Serotonergic influences on eating behaviour

Lora Heisler
The energy balance equation

Intake = Expenditure

Neutral energy state
Stable weight

Intake < Expenditure
Negative energy state
Weight loss

Intake > Expenditure
Positive energy state
Weight gain

Calories
Thermogenesis
Physical activity
Basal metabolism
Obesity Treatment Targets

Food Intake – central

- Neurotransmitters: 5-HT, adrenaline, noradrenaline, histamine
- Neuropeptides: POMC, AgRP, NPY, Orexin, CRH
- Cannabinoids

Food Intake – peripheral

- GI peptides: CCK, GLP1, PYY, Ghrelin
- Pancreatic peptides: Insulin, glucagon, amylin
- Adipokines: Leptin, adiponectin

Physical activity

Thermogenesis

- Thyroid hormones
- β-adrenergic agonists
- Uncoupling proteins

Fat metabolism

- Adipocyte differentiation
- Adipogenesis
- Apoptosis

Fat absorption

- Lipase inhibitors
- Fatty acid transporters
5-HT medications at forefront of obesity treatment

Adapted from Heisler et al., Pharm Biochem Beh, 1997
5-HT medications withdrawn from clinical use
5-HT$_{2C}$ Receptors are primary target

Adapted from Lam & Heisler, *Expert Reviews in Molecular Medicine*, 2007
Melanocortin: Principal energy balance mediator

Adapted from Yeo and Heisler, *Nature Neurosci* 2012
Garfield et al., *Trends in Endo and Metab* 2009
Proposed Model:

- $G_q$ 5-HT$_{2C}$Rs are expressed with POMC
- $G_i$ 5-HT$_{1B}$Rs can indirectly influence POMC activity via GABA disinhibition
- MC4-Rs are required for 5-HT$_{2C}$R agonists to suppress food intake
5-HT$_2$C Rs are positioned to influence ARC POMC

Serotonin 5-HT$_2$C Receptor Agonist Promotes Hypophagia via Downstream Activation of Melanocortin 4 Receptors

Daniel D. Lam, Magdalena J. Przydzial, Simon H. Ridley, Giles S. H. Yeo, Justin J. Rochford, Stephen O’Rahilly, and Lora K. Heisler

Tony Coll’s POMC tau lacZ line, 5-HT$_2$C R antibody
5-HT$_{2C}$R agonists activate ARC POMC neurons

Serotonergic Drugs Dose-Dependently Depolarize GFP-POMC Neurons

In vivo, wild type

5-HT\textsubscript{2C}R-mediated energy balance via Pomc

Yong Xu et al, *Neuron* 2008 Joel Elmquist
Clinical significance of 5-HT$_{2C}$R agonists

FDA approves lorcaserin, first weight-loss drug since 1999

Once the Drug Enforcement Administration clears it, the drug will be marketed in the U.S. under the name Belviq. But the FDA's approval comes with a warning.

June 27, 2012 | By Melissa Healy, Los Angeles Times
Are ARC Pomc peptides the neurochemical mediators of lorcaserin?
Generation of 5-HT$_{2c}$R$^{\text{Cre}}$ mouse line and 5-HT$_{2c}$R$^{\text{YFP}:\text{POMC}^{\text{dsRED}}}$
Re-activation of Pomc gene in 5-HT$_{2C}$R expressing neurons
- Inactivation of *Pomc* gene in the ARC abrogates the appetite suppressive effect of lorcaserin

- ARC *Pomc* derived peptides are the neurochemical mediator communicating lorcaserin’s therapeutic appetite-suppressive effect
ARC POMC peptides are required for lorcaserin to suppress appetite.
Aging impairs Pomc tone

Rapamycin Ameliorates Age-Dependent Obesity Associated with Increased mTOR Signaling in Hypothalamic POMC Neurons

Shi-Bing Yang,1 An-Chi Tien,2 Gayatri Boddupilli,1,4 Allison W. Xu,5 Yuh Nung Jan,1 and Lily Yeh Jan1,*

Yang et al. 2012 (Neuron)

Burke et al., Endocrinology 2014
Lorcaserin over-rides diminished Pomc function with age

Burke et al., Endocrinology 2014
New drug may end the curse of the middle age spread

Sarah Knapton
Published 13/08/2014 | 00:00

Scientists discover secret to losing weight in middle-age

Scientists believe they have discovered what causes the middle age spare tyre.

Lorcaserin over-rides diminished Pomc function with age

Burke et al., Endocrinology 2014
ARC Pomc peptide post-translational processing is impaired with diet-induced obesity

Rapamycin Ameliorates Age-Dependent Obesity Associated with Increased mTOR Signaling in Hypothalamic POMC Neurons

Shi-Bing Yang, An-Chi Tien, Gayatri Boddupalli, Allison W. Xu, Yuh Nung Jan, and Lily Yeh Jan

Obesity Induces Hypothalamic Endoplasmic Reticulum Stress and Impairs Proopiomelanocortin (POMC) Post-translational Processing

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Isin Çakır, Nicole E. Cyr, Mario Perello, Bogdan Patedakis Litvinov, Amparo Romero, Ronald C. Stuart, and Eduardo A. Niinimäki

A

7mg/kg

B

DIO mice
Lorcaserin overcomes impaired Pomc function with age and diet
Can a $5\text{HT}_{1B}$R agonist prevent age and HFD inhibitory tone onto Pomc?

### Proposed Model:
- $G_q$ $5\text{HT}_{2C}$Rs are expressed with POMC
- $G_i$ $5\text{HT}_{1B}$Rs can indirectly influence POMC activity via GABA disinhibition
- MC4-Rs are required for $5\text{HT}_{2C}$R agonists to suppress food intake
5-HT₁B R agonists reduce an inhibitory input onto ARC Pomc

Michael Cowley - *Neuron* 2006
Combined 5-HT$_{2C}$R/5-HT$_{1B}$R agonists potentiate satiety

5-HT$_{2C}$R agonist WAY 161503
5-HT$_{1B}$R agonist CP 94,253

Doslikova et al. J Neurosci 2013
Proposed Model:

- $G_q\ 5-HT_{2C}$ Rs are expressed with POMC
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- MC4-Rs are required for $5-HT_{2C}$R agonists to suppress food intake
5-HT$_{2C}$R agonists require MC4R to suppress appetite

Genetic inactivation of *Mc4r*, but not *Mc3r* attenuates responses to d-fenfluamine hypophagia

Re-expression of *Mc4r* only in Sim1 neurons restores d-fenfluramine anorexia in *Mc4r* nulls

(Adapted from Heisler et al., *Neuron* 2006)

(Yong Xu et al. *J. Neurosci* 2010)
SUMMARY

- ARC POMC is required for normal appetite and body weight regulation.
- Age and diet impair ARC Pomc basal activity and post translational processing.
- The subset of ARC POMC expressing 5-HT\textsubscript{2C}R are critical for appetite and glucoregulatory functions.
- 5-HT\textsubscript{2C}R agonist lorcaserin was able to bypass reduced Pomc function to suppress appetite.
- Combination of a 5-HT\textsubscript{2C}R agonist with a 5-HT\textsubscript{1B}R agonist significantly increased appetite suppression via an elevation of the number of Pomc neurons activated.
- Modulation of aspects of this discrete circuit may yield a more effective obesity pharmacotherapy.
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