Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

Consortium leader

PETER PAZMANY CATHOLIC UNIVERSITY

Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

The Project has been realised with the support of the European Union and has been co-financed by the European Social Fund ***

**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

***A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

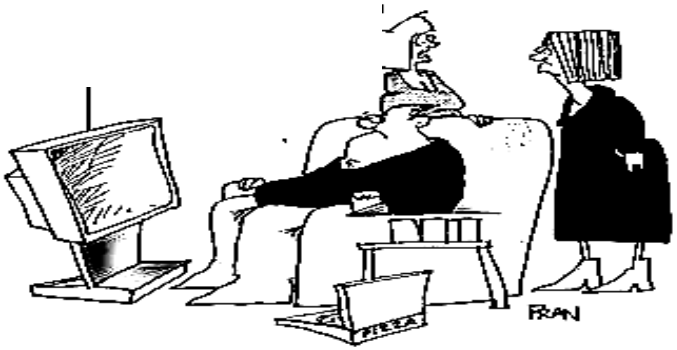
BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

REGULATION OF FEEDING

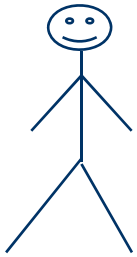
(Táplálkozás szabályozás)

ZSOLT LIPOSITS



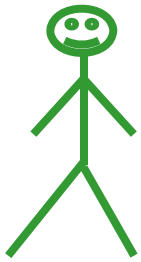
HE'S IN TRAINING FOR THE MARATHON. HE WATCHES IT EVERY YEAR

LEAN



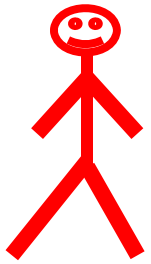
ENERGY INTAKE < ENERGY EXPENDITURE

NORMAL



ENERGY INTAKE = ENERGY EXPENDITURE

OBESE



ENERGY INTAKE > ENERGY EXPENDITURE

OBESITY

TYPE 2 DIABETES

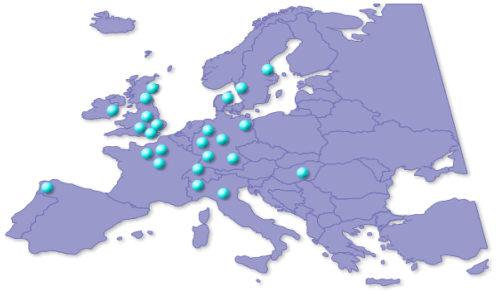
- Obesity and type-2 diabetes (diabesity) are a major global health problem
- In the European Union type 2 diabetes costs 15 b Euros per year
- By 2010, approximately 33 million Europeans will suffer from diabetes
- Obesity, which is a major recognised risk factor for type 2 diabetes, is rapidly increasing in prevalence, resulting in a diabesity epidemic
- For most people, neither dieting nor current pharmacological interventions are effective in achieving long-term weight reduction
- To treat diabesity, we must develop approaches to modulate the ways in which the brain controls metabolism, body weight and composition

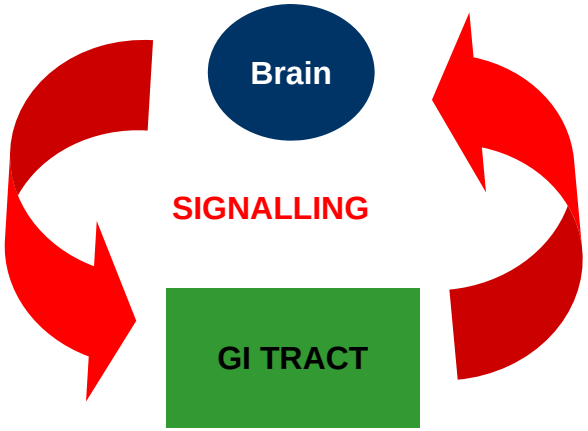
DIABESITY

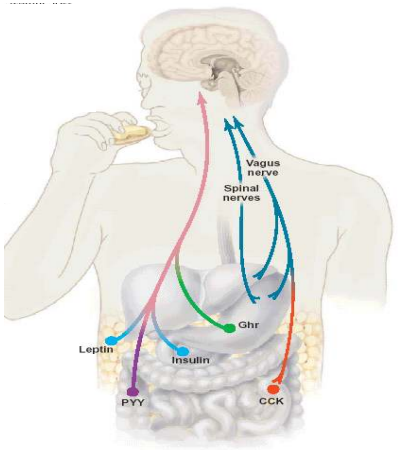
Novel molecular targets for obesity and type 2 diabetes

Sixth Framework Programme (2002-2006)

heart disease (cardiovascular disease)
blindness (retinopathy)
nerve damage (neuropathy)
kidney damage (nephropathy)

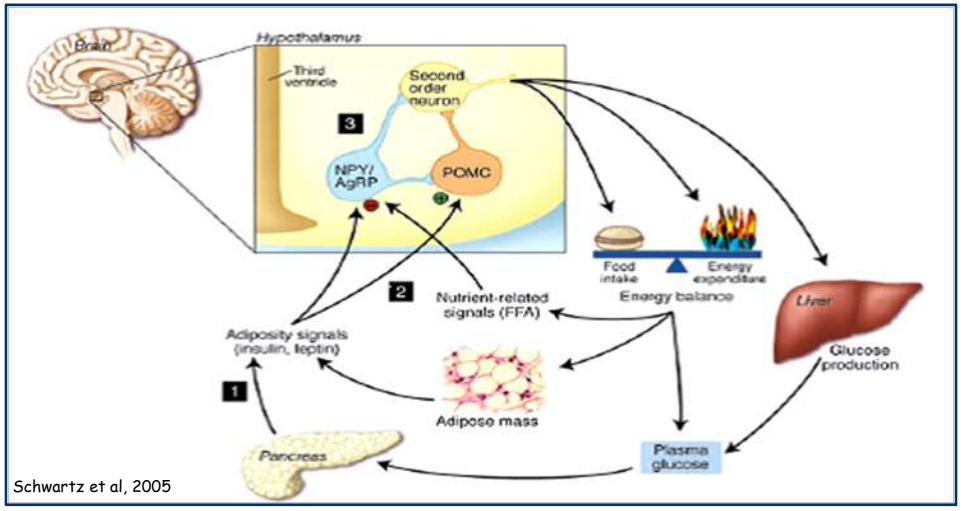


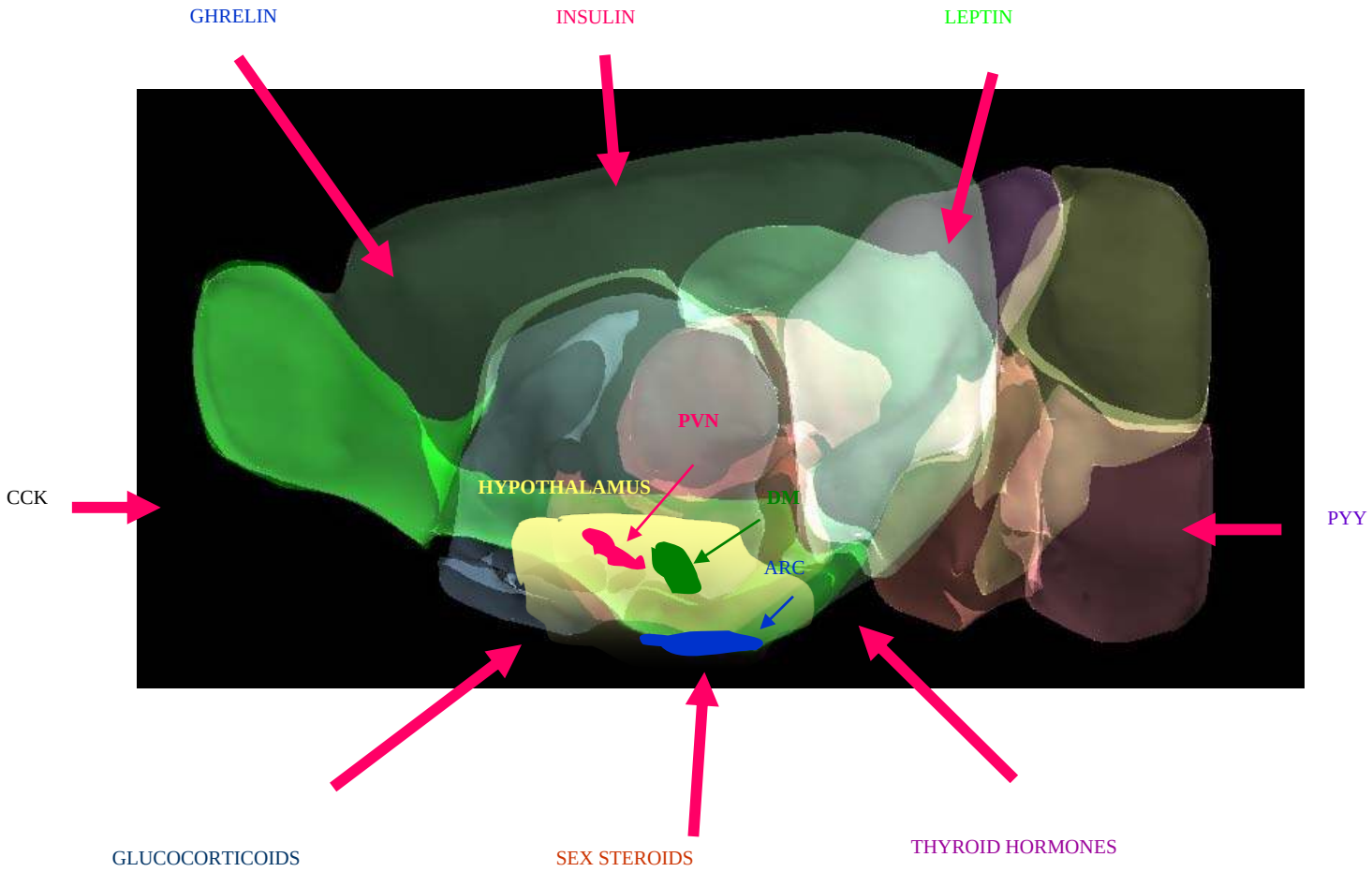




Satiety hormones
Leptin
Insulin
PYY
CCK

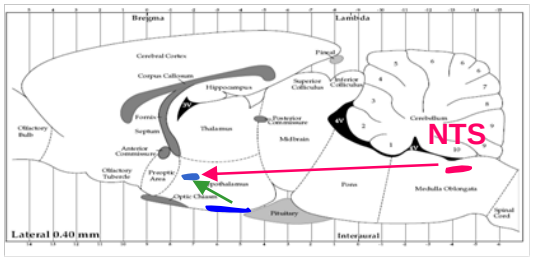
Hunger hormone
Ghrelin

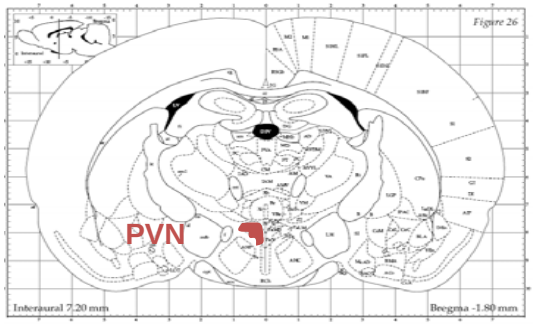


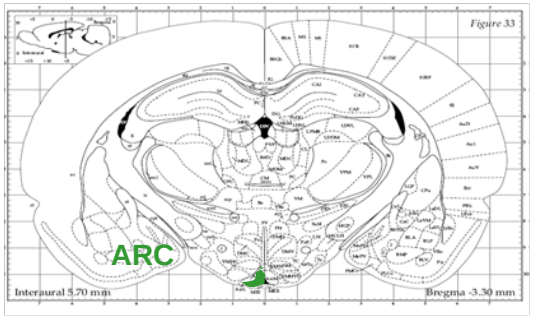

GHRELIN
INSULIN
LEPTIN
PVN
HYPOTHALAMUS
DM
ARC
CCK
PYY
GLUCOCORTICOIDS
SEX STEROIDS
THYROID HORMONES

INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

Regulation of feeding







AUTONOMIC CENTERS

PITUITARY- ADRENAL & THYROID AXES

POSTERIOR PITUITARY

SECOND ORDER EFFECTOR NEURONS

OREXIGENIC
ANOREXIGENIC
OUTFLOWS

FIRST ORDER SENSOR NEURONS

METABOLIC SIGNALS

TRH
CRH

OXY
VAS

FOOD INTAKE
ENERGY EXPENDITURE
WATER, ELECTROLYTE
ADAPTATION

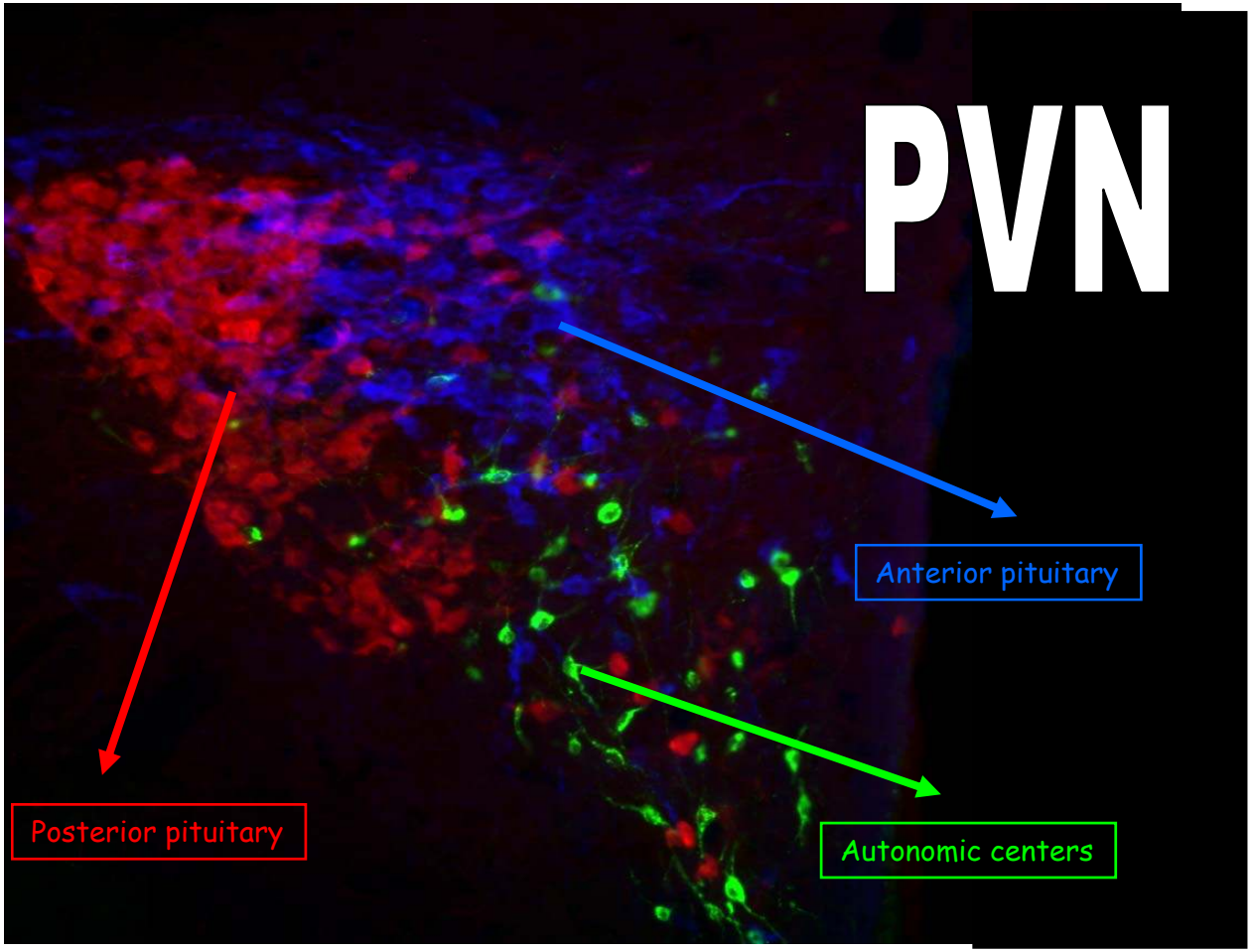
MCH

OREXIN

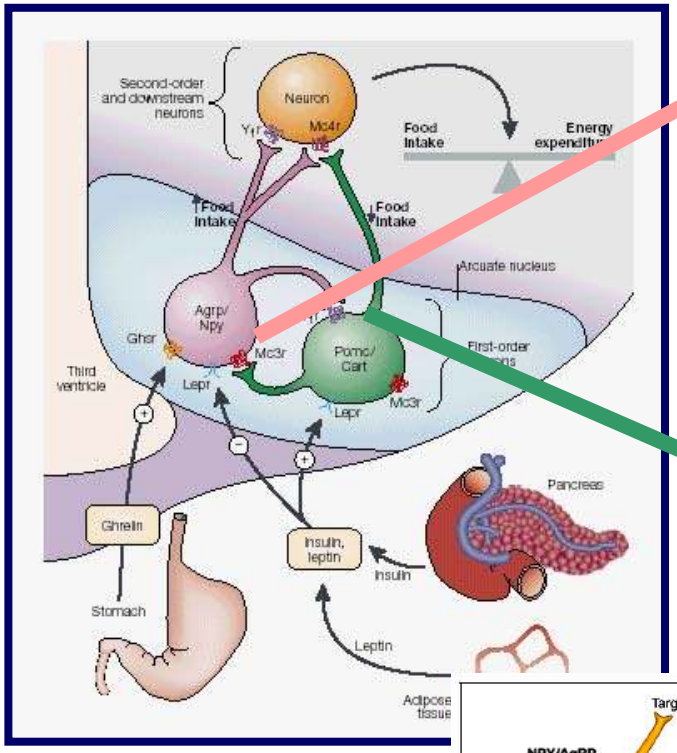
NPY
AGRP

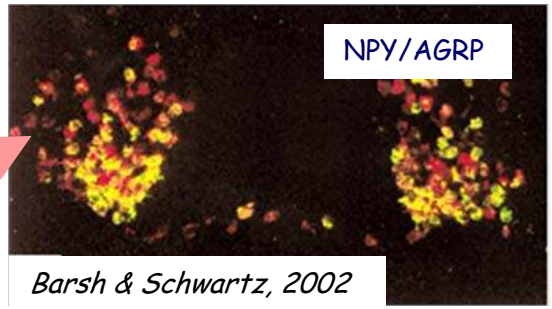
α-MSH
CART

INSULIN
GHRELIN
LEPTIN
GLUCOCORTICOIDS

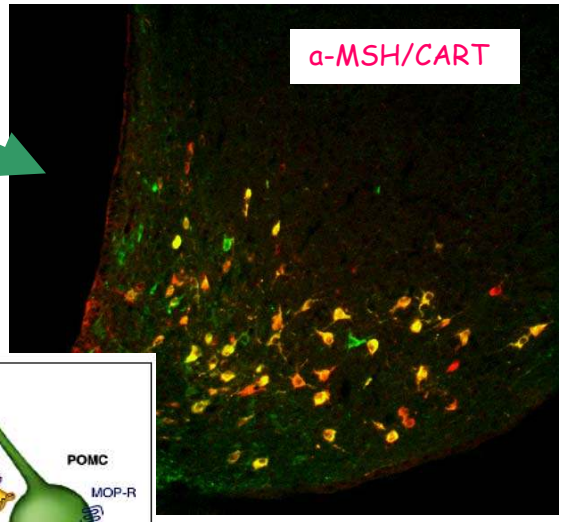

PVN
Anterior pituitary
Posterior pituitary
Autonomic centers

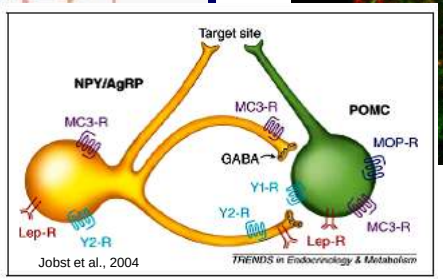
The sensor system



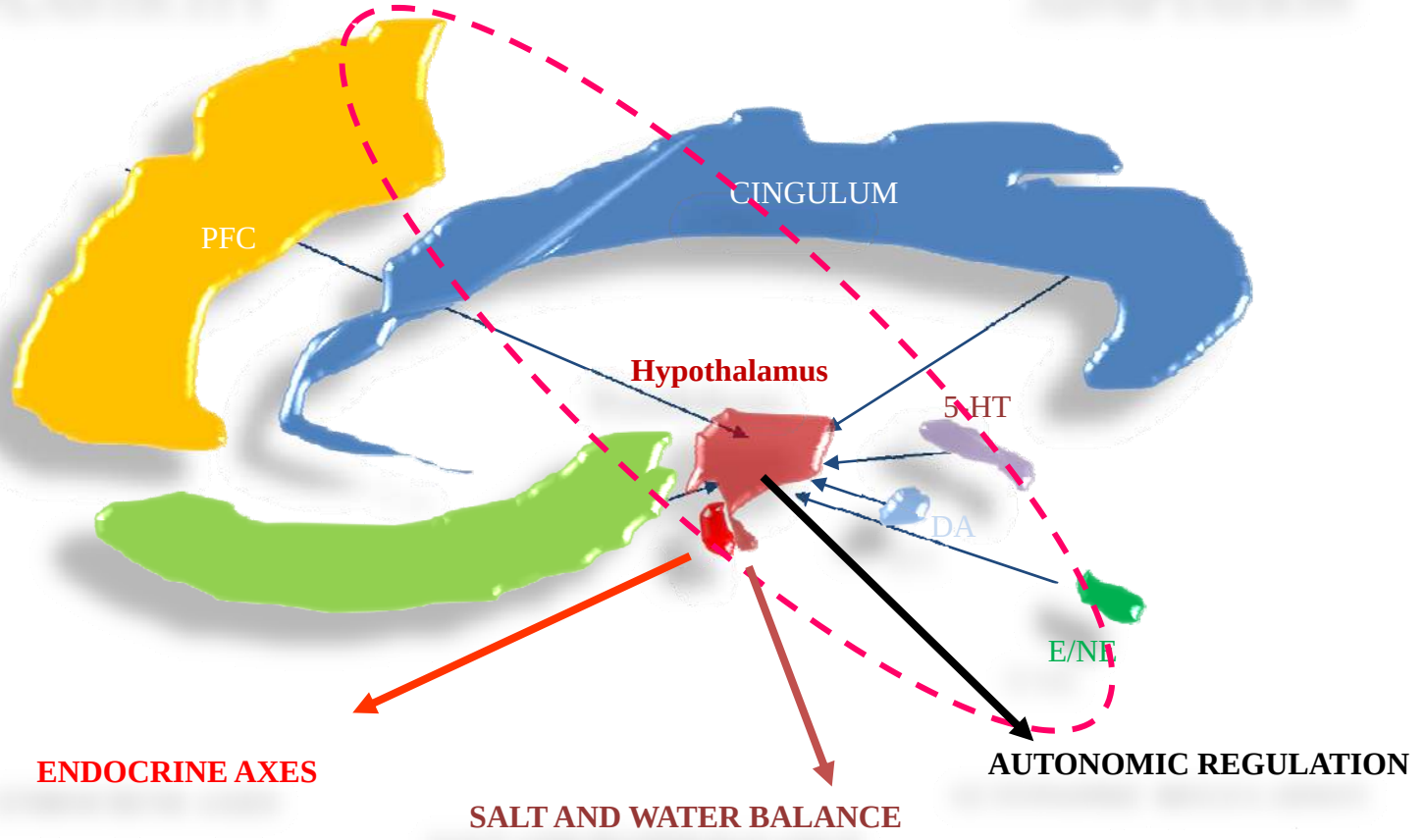


Barsh & Schwartz, 2002

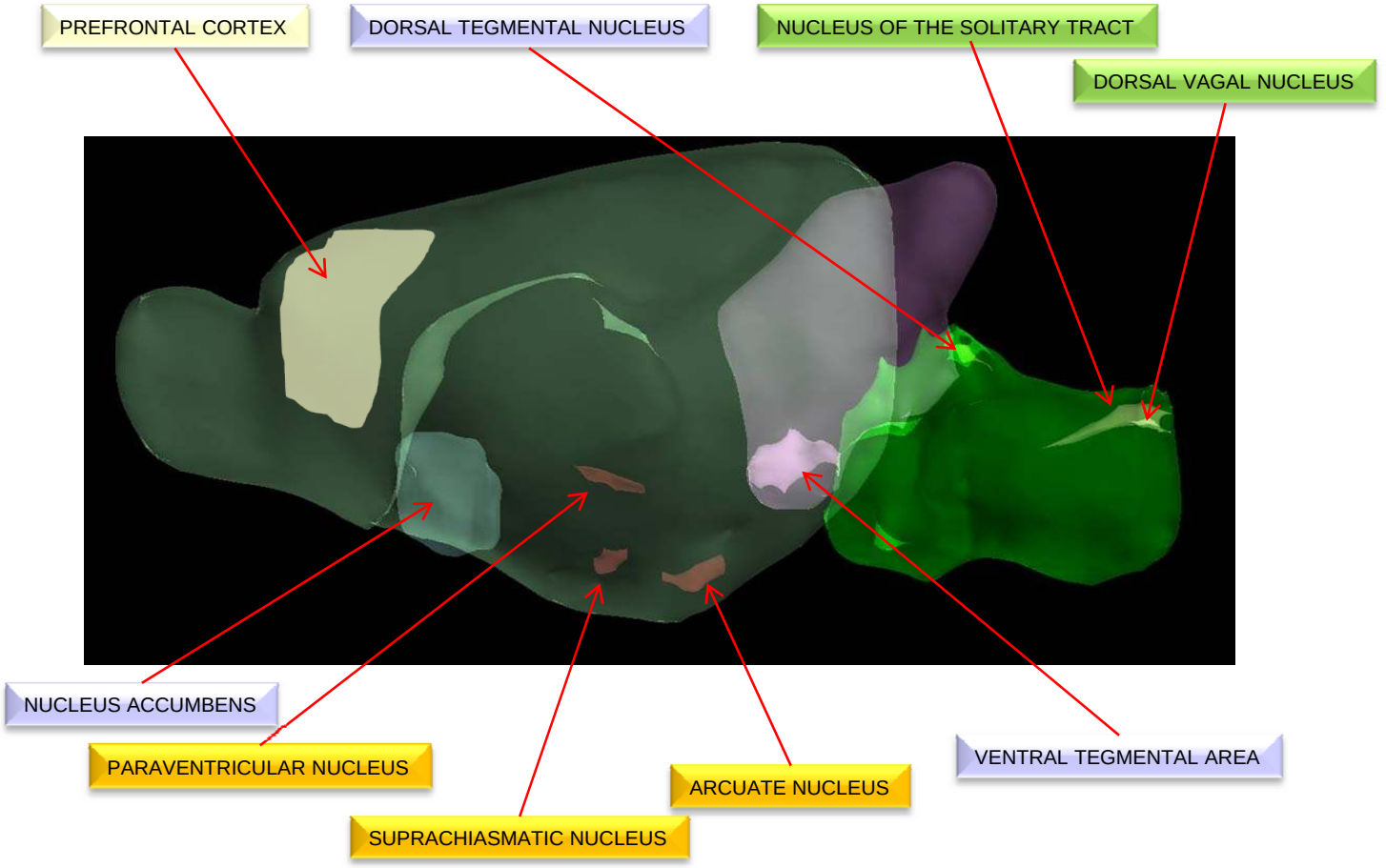




PLASTICITY ADAPTATION



Lateral view of the transparent rodent brain



The relation of various hypothalamic lesions to adiposity in the rat
A. W. Hetherington, S. W. Ranson

The Journal of Comparative Neurology
76: 475-499 (1942)

Hypothalamic lesions and adiposity in the rat
A. W. Hetherington, S. W. Ranson

The Anatomical Record
78: 149-172 (1940)

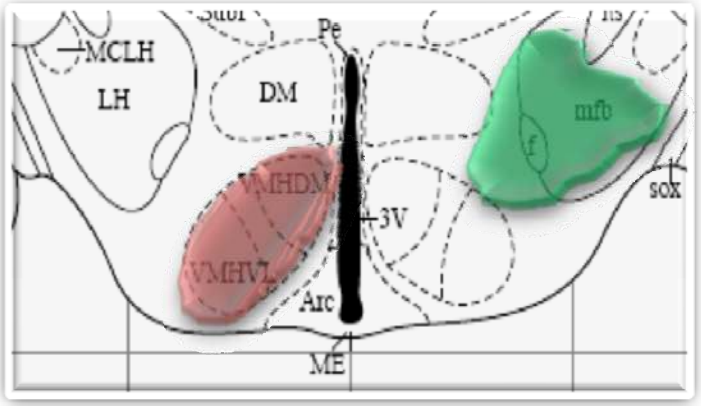
Lesion of VMH

↓

Destruction of satiety centre

↓

Weight gain



Lesion of LH

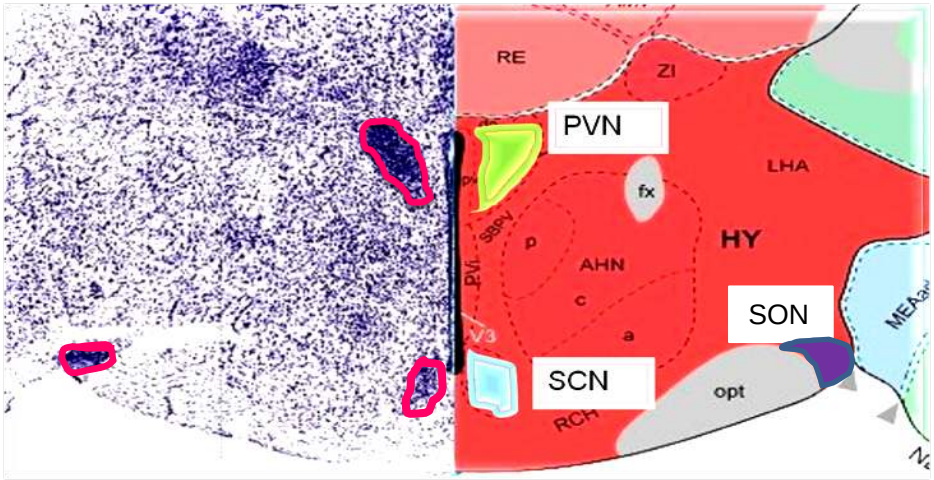
↓

Disruption of feeding centre

↓

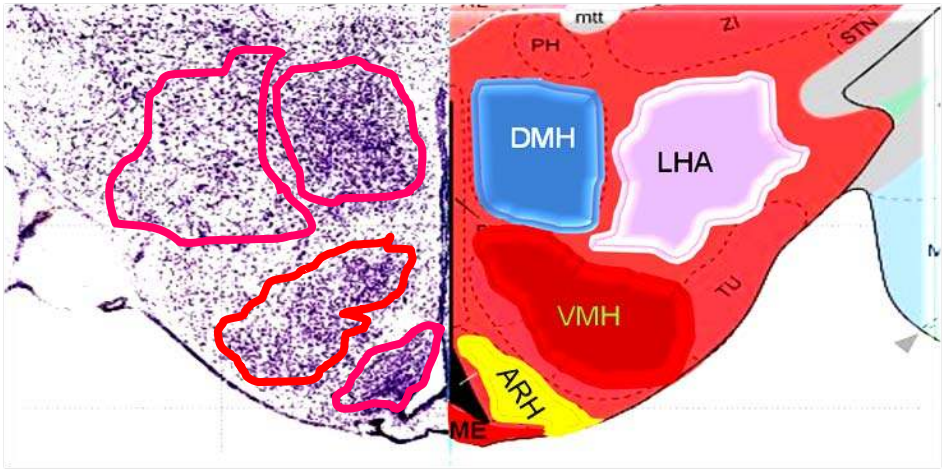
Weight loss

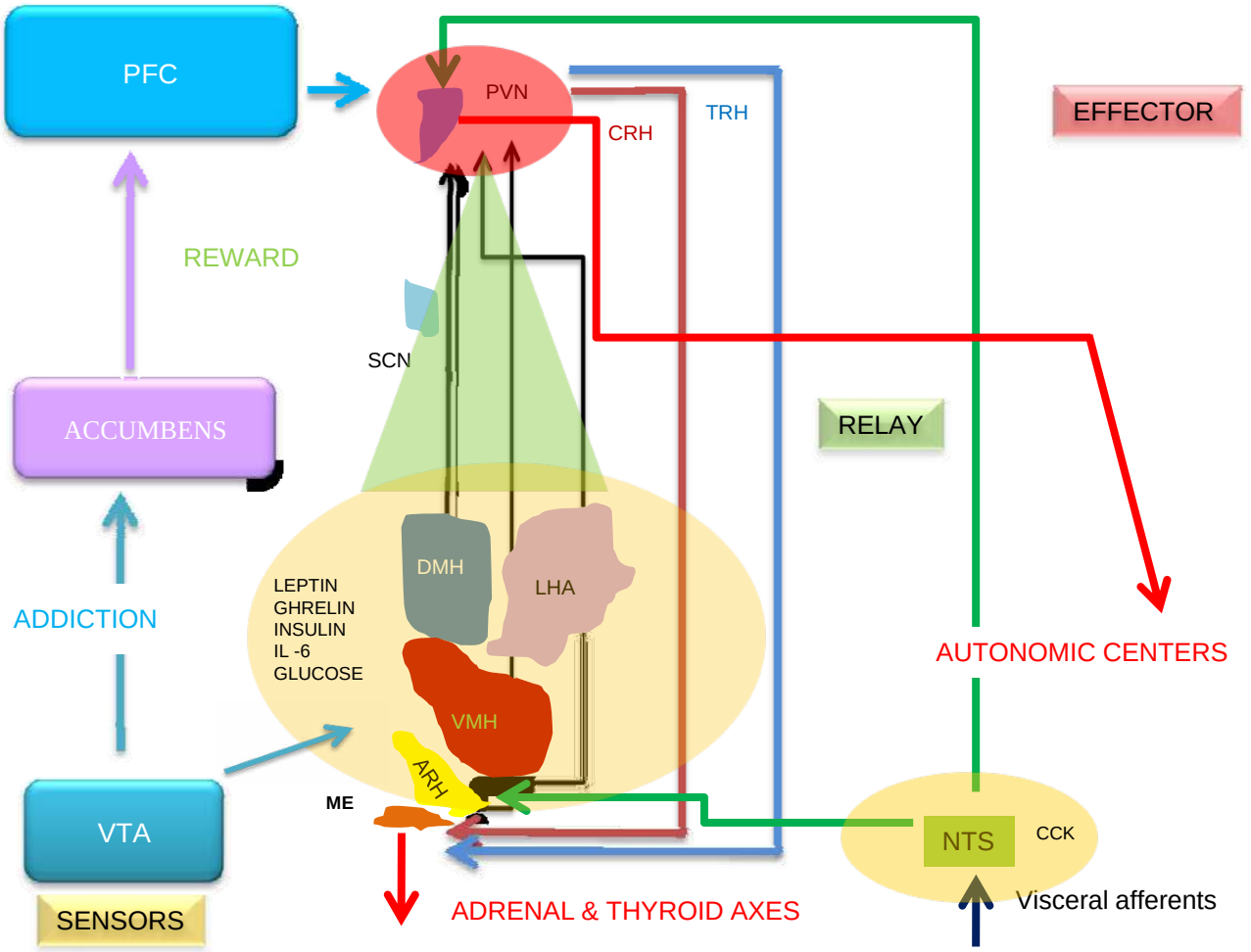
Hypothalamic nuclei regulating food intake and energy expenditure



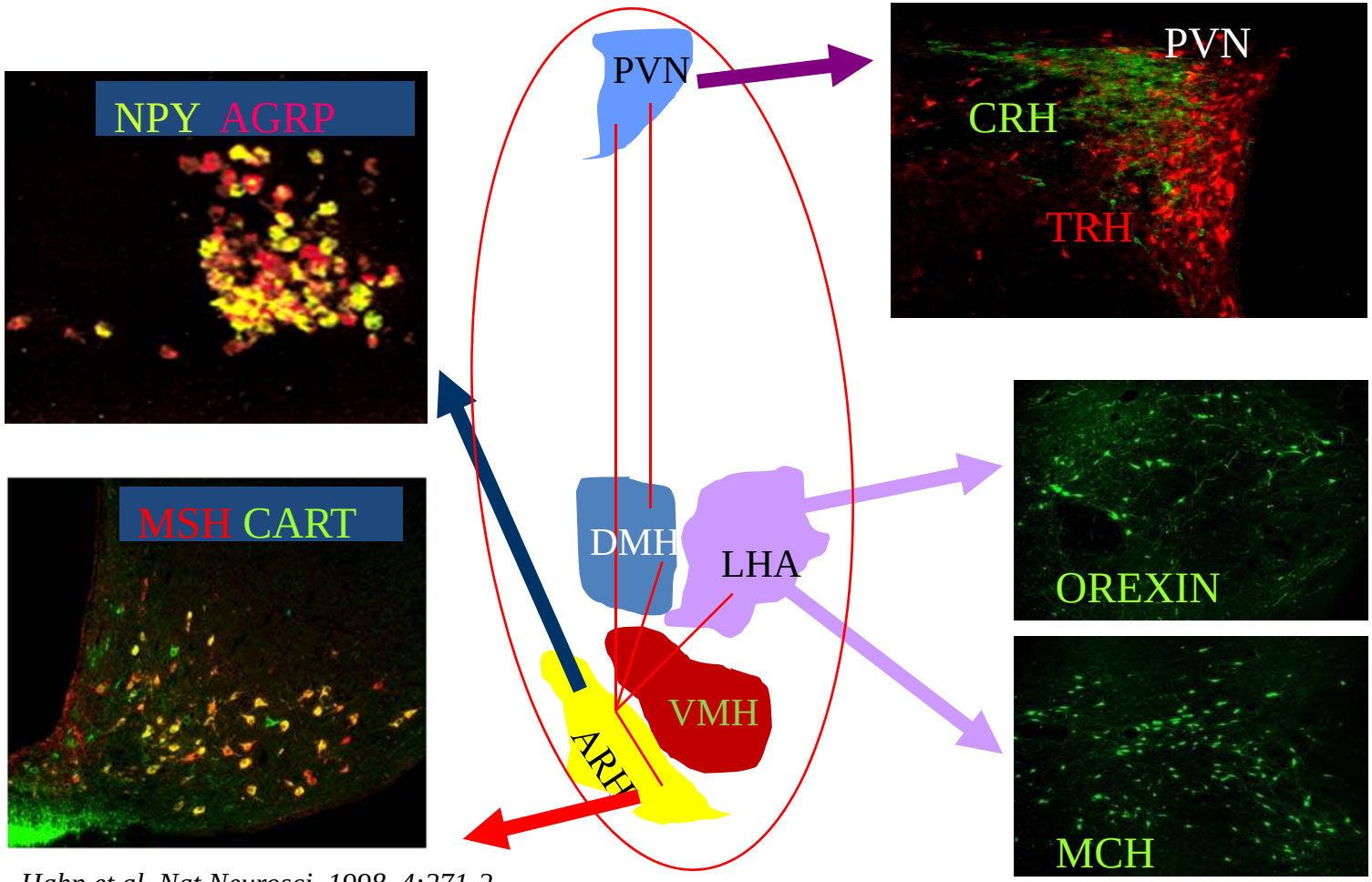
ROSTRAL

CAUDAL

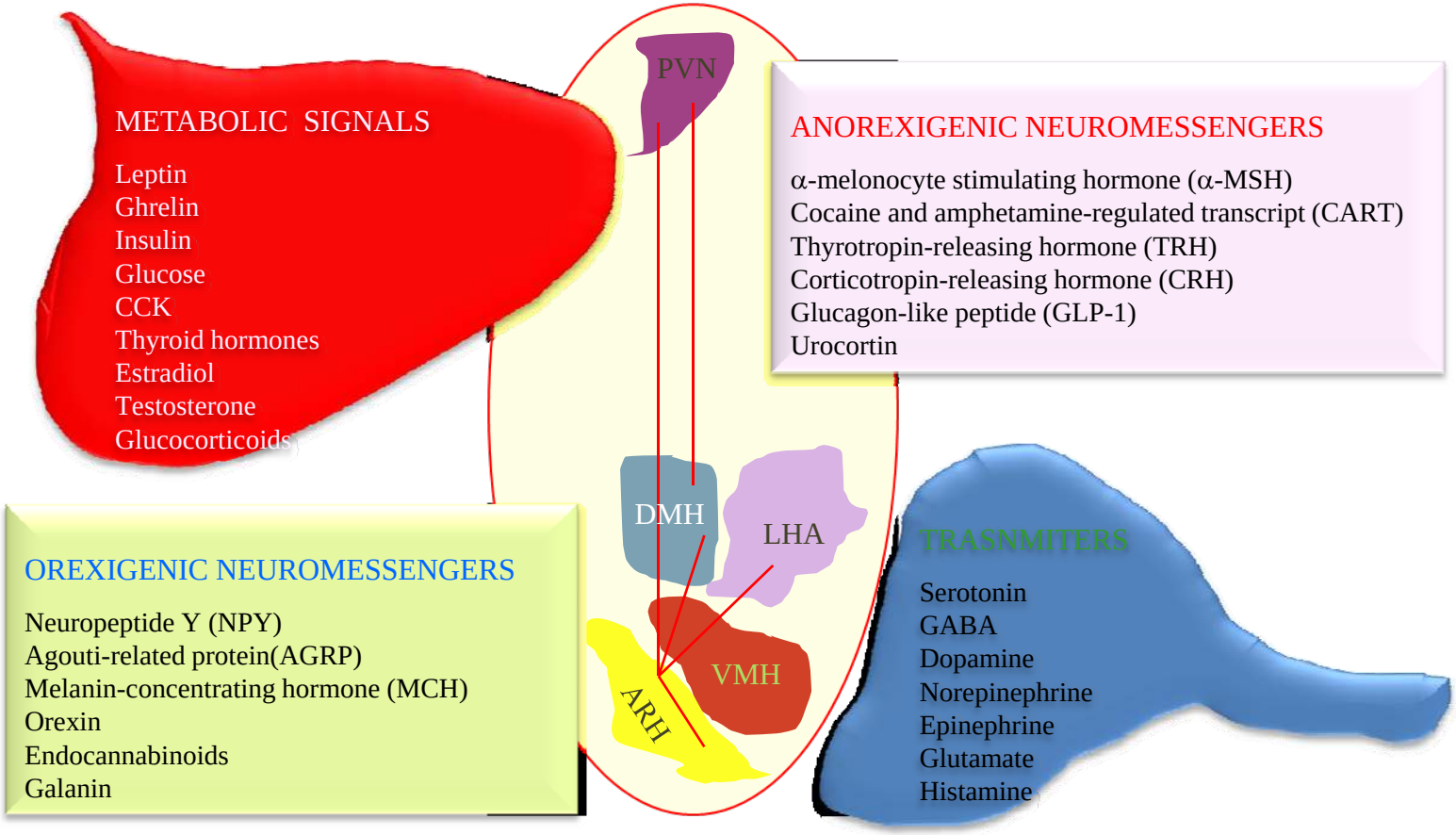



PFC
PVN
CRH
TRH
EFFECTOR
REWARD
SCN
ACCUMBENS
RELAY
DMH
LHA
LEPTIN
GHRELIN
INSULIN
IL -6
GLUCOSE
ADDICTION
AUTONOMIC CENTERS
VMH
ARH
ME
VTA
NTS
CCK
SENSORS
ADRENAL & THYROID AXES
Visceral afferents

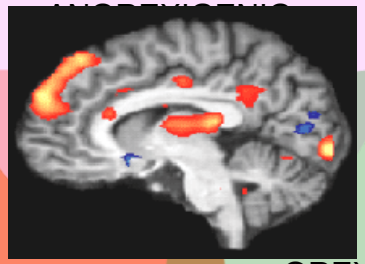
Regulation of feeding



Hahn et al, Nat Neurosci. 1998, 4:271-2
Fekete et al, J Neurosci. 2000; 20:9224-34


METABOLIC SIGNALS
Leptin
Ghrelin
Insulin
Glucose
CCK
Thyroid hormones
Estradiol
Testosterone
Glucocorticoids
PVN
ANOREXIGENIC NEUROMESSENGERS
α-melonocyte stimulating hormone (α-MSH)
Cocaine and amphetamine-regulated transcript (CART)
Thyrotropin-releasing hormone (TRH)
Corticotropin-releasing hormone (CRH)
Glucagon-like peptide (GLP-1)
Urocortin
DMH
LHA
VMH
ARH
OREXIGENIC NEUROMESSENGERS
Neuropeptide Y (NPY)
Agouti-related protein(AGRP)
Melanin-concentrating hormone (MCH)
Orexin
Endocannabinoids
Galanin
TRASNMITERS
Serotonin
GABA
Dopamine
Norepinephrine
Epinephrine
Glutamate
Histamine

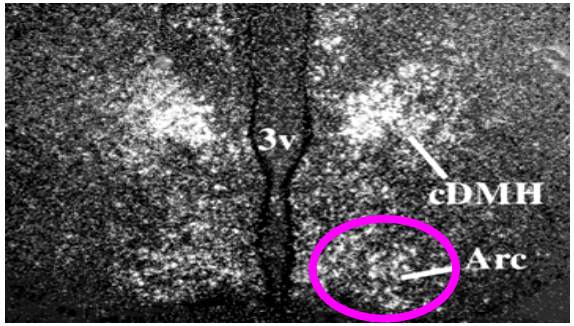
Hypothalamic kaleidoscope



Führer et al, Obesity, 2008,16:945-50

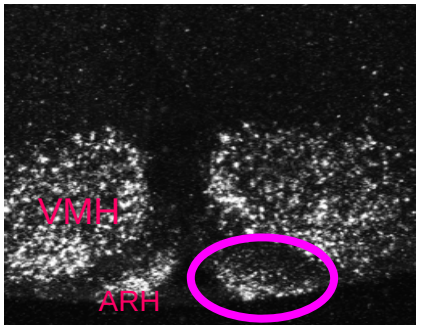
Monitoring and processing of metabolic signals by hypothalamic nuclei

LEPTIN RECEPTOR mRNA

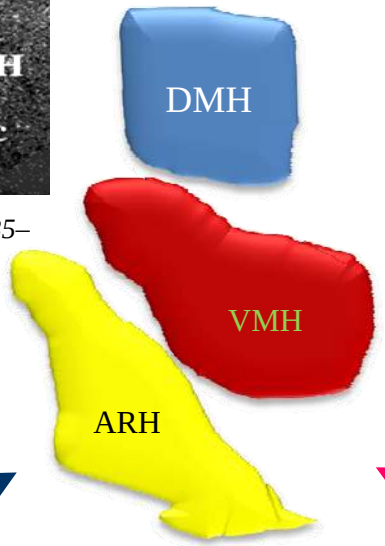


Elmquist et al., J Comp Neurol , 1998, 395:535–47

GHRELIN RECEPTOR mRNA



Hrabovszky et al, 2010, unpublished

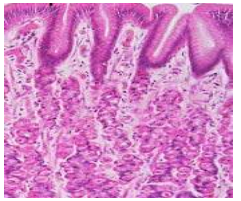


FAT

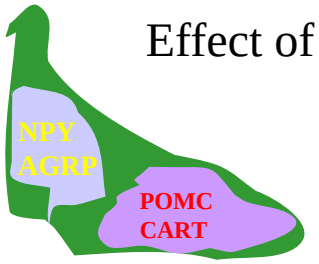
LEPTIN

GHRELIN

STOMACH

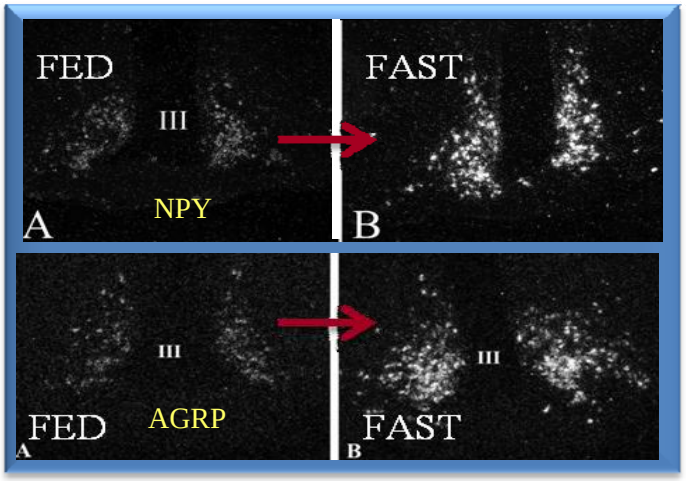


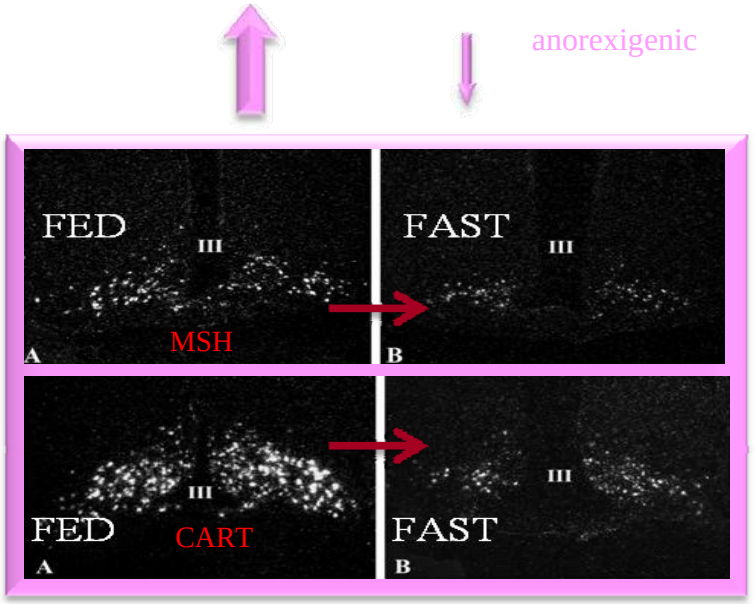
Effect of fasting on the expression of orexigenic and anorexigenic peptide mRNAs in the arcuate nucleus



orexigenic

anorexigenic

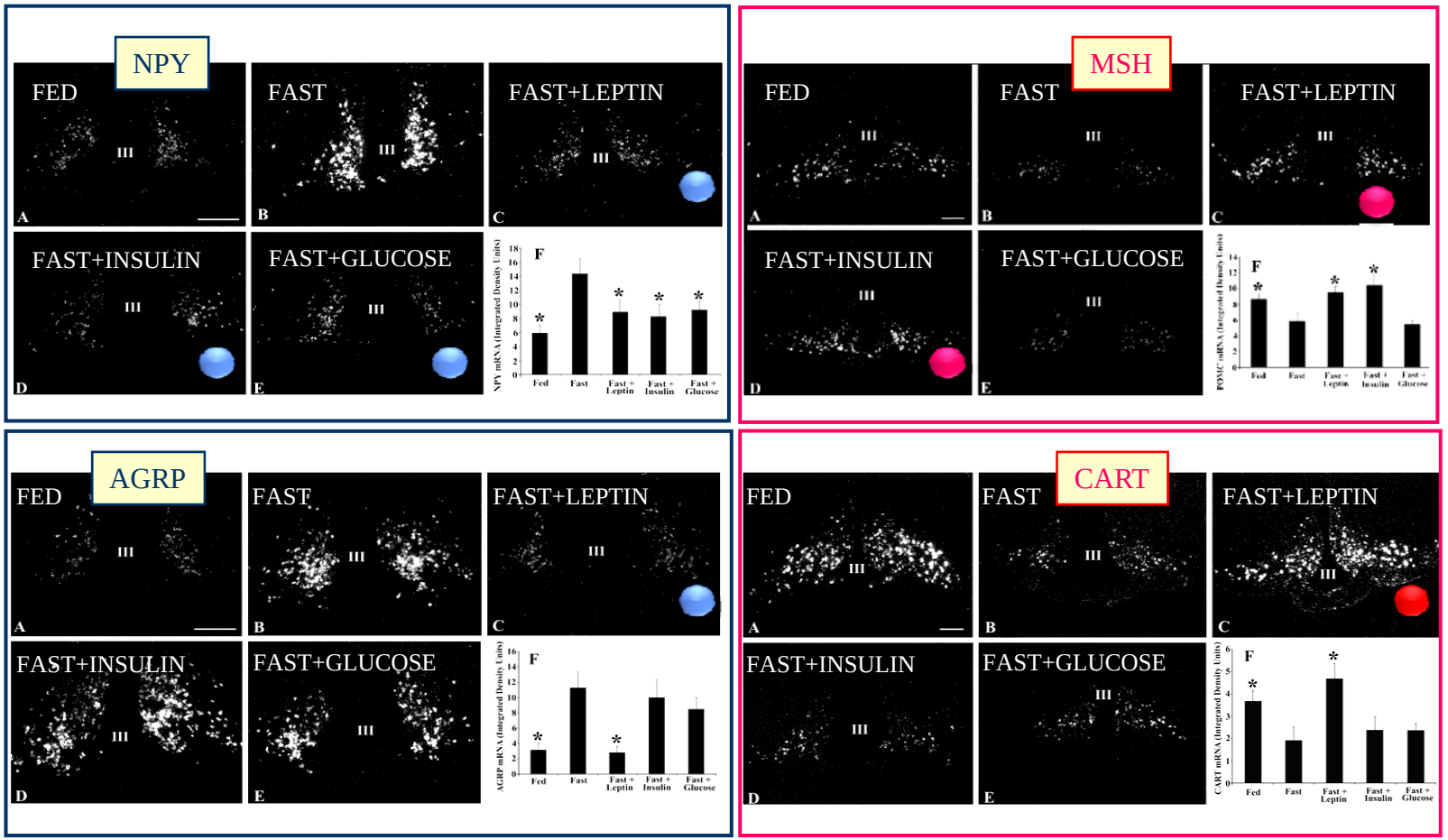


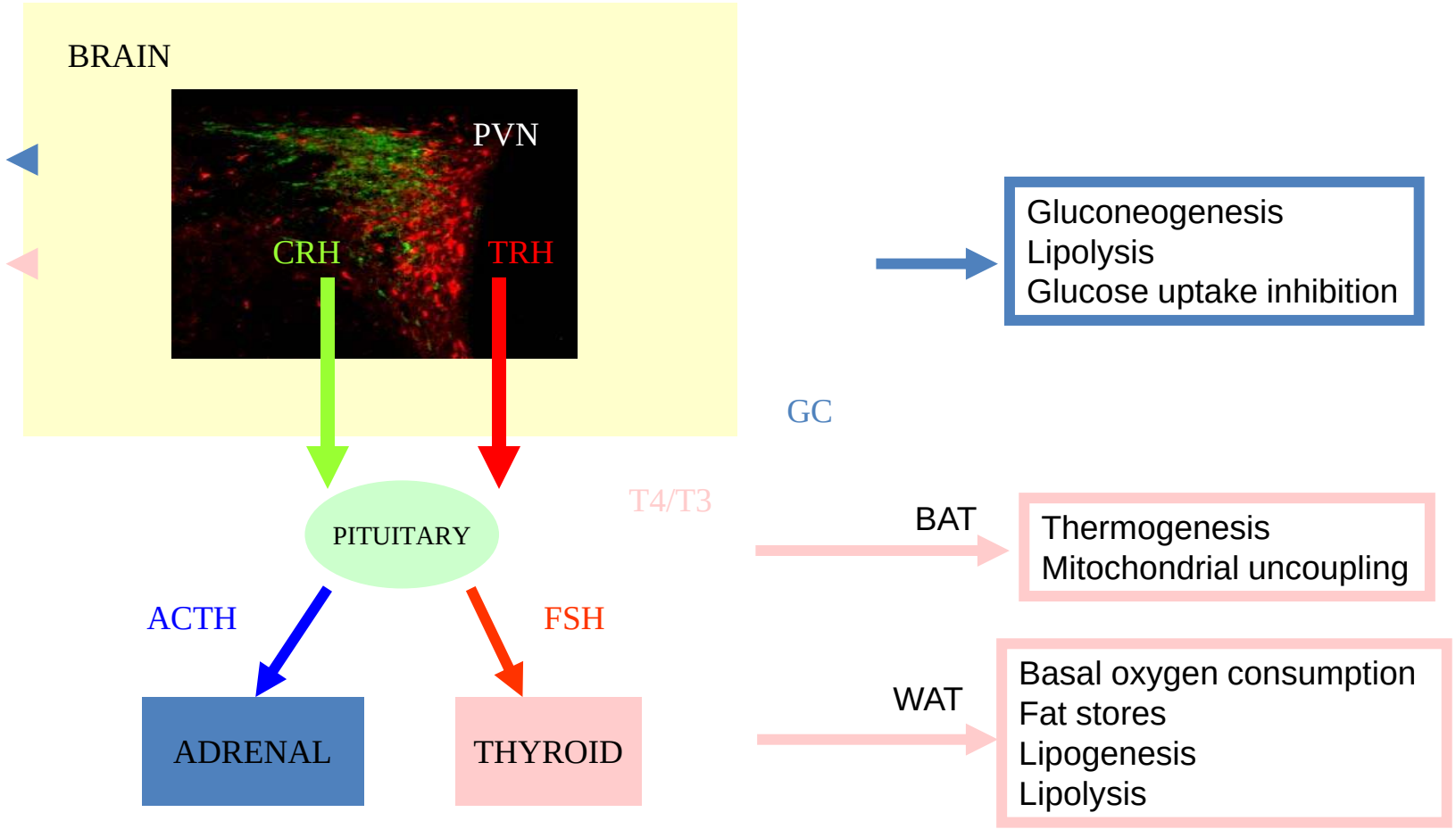


Lechan RM, Fekete C. Prog Brain Res. 2006,153:209-35.

Effects of central leptin, insulin and glucose administration on the peptidergic neurons of the arcuate nucleus

Fekete et al., Endocrinology, 2006, 147:520-9

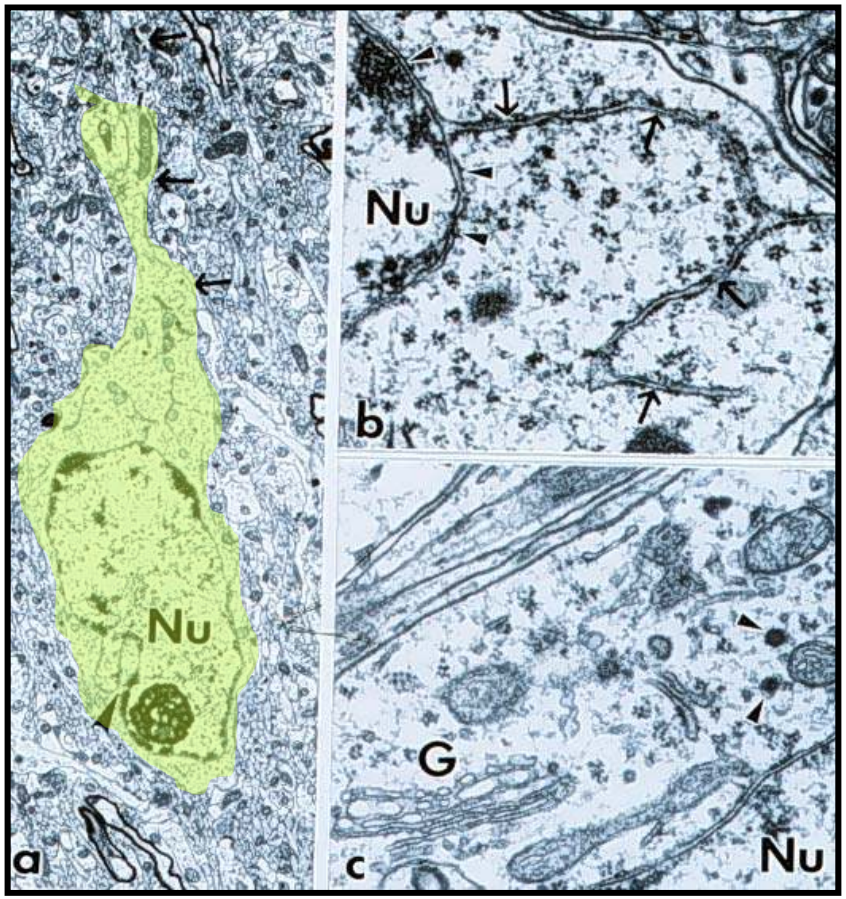



BRAIN
PVN
CRH
TRH
PITUITARY
ACTH
FSH
ADRENAL
THYROID
GC
T4/T3
BAT
WAT
Gluconeogenesis
Lipolysis
Glucose uptake inhibition
Thermogenesis
Mitochondrial uncoupling
Basal oxygen consumption
Fat stores
Lipogenesis
Lipolysis

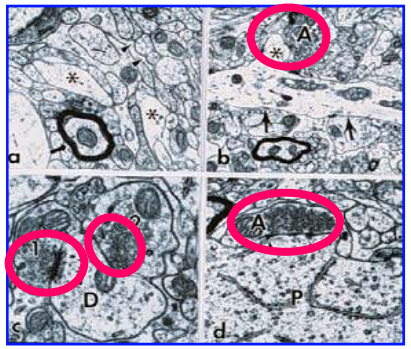
Origin, chemical nature and regulatory effects of synaptic afferents to CRH and TRH neurons

ULTRASTRUCTURE OF PARVICELLULAR NEURONS

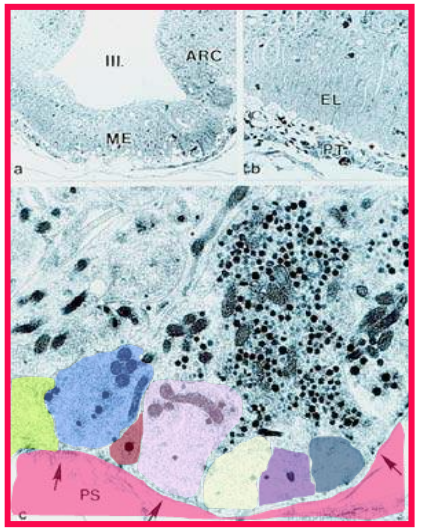
CELL BODIES



INPUT

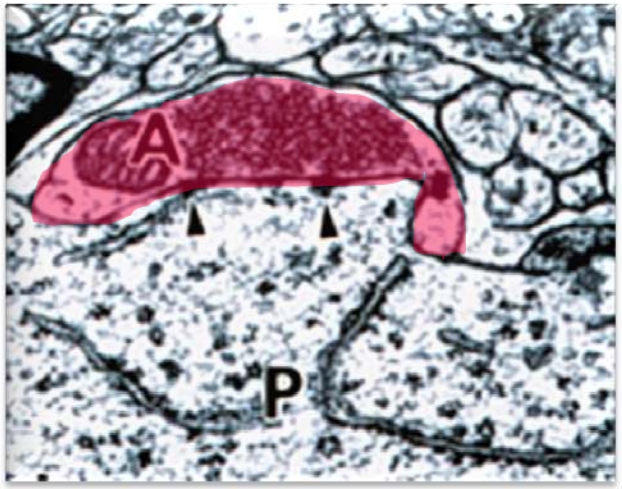


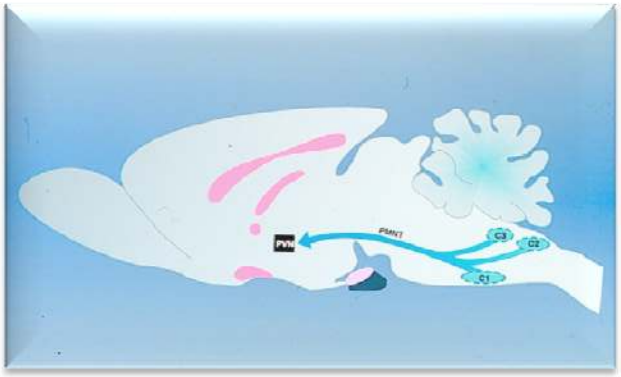
OUTPUT

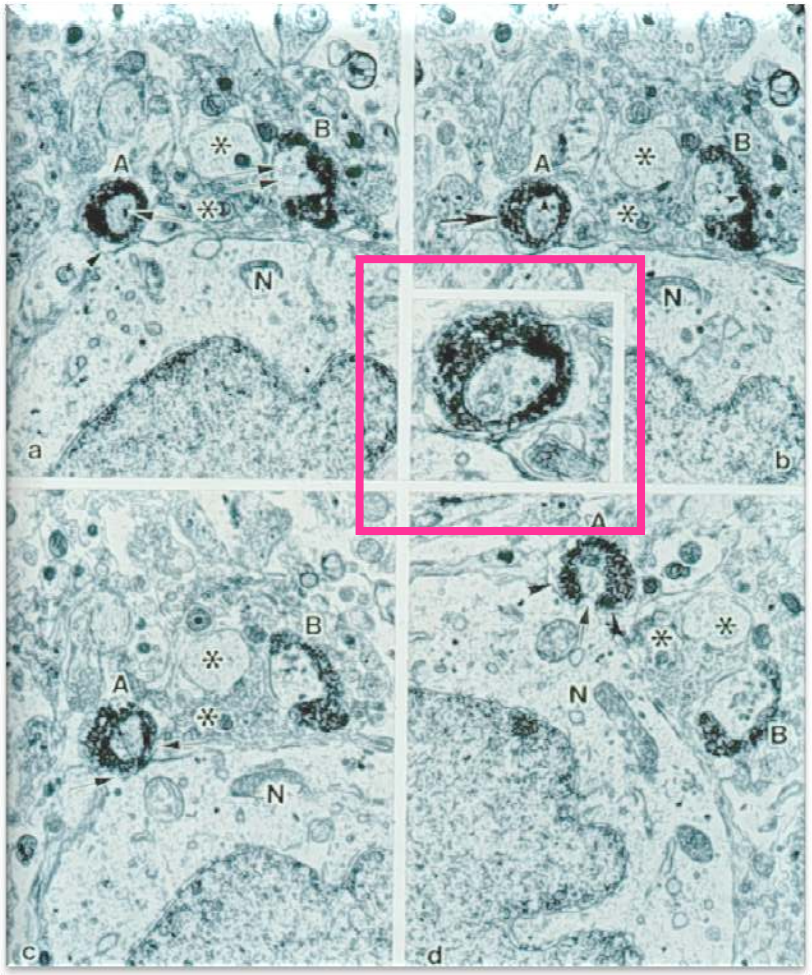


Liposits Zs, Crit. Rev. Neurobiol. 1993;7:89-162

ADRENERGIC INPUT TO THE PVN

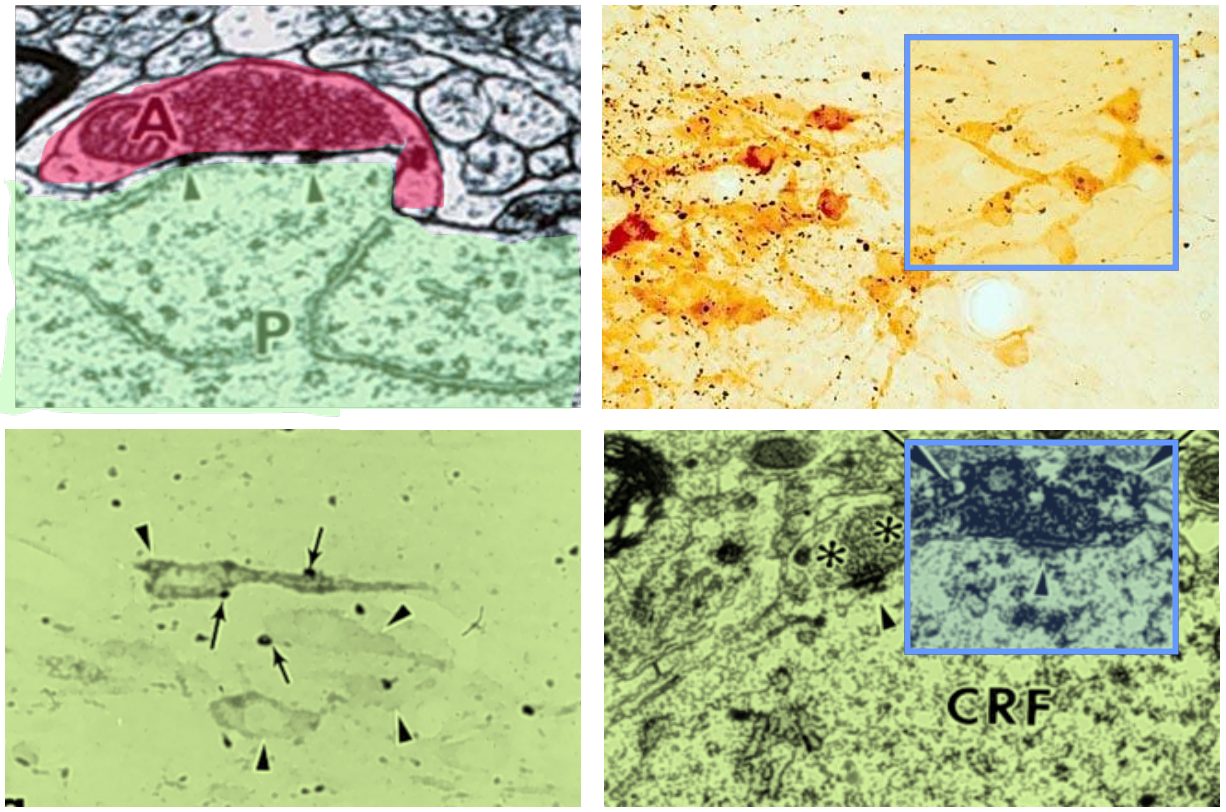






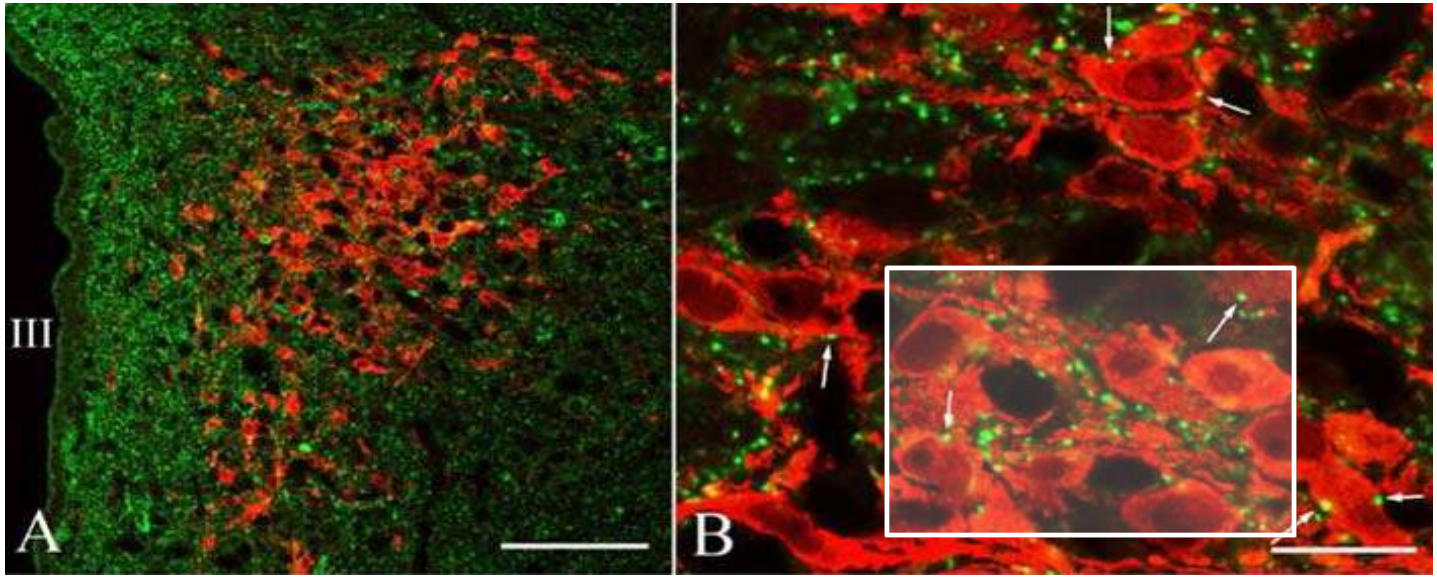
Liposits Z, Phelix C, Paull WK: Histochemistry, 1986;84:105-20.

CATECHOLAMINERGIC NEURONAL INPUT TO CRH NEURONS



Liposits Z, Phelix C, Paull WK: Histochemistry. 1986;84:201-5.

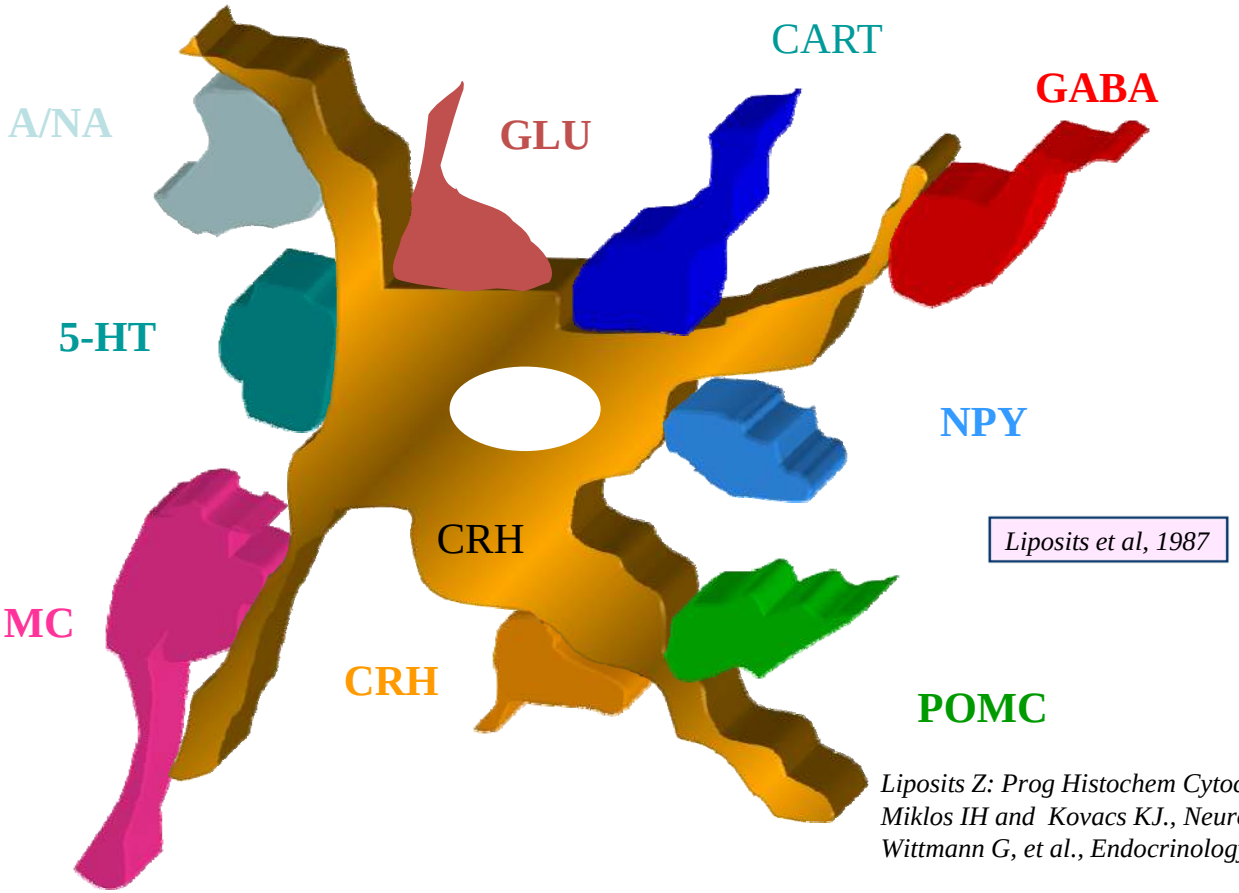
Glutamatergic innervation of hypophysiotropic CRH neurons



VGLUT-2 + CRH

Wittmann G, et al.: Brain Res. 2005;1039:53-62.

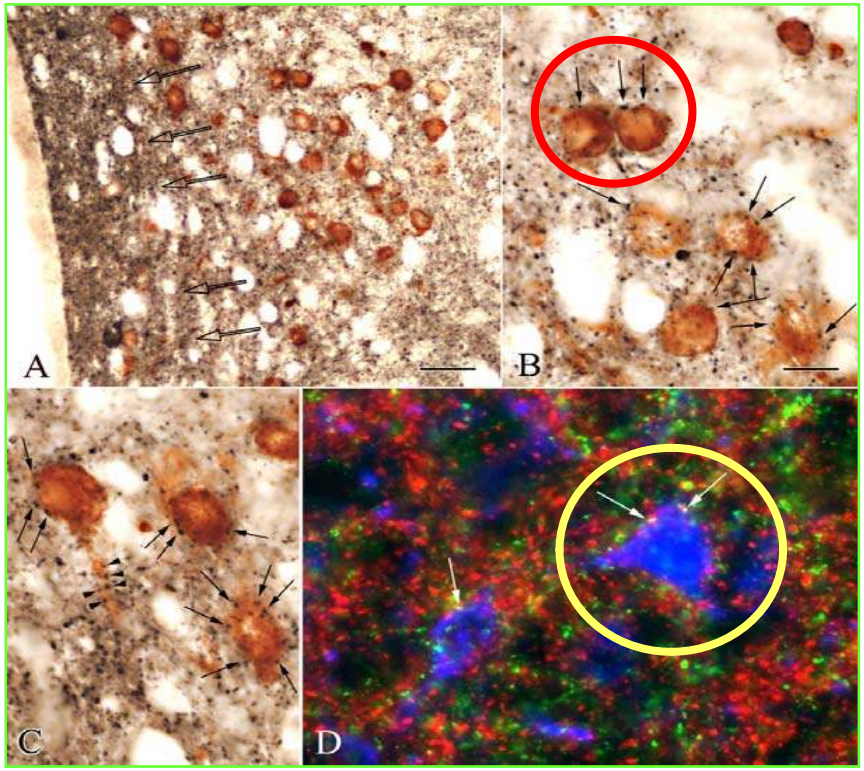
Peptides and transmitters in boutons synapsing with CRH neurons



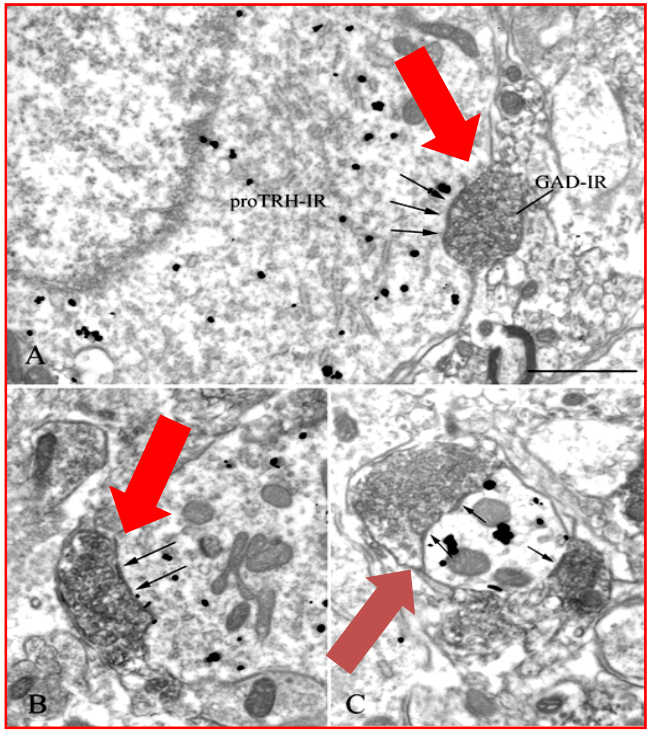
Liposits et al, 1987

Liposits Z: Prog Histochem Cytochem. 1990;21:1-98.
Miklos IH and Kovacs KJ., Neuroscience. 2002;113:581-92.
Wittmann G, et al., Endocrinology. 2005;146(7):2985-91.

GABA-ergic innervation of hypophysiotrophic TRH neurons



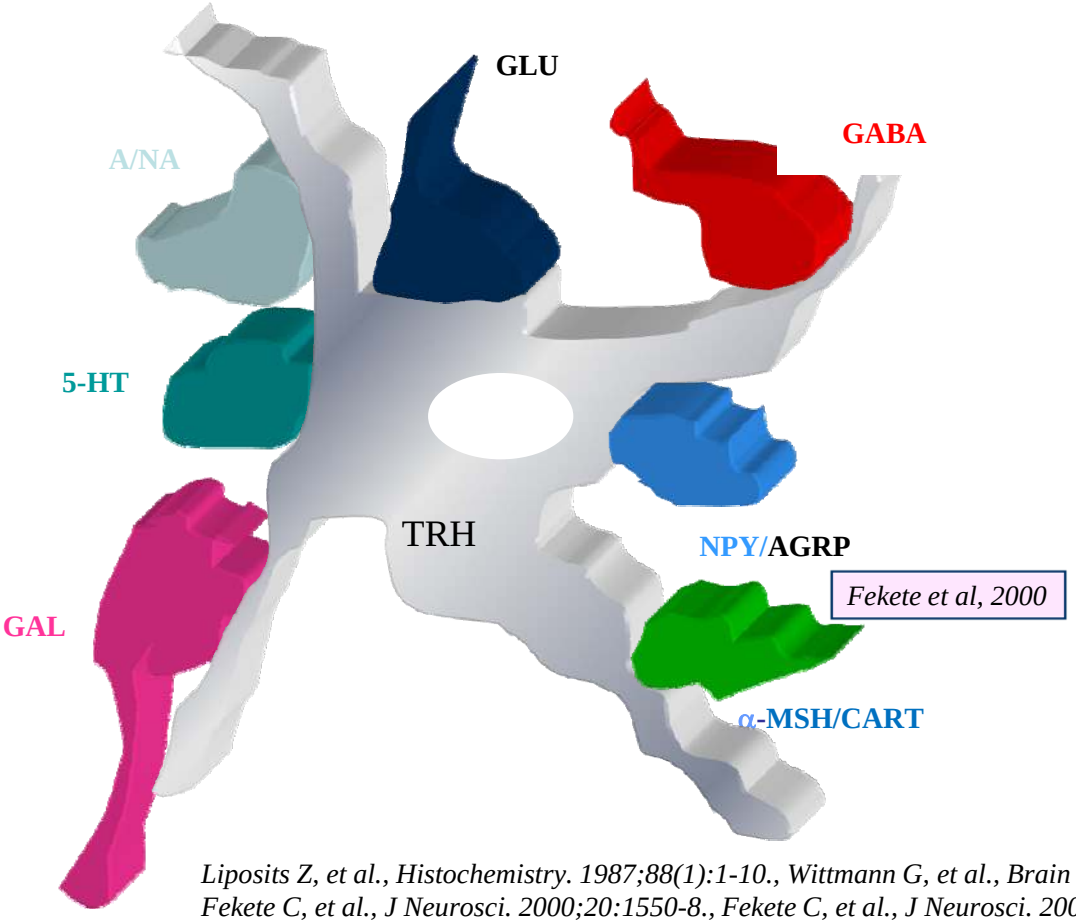
Axo-somatic



Axo-dendritic

Fekete C, et al.: Brain Res. 2002;957:251-8.

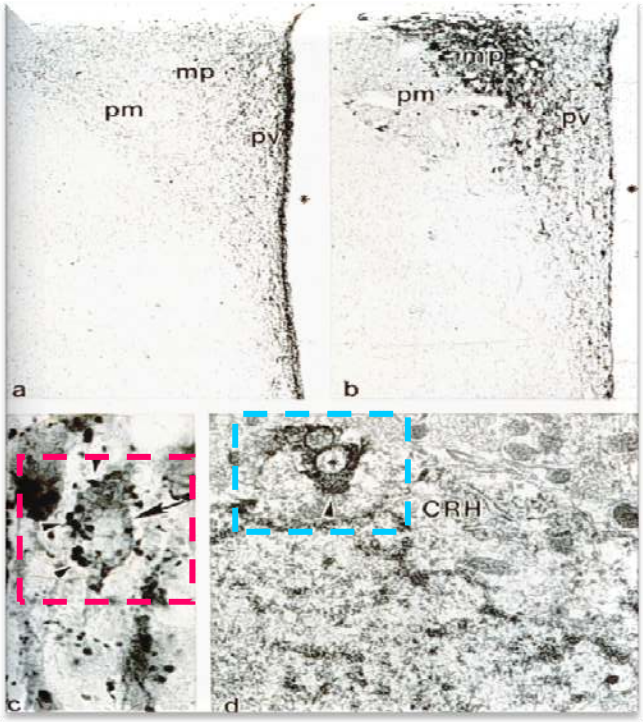
Synaptic modulators of TRH neurons

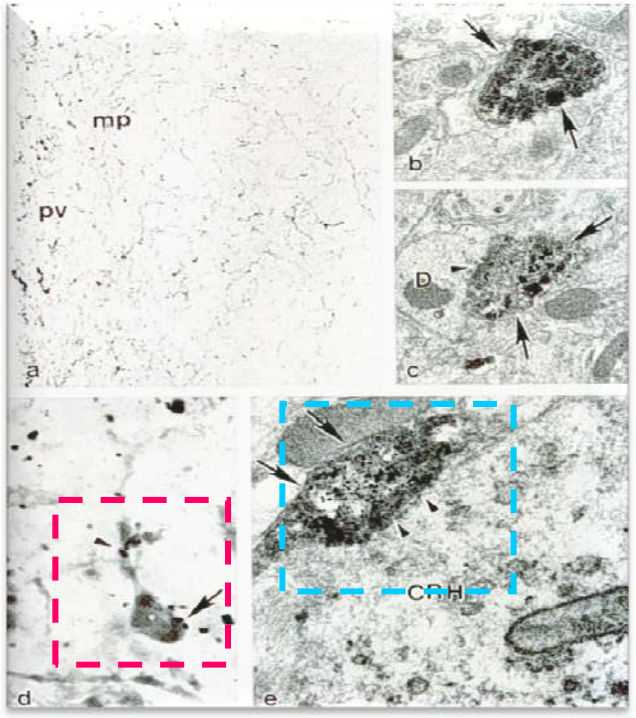


Liposits Z, et al., Histochemistry. 1987;88(1):1-10., Wittmann G, et al., Brain Res. 2004;1002:43-50., Fekete C, et al., J Neurosci. 2000;20:1550-8., Fekete C, et al., J Neurosci. 2000;20:9224-34., Fekete C, et al.: Brain Res. 2002;957:251-8., Wittmann G, et al.: Brain Res. 2005;1039:53-62.

Impact of feeding-related systems on hypophysiotrophic CRH and TRH neuron populations

Innervation of PVN and hypophysiotrophic CRH neurons
by NPY and POMC axons





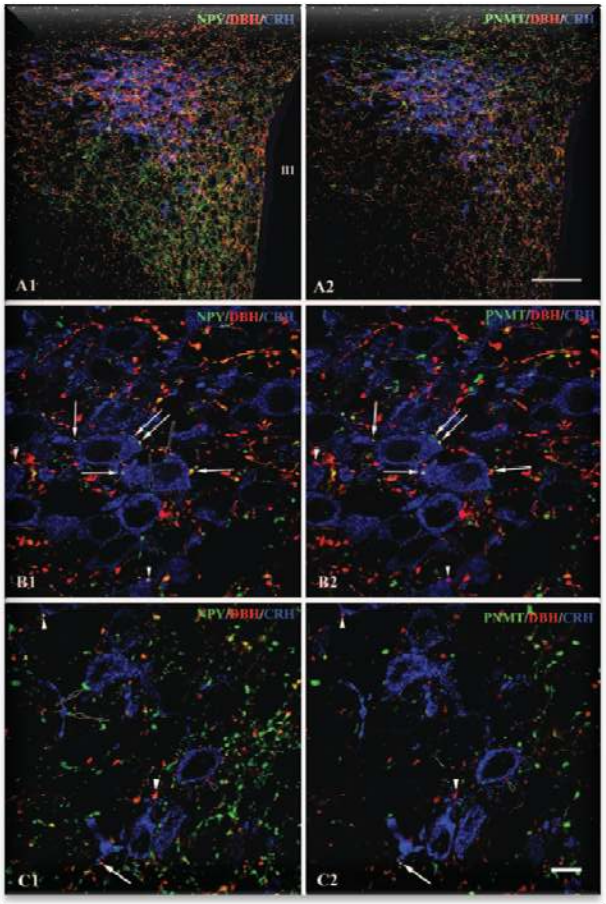
NPY

Liposits Z, Sievers L, Paull WK., Histochemistry. 1988;88:227-34.

POMC

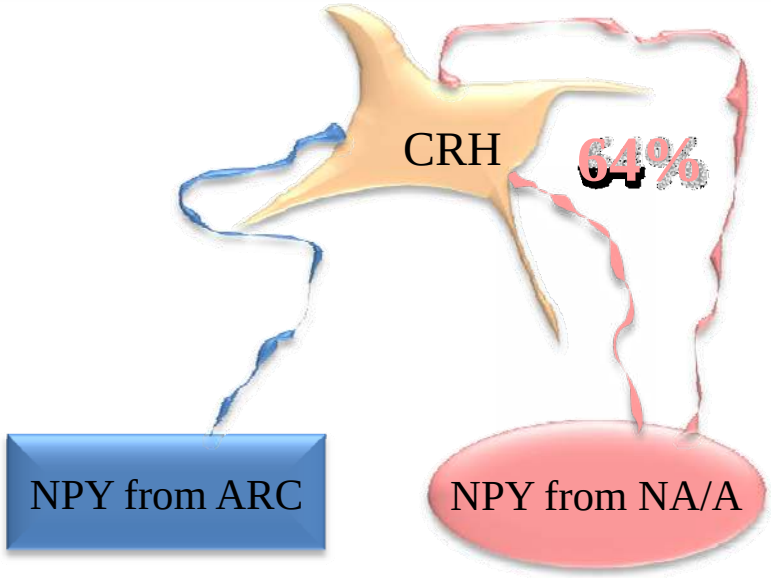
Origin of NPY innervation of CRH neurons

Quantitative analysis of quadruple-labeling immunofluorescence (PNMT/DBH/**NPY**/CRH) in intact rats



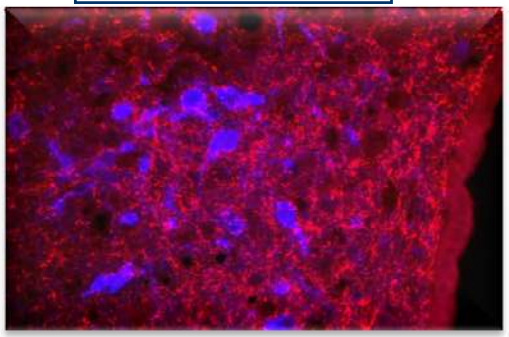
Füzesi et al, Endocrinology, 2007,148:5442-50

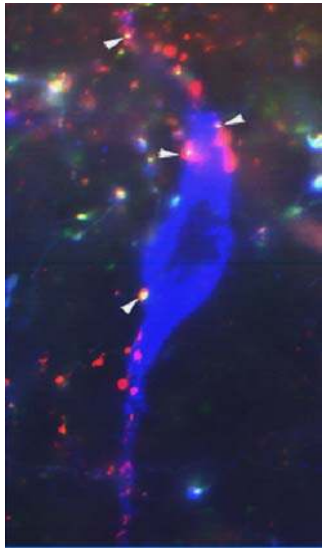
Type of NPY-IR bouton	Percentage of CRH neurons contacted (%)	Average number of NPY-IR varicosities per innervated CRH neuron	Percentage of all NPY-IR boutons in contact with CRH neurons (%)
Single-labeled NPY	89.0 5.3	5.3 0.8	36.6 3.1
DBH/**NPY**	82.8 6.2	3.5 0.8	22.2 3.0
PNMT/DBH/**NPY**	94.2 1.1	5.5 0.4	41.2 5.6
All NPY	100	12.9 2.0	100

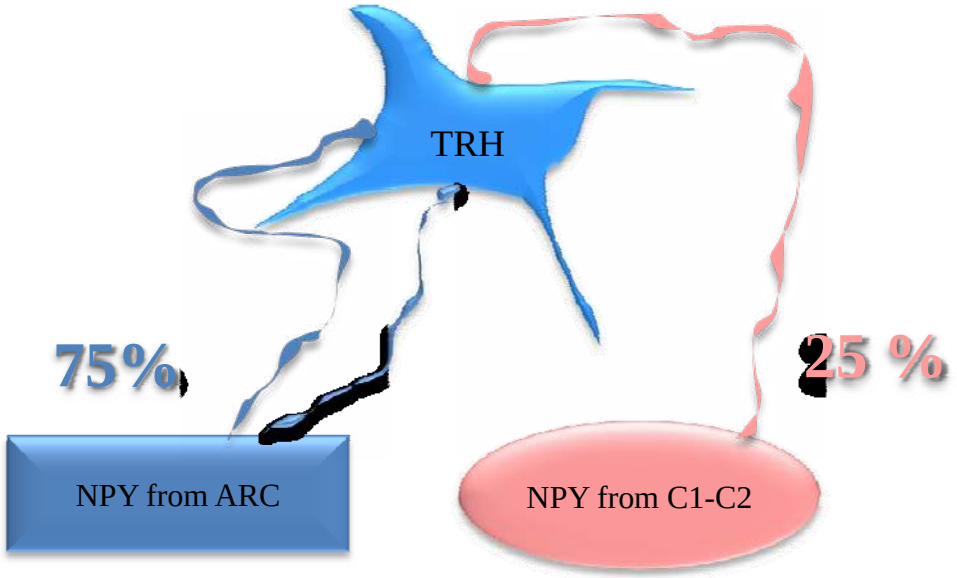


Origin of NPY-ergic afferents to TRH neurons

NPY-ergic innervation of TRH neurons



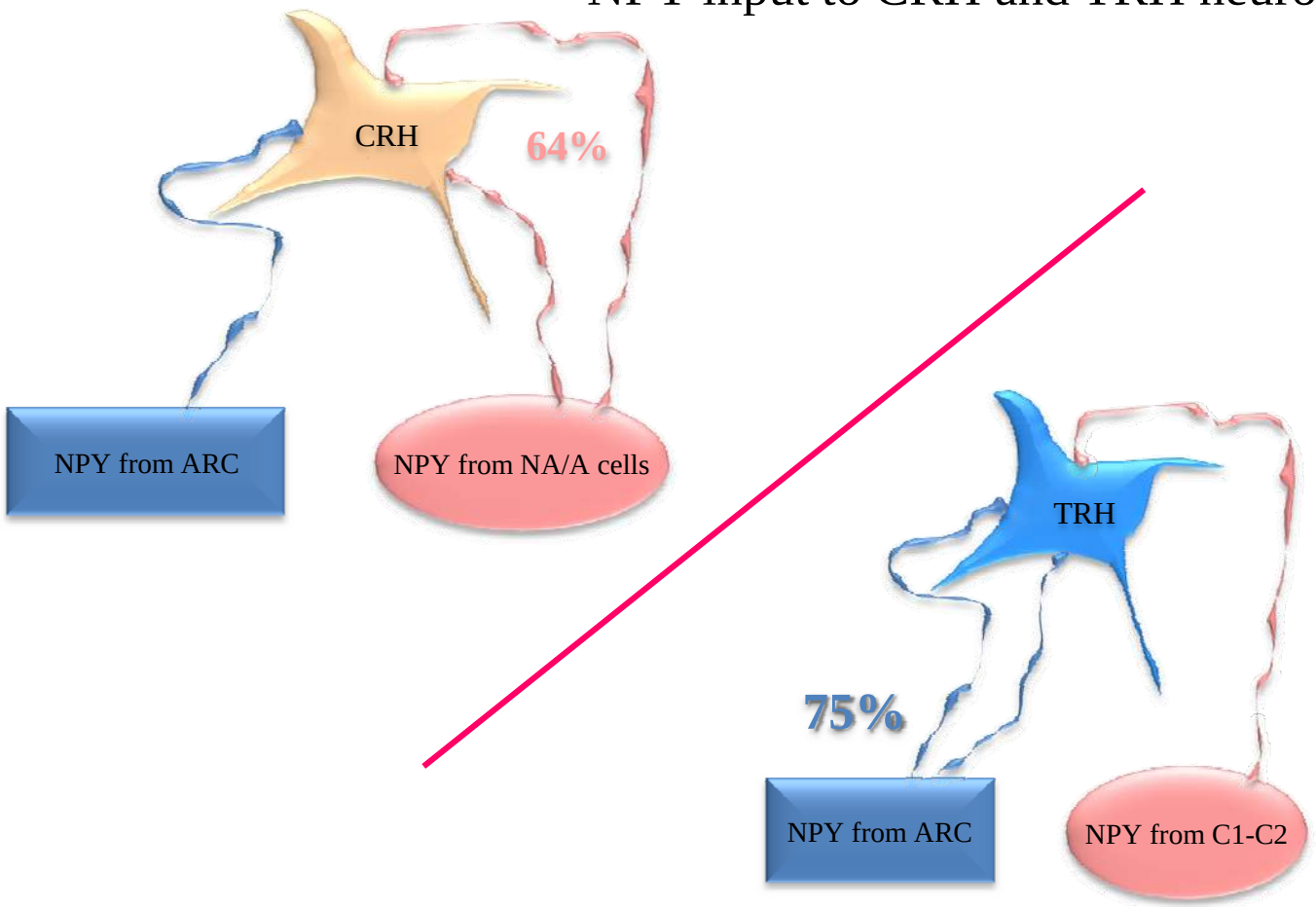




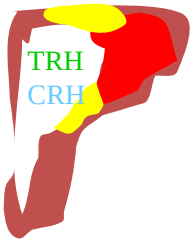
Colocalization of NPY and PNMT in axons innervating TRH neurons

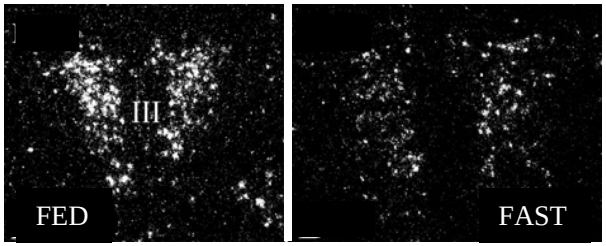
Wittmann G. et al., Neurosci Lett. 2002;324:69-73

NPY input to CRH and TRH neurons

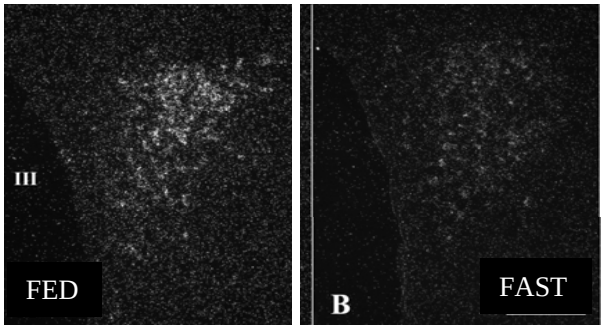


Impact of fasting on the expression of feeding-related peptide mRNAs





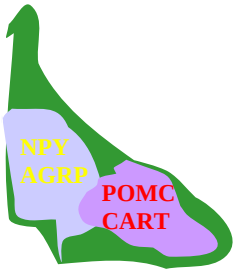
TRH mRNA

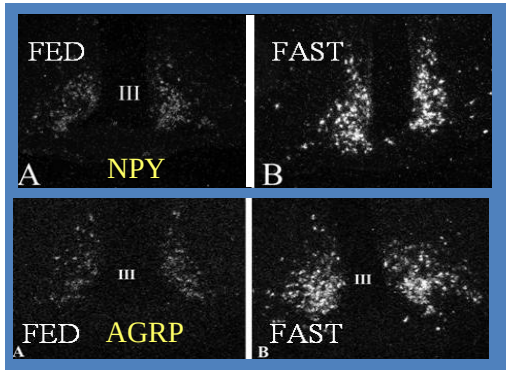


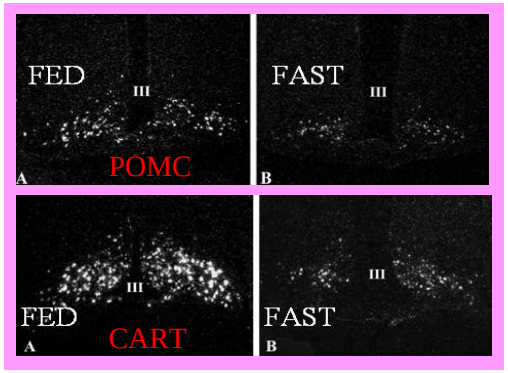
CRH mRNA

anorexigenic

orexigenic

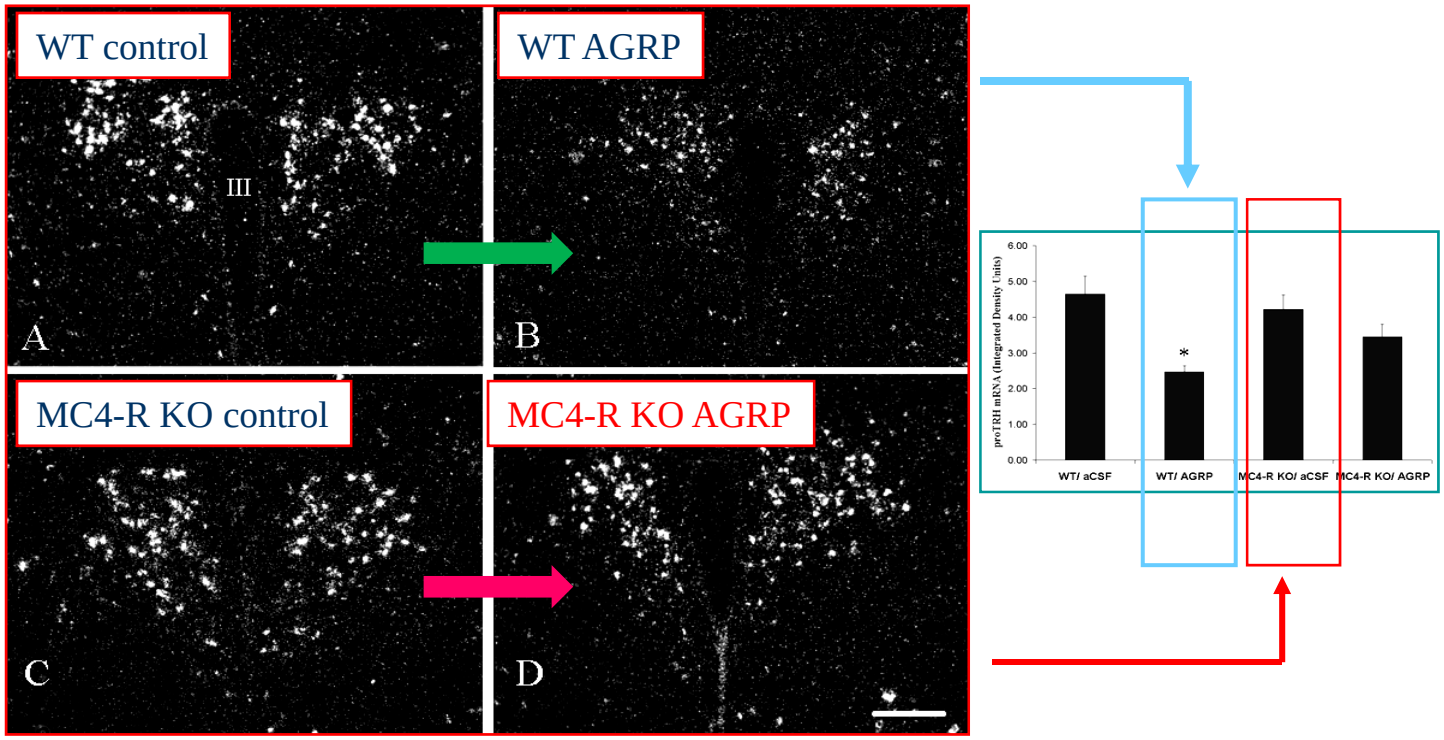






Lechan RM, Fekete C. Prog Brain Res. 2006;153:209-35.

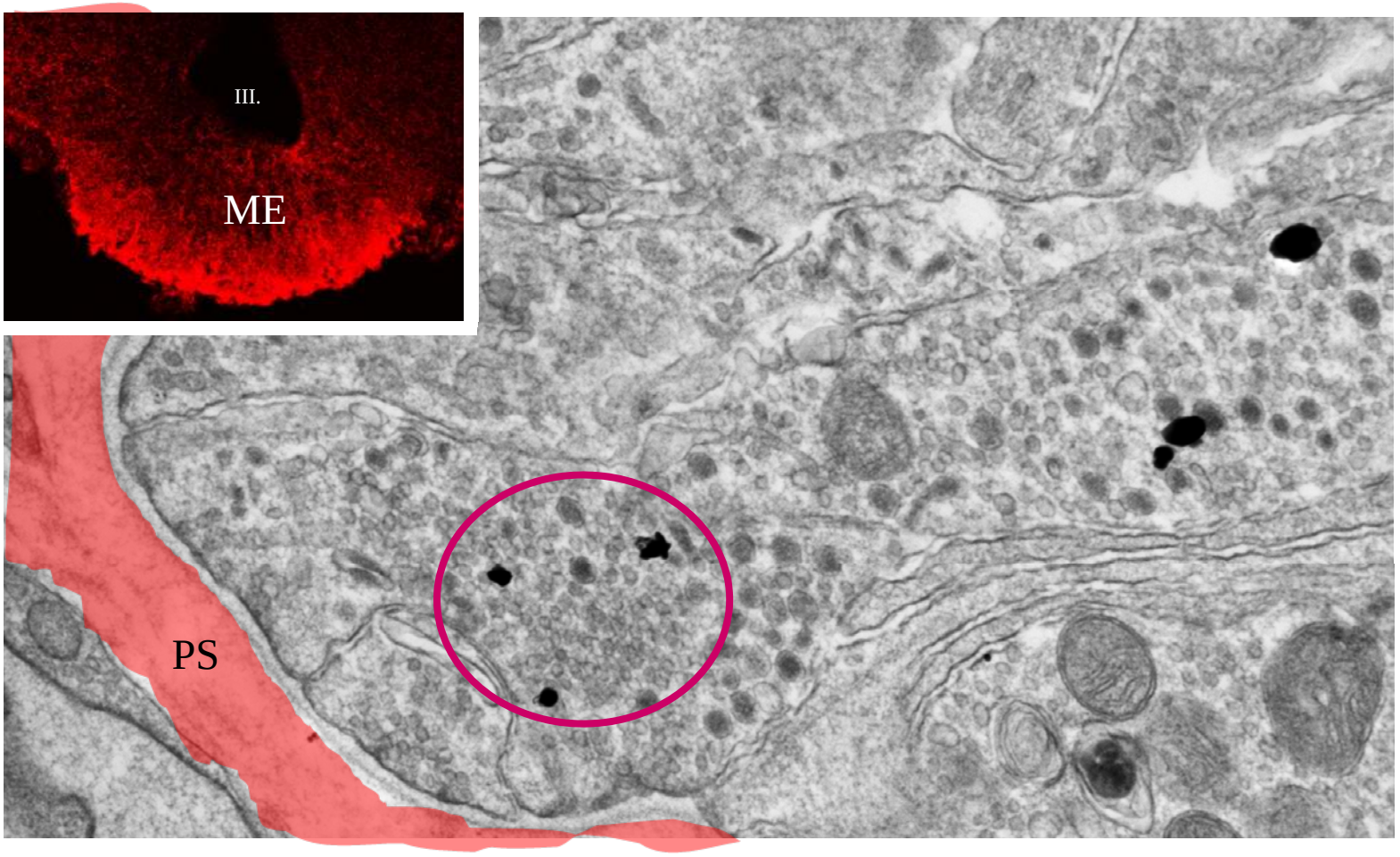
Effects of AGRP on the TRH mRNA levels in the PVN of WT and MC4-R KO mice



Fekete C. et al., Endocrinology. 2004;145:4816-21.

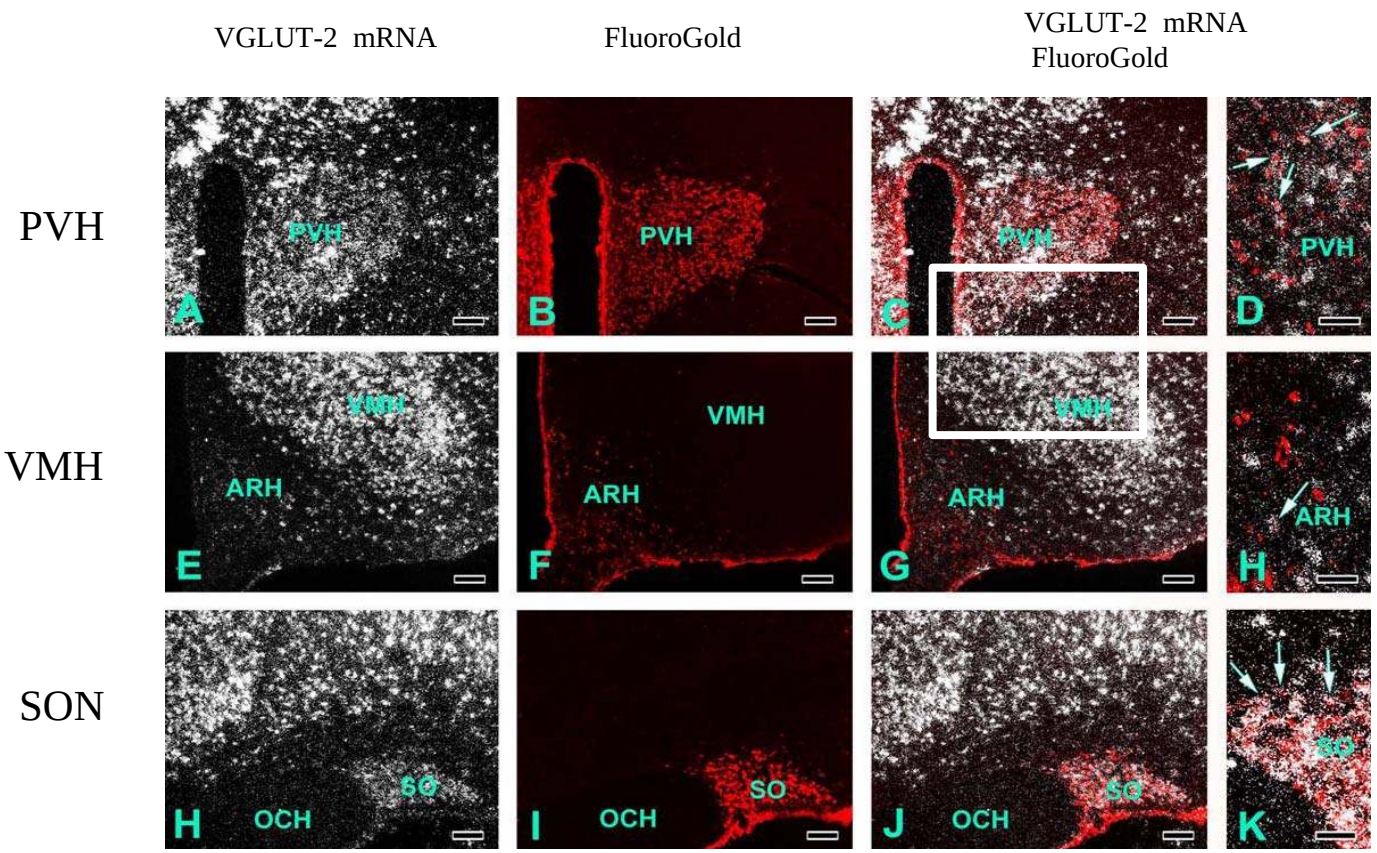
The novel glutamatergic phenotype of TRH and CRH neurons

VGLUT-2 IMMUNOREACTIVITY IN AXONS OF MEDIAN EMINENCE



Hrabovszky et al., Neuroscience. 2007, 23;144:1383-92.

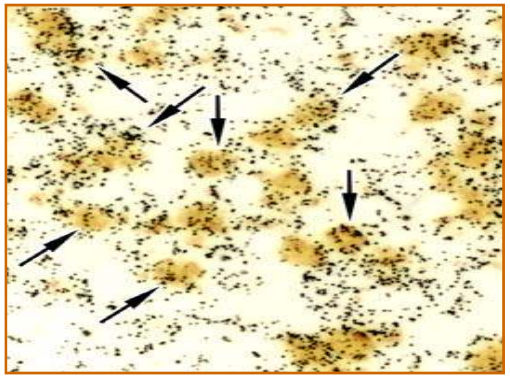
Localization of VGLUT-2 mRNA and retrogradely transported FluoroGold in the hypothalamus



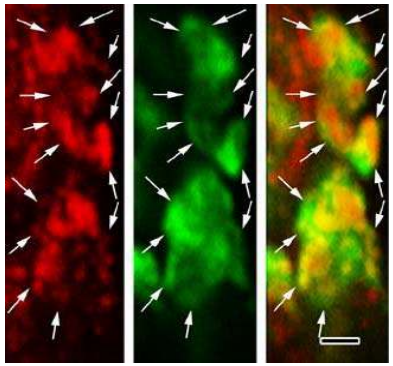
Hrabovszky E, et al., Neuroscience. 2007, 23;144:1383-92.

Expression of VGLUT-2 mRNA in neurosecretory systems

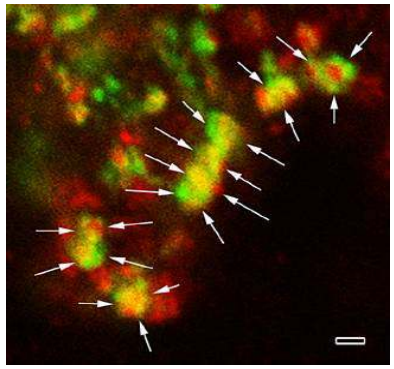
VGLUT-2 mRNA
CRH mRNA

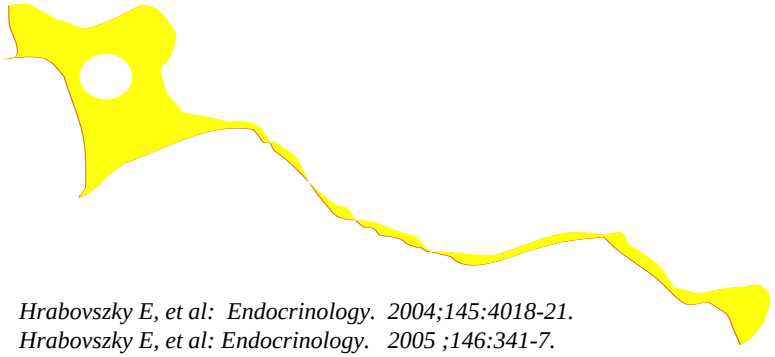


VGLUT-2-IR
CRH-IR



VGLUT-2-IR
TRH-IR

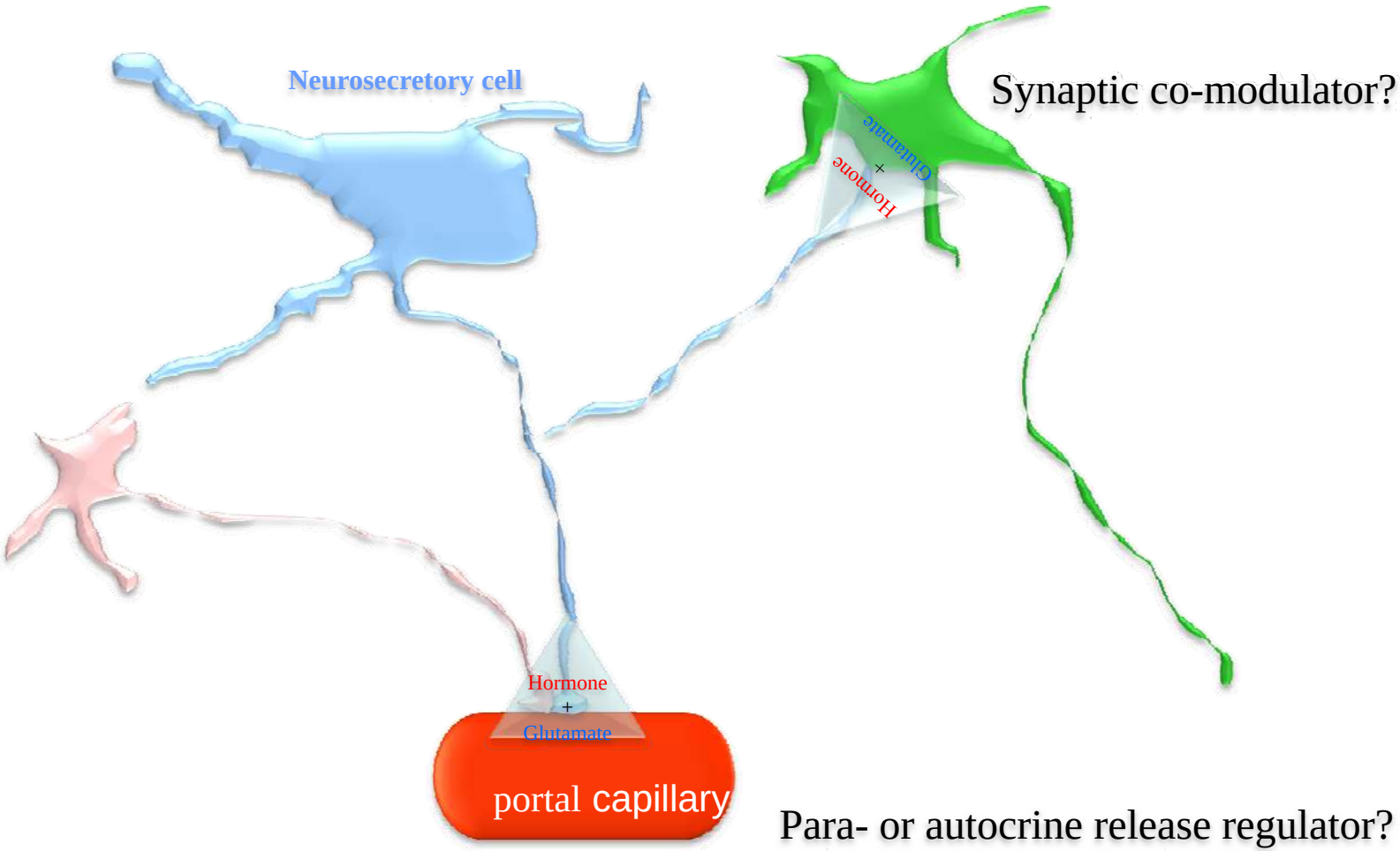




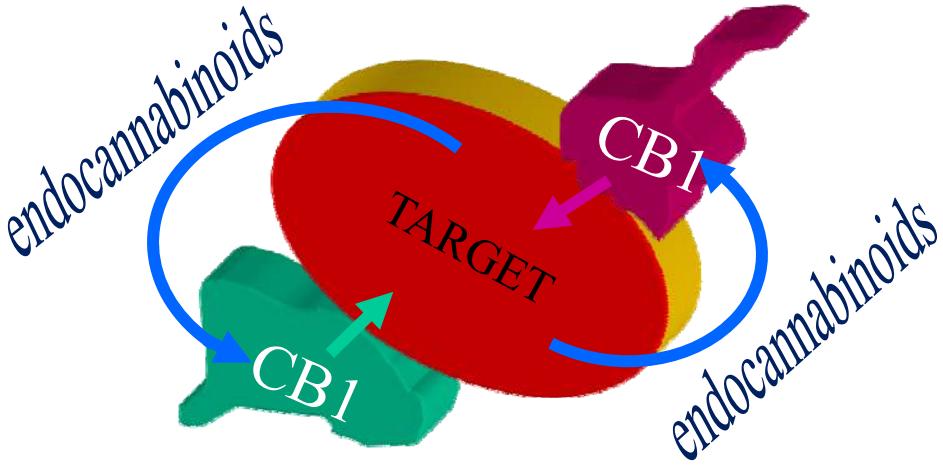
CRH
TRH
LHRH
SS
VP
OXY

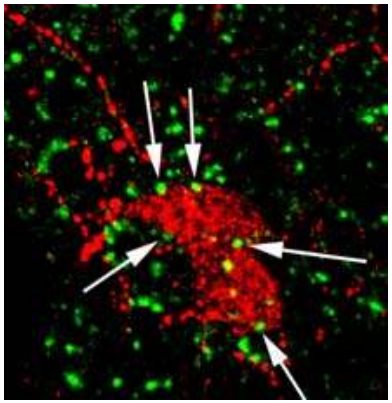
+ VGLUT-2

Hrabovszky E, et al: Endocrinology. 2004;145:4018-21.
Hrabovszky E, et al: Endocrinology. 2005 ;146:341-7.
Hrabovszky E, et al: Eur J Neurosci. 2005;21:2120-6.
Hrabovszky E, et al: Neurochem Int. 2006;48:753-61.


Neurosecretory cell
Synaptic co-modulator?
Glutamate
+
Hormone
Hormone
+
Glutamate
portal capillary
Para- or autocrine release regulator?

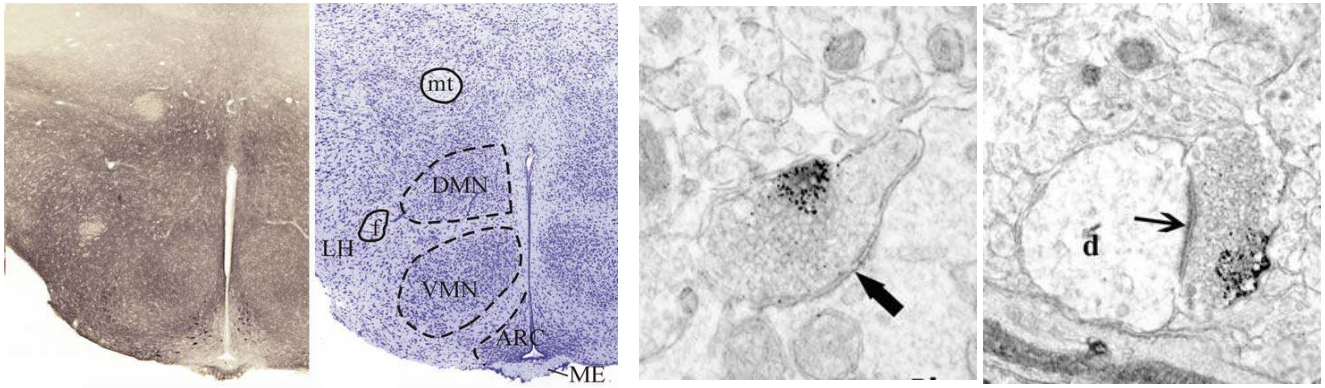
Retrograde endocannabinoid signaling in hypothalamic feeding centers

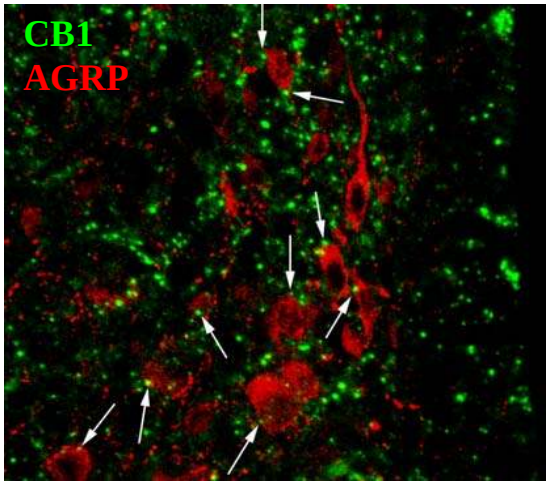


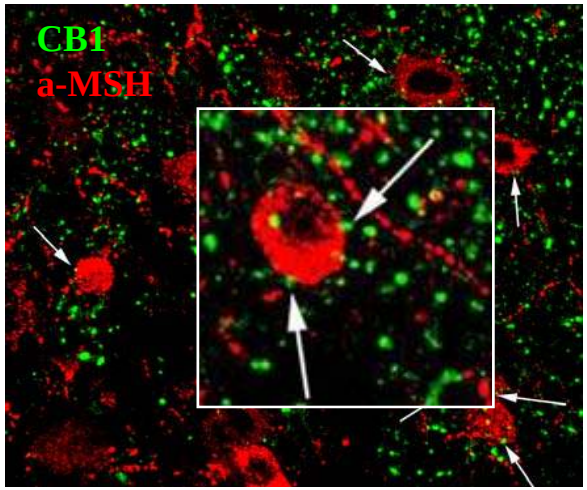


CB1-IR innervation of the arcuate nucleus

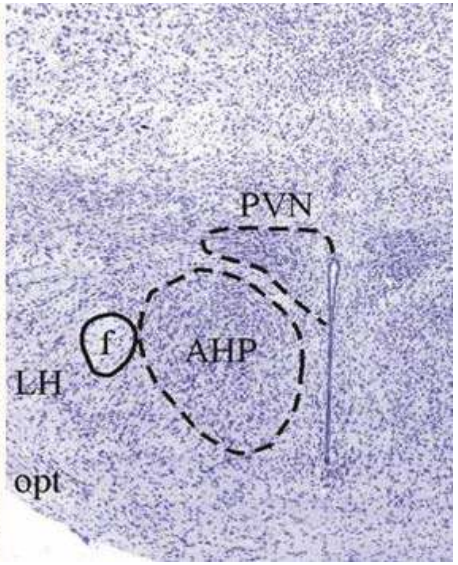
CB1-IR | Nissl | Symmetric synapse | Asymmetric synapse







Wittmann G. et al., J. Comp. Neurol, 2007 ,10;503:270-9.

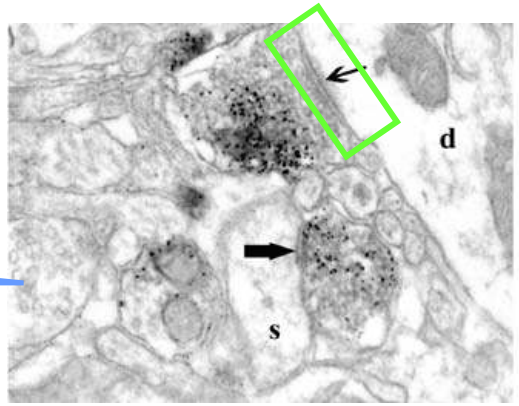


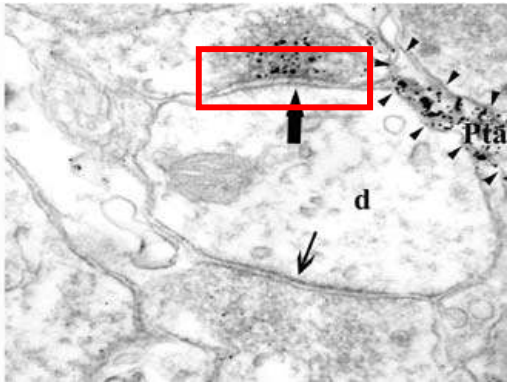
PVN

Localization of CB1 receptor in excitatory and inhibitory pre-synaptic terminals of parvicellular neurons in PVN

Inhibitory

CB1



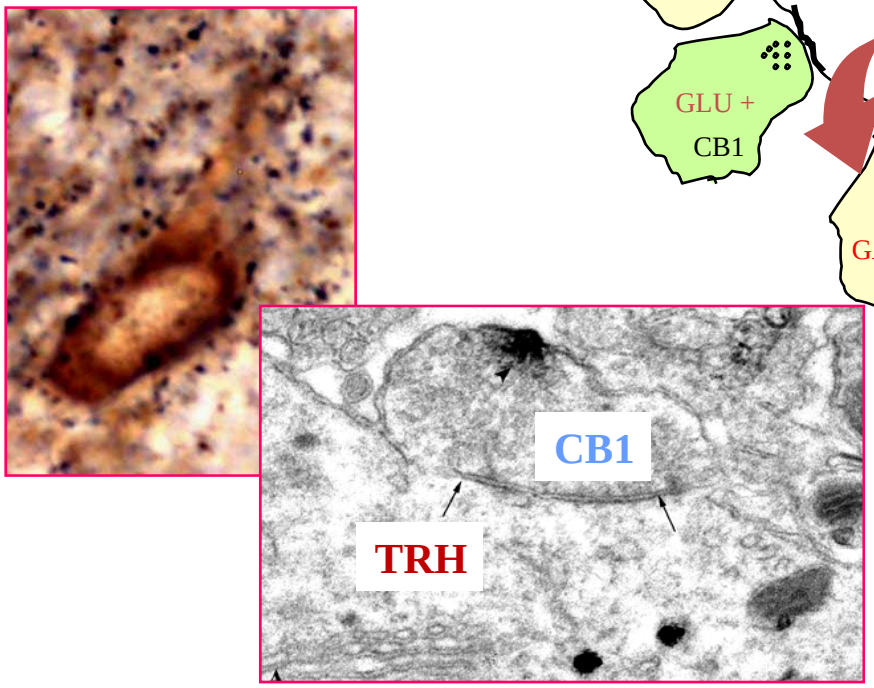


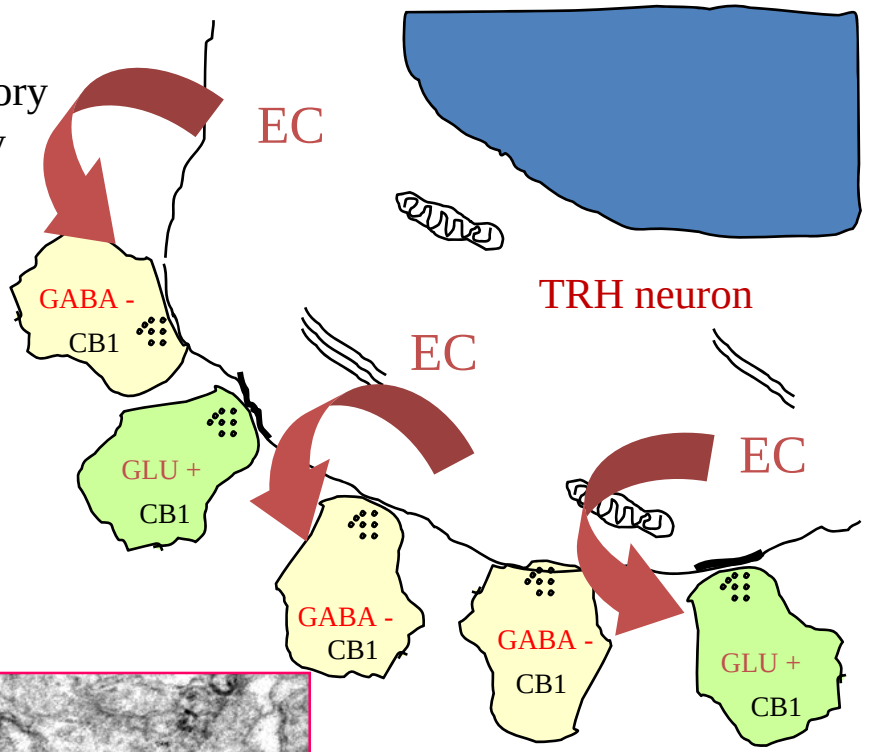
Excitatory

Wittmann G. et al., J. Comp. Neurol, 2007 ,10;503:270-9.

Modulation of excitatory and inhibitory synaptic inputs to TRH neurons by endogenous cannabinoids

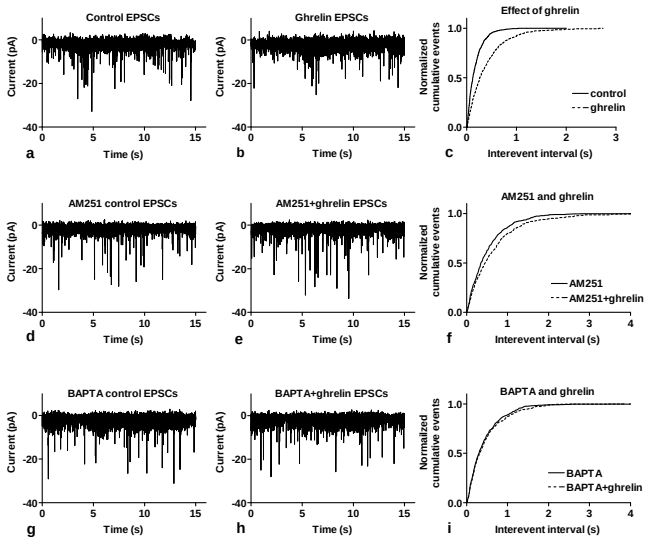
Innervation of TRH neurons by CB1-IR axons

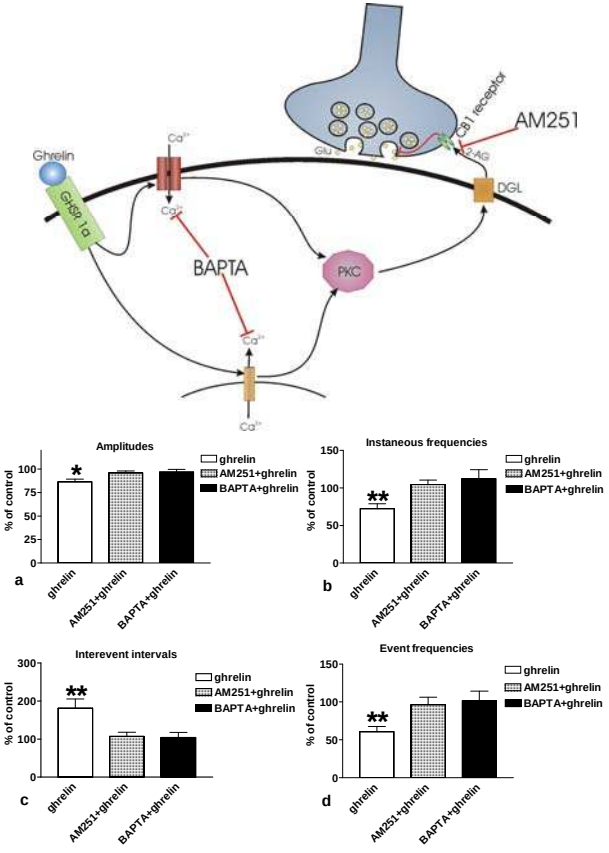




Deli et al. et al.: Endocrinology, 2009,150:98-103

Cooperation between ghrelin and endocannabinoid signaling mechanisms

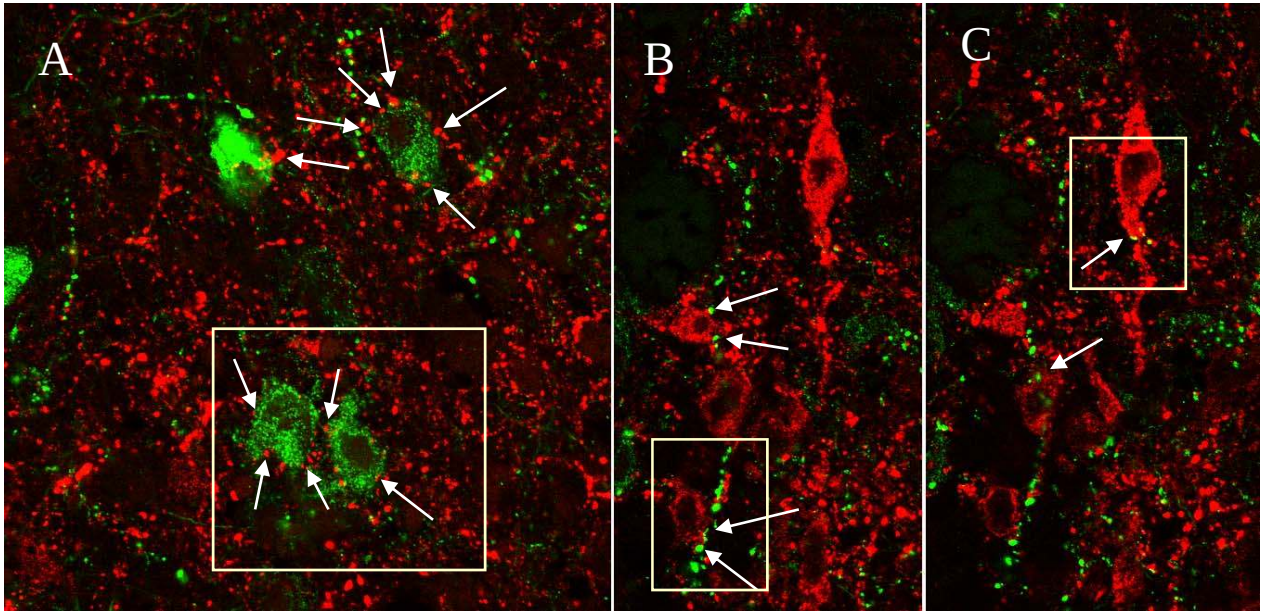




Kola et al., PLoS One. 2008 Mar 12;3(3):e1797.

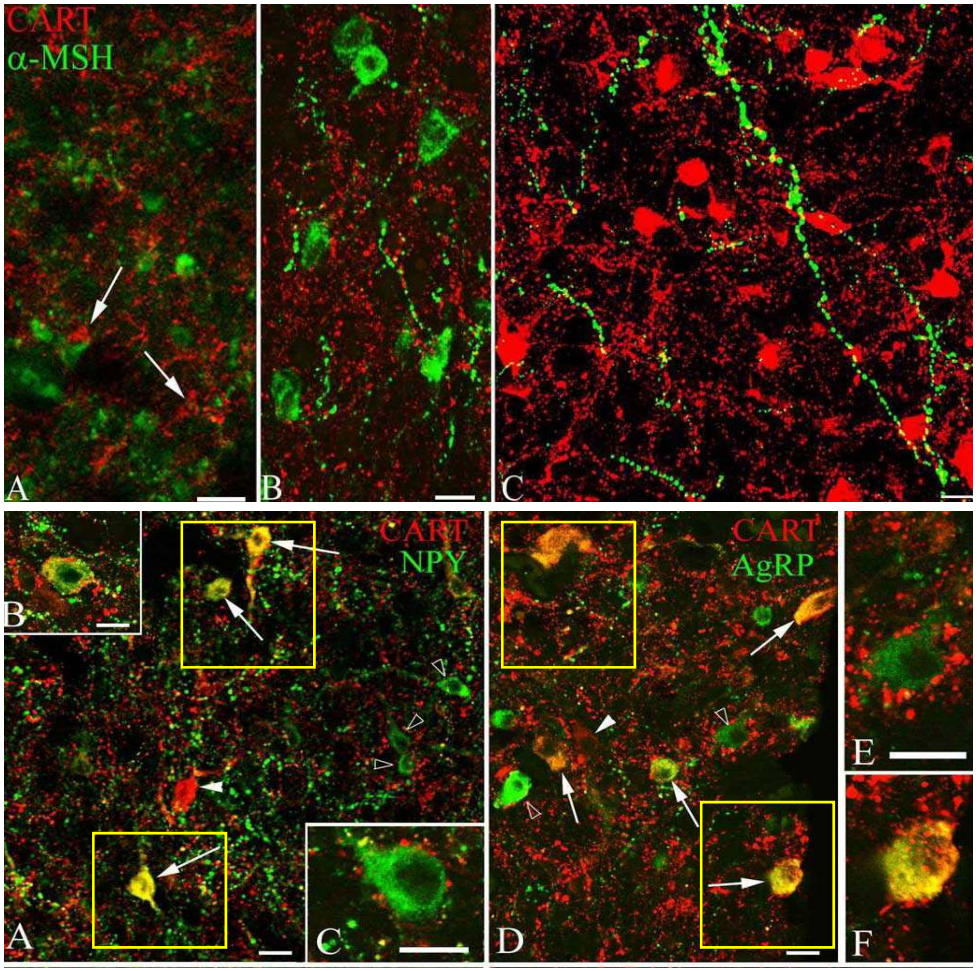
Organization and specific features of the human hypothalamic feeding centers

Reciprocal connection between α-MSH- and NPY-producing neurons in the infundibular nucleus of the human hypothalamus



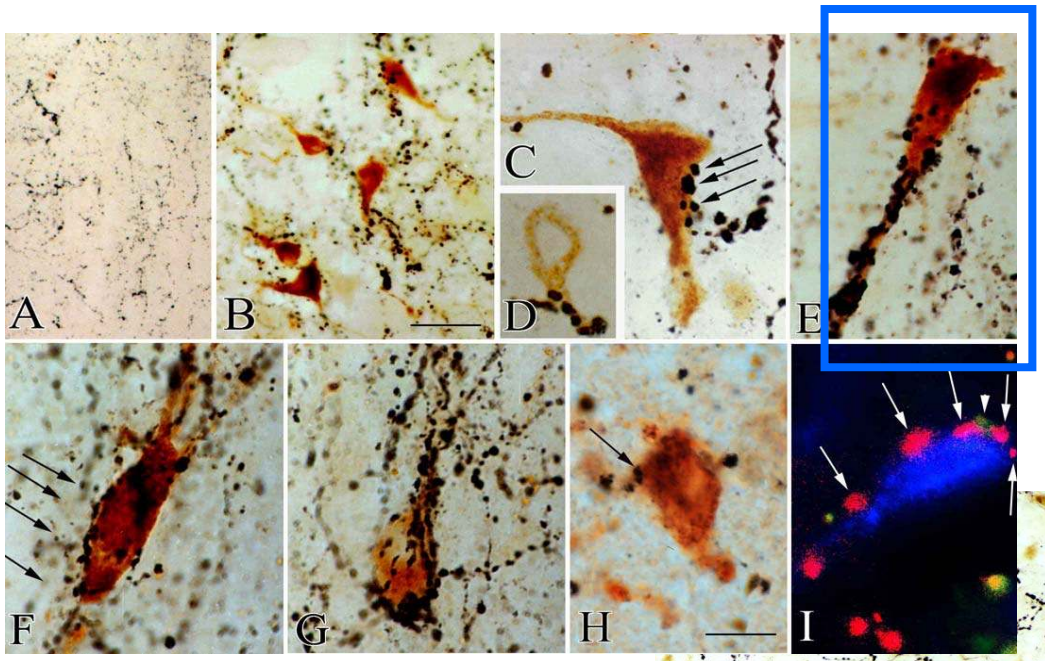
Menyhért J. et al., Brain Res. 2006;1076:101-5.

α-MSH cells do not express CART in humans



Menyhért J. et al., Endocrinology, 2007,148:4276-81

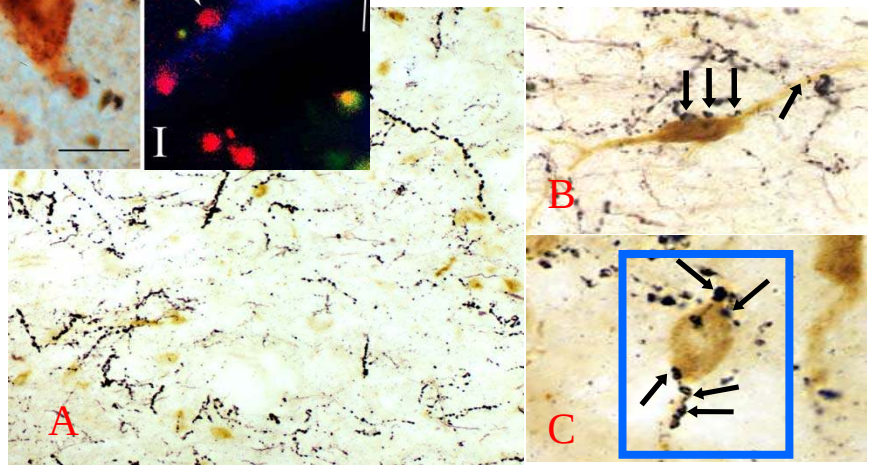
NPY-IR and α-MSH-IR innervation of the CRH-IR neurons in the paraventricular nucleus of the *human* hypothalamus



NPY

Mihaly E. et al., J Comp Neurol. 2002;446:235-43

α-MSH



Mihály E. et al., 2007, unpublished

Characteristics of neuronal networks regulating feeding in humans