A compelling body of research over the last two decades has established that chronic inflammation in adipose tissue makes a key contribution to insulin resistance in obesity (reviewed in Ref. 1). Adipocyte expansion in obesity is frequently accompanied by an induction of inflammatory mediators and cytokines, including (but not limited to) TNFα (2), IL-1β and IL-6, plasminogen activator inhibitor-1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1) (3). The majority of these inflammatory signals are produced by bone marrow-derived macrophages, which infiltrate adipose tissue as monocytes and become activated proinflammatory macrophages (4, 5). Macrophage-derived cytokines contribute to insulin resistance in adipose tissue by interfering with insulin signaling in neighboring adipocytes (6, 7). Accordingly, genetic ablation of inflammatory signaling in myeloid cells has been shown to protect mice from diet-induced glucose intolerance and insulin resistance (8), and antiinflammatory therapeutics have recently been found to improve glycemic control in patients with type 2 diabetes (9, 10).

However, it is not well studied in this context that the central nervous system, via an inflammatory reflex involving the vagus nerve (and its major neurotransmitter, acetylcholine), can exert a tonic inhibition on cytokine production in immune cells (reviewed in Ref. 11). The existence of this mechanism, termed the ‘cholinergic antiinflammatory pathway,’ was first suggested in studies of animal models of sepsis, where hyperthermia induced by ip administration of IL-1β could be blocked by subdiaphragmatic vagotomy (12). Moreover, direct electrical stimulation of the vagus nerve suppressed elevations of circulating TNFα in a rat model of endotoxic shock (13). This and other key observations at the time delineated a reflex arc originating in vagal afferent fibers, which gather sensory information pertaining to noxious stimuli (pressure, temperature, inflammation) from the viscera and relay this information to the nucleus tractus solitarius in the medulla oblongata, which coordinates autonomic functions. In concert with other nuclei, including the dorsal motor nucleus of the vagus, an appropriate response is initiated and transmitted along preganglionic vagal efferents (14). These vagal efferents inhibit innate immune responses via acetylcholine and the nicotinic acetylcholine receptor subunit α7 (α7nAChR), expressed by cytokine-producing immune cells (15). In this issue of Endocrinology, Hang Shi and colleagues (16) provide fascinating new evidence to demonstrate that chronic activation of the cholinergic antiinflammatory pathway by nicotine, a nAChR agonist, can ameliorate obesity-induced inflammation and insulin resistance in mice, and that these effects are dependent upon α7nAChRs.

Before this study cholinergic antiinflammatory signaling in adipose tissue had not been studied, and the issue of whether adipose tissue possesses significant parasympathetic innervation is itself controversial (17, 18). Regardless, the authors detected mRNA expression of both α7nAChR and the acetylcholine-degrading enzyme butyrylcholinesterase (BChE) in mouse white adipose tissue. Notably, α7nAChR expression was higher in adipose tissue-derived macrophages than in isolated adipocytes, and levels of BChE expression mRNA and protein in white adipose tissue showed dynamic changes in response to chronic nicotine treatment (up-regulated) and genetic or diet-induced obesity (down-regulated). It is quite likely

Abbreviations: BChE, Butyrylcholinesterase; MCP, monocyte chemoattractant protein; α7nAChR, nicotinic acetylcholine receptor subunit α7.
that these changes in BChE expression occurred in the nonadipocyte fraction of adipose tissue, as a recent study of human omental fat showed that BChE mRNA expression was significantly higher in the stromal-vascular fraction than in adipocytes (19).

Next, the authors administered nicotine chronically to db/db and diet-induced obese mice, at a dose that did not affect food intake or body weight. Nicotine reduced fed and fasting blood glucose concentrations in the db/db mice and ameliorated glucose intolerance and improved whole-body insulin action in the diet-induced obese mice. Nicotine treatment did not affect these variables in lean mice. Consistent with the above effects on glucose homeostasis, examination of the skeletal muscle, liver, and adipose tissue of db/db or diet-induced obese mice revealed that the insulin signaling defects in these tissues were nearly completely reversed by chronic nicotine treatment, to levels observed in wild-type chow-fed mice. The salutary effects of nicotine treatment extended to a suppression of serum TNFα concentrations and a reduced expression of inflammatory signals (including TNFα, IL-1β, IL-6, MCP-1) and the macrophage marker F4/80 in adipose tissue.

Wang et al. (16) then tested whether the beneficial effects of chronic nicotine treatment were dependent upon α7nAChR, the nicotinic acetylcholine receptor present upon macrophages, by studying α7nAChR-null mice. Mice lacking α7nAChR are viable and have no gross phenotypic abnormalities (20) and have been reported to have higher serum concentrations of TNFα, IL-1β, and IL-6 relative to wild-type mice after endotoxic shock (15). As expected, isolated macrophages from α7nAChR-deficient mice showed greater stearic acid–induced induction of TNFα, IL-1β, and IL-6 mRNA expression relative to wild-type macrophages; and nicotine suppressed these effects in wild-type macrophages but not in those derived from α7nAChR-deficient mice.

The overall relevance of the cholinergic antiinflammatory pathway in insulin resistance was then investigated in whole-animal studies of glucose homeostasis, including hyperinsulinemic-euglycemic clamps. α7nAChR-deficient mice displayed mild hyperinsulinemia on a chow diet; while on a high-fat diet, glucose intolerance, insulin resistance, and insulin signaling in muscle were worsened by the lack of α7nAChRs. Examination of adipose tissue from α7nAChR-null mice revealed a dramatic increase in F4/80-positive, CD11c-positive (indicating classically activated) macrophage content; in mice on a high-fat diet, the effects of α7nAChR deficiency on activated macrophage content were even greater, and adipose tissue expression of TNFα and MCP-1 was doubled relative to wild-type mice. Lastly, insulin signaling in skeletal muscle and liver was significantly impaired in α7nAChR-knockout animals on a high-fat diet, relative to wild-type mice, and the expression of gluconeogenic enzymes in the liver of α7nAChR-null mice was increased. One caveat of the study by Wang et al. (16) is that definitive proof for the involvement of α7nAChR-mediated suppression of inflammation in insulin resistance will likely require either selective deletion of α7nAChR from macrophages or transfer of α7nAChR-deficient macrophages to wild-type mice.

By widening the scope of inflammatory conditions suppressed by the cholinergic antiinflammatory pathway to adipose tissue insulin resistance, these new findings may uncover new targets for the treatment and prevention of metabolic disease. Both cholinergic agonists and vagal nerve stimulation have been shown to ameliorate inflammation in animal models of sepsis, hemorrhagic shock, ischemia/reperfusion, pancreatitis, arthritis (21), and inflammatory bowel disease (22). Interestingly, human obesity is itself characterized by a reduced vagal tone, which increases with exercise and weight loss (23). There is some evidence to suggest that vagal function may predict inflammatory disease: a recent cross-sectional study of >600 healthy human adults obtained evidence for independent relationships between vagally-mediated heart rate variability and both white blood cell count and circulating concentrations of C-reactive protein (24).

Perhaps more importantly, this study also contributes to the emerging view that circuits originating in the central nervous system, including those involved in energy balance, not only influence glucose homeostasis directly but also indirectly by influencing macrophage infiltration, activation, and the production of proinflammatory signals in peripheral tissues. The nucleus tractus solitarius is one of the main areas receiving afferent vagal inputs in the cholinergic antiinflammatory pathway and is also a critical extra-hypothalamic site of leptin action for feeding behavior (25). Leptin itself has been recently shown to improve survival in a murine model of sepsis (26). It would be of considerable interest to examine the relationships between established central regulators of energy homeostasis and cholinergic antiinflammatory vagal outflow. In this regard, it is notable that intracerebroventricular and peripheral administration of a selective melanocortin-4 receptor agonist, ACTH-(1–24), increases neural efferent activity along the vagus nerve and blunts increases in both the hepatic expression and circulating concentrations of TNFα in a rat model of hemorrhagic shock (27, 28). Identification of central nervous system circuits linking excessive caloric intake with adipose tissue inflammation and insulin resistance might allow us to ‘turn down the heat’ in adipose tissue and alleviate the global conflagration of insulin resistance and type 2 diabetes (29).
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