Tracing the Effect of the Melanocortin-4 Receptor Pathway in Obesity: Study Design and Methodology of the TEMPO Registry

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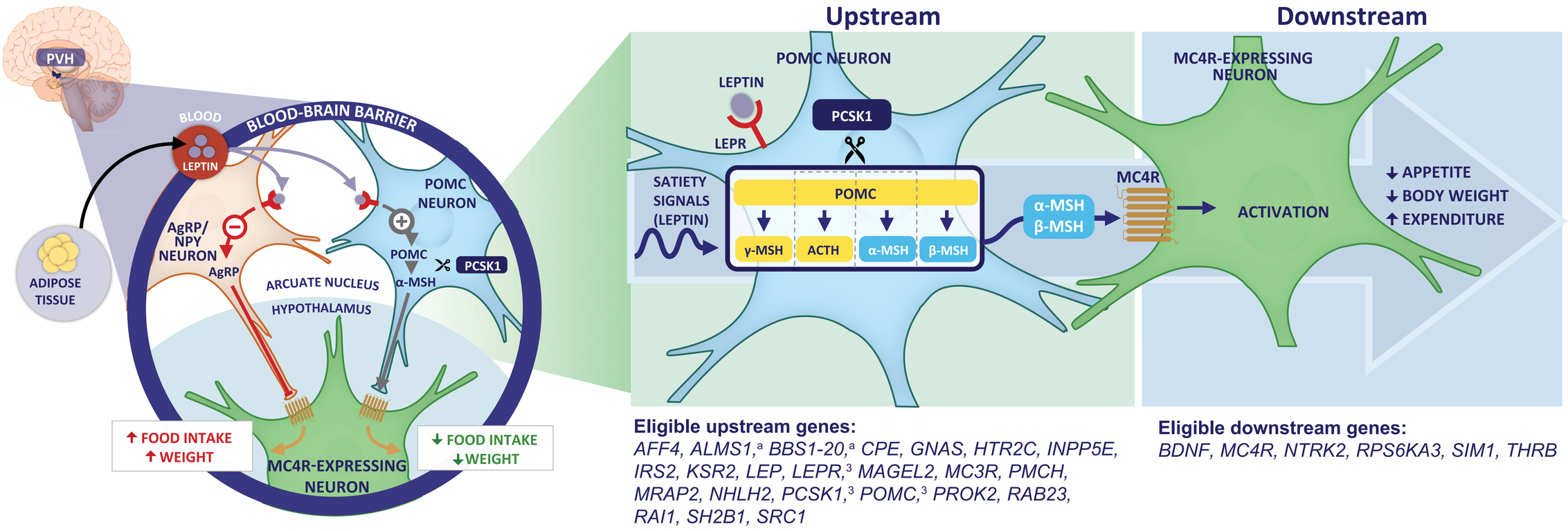
Figure 1. The melanocortin-4 receptor signaling pathway, a component of the central melanocortin pathway, plays a vital role in regulating appetite and energy balance, and mutations in this pathway can result in rare genetic disorders of obesity.[1,2]



Eligible upstream genes:
AFF4, ALMS1,[a] BBS1-20,[a] CPE, GNAS, HTR2C, INPP5E, IRS2, KSR2, LEP, LEPR,[3] MAGEL2, MC3R, PMCH, MRAP2, NHLH2, PCSK1,[3] POMC,[3] PROK2, RAB23, RAI1, SH2B1, SRC1

Eligible downstream genes:
BDNF, MC4R, NTRK2, RPS6KA3, SIM1, THRB

AgRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PVH, paraventricular nucleus of hypothalamus. [a]Only if there is no evidence of clinical syndromic features, likely heterozygous patients only.

Summary

- **The TEMPO registry enrolls patients with rare genetic disorders of early-onset severe obesity resulting from genetic variants in the MC4R pathway**
- **The registry provides insights into the overall course and disease burden of rare disorders of obesity**
- **Health care providers may use this resource to improve the identification, diagnosis, and treatment of genetic disorders in patients with obesity**

Introduction

- Rare genetic disorders of obesity characterized by dysfunction of the melanocortin-4 receptor (MC4R) pathway include *MC4R*, *POMC*, *PCSK1*, *LEPR*, and *LEP* genetic deficiencies; Bardet-Biedl syndrome; and Alström syndrome[4,5]
- The MC4R pathway, which is a component of the central melanocortin pathway, regulates satiety and energy balance[2,4]
  - Deleterious gene mutations in this pathway may result in early-onset severe obesity and insatiable/excessive hunger (Figure 1)[4-6]
- Diagnosing, evaluating, and managing genetic disorders of obesity may address unmet treatment needs[7]

Objective

- To evaluate the burden of rare genetic disorders of obesity on participants, caregivers, healthcare providers, and the healthcare system

Study Design and Methodology

The TEMPO Registry

- The TEMPO registry is a voluntary, prospective, open-ended registry of individuals with rare genetic disorders of obesity in which the MC4R pathway is implicated in early-onset severe obesity and insatiable/excessive hunger
- This registry captures data entered by the patient; caregiver; and treating, diagnosing, or primary care healthcare provider using electronic survey tools administered at baseline and annually thereafter
- Electronic surveys are HIPAA (Health Insurance Portability and Accountability Act of 1996) compliant

Referral

- Eligible participants are referred to the TEMPO study in either of the following ways:
  - Referral by the healthcare provider to coordinating centers
  - Inclusion after positive identification through an industry-sponsored genetic screening study

Eligibility and Enrollment

Key Inclusion Criteria

- Patients aged ≥2 years with the following criteria are eligible for inclusion:
  - Body mass index (BMI) >1.4 times that of the age- and sex-adjusted 95th percentile value (in patients aged 2 to 17 years)
  - BMI >40 kg/m^2 (in patients aged ≥18 years)
- Patients are eligible if homozygous, compound heterozygous, heterozygous, or composite heterozygous mutations upstream or downstream of the MC4R are detected (Figure 1)

Key Exclusion Criteria

- Patients with syndromic disorders of obesity such as Bardet-Biedl syndrome or Alström syndrome will be excluded if they demonstrate clinical manifestations of the disease other than obesity and hyperphagia
  - Individuals identified with mutations consistent with Prader-Willi syndrome, Bardet-Biedl syndrome, or Alström syndrome are referred to existing registries

Enrollment

- The Registry Coordinating Center is responsible for obtaining consent from adult patients and caregivers of minor patients (and assent from minors when appropriate), screening patients, and enrolling patients in the registry
- Eligible patients and caregivers are enrolled after providing written consent and are informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care

Electronic Surveys

Baseline

- Following enrollment, baseline electronic surveys are completed
  - Healthcare providers complete the baseline healthcare provider survey tool, reporting patient baseline demographics and disease characteristics
  - Patients and caregivers complete their respective baseline survey tools, answering questions on the burden of disease

Baseline surveys collect the following information:

- Demographics[a]
- Medical history[b]
- Pedigree of obesity history[c]
- Genetic testing[d]
- Resource utilization[e]
- Eating habits and hunger[f]
- Symptoms and comorbidities present
- Development and education[g]
- Social and emotional impact[h]

[a]Including sex and age. [b]eg, height; weight; age at which obesity was identified; hair color; gastrointestinal complications in early life; comorbidities; medical treatment history; and current medication, surgeries, and other disorders. [c]As available; relevant family members, as well as early mortality of siblings and obesity or PCSK1-related symptoms or surgical intervention. [d]Identifying gene(s) of interest. [e]eg, hospitalizations, assistive devices, productivity/income loss, medications. [f]eg, level of hunger, nocturnal eating, choking episodes. [g]eg, learning disabilities and developmental delays, interruptions to education. [h]eg, bullying, limitations on activities, health concerns.

Annual Follow-ups

- Enrolled patients, caregivers, and healthcare providers are contacted annually by the Registry Coordinating Center to complete an online follow-up survey, which includes a smaller subset of questions from the baseline survey
- The period of follow-up is open ended

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided by MedThink SciCom (support from Deirdre Rodeberg, PhD, and David Boffa, ELS) and funded by Rhythm Pharmaceuticals, Inc.

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