The Hunger Games

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Prader–Willi syndrome

Prader–Willi syndrome (/ˈprɔdər ˈvɪli/, abbreviated P.W.S) is a rare genetic disorder in which seven genes (or some subset thereof) on chromosome 15 (q 11–13) are deleted or unexpressed (chromosome 15q partial deletion) on the paternal chromosome. It was first described in 1956 by Andrea Prader (1919–2001), Heinrich Willi (1900–1971), Alexis Labhart (1916–1994), Andrew Ziegler, and Guido Fanconi of Switzerland.[1] Characteristic of PWS is "low muscle tone, short stature, incomplete sexual development, cognitive disabilities, problem behaviors, and a chronic feeling of hunger that can lead to excessive eating and life-threatening obesity."[2] The incidence of PWS is between 1 in 25,000 and 1 in 10,000 live births.

The maternal origin of the genetic material that is affected in the syndrome is important because the particular region of chromosome 15 involved is subject to parent of origin imprinting, meaning that for a number of genes in this region only one copy of the gene is expressed while the other is silenced through imprinting. For the genes affected in PWS, it is the maternal copy that is usually imprinted (and thus is silenced), while the mutated paternal copy is not functional.[3]

This means that while most people have one working and one silenced set of these genes, people with PWS have a non-working set and a silenced set. If the maternally derived genetic material from the same region is affected instead, the sister syndrome Angelman syndrome is the result.[4]

With the recent benefits of early diagnosis and ongoing interventions, the obesity rate among children with Prader–Willi Syndrome has decreased to be similar to the typical population. With behavioural therapy and other treatments, the effects of the syndrome can be reduced.[5]
Neural Mechanisms Underlying Hyperphagia in Prader-Willi Syndrome


Relatively few studies have systematically investigated brain structure and function in PWS. Postmortem anatomical and histopathological studies have shown enlarged lateral ventricle volume (13–15), cerebellar dentate nucleus abnormalities (13,16), neuron cell layer disorganization and cell loss (13,16), and frontal cortical atrophy (15,16). Leonard et al. (17) reported abnormal sylvian fissure asymmetry in one half of their PWS sample. Despite its central role in regulating food intake, there seem to be inconsistent findings related to abnormalities in the hypothalamus. For example, individuals with PWS have decreased cerebrospinal fluid (CSF) levels of orexin/hypocretin-1, a hypothalamic neuropeptide that regulates sleep cycles (18). However, Cacciarini et al. (19) failed to reveal gross structural abnormalities in the hypothalamus in PWS. Paraventricular hypothalamic oxytocin cells seem to be selectively decreased in PWS (20), although others report elevated CSF levels of oxytocin (21). Finally, compared with controls, individuals with PWS exhibit similar patterns of receptor expression of the orexigenic hormone, ghrelin, in several brain regions (22), despite elevated plasma ghrelin levels in PWS compared with both obese and lean individuals (23).

Functional magnetic resonance imaging (fMRI) provides a non-invasive measure of brain function. A recently published fMRI study of three individuals with PWS showed delayed signal reduction after glucose administration in the hypothalamus, ventromedial prefrontal cortex, and nucleus accumbens, with signal increase in the dorsolateral prefrontal cortex (24). Individuals with PWS had a mean signal reduction latency of 24 minutes after glucose ingestion, compared with a 15-minute mean latency in obese individuals. These findings provide evidence for dysfunction in neural satiety mechanisms in individuals with PWS.
synaptic plasticity & the hunger circuit

interoceptive sensory neurons monitor metabolic signals to regulate:

- hunger
- food seeking
- food consumption

During fasting
- undergo structural changes that cause them to become more active

the AgRP neurons that drive feeding behaviors
- which makes them more responsive to hunger-promoting neural stimuli
why plasticity?

biggest daily challenge

finding food

to survive

brain’s feeding drive may be adaptive
The main characters in the hunger games:

- **AgRP (agouti-related peptide)** drives eating and weight gain.
- **POMC (pro-opiomelanocortin)** inhibits feeding which leads to satiety and weight loss.

*Starvation sensitive*
Switching AgRP on

When AgRP neurons are artificially switched on, the animals eat voraciously – consuming up to 4x more food. They will also work harder to get food.

So, what regulates their activity?
Anatomical map of multiple AGRP axon projections.

Projections that have been directly implicated in food intake are marked with **blue lines.**

ARC: hypothalamic arcuate nucleus, BST: bed nucleus of the stria terminalis, NTS: nucleus of the solitary tract, PBN: parabrachial nucleus, PAG: periaqueductal gray.

Functional circuit map of synaptic targets

- Baseline
- Activated
- Inhibited
- Not connected
- Inhibition
- GABA release

“In behavioral experiments, test if activation of the presynaptic population or inhibition of the postsynaptic population are each sufficient for the behavioral response.”
Functional test of circuits between molecularly defined cell types.

Occlusion strategies for inhibitory synaptic connections

What is the interaction between the AgRP neurons and POMC neurons?

Would the AgRP-POMC interaction be a critical control point for feeding behavior?

Recall: POMC (Pre-opiomelanocortin) expressing neurons inhibit feeding.
Testing AgRP-POMC interactivity

Matrix of possible monosynaptic interactions between AgRP and POMC neurons in the ARC.

Optogenetics: controlling cell function with light

A brief description of the basic steps required to control cellular function with optogenetics is presented.

How optogenetics works

A light-sensitive protein from algae

Take the gene for this protein...

...and insert the DNA into specific neurons in the brain

Neurons communicate by “firing.” This is an electrical signal created by opening & closing ion channels.

So now you can cause neurons to fire just by flashing blue light!

With the right combination of neurons, you can activate an entire brain circuit to control specific behaviors (like movement)
Channelrhodopsin-assisted circuit mapping

AgRP neurons were rendered photo-excitable with channelrhodopsin-2

Left, cell-attached recording showing inhibition of a POMC neuron during AGRP neuron photostimulation with no blockers present. Right, AGRP neuron inhibition of spontaneous POMC firing was sensitive to PTX, demonstrating a requirement for GABA release.

1. Selective activation of AgRP $\rightarrow$ POMC synaptic connections strongly inhibited POMC neuron activity.

2. Chronic suppression (24 h) of POMC neurons does increase food intake. **POMC neuron suppression does not acutely activate feeding behavior but does influence long-term food intake.**

Suppression of POMC neuron activity by AgRP neurons is not required for acute feeding.
PVH lesions lead to hyperphagia and obesity

“Photoactivation of AgRP → PVH axons elicited food intake with similar magnitude as stimulating AgRP-expressing somata in the ARC.”

AgRP neurons increase feeding by inhibiting neurons in the PVH and food deprivation increases synaptic drive onto PVH.
PVH has multiple cell types

Oxytocin neuron loss in PVH is implicated in PWS

Prader-Willi Syndrome

AgRP $\rightarrow$ high connection probability to PVH Oxytocin neurons
pharmacological inhibition of PBN promotes feeding

Photoactivation of AgRP → PBN axons DID NOT significantly increase feeding.
Do AgRP neurons show structural changes with activity?

recall:

- Glutamate is the main excitatory neurotransmitter in the CNS.
- Synaptic plasticity can occur when Glutamate binds to NMDA \( \rightarrow \text{Ca}^{++} \rightarrow \) signal transduction pathways

Genetically engineered two types of mice:

1. No NMDA receptors on AgRP neurons.
2. No NMDA receptors on POMC neurons
what happened?

**mice w/o NMDAR on POMC**
- no change in feeding behavior

**controls**
- 24hr fast → increased dendritic spines on AgRP neurons; then refed (hunger alleviated) number of spines on AgRP dendrites dropped back down to baseline

**mice w/o NMDAR on AgRP**
- ate a lot less than controls
- more lean than controls
- 24hr fast → no effect on dendritic spines on AgRP neurons

“Structural plasticity of excitatory glutamate synapses on AgRP neurons is an important regulator of feeding behavior.”