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Activating Leptin Receptors in the Central Nervous System Using Intranasal Leptin

A Novel Therapeutic Target for Sleep-disordered Breathing

In addition to serving as a tissue for energy storage, adipose tissue has become a well-recognized endocrine organ that secretes a variety of adipokines with important pleiotropic functions. One of these adipokines is leptin, discovered in 1994 by Zhang and colleagues (1). Much of the research on leptin has focused on its role on metabolism, particularly in central nervous system regulation of energy homeostasis and obesity, as well as its peripheral effects on obesity-related cardiometabolic diseases. The excess adiposity in obese humans leads to high circulating levels of leptin. Paradoxically, despite leptin's well-described effects on suppressing appetite and increasing energy expenditure, these individuals remain obese, reflecting a state of leptin resistance (2). A few years after its discovery, it became evident that leptin has a significant effect on ventilation and control of breathing (3, 4). At the central nervous system level, leptin increases the hypercapnic ventilatory response. Yet, severely obese patients afflicted with obesity hypoventilation syndrome (OHS) continue to hypoventilate despite having high circulating levels of leptin, in line with leptin resistance. Further evidence in support of leptin resistance at the central nervous system level comes from experiments in which parenterally administered recombinant leptin was shown to be largely ineffective in reducing weight in the vast majority of obese individuals (5). For leptin to affect the respiratory center and increase minute ventilation, it has to first cross the blood–brain barrier (BBB). One proposed

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mechanism for leptin resistance is impaired leptin transport across the BBB (6).

Against this background, in this issue of the *Journal*, Berger and colleagues (pp. 773–783) postulated that intranasal administration of leptin could bypass the BBB and thus promote its physiologic action on the control of respiration and the upper airway, consequently mitigating sleep-disordered breathing (SDB) (7). The finding that intranasal leptin can alleviate hypoventilation and upper-airway obstruction in an obese mice model is exciting because it provides a much-needed novel therapeutic approach for the management of SDB. Since its introduction in 1981, positive airway pressure (PAP) therapy has remained the gold standard treatment for SDB (8). However, despite its high effectiveness, PAP therapy has low clinical efficacy, primarily due to suboptimal adherence in a large proportion of patients (9). Moreover, approximately 25% of patients with OHS remain hypercapnic despite high levels of adherence to nocturnal PAP therapy (10). As such, it is not surprising that there has been much interest in discovering novel therapeutic targets and modalities (11–13). Any therapy that is able to effectively maintain upper-airway patency and normalize ventilation throughout the entire sleep period will go a long way toward improving long-term health outcomes in patients with SDB, and will be a welcome addition to our armamentarium to treat disordered breathing during sleep. One concern regarding ventilatory stimulants is exposing the upper airway to increasingly negative intrathoracic pressure, thereby promoting upper-airway collapse. However, Berger and colleagues demonstrated that intranasal leptin improves inspiratory flow limitation despite its ventilatory stimulant effect (7). This finding, in conjunction with transneuronal tracer experiments, suggests that at the central nervous system level, leptin can simultaneously improve ventilatory response and upper-airway tone through synaptic connections between leptin receptor–expressing cells and hypoglossal and phrenic motor neurons.

Although prior work has explored the effect of intranasal leptin administration on reducing food intake in rats (14, 15), Berger and colleagues provide a very elegant, albeit preliminary, physiological demonstration of how leptin delivered intranasally can overcome "central leptin deficiency" and lead to demonstrable improvement in upper-airway resistance and ventilation in a murine model (7). However, as with any well-designed and novel animal experiment, there are many unanswered questions. First and foremost, the demonstration of an acute effect of intranasal leptin has less clinical relevance for managing a chronic disease such as SDB. Therefore, more research is needed to demonstrate the long-term efficacy of intranasal leptin in alleviating SDB. In theory, if this acute effect is sustained after repeated administrations without significant side effects, the long-term modulation of cerebral areas that control appetite as well as breathing may have further desirable effects on health beyond those of improving SDB and ventilation. Such effects cannot be assumed until the experiments are done and new evidence becomes available. It also remains unclear whether improvement in ventilation during sleep would be sustained during wakefulness to ameliorate daytime hypoventilation, a hallmark of OHS. Second, the exact mechanism by which intranasal leptin exerts its action of relieving SDB needs to be further elucidated. The use of the intranasal route stemmed from its ability to bypass leptin resistance, which is attributed, at least in part, to limited permeability of the BBB to leptin. However, recent work suggests that leptin transport into cerebrospinal fluid is intact in obese mice (16). Although this does not contradict the finding that intranasal leptin, and not intraperitoneal leptin, relieved SDB, it is clear that much more needs to be explored regarding the traffic of leptin into the central nervous system and its mechanisms of actions on various parts of the brain. Prior studies exploring the effect of intranasal leptin on appetite and weight in mice and rats used substantially lower concentrations (0.1 or 0.2 mg/kg) (14, 15) than the current study, in which the delivered dose was 0.4 mg/kg. Whether the dose needs to be adjusted based on the therapeutic goal (i.e., appetite vs. respiratory modulation) also requires further investigation. Lastly, further research is needed to identify the patient population that will be most responsive to this therapeutic modality.

Although we are excited by this novel finding of intranasal leptin in the murine model, the translation to humans cannot be taken on a mere leap of faith, as men are not mice. The sleep medicine community eagerly awaits additional experiments and clinical trials exploring intranasal leptin in the management of SDB. ■

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The Acid-Fast Bacilli Smear: Hail and Farewell

When Robert Koch reported his discovery of the tubercle bacillus in 1882 in a lecture and in the scientific paper he published just a few weeks later in *Berliner Medicinische Wochenschrift*, he described the staining techniques that allowed him to see the rod-shaped bacteria that he had successfully isolated and grown in pure culture (1). Paul Erlich had attended Koch's lecture and quickly refined the staining technique, making it easier and quicker. Shortly thereafter, Ziehl and Neelsen further modified the technique and developed the method basically still used today. By 1883, Koch recognized that the development of a relatively simple and rapid staining method had important implications for patient care. He wrote, "It was soon found that with Ehrlich's method of staining, the recognition of tubercle bacilli could readily be made use of in diagnosis. We owe it to this circumstance alone that it has become a general custom to search for the bacilli in the sputum" (2).

The acid-fast bacilli (AFB) smear remains the main mode of diagnosis of tuberculosis in most of the places in the world where tuberculosis is common. If tuberculosis were something like beer brewing, or cheesemaking, this kind of artisanal approach to diagnosis might seem authentic and appealing. But tuberculosis is not beer brewing or cheesemaking, and the persistence of a 19th-century technique for diagnosing the world's leading cause of death resulting from a single infectious agent in the 21st century is a disgrace. By now, it is well-appreciated that smears detect only about half of all cases of culture-positive tuberculosis, and quality control is notoriously difficult, especially in places where it is relied on most heavily (3, 4). The article in this issue of the *Journal* by Lee and colleagues (pp. 784–794) provides further evidence that it is time for the AFB smear to find its place in medical museums and history books, rather than in modern diagnostic labs (5).

Sputum samples were collected from each of nearly 3,000 consecutive patients being evaluated for possible tuberculosis. One aliquot was analyzed using semiquantitative nucleic acid amplification with GeneXpert MTB/RIF, and one was analyzed by conventional AFB smear microscopy and culture. Culture results were considered the gold standard for a diagnosis of tuberculosis.

The results were clear and convincing. Overall, 8.9% of patients provided samples that were culture positive for *Mycobacterium tuberculosis.* Of those, 102 had AFB smear-positive sputum and 161 were smear negative. In addition, another 9% (265) of patients were culture positive for nontuberculous mycobacteria, and 82 of those patients were AFB smear positive. Overall, then, the sensitivity of AFB smear was 38.8%, and the specificity was 96.7%. This compares with a sensitivity of 74.1% and a specificity of 97.5% for Xpert. Notably, AFB smear sensitivity varied by time of collection (morning samples had greater yield than spot samples), but this was not true for Xpert. Results from Xpert were reported back to clinicians on average about 16 hours faster than results from AFB smears. Thus, Xpert results overall were more accurate, available more quickly, and less affected by several operational issues than were AFB smears.

This article amplifies results of many earlier, smaller, or laboratory-based studies that showed the promise of nucleic acid amplification-based tuberculosis diagnostics (6–9). Indeed, uptake of Xpert has been advancing around the world in both resource-rich and resource-limited settings and in countries with both high and low burdens of tuberculosis (10). Technological advances that will make it easier to use this test at the point of care will likely accelerate this trend. Still, there has been reluctance and even opposition to making this test the standard initial means of diagnosis for suspected pulmonary tuberculosis (11). Objections have been raised that the test is too costly, requires too much maintenance, does not provide information regarding infectiousness, and does not allow a clinician to assess response to therapy in the way that a decreasing AFB smear grade does. In addition, an early paper noted that introduction of Xpert in South Africa had not resulted in a decrease in TB mortality in the communities in which it was being used, although there was realization that this was mostly a systems issue (12).

These concerns are real, but we should also not overestimate the performance of AFB smears, especially in many high-burden countries, where quality control is chronically terrible. Cost is a serious issue, and national tuberculosis control programs, ministries of health, advocacy groups, and others should work hard to negotiate reasonable prices. Still, we should accept the fact that newer tools (diagnostics, drugs, and vaccines) are likely to have some additional costs associated with them under any circumstances. This is the cost of progress, and improving the lives of patients by allowing them access to the best diagnostics and drugs should be a priority that competes with other budgetary demands. In addition,

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