Poels, Piette, Scheen, & Paquot, 2014; Nathan, 2008; Pavlov & Tracey, 2012; Saltiel & Olefsky, 2017; Shoelson et al., 2007). Several cytokines and adipokines are key molecular mediators of obesity- and MetS-associated inflammation (Elks & Francis, 2010). The pro-inflammatory cytokine TNF substantially contributes to and even directly induces insulin resistance (Elks & Francis, 2010; Pavlov & Tracey, 2012; Shoelson et al., 2007). IL-1 β generated through activation of NLR family pyrin domain-containing 3 (NLRP3) inflammasome in macrophages infiltrating visceral adipose tissue mediates insulin resistance in obesity and MetS and progression to type 2 diabetes (Esser et al., 2014). IL-6 also contributes to insulin resistance and has pro-coagulant properties (Elks & Francis, 2010; Pavlov & Tracey, 2012; Shoelson et al., 2007). In contrast, the anti-inflammatory cytokine IL-10 promotes insulin sensitivity (Pavlov & Tracey, 2012; van Exel et al., 2002). Adiponectin is an adipokine with anti-inflammatory, anti-atherogenic and insulin-sensitizing properties (Eckel et al., 2005; Ouchi, Parker, Lugus, & Walsh, 2011; Pavlov & Tracey, 2012; Tilg & Moschen, 2006). In addition, adiponectin has anti-steatotic, hepatoprotective, and anti-fibrotic effects (Gatselis, Ntaios, Makaritsis, & Dalekos, 2014). Adiponectin suppresses macrophage activation and release of pro-inflammatory cytokines, including TNF (Ouchi et al., 2011; Tilg & Moschen, 2006). Conversely, adiponectin expression is negatively regulated by TNF (Ouchi et al., 2011). Adiponectin levels are reportedly decreased in obesity and MetS (Kern, Di Gregorio, Lu, Rassouli, & Ranganathan, 2003; Pavlov & Tracey, 2012). In contrast, plasma levels of the adipokine leptin are increased and this leptinemia results in activation of pro-inflammatory signaling, insulin resistance (Avtanski, Pavlov, Tracey, & Poretzky, 2019; Eckel et al., 2005; Elks & Francis, 2010; Pavlov & Tracey, 2012; Tilg & Moschen, 2006), and increased thrombosis and arterial distensibility in obese patients (Konstantinides, Schäfer, Koschnick, & Loskutoff, 2001; Singhal et al., 2002). Inflammation is an important therapeutic target in obesity and MetS (Esser, Paquot, & Scheen, 2015; Sutherland et al., 2004; Tilg & Moschen, 2006). However, instead of employing monotherapies, targeting individual cytokines or adipokines, it would be much more efficient to explore upstream physiological

mechanisms that control multiple cytokines and exert beneficial metabolic effects (Chang et al., 2019; Pavlov & Tracey, 2012).

4. COVID-19, inflammation, and obesity

The ongoing COVID-19 pandemic has shaken the foundations of our modern healthcare because of its rapid spread and the lack of both highly efficacious treatments and a vaccine. Obese patients are a high risk category for COVID-19. In COVID-19 without or with obesity, inflammation has a key role in pathogenesis and presents a currently explored therapeutic target (Fig. 1).

4.1. Inflammation as a therapeutic target in COVID-19

COVID-19 has pulmonary and many extra-pulmonary manifestations, and we are still learning about the specifics of its pathobiology (Prompetchara, Ketloy, & Palaga, 2020). Previous experience with highly pathogenic coronaviruses, such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) indicates a key pathogenic role of excessive inflammation linked to severe pneumonia, acute lung injury, and acute respiratory distress syndrome (ARDS) (Channappanavar & Perlman, 2017). Aberrant systemic inflammation and increased systemic levels of IL-6, TNF, and other cytokines have been indicated in patients with COVID-19 and positively correlated with disease severity (Gong et al., 2020; Henderson et al., 2020; Huang et al., 2020; Mehta et al., 2020; Prompetchara et al., 2020). Although children and adults have similar rates of COVID-19 infection, developing the disease in the pediatric population is generally less likely and less severe (Bi et al., 2020; Steinman, Lum, Ho, Kaminski, & Steinman, 2020) and as recently proposed, providing insights into this phenomenon may inform new strategies for targeting key pathogenic mechanisms (Steinman et al., 2020). Among other features, the lower pro-inflammatory cytokine production was suggested as a potential mechanism reducing the development of COVID-19 in children (Steinman et al., 2020). While exacerbated COVID-19 in previously healthy children and adolescents has been linked to a multisystem inflammatory syndrome (Feldstein et al., 2020), this condition is rare (Belot & Levy-Bruhl, 2020). Some patients with COVID-19 require hospitalization and further management in intensive care units (ICUs), which is directly related to the necessity to treat severe pneumonia and ARDS (Rodriguez-Morales et al., 2020). Respiratory failure from ARDS is a major cause of mortality in these patients (Rodriguez-Morales et al., 2020; Ruan, Yang, Wang, Jiang, & Song, 2020). Targeting the cytokine storm in COVID-19 patients has been explored in the current desperate search for efficacious treatments (Mehta et al., 2020). Clinical trials with an anti-IL-6 therapy (monoclonal antibodies) are ongoing (<https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/interleukin-6-inhibitors>) and anti-TNF therapies have been proposed (Feldmann et al., 2020). Recently reported results from a randomized, placebo-controlled, double-blind study revealed a lack of significant effects of IL-6 receptor blockade by tocilizumab in preventing intubation or death in moderately ill hospitalized COVID-19 patients (Stone et al., 2020). Chloroquine and hydroxychloroquine - anti-malaria drugs, which have been used off-label in the treatment of inflammatory and autoimmune conditions, have been also used in COVID-19 patients. Results from observational studies however, did not show any benefit of hydroxychloroquine in hospitalized patients with COVID-19 in terms of the composite end point of intubation or death (Geleris et al., 2020). Oral or intravenous dexamethasone (6mg) once daily in 2,104 patients with COVID-19 vs 4,321 on a standard medical care lowered the 28-day mortality of patients with invasive mechanical ventilation or oxygen alone, but did not improve survival of patients with no respiratory support (Group et al., 2020). Dexamethasone has now been frequently used in the treatment of hospitalized patients with COVID-19 in the United States and other countries. While suppressing deleterious

inflammation in the context of COVID-19 is beneficial, the danger of inducing an immunosuppressive state should also be considered to avoid complications such as bacterial and fungal infections (superinfections) (Mehta et al., 2020; Ritchie & Singanayagam, 2020). Of note, the previous use of dexamethasone in patients with SARS-CoV and MERS-CoV is associated with mixed results and even cases of exacerbated disease (Channappanavar & Perlman, 2017).

4.2. Obesity and COVID-19

Obese patients with COVID-19 are a specifically vulnerable category reflecting increased hospitalizations, ICU admissions, and mortality (Gao et al., 2020; Hamer, Gale, et al., 2020; Lighter et al., 2020; Richardson et al., 2020) (Fig. 1). A large observational study with 387,109 hospitalized men and women found that both overweight and obesity were risk factors for severe COVID-19 infection (Hamer, Kivimäki, Gale, & Batty, 2020). Even in relatively mild cases of COVID-19, overweight and obesity, defined by a body mass index (BMI) ≥ 24 and/or abnormal liver function (aminotransferase >40 U/L) are significant contributors to prolonged hospitalization (Hu et al., 2020). The presence of diagnosed NAFLD additionally worsens COVID-19 progression compared with obesity without NAFLD (Zheng et al., 2020). Obesity (defined by BMI of at least 30) in patients with COVID-19 and specifically those who are younger than 60 years is a significant risk factor for ICU admission (Lighter et al., 2020). Another recent study also identified a significant correlation between obesity, severe COVID-19 and the need of ICU admission (Caussy et al., 2020). The severity of obesity based on BMI also was positively correlated with COVID-19 severity and the requirement of invasive mechanical ventilation (Caussy, Wallet, Laville, & Disse, 2020; Simonnet et al., 2020). A clear positive correlation between higher BMI and risk for death was very recently identified in 6,916 patients with COVID-19; higher BMI was associated with increased death rates specifically in younger adults and male patients ("Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization,"). Among various factors, obesity and hypertension with higher prevalence among African Americans may be important underlying events in the reportedly disproportional and more severe impact of COVID-19 on this population in the United States (Carethers, 2020; Shah, Sachdeva, & Dodiuk-Gad, 2020; Yancy, 2020).

The mechanisms linking obesity and obesity-related conditions with COVID-19 severe progression and increased death rates remain unknown. Pulmonary alterations in obesity such as increased airway closure and exacerbated airway reactivity, and inhomogeneity of ventilation predominantly directed towards the upper lobes, predispose to an exacerbated lower respiratory tract infection and increased disease severity (Prompetchara et al., 2020; Sattar, McInnes, & McMurray, 2020; Zheng et al., 2020). The obesity-related low-grade inflammation also presents an altered biological set point that may substantially predispose and contribute to increased COVID-19 severity (Hamer, Kivimäki, et al., 2020; Michalakakis & Ilias, 2020; Sattar et al., 2020). Endothelial dysfunction driven by vascular inflammation and oxidative stress in obesity and MetS (Engin, 2017; Grattagliano, Palmieri, Portincasa, Moschetta, & Palasciano, 2008; Virdis et al., 2019) may also be specifically linked to exacerbation of thromboembolic events and cardiovascular complications in patients with COVID-19 (Long, Brady, Koyfman, & Gottlieb, 2020; Spyropoulos & Weitz, 2020; Vrints et al., 2020). It is worth noting that obesity has been indicated as a risk factor for other viral infections. Obesity-associated type 2 diabetes and hypertension have been identified as major risk factors for increased MERS-CoV disease severity (Banik, Alqahtani, Booy, & Rashid, 2016; Garbati et al., 2016). Obesity and morbid obesity have also been significantly correlated with increased hospitalizations and mortality due to the 2009 pandemic of influenza A H1N1 infection (Honce & Schultz-Cherry, 2019; Louie, et al., 2009; Morgan et al., 2010). Having an effective and safe vaccine should undoubtedly alleviate the COVID-19 crisis.

However, as previously shown, even vaccinated obese patients remain at risk of respiratory influenza infections (Neidich et al., 2017). The possibility of having a weaker COVID-19 vaccine effect on obese patients in the future should be considered.

5. The vagus nerve and the inflammatory reflex: mechanistic insights into inflammatory regulation and current clinical translation

The vagus nerve is the largest parasympathetic nerve, which provides a major conduit of brain – periphery communication. It contains efferent (motor) fibers originating in the brainstem dorsal motor nucleus of the vagus (DMN) and nucleus ambiguus (NA), and innervates many peripheral organs (Metz & Pavlov, 2018; Pavlov & Tracey, 2012) (Fig. 2). Other, afferent (sensory) fibers - the majority (about 80%) of this complex nerve, with cell bodies in the nodose ganglion, and peripheral and central axonal projections, send signals to the brainstem nucleus tractus solitarius (NTS) (Berthoud & Neuhuber, 2000; Pavlov et al., 2018) (Fig. 2). DMN, NTS, and the closely located circumventricular formation - area postrema form the dorsal vagal complex, where sensory, hormonal and metabolic inputs are integrated and coordinated through neuronal interactions with other brainstem regions and higher (forebrain) areas (Pavlov, Wang, Czura, Friedman, & Tracey, 2003). Neural circuitries mediating communication between the dorsal vagal complex, rostroventrolateral medulla, locus coeruleus, insular cortex, hypothalamus, hippocampus and other constituents of the limbic system form a *central autonomic network* (Benarroch, 1993) that controls and coordinates vagus nerve regulatory output (B. Bonaz, Sinniger, & Pellissier, 2017; Pavlov et al., 2003). Bidirectional communication through the vagus nerve allows an instantaneous reflex neural control of physiological functions, including respiratory, cardiac, gastrointestinal, hepatic, and pancreatic (Metz & Pavlov, 2018; Pavlov & Tracey, 2012). Recent discoveries revealed a new and important role of the vagus nerve within a physiological mechanism that utilizes afferent and efferent signaling in controlling cytokine levels and inflammation - *the inflammatory reflex* (Tracey, 2002) (Fig. 2). The neuro-immune dialogue through the vagus nerve takes place utilizing a “common language”; afferent vagal neurons express receptors for cytokines and other inflammatory molecules, while immune cells express receptors for acetylcholine and even synthesize acetylcholine and other neurotransmitters (Olofsson et al., 2017; Terrando & Pavlov, 2018). The expression of IL-1 β and TNF receptors, and TLR4 on afferent vagal neurons is key for sensing cytokines, LPS and other inflammatory molecules and activating signaling to NTS (Chavan et al., 2017; Zanos et al., 2018). In turn, activation of efferent vagus nerve signaling results in the release of acetylcholine with an anti-inflammatory function in peripheral organs, including the heart, liver, pancreas, lungs, and gastrointestinal (GI) tract (Pavlov & Tracey, 2012) (Fig. 2). Acetylcholine binding to the alpha7 nicotinic acetylcholine receptor (α 7nAChR) on macrophages and other immune cells plays an essential role in translating cholinergic anti-inflammatory output (Olofsson et al., 2012; Wang et al., 2003). Advances in understanding the efferent arm of the inflammatory reflex have also revealed that DMN efferent cholinergic fibers interact with the splenic catecholaminergic neurons in the celiac/superior mesenteric ganglion complex (Kressel et al., 2020; Murray, Barboza, Rude, Brust-Mascher, & Reardon, 2019; Pavlov & Tracey, 2015). Electrical vagus nerve stimulation (VNS) activates the release of norepinephrine in spleen, which interacts with the β 2 adrenergic receptor on a subset of CD4+ T lymphocytes, which contain functional choline acetyltransferase - the main acetylcholine synthesizing enzyme (Rosas-Ballina et al., 2011). This chain of molecular events results in increased splenic acetylcholine, which further interacts with α 7nAChR on macrophages to suppress pro-inflammatory cytokine production (Rosas-Ballina et al., 2011). Downstream of α 7nAChR, suppression of NF- κ B nuclear translocation (Guarini et al., 2003; Parrish et al., 2008), JAK2/STAT3 activation (de Jonge et al., 2005), mitochondrial α 7nAChR-mediated inflammasome modulation (Lu et al., 2014), and adenylyl cyclase 6 signaling (Tarnawski et al., 2018) mediate suppression of TNF and other pro-inflammatory cytokine synthesis in

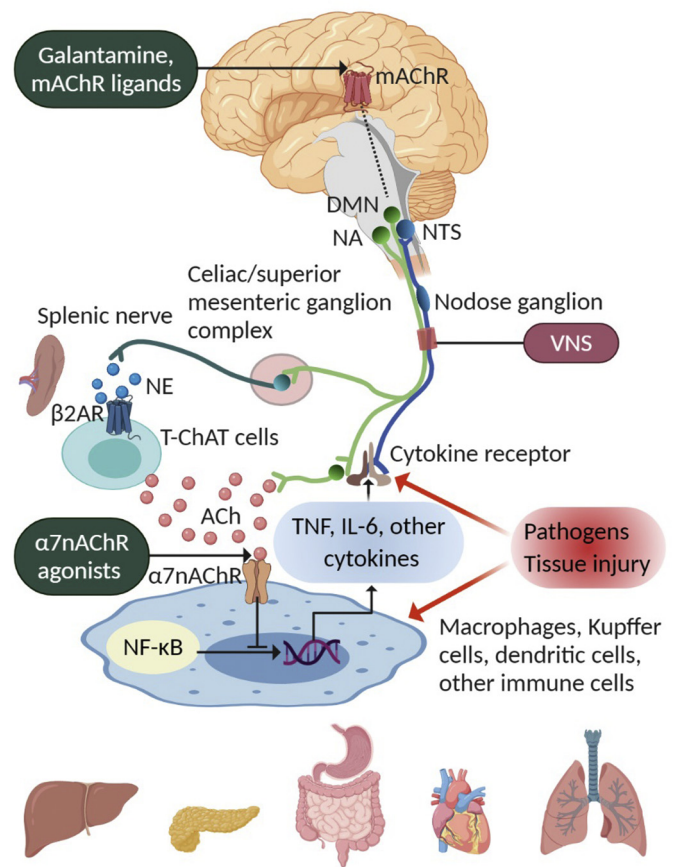


Fig. 2. The inflammatory reflex. Pathogen invasion and tissue injury cause innate immune responses and inflammation with the release of cytokines through interaction of pathogen associated molecular patterns and danger associated molecular patterns with TLRs, NLRs, and other pattern-recognition receptors (not shown) on macrophages and other immune cells. These interactions trigger intracellular cascade mechanisms, including NF- κ B nuclear translocation and inflammasome activation with the release of TNF, IL-1 β , IL-6 and other cytokines. These cytokines activate signals along afferent (sensory) vagus neurons residing in the nodose ganglion and terminating in the brainstem NTS. Pathogens can also directly trigger sensory neuronal activation. The signals are further communicated to DMN with the generation of efferent (motor) vagus nerve (in green) signaling with the release of ACh in innervated organs, including the liver, pancreas, gastrointestinal tract, heart and lungs. Another source of efferent vagus neurons is NA. Efferent vagus neurons interact with splenic neurons in the celiac/superior mesenteric ganglion complex. Activation of the vagus nerve – splenic nerve axis results in the release of NE that binds β 2AR on a subset of T cells, containing ChAT, the ACh synthesizing enzyme (T-ChAT cells). ACh released from post-ganglionic vagus neurons or from T-ChAT cells interacts with α 7nAChR on macrophages and other immune cells. Activation of this receptor results in inhibition of NF- κ B nuclear translocation leading to suppression of TNF and other pro-inflammatory cytokine synthesis. Other intracellular mechanisms downstream of α 7nAChR include activation of JAK2/STAT3, inflammasome inhibition, and adenylyl cyclase 6 signaling (not shown). The inflammatory reflex can be activated by VNS or using α 7nAChR agonists. Efferent vagus nerve signaling in the inflammatory reflex can also be activated through brain mAChR-mediated mechanisms by galantamine or mAChR ligands. ACh, acetylcholine; α 7nAChR, alpha7 nicotinic acetylcholine receptor; β 2AR, beta adrenergic receptor; ChAT, choline acetyltransferase; DMN, dorsal motor nucleus of the vagus; IL-1 β , interleukin 1beta, IL-6, interleukin 6; JAK2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3; mAChR, muscarinic acetylcholine receptor; NE, norepinephrine; NA, nucleus ambiguus; NF- κ B, nuclear factor kappa-B; NTS, nucleus tractus solitarius; NLRs, nucleotide-binding oligomerization domain-like receptors; TLRs, toll like receptors; TNF, tumor necrosis factor; VNS, vagus nerve stimulation. See text for details. (Figure created using Biorender).

different inflammatory conditions (Fig. 2). These discoveries improved our understanding of the regulation of inflammation and indicated possibilities for new therapeutic exploration (Hoover, 2017). The efficacy of VNS in suppressing TNF and other pro-inflammatory cytokine levels and in alleviating disease severity has been demonstrated in many animal models of acute and chronic inflammatory conditions (Pavlov & Tracey,

2015), including arthritis (Levine et al., 2014) and inflammatory bowel disease (IBD) (Meregnani et al., 2011).

This research culminated in the recent successful utilization of bioelectronic VNS in the treatment of patients with rheumatoid arthritis (Genovese et al., 2020; Koopman et al., 2016) and Crohn's disease (one of the two major IBD types) (Bonaz et al., 2016; Sinniger et al., 2020) – chronic conditions characterized with immune and metabolic dysregulation. Current treatments for rheumatoid arthritis and IBD are mainly biologicals with significant side effects and many patients do not respond to treatment. In an open-label study with patients with rheumatoid arthritis, brief regimens of bioelectronic VNS for one to four times per day significantly alleviated the disease severity in two groups of patients (Koopman et al., 2016). The first group consisted of seven patients in the early disease stage, unresponsive to methotrexate, and not previously receiving a biological TNF antagonist or failing treatment with TNF antagonists due to toxicity. The second group included patients who failed methotrexate and at least two other treatments, including anti-TNF, anti-IL-6 receptor, anti-CD20 antibodies, and/or a T-cell co-stimulation inhibitor. VNS therapeutic efficacy was associated with significantly inhibited TNF production (Koopman et al., 2016). Technological advances resulted in designing a novel miniaturized implantable device for VNS, and results about the safety and efficacy of this device in patients with rheumatoid arthritis were very recently reported (Genovese et al., 2020). In a multicenter, randomized, sham (placebo)-controlled study trial, VNS (for 1 min daily or for 1 min four times daily for 12 weeks) via this implanted miniaturized neurostimulator was found well tolerated and with significant efficacy in reducing disease indices in 50% of the patients with multidrug-refractory disease (Genovese et al., 2020). In patients with mild to active Crohn's disease, chronic VNS induced a disease remission at 6 months in the majority of the patients (B. Bonaz et al., 2016). In parallel, VNS improved disease-related biological parameters, including C-reactive protein and/or fecal calprotectin and perceived abdominal pain (Bonaz et al., 2016). At 12 months, the vagal tone and the inflammatory state in these patients were improved and patients remained in clinical or endoscopic remission (Sinniger et al., 2020). As the authors note, these promising results provide a rationale for a further larger randomized double-blind controlled study (Sinniger et al., 2020).

These preclinical and clinical advances considerably contributed to and streamlined the rapidly developing field of *Bioelectronic Medicine* (Pavlov & Tracey, 2019a). Bioelectronic VNS has now been explored in the treatment of numerous disorders and conditions including inflammatory and autoimmune diseases, pain, bleeding, heart failure, and the current opioid epidemic in the United States (Czura et al., 2010; DiCarlo et al., 2018; Koopman et al., 2016; Pavlov & Tracey, 2019a; Qureshi, Datta-Chaudhuri, Tracey, Pavlov, & Chen, 2020; Sharma et al., 2020). Implanted device-generated VNS, similar to VNS that is clinically-approved for the treatment of pharmacoresistant epilepsy and depression has been increasingly utilized and the underlying bioelectronic technology improved (Levine, Faltys, & Chernoff, 2019). In addition, there is a great interest in using non-invasive VNS approaches. For instance, stimulation of a branch of the vagus nerve that innervates the outer ear – transcutaneous auricular VNS or placing a bioelectronic device (gammaCore) on the skin of the neck to stimulate the cervical vagus nerve are currently being explored (Addoriso et al., 2019; Clancy et al., 2014; Kong, Fang, Park, Li, & Rong, 2018; Lerman et al., 2016; Muthulingam et al., 2019; Mwamburi, Tenaglia, Leibler, & Staats, 2018; Qureshi et al., 2020; Tarn, Legg, Mitchell, Simon, & Ng, 2018). In addition to VNS, noninvasive ultrasound stimulation has been successfully explored in treating inflammation in rodents. Targeted ultrasound stimulation of the spleen – an organ component of the inflammatory reflex, alleviates inflammation in murine endotoxemia (Cotero et al., 2019) and inflammatory arthritis in mice (Zachs et al., 2019). This non-invasive approach remains to be evaluated in human inflammatory conditions.

Studying the vagus nerve and the inflammatory reflex in bioelectronic medicine also led to identifying several pharmacological

cholinergic modalities with anti-inflammatory properties (Pavlov, 2019; Pavlov et al., 2018). The discovery that $\alpha 7nAChR$ on macrophages and other immune cells mediates the anti-inflammatory cholinergic output of the inflammatory reflex led to successful evaluation of small molecule $\alpha 7nAChR$ agonists as anti-inflammatory agents (Chatterjee et al., 2017; Parrish et al., 2008; Pavlov et al., 2007; Sitapara et al., 2020; Wang et al., 2003) (Fig. 2). The inflammatory reflex can be activated in the brain through muscarinic receptor acetylcholine receptor (mAChR)-mediated cholinergic signaling (Pavlov et al., 2006; Pavlov & Tracey, 2017). Centrally-acting M1mAChR agonists and other mAChR ligands have been shown to suppress peripheral pro-inflammatory cytokine release through vagus nerve mediated mechanisms (Lehner et al., 2019; Pavlov & Tracey, 2015, 2017) (Fig. 2). Using advanced optogenetic stimulation and mice with specific forebrain genetic deletion of the vesicular acetylcholine transporter – a critical molecule for neuronal acetylcholine release indicated a specific role for forebrain cholinergic signaling in the regulation of peripheral inflammation (Lehner et al., 2019). The inflammatory reflex can be also activated by the AChE inhibitors (Ji et al., 2014; Metz & Pavlov, 2020; Pavlov et al., 2009). One such compound is galantamine – a centrally-acting cholinergic drug, which is clinically-approved for the treatment of cognitive deterioration in Alzheimer's disease (Birks, 2006; Prvulovic, Hampel, & Pantel, 2010) (Fig. 2). The anti-inflammatory and disease alleviating efficacy of galantamine have been demonstrated in animals with endotoxemia, sepsis, inflammatory bowel disease, post-operative cognitive deterioration, and many other disorders (Ji et al., 2014; Metz & Pavlov, 2020; Pavlov, 2019; Pavlov & Tracey, 2015).

6. The vagus nerve and the inflammatory reflex in the metabolic and immune regulation in obesity

The vagus nerve functions as a major communication channel between the brain and periphery and regulates feeding behavior and metabolism. There is a relationship between altered afferent and efferent vagus nerve activity and impaired metabolic and immune regulation in obesity and MetS. Bioelectronic VNS and pharmacological activation of neural signaling in the inflammatory reflex ameliorates both metabolic derangements and inflammation (Fig. 3).

6.1. The vagus nerve in obesity and MetS

Afferent vagus nerve projections to the GI tract and the hepatic portal system play a major role in communicating alterations in peripheral metabolic homeostasis, including changes in cholecystokinin, lipids, leptin, insulin and glucose levels to the brain (Pavlov & Tracey, 2012). In a reflex manner, efferent vagus nerve innervations of the heart, liver and pancreas provide cardio-metabolic regulatory output (Pavlov & Tracey, 2012). Cholecystokinin- and leptin-induced afferent vagus nerve activity importantly mediates satiety and regulates feeding behavior (Berthoud, 2008; Owyang & Heldsinger, 2011; Smith, Jerome, Cushin, Eterno, & Simansky, 1981). Cholecystokinin, released as a result of intestinal lipid accumulation also causes activation of afferent signaling and subsequent efferent vagus nerve output to liver that suppresses hepatic gluconeogenesis (Wang et al., 2008). There is experimental evidence of dysregulation in vagal afferent signaling in obesity (Pavlov & Tracey, 2012). High-fat diet-induced obesity causes leptin resistance in afferent vagal neurons, indicated by increased expression of suppressor of cytokine signaling 3, an inhibitor of signal transducer and activator of transcription 3 phosphorylation – a critical step in leptin receptor-mediated intracellular signaling (de Lartigue, Barbier de la Serre, Espero, Lee, & Raybould, 2011). Attenuation of glucose-triggered activation of afferent vagus nerve signaling has been identified as a characteristic feature of type 2 diabetes in rats (Lee et al., 2012). Applying chronic cervical VNS significantly suppresses food intake, body weight gain, and epididymal fat, and decreases serum leptin levels in animals with high fat diet-induced obesity compared with sham stimulation (Gil,

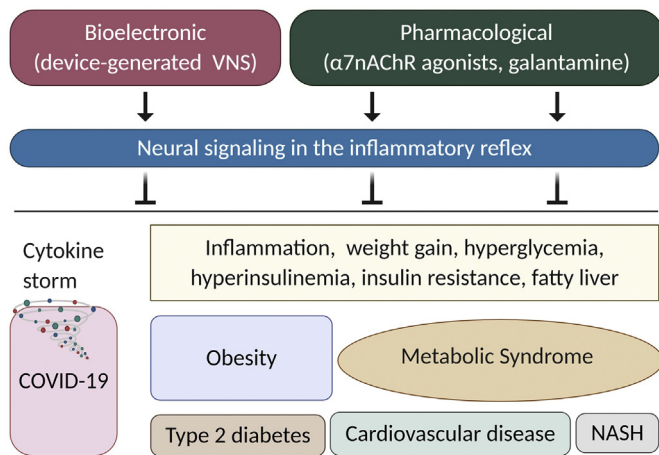


Fig. 3. Emerging bioelectronic and pharmacological cholinergic treatments for obesity, metabolic syndrome, and COVID-19 based on the vagus nerve and the inflammatory reflex. There is growing preclinical and clinical evidence that bioelectronic device-generated VNS – invasive and non-invasive can be used to treat obesity, MetS and obesity-driven disorders, including type 2 diabetes, cardiovascular disease and NASH. Pharmacological modalities, including the acetylcholinesterase inhibitor galantamine and $\alpha 7nAChR$ agonists also alleviate inflammation and several other pathological features of obesity and obesity-associated diseases. Alleviating inflammation and metabolic derangements in obesity and MetS reduces the risk of chronic diseases. This will also result in ameliorating the risk for severe COVID-19. Bioelectronic VNS and pharmacological cholinergic modalities are currently being explored in suppressing the cytokine storm in direct treatments of COVID-19. $\alpha 7nAChR$, alpha7 nicotinic acetylcholine receptor; COVID-19, coronavirus disease 2019; NASH, non-alcoholic steatohepatitis; MetS, metabolic syndrome; VNS, vagus nerve stimulation. See text for details. (Figure created using Biorender).

Bugajski, & Thor, 2011). Stimulating satiety signals along the afferent vagus fibers is at least partially responsible for these beneficial effects (Gil et al., 2011). The latest developments in bioelectronics and mechanistic insight into the GI regulatory functions of the vagus nerve have led to the development of a battery-free device that works in synchronicity with stomach peristalsis to stimulate signaling through the afferent vagus nerve (Yao et al., 2018). Modulation of afferent vagus nerve activity using this self-powered device results in significant and sustained weight loss in animals (Yao et al., 2018). A recent study utilizing single-cell RNA sequencing and other advanced approaches provided a detailed map of vagal sensory neuronal subpopulations innervating the GI tract and insights into their role in the regulation of feeding (Bai et al., 2019). These findings (Bai et al., 2019; Yao et al., 2018) are of considerable interest for further development of bioelectronic technology to specifically target afferent vagus nerve activity for therapeutic benefit in obesity. Chronic VNS significantly lowers body weight, decreases food consumption, and improves glucose homeostasis in obese minipigs and rats (Malbert, Picq, Divoux, Henry, & Horowitz, 2017; Val-Laillet, Biraben, Randuineau, & Malbert, 2010). A very recent study indicated a role for vago-vagal reflex mechanisms in the beneficial effects of chronic subdiaphragmatic VNS in animals with high-fat diet obesity (Dai, Yin, & Chen, 2020). VNS for 4 weeks suppresses food intake and body weight (Dai et al., 2020). It simultaneously decreases sympathetic input and increases vagal tone assessed by heart rate variability (HRV) analysis, and increases levels of pancreatic polypeptide – a surrogate marker of efferent vagus nerve cholinergic activity (Dai et al., 2020). The efficacy of chronic cervical left VNS through an implanted electrode and bioelectronic interface for 12 weeks in rats with high-fat diet-induced obesity and MetS was also recently demonstrated (Samniang et al., 2016). In this study VNS, compared with sham stimulation, significantly reduced visceral fat depositions, plasma insulin, and insulin resistance (homeostatic model assessment for insulin resistance, HOMA-IR), total cholesterol and triglycerides, decreased blood pressure, and ameliorated cardiac mitochondrial dysfunction (Samniang et al.,

2016). In addition, VNS significantly decreased systemic TNF levels and increased adiponectin levels (Samniang et al., 2016). Non-invasive auricular VNS has also been explored in the setting of obesity. Chronic auricular VNS results in a significant decrease in both body weight and abdominal (visceral) adipose tissue content in rats with high-fat diet-induced obesity (H. Li et al., 2015).

There is growing evidence for beneficial metabolic effects of vagus nerve signaling in humans. The use of device-generated VNS in patients with pharmaco-resistant epilepsy is associated with significant weight loss (Burneo, Faught, Knowlton, Morawetz, & Kuzniecky, 2002). VNS treatment for 2 years of patients with treatment-resistant depression also results in highly significant weight loss without additional dieting or exercising (Pardo et al., 2007). It should be also noted that the VNS effect is reportedly more pronounced in patients with higher initial BMI and obesity (Pardo et al., 2007). Maintaining intact vagus nerve signaling following bariatric surgery for achieving and maintaining weight loss has also been acknowledged (Bueter et al., 2010). Surgical VNS is related to a decreased weight gain, and vagal sparing during bariatric surgery can facilitate weight loss (Li et al., 2011). Obesity, MetS and many other conditions, associated with chronic inflammation are characterized by autonomic dysfunction, manifested by increased sympathetic activity and decreased vagal tone (Carnethon, Jacobs Jr., Sidney, & Liu, 2003; Karason, Molgaard, Wikstrand, & Sjostrom, 1999). A strong correlation between autonomic dysregulation with diminished vagus nerve activity (indicated by impaired heart rate recovery following exercise cessation) and impaired glucose homeostasis, and type 2 diabetes development has been reported (Carnethon et al., 2003). Restoring the autonomic balance by VNS restores the anti-inflammatory, but also other functions of the vagus nerve, which are compromised. Non-invasive VNS is becoming an increasingly attractive approach for therapeutic interventions and modulation of autonomic regulation. Results from a recent study of non-invasive auricular VNS once daily for two weeks in individuals aged 55 and above demonstrated improved vagal tone and autonomic regulation, sleep quality, and overall quality of life, as compared to sham stimulation (Bretherton et al., 2019). The autonomic balance was specifically improved in people with higher baseline sympathetic prevalence (Bretherton et al., 2019). As sympathetic predominance is associated with hypertension, these findings suggest that VNS may be a viable option to improve autonomic balance and counteract hypertension. Another study demonstrated that auricular VNS significantly increased HRV and decreased sympathetic activity (Clancy et al., 2014). Although the study was performed in healthy individuals, this approach is of considerable interest for many disorders characterized with autonomic dysregulation, including obesity, MetS and hypertension (Clancy et al., 2014). In a study of 1,883 individuals (18-65 years old), a decreased vagus nerve activity and increased sympathetic activity were significantly associated with MetS (Licht et al., 2010). Autonomic dysregulation and impaired sympatho/vagal balance, determined by low frequency/high frequency ratio of HRV is demonstrated in animals with high-fat diet-induced obesity and MetS (Samniang et al., 2016). Importantly, chronic bioelectronic VNS for 12 weeks significantly improves the LF/HF ratio of HRV, in parallel with anti-inflammatory and beneficial cardio-metabolic effects (Samniang et al., 2016).

In addition to device-generated bioelectronic VNS, other approaches, including complementary and alternative medicine therapies, such as meditation, hypnosis, acupuncture, and biofeedback have been shown to alter autonomic regulation towards an increase in vagus nerve activity and to suppress inflammation (Bonaz et al., 2017; Oke & Tracey, 2009; Song et al., 2012; Tracey, 2002). Of note, alternative and complementary medicine approaches have been implicated in the clinical management of obesity and MetS. Acupuncture has been utilized as an alternative approach in the treatment of obesity (Lacey, Tershakovec, & Foster, 2003; Zhang, Zhou, Wang, Xu, & Zhang, 2018). The use of meditation, yoga, and other mind-body practices is associated with a favorable cardiometabolic risk profile, including lower BMI, triglyceride and

glucose levels, and a lower occurrence of MetS (Younge et al., 2015). These practices can be useful in lowering the cardiovascular risk and improving MetS features (Anderson & Taylor, 2011; Levine et al., 2017).

6.2. Cholinergic signaling in obesity and MetS: mechanisms and pharmacological therapeutic utilization

Active research has characterized an essential role for brain and peripheral cholinergic signaling and the $\alpha 7$ nAChR in metabolic homeostasis and inflammatory regulation in obesity. Cholinergic signaling in the brain is implicated in the regulation of feeding. In addition to being a non-specific $\alpha 7$ nAChR agonist, nicotine is a known appetite suppressor, acting on $\alpha 3\beta 4$ nAChRs in the pro-opiomelanocortin neuronal circuit in the arcuate nucleus of the hypothalamus and in other brain sites (Chang et al., 2019). Studies utilizing selective optogenetic cholinergic modulation in mice highlighted the regulatory role of forebrain cholinergic signaling in feeding behavior – while cholinergic activation decreases food intake, cholinergic suppression has the opposite effect (Herman et al., 2016). Reportedly, a multi-synaptic brain network including the hypothalamic arcuate nucleus mediates forebrain cholinergic regulation of feeding (Herman et al., 2016). Hypothalamic cholinergic signaling via mAChRs regulates metabolic processes, including hepatic glycogen synthesis and pancreatic exocrine secretion through vagus nerve-mediated circuitry (Chang et al., 2019).

The relationship between cholinergic $\alpha 7$ nAChR-mediated signaling and alterations in inflammation, insulin sensitivity, and other metabolic indices was highlighted in *Rip-cre⁺ Pten^{fllox/fllox}* mice. In these mice, the insulin-2 promoter (*Rip*)-mediated deletion of *Pten*, a gene encoding a negative regulator of phosphoinositide 3-kinase signaling, results in increased hypothalamic PI3K, but also in enhanced NTS and DMN neuronal activity (Wang et al., 2014). These alterations, indicative for activation of brain constituents of the inflammatory reflex are associated with higher gene expression of anti-inflammatory M2 splenic and peritoneal macrophage markers, including *Chil3*, *Mgl2*, *Mrc2* and *Arg1* (mRNA expression), and lower pro-inflammatory M1 markers such as *Ccl2* and *Il1b* (mRNA expression) (L. Wang et al., 2014). In addition, decreased systemic TNF levels, increased IL-10 and adiponectin levels, and increased peripheral insulin sensitivity are detected. Cholinergic signaling within the inflammatory reflex is an important determinant of these beneficial metabolic and anti-inflammatory alterations, because they are significantly abrogated in mice treated with a pharmacological nAChR antagonist and in the context of $\alpha 7$ nAChR deficiency (Wang et al., 2014). *Rip-cre⁺ Pten^{fllox/fllox}* mice, compared with littermate controls, are significantly protected against high-fat diet-induced obesity alterations, including hyperglycemia, insulin resistance, inflammation, and NAFLD (Wang et al., 2014). However, cervical unilateral vagotomy abolishes this protective phenotype, which directly points to a key role of vagus nerve signaling (Wang et al., 2014).

Preclinical insights indicate the therapeutic efficacy of $\alpha 7$ nAChR agonists in animals with obesity, MetS, and related diseases (Chang et al., 2019; Pavlov & Tracey, 2012). Treatment with nicotine suppresses visceral adipose tissue and plasma TNF levels in mice with high-fat diet-induced obesity and db/db mice and reduces macrophage infiltration of adipose tissue (Wang, Yang, Xue, & Shi, 2011). Oral administration of a selective $\alpha 7$ nAChR agonist (TC-7020) to db/db mice decreases plasma TNF levels and reduces weight gain, food consumption and glucose and triglyceride levels (Marrero et al., 2010). Interestingly, the expression of $\alpha 7$ nAChR in human adipocytes is suppressed in subjects with obesity and weight loss partially restores expression of $\alpha 7$ nAChR (Cancellato et al., 2012). In the context of NASH, $\alpha 7$ nAChR KO mice develop excessive hepatic fibrosis, associated with higher plasma transaminase levels, and significantly increased Col1a1 gene-encoding alpha-1 type I collagen (mediating liver fibrosis) *Ccl2* and *Tnf* mRNA gene expression (Kimura et al., 2018).

Treatment of mice with high-fat diet-induced obesity and MetS with the centrally-acting AChE inhibitor galantamine significantly suppresses weight gain, food intake, abdominal white adipose depots, the pro-inflammatory state, insulin and glucose levels, insulin resistance, and hepatic steatosis (Satapathy et al., 2011). The therapeutic efficacy of galantamine has also been demonstrated in murine models of diabetes (Ali, El-Abhar, Kamel, & Attia, 2015; Hanes et al., 2015). As noted above, galantamine is a clinically-approved drug for the treatment of Alzheimer's disease in the United States and many European countries (Hampel et al., 2018; Prvulovic et al., 2010). The preclinical efficacy of galantamine and the abundant information about the safety profile of this drug facilitated studying galantamine in patients with MetS, in a randomized, placebo-controlled, double blind trial (Consolim-Colombo et al., 2017). Treatment with clinically-approved low doses of this drug for 12 weeks, significantly suppresses plasma TNF and leptin levels, and increases IL-10 and adiponectin levels (Consolim-Colombo et al., 2017). Galantamine also significantly decreases insulin levels and alleviates insulin resistance (HOMA-IR) in MetS patients compared with placebo. In addition, galantamine treatment alters autonomic regulation (based on HRV analysis) towards increased vagal contribution (Consolim-Colombo et al., 2017). In addition to inflammation, oxidative stress is a major driver of metabolic dysregulation and pathogenesis in obesity and MetS (Carrier, 2017; Van Guilder, Hoetzer, Greiner, Stauffer, & Desouza, 2006); galantamine also alleviates oxidative stress in patients with MetS (Sangaletti et al., 2020). Obesity and MetS are associated with a significant risk for cardiovascular disease, including congestive heart failure, stroke, myocardial infarction and increased cardiovascular mortality (Grundy, 2004; Kenchaiah et al., 2002; Van Gaal, Mertens, & De Block, 2006). Galantamine has cardio-protective effects; treatments with galantamine and other centrally-acting AChE inhibitors of patients with Alzheimer's disease, significantly correlate with a lower risk of myocardial infarction and death (Nordstrom, Religa, Wimo, Winblad, & Eriksdotter, 2013). The prevalence of obesity is rising in all age categories, including children (Ebbeling et al., 2002). Effective and safe pharmacological treatments are needed for childhood obesity, which in addition to immediate complications, is linked to increased risks of illness and mortality later in life (Ebbeling et al., 2002). Galantamine has been studied in children with autism spectrum disorder; improvements in core and associated symptoms of the disease and no significant adverse effects have been indicated (Chaleiha et al., 2014). As recently reported 10-17 year old US youth with autism spectrum disorder have significantly higher odds of being overweight and obese compared with typically developing children (Healy, Aigner, & Haegele, 2019). The prevalence of severe obesity is reportedly higher in children with autism spectrum disorder with increasing age and specially for the 6-11 year-old age group compared with the general population (Pham, Silver, Haq, Hashmi, & Eissa, 2020). Future studies with galantamine in pediatric obesity and MetS can be considered.

Peripheral chronic inflammation, inflammation in the CNS (neuroinflammation) and metabolic dysregulation in obesity, MetS, and type 2 diabetes have been linked to cognitive impairment and increased risk of dementia (Biessels, Strachan, Visseren, Kappelle, & Whitmer, 2014; Guillemot-Legris & Muccioli, 2017; Strachan, Reynolds, Marioni, & Price, 2011). The brain cholinergic system is an essential regulator of cognition, including attention, learning and memory, and provides key opportunities for therapeutic exploration (Ballinger, Ananth, Talmage, & Role, 2016; Hampel et al., 2018; Schroeder, Wecker, & Philpot, 2016). In this context, the cognitive effects of the cholinergic drug galantamine add another advantage to its further development in obesity-driven disorders. VNS also positively affects cognition, and specifically domains of verbal recognition, memory, and executive function (Groves & Brown, 2005; Vonck et al., 2014).

These preclinical insights and clinical developments justify further exploration of VNS and cholinergic modalities in obesity, MetS, and other obesity-driven disorders.

7. Bioelectronic VNS and pharmacological cholinergic modalities for COVID-19

There is a growing interest in using VNS and cholinergic therapeutics in the treatment of COVID-19 patients. This is based on insights into the inflammatory reflex, cholinergic signaling, and advances in bioelectronic medicine. Reviews, editorials and commentaries enthusiastically discuss the topic and propose treatments (Andersson, Ottestad, & Tracey, 2020; Bonaz, Sinniger, & Pellissier, 2020; Farsalinos et al., 2020; Mazloom, 2020; Staats et al., 2020). Early clinical experience with some patients with COVID-19 benefiting from non-invasive VNS was also reported (Staats et al., 2020). The abundant rationale has started to materialize in performing several clinical trials with VNS and a cholinergic drug in patients with COVID-19 (Fig. 3). The rationale is broadly based on suppressing the cytokine storm, which should be beneficial in alleviating disease severity. Currently, four ongoing trials utilize non-invasive VNS in patients with COVID-19. The device used in two of the trials: (<https://clinicaltrials.gov/ct2/show/NCT04368156?term=vagus&cond=COVID&draw=2&rank=1>); (<https://clinicaltrials.gov/ct2/show/NCT04382391?term=vagus&cond=covid&draw=2&rank=4>) is gammaCore® for a non-invasive stimulation of the left cervical vagus nerve. Two other clinical trials utilize devices for auricular VNS (<https://clinicaltrials.gov/ct2/show/NCT04379037?term=vagus&cond=COVID&draw=2&rank=2>); (<https://clinicaltrials.gov/ct2/show/NCT04341415?term=vagus&cond=COVID&draw=2&rank=3>).

The efficacy of the AChE inhibitor pyridostigmine, which is clinically-approved for the treatment of myasthenia gravis and exhibits immunomodulatory and anti-inflammatory properties in patients with human immunodeficiency virus (HIV)-infection (Valdes-Ferrer et al., 2017), is currently being tested in a placebo-controlled trial with patients with COVID-19 (<https://clinicaltrials.gov/ct2/show/NCT04343963?term=cholinergic&cond=COVID&draw=2&rank=1>) (Fragoso-Saavedra et al., 2020). The utility of galantamine in treating COVID-19 patients was also recently proposed (Ahmad, 2020).

There is also a growing interest in using nicotine – a non-selective $\alpha 7$ nAChR agonist in treating COVID-19 patients (Farsalinos, Barbouni, & Niaura, 2020; Farsalinos, Niaura, et al., 2020; Kaur & Rinkoo, 2020; Tindle, Newhouse, & Freiberg, 2020). As recently suggested, COVID-19 may affect nAChRs and diminish anti-inflammatory cholinergic signaling. Accordingly, it was proposed that the use of nicotine could restore cholinergic signaling through nAChRs and inhibit the release of pro-inflammatory cytokines, thus suppressing or preventing the cytokine storm (Farsalinos, Niaura, et al., 2020). As recently noted, it is important to distinguish treatment with medicinal nicotine, which is FDA-approved, from cigarette smoking (Tindle et al., 2020). For reasons discussed in previous sections, bioelectronic VNS and pharmacological cholinergic modalities could be specifically beneficial for obese patients with COVID-19.

Many hospitalized and ICU patients with COVID-19 survive the disease. Some of them survive severe complications, including ARDS and sepsis. Is the hospital discharge the end of their ordeal? There is no clear answer to this question yet, and these patients remain to be carefully evaluated. However, current knowledge of patients surviving critical illness, including sepsis and ARDS paints a gloomy picture of multiple functional disabilities, immune dysregulation, neurological complications, including cognitive deterioration, and increased mortality (Hopkins, Gale, & Weaver, 2006; Mostel et al., 2019; Pavlov et al., 2018). Therefore, long-term complications in COVID-19 survivors can be anticipated and those with obesity may continue to be at increased risk. Evaluating the distinct features of a possible COVID-19 chronic illness will inform future recovery and rehabilitation approaches. Bioelectronic, non-invasive VNS, galantamine and other cholinergic modalities might also be used in such approaches.

8. Conclusions

The current viral COVID-19 pandemic has alarmingly added a major problem to the long list of obesity-associated risk factors. Obesity and COVID-19 can be a deadly combination, which has been the tragic reality for many. The prospect that there will be ample time to find efficient strategies for obesity management has to be revised; exploring new therapeutic approaches to improve the gloomy outlook has never been of such a high priority. Bioelectronic medicine, driven by new insights into neural regulatory functions and technological developments has started to provide novel treatment options for various diseases (Olofsson & Tracey, 2017; Pavlov et al., 2019; Pavlov & Tracey, 2019b; Pavlov & Tracey, 2019a) and generated interest among medical professionals, patients, caregivers, and industry (Building a bioelectronic medicine movement 2019: insights from leaders in industry, academia, and research, 2020; Pavlov & Tracey, 2019a). Important areas of current exploration of bioelectronic VNS and specifically its non-invasive forms are obesity and MetS. Current findings also indicate the translatability of knowledge generated with the clinically-approved drug AChE inhibitor galantamine in clinical settings of obesity and MetS. In addition to their anti-inflammatory effects, both VNS and galantamine have beneficial metabolic efficacy, including suppression of body weight gain, improvements in glucose homeostasis, and amelioration of insulin resistance. These findings provide a solid rationale for further development of VNS and pharmacological cholinergic modalities as stand-alone treatments or as additive (to dieting and exercising) therapies in obesity and MetS. Results from ongoing clinical trials with VNS and cholinergic treatments in patients with COVID-19 will allow to assess efficacy and possibly optimize these treatments for the active disease, post-COVID-19 chronic syndromes, or other viral outbreaks in the future, in which obese patients will remain a vulnerable category.

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Declaration of Competing Interest

V.A.P. has co-authored patents broadly relevant to the content of this review. He has assigned his rights to the Feinstein Institutes for Medical Research.

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