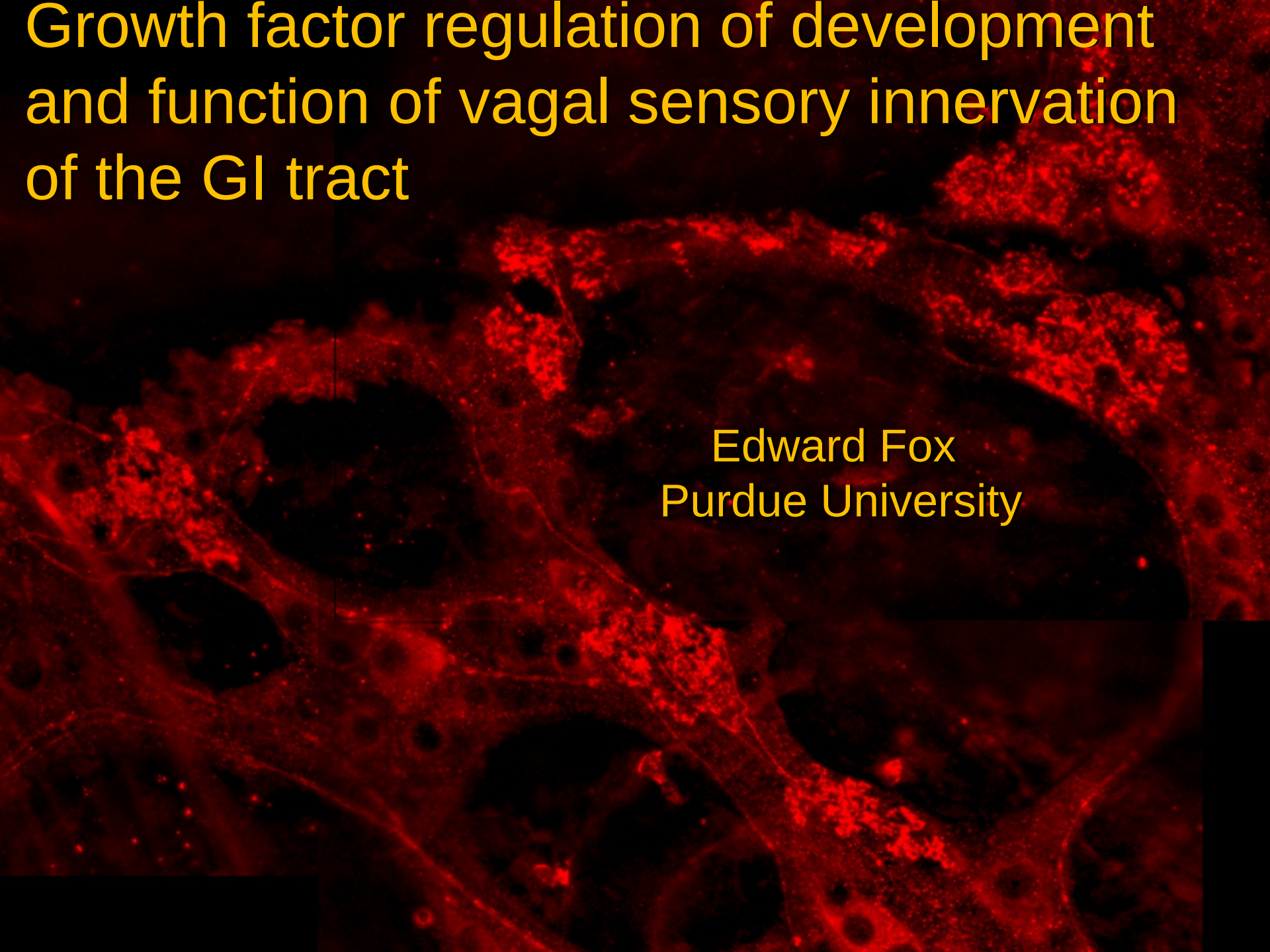
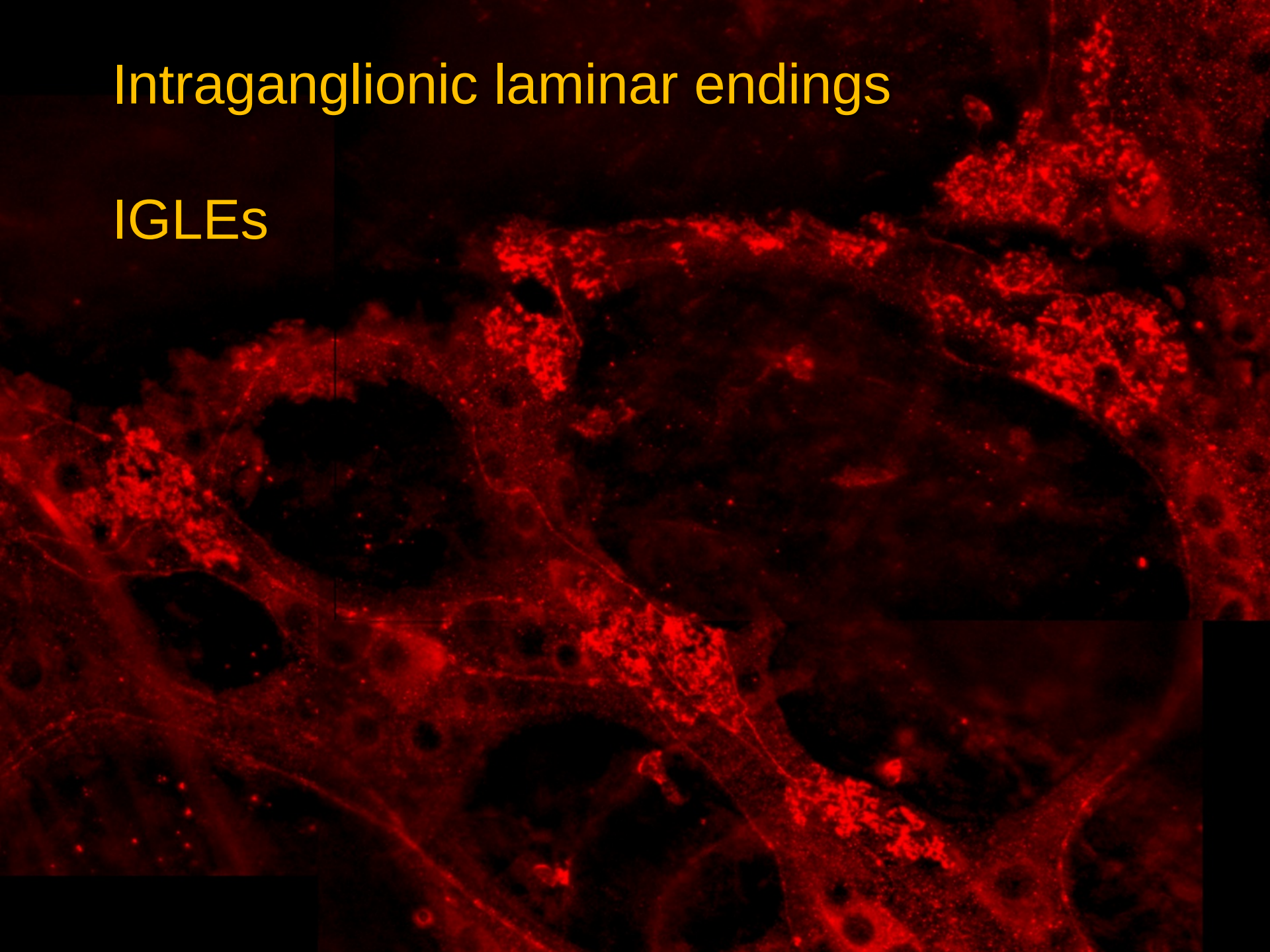
Growth factor regulation of development and function of vagal sensory innervation of the GI tract

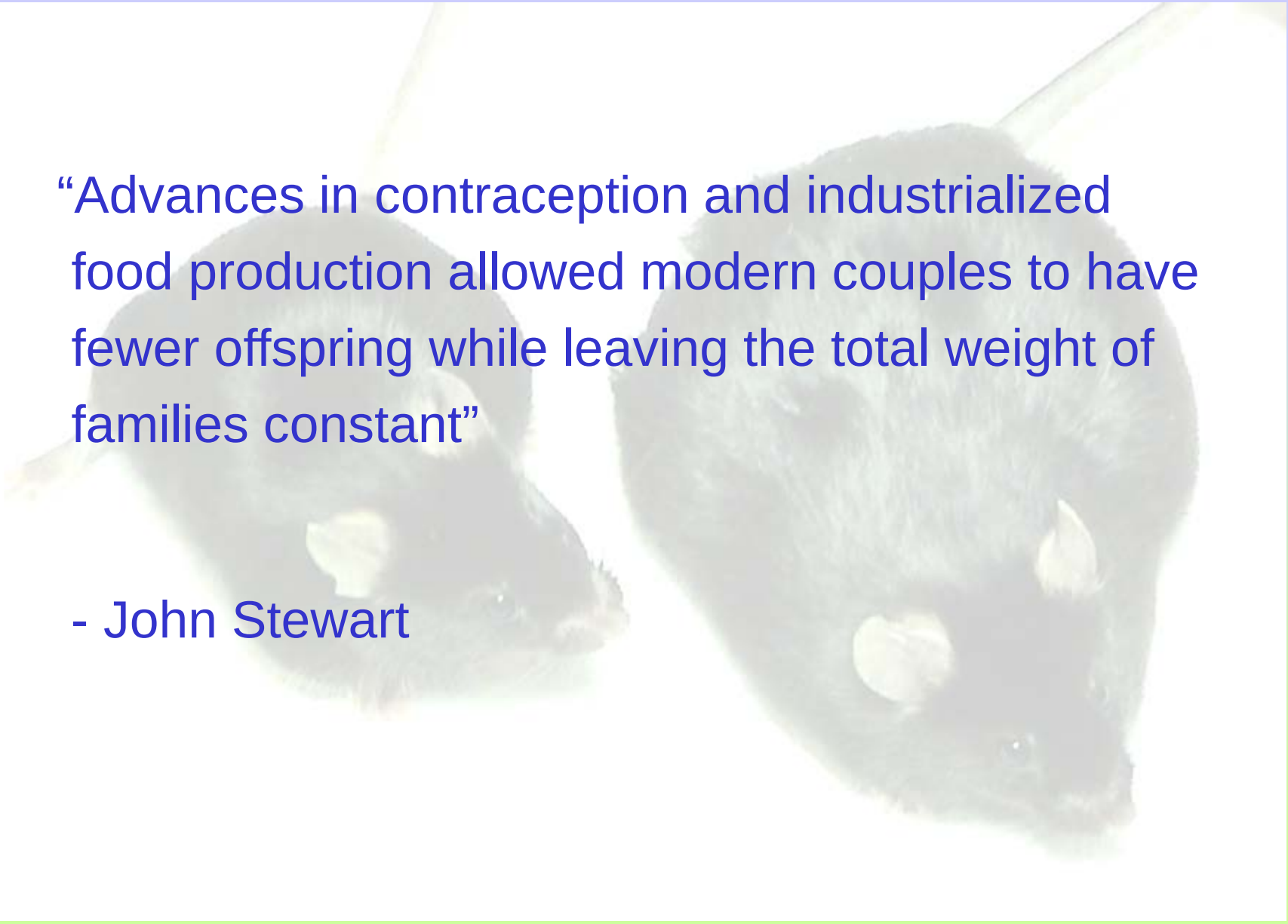


Edward Fox
Purdue University

Intraganglionic laminar endings

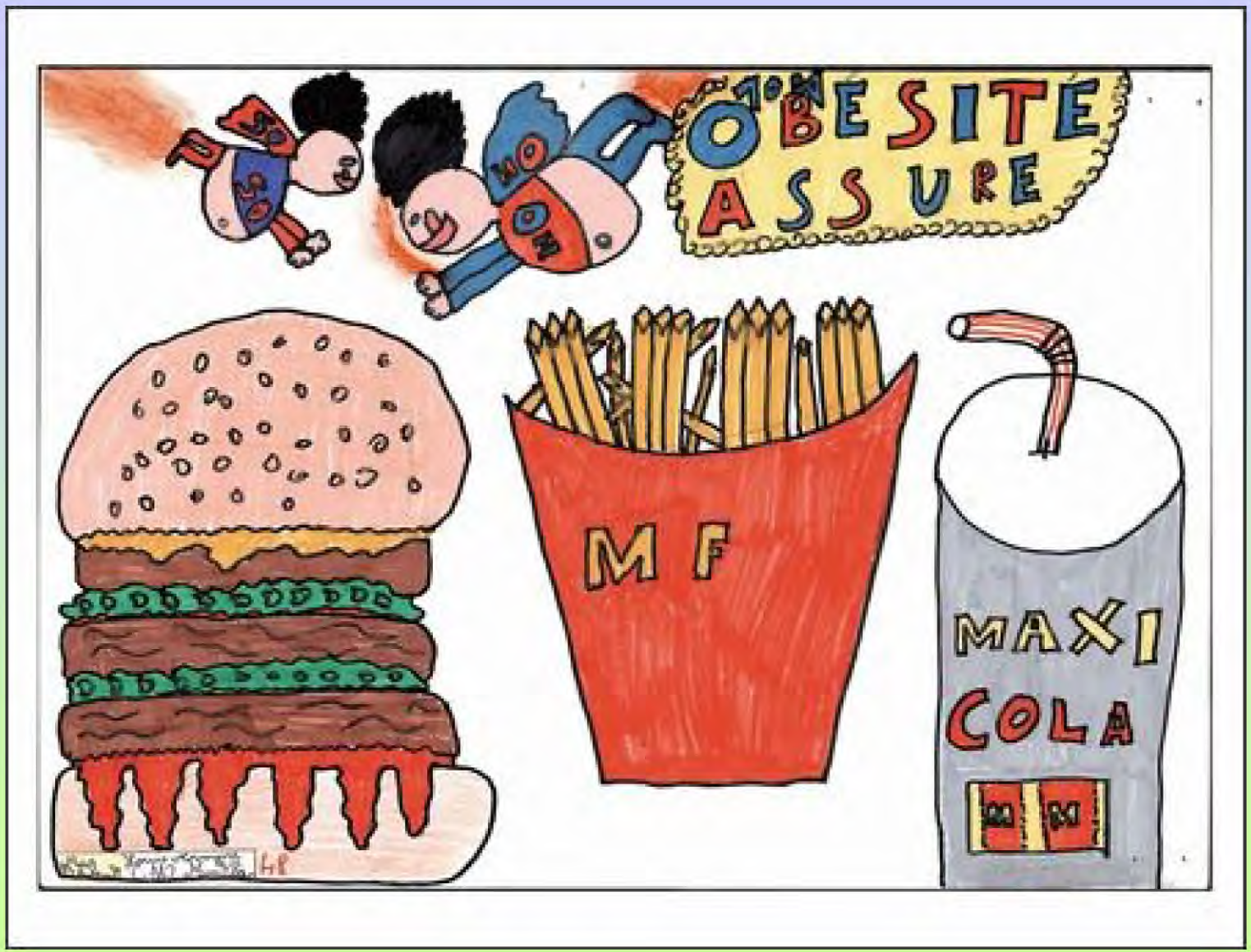
IGLEs





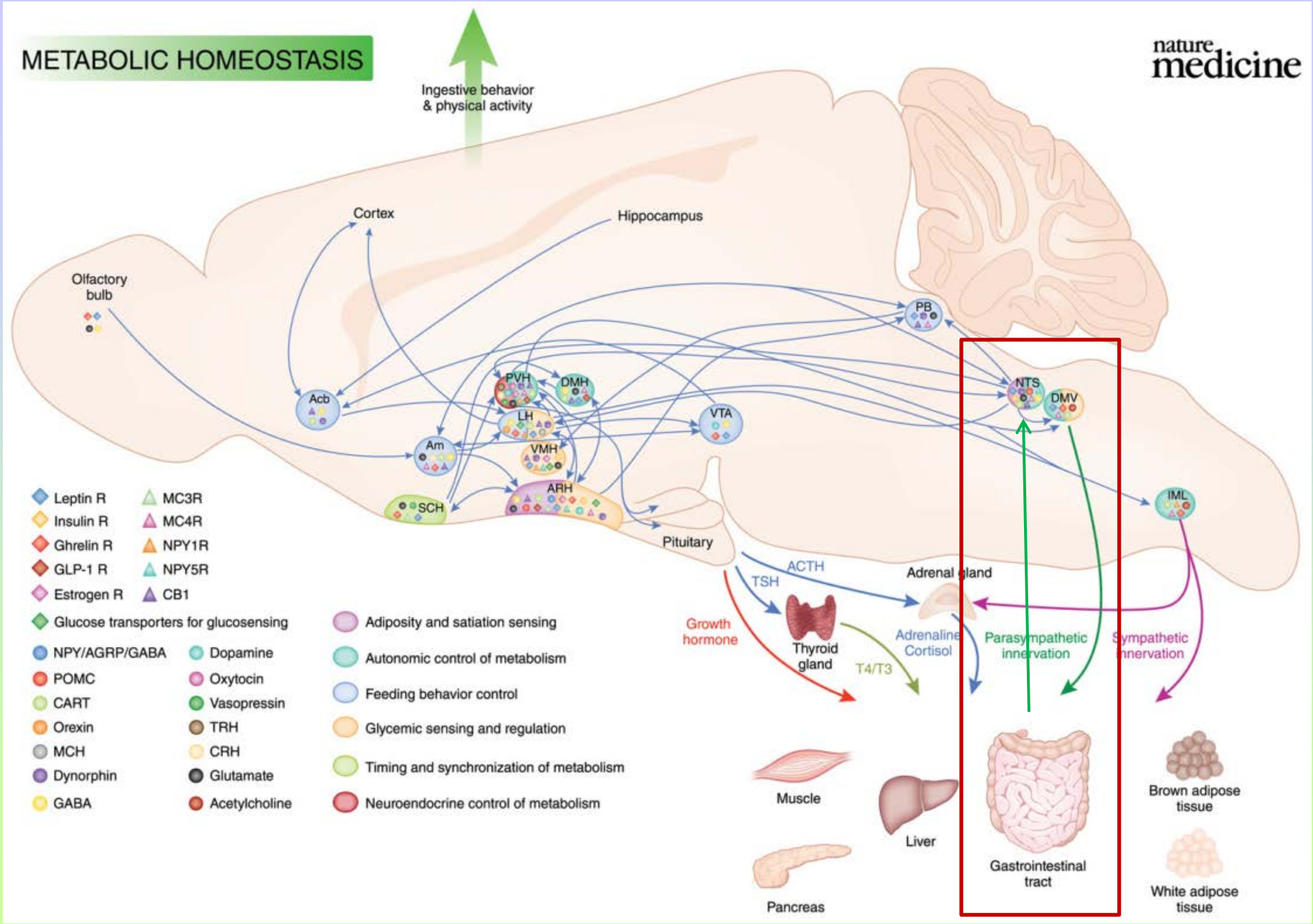
"Advances in contraception and industrialized food production allowed modern couples to have fewer offspring while leaving the total weight of families constant"

- John Stewart


OBESITE
ASSURE
MF
MAXI
COLA

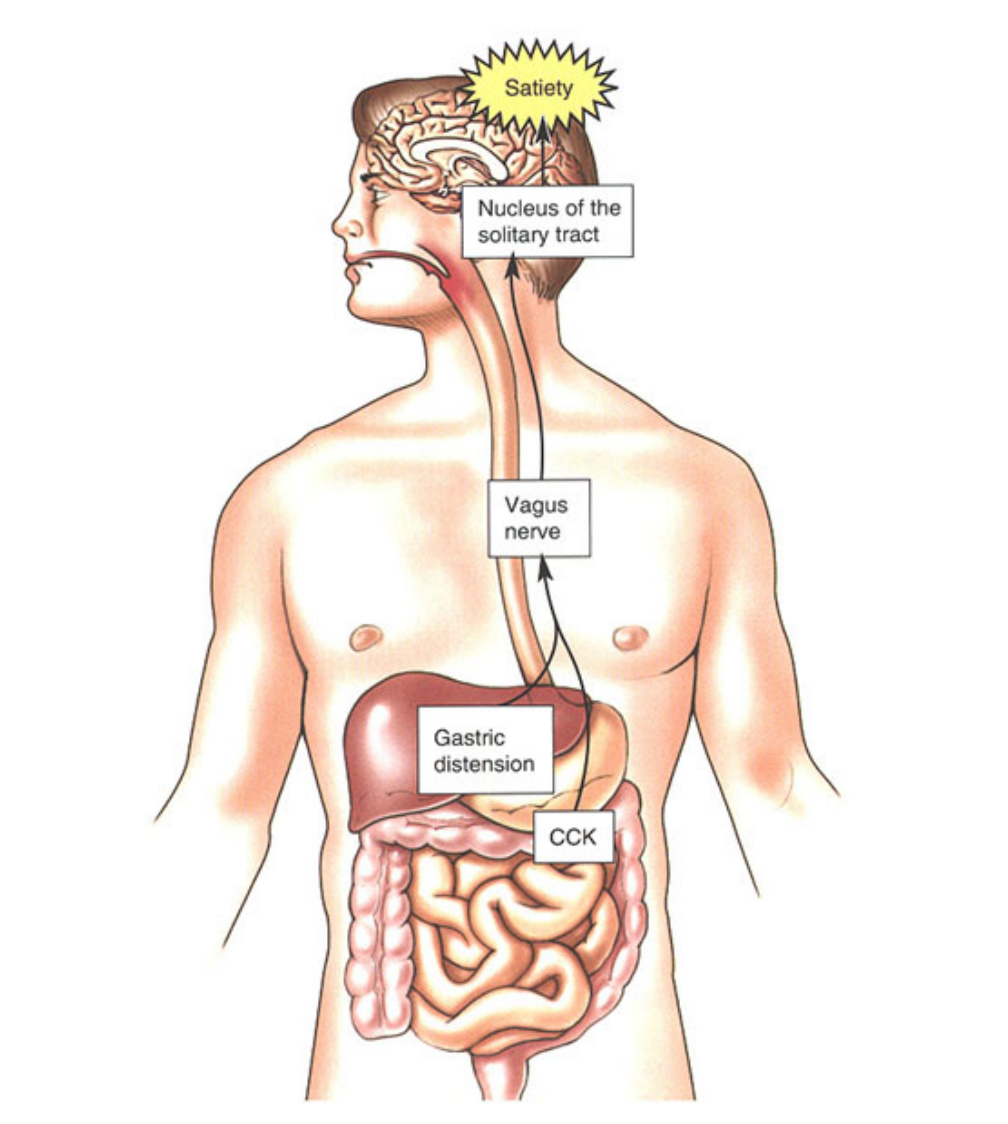
- Vagus Nerve
- Neurotrophins & Vagal GI afferents
- Neurotrophin knockouts in the GI tract

  => development of vagal GI afferents
  => feeding behavior



Yi, Zeltser, & Tschop

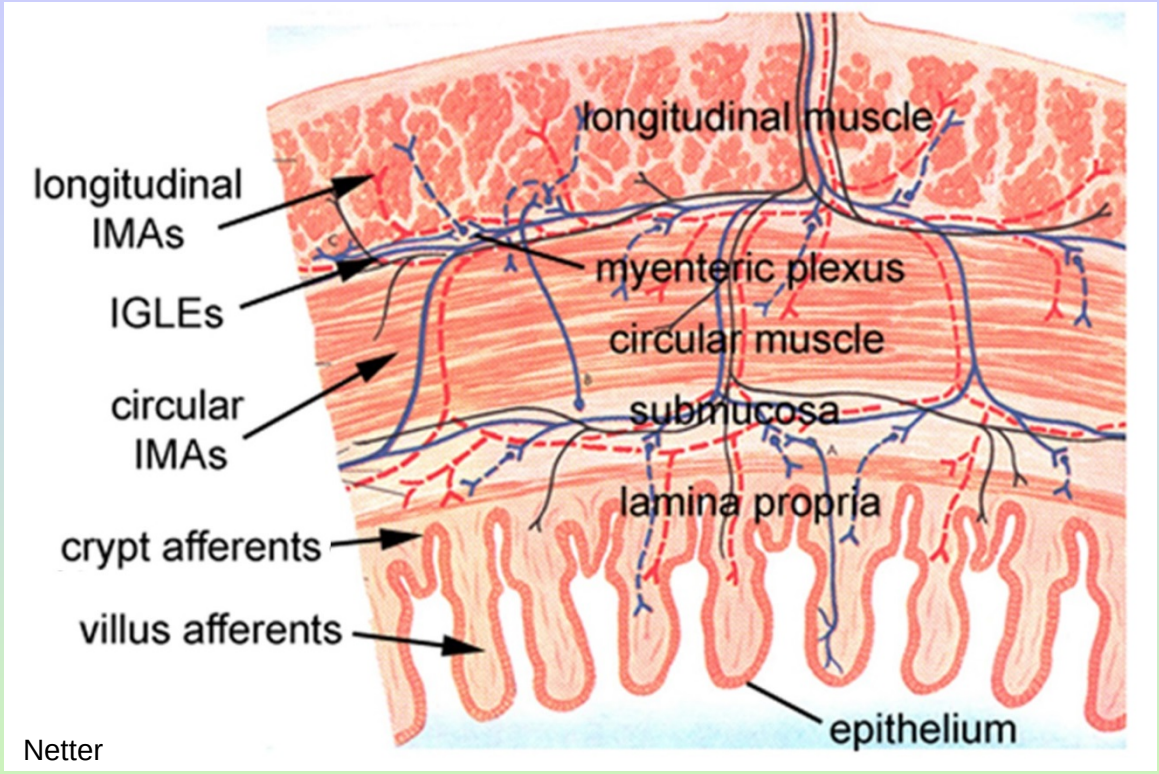
Vagal afferents signal satiation



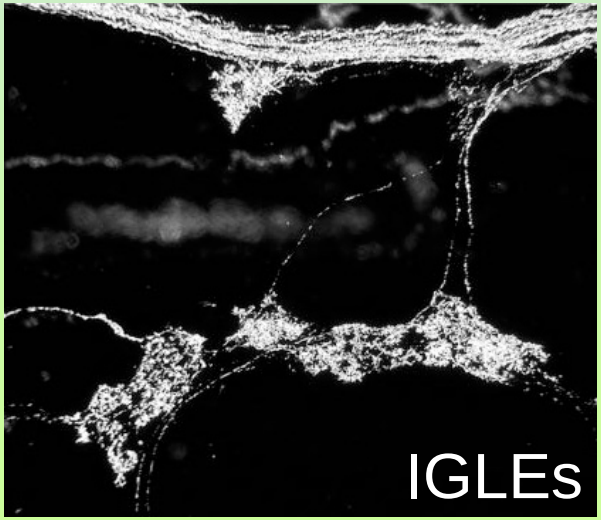
Woods et al., Science 280:1378 1998

There are many types of GI vagal afferents

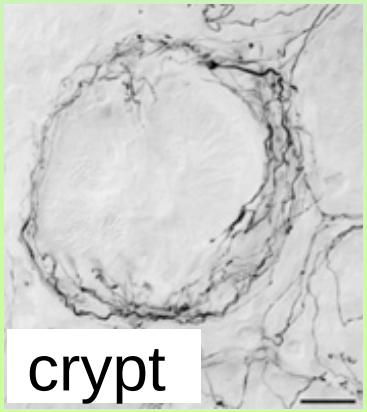
Fox et al., 2002



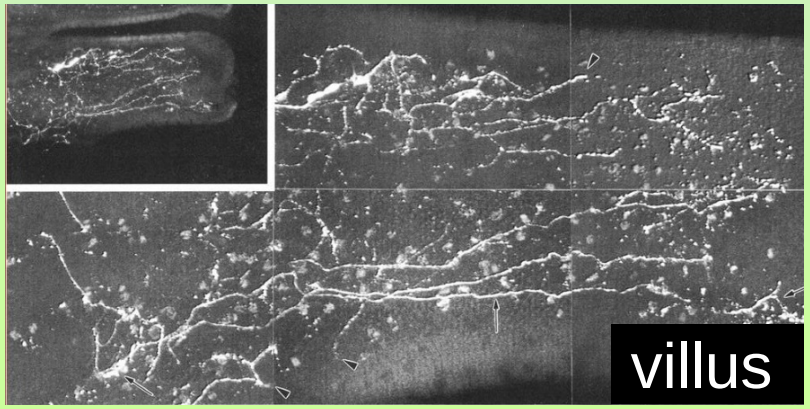
Netter



Fox et al., 2001



Powley et al., 2011

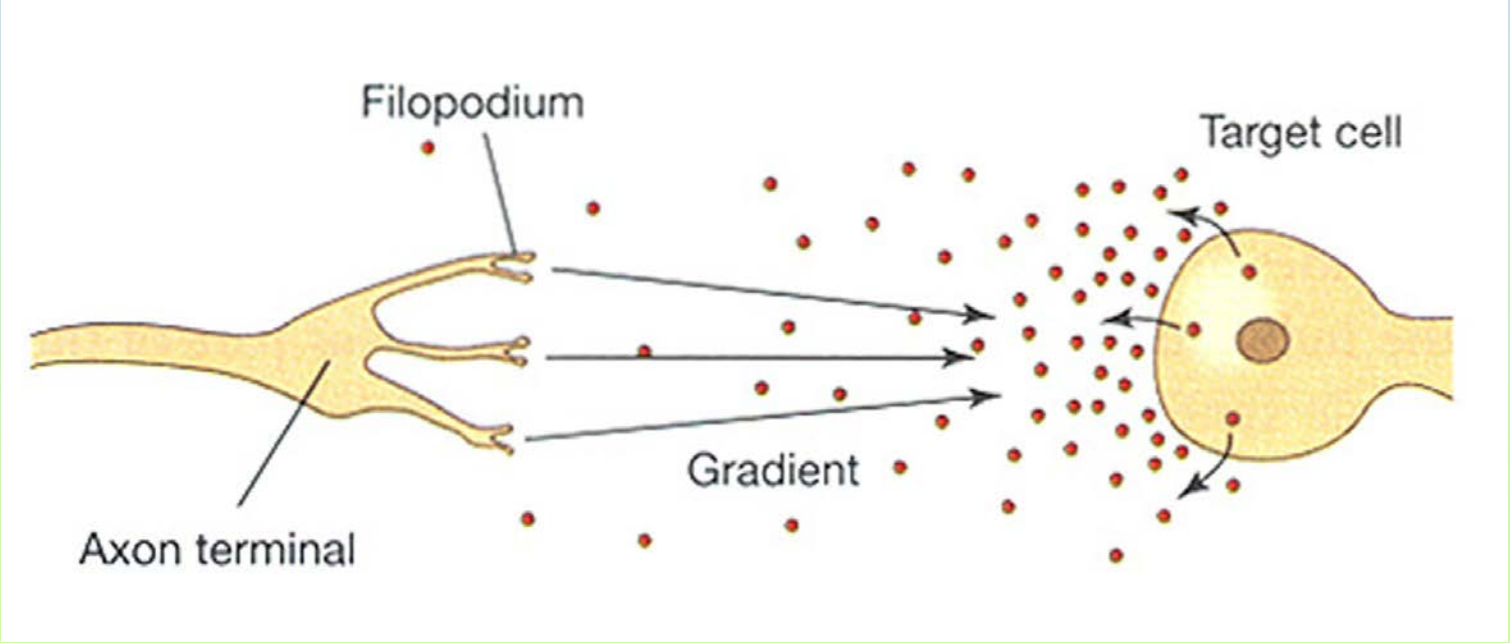


Berthoud et al., 1995

Growth factors: neuron survival

neuron differentiation

axon growth / guidance

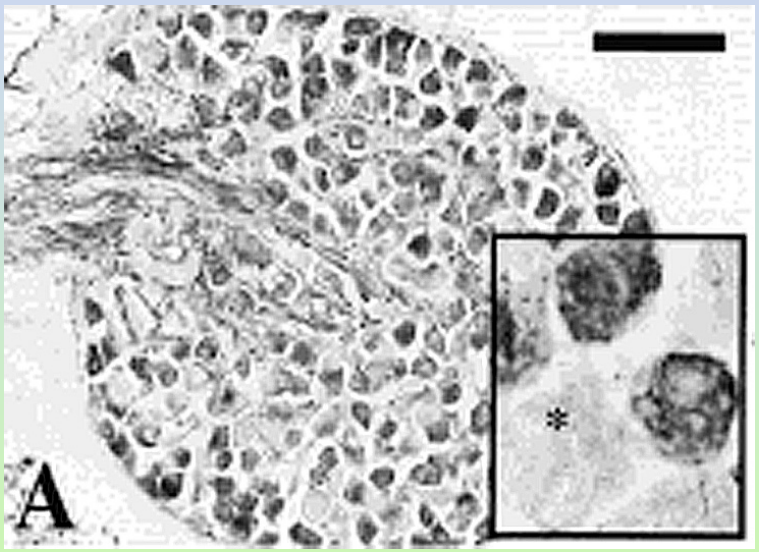


Brain-derived neurotrophic factor (BDNF)

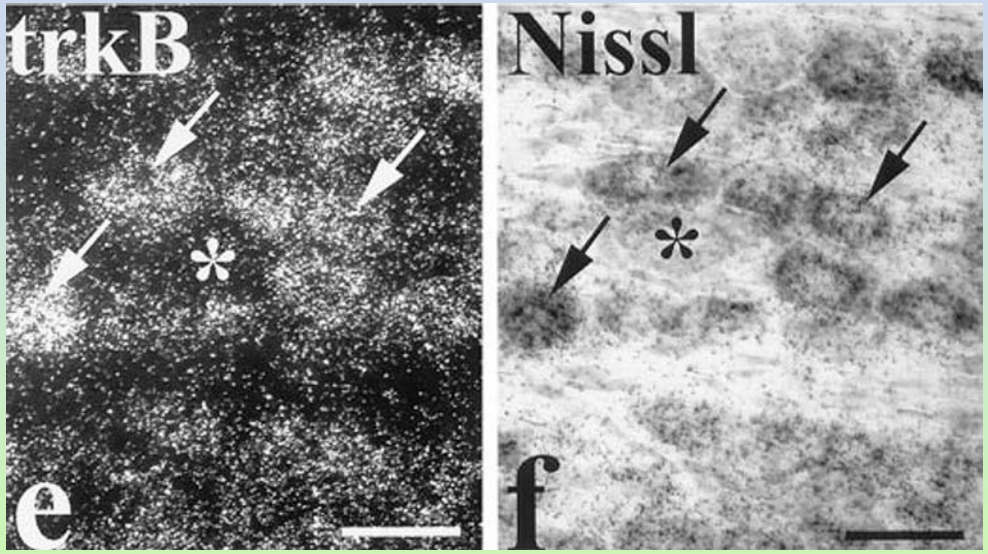
Evidence for Role in Development of Vagal Sensory Innervation of the GI Tract

TrkB is expressed in vagal sensory neurons

protein (IHC)



mRNA (ISH)

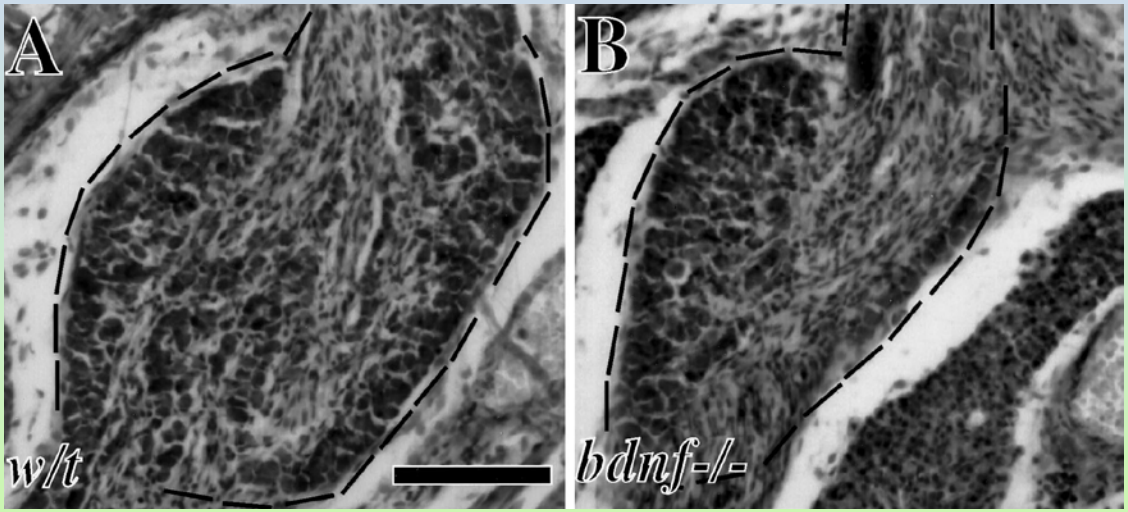


Wiklund & Ekstrom J Neurobiol, 45:142 2000

Michael & Priestley J Neurosci, 19:1844 1999

BDNF KO mice have 59% loss of vagal sensory neurons

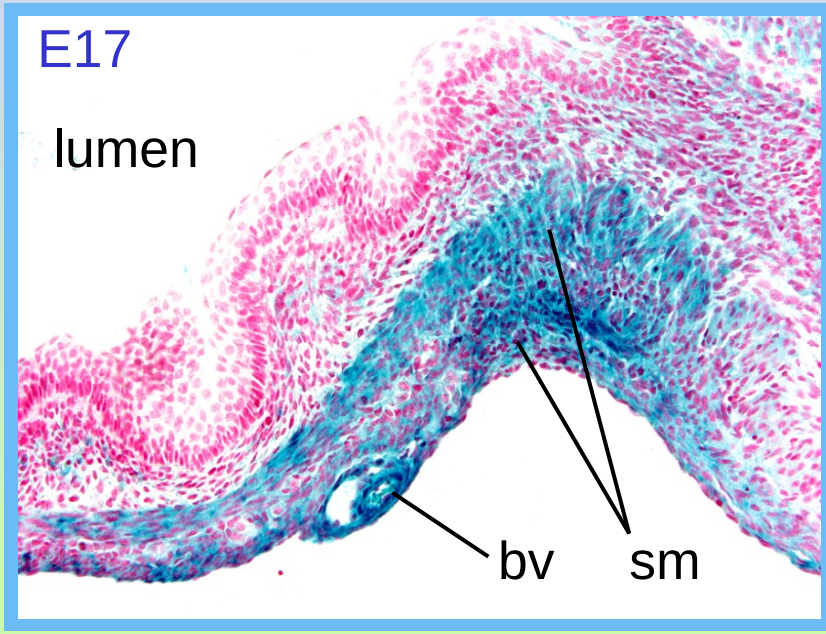
Wild type BDNF -/-



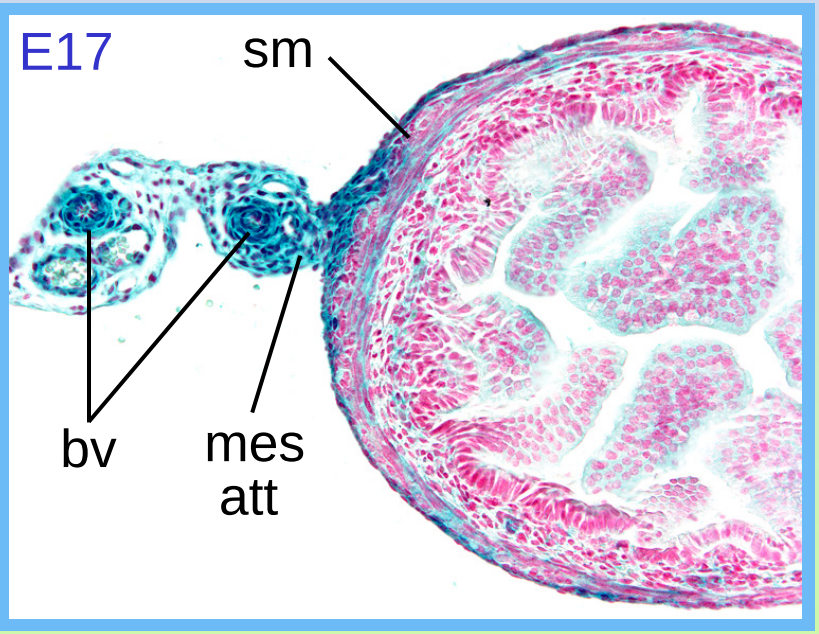
Elshamy & Ernfors J Neurosci 17: 8667 1997

BDNF is present in embryonic and early postnatal GI tract

Stomach



Intestine

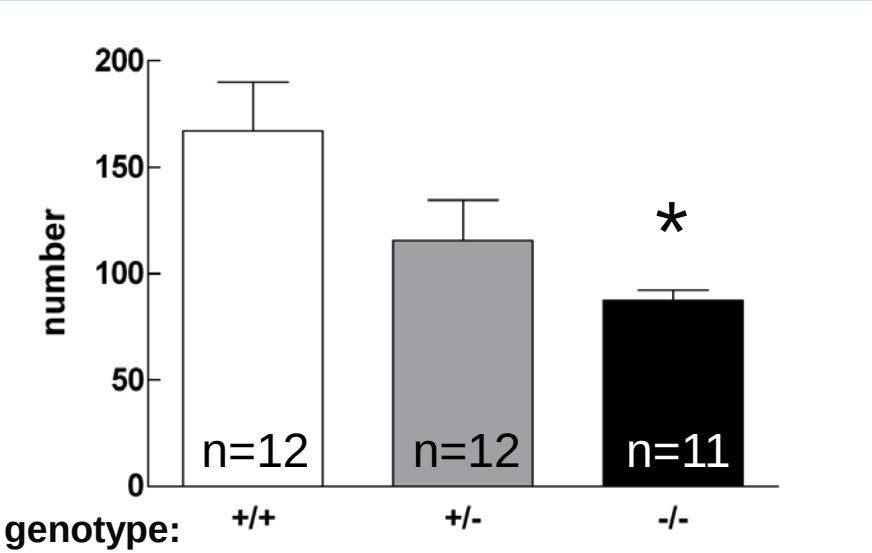


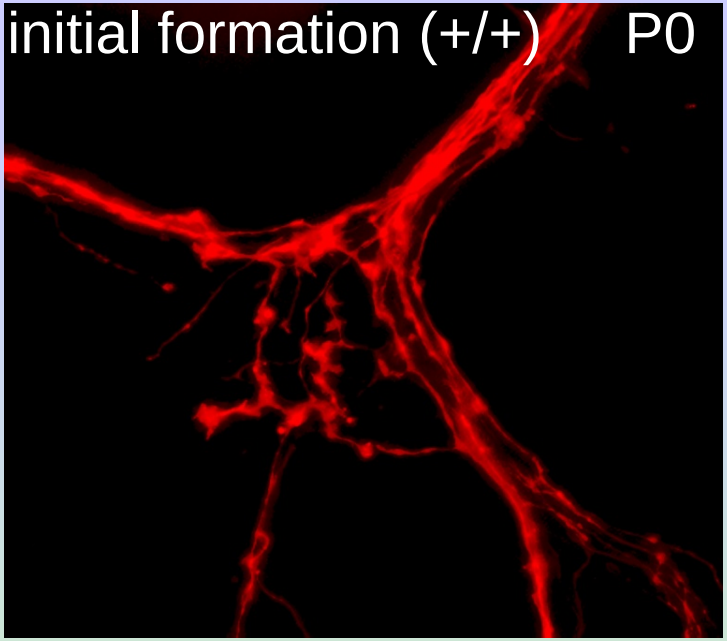
Fox & Murphy 2008

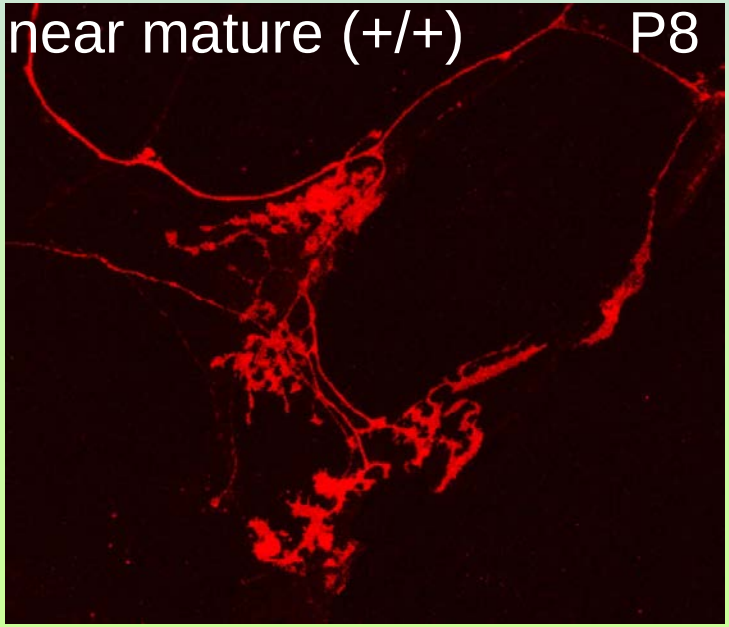
Global BDNF KO P0

→ 50% decrease

IGLE number

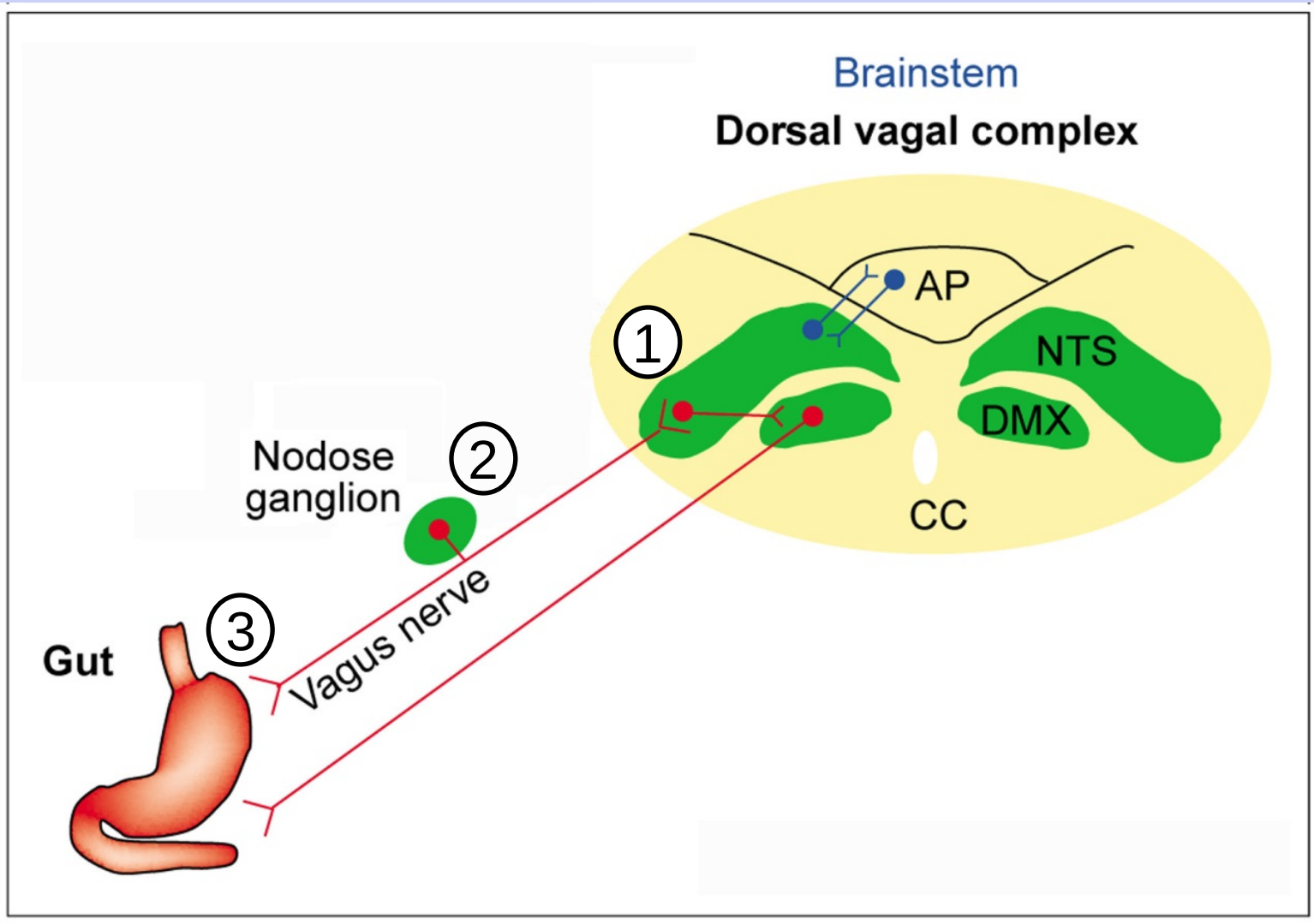






Murphy & Fox 2008

Sites of BDNF Expression that Influence Vagal Development



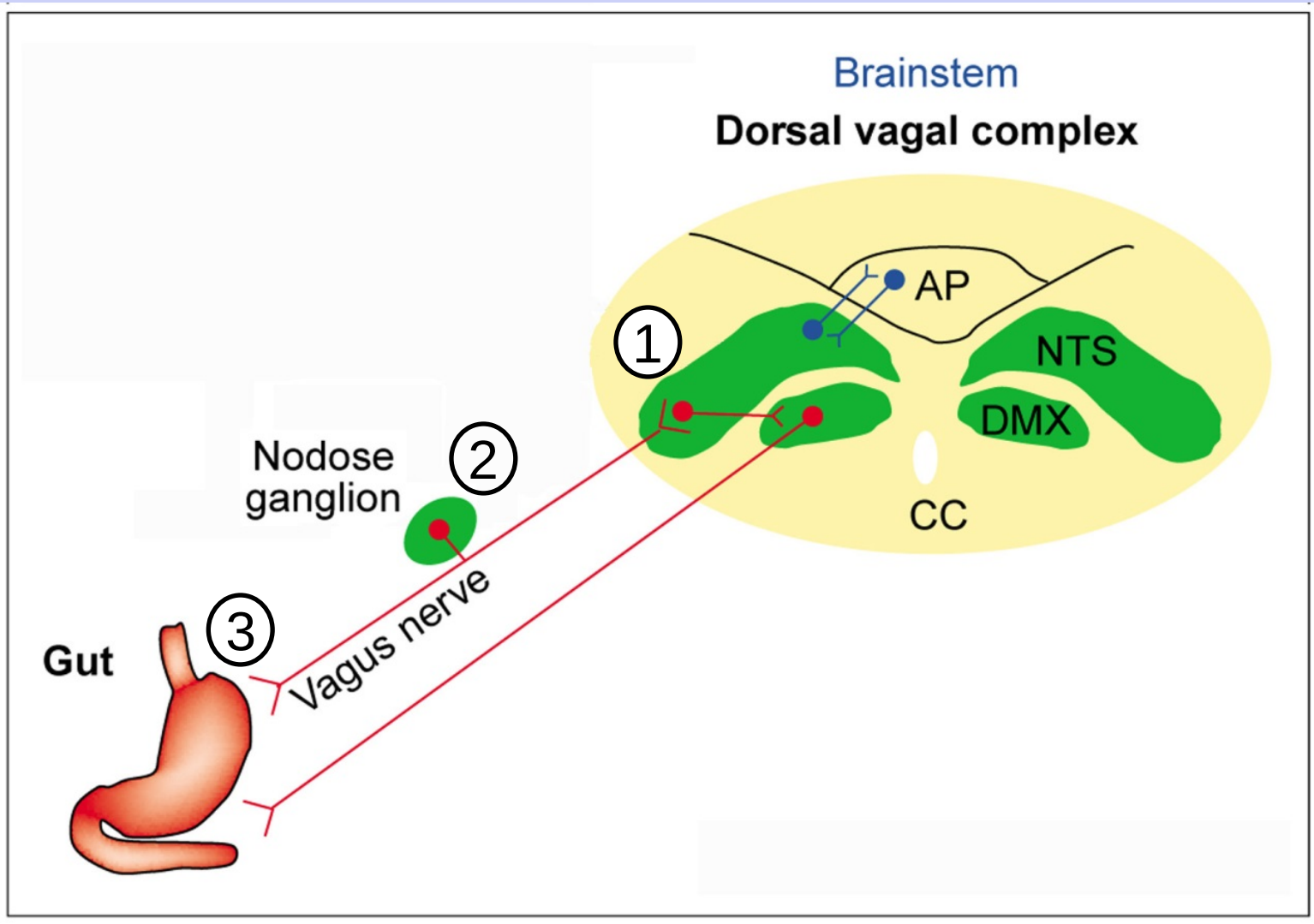
Modified from Lawrence & Luckman, Trends in Endocrinol Metabol,14, 60, 2003

Neurotrophic Hypothesis

Oppenheim 1991:

- neurons are overproduced during development
- neurons compete for limiting amounts of target-derived neurotrophic factors
- neurotrophic factors support neuron survival by preventing apoptosis

Sites of BDNF Expression that Influence Vagal Development

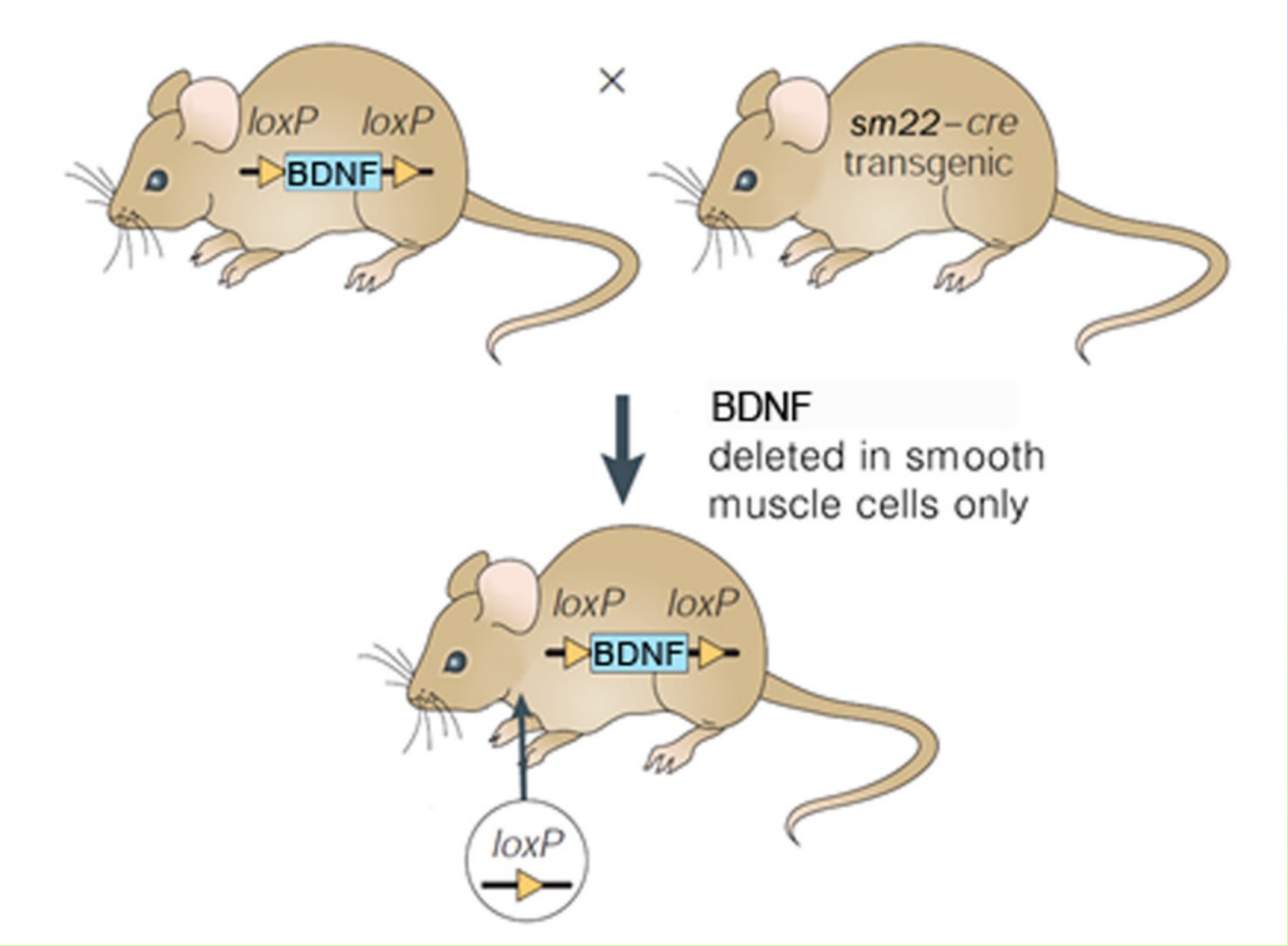


Modified from Lawrence & Luckman, Trends in Endocrinol Metabol,14, 60, 2003

Predictions: SM-BDNF KO Effects

- decreased numbers of vagal sensory neurons
- decreased survival of IGLE innervation of GI tract
- decreased vagal satiation signaling (increased meal size)

Smooth-muscle specific *BDNF* KO



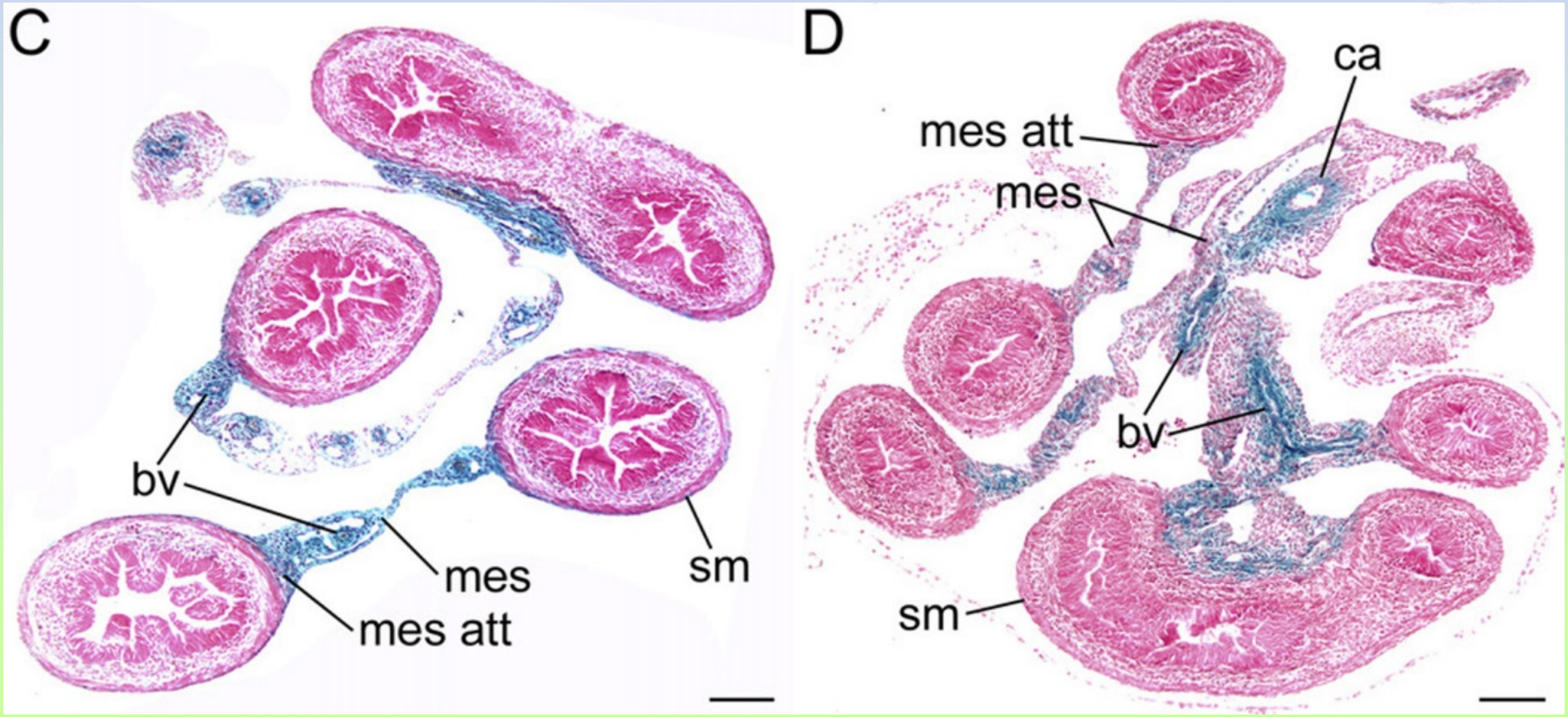
Modified from Mak et al., Nat Rev Immunol, 1:11 2001

BDNF Expression Compared with SM-BDNF KO

INTESTINE (E14-15)

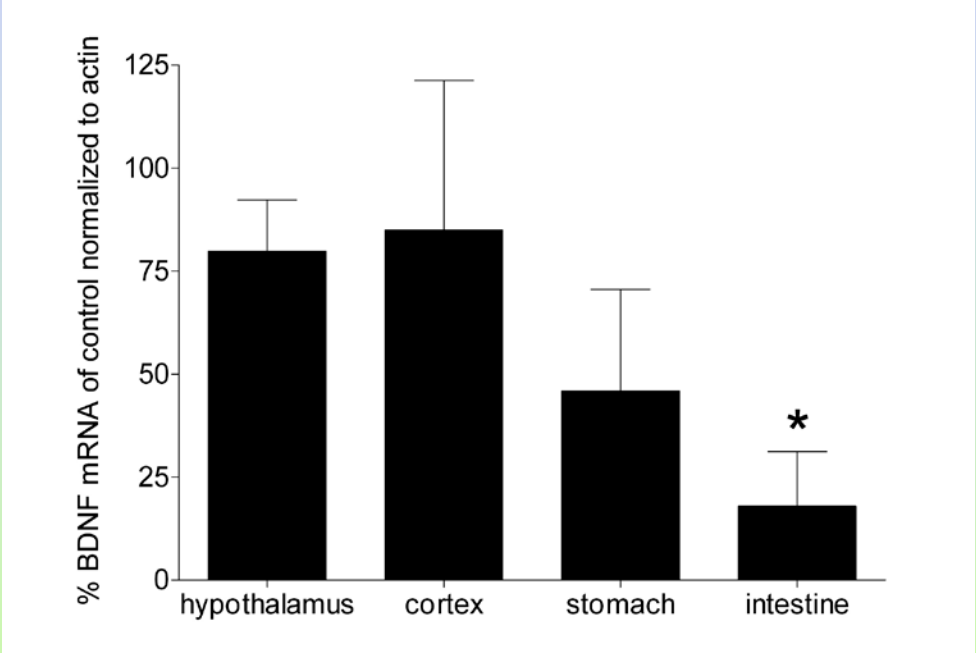
BDNF Expression

SM-BDNF KO



Fox et al., Neurosci 229, 176, 2013

SM-BDNF KO Reduced BDNF mRNA in the Intestine

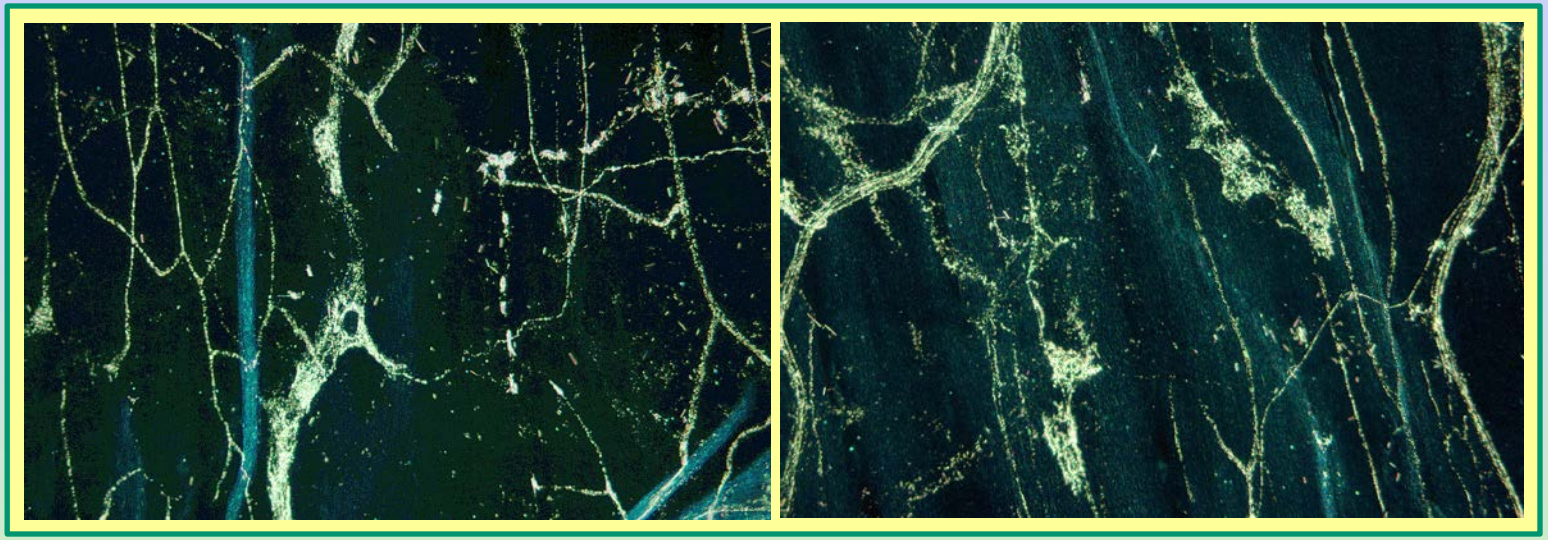


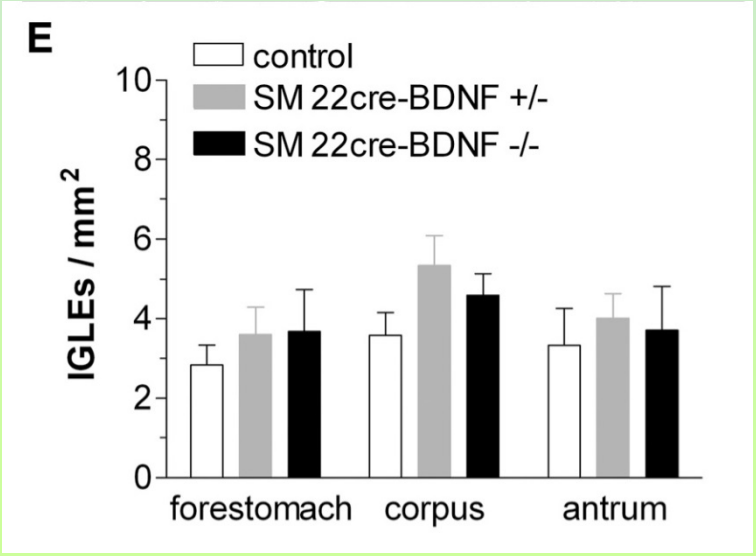
Biddinger & Fox, J Neurosci 34, 10379, 2014

SM-BDNF KO does not Alter Gastric IGLEs

control

SM-BDNF KO



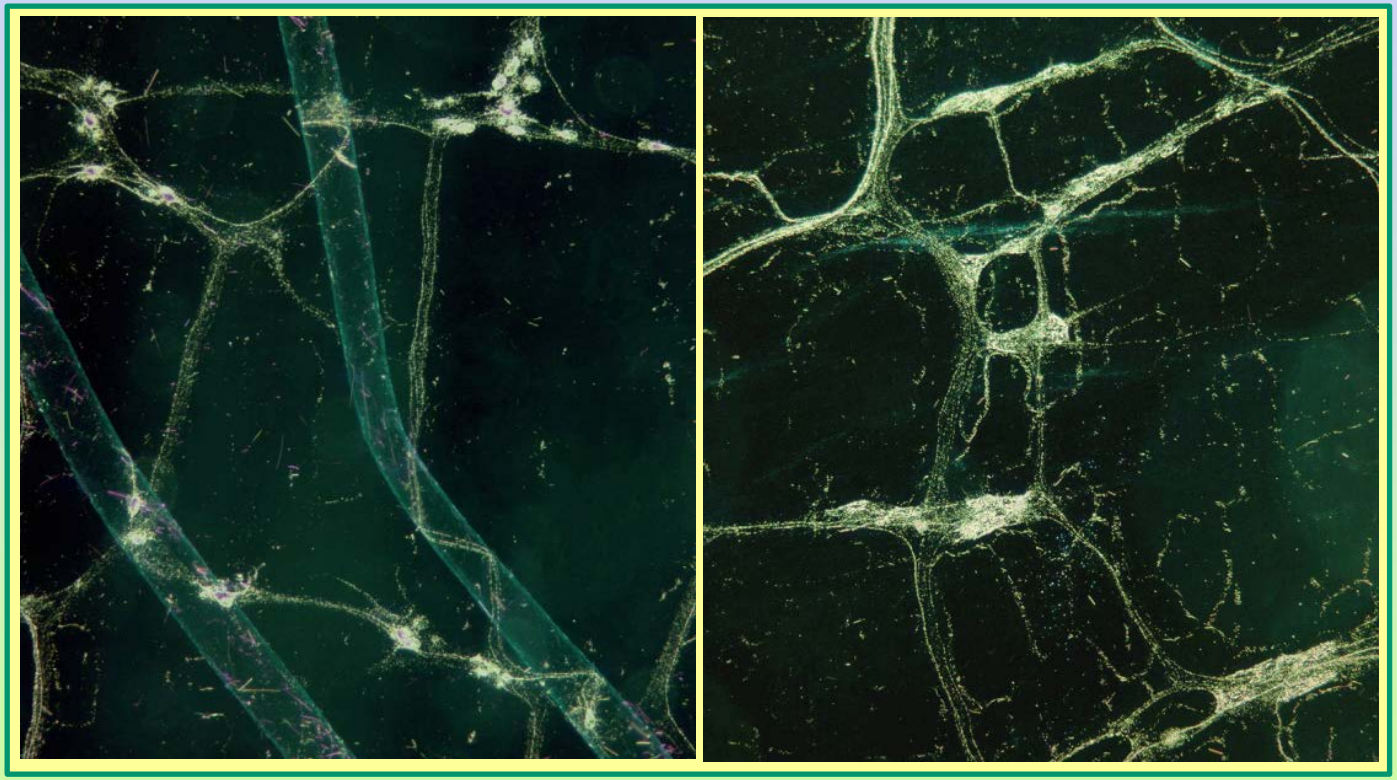


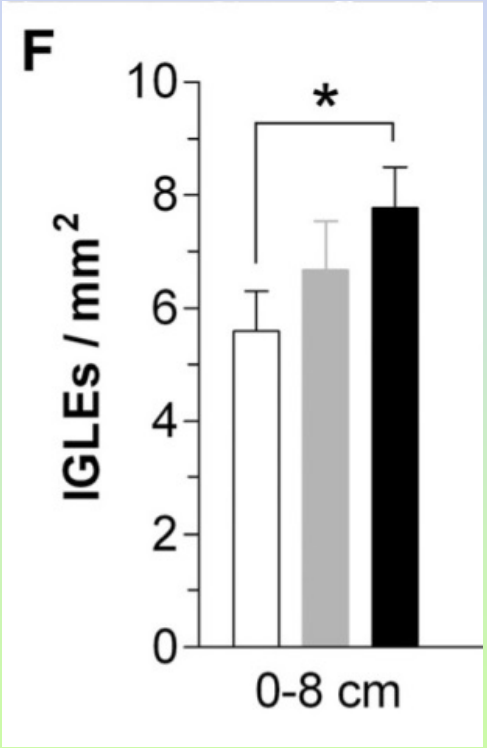
Biddinger & Fox, J Neurosci 34, 10379, 2014

SM-BDNF KO Increases Intestine IGLE Density

control

SM-BDNF KO

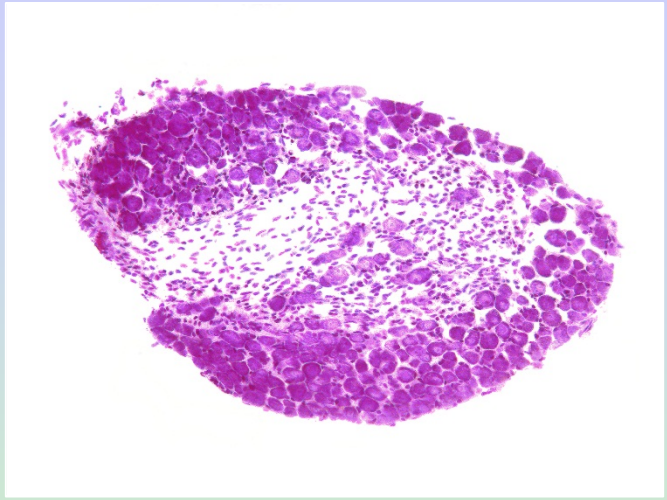




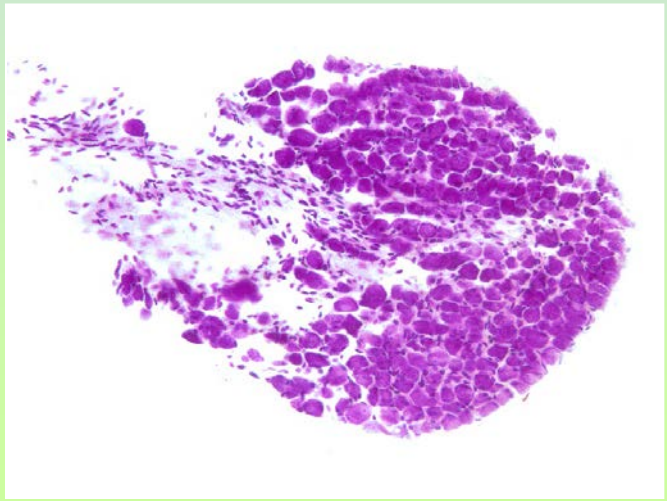
Biddinger & Fox, J Neurosci 34, 10379, 2014

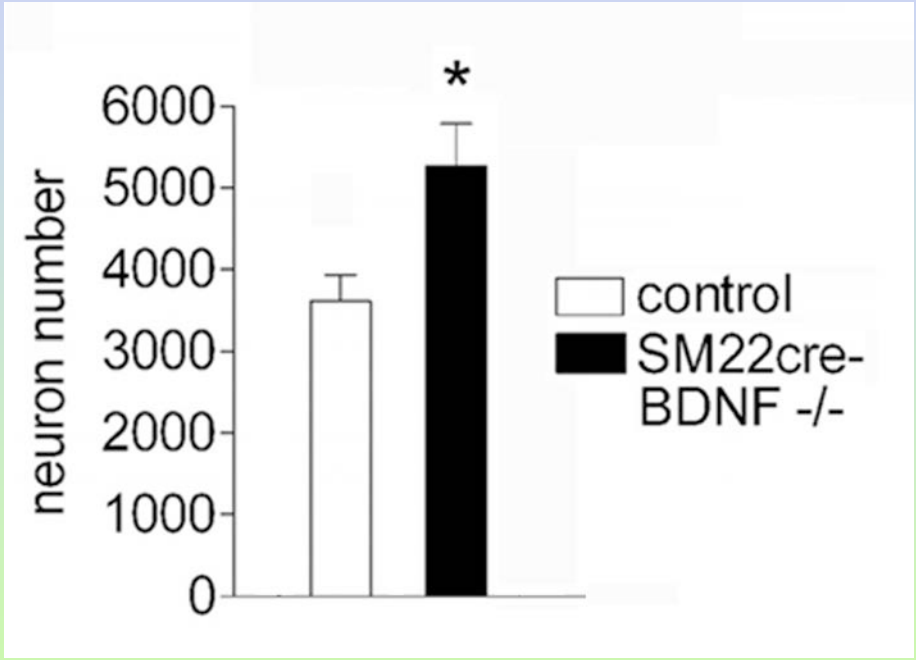
SM-BDNF KO Increases Vagal Sensory Neuron Number

Control



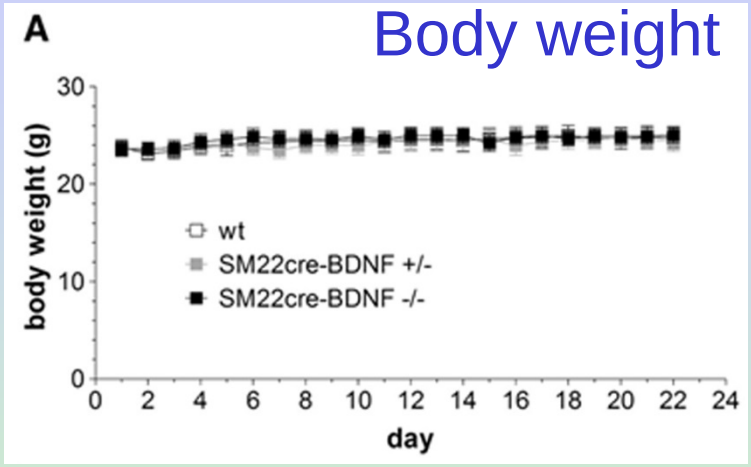
SM-BDNF KO

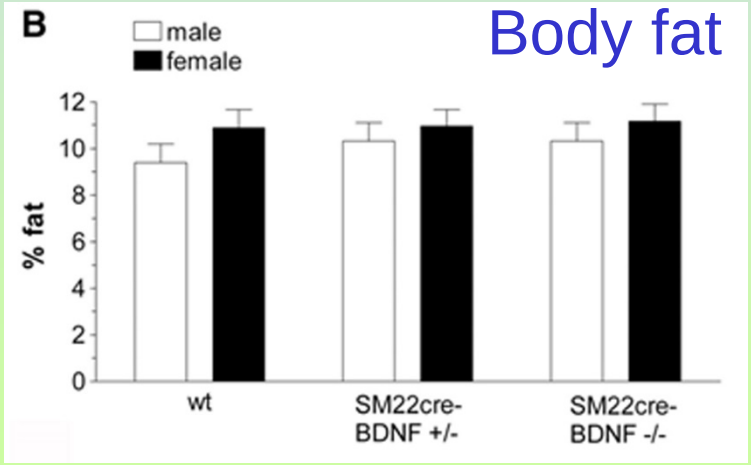


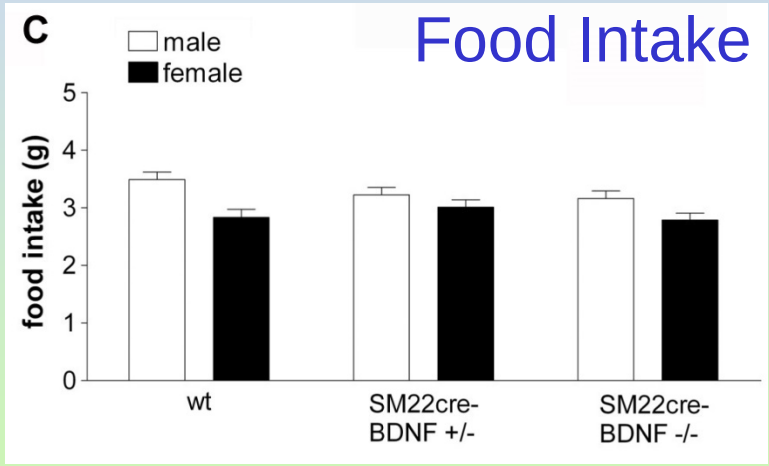


Biddinger & Fox, J Neurosci 34, 10379, 2014

SM-BDNF KO has No Effect on Body Weight or Daily Food Intake



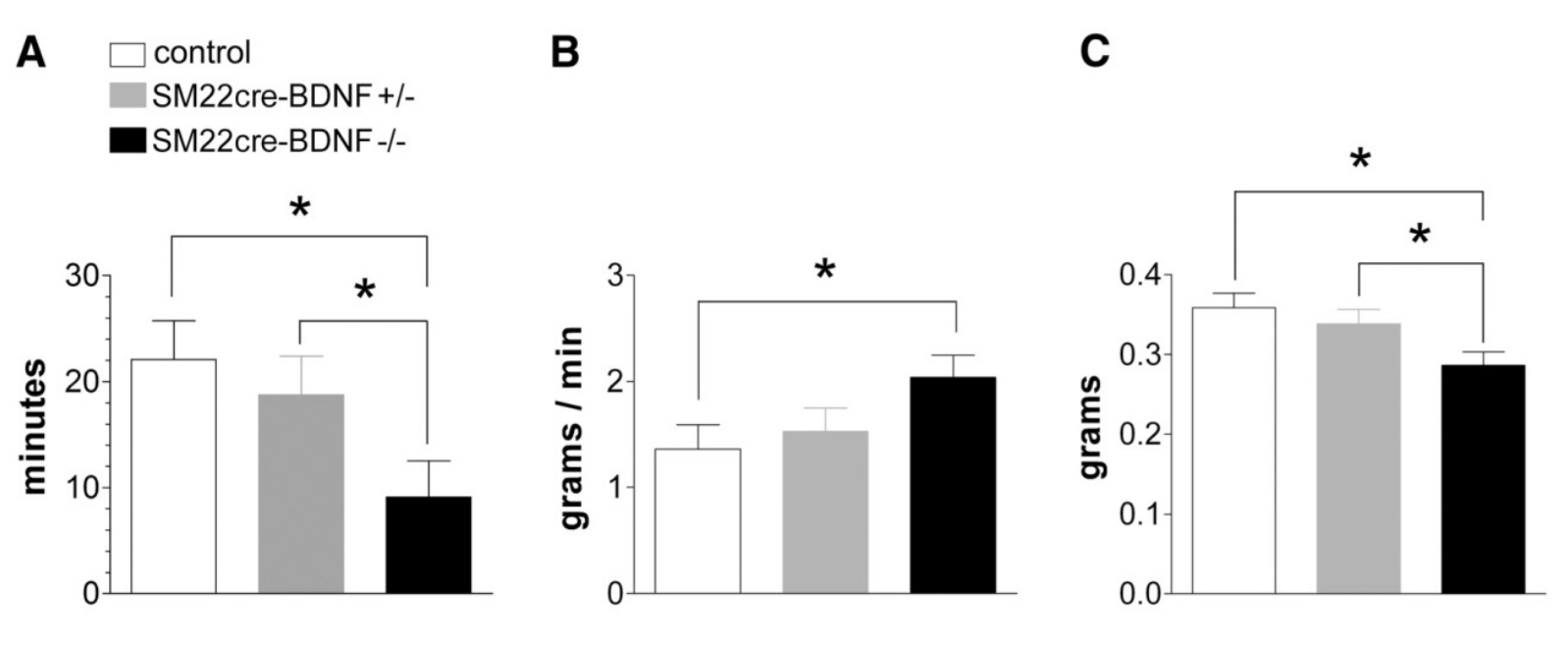




Biddinger & Fox, J Neurosci 34, 10379, 2014

SM-BDNF KO Reduces Meal Duration and Meal size

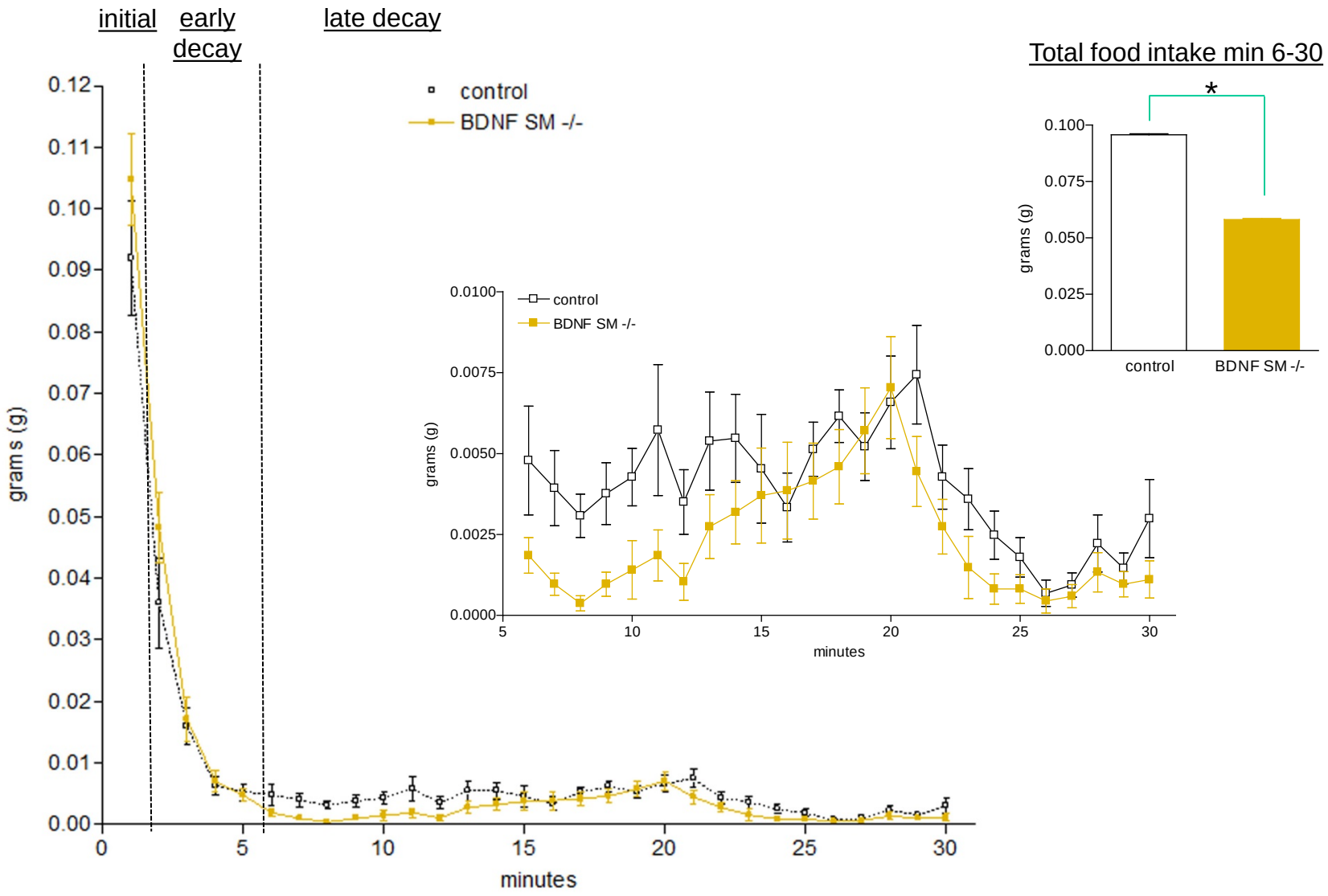
=> Suggests Increased Satiation Signaling



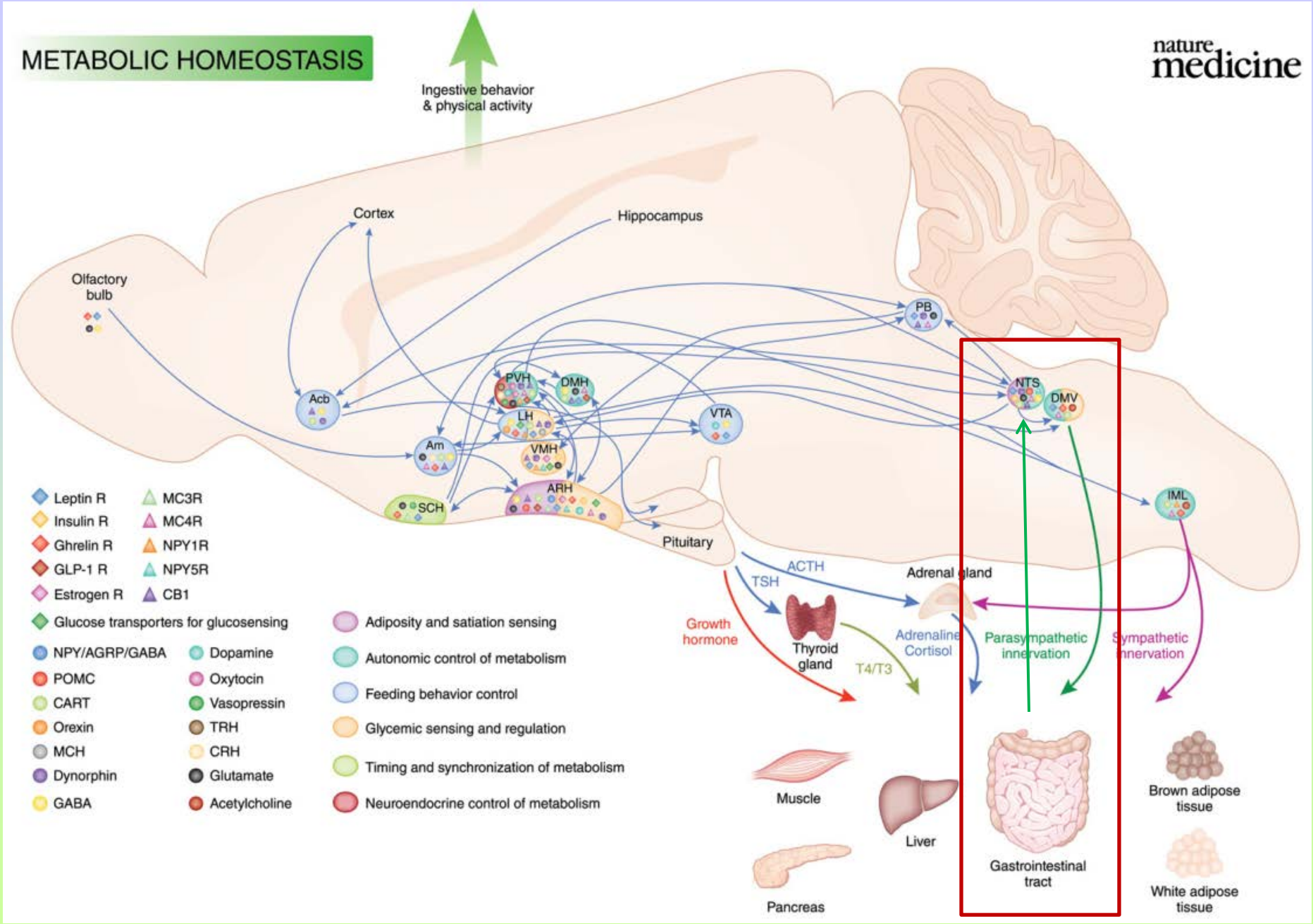
meal duration eating rate meal size

Biddinger & Fox, J Neurosci 34, 10379, 2014

SM-BDNF KO Increases Suppression of Feeding
=> Consistent with Increased Satiation Signaling



Biddinger & Fox, J Neurosci 34, 10379, 2014



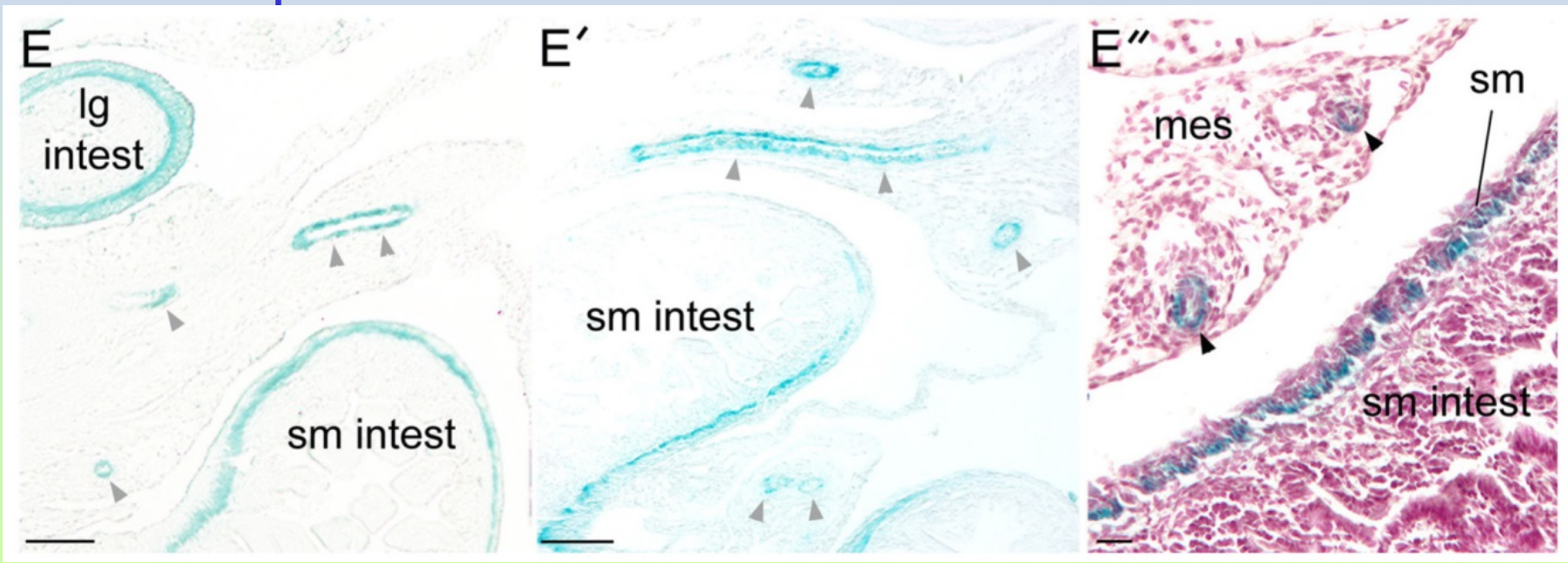
Yi, Zeltser, & Tschop

Summary: SM-BDNF KO Effects

- increased intestinal IGLE innervation
- meal analyses suggest increased satiation signaling
- increased numbers of vagal sensory neurons
  - suggests BDNF in GI smooth muscle normally decreases survival of IGLEs
  - not consistent with neurotrophic hypothesis
  - may be mediated by BDNF activation of trkB-p75

NT-3 Expression Compared with SM-NT-3 KO Mesenteric Blood Vessels

NT-3 Expression SM-NT-3 KO SM-NT-3 KO



(E15-17)

Fox et al., Am J Physiol 305, R1307, 2013

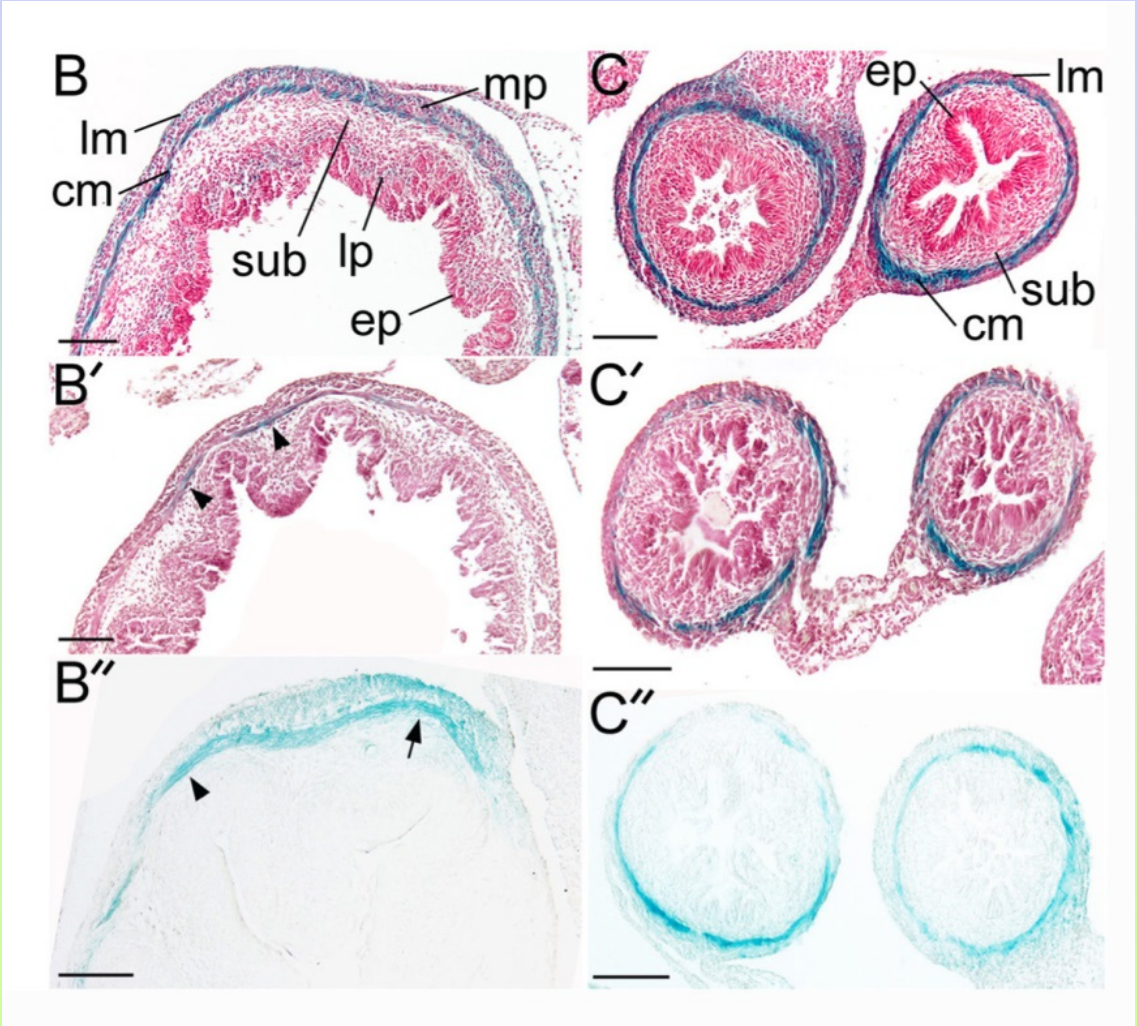
NT-3 Expression Compared with SM-NT-3 KO

(E15-17) stomach intestine

NT-3 Expression

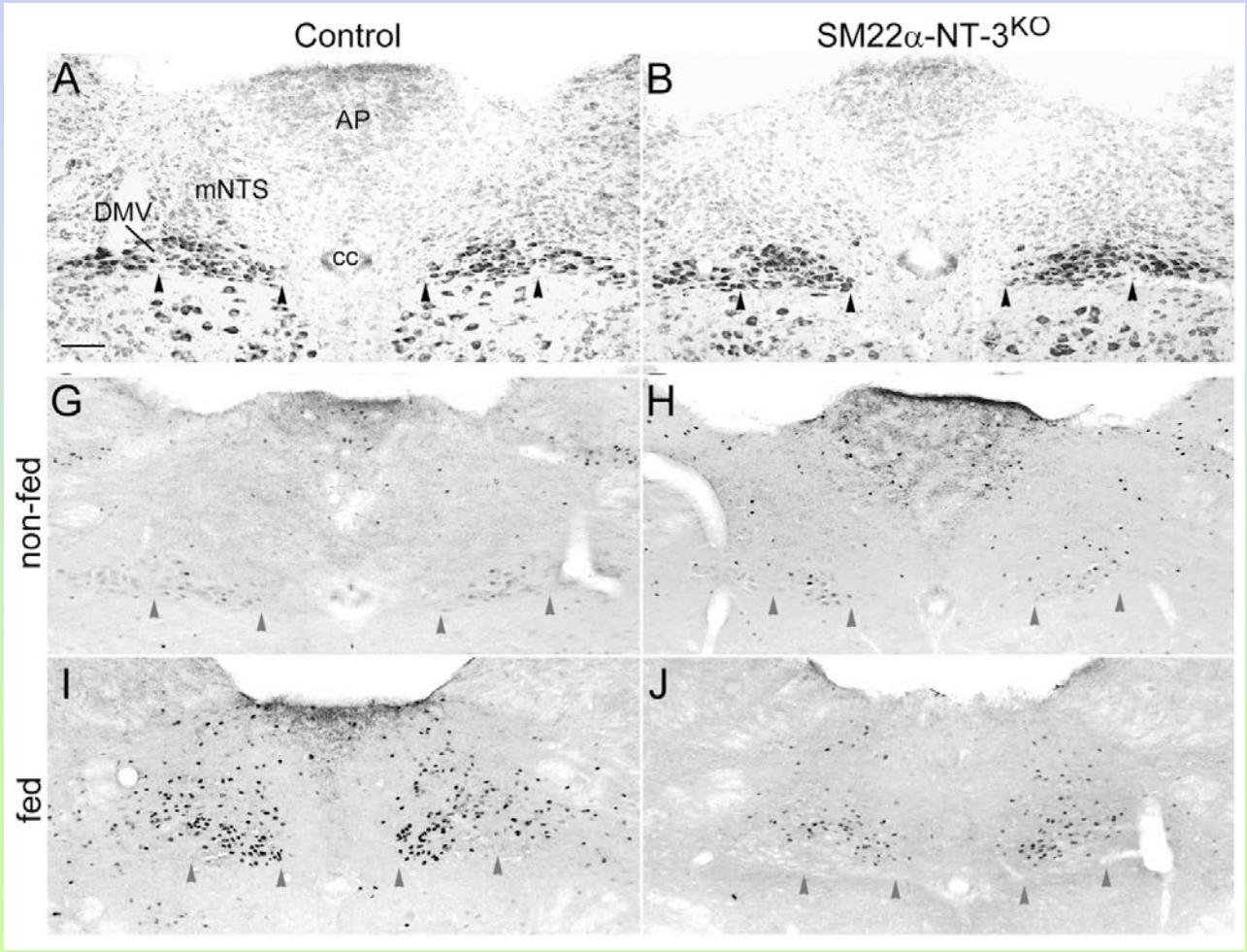
SM-NT-3 KO

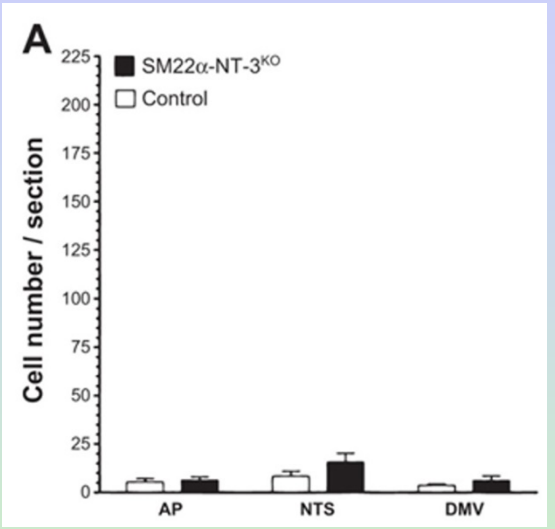
SM-NT-3 KO

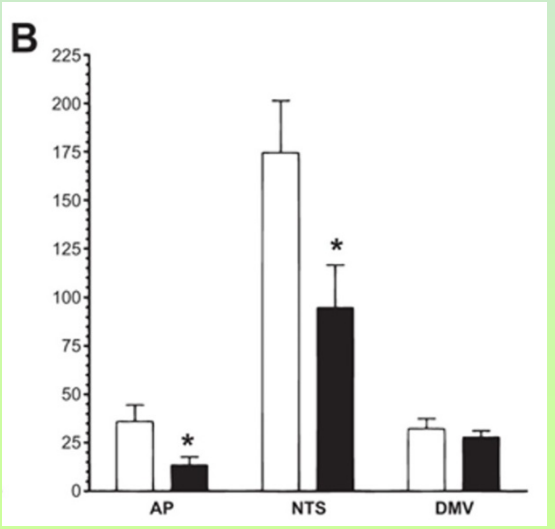


Fox et al., Am J Physiol 305, R1307, 2013

SM-NT-3 KO Reduces Vagal Activation by Consumption of a Large Meal

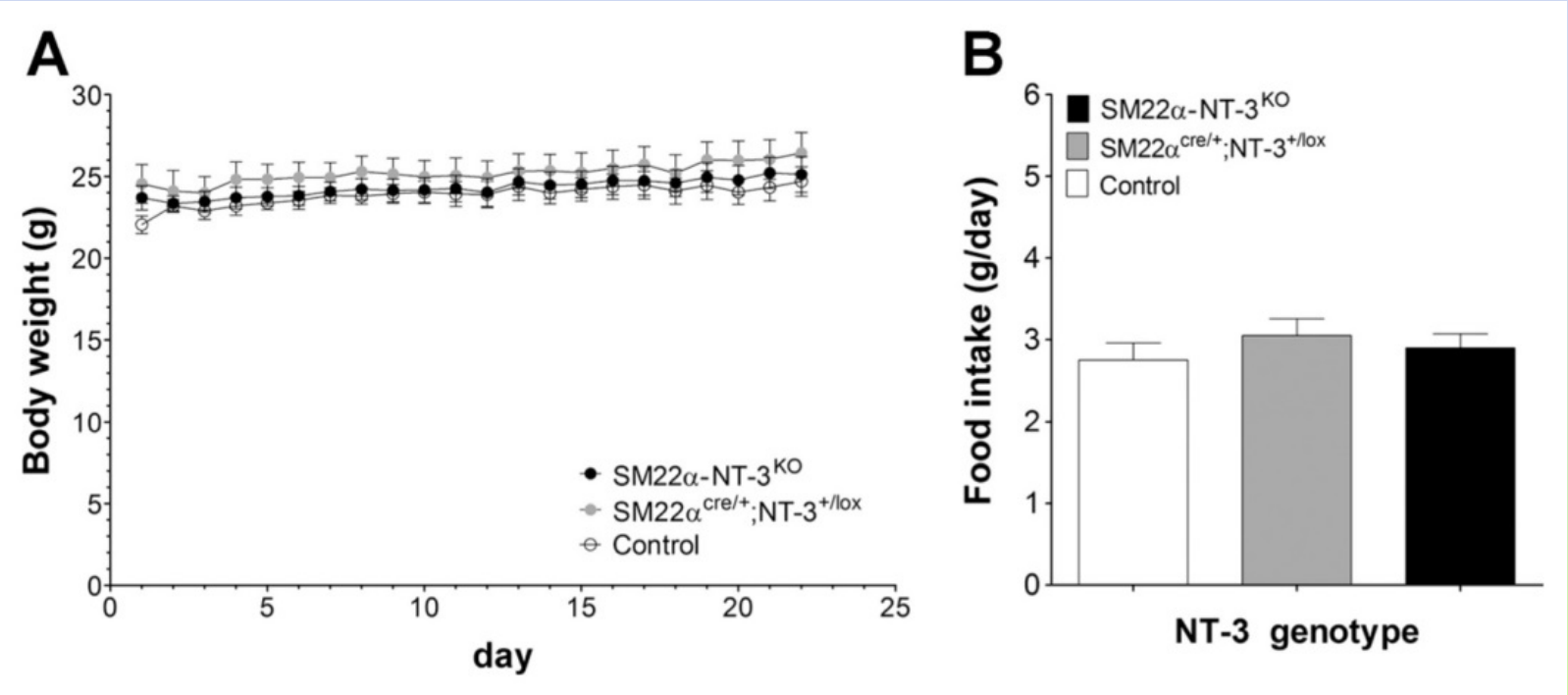






Fox et al., Am J Physiol 305, R1307, 2013

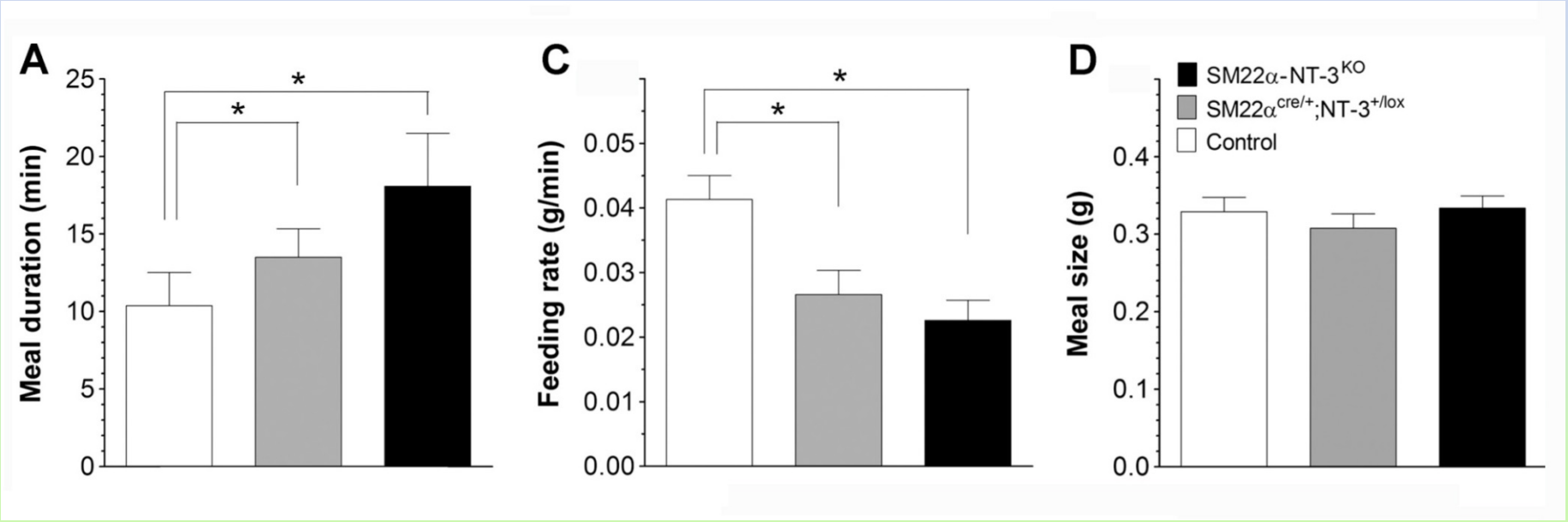
SM-NT-3 KO has no Effect on Body Weight or Daily Food Intake



Fox et al., Am J Physiol 305, R1307, 2013

SM-NT-3 KO Increases Meal Duration

=> Suggests Decreased Satiation Signaling

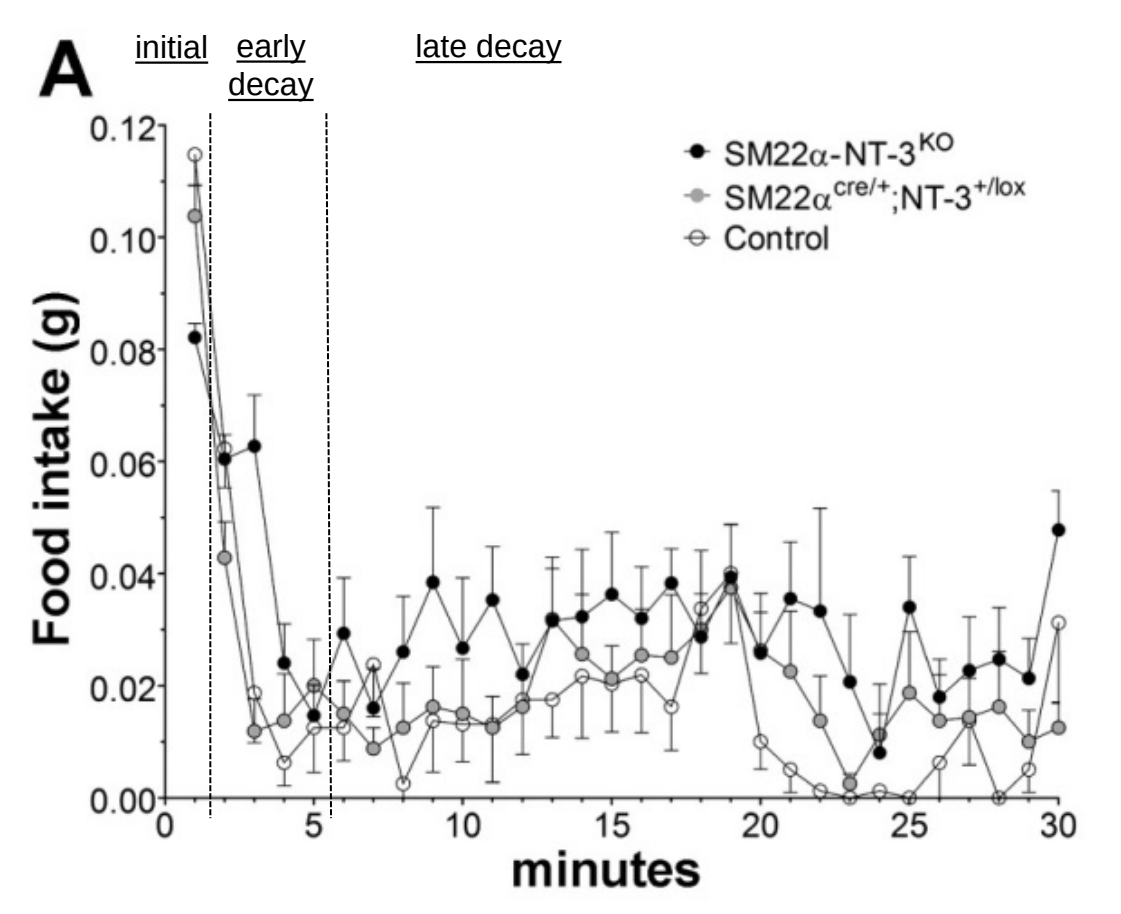


meal duration eating rate meal size

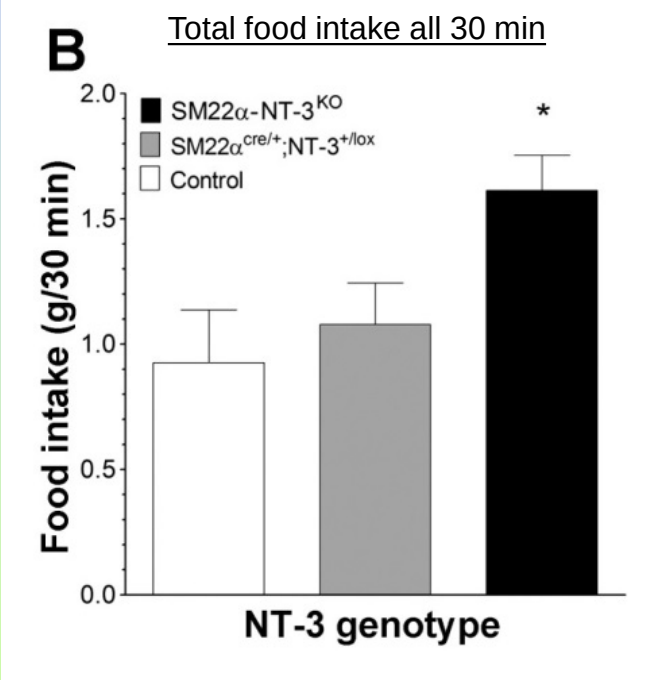
Fox et al., Am J Physiol 305, R1307, 2013

SM-NT-3 KO Reduces Suppression of Feeding

=> Consistent with Decreased Satiation Signaling



eating rate



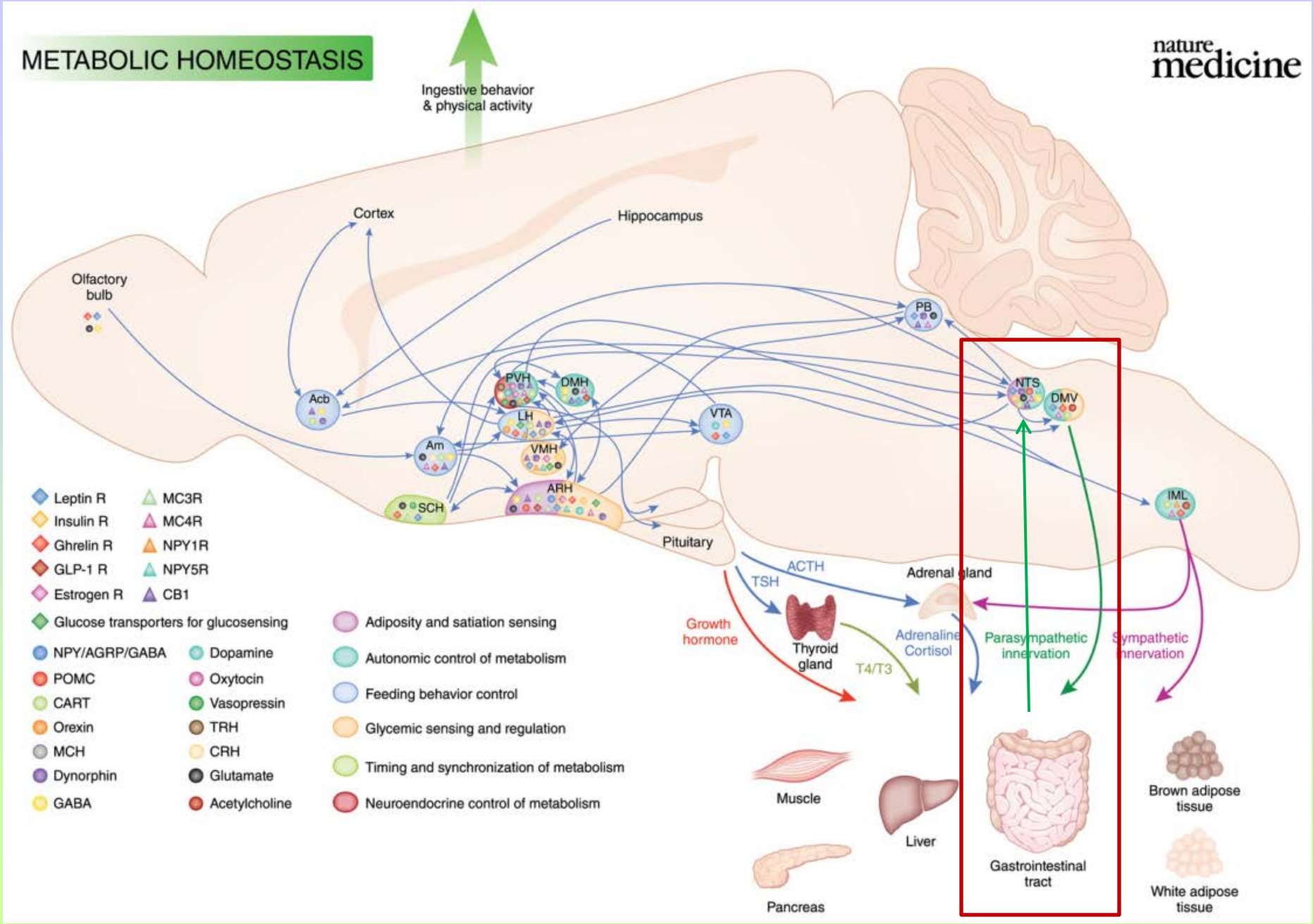
meal size

Fox et al., Am J Physiol 305, R1307, 2013

Summary: SM-NT-3 KO Effects

- decreased vagal activation of brainstem by large meal
- increased meal duration
- increased 1st meal size

=> suggests decreased satiation signaling



Yi, Zeltser, & Tschop

Conclusions

- Effects of smooth muscle KO's of BDNF & NT-3:

  - SM-BDNF KO: increased intestinal innervation & satiation

  - SM-NT-3 KO: decreased vagal signaling & satiation

- Implications?

  - selective pharmacological or electrophysiological activation (or inhibition) of intestinal IGLE pathway could reduce (or increase) meal size.

  - in conjunction with other treatments may help treat obesity and eating disorders such as anorexia and bulimia

Acknowledgements

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Amber Worman
Phyllis Zickmund

Talal Karam
Tammy Dilden

Kevin Jones, Univ Colorado

Guoping Fan, UCLA

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