An X on the Map for Sleep Apnea's Holy Grail: Drug Therapy

Obstructive sleep apnea was supposed to be an easy target for drug therapies. Characterized decades ago, the pathophysiology of sleep apnea requires sleep state–dependent reductions in pharyngeal dilator activity (1, 2). Specifically, in obstructive sleep apnea, increased activity of upper airway dilator muscles across wakefulness ensures airway patency (3). In sleep, normal sleep state–dependent reductions in muscle tone result in relaxation of upper airway dilators, leading to collapse of the upper airway with resultant obstructive apneas (complete collapse) and hypopneas (partial collapse). One of the critical upper airway dilator muscles for airway patency is the genioglossus (tongue) muscle, which is innervated by the hypoglossal nerve (4). Armed with the understanding that sleep apnea involves a clear sleep state–dependent effect on this important dilator muscle and its nerve, researchers needed only to determine the neurochemical source of sleep-dependent inhibition of the hypoglossal nerve and then replace the neurochemical across sleep in the form of drug therapy, and we would obviate the need for cumbersome positive airway pressure machines. Excitatory receptor subtypes were then identified in the hypoglossal nucleus, and relevant agonists for the receptors were explored for effects on obstructive sleep-disordered breathing in animal models and in humans (5). Identified targets, however, largely had the untoward effect of promoting wakefulness and/or were no match for powerful sleep state–dependent hyperpolarization of hypoglossal motoneurons (5). Failure to identify a universally effective pharmacologic therapy for obstructive sleep apnea prompted development of a second mechanical therapy for sleep apnea, electric hypoglossal nerve stimulation (6, 7). Although this therapy has been effective in some individuals, it is expensive; it requires implantation of a foreign body and does not fully alleviate sleep-disordered breathing events in all individuals (8).

Enter chemogenetics. If the ideal receptor is not present on hypoglossal neurons to allow sufficient excitation across sleep to maintain a patent upper airway, it is now possible to place an exogenous receptor genetically onto target neurons. The ideal designer receptor would be one not found in the brain, or elsewhere, so that off-target effects of the drug could be avoided, and one that is receptive to an otherwise inert ligand that readily crosses the blood–brain barrier and has no active metabolites, which could also induce undesired effects. In this issue of the *Journal*, Fleury Curado and colleagues (pp. 102–110) tested the effectiveness of using a chemogenetic approach to treat upper airway flow limitation (9). Specifically, the researchers delivered an excitatory designer receptor by way of an adeno-associated viral vector injected into the tongue of a mouse model. The vector was then carried retrogradely to hypoglossal motoneurons and established as a new receptor (9). It is important to note that there is no widely available animal model of obstructive sleep apnea, and for this reason, the group used a model of obesity hypoventilation with inspiratory airflow limitation but without apnea (10). This is not an insignificant consideration, as it is entirely possible that complete airway collapse, as in an obstructive apnea, requires far greater hypoglossal activation to resolve the hysteresis resulting from increased surface tension at the site of collapse. With that caveat, the group was able to show quite convincingly that a viral vector could be injected into the tongue to deliver a designer receptor retrogradely to hypoglossal motoneurons and that administration of a selective agonist for the excitatory receptor could indeed markedly increase tonic muscle activity. In addition to increasing the genioglossal tonic and phasic muscle electromyographic activity, the research team demonstrated that administration of the designer ligand increased metabolic activity specifically in the genioglossus muscle in the model and increased upper airway cross-sectional area. Notably, the latter two effects were measured in anesthetized animals. Thus, this chemogenetic approach is potent enough to counter the significant inhibitory effects of anesthesia on muscles, lending further support for the feasibility of this approach in sleep apnea and its use also in patients with sleep apnea requiring anesthesia. Whether the designer receptor remains localized long term exclusively to hypoglossal motoneurons, or whether this may jump transsynaptically to additional brain regions, will require longer-term studies and potentially refinement of the viral vector and/or receptor-ligand pair.

Nonetheless, there are clear advantages with this general direction as a therapeutic approach for obstructive sleep apnea. Unlike hypoglossal nerve stimulation, the vector carrying the target receptor to the desired motoneurons can be placed specifically in protractor components of the genioglossus muscle, and as a less invasive procedure and as a procedure potentially done under local anesthesia, exogenous delivery of the designer receptor could be done gradually over time, allowing titration of the therapy to successful resolution of obstructive sleep-disordered breathing. Additionally, this is a therapy that would not be limited to one nerve but in theory could be injected serially into additional pharyngeal muscles to augment the effect. Moreover, for such localized effects, very little virus is needed to deliver the designer receptor to its target motoneuron if delivered in this present study as retrograde transfer from muscles. A wonderful next step would be to bring back the Hendricks bulldog model of sleep apnea (11) for longer-term studies on safety, viral localization, and effectiveness of therapy on apneic events.

Given the overall promise of chemogenetics in general for treating a vast array of disorders, newer receptors and ligands are being developed. Recently, a chimeric ion channel was developed to conduct cations in response to the antismoking drug, varenicline, which readily crosses the blood–brain barrier and can be given to activate the designer receptor at concentrations far lower than that needed to activate nicotinic receptors (12). This approach may allow improved excitability of hypoglossal motoneurons across REM sleep. At the same time, the

techniques to assess activation used in the present paper by Fleury Curado and colleagues (positron emission tomography and magnetic resonance imaging) to measure effect on airway dimensions may be helpful to determine optimal delivery of chemogenetic receptors. At long last, it does seem hopeful that we are palpably closer to an elusive drug therapy for obstructive sleep apnea. ∎

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References

1. Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. *Eur Respir J* 1995;8:1161–1178.
2. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90:47–112.
3. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Invest* 1992;89:1571–1579.
4. Phillipson EA. Regulation of breathing during sleep. *Am Rev Respir Dis* 1977;115:217–224.
5. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. *J Appl Physiol (1985)* 2014;116:325–336.
6. Decker MJ, Haaga J, Arnold JL, Atzberger D, Strohl KP. Functional electrical stimulation and respiration during sleep. *J Appl Physiol (1985)* 1993;75:1053–1061.
7. Smith PL, Eisele DW, Podszus T, Penzel T, Grote L, Peter JH, *et al*. Electrical stimulation of upper airway musculature. *Sleep* 1996;19(Suppl):S284–S287.
8. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, *et al*.; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139–149.
9. Fleury Curado T, Pho H, Freire C, Amorim MR, Bonaventura J, Kim LJ, *et al*. Designer receptors exclusively activated by designer drugs approach to treatment of sleep-disordered breathing. *Am J Respir Crit Care Med* 2021;203:102–110.
10. Fleury Curado T, Pho H, Berger S, Caballero-Eraso C, Shin MK, Sennes LU, *et al*. Sleep-disordered breathing in C57BL/6J mice with diet-induced obesity. *Sleep (Basel)* 2018;41:zsy089.
11. Hendricks JC, Kline LR, Kovalski RJ, O'Brien JA, Morrison AR, Pack AI. The English bulldog: a natural model of sleep-disordered breathing. *J Appl Physiol (1985)* 1987;63:1344–1350.
12. Magnus CJ, Lee PH, Bonaventura J, Zemla R, Gomez JL, Ramirez MH, *et al*. Ultrapotent chemogenetics for research and potential clinical applications. *Science* 2019;364:eaav5282.

⊗ Operational Research on the Treatment of Drug-Resistant Tuberculosis: Exciting Results That Need to Be Protected

Despite worldwide efforts to improve tuberculosis (TB) control, including the introduction of molecular diagnostics, and a global focus on treatment of diagnosed patients, many high-burden TB countries will not meet 2020 milestones for TB control (1). An important underlying reason for failure to meet these targets is the challenge to successfully treat drug-resistant (DR) TB. Until recently, second-line TB regimens have been poorly active, requiring prolonged duration, with high pill burden including routine inclusion of injectable agents and substantial severe adverse effects (2).

Over the past 10 years, the introduction of new antimycobacterial drugs has facilitated the construction of innovative new regimens for the treatment of DR-TB. Critical new drugs include bedaquiline (World Health Organization Class A), a novel diarylquinoline antibiotic that acts to inhibit the mycobacterial ATP synthase proton pump, and delamanid (World Health Organization Class C), a nitroimidazole, which interferes with the production of the mycobacterial cell wall through inhibition of mycolic acid synthesis (1).

These new regimens allow for significantly shorter treatment duration compared with older-generation second-line regimens and have revolutionized DR-TB therapy by achieving substantially higher cure rates, with improved adverse effect profiles, and are more amenable to decentralized outpatient administration (1, 3).

In this issue of the *Journal*, Franke and colleagues (pp. 111–119) report on rates of 6-month sputum TB culture conversion using new treatment regimens in a large multinational DR-TB prospective cohort (4). Eligible patients were acid-fast bacilli smear positive at baseline and were initiated on bedaquiline, delamanid, or both as key components of the treatment regimen. In this study, 6-month TB culture conversion was used as the primary outcome, which has been previously used as a surrogate for end-of-treatment outcome in patients with DR-TB treated with older second-line regimens (5). Strengths of this study include its large sample size, with patients recruited in 17 geographically diverse, low- and middle-income countries, primarily Kazakhstan, Georgia, Bangladesh, and Pakistan, the prospective enrollment of patients, inclusion of HIV-infected and HIV-uninfected patients, and the statistical analyses and operational study design. Because diagnostics and DR-TB treatment and care were provided as per routine practices, study results should be considered generalizable to clinical DR-TB programs in high-burden settings.

Compared with earlier operational studies of DR-TB treatment using older second-line DR-TB regimens, which demonstrated