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Metabolic Precision Medicines: Curing POMC Deficiency

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Pro-opiomelanocortin deficiency is a rare cause of severe intractable obesity. Two patients have experienced dramatic weight loss in response to setmelanotide, a melanocortin-4 receptor activator. The drug has potential in broader populations, but caution is warranted as it may act at other melanocortin receptors.

In 1997, Heiko Krude and Annette Grüters, pediatric endocrinologists in Berlin, were investigating two pale-skinned, red-haired children with the unusual combination of extreme, early-onset obesity and adrenal insufficiency. Based on their knowledge of the biological effects of the range of peptides derived from the pro-opiomelanocortin pro-peptide, they hypothesized that these children might have a defect in the POMC gene. Genetic analysis proved them to be correct: the patients were either homozygous or compound heterozygous for nonsense mutations that prevented the production of all of the biologically active products of the POMC gene (Krude et al., 1998). Adrenal insufficiency was explained by lack of ACTH action on the adrenal cortex, pale skin and red hair by lack of α-MSH action on melanocytes, and the obesity by lack of MSH peptides in the hypothalamus acting on downstream neurons expressing melanocortin-4 receptors (MC4Rs). Whereas adrenal insufficiency is treatable with hydrocortisone, until now, no specific treatment has been available for the obesity. In the current issue of *The New England Journal of Medicine*, Krude and colleagues, 19 years after the first report of POMC deficiency, describe the dramatic impact of a synthetic melanocortin (MC) in this condition (Kühnen et al., 2016).

In the brain, POMC is selectively expressed in areas including the arcuate nucleus of the hypothalamus where its constituent MC peptides agonize downstream MC4Rs, which are known to play an essential role in the control of food intake and systemic metabolism. Under physiological conditions, leptin stimulates POMC neurons. However, approaches targeting the MC system have so far been largely unsuccessful. Administration of leptin has to date proved insufficiently efficacious in lowering body weight except in cases of severe leptin deficiency (Farooqi et al., 2002; Myers et al., 2012). MC4R agonists, on the other hand, were until now precluded from clinical use due to unacceptable adverse effects, including hypertension (Greenfield et al., 2009). Kühnen et al. now report that the synthetic MC setmelanotide can correct obesity in patients with congenital POMC deficiency, without causing major adverse effects (Kühnen et al., 2016). In two morbidly obese POMC-deficient patients, one of whom was described in the original paper (Krude et al., 1998), three months of daily subcutaneous setmelanotide decreased body weight by 13.4% (25.8 kg) and 16.6% (20.5 kg), respectively. Weight loss was accounted for largely by fat mass and was accompanied by a decrease in appetite. In one patient, temporary discontinuation of treatment resulted in immediate weight regain, while subsequent drug administration for 42 weeks led to a loss of 51 kg. Notably, setmelanotide resulted in darkening of the skin and hair, suggesting that it must also be active on melanocortin-1 receptors (MC1Rs) that are expressed on melanocytes.

The MC4R is involved in the central control of sympathetic tone to blood vessels, and MC4R agonist administration has been associated with marked increase in blood pressure (Greenfield et al., 2009). It is surprising, but reassuring, that setmelanotide did not cause this problem either in the two POMC-deficient patients or in over 200 other human phase 1b/2a trial participants for obesity (Gottesdiener et al., 2015). Why this particular agent avoids the cardiovascular toxicity seen with other related drugs remains unknown.

Might setmelanotide play a broader role in the treatment of obesity? There are other forms of monogenic obesity e.g., Prader-Willi syndrome or leptin receptor deficiency, where effective therapies are lacking, and setmelanotide could theoretically have an impact. Modest reductions in POMC, such as those seen in heterozygote carriers of nonsense mutations (Farooqi et al., 2006), are associated with increased adiposity, and it is therefore likely that some individuals with "common" obesity might have lowered POMC-ergic tone and be sensitive to this agent. Developing reliable biomarkers to identify such individuals would be helpful. Recent pre-clinical studies reported that MCR4 agonists can amplify GLP-1-induced weight loss in diet-induced obese mice, so novel combinatorial approaches may have therapeutic promise (Clemmensen et al., 2015; Tschöp et al., 2016).

This elegant example of "precision medicine" shows the enduring importance of rare human disorders in advancing our understanding of pathophysiology

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and discovering new and improved therapeutics. Critical to such success is the continued existence of physicians with sufficient scientific curiosity and training to see and seize the opportunity to advance science through the rigorous investigation of patients with atypical presentations and mysterious diseases. It also demonstrates the importance of a vibrant biotechnology industry committed to working with academics to test their drugs in specific scenarios, including use in ultra-orphan diseases that are outside the usual industry paradigm.

The MC agonist setmelanotide has had a transformative effect on the health and lives of these two severely afflicted patients, and it is beyond doubt that its long-term administration would be efficacious in other cases of this extremely rare disease. However, as has been the case with leptin, it is a long and uncertain path from the treatment of severe hormonal deficiency causing a rare disease to a treatment for more common forms of obesity. Leptin is extremely specific and safe, but lacks sufficient efficacy in common obesity, at least in the way it has been used to date. Setmelanotide clearly stimulates the MC1R, resulting in changes in skin and hair pigmentation, and there are at least theoretical concerns that chronically stimulating melanocytes might promote the development of melanocytic tumors. However, this is a time to celebrate this milestone in metabolic precision medicine, which has brought great clinical benefit to two patients and raises hopes of broader therapeutic efficacy.

However, without wishing to "spoil the party," it is also worth starting a conversation in the broader biomedical community about a dilemma that is likely to increasingly present itself as we test novel therapeutics in very rare diseases. What will we do when we have a drug that is spectacularly effective in a tiny number of patients with a specific condition, but where it is not commercially viable to guarantee lifelong treatment? In the obesity field, we are already witnessing this challenge with congenital leptin deficiency, where there are several untreated patients in countries where the company that produces leptin does not have the infrastructure to deliver the drug. What will happen to the patients with POMC deficiency if it turns out that setmelanotide is not commercializable for use in larger populations? We need to start thinking about how all interested parties, including companies, doctors, and governments, might best work together to ensure that people do not succumb to eminently treatable hormonal deficiency diseases just because they have been doubly unfortunate—in the genetic lottery and in the risky game that is drug development.

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