DCCR-Mediated Agonization of the ATP-sensitive Potassium Channel: A Proposed Mechanism of Action to Treat Hyperphagia in PWS Patients

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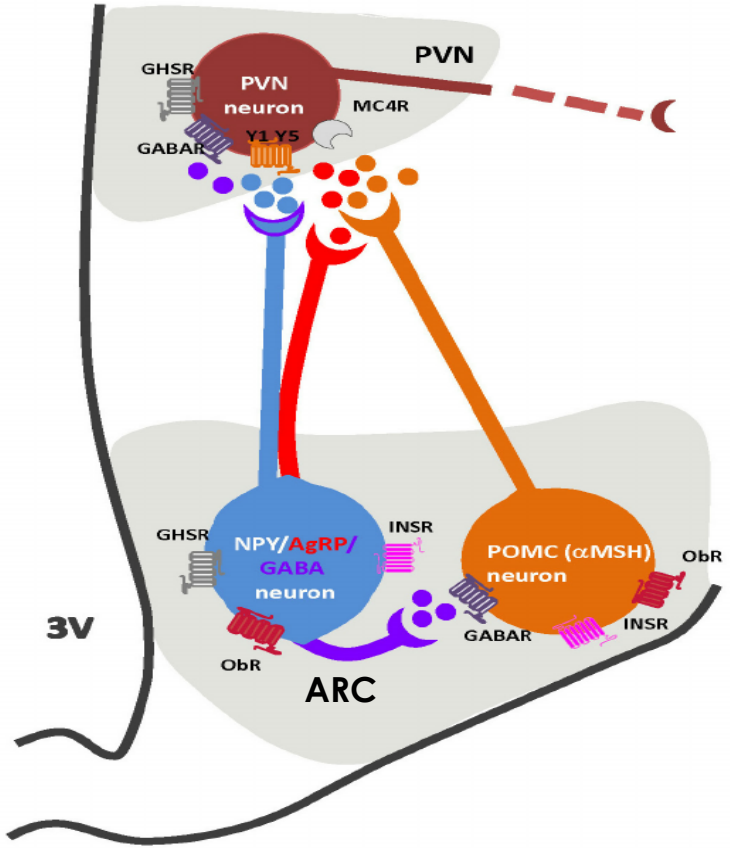
Key neurons regulating appetite located in ARC

- Appetite- regulating neurons are located in the arcuate nucleus of the hypothalamus
  - NAG neurons → orexigenic
  - POMC neurons → anorexigenic
- Peripheral signals related to energy status regulate these neurons
  - leptin, insulin and ghrelin



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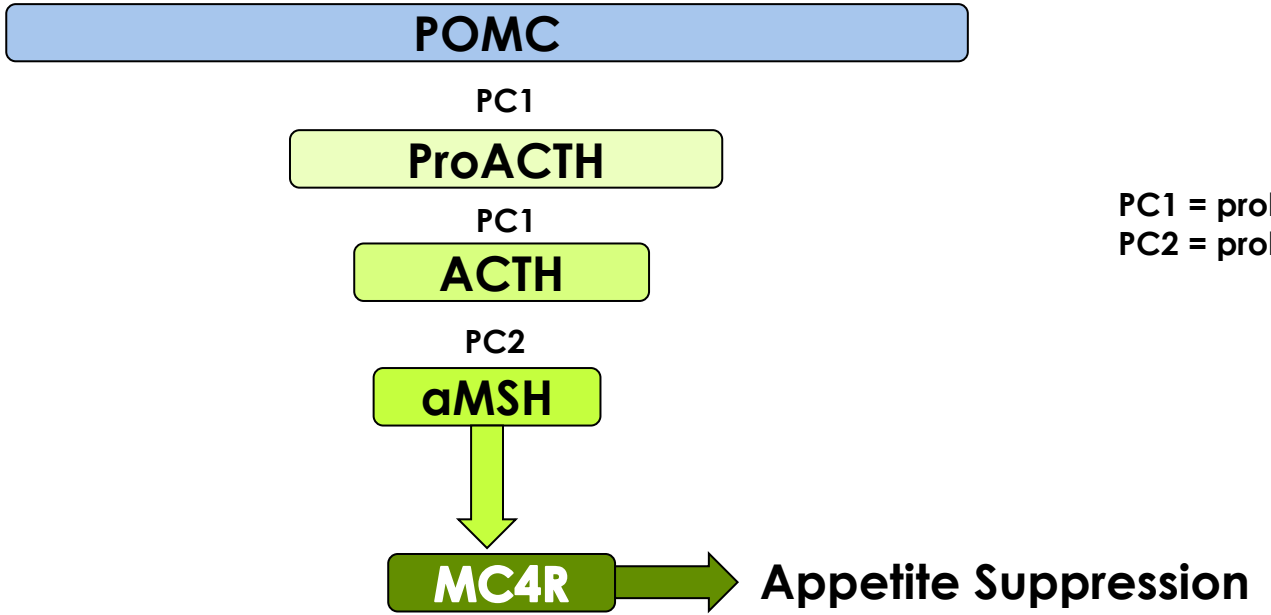
POMC is cleaved to yield aMSH which interacts with MC4R to suppress appetite



PC1 = prohormone convertase 1
PC2 = prohormone convertase 2

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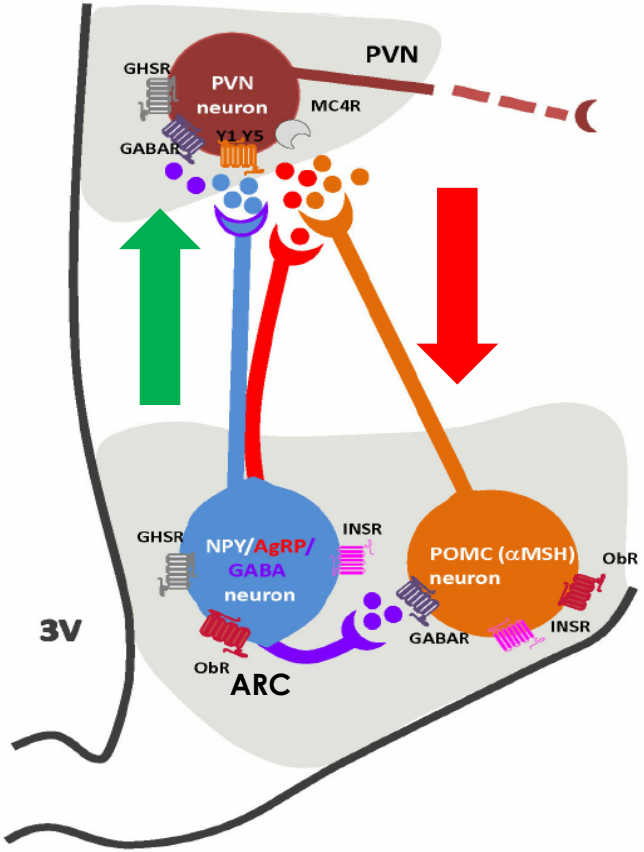
Appetite stimulatory effects and regulation of NAG neurons

Neuro-transmitter	Direct appetite stimulation	Indirect appetite stimulation
NPY	Most potent endogenous appetite stimulatory peptide	Downregulates PC2, limiting aMSH production from POMC
AgRP		Antagonist/inverse agonist of MC4R
GABA	Potent appetite stimulant	Inhibits POMC neurons



Elevated NPY and AgRP drive hyperphagia in PWS

- SNORD116, in the PWS critical region, has an important role in the control of NAG neuronal functions[1]
- Lack of SNORD116 in NAG neurons leads to the upregulation of NPY mRNA consistent with the hyperphagic phenotype[1]
- Hypothalamic AgRP and NPY remain elevated following refeeding in association with hyperphagia in SNORD116p-/m+ mice[2]
- Based on these models, dysregulation of NAG neurons due to lack of SNORD116 leads to increased orexigenic signaling and markedly impaired POMC signaling.

1. Qi et al. Snord116 is critical in the regulation of food intake and body weight. Sci Rep 2016; 6:18614
2. Burnett et al. Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome. J Clin Invest 2017; 127(1):293-305

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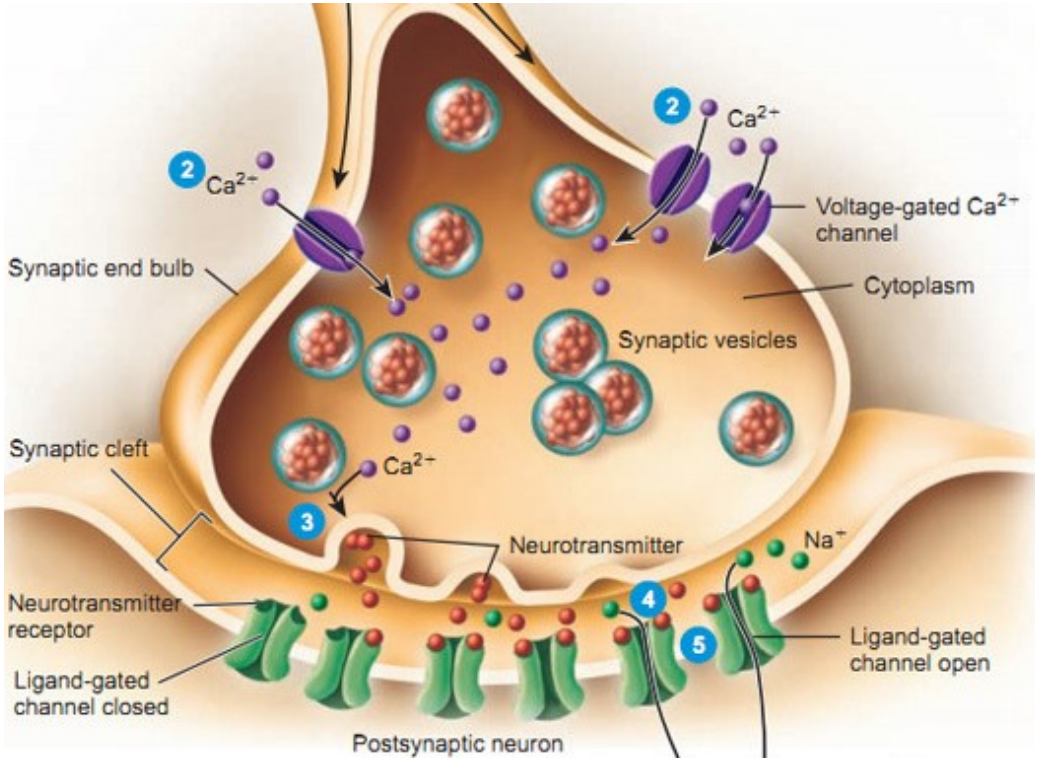
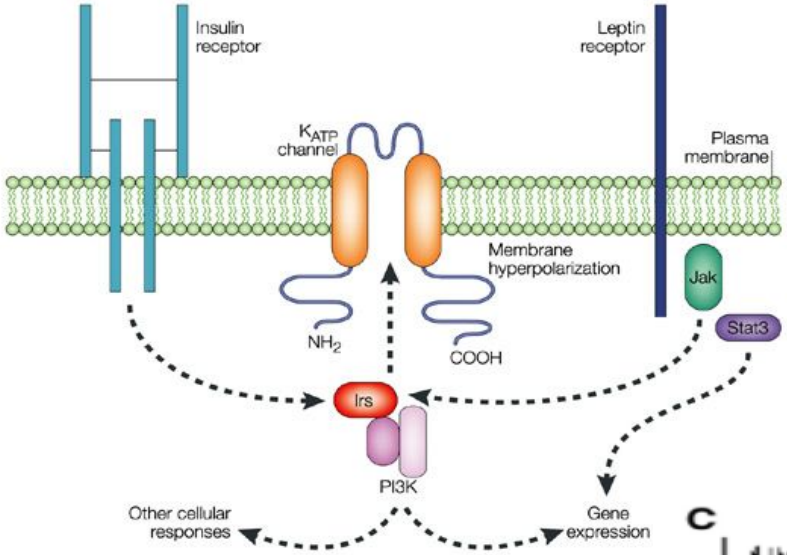
Regulation of secretion of NPY and AgRP

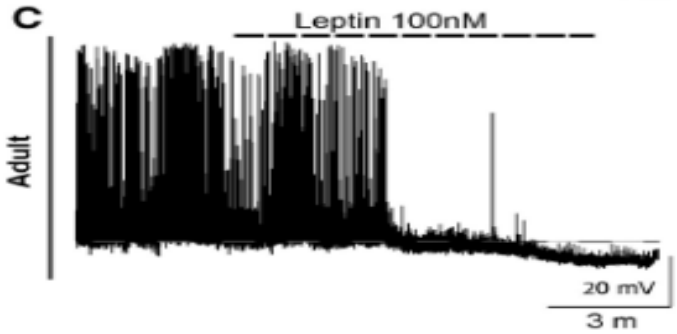


- NPY and AgRP are co-localized to vesicles in the NAG neurons
- The are co-secreted (with GABA) due to changes in the resting membrane potential of the NAG neurons
  - Depolarization → Ca^{2+} enters the cell → secretion of vessicles
  - Hyperpolarization prevents Ca^{2+} from entering the cell, and prevents secretion

Leptin and insulin regulate NPY and AgRP secretion



- Leptin is the predominant hormone regulating NAG neurons
- Insulin has an identical regulatory role
- Leptin and insulin control NPY and AgRP secretion by opening the K_{ATP} channel thereby hyperpolarizing the plasma membrane
- The K_{ATP} channel serves a central role in leptin's and insulin's regulation of appetite



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Can direct agonization of the K_{ATP} channel contribute to improvements in hyperphagia?

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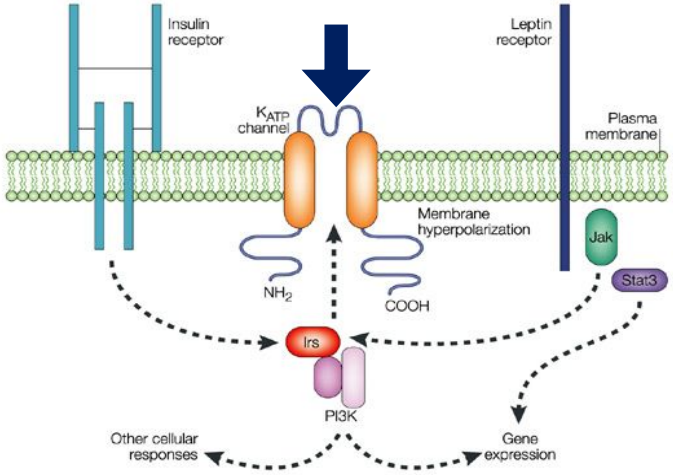
DCCR, a K_{ATP} channel agonist, directly regulates NPY and AgRP secretion



- DCCR, on administration, releases diazoxide choline over 24 hours[1]
- Diazoxide choline hydrolyzes to diazoxide, a potent K_{ATP} agonist
- Diazoxide crosses the BBB to act centrally[2]
- Diazoxide hyperpolarizes NAG neurons more extensively than leptin which amplifies the regulation of NPY and AgRP secretion by leptin and insulin.

1. Salehi et al. Pharmacokinetics of diazoxide choline controlled-release tablets, a once a day treatment being evaluated in patients with Prader-Willi syndrome. ESPE 2018
2. Kishore et al. Activation of K_{ATP} channels suppresses glucose production in humans. J Clin Invest 2011; 121(12):4916-4920
3. Baquero et al. Developmental switch of leptin signaling in arcuate nucleus neurons. J Neurosci 2014; 34(30):9982-9994

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Diazoxide has anorexigenic effects in models of NPY-driven hyperphagic obesity

Model	Caloric intake	Weight	Body fat	Glycemic control	Circulating lipids
Magel2 mouse		Weight loss	Loss of body fat	Improved	--
Zucker Fatty rat	Reduced	Reduced rate of gain	Reduced body fat	Improved	Improved
Zucker Diabetic Fatty rat	Reduced	Reduced rate of gain	--	Improved	Improved
db/db mouse	Reduced	--	--	--	--
OLETF rat	Reduced	Reduced rate of gain	Reduced body fat	Improved	Improved
Hypothalamic injury rat	Reduced	--	--	--	--
Hypothalamic injury chicken	Reduced	--	--	--	--
Streptozotocin diabetic rat	--	Reduced rate of gain	--	Improved	--
High Fat Diet Induced Obese mouse	Reduced	Weight loss or reduced rate of gain	Loss of body fat	Improved	Improved

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Clinical Study PC025: Phase II study of DCCR in PWS patients

- Clinical study at UC Irvine
  - 10-week open-label treatment phase
  - 4-week double-blind treatment phase
- Doses titrated between1.5 mg/kg to 4.2 mg/kg at the discretion of the investigator
- Enrolled 13 obese and overweight subjects with genetically confirmed PWS (8 male, 5 female) between 11 and 21 years old.
- Hyperphagia was evaluated at each study visit using a modified-Dykens hyperphagia questionnaire completed by the caregiver

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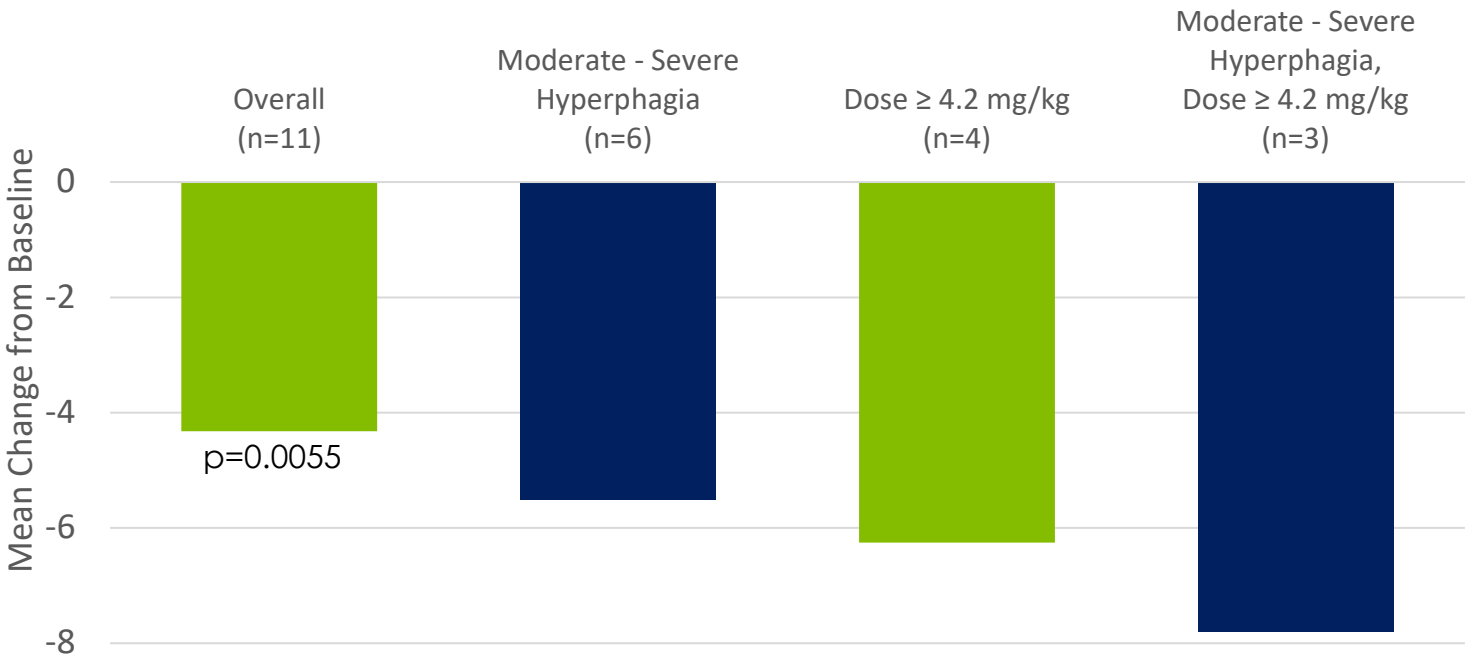
PC025 Hyperphagia Mean Change from Baseline During Open-Label Treatment

Greater at Highest Dose and Moderate-Severe Hyperphagia



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Conclusions

- Part of the hyperphagia in PWS may be driven by excessive secretion of NPY and AgRP by NAG neurons
- Leptin and insulin regulate the secretion of NPY and AgRP by agonizing the K_{ATP} channel
- DCCR can directly agonize the K_{ATP} channel which amplifies leptin's and insulin's regulation of NAG neurons, therefore lowering NPY and AgRP secretion
- Directly agonizing the K_{ATP} channel in NAG neurons is an effective means to reduce hyperphagia in NPY-driven hyperphagic animal
- Reduction in hyperphagia observed in a Phase II clinical study of DCCR (PC025)
- A phase III study, C601, is underway to confirm the efficacy of DCCR in PWS patients

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