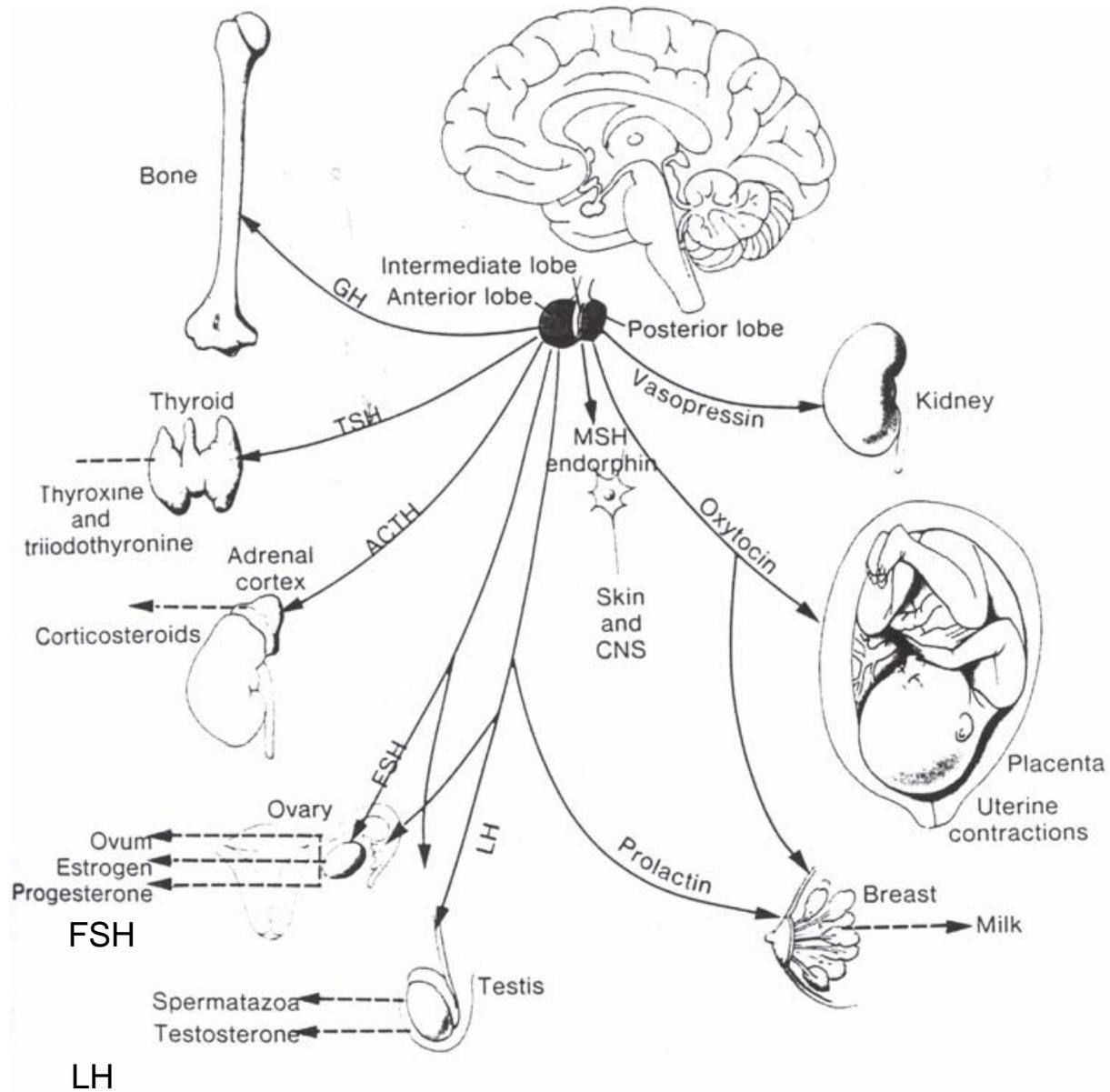


# **HYPOTHALAMUS AND NEUROENDOCRINE SYSTEMS**

- **Boundaries, Subdivisions, Hypothalamic Nuclei**
- **Connections of the Hypothalamus**
- **Magno- and Parvocellular Neurosecretory System**
- **Hypothalamic Organization**
- **Reflex Control of Vasopressin and Oxytocin Secretion**
- **Central Control of Osmo-Volume regulation. Thirst. Drinking**
- **Brain-Pituitary Gonadal Axis**
- **Brain-Pituitary-Adrenal Axis. Stress**
- **Behavioral State Control**

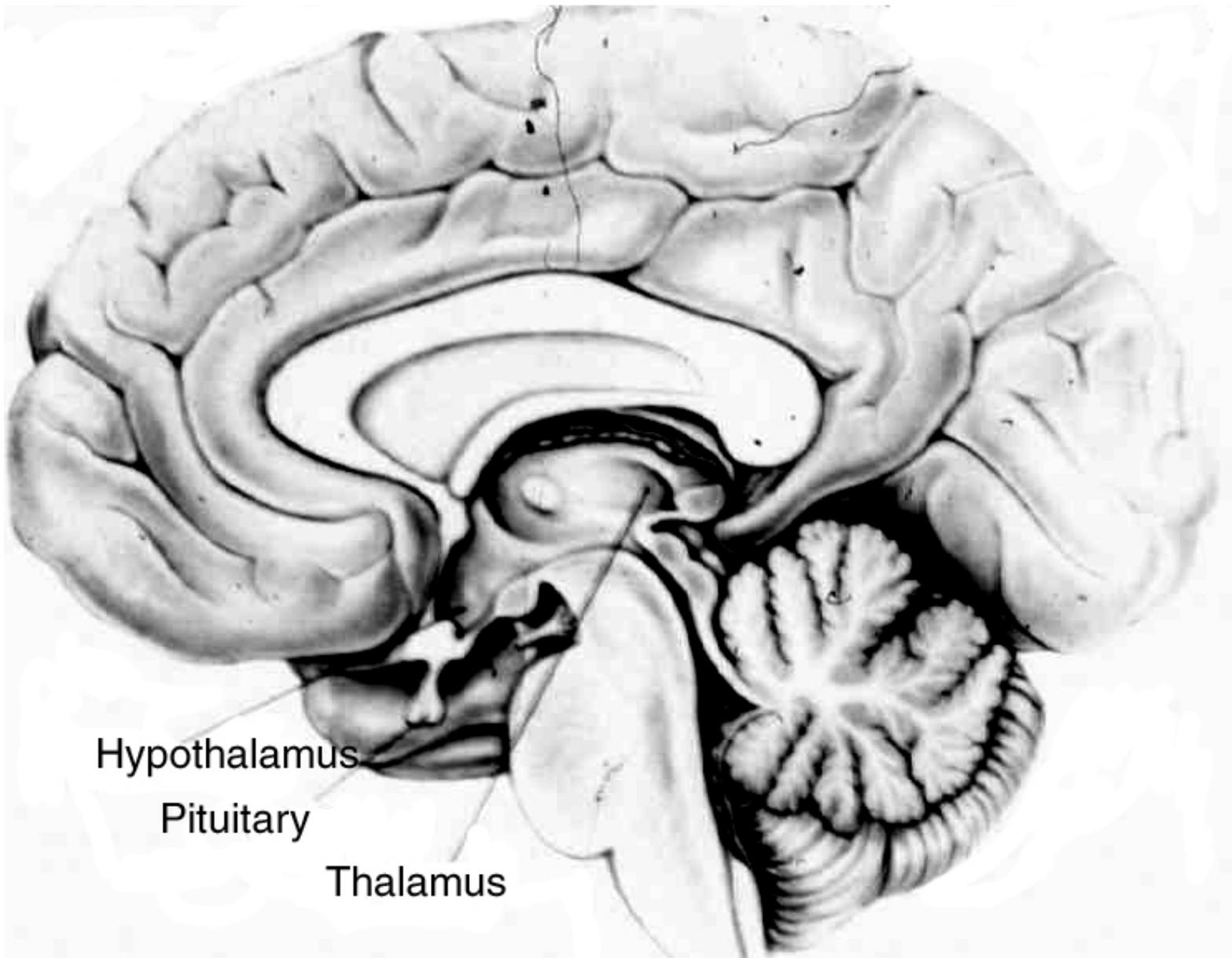
<b>Process</b>	<b>System or Activity</b>	<b>Effect</b>
Autonomic	Cardiovascular	Blood flow ( ↓ or ↑ ) <sup>*</sup> Vasodilation or vasoconstriction
	Thermoregulatory	Blood flow, shivering, panting
	Visceral	Digestive acid secretion ( ↑ )
Behavioral	Sexual	Sexual receptivity ( ↑ )
	Maternal	Nest building
	Emotional	Aggression ( ↑ )
	Ingestive	Eating and drinking ( ↑ or ↓ )

<sup>\*</sup> ↑ , increase; ↓ , decrease



### NEUROENDOCRINE REGULATORS OF HYPOTHALAMIC ORIGIN

<b>System Regulated</b>	<b>Site of Regulation</b>	<b>Action</b>	<b>Hypothalamic Regulator</b>
Thyroid gland	Adenohypophysis	Stimulation of thyrotrophin secretion	Thyrotrophin-releasing hormone
Adrenal cortex	Adenohypophysis	Stimulation of adrenocorticotrophin secretion	Corticotrophin-releasing hormone
Gonads	Adenohypophysis	Stimulation of luteinizing hormone and follicle-stimulating hormone secretion	Gonadotropin-releasing hormone
Muscle, bone, liver	Adenohypophysis	Stimulation or inhibition of growth hormone secretion	Growth hormone-releasing hormone, somatostatin
Milk synthesis and secretion from the mammary gland	Adenohypophysis	Inhibition of prolactin secretion	Dopamine
Cardiovascular, renal	Vascular smooth muscle, renal tubule	Vasoconstriction, water reabsorption	Vasopressin (antidiuretic hormone)
Mammary gland, uterus	Smooth muscle of mammary ducts and uterus	Increase intramammary pressure, inducing milk ejection; increase uterine contraction in labor	Oxytocin



Hypothalamus

Pituitary

Thalamus

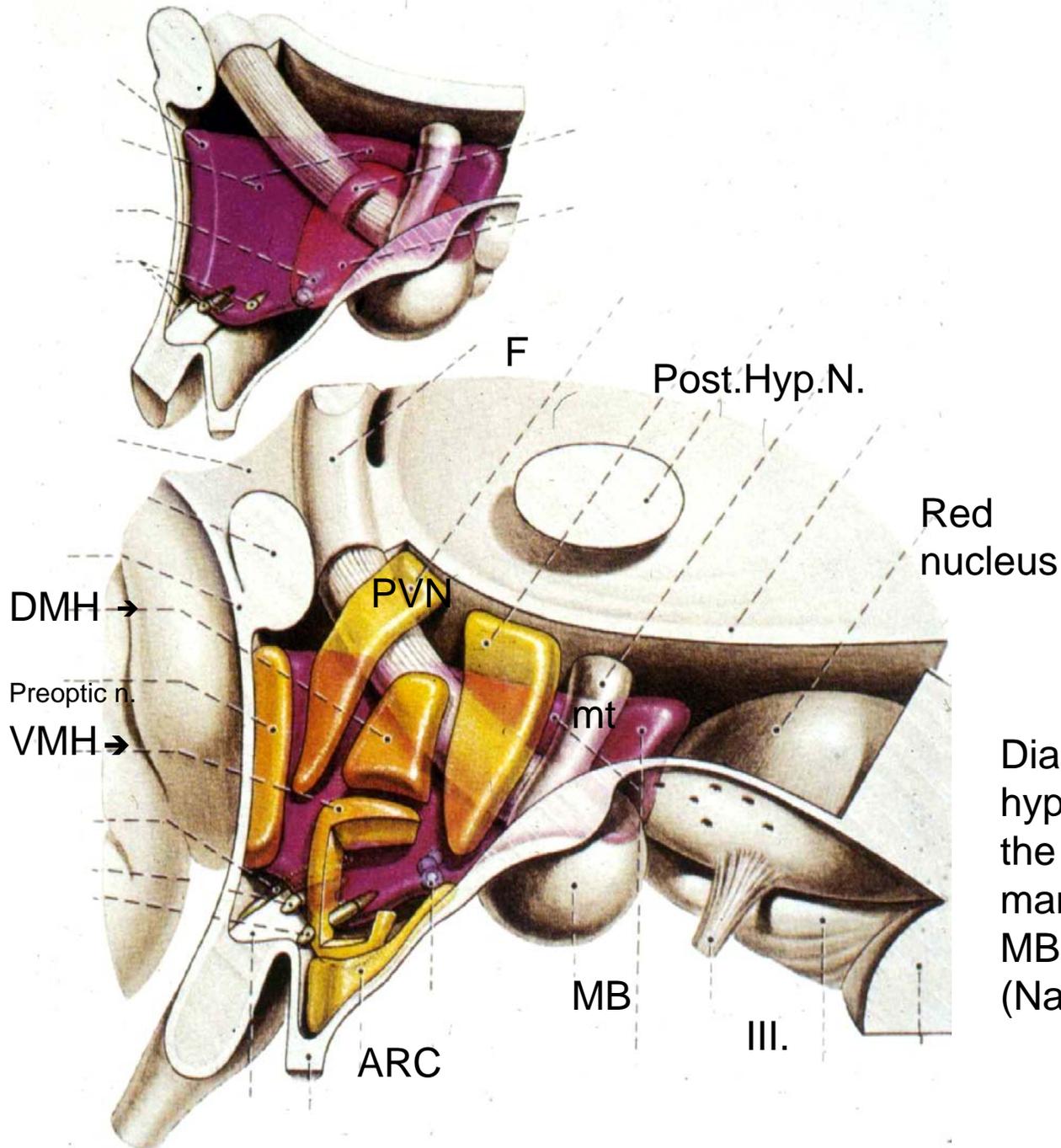
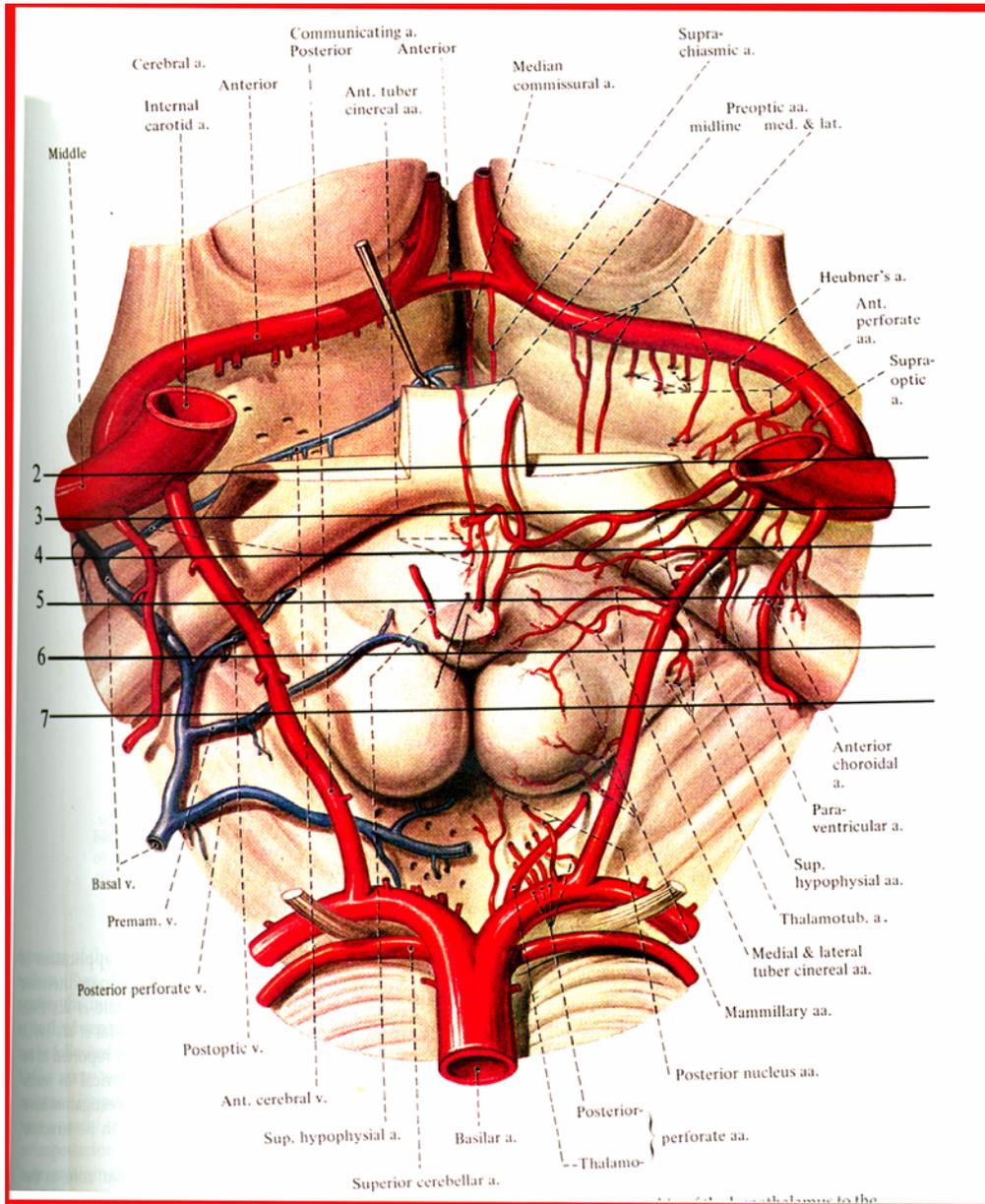
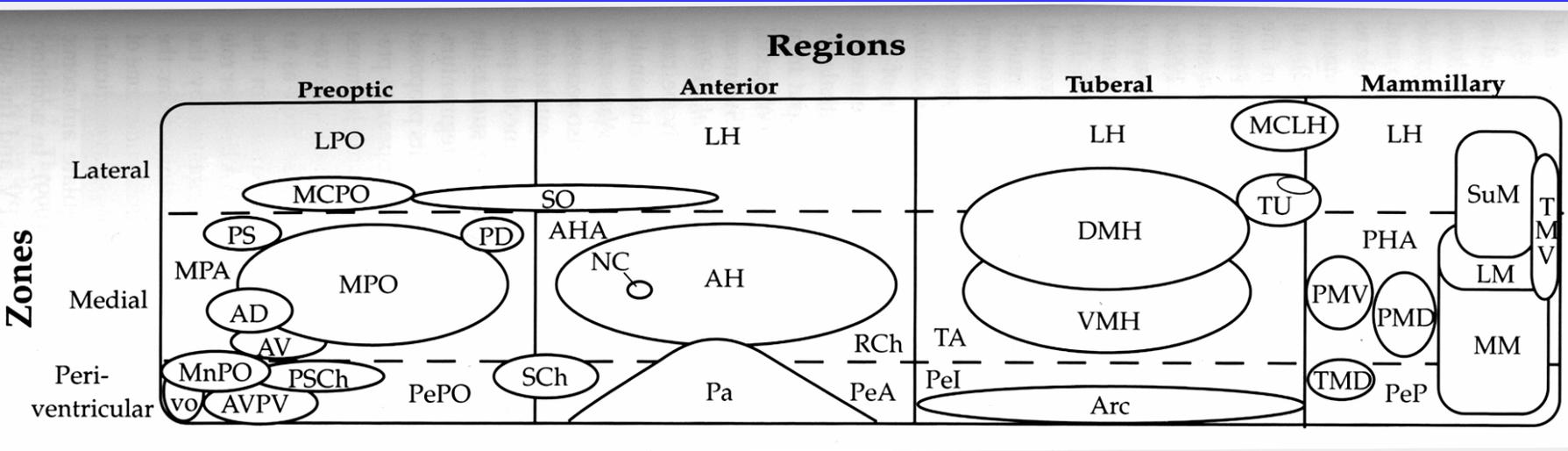


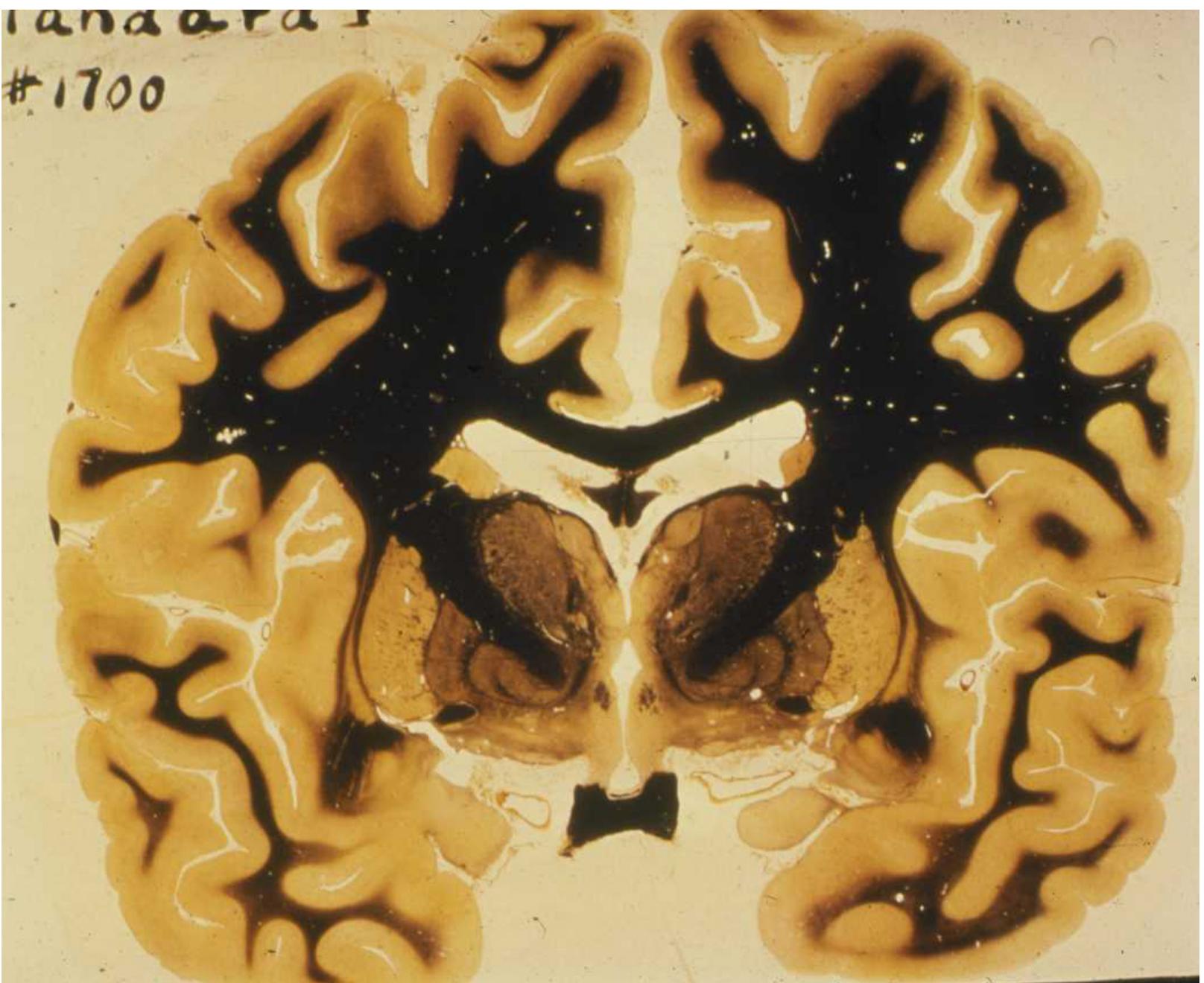
Diagram to show the major hypothalamic nuclei lateral to the fornix (F) and mammillothalamic tract (mt). MB= mammillary body. (Nauta, 1969).



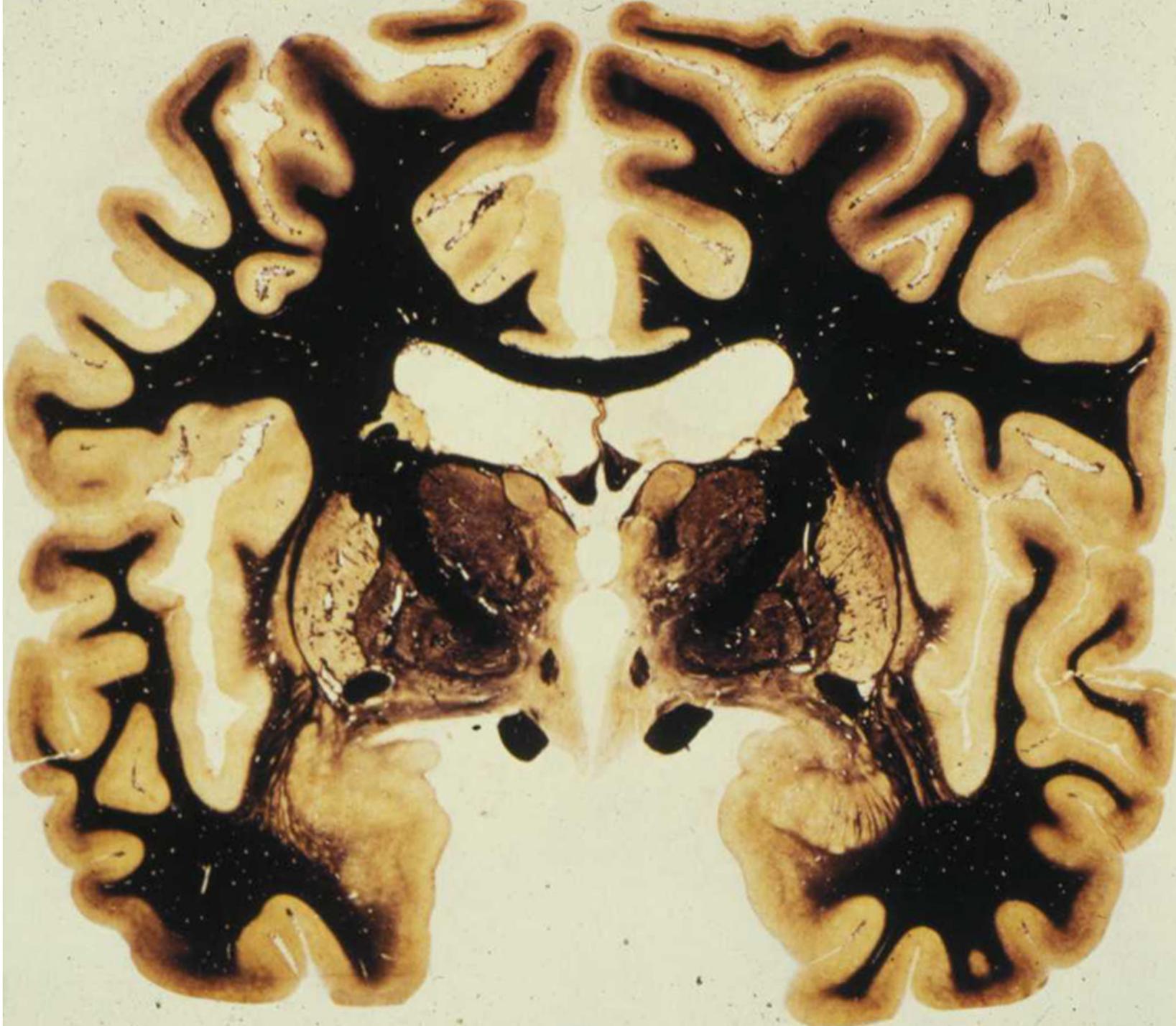
Basal surface of the brain showing the hypothalamus (Haymaker and Nauta, 1969)

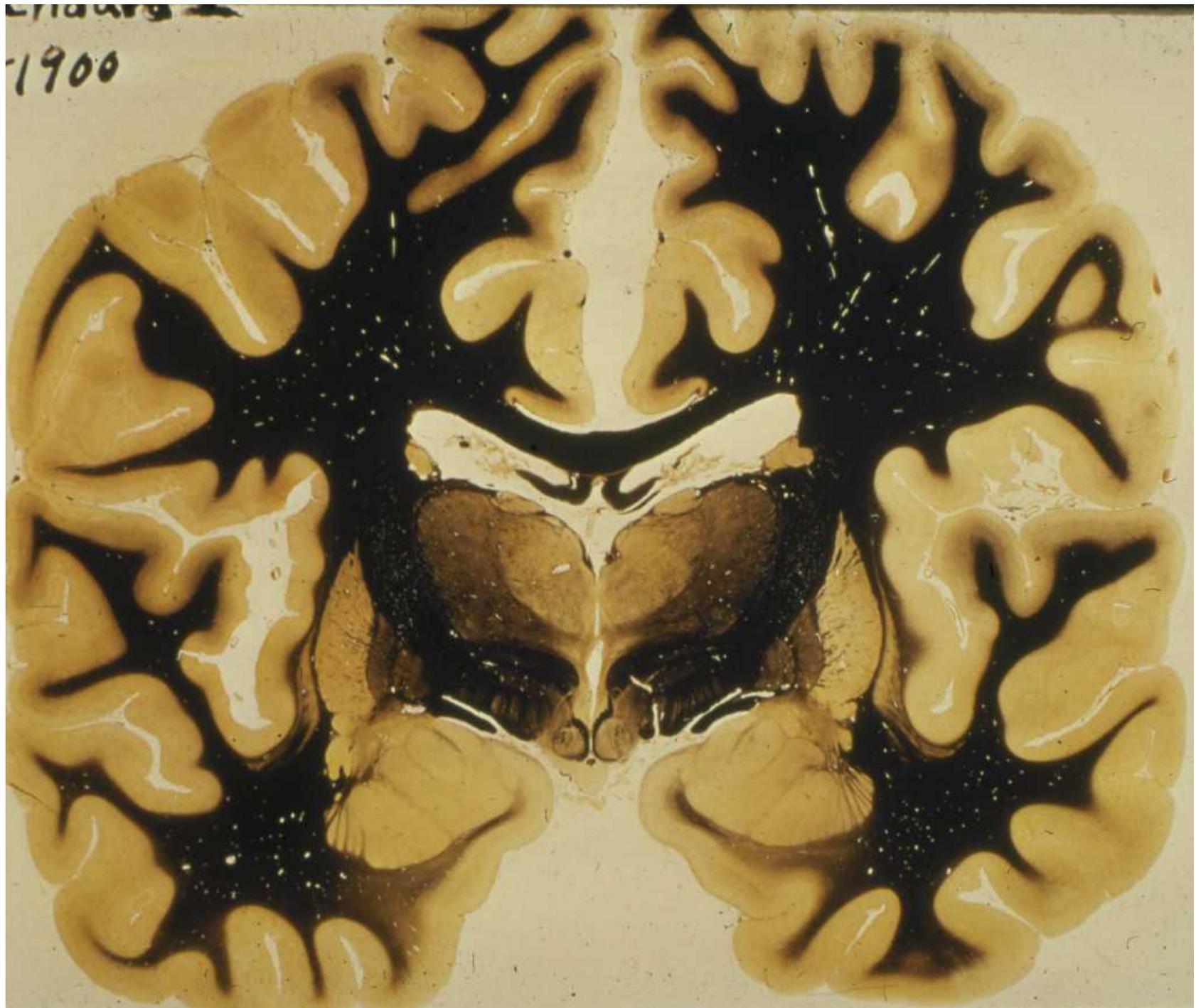
# ORGANIZATION OF THE HYPOTHALAMUS (from Simerly, 2004)

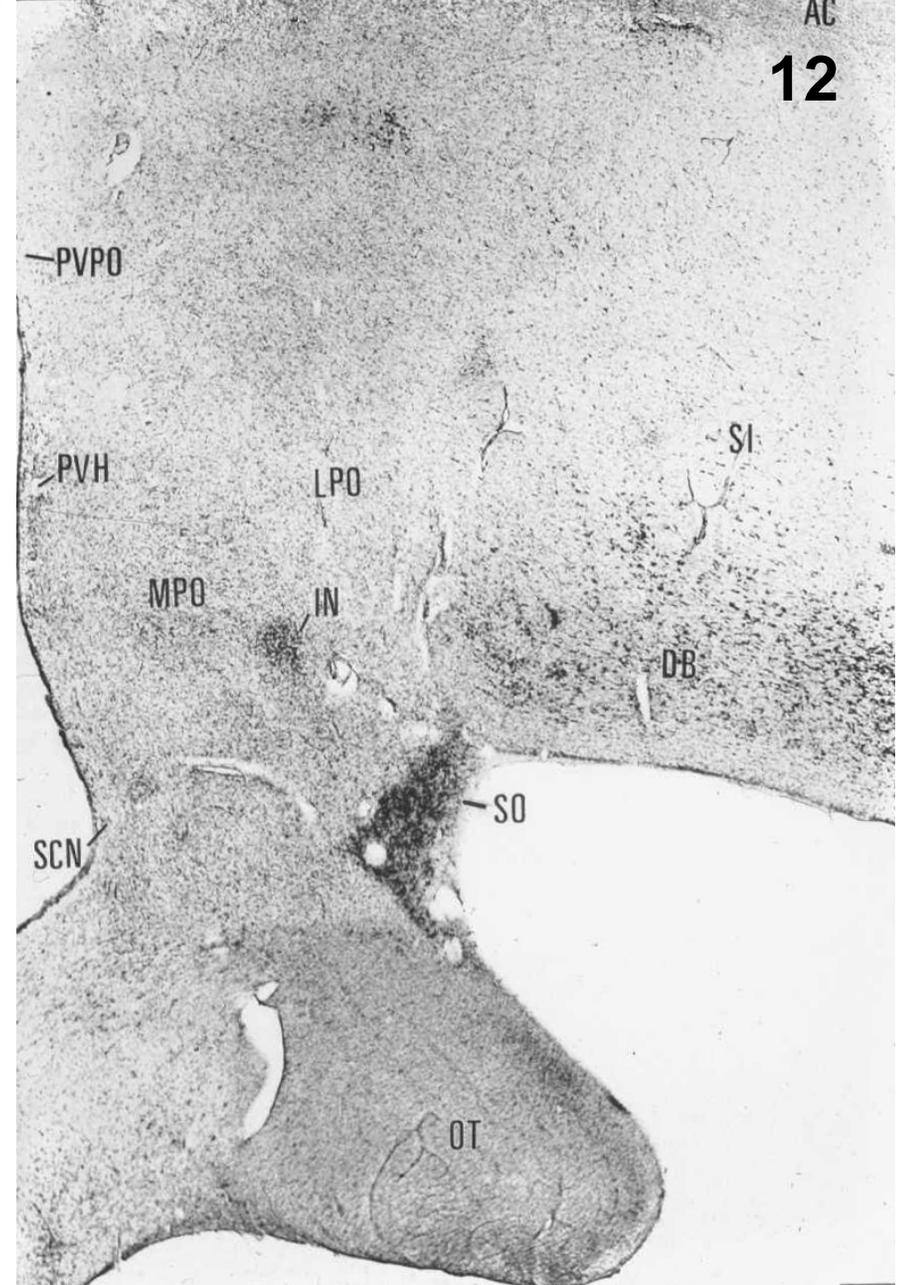
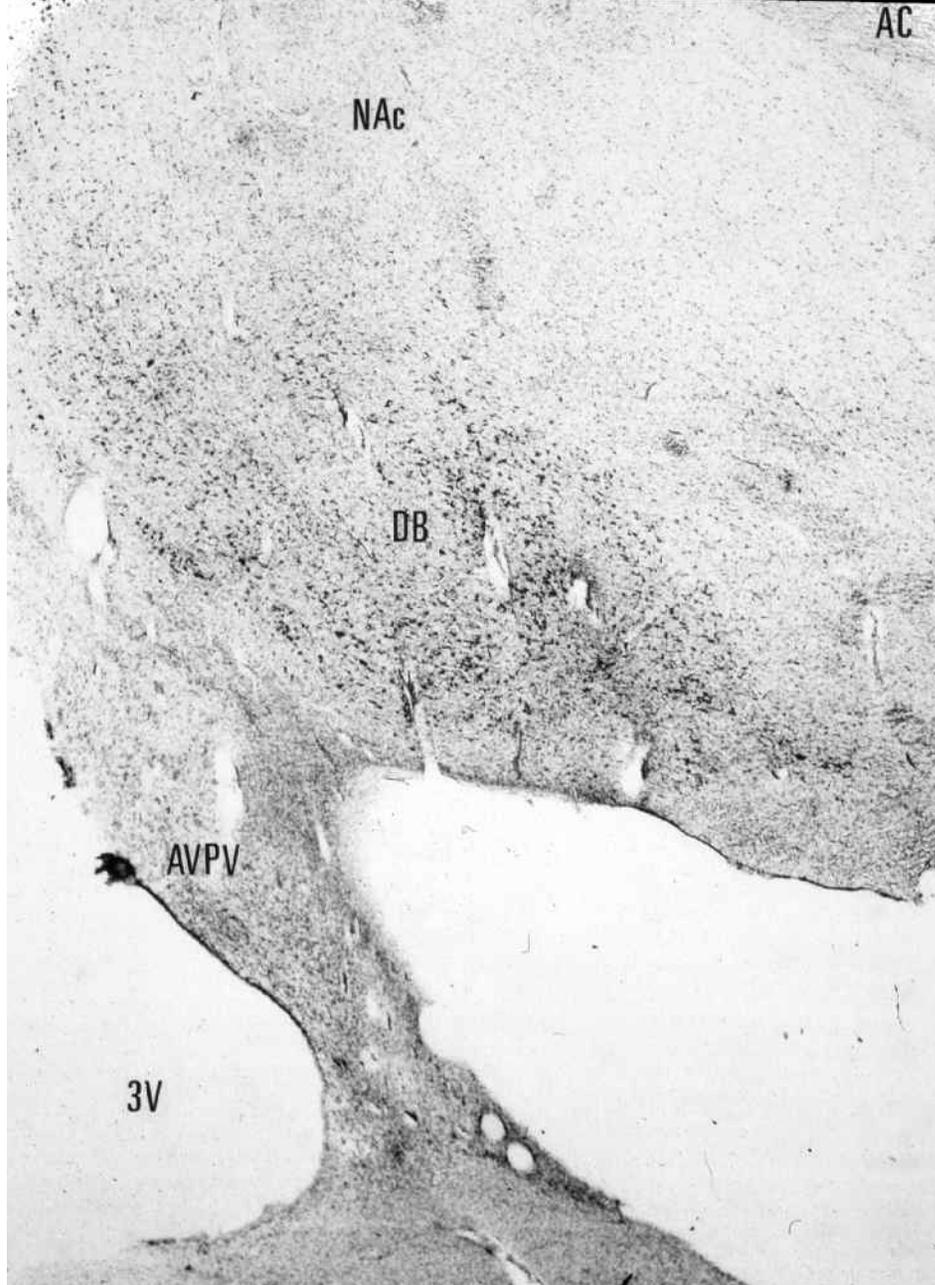




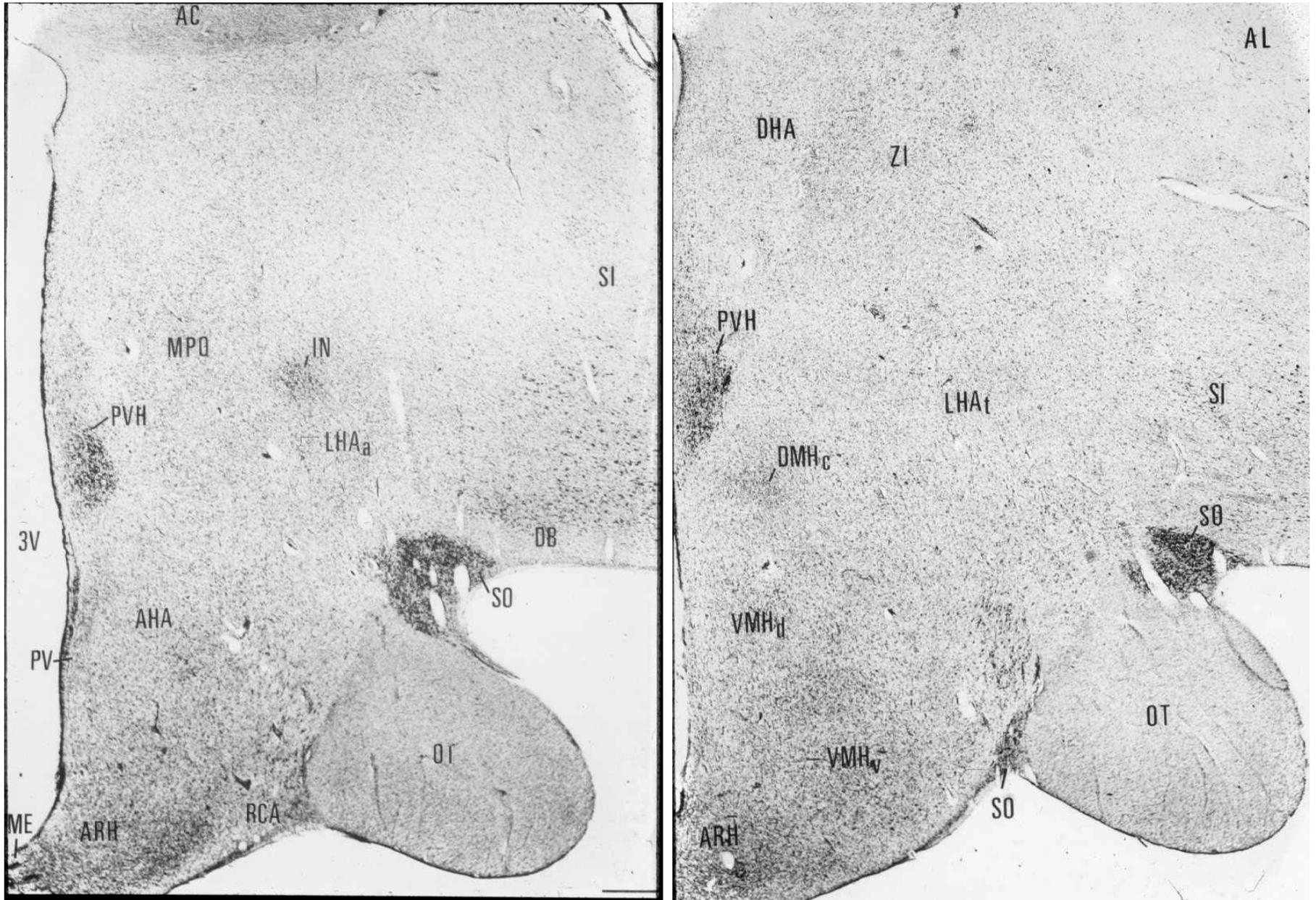
Myelin-stained sections of the human brain cut in the frontal plane for orientation.  
(From the Jakoblev collection).



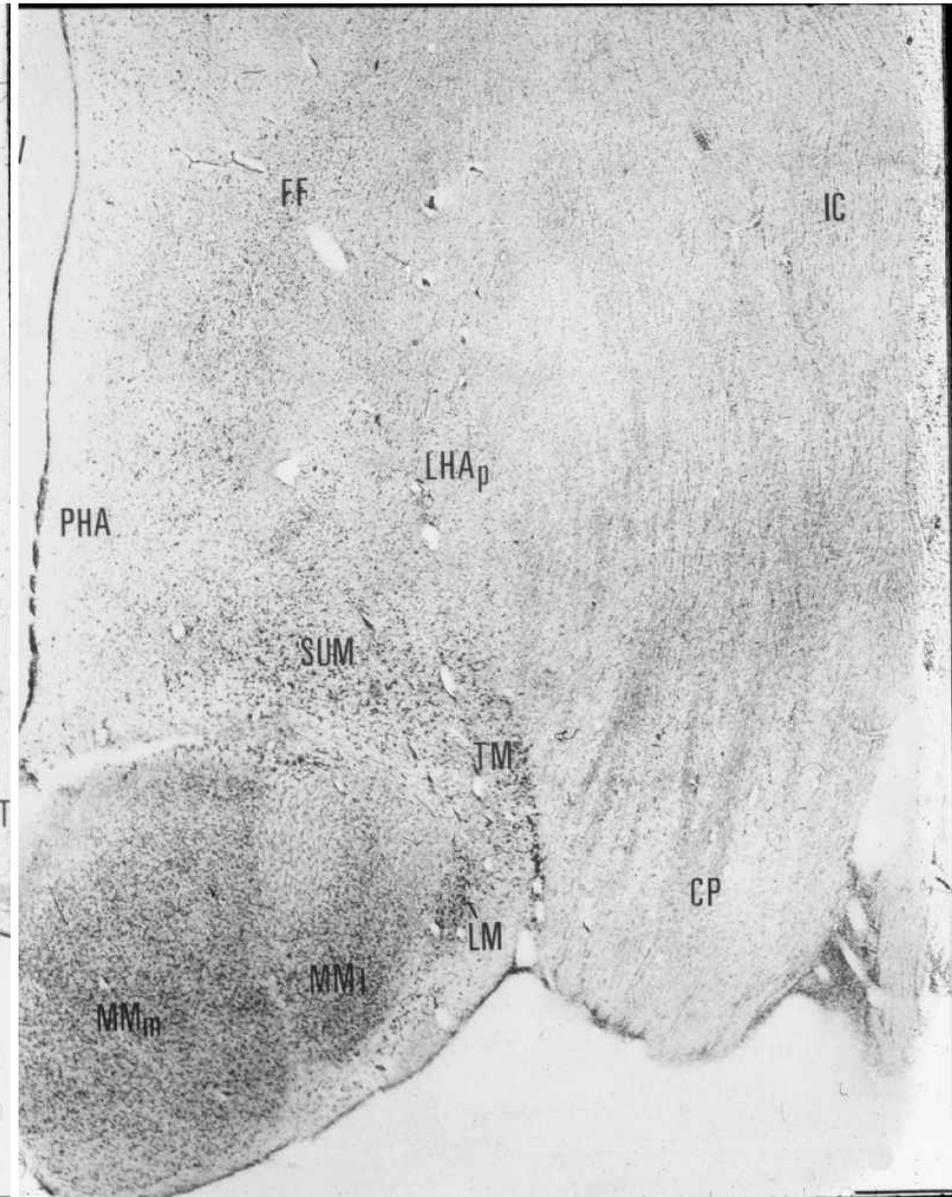
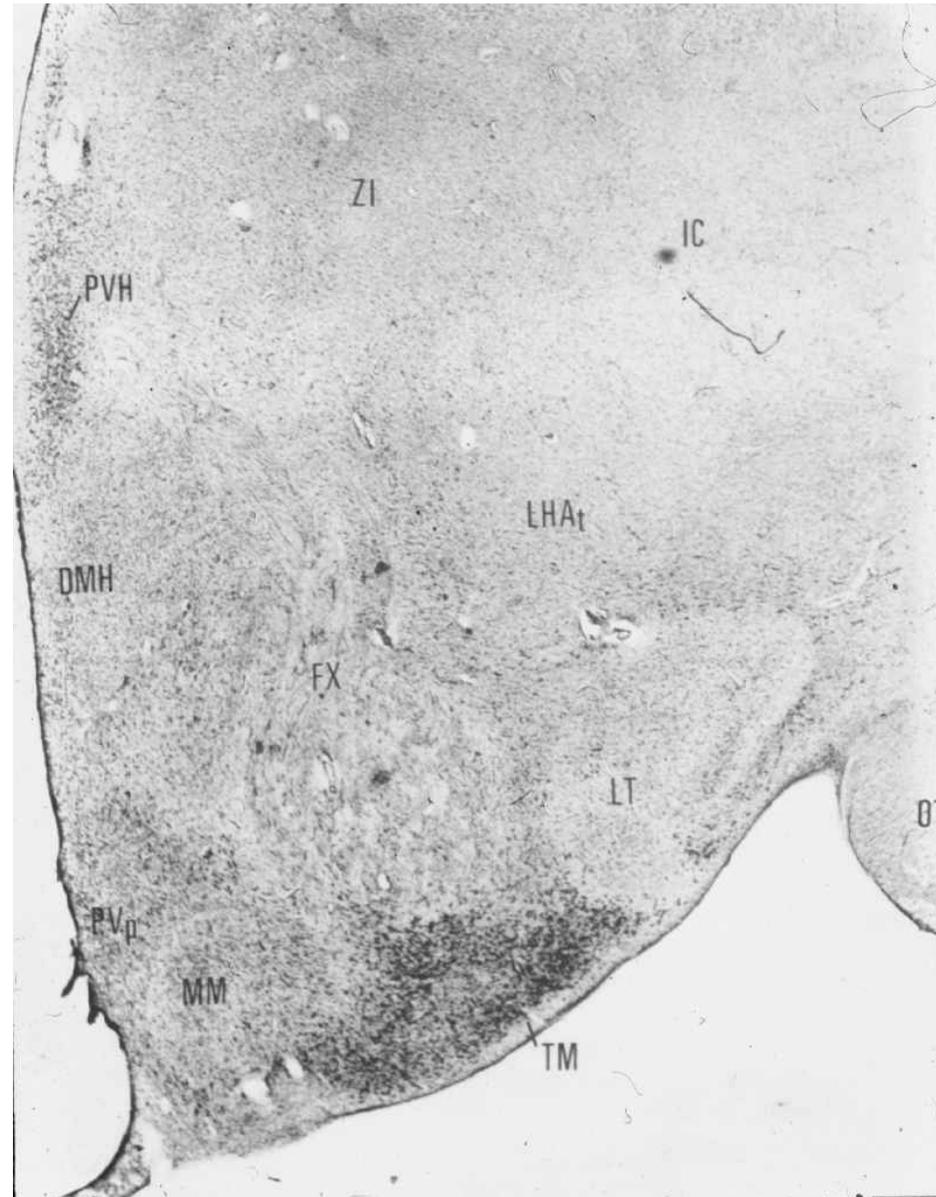




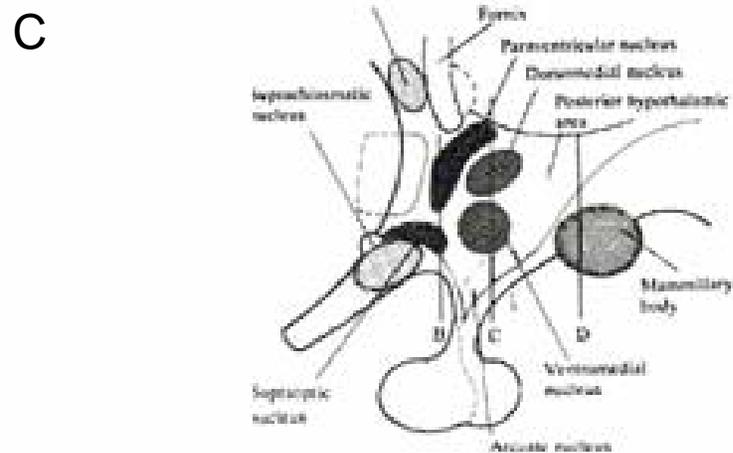
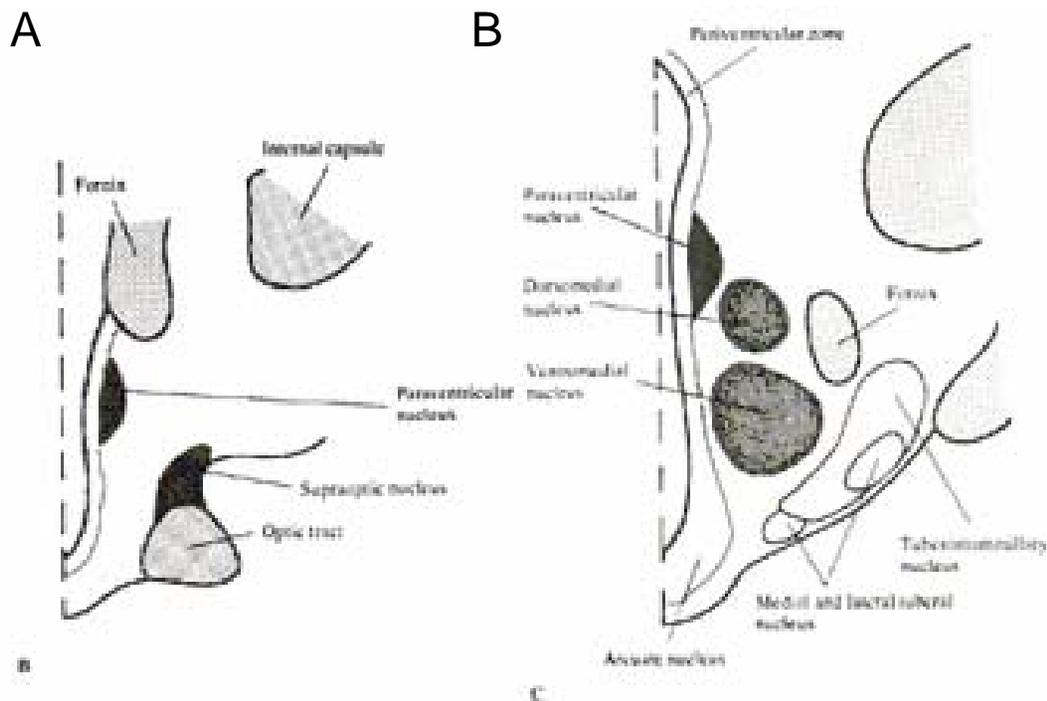
Nissl-stained coronal sections through the human hypothalamus (Saper, 2004).  
MPO=medial preoptic nucleus; PVH=paraventricular hypothalamic nucleus; S=supraoptic nucleus; SCN=suprachiasmatic nucleus.



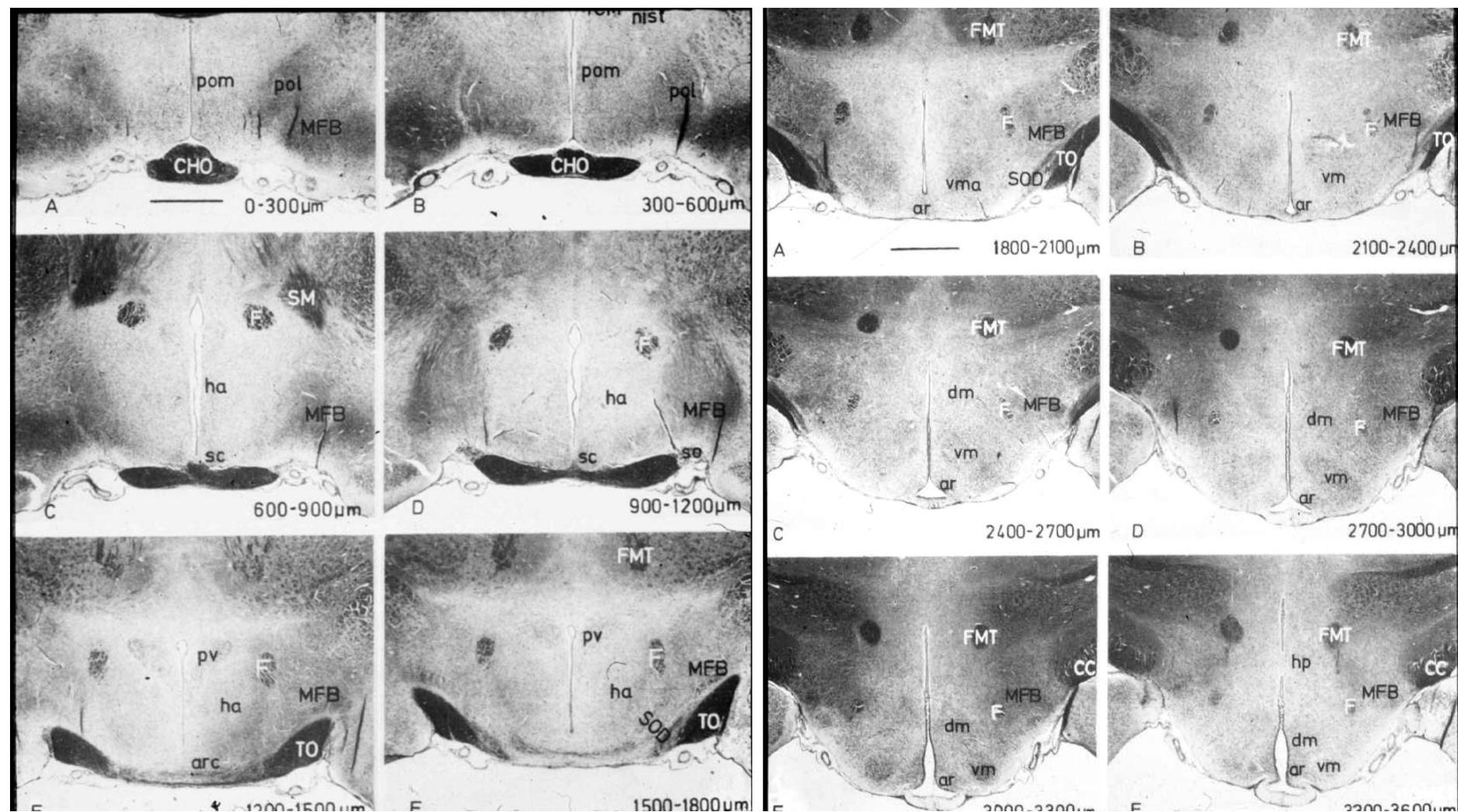
ARH=arcuate nucleus; AHA=anterior hypothalamic area; VMH=ventromedial hypothalamic nucleus



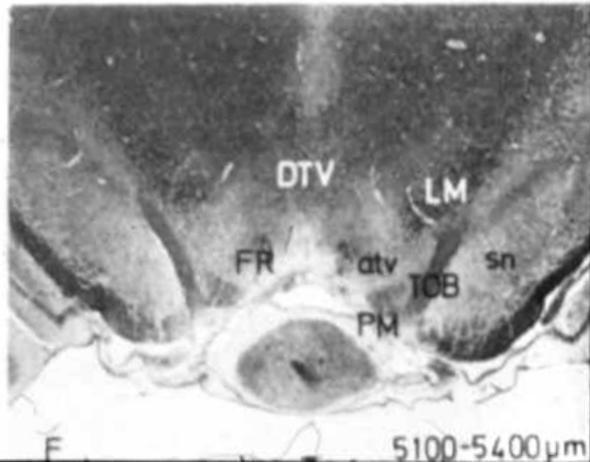
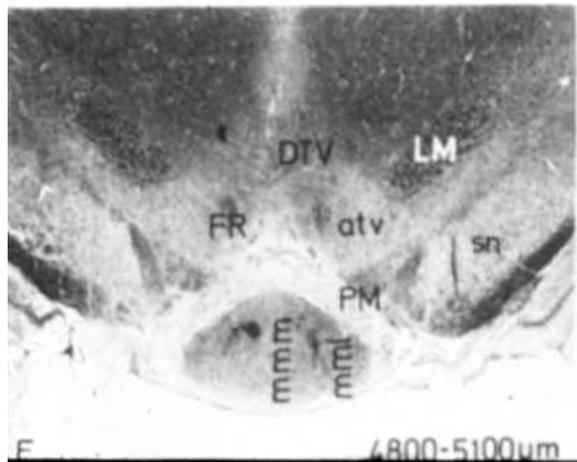
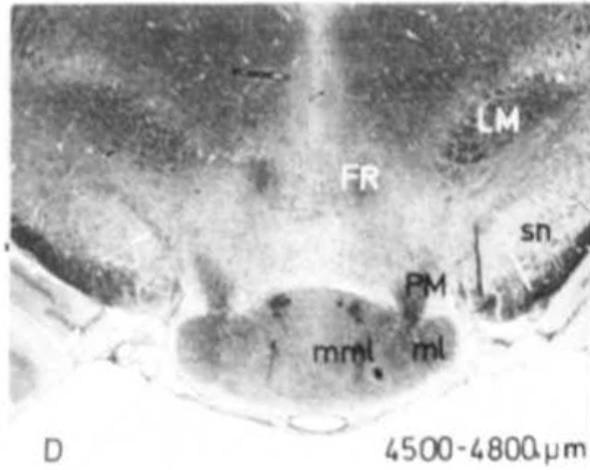
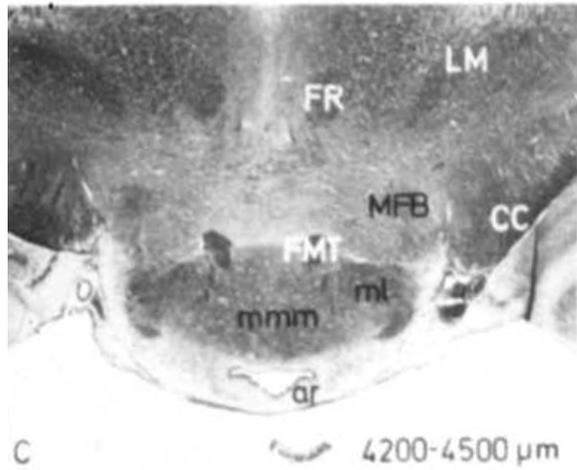
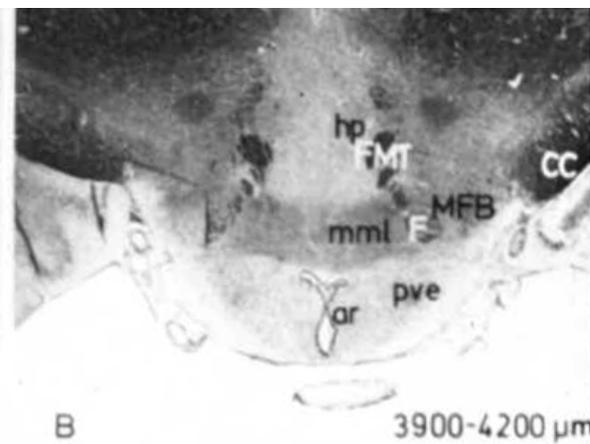
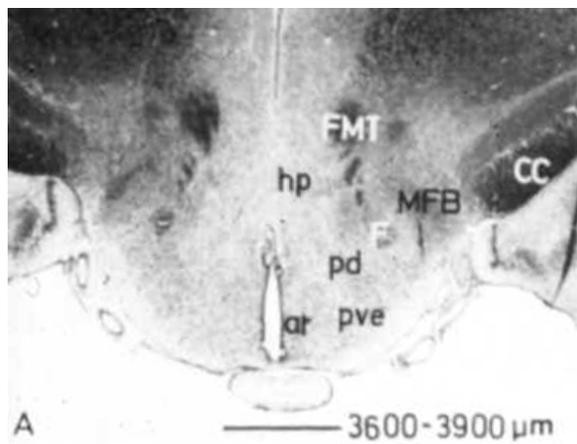
DMH: dorsomedial hypothalamic nucleus;  
 TM=tuberomammillary nucleus; MM=mammillary body



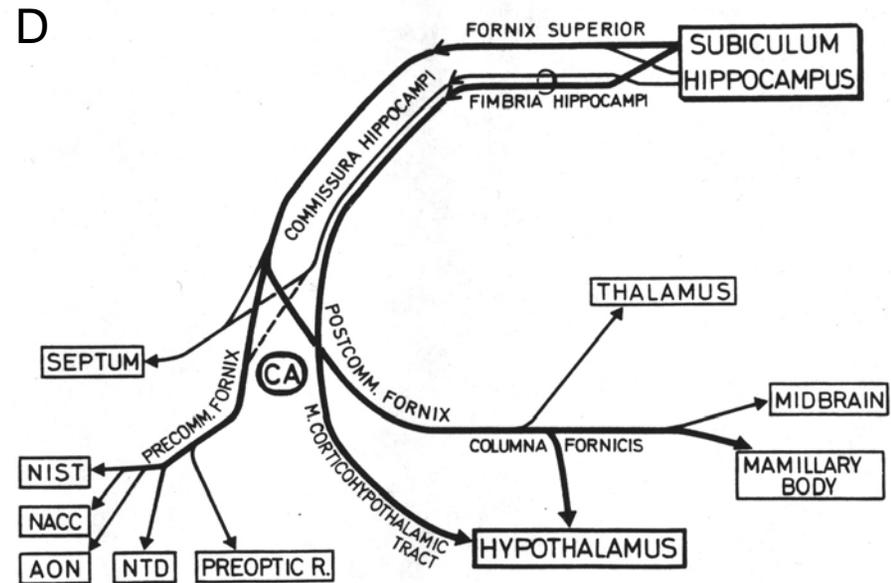
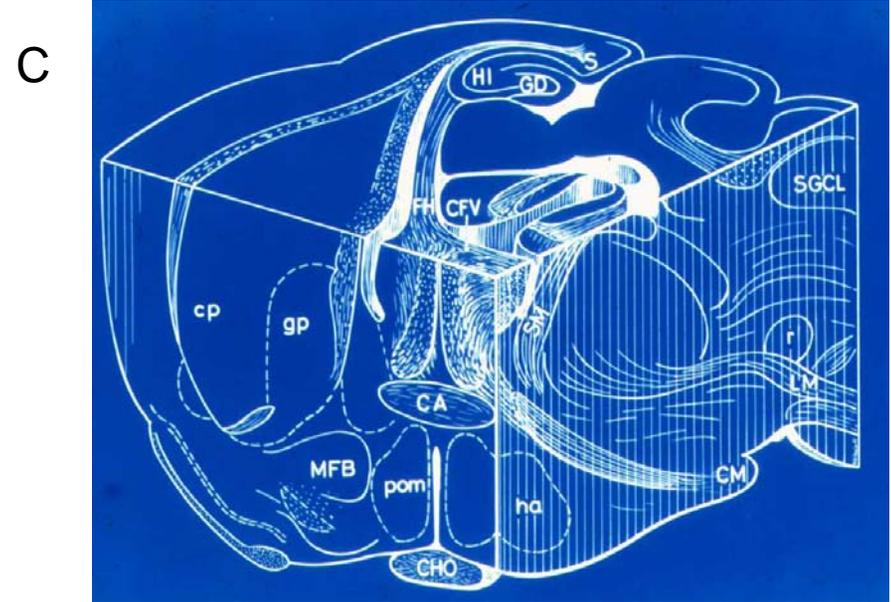
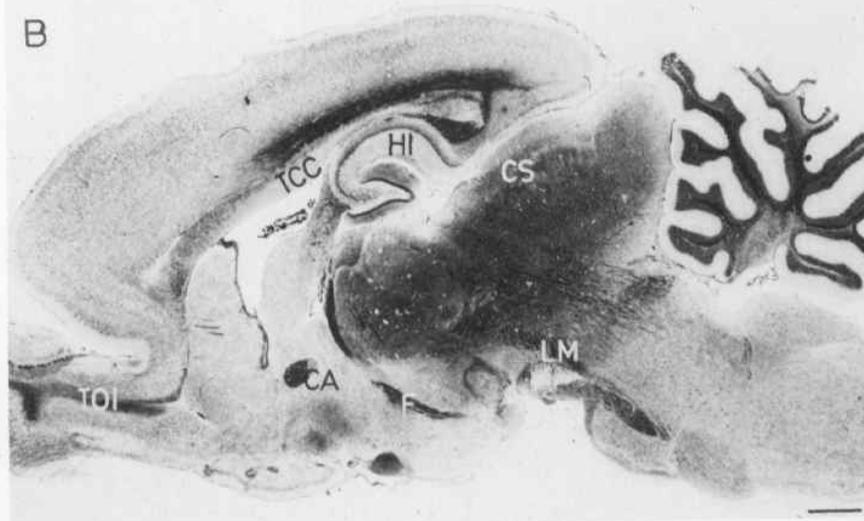
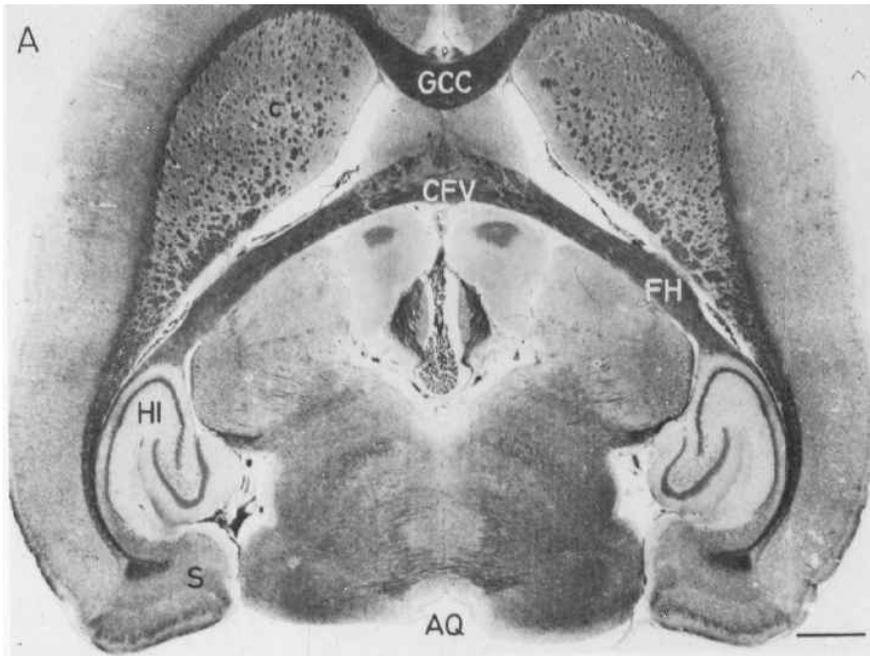
A-B Coronal, C sagittal scheme to show hypothalamic nuclei (From Heimer, 1994)



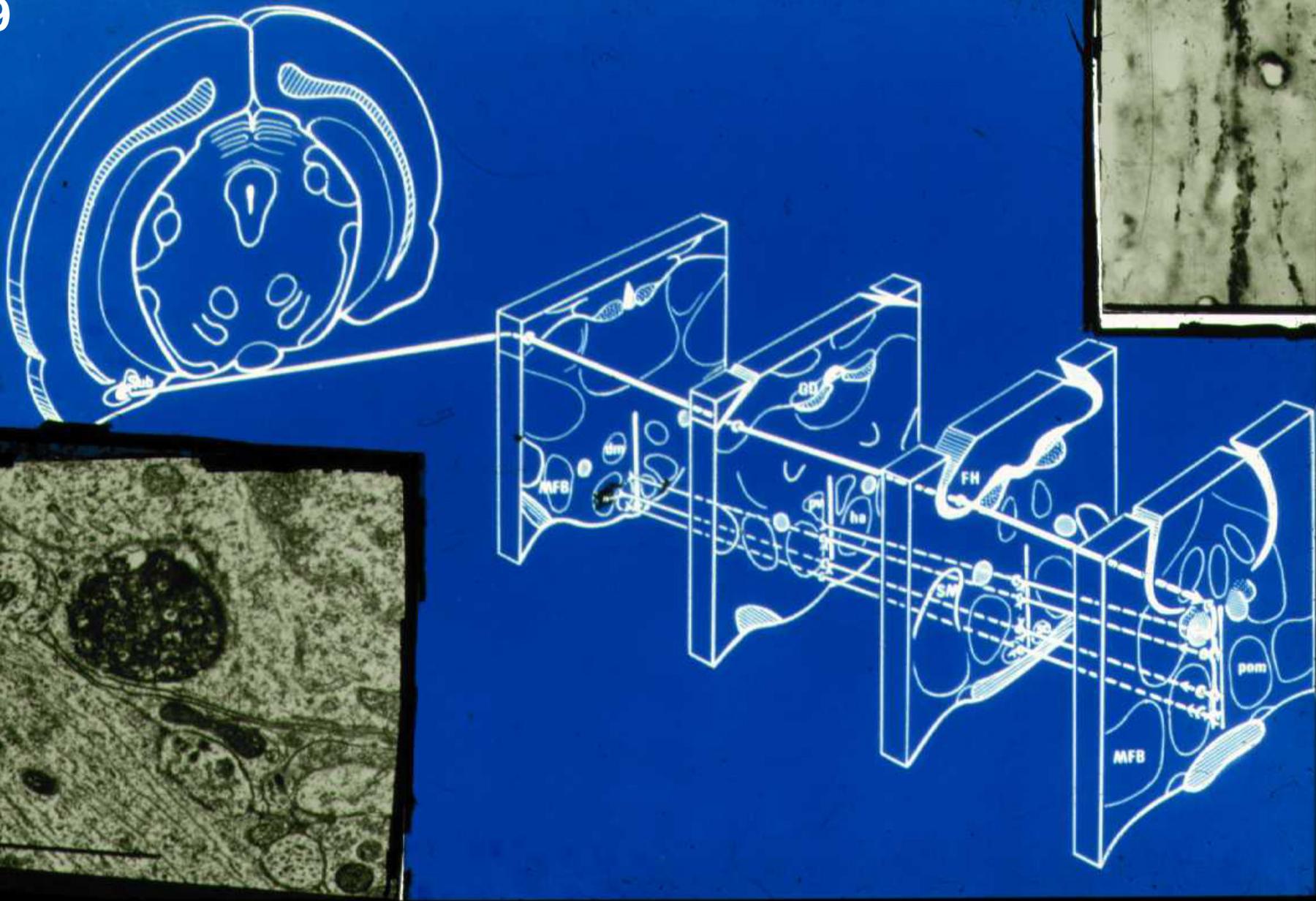
Coronal series of rat brain sections through the rat hypothalamus, stained with Luxol Fast Blue-CV (From Palkovits)



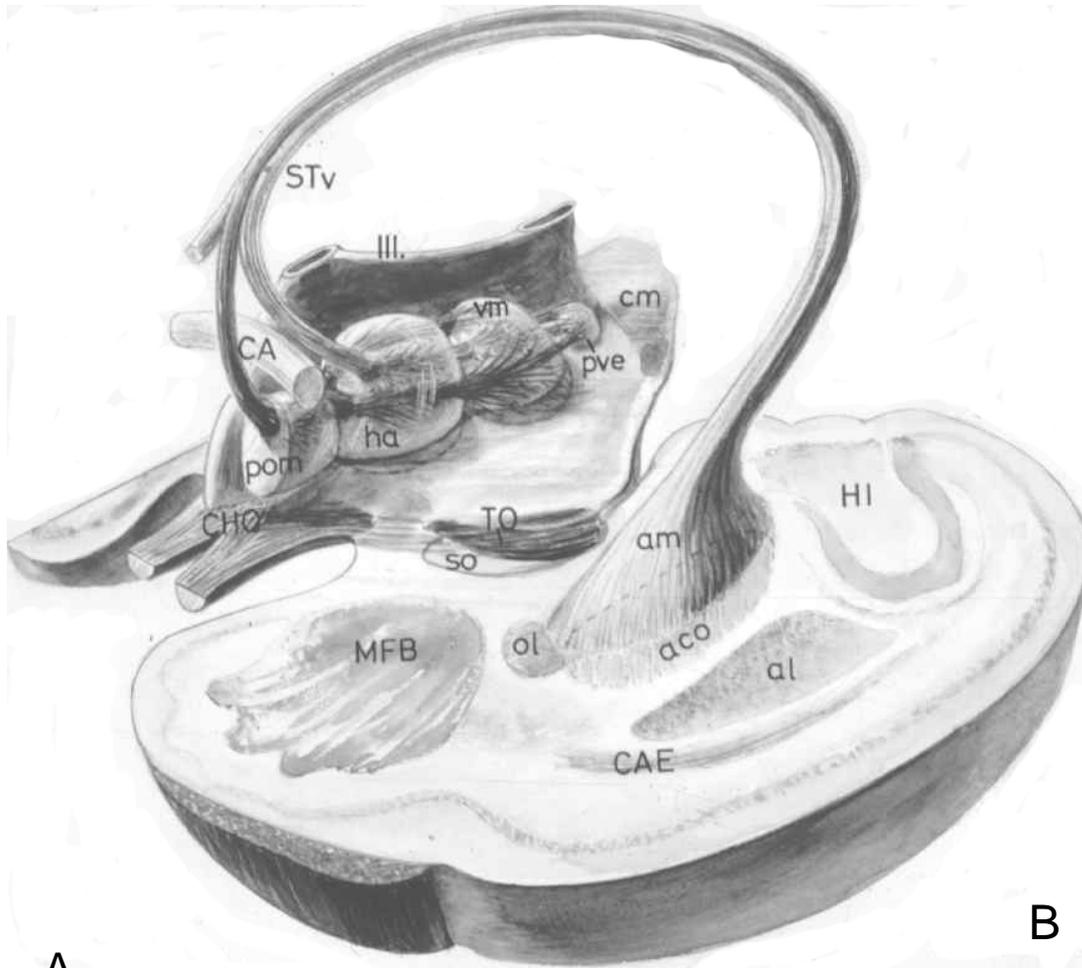
# HIPPOCAMPAL EFFERENTS TO THE HYPOTHALAMUS <sup>18</sup>



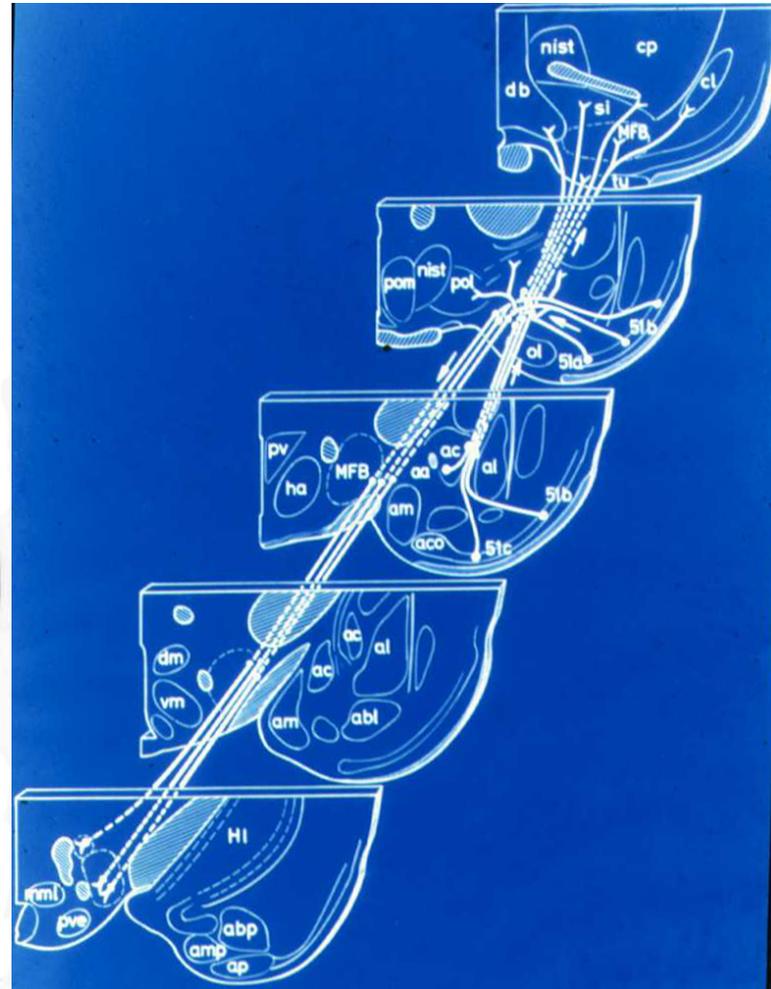
From Palkovits-Zaborszky, 1979)



Scheme, to show the origin, course (upper right inset; silver impregnation) and termination (lower left inset; electron micrograph with degenerated terminal after ventral subicular lesion) in the arcuate nucleus of the medial corticohypothalamic tract .

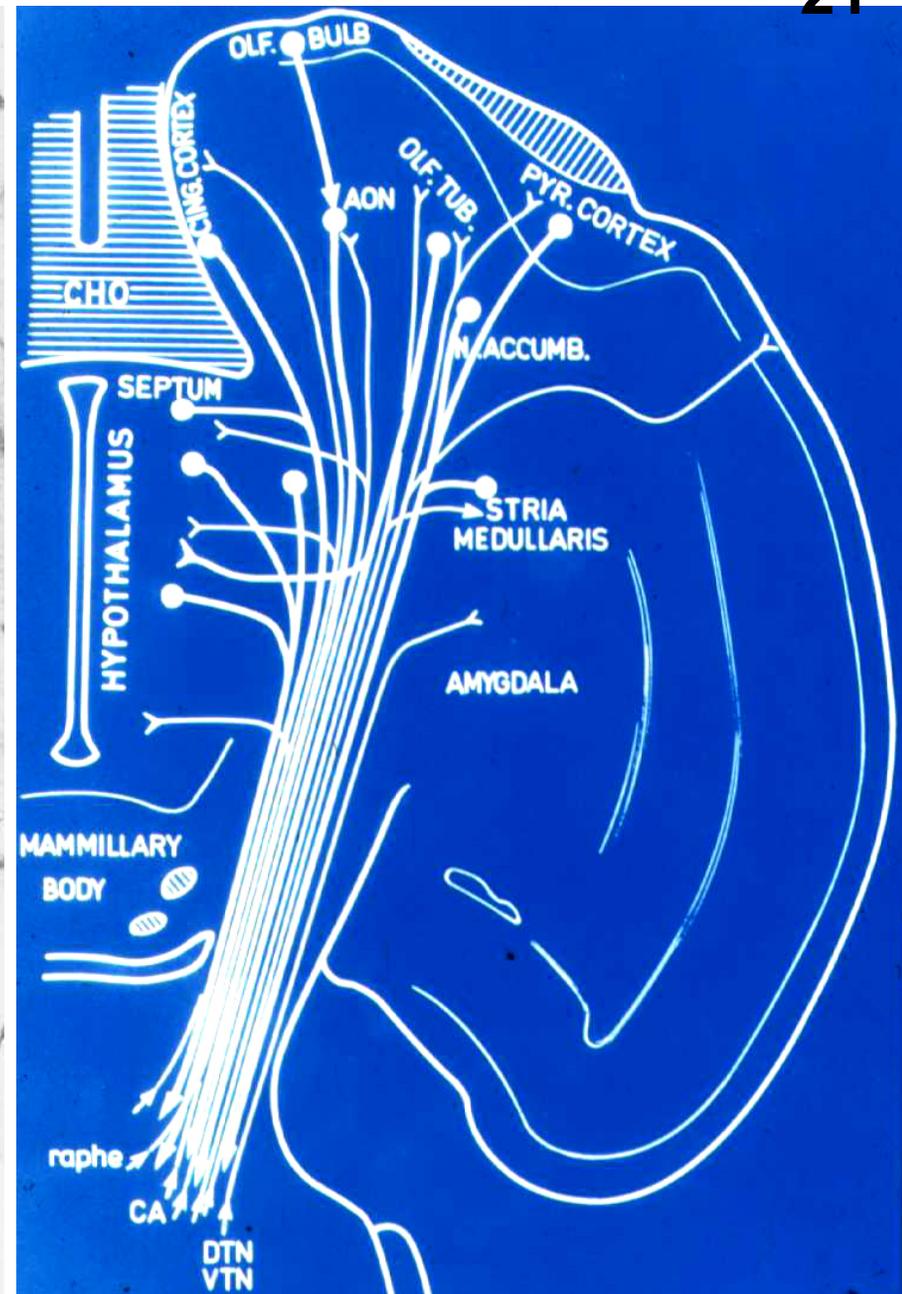
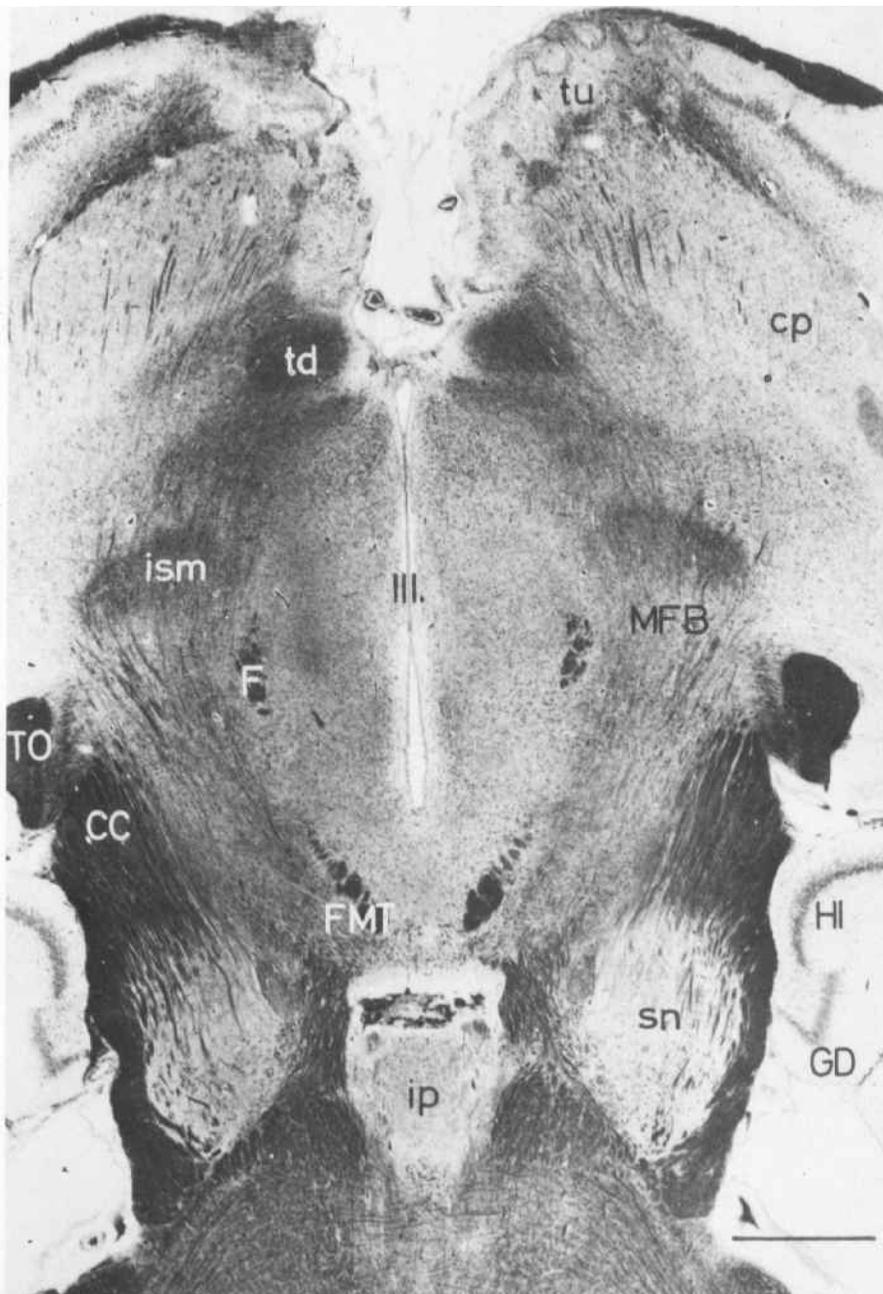


A

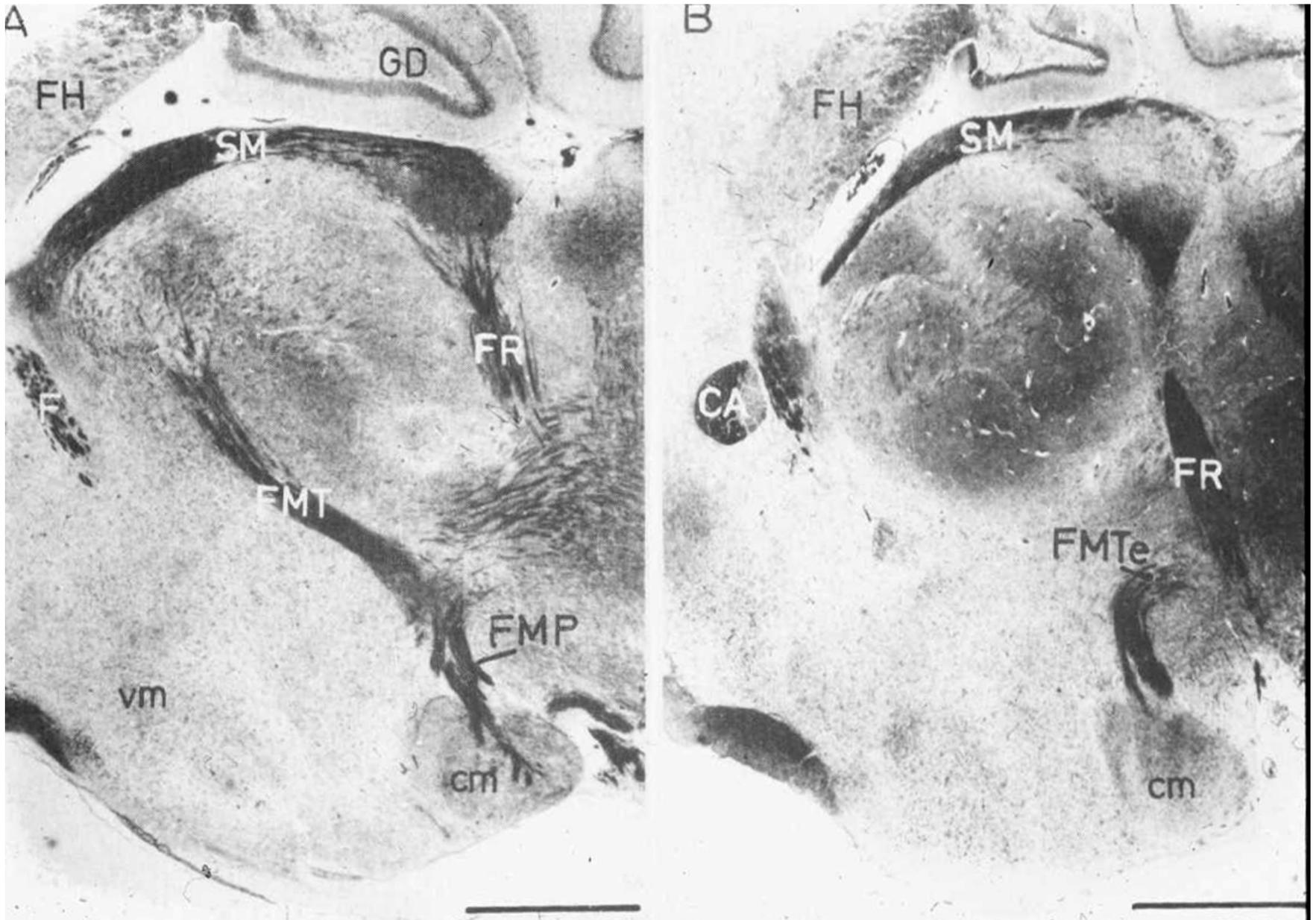


B

A: Schematic 3D-drawing to show the course of the stria terminalis, B: ventral amygdalofugal pathway (From Palkovits-Zaborszky, 1979)



Horizontal section to show the topography and distribution of the **medial forebrain bundle (MFB)**



Sagittal sections to show the course of the mammillothalamic tract (FMT), fasciculus mammilaris princeps (FMP), fornix (F), stria medullaris (SM) and fasciculus retroflexus (habenulo-interpeduncular tract).

# MAJOR AFFERENTS TO THE HYPOTHALAMUS

Cortical input: Prefrontal (infralimbic, prelimbic), Insular cortex to Lateral Hyp.  
area

Sensory: viscerosensory (via the NTS, parabrachial area)

olfactory (via relays in the olfactory tubercle and various amygdaloid nuclei)

visual (retinohypothalamic tract to SCN, the circadian pacemaker)

auditory to preoptic area (polysynaptic)

Monoaminergic input from the brainstem

Projections from limbic regions (hippocampus, amygdala)

Blood-born stimuli: circumventricular organs (SFO, OVLT, median eminence ) steroid feedback

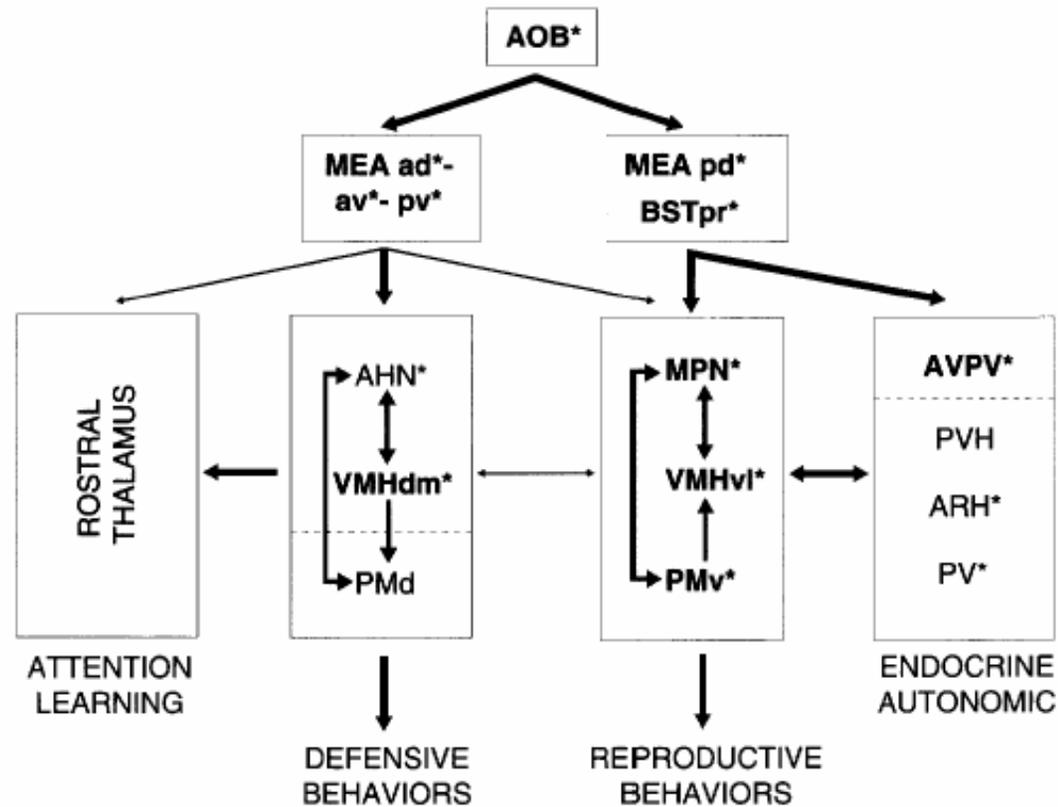


Fig. 2. Pheromonal information from the accessory olfactory bulb influences social behaviors through two pathways that involve distinct subnuclei of the medial amygdalar nucleus and principal nucleus of the BST. In turn, these cell groups innervate distinct subsystem of the hypothalamus that are involved in the expression of defense or reproductive behaviors respectively via differential projections to the brainstem. The hypothalamic defense subsystem also projects densely to several nuclei in the rostral thalamus, whereas the reproductive subsystem is bidirectionally connected with the periventricular zone of the hypothalamus, which also receives direct projections from the posterodorsal part of the medial amygdalar nucleus and the principal nucleus of the BST (through the anteroventral periventricular nucleus). Bold characters are used to identify anatomical structures that are sexually dimorphic, and asterisks (\*) indicate structures that express gonadal steroid hormone receptors.

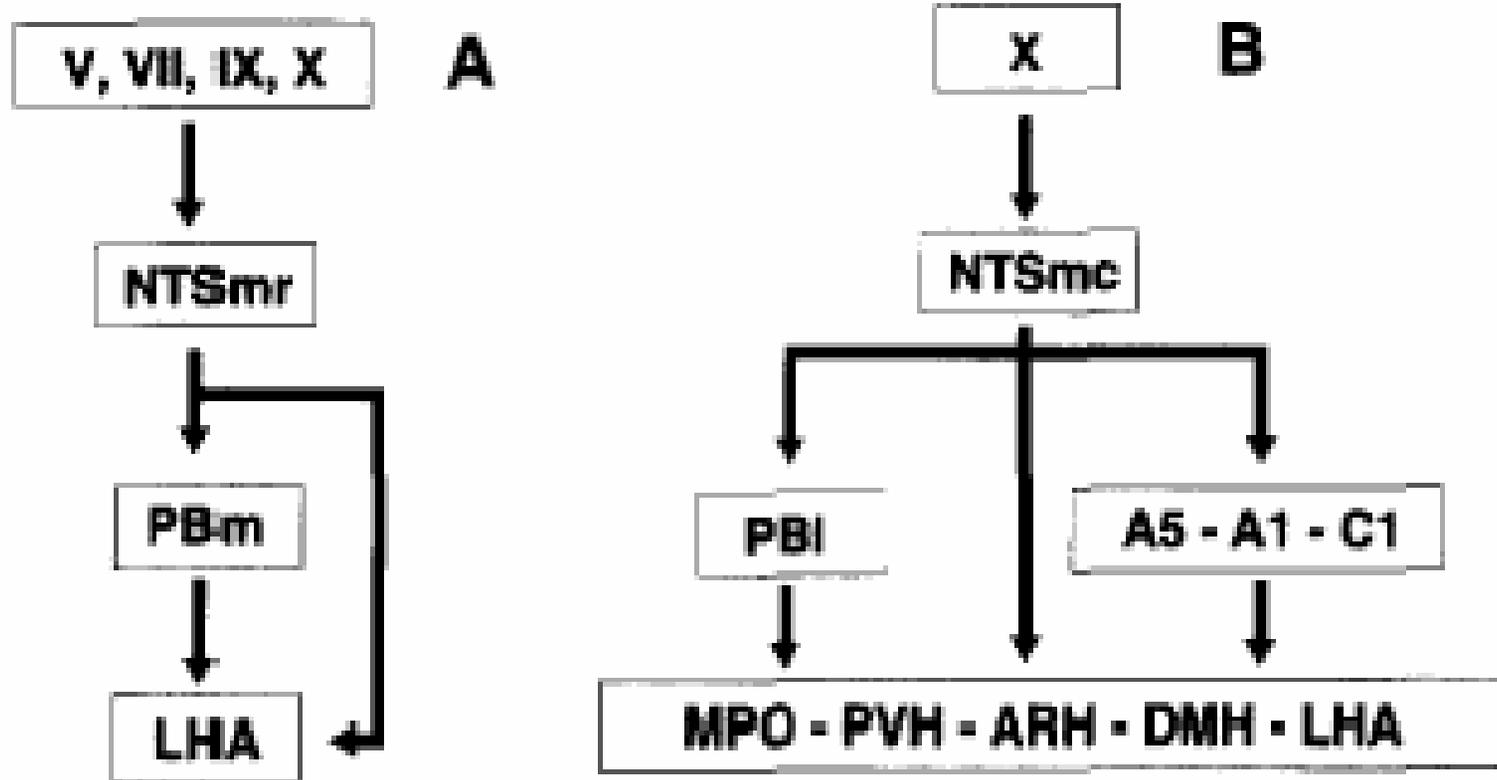
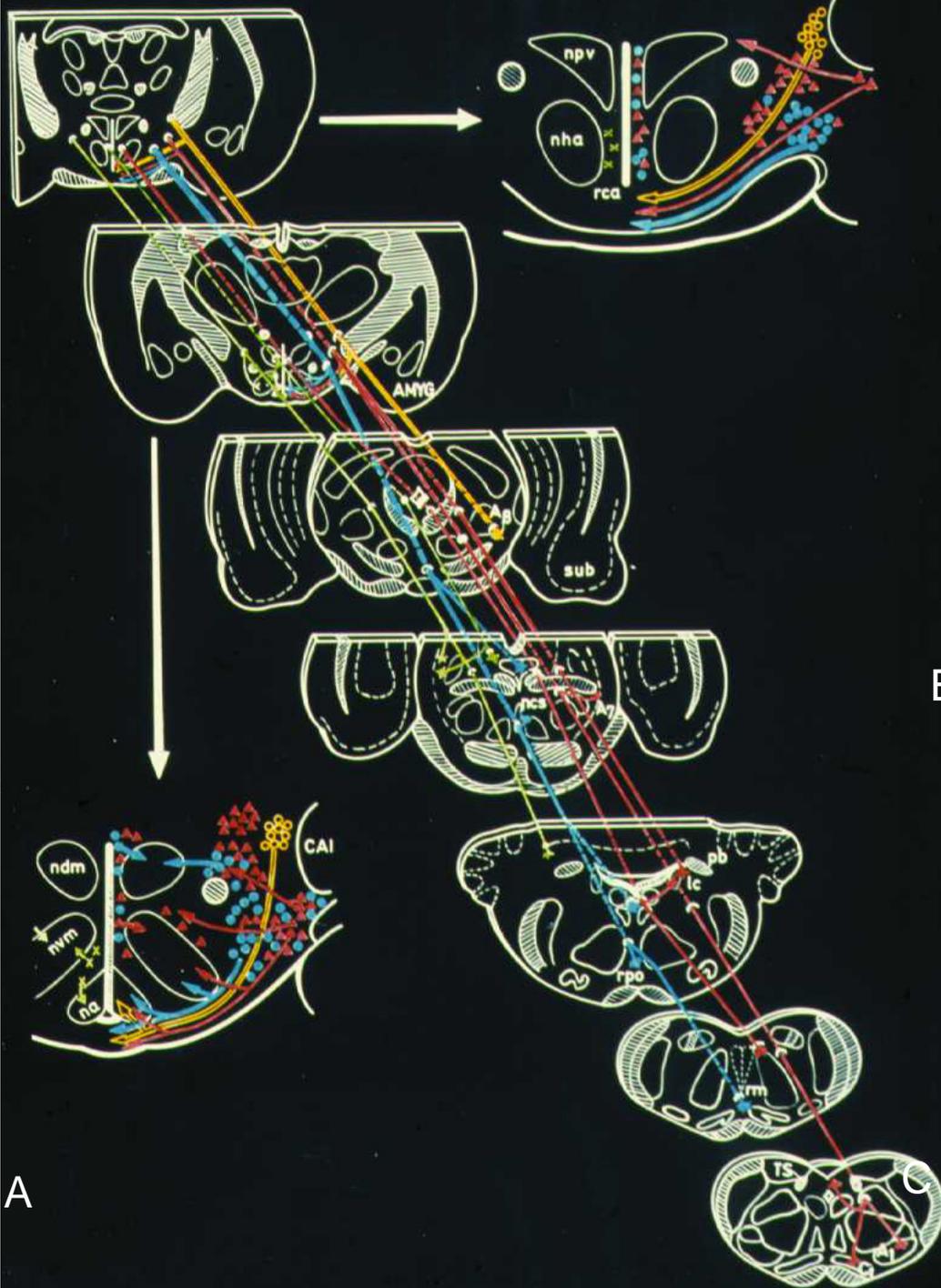


Fig. 3. Schematic representation of the organization of ascending gustatory (A) and visceral (B) pathways to the hypothalamus.



B

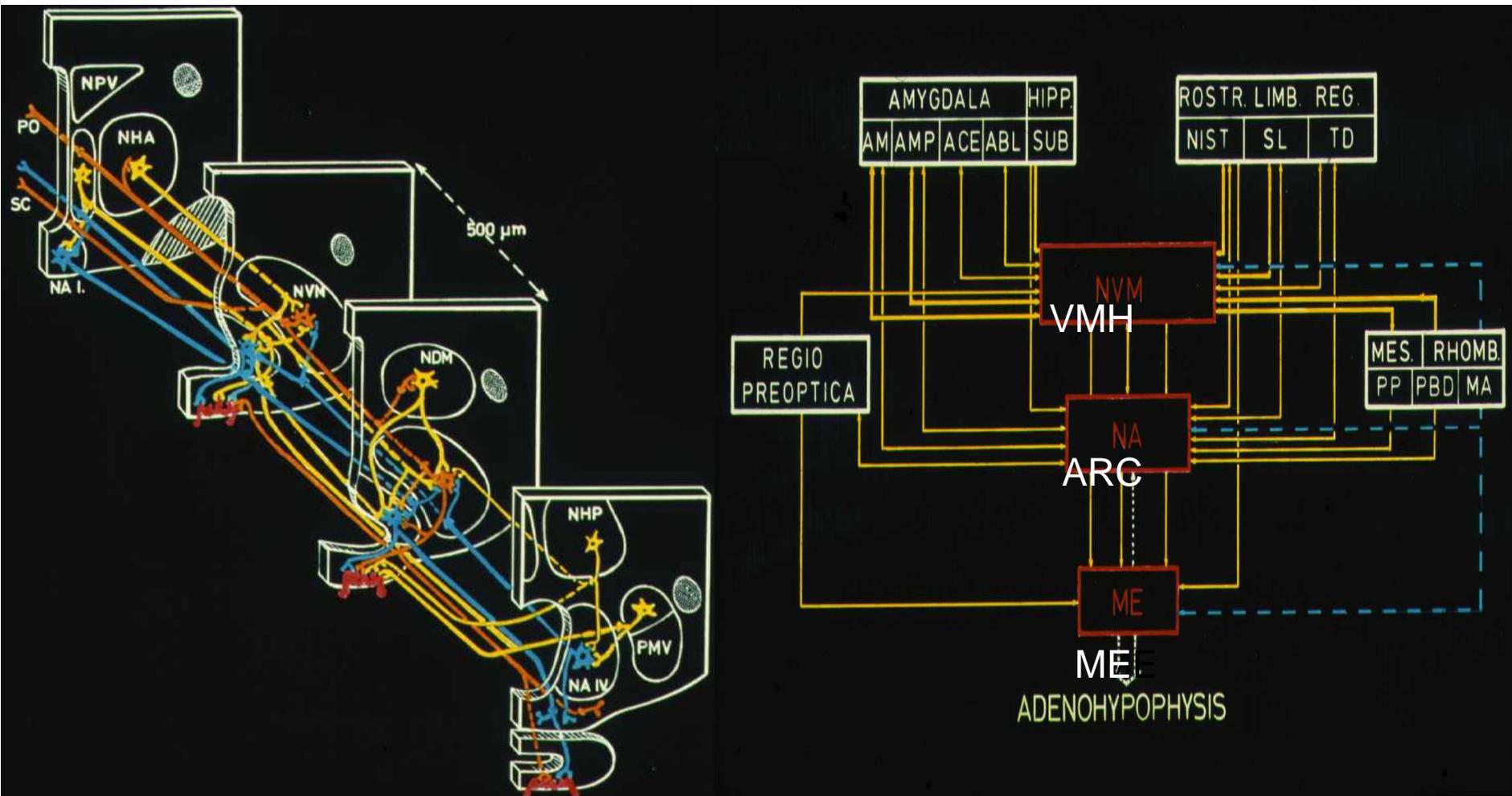
**BRAINSTEM INPUTS.** Among brainstem inputs are prominent projections from the nucleus of the solitary tract (NTS) that receives input from the major visceral organ by way of the glossopharyngeal (IX) and vagal (X) cranial nerves. In monkey and human, visceral afferents from the NTS are relayed to the hypothalamus via the parabrachial nucleus. Neurons in the PVN and lateral hypothalamic area receive direct input from the NTS. Among important brainstem source of afferents to the hypothalamus are the monoaminergic cell groups (locus coeruleus, raphe, A8 dopaminergic A1, A2 noradrenergic and adrenergic cells).

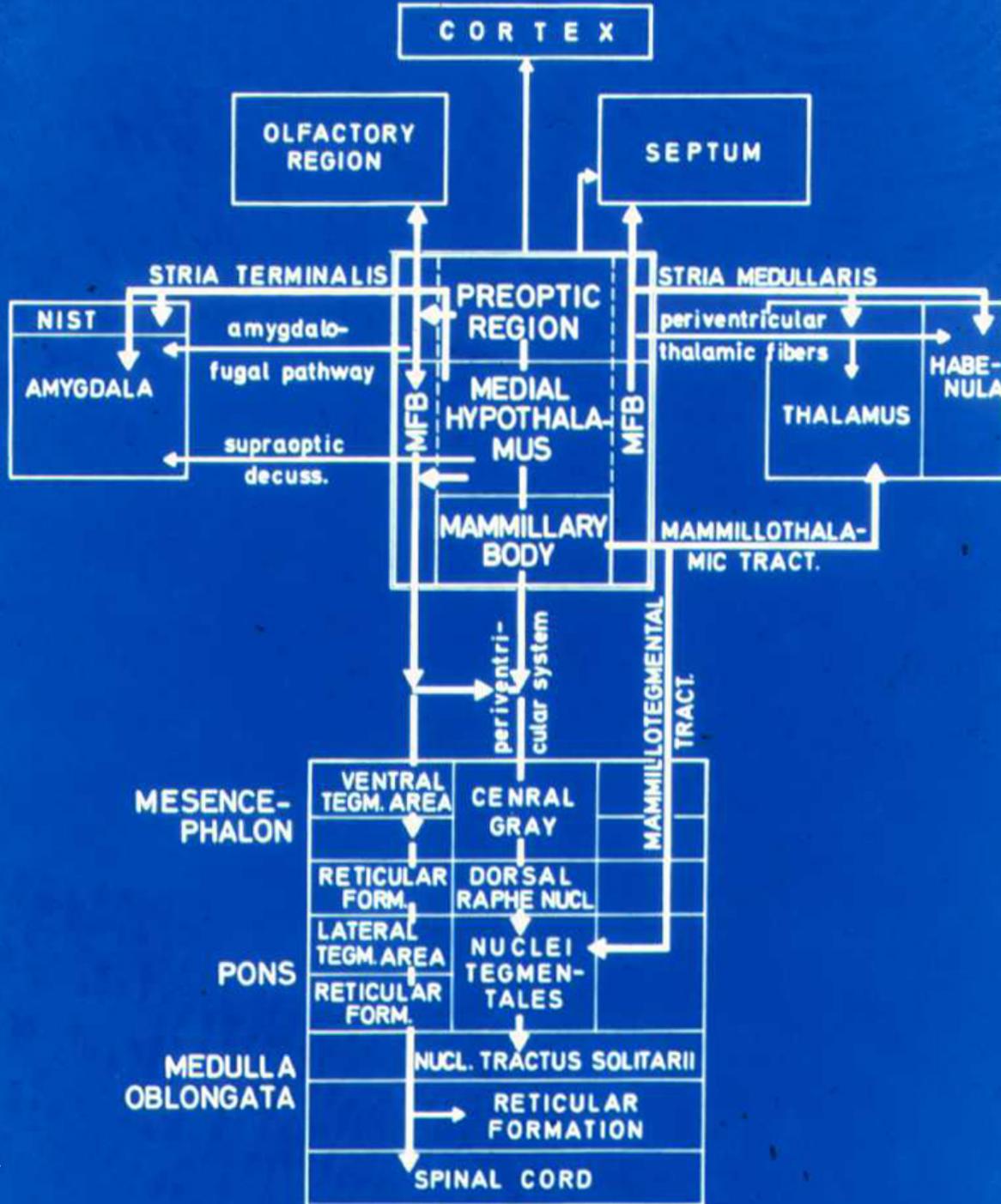
A

# THE MAIN OUTFLOW OF HYPOTHALAMIC NUCLEI ARE

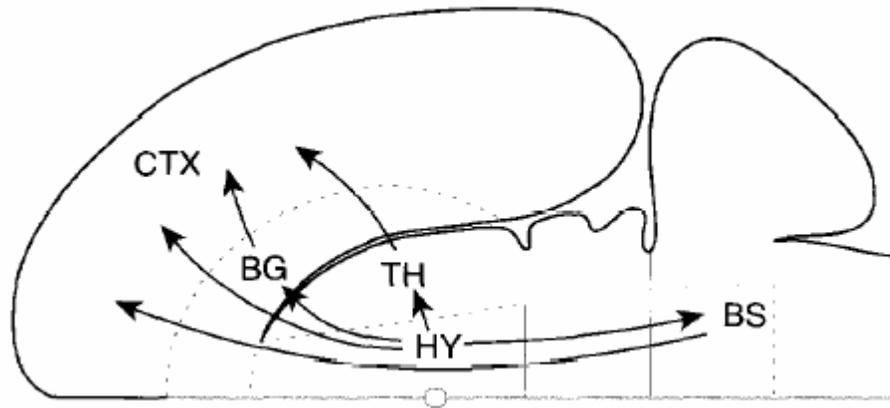
- Median eminence
- Posterior pituitary
- Sympathetic and PS preganglionic cell groups in the brainstem and spinal cord
- Thalamus, amygdala, basal forebrain, cerebral cortex, PAG, parabrachial area, NTS

# Intrahypotahalmic connections and projections to the median eminence-anterior pituitary



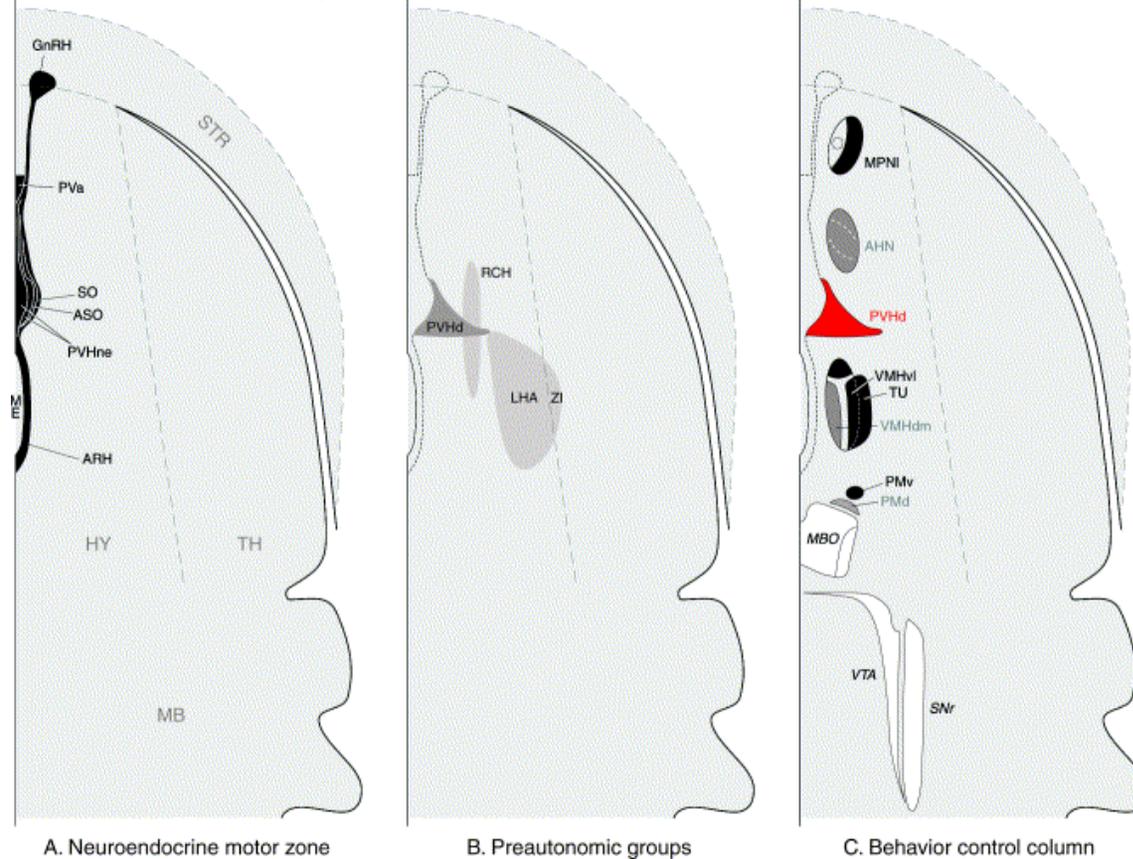


**Hypothalamic efferents**  
 a) to the brainstem and spinal cord **sympathetic and parasympathetic preganglionic cell groups** to influence autonomic functions; b) projections to the amygdala, cerebral cortex, brainstem and thalamus to **modulate behavioral functions**



Direct hypothalamocortical fibers (orexin, GABA, MCH, histamin); hypothalamic fibers via the basal forebrain cholinergic and GABAergic neurons; hypothalamic fibers via the thalamus and hypothalamic fibers via the brainstem cells that in turn project to the cerebral cortex.

CTX=cerebral cortex; BG=basal ganglia; TH=thalamus; HY=hypothalamus (Risold et al., 1997).

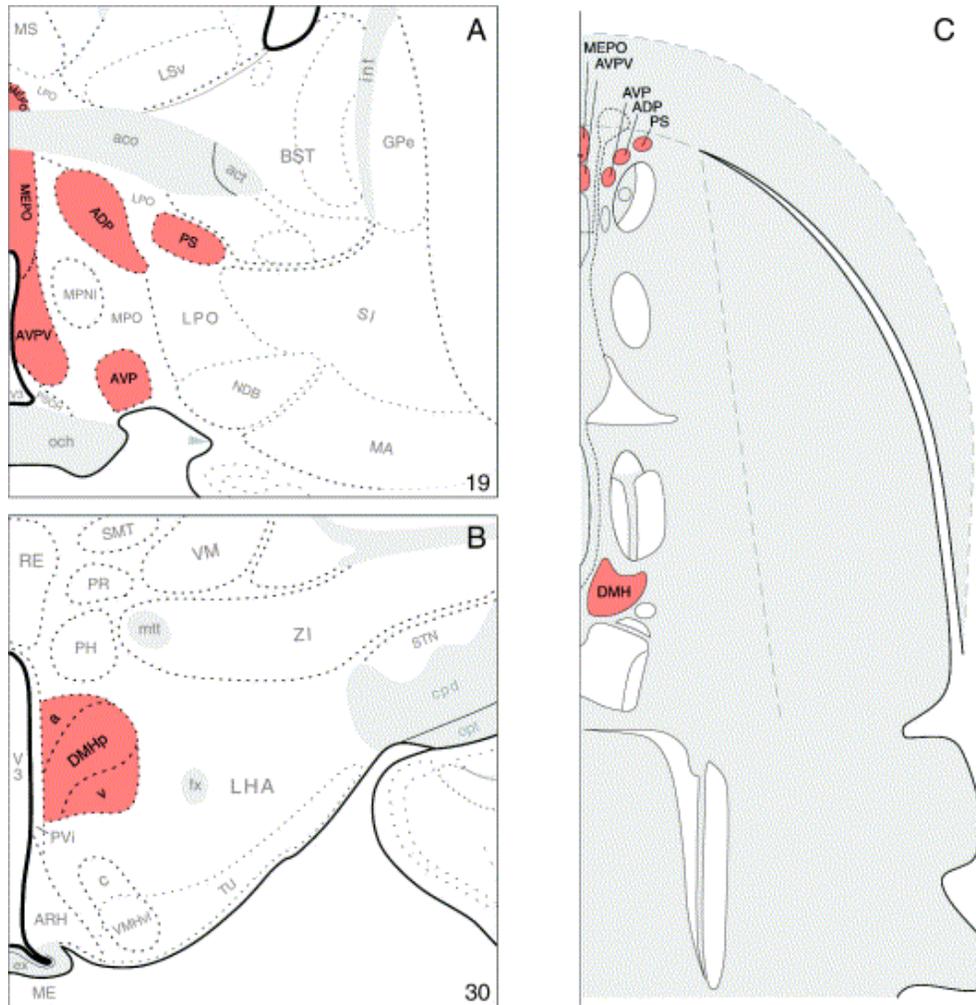


Schematic horizontal views of the rat (A) neuroendocrine motor zone, which is centered in the traditional periventricular zone of the hypothalamus; (B) preautonomic cell groups centered in the hypothalamus; and (C) the behavior control column in ventromedial regions of the hypothalamus and midbrain (upper brainstem). In (C), red indicates the part of the behavior control column most directly concerned with modulating ingestive behavior, black indicates nuclei in the column most closely associated with reproductive behavior, dark gray indicates nuclei in the column most closely associated with defensive (agonistic) behaviors, and white indicates nuclei most closely associated with exploratory or foraging behavior (From Thompson and Swanson, 2003).

GnRH=gonadotropin-releasing hormone; PVa, PVHne=components of the paraventricular hypothalamic n.; SO=supraoptic; ASO=accessory supraoptic nucleus; ARH=arcuate nucleus; PVHd=paraventricular dorsal part; RCH=retrochiasmatic; LHA=lateral hypothalamic area; ZI=zona incerta; MPNI=medial preoptic; AHN=anterior hypothalamic; VMH=ventromedial hypothalamic; PMv, PMd=ventral and dorsal preammillary nuclei

# HYPOTHALAMIC 'VISCEROMOTOR PATTERN GENERATORS' (HVPG)

32



The six nuclei of the hypothalamic visceromotor pattern generator (HVPG: highlighted in red). (A,B) Drawings of transverse sections through the rat hypothalamus to show the location of the DMH in the tuberal region (B), as well as five small cell groups in the preoptic region with which the DMH shares dense bidirectional connections (A). Level A is rostral to level B, as can be appreciated from the schematic horizontal view of the rat brain.

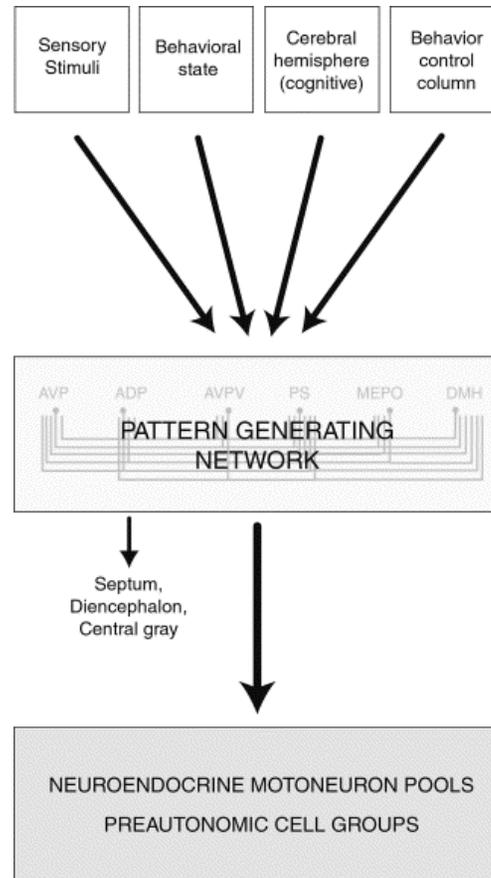
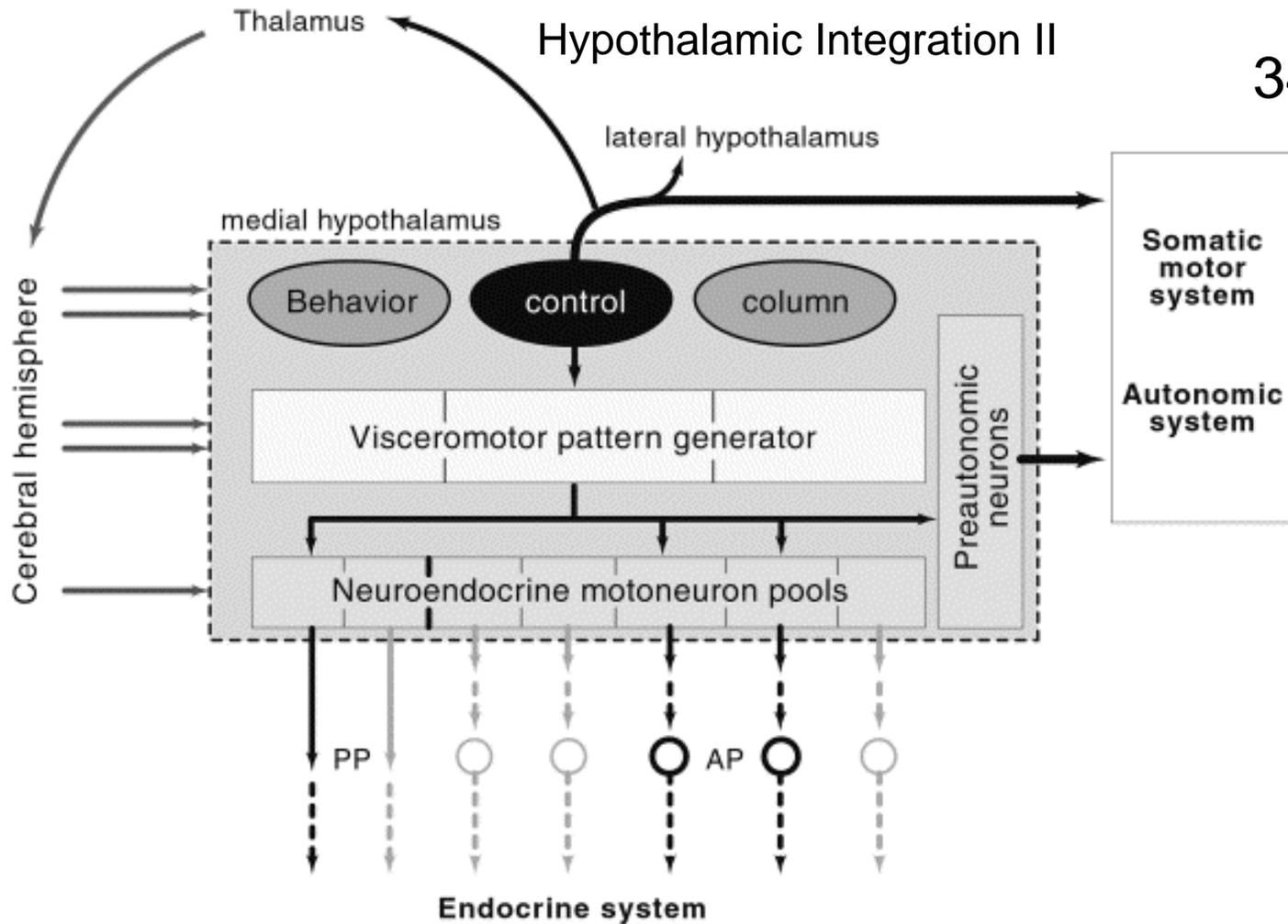
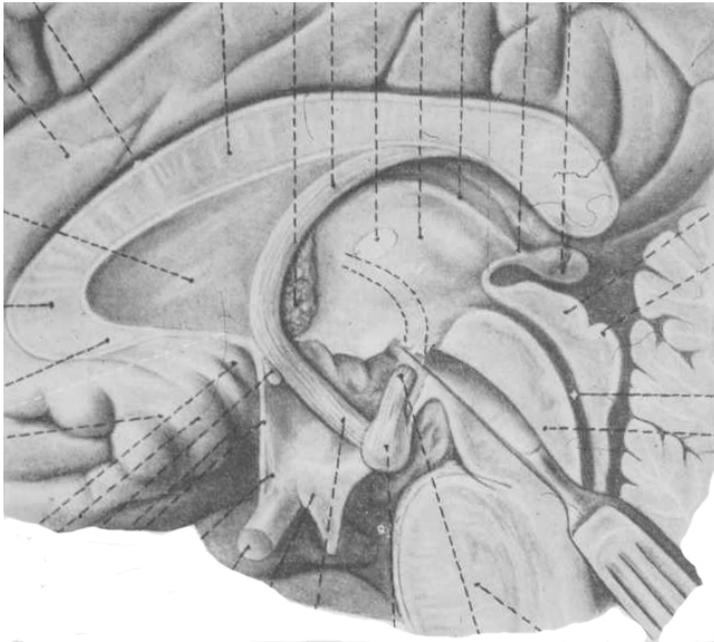


Diagram to show the basic classes of known neural inputs to the visceromotor pattern generator network, along with its major output to neuroendocrine motoneuron pools and preautonomic cell groups, and its generally less massive output to other, nearby brain regions. The HVPN projects directly to neurons that innervate the posterior pituitary (magnocellular neurosecretory) and to neurons that directly control anterior pituitary secretion (parvocellular neurosecretory). The most direct HVPN influences on sympathetic and parasympathetic preganglionic neurons appear to be relayed via inputs to the descending division of the PVN. Components of the behavioral control column is depicted in Fig. The behavioral state control input arises primarily in the suprachiasmatic nucleus (From Thompson and Swanson, 2003).

# Hypothalamic Integration II



Model of the basic plan of the hypothalamus. It is convenient to start with the activation of a particular node (black) in the behavior control column. Note two classes of output. One consists of 'descending' projections to brainstem, and in some cases spinal, regions associated with the somatic and/or autonomic motor systems, 'ascending' projections to thalamocortical loops, and projections to the adjacent lateral hypothalamic area, which may be concerned with modulating behavioral state. The other class of output from behavior control column nuclei is to the HVPG network, in preference to neuroendocrine motoneuron pools themselves. Each node in the HVPG network projects to a unique set of neuroendocrine motoneuron pools and preautonomic cell groups in the PVH. Note that various parts of the cerebral hemispheres appear to have glutamatergic (from the prefrontal cortex and subiculum of the hypothalamus) inputs to the medial hypothalamus. The medial amygdala, the lateral septum and the bed nucleus of the stria terminalis project with GABAergic input to the HVPG network and the neuroendocrine motor zone.

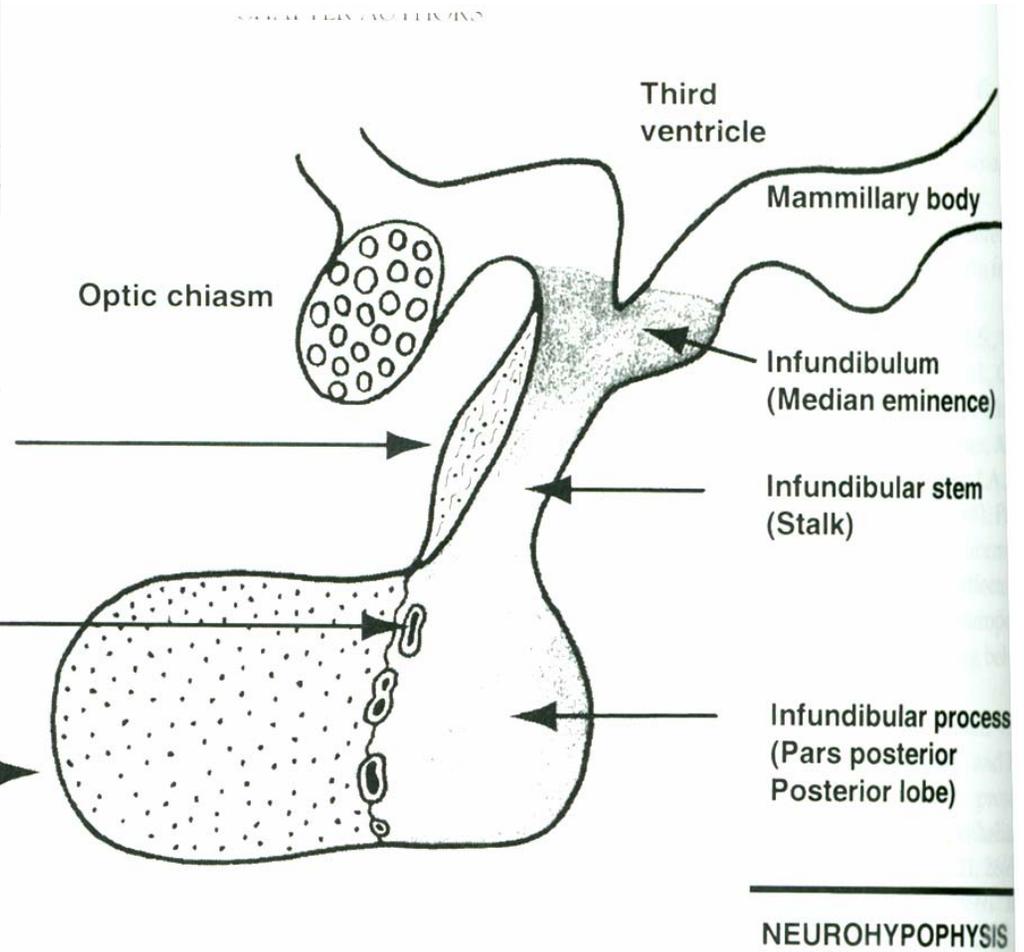


Pars tuberalis  
(Pars infundibularis)

Pars intermedia  
(intermediate lobe)

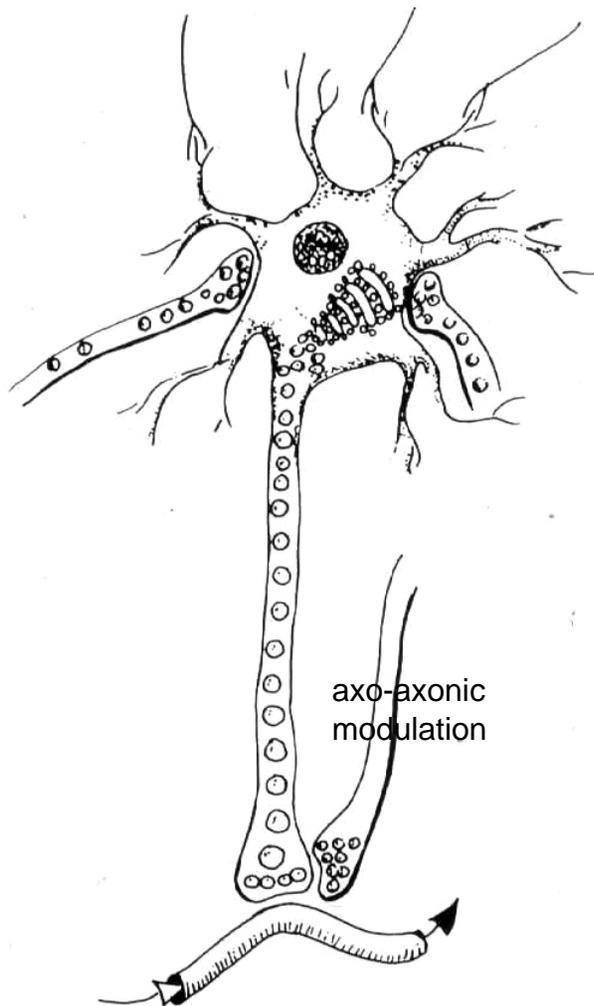
Pars distalis  
(Pars anterior  
Anterior lobe)

ADENOHYPOPHYSIS



A

## Neurosecretion



Receptor

Genetic Control

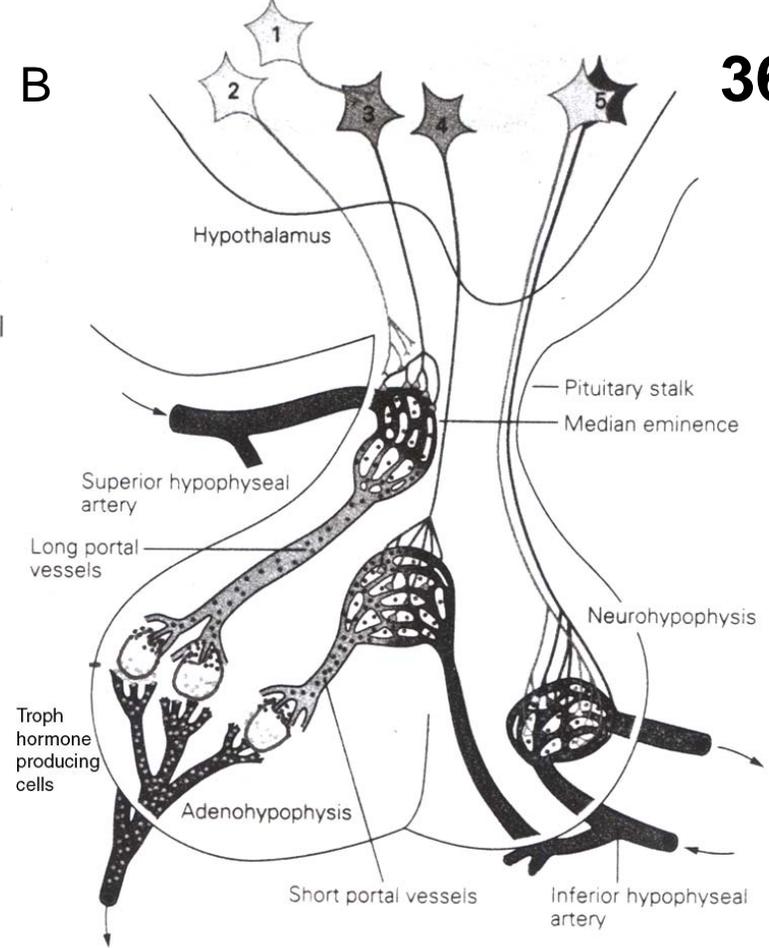
Biosynthesis  
and Packaging

Axon Transport

axo-axonic  
modulation

Release

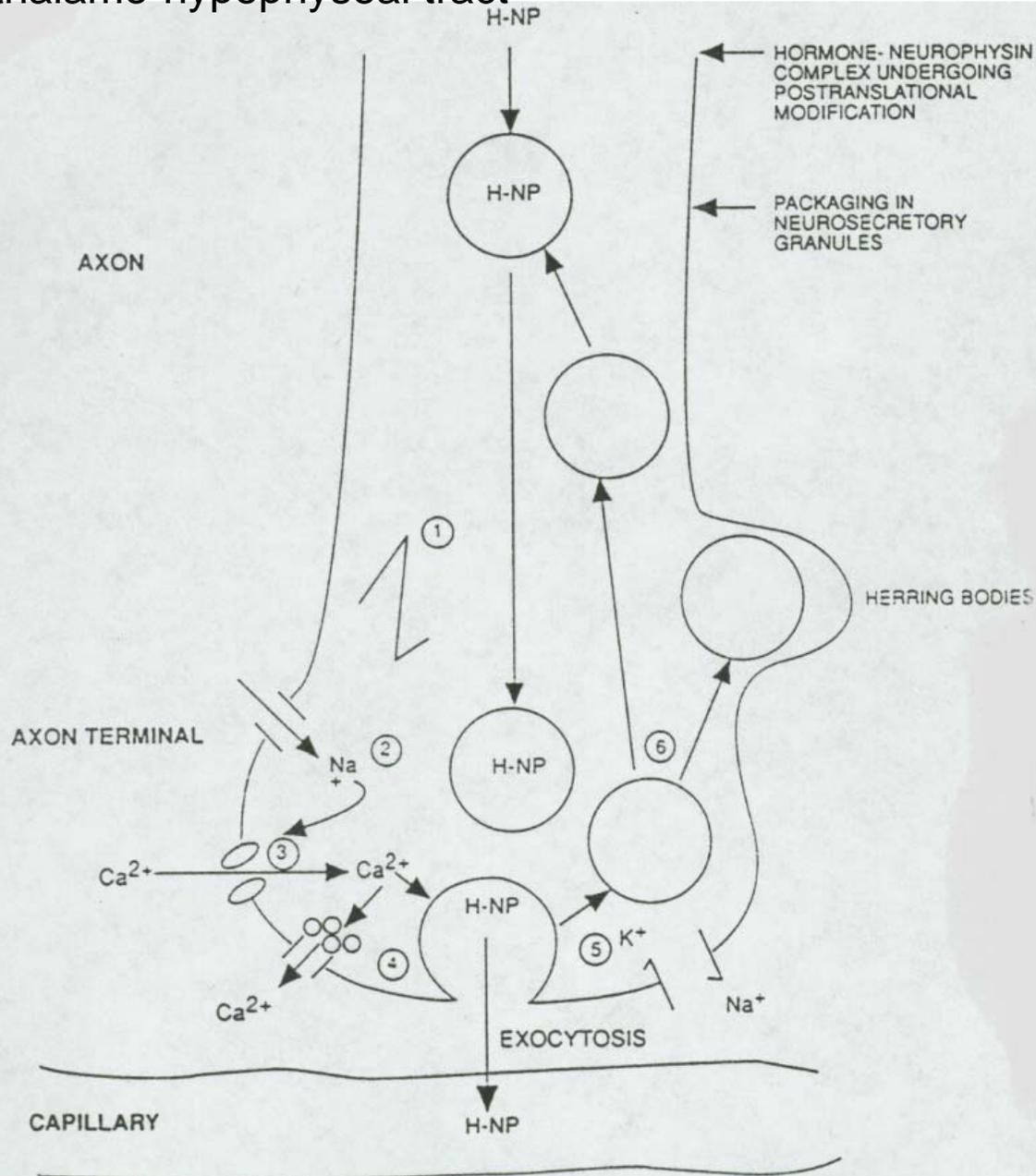
B



36

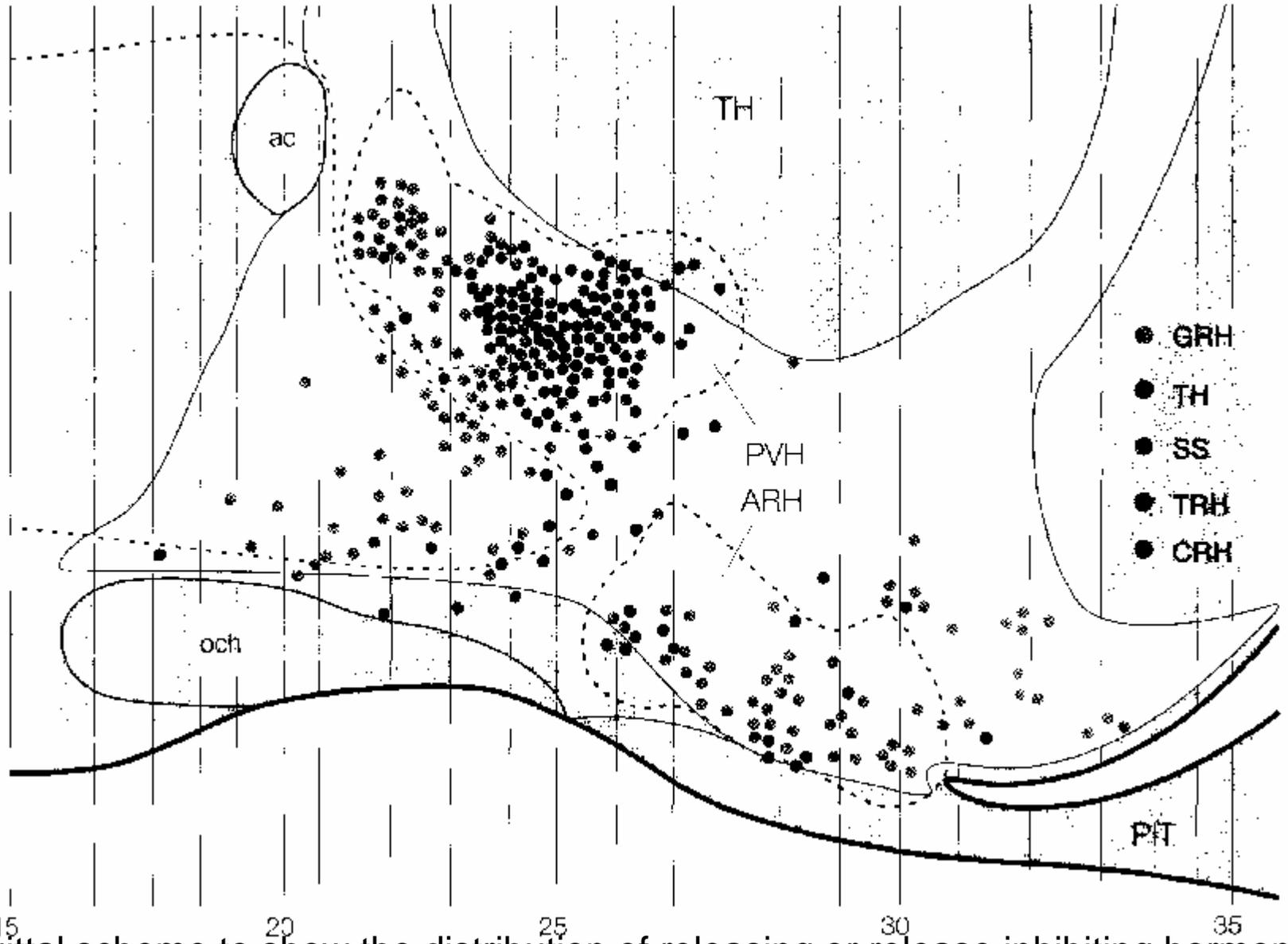
A: hypothalamic neuroendocrine cells release secretory products into the blood stream. B: Control of the anterior and posterior pituitary by the hypothalamus. 1: axodendritic or axosomatic input to a neurosecretory cells; 2: monoaminergic axons from the brainstem can affect neurosecretory axons in the median eminence via axo-axonic interaction; 3-4: parvocellular neurosecretory axons release their hormones into the hypothalamo-portal circulation; 5: magnocellular neurosecretory axons terminating in the posterior pituitary and release their hormones into the general circulation.

# Mechanism of transport, package and secretion of neurophysin-peptide complex in the hypothalamo-hypophyseal tract



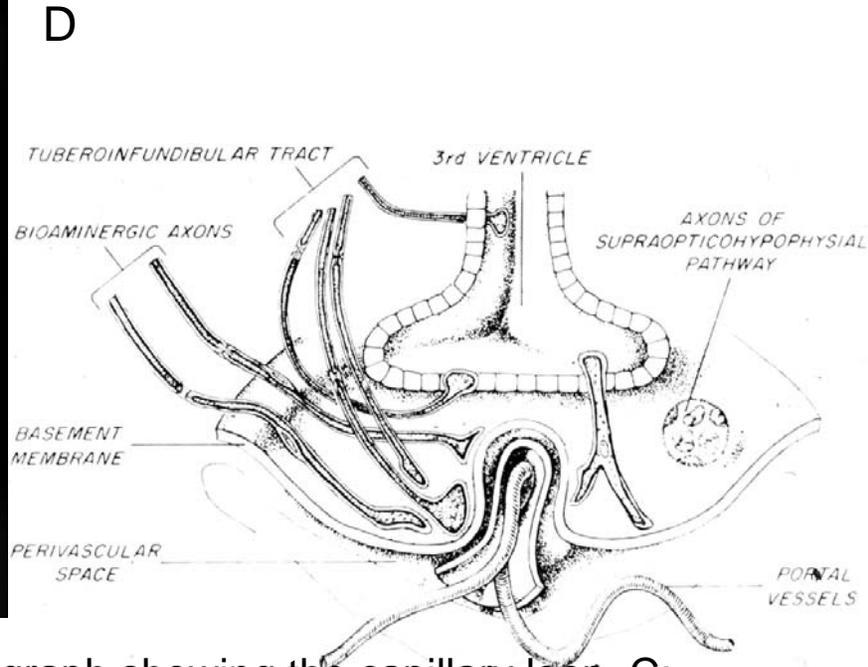
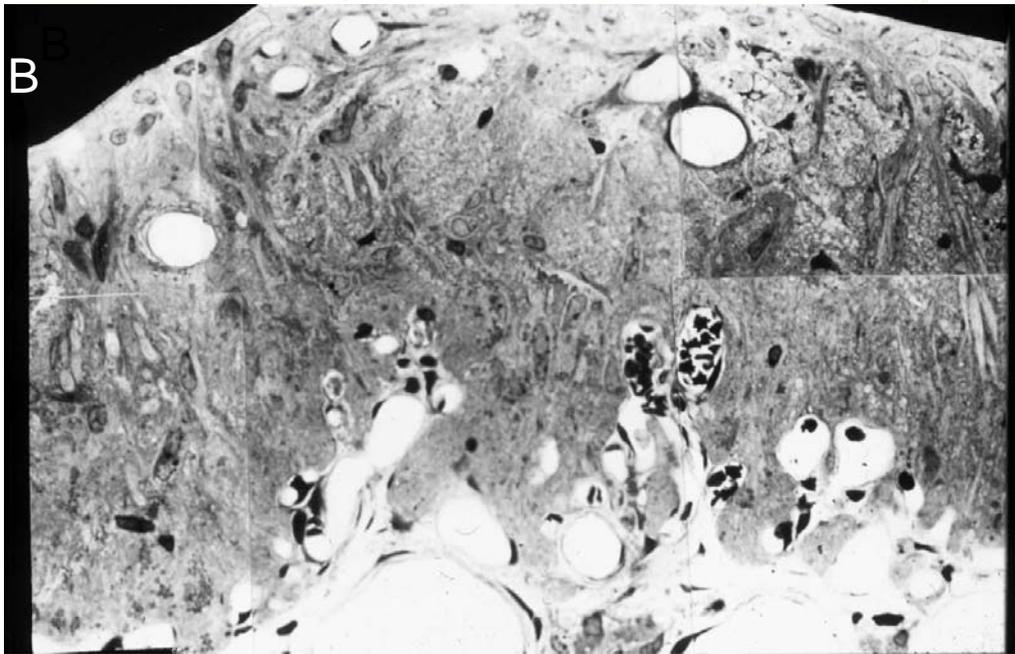
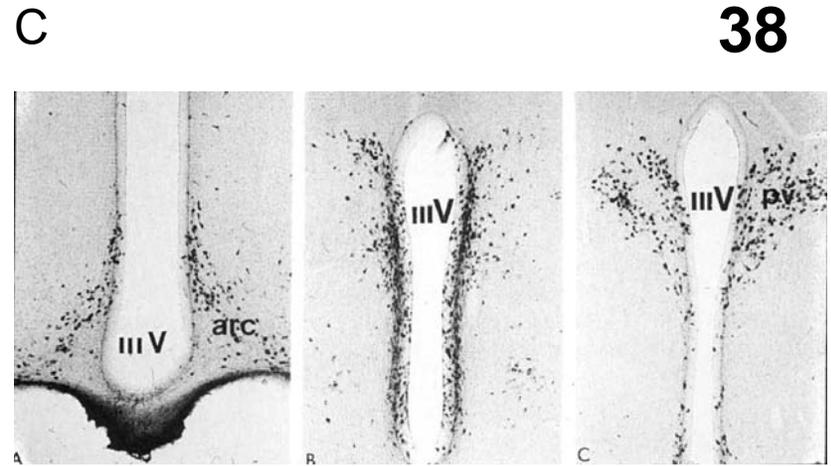
As the hormone neurophysin complex is transported down the axons in the hypothalamo-hypophyseal tract, additional post-translational processing is taking place. The mature complex is then packaged into the neurosecretory granules, whose arrival at the axon terminal coincides with the arrival of the action potential (1). The membrane of the granule fuses with the axon terminal membrane and the product is exocytosed. The action potential causes entry of sodium (2) and calcium (3). The intracellular calcium is packaged into microvesicles (4) and extruded and the membrane potential is restored by a sodium-potassium pump (5). The membranes of the evacuated neurosecretory granules are reformed (6) and packaged into lysosomes and degraded or recycled in areas of non-terminal swelling known as Herring bodies. From Kandell and 36a Schwartz

A. Parvicellular neurosecretory motor zone

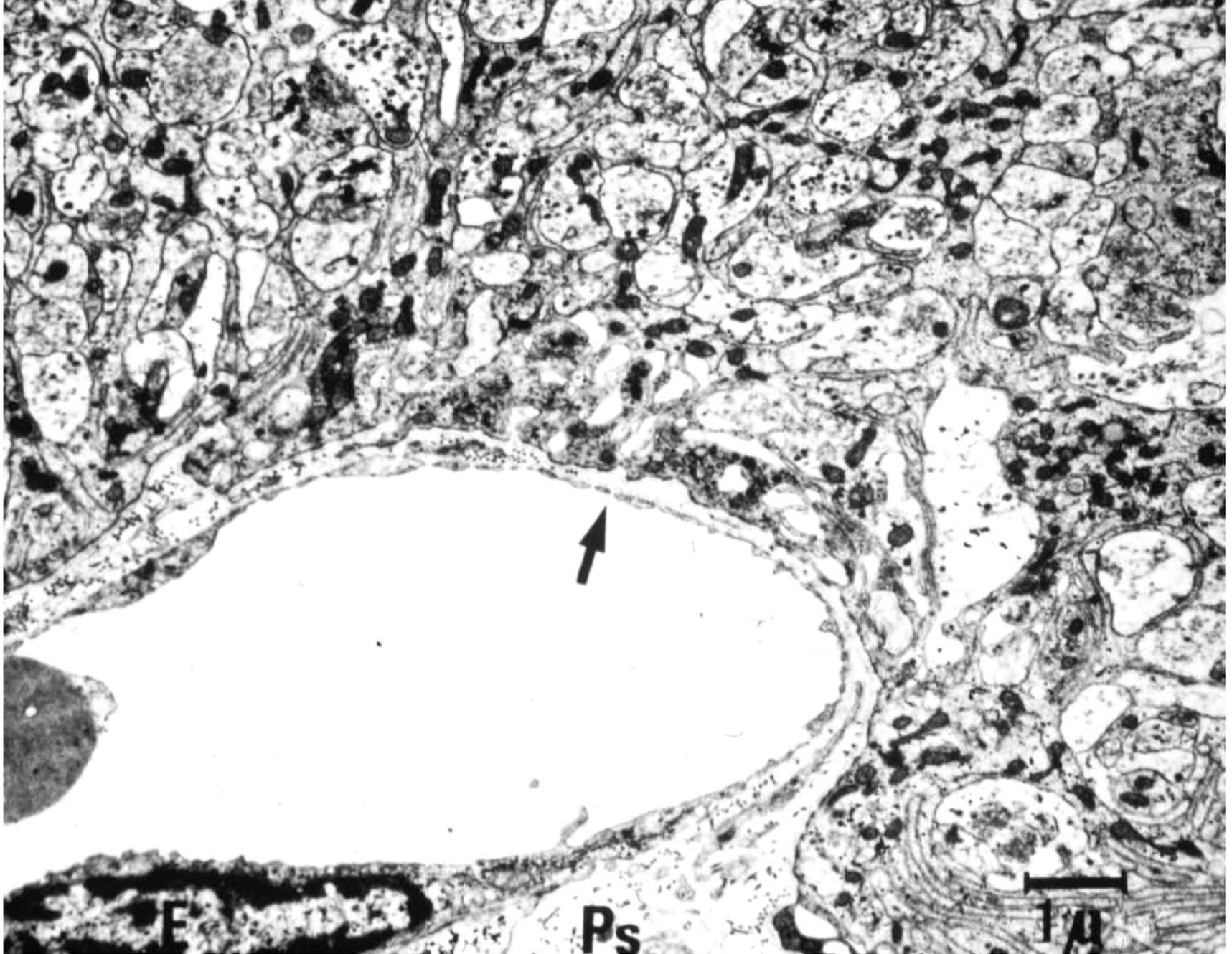


Sagittal scheme to show the distribution of releasing or release inhibiting hormones. From Markakas and Swanson, 1997)

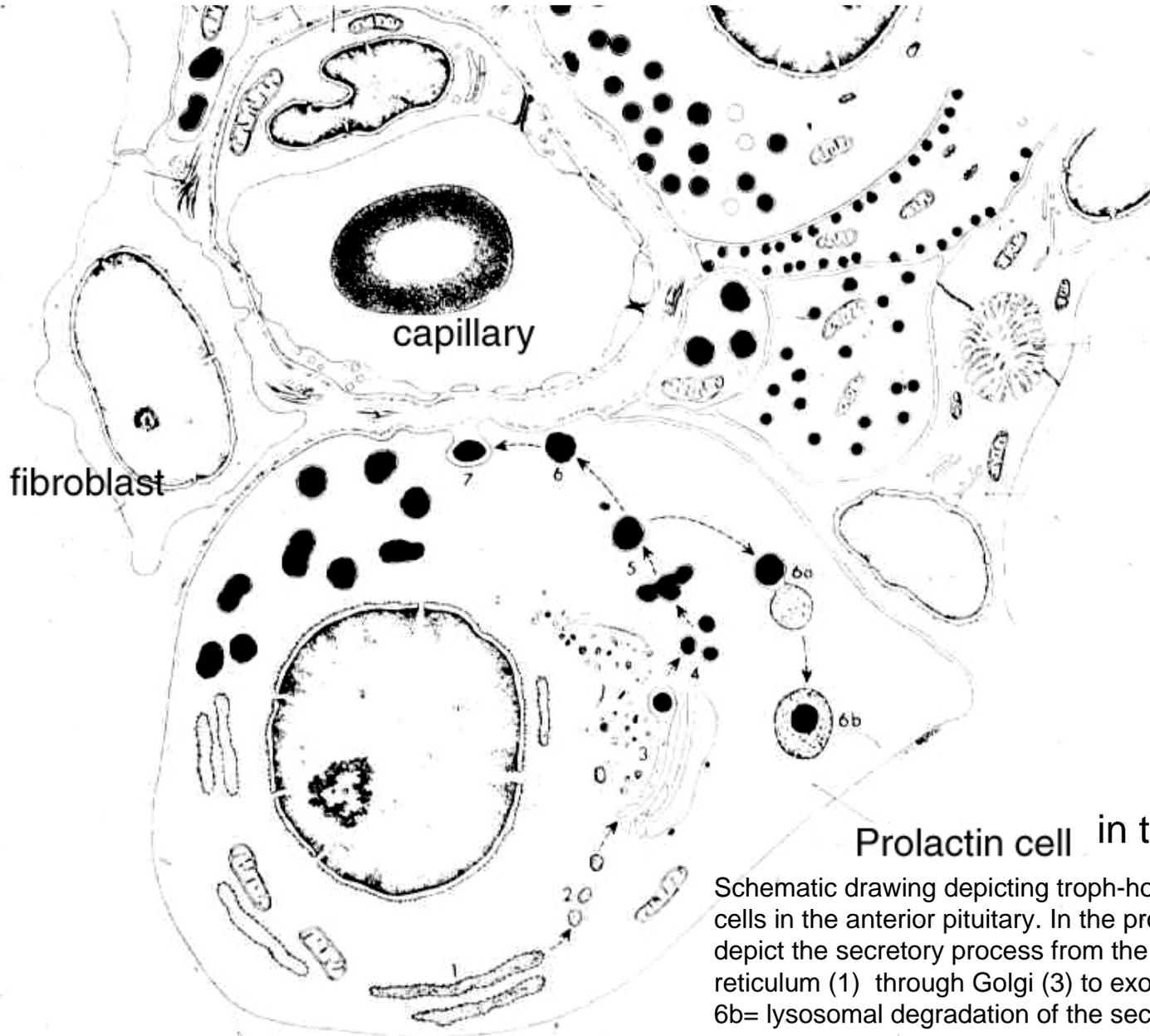
# Organization of the median eminence



Schemes (A,D) and photomicrographs. B: photomicrograph showing the capillary loop. C: distribution of somatostatin-containing neurons (From Lechan)



Electronmicrograph to show the fenestrated capillaries (arrow) of the median eminence



**Prolactin cell in the pituitary**

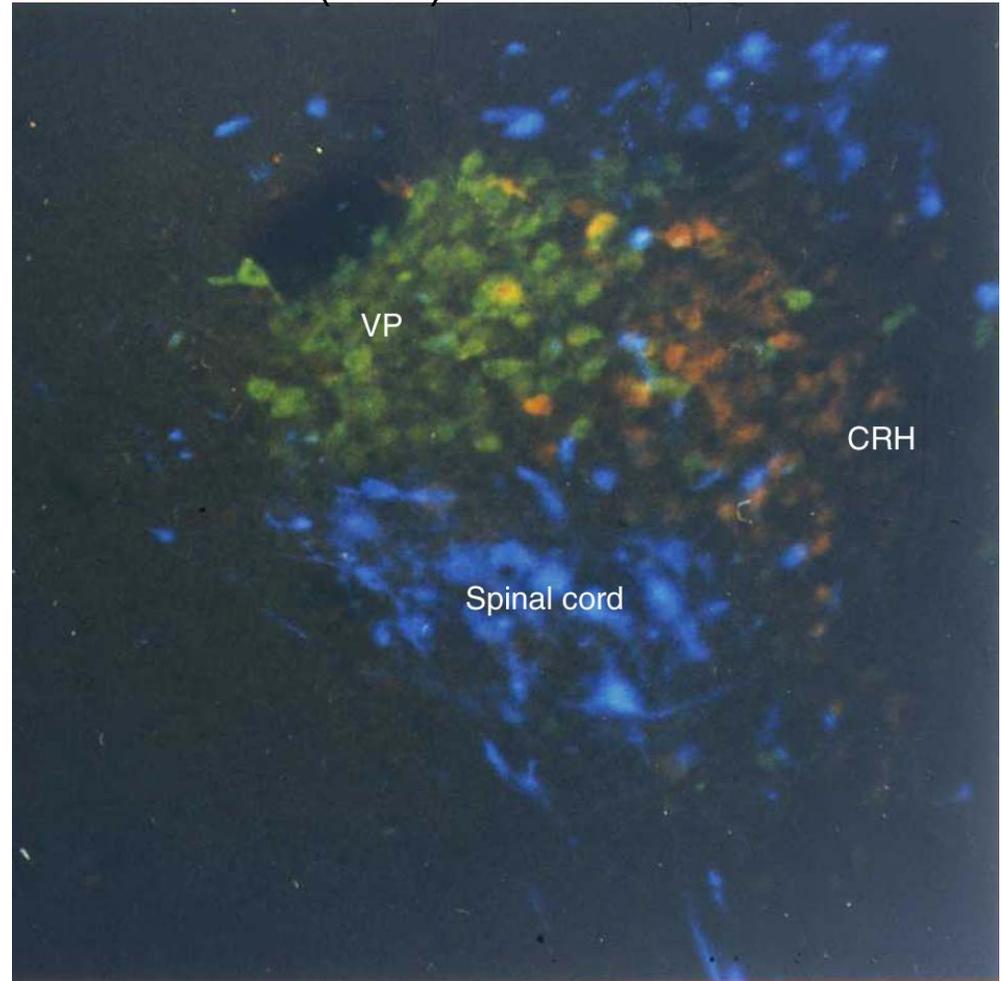
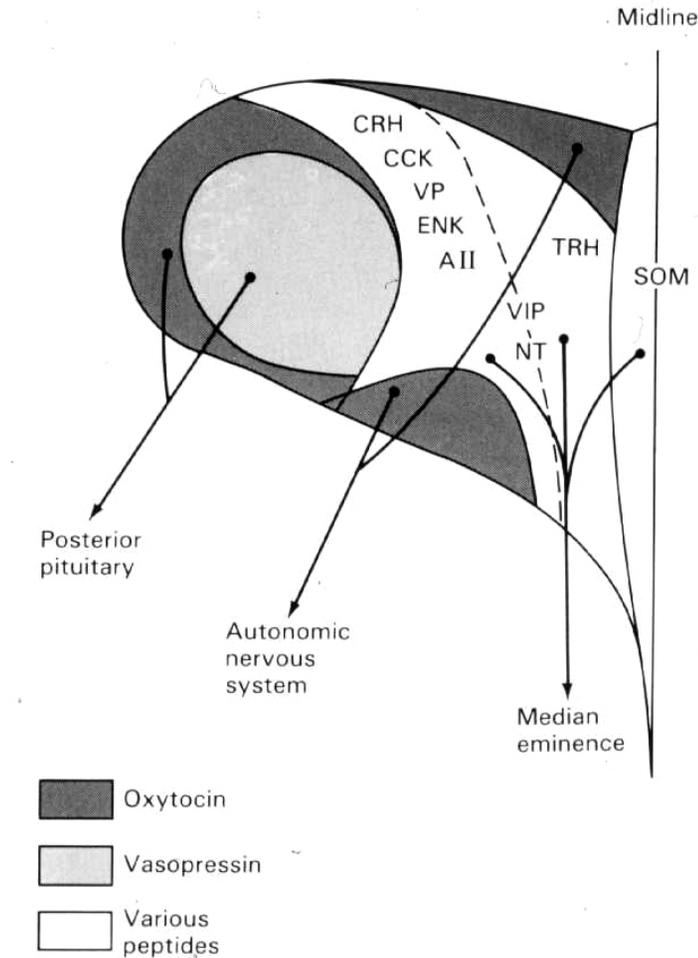
Schematic drawing depicting troph-hormone producing cells in the anterior pituitary. In the prolactin cell 1-7 depict the secretory process from the endoplasmic reticulum (1) through Golgi (3) to exocytosis (7). 6a-6b= lysosomal degradation of the secretory product..

# Hypothalamic

# Anterior Pituitary

<b>Releasing</b>	<b>Hormone</b>
TRH	Thyrotropin
CRH	ACTH, $\beta$ -lipotropin
GnRH	LH, FSH
GHRH	Growth Hormone
PRF	Prolactin
MSHRF	$\alpha$ -MSH
<b>Inhibiting</b>	
PRIF	Prolactin
GHRIH	Growth Hormone
MSHIF	$\alpha$ -MSH

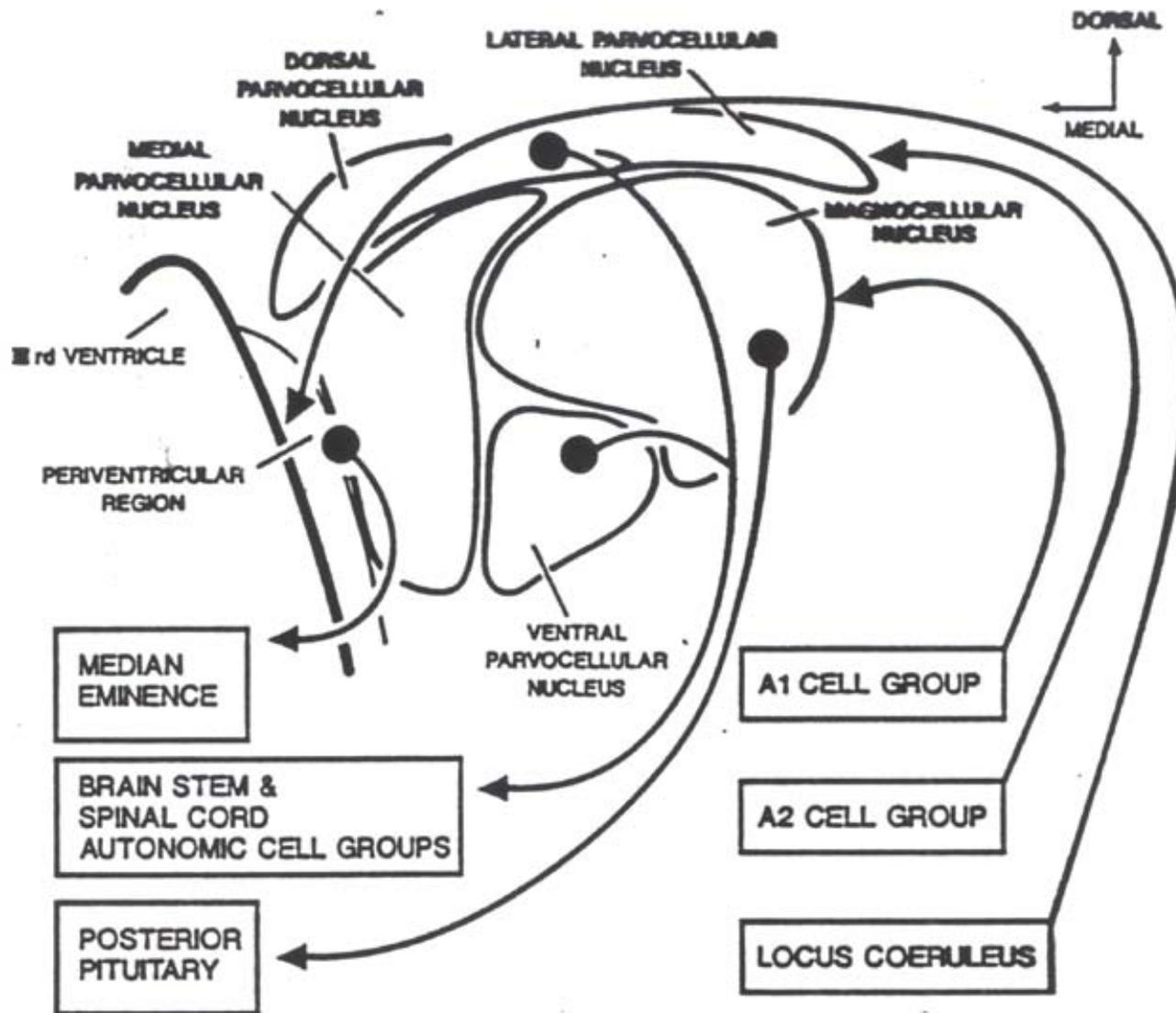
# HYPOTHALAMIC INTEGRATION AT THE LEVEL OF THE PARAVENTRICULAR HYPOTHALAMIC NUCLEUS (PVN)



A

B

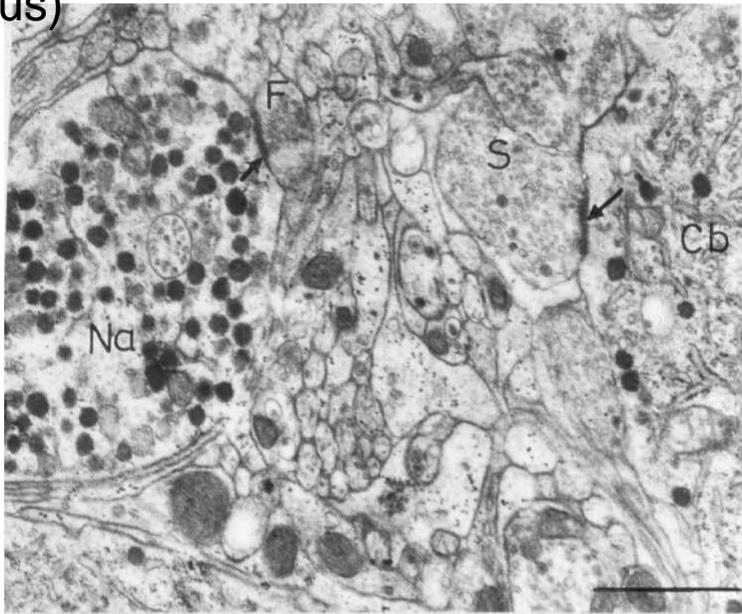
A: Subdivision of the paraventricular hypothalamic nucleus showing the separation of magnocellular (oxytocin, vasopressin) and parvocellular neurons (from Swanson). B: CRH cells yellow, vasopressin cells green, neurons projecting to the spinal cord blue (from Sawchenko)



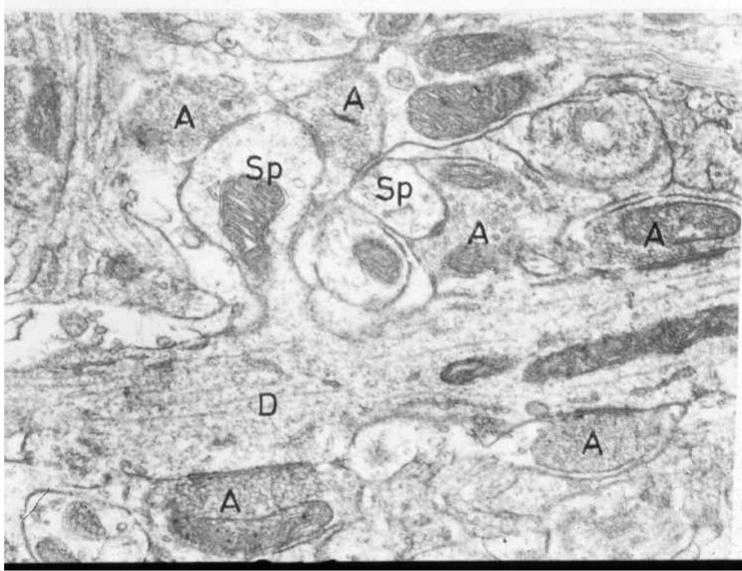
Schematic drawing to show the major subdivisions, afferent and efferent connections of the PVN (Swanson and Sawchenko)

# HYPOTHALAMIC INTEGRATION AT THE CELLULAR LEVEL (supraoptic nucleus)

A

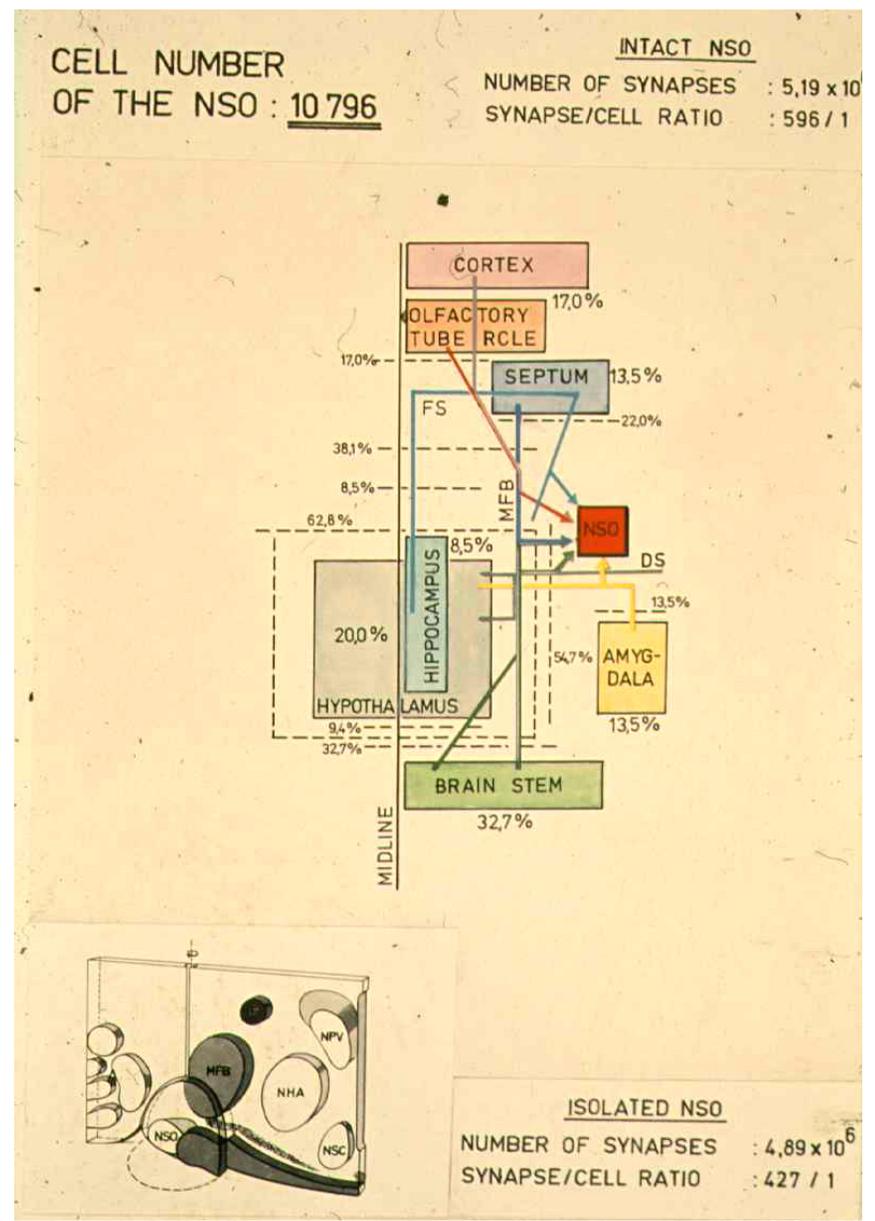


B

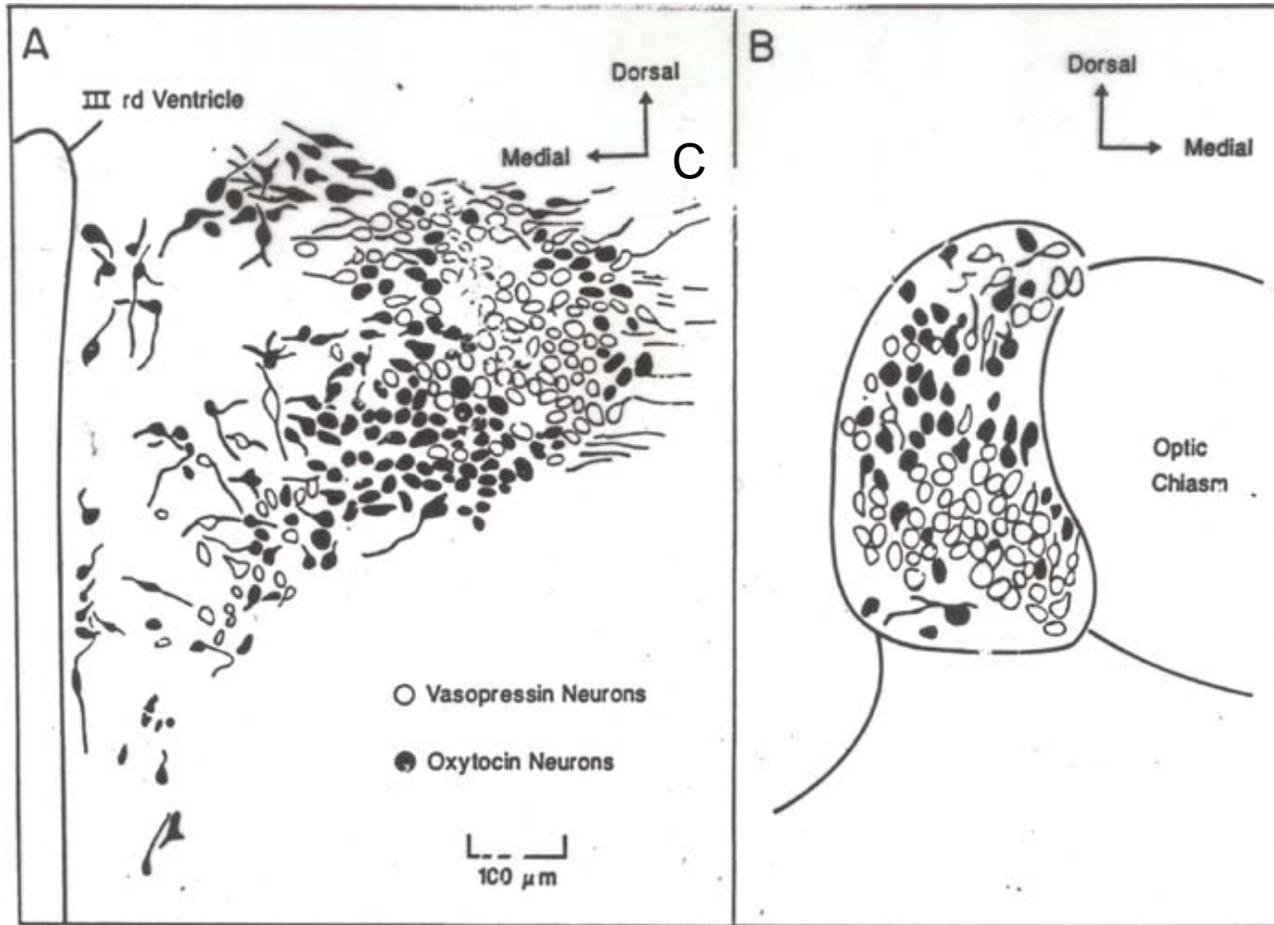


**A:** Neurosecretory axon (Na) from the SON. A in (B) marks axon terminals containing clear vesicles.

C

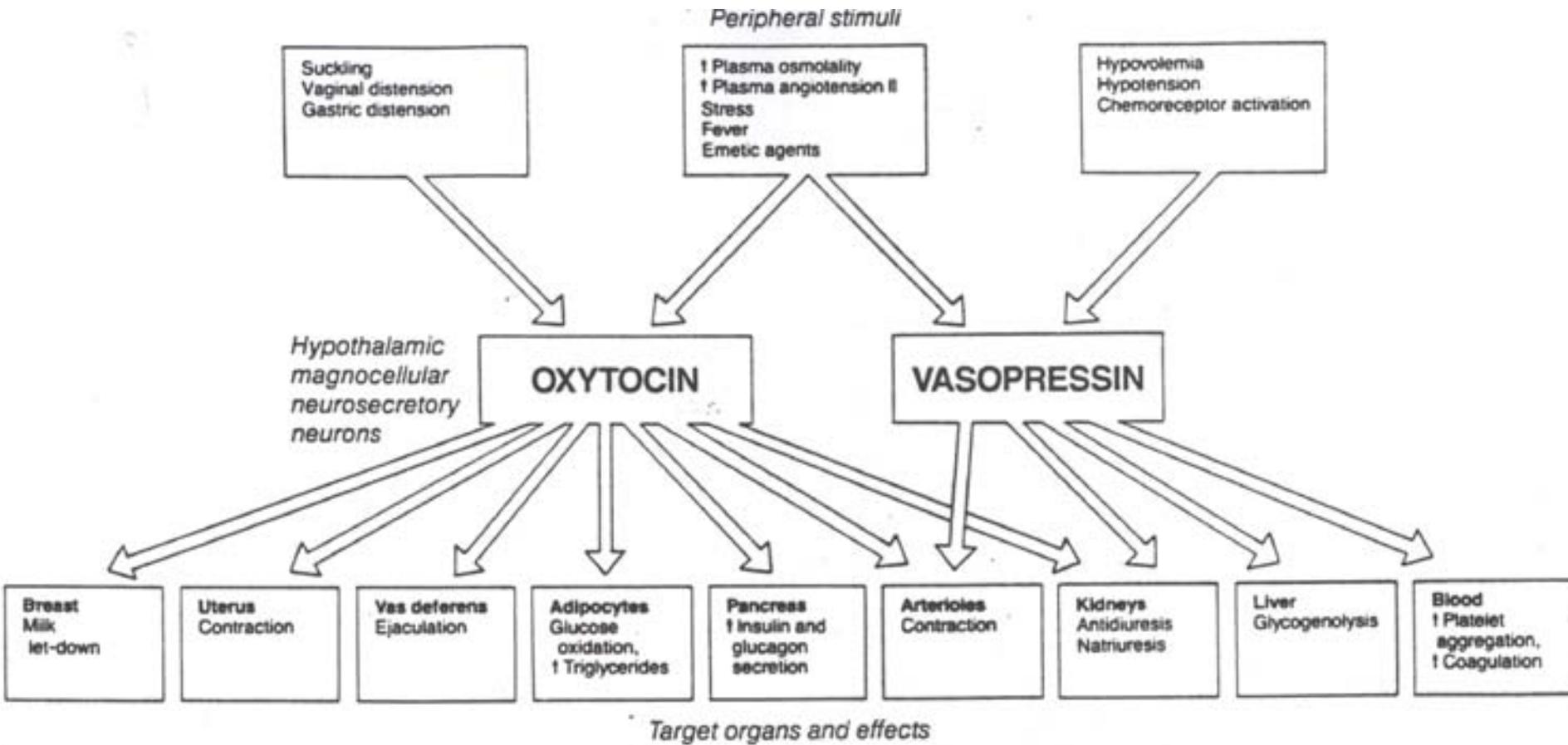


Number and distribution of various synaptic input in the SON  
 From Zaborszky et al., 1975)



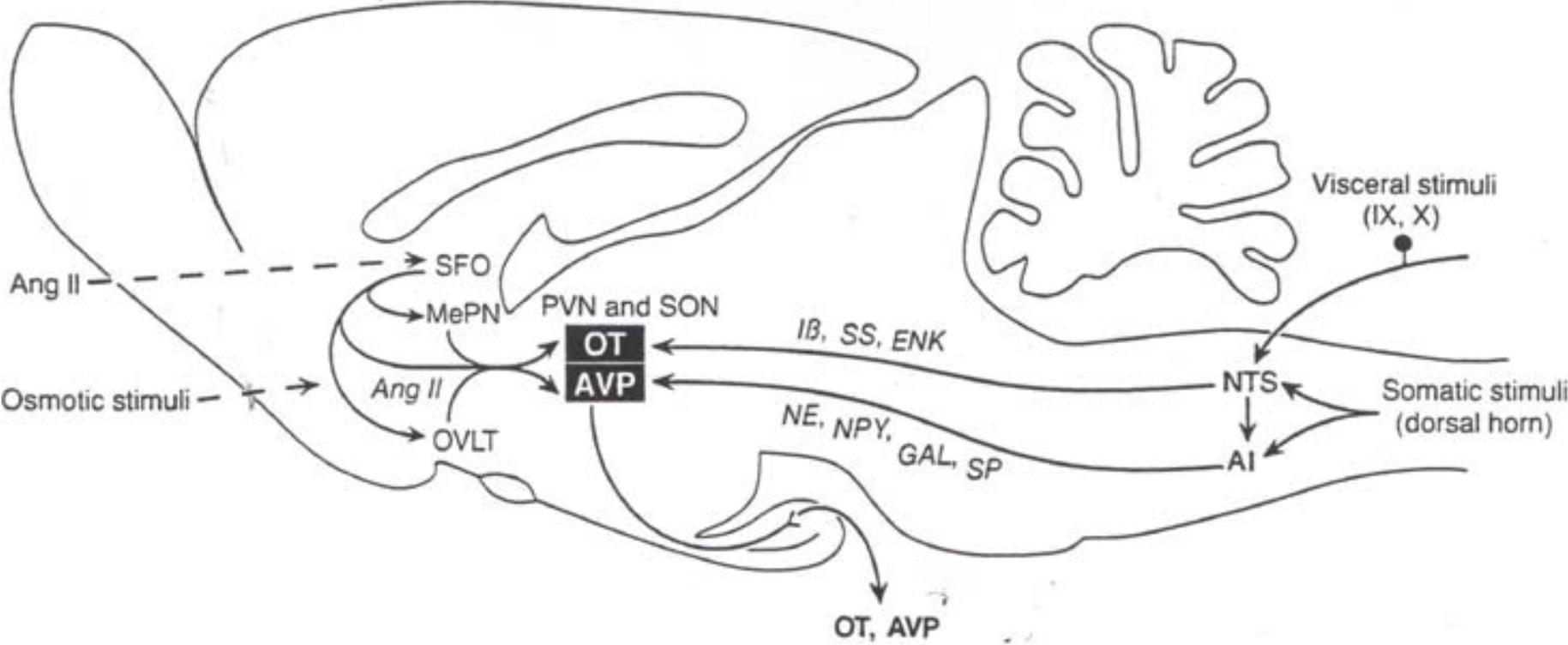
A-B: Distribution of oxytocine and vasopressin-containing neurons in the PVN (A) and (B) SON.

C

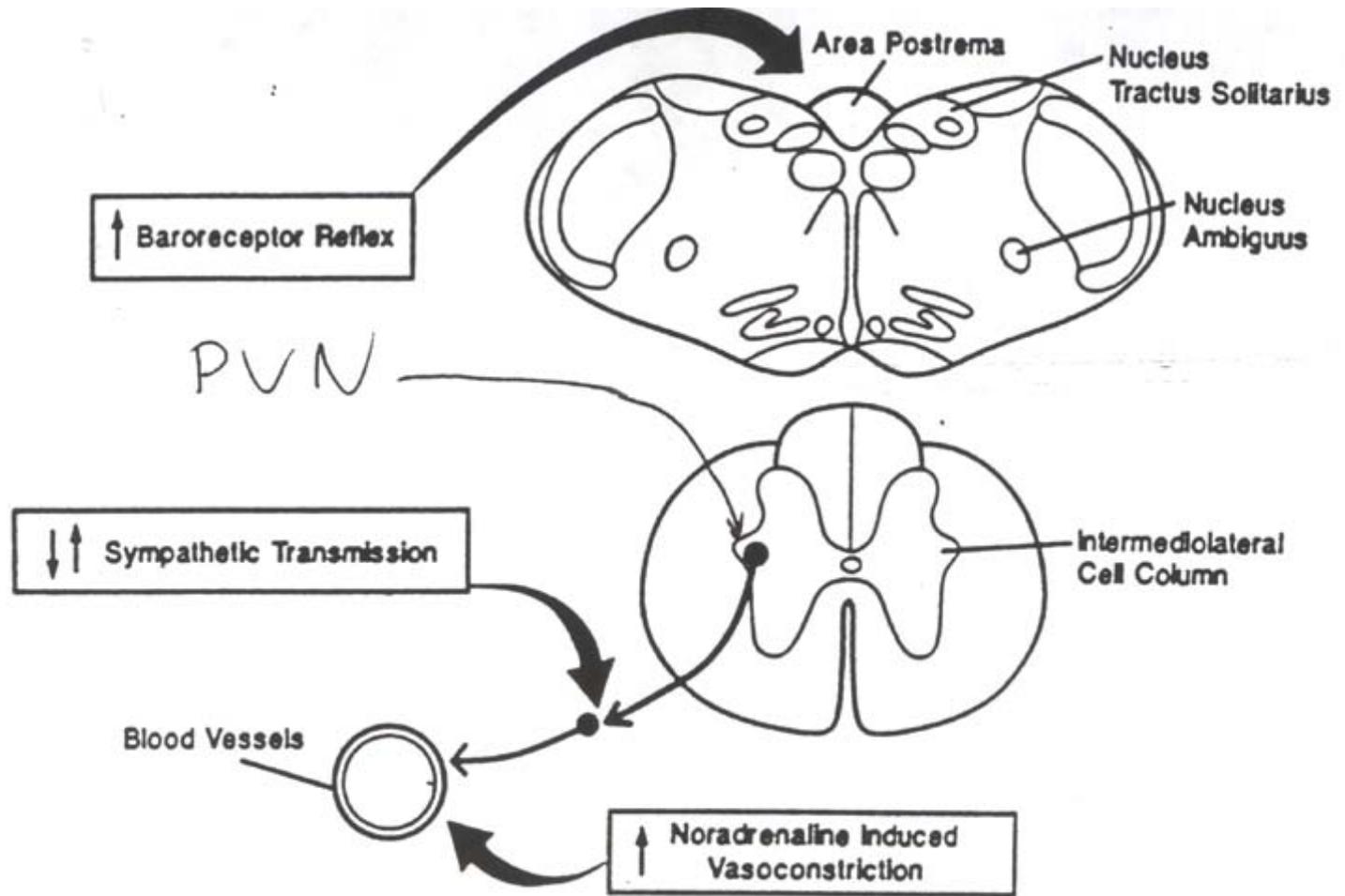


Schematic diagram of the peripheral stimuli known to elicit coordinated and preferential release of oxytocin and vasopressin from hypothalamic magnocellular neurons, as well as the resultant effect of these hormones on distant target organs. (Sawchenko).

# Main inputs to OT and VP secreting neurons of the paraventricular nucleus

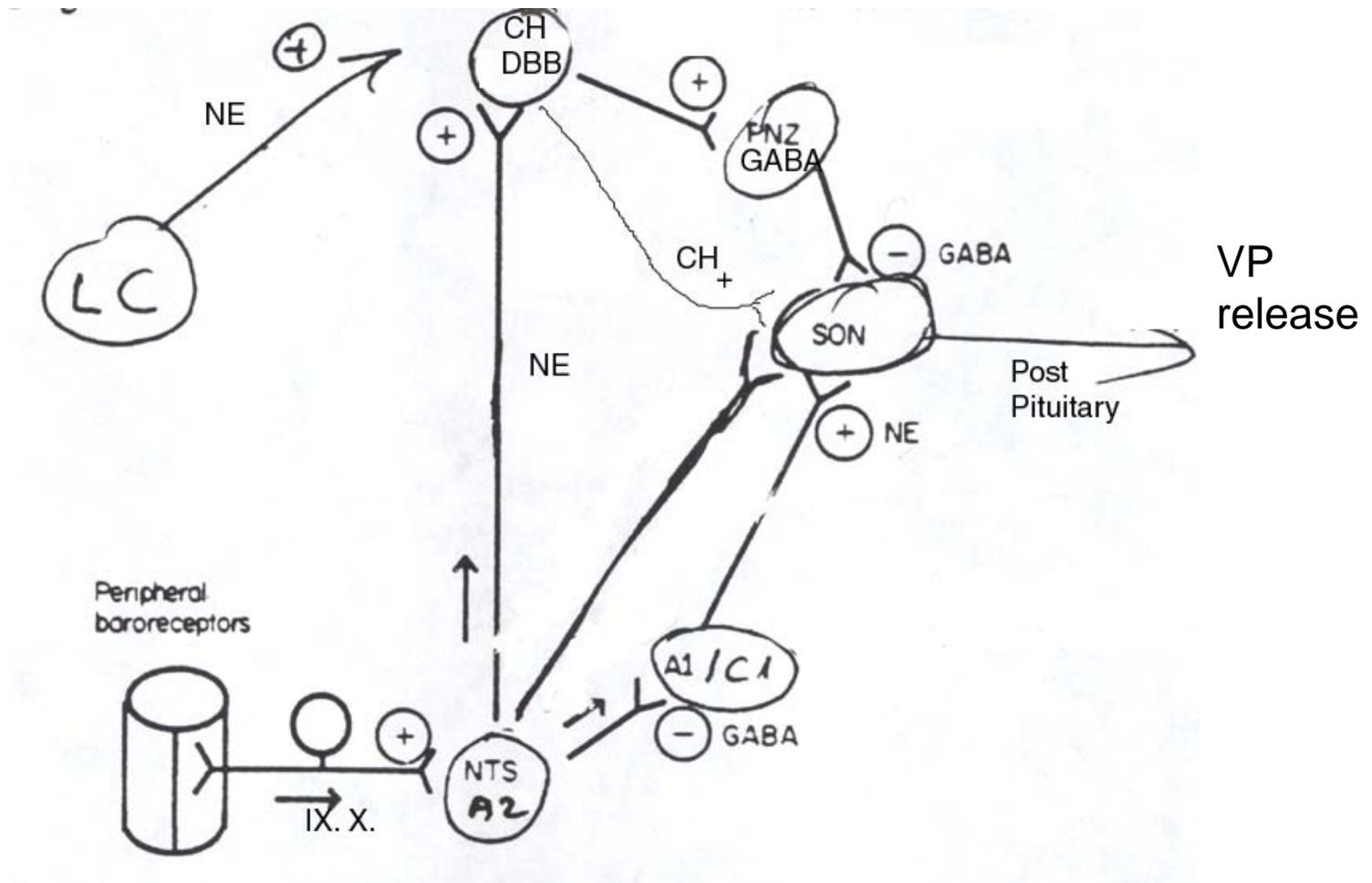


A schematic drawing of a sagittal section through the rat brain to summarize current understanding of **central mechanisms of vasopressin (AVP) and oxytocin (OT) secretion** (Sawchenko). Osmoreceptors are located near the OVLT and the neighboring medial preoptic area.



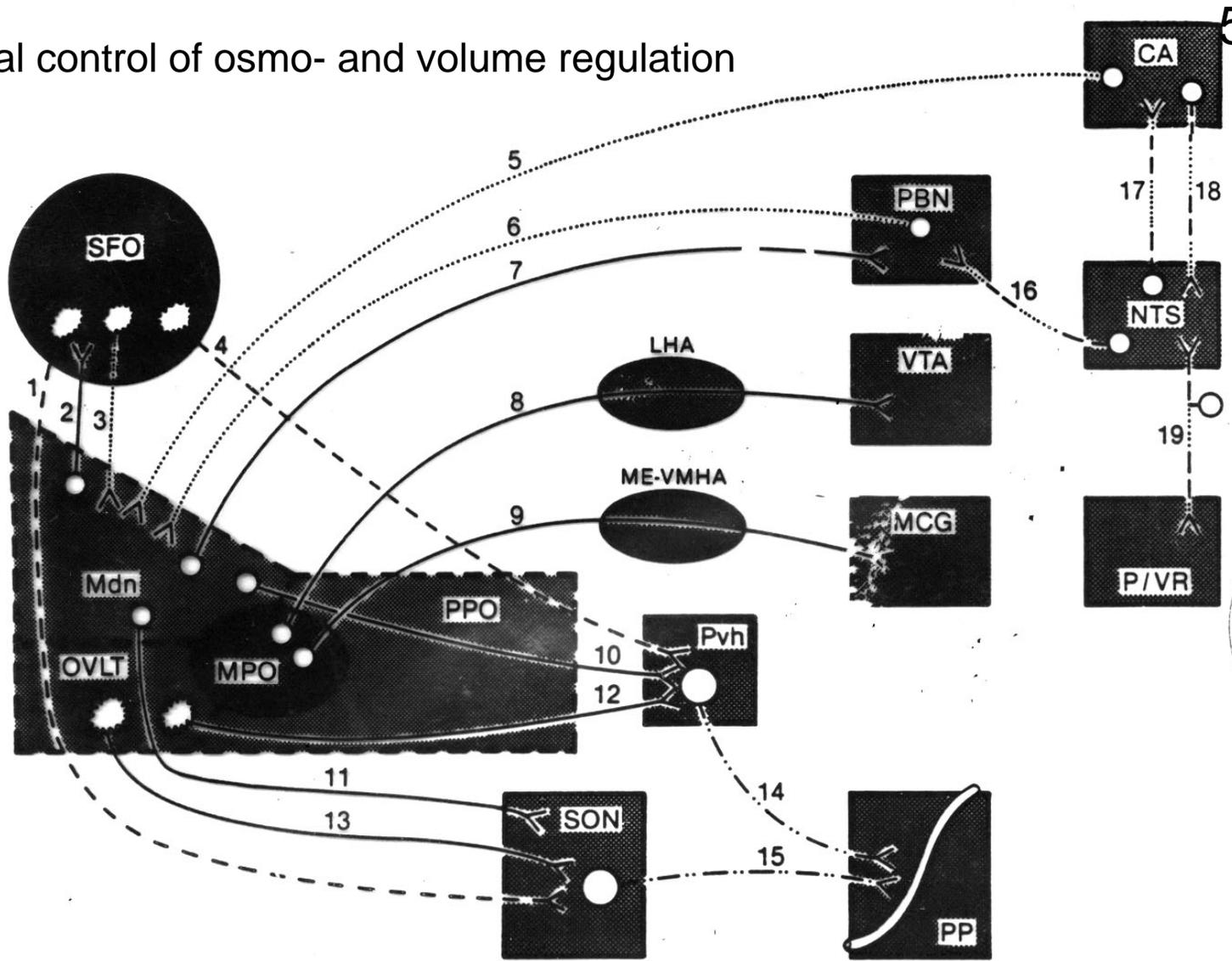
**Vasopressin acts at three different sites** in the body to modify cardiovascular function. It can potentiate the vasoconstrictor action of noradrenaline at blood vessels, modulate sympathetic transmission, and affect the baroreceptor reflex by a central effect mediated by the area postrema

# Pathways mediating baroreceptor-induced inhibition of vasopressin secretion in the supraoptic nucleus



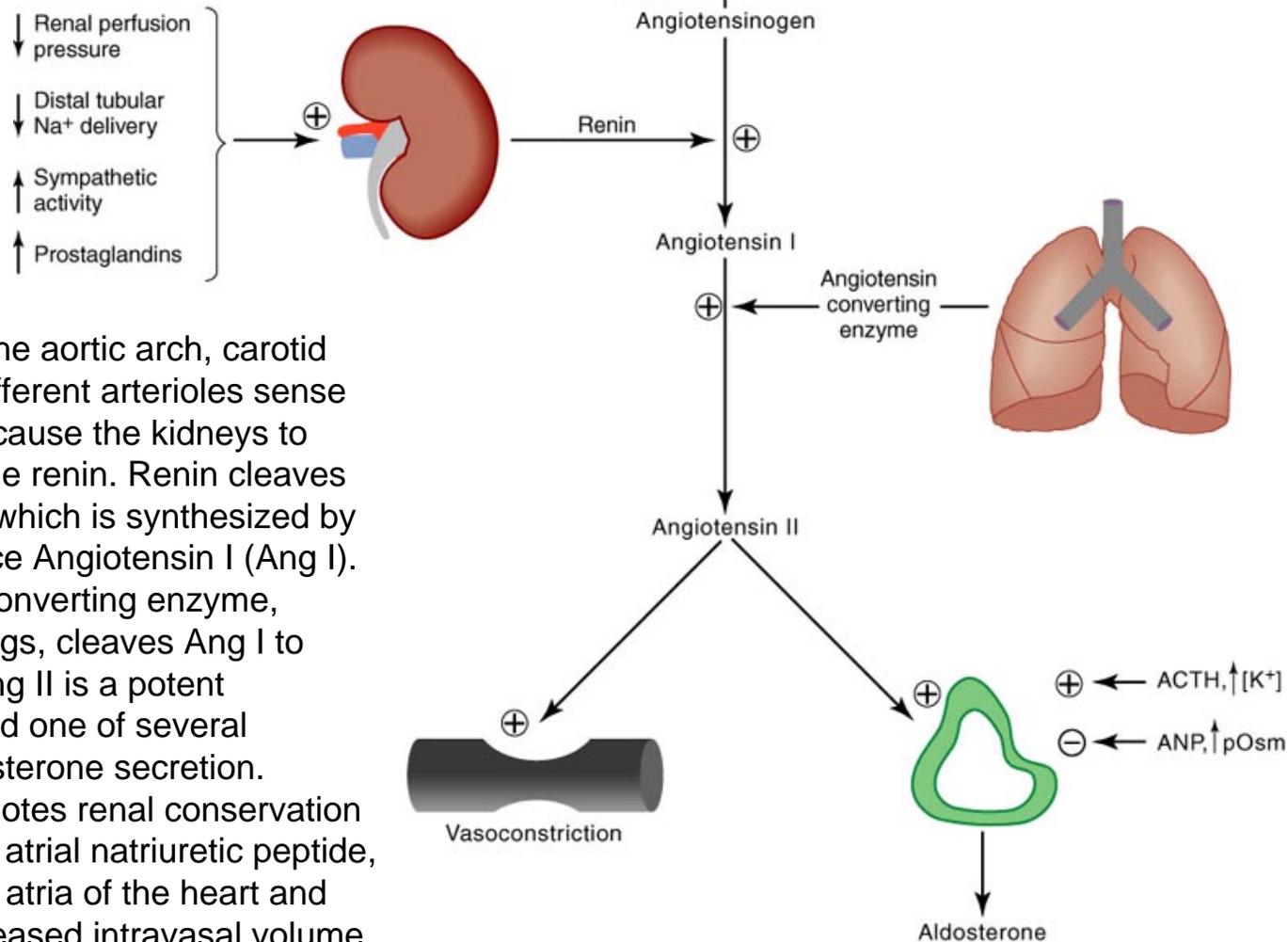
LC=locus coeruleus, NTS=nucleus tractus solitarius, A2= noradrenergic neurons within the NTS area; A1/C1= adrenergic-noradrenergic neurons in the ventrolateral medulla, CH=cholinergic neurons in the diagonal band, PNZ= perinuclear zone around the SON containing GABAergic neurons (after J. Jhamandas)

# Central control of osmo- and volume regulation



SFO: subfornical area; The large black island is the AV3V (anteroventral 3<sup>rd</sup> ventricle area) that encompasses the OVLT (organon vasculosum laminae terminalis and various preoptic cell groups that contain osmoreceptors; S)N: supraoptic nucleus; Pvh: paraventricular nucleus; PBN+parabrachial nucleus in the brainstem (viscerosensory relay); VTA: ventral tegmental area (dopaminergic cells); ME-VMH (median eminence-ventromedial hyp, n); PP:posterior pituitary (termination of fibers from the SON and Pvh); CA=catecholaminergic cell groups in the medulla; NTS: n. tractus solitarii (termination of vagal and glossopharyngeus viscerosensory axons); P/VR=mecahnoreceptors in the pulmonary artery and vena cava.

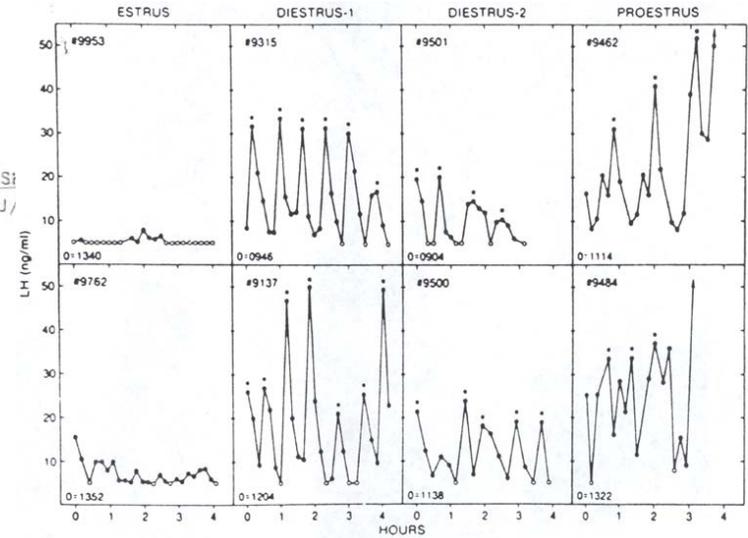
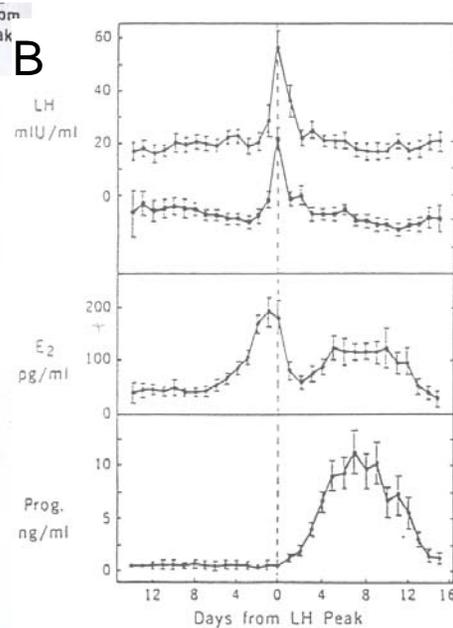
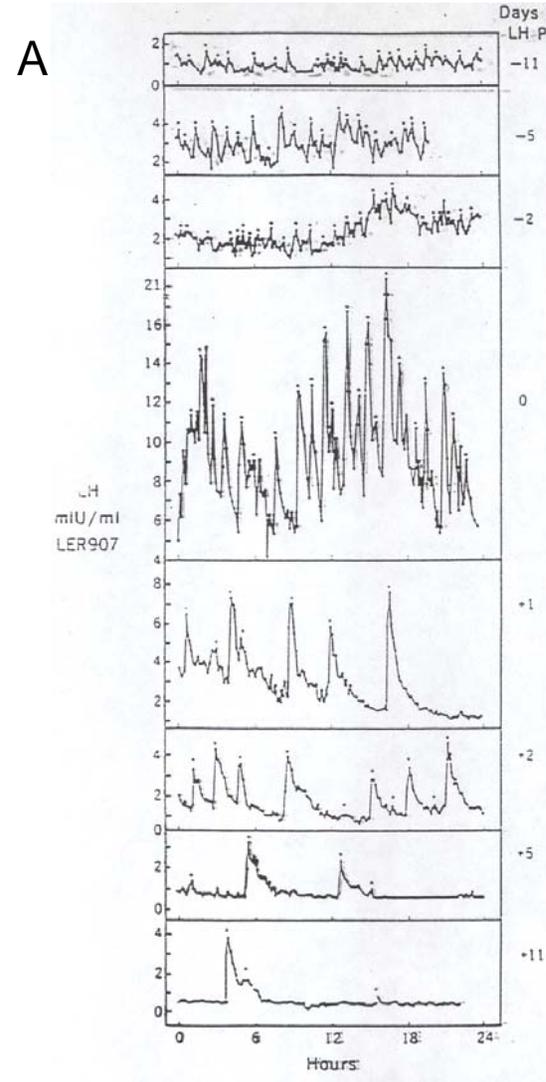
# PERIPHERAL MECHANISMS OF OSMO- AND VOLUME REGULATION



Baroreceptors in the aortic arch, carotid sinus, and renal afferent arterioles sense hypovolemia and cause the kidneys to secrete the enzyme renin. Renin cleaves angiotensinogen, which is synthesized by the liver, to produce Angiotensin I (Ang I). The angiotensin-converting enzyme, primarily in the lungs, cleaves Ang I to produce Ang II. Ang II is a potent vasoconstrictor and one of several stimulants of aldosterone secretion. Aldosterone promotes renal conservation of Na<sup>+</sup> ions. ANP, atrial natriuretic peptide, synthesized in the atria of the heart and released with increased intravascular volume to stimulate aldosterone secretion in the adrenal cortex (Stricker and Verbalis, 2002)



# Pulsatile/Diurnal/Seasonal Release of GnRH/LH/FSH <sup>53</sup>



- Frequency and amplitude of LH pulses on selected days of the normal human menstrual cycle. The days of the cycle are indicated relative to the day of the LH surge (day 0). Significant LH pulses are indicated (dot). During the follicular phase (days -11 to -2) low-amplitude LH pulses occur almost hourly. On the day of the LH peak, the frequency of the LH pulses remains circrchoral but the amplitude is increased. During the luteal phase, the LH pulse frequency is reduced.

**B:** LH, FSH, E<sub>2</sub> and progesteron levels throughout the cycle of nine women. **C:** Concentrations of LH in peripheral plasma obtained at 10-min intervals for 4 hr from two rats during each day of the 4-day estrus cycle.

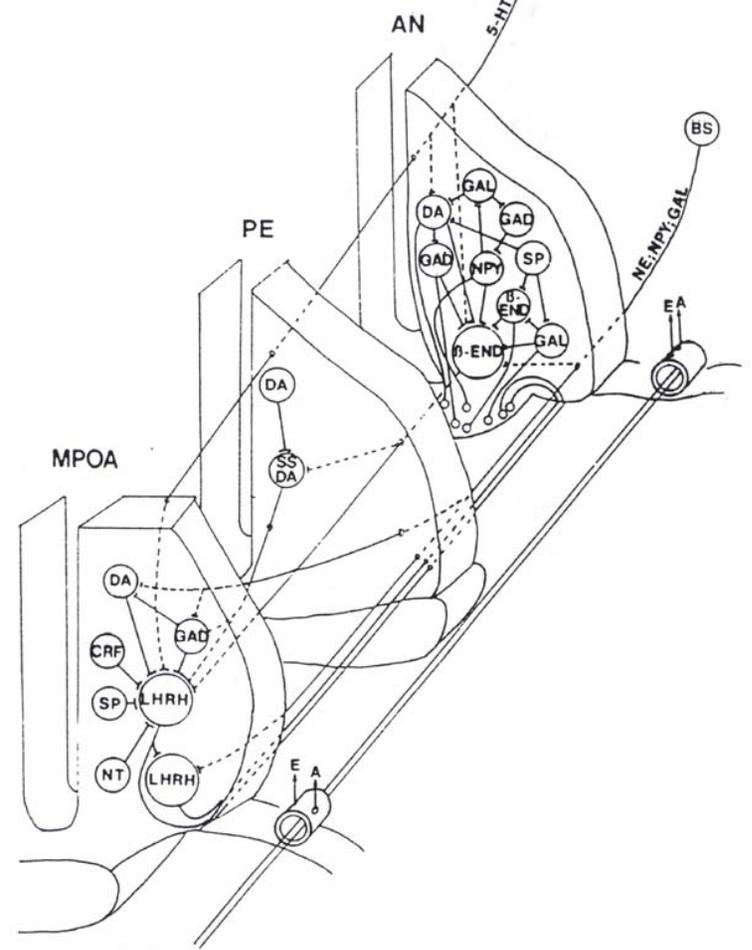
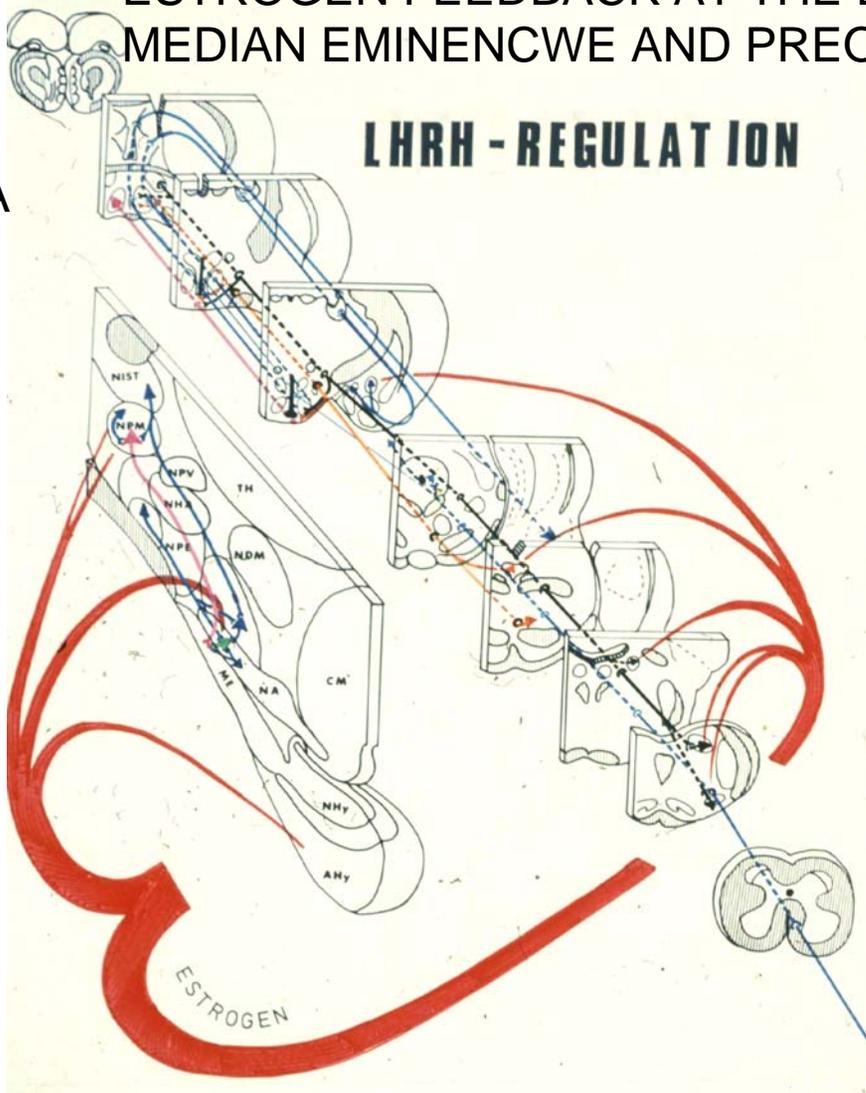
# ESTROGEN FEEDBACK AT THE LEVEL OF THE ANTERIOR PITUITARY, MEDIAN EMINENCE AND PREOPTIC REGION

54

B

## LHRH - REGULATION

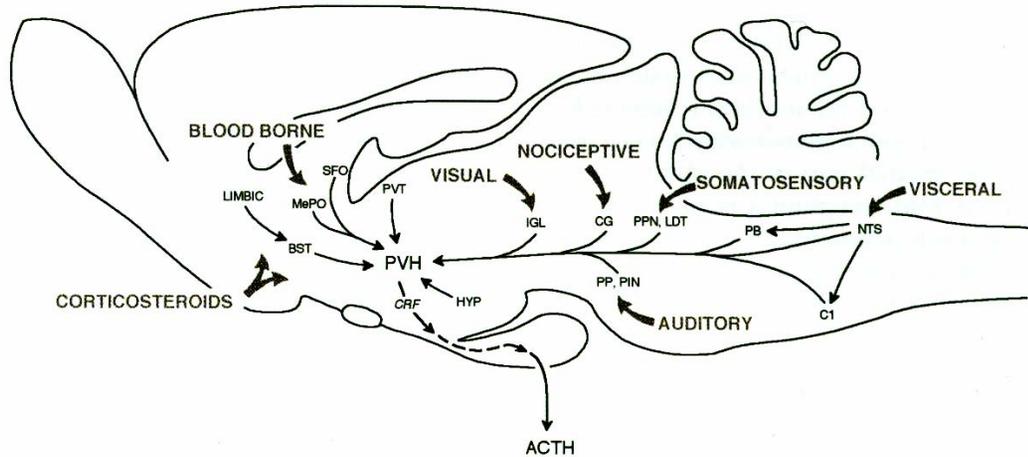
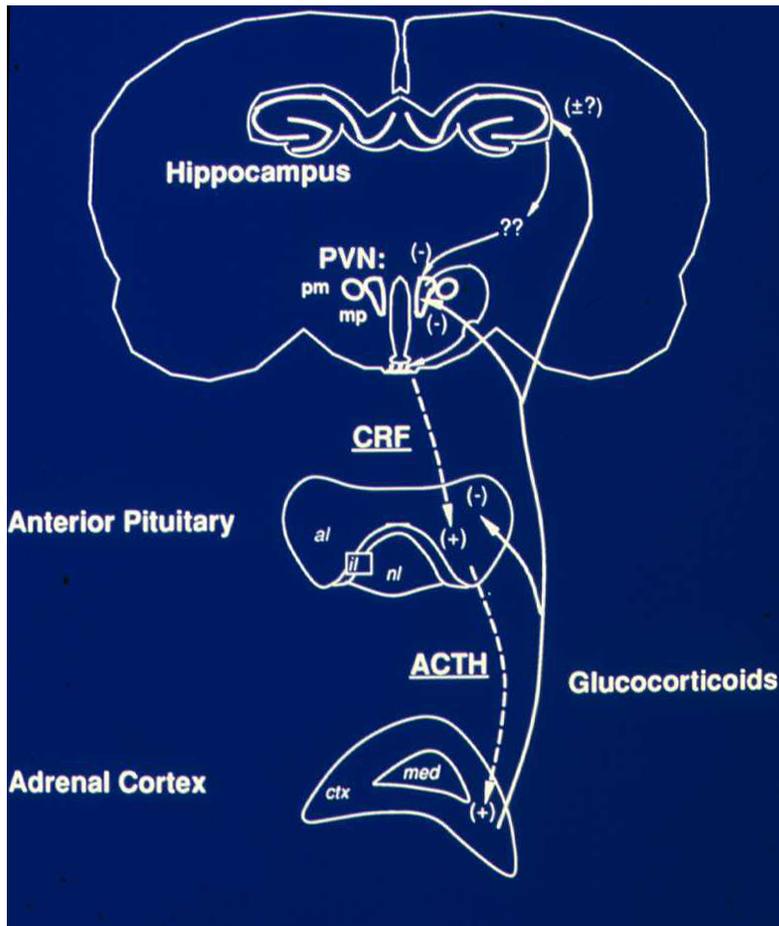
A



**A:** Schematic representation of estrogen feedback at the level of the anterior pituitary, median eminence and preoptic region of the hypothalamus. Note that LHRH neurons in the preoptic area (pink) do not possess estrogen receptors (ER) but receive input from estrogen sensitive neurons (blue) in the arcuate nucleus (Beta-endorphin) and from brainstem monoaminergic cell groups (right part of A). **B:** Schematic representation of the main synaptic interconnections between estrogen-sensitive systems and LH-RH-producing neurons. RN: raphe nuclei, BS: brainstem, E: circulating estrogens, A: circulating androgens.

# ESTROGEN AND COGNITION

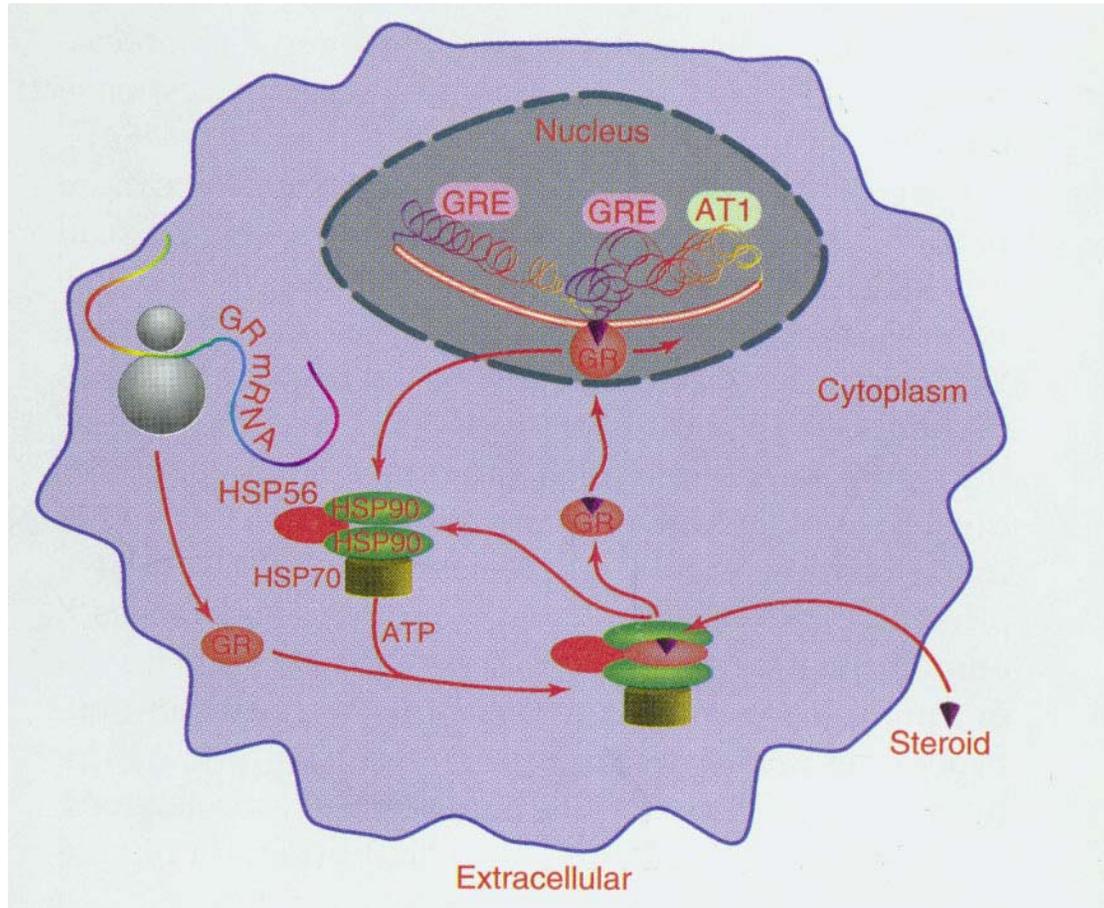
- Estrogen levels are correlated positively with spine density in CA1
- Estrogen cooperate with NGF in BF cholinergic neurons
- Estrogen increases NMDA receptors and enhances LTP
- There are sex differences in the rate of development of age related impairments in spatial reference memory
- Estrogen protect B-amyloid exposure induced cell death



**B:** Sagittal drawing of the rat brain illustrating the main input to CRF producing cells in the PVN (From Simerly et al., 2004).

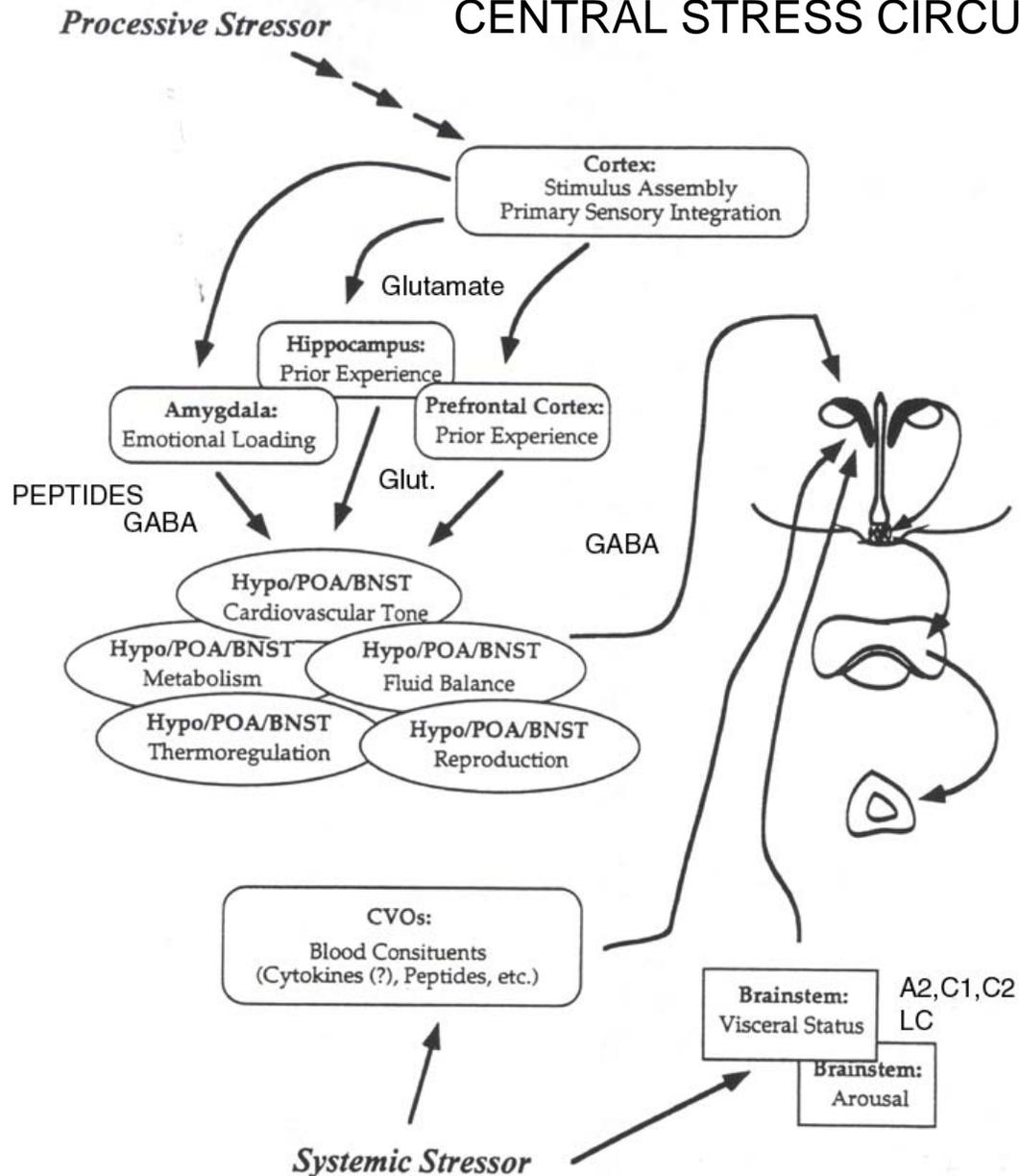
**A:** Schematic representation of the brain-pituitary-adrenal axis showing that CRF travels in the axons from the PVN to the median eminence where CRF is released to the portal vessels to stimulate ACTH secretion from the anterior pituitary. ACTH acts at the adrenal cortex to induce the biosynthesis and release of glucocorticoids. These are released into the general circulation to mediate the stress response and feedback in a negative manner at the pituitary and the CRF neurons of the PVN. The hippocampus act via the subiculum-bed nucleus of the stria terminalis-[BST]-PVN route to inhibit CRF secretion ('A' courtesy of Dr. Cullinan).

## Model of glucocorticoid receptor (GR) function



Once translated in the cytoplasm, GR is quickly stabilized by a complex including heat-shock protein (HSP) subtypes. Circulating steroids, including corticosteroids, easily cross cell membranes to access the cytoplasm from the vasculature and bind to GR. Activation of the GR by steroid binding induces its separation from the HSP complex and its translocation to the nucleus, where it interacts with DNA to activate or inhibit gene transcription.

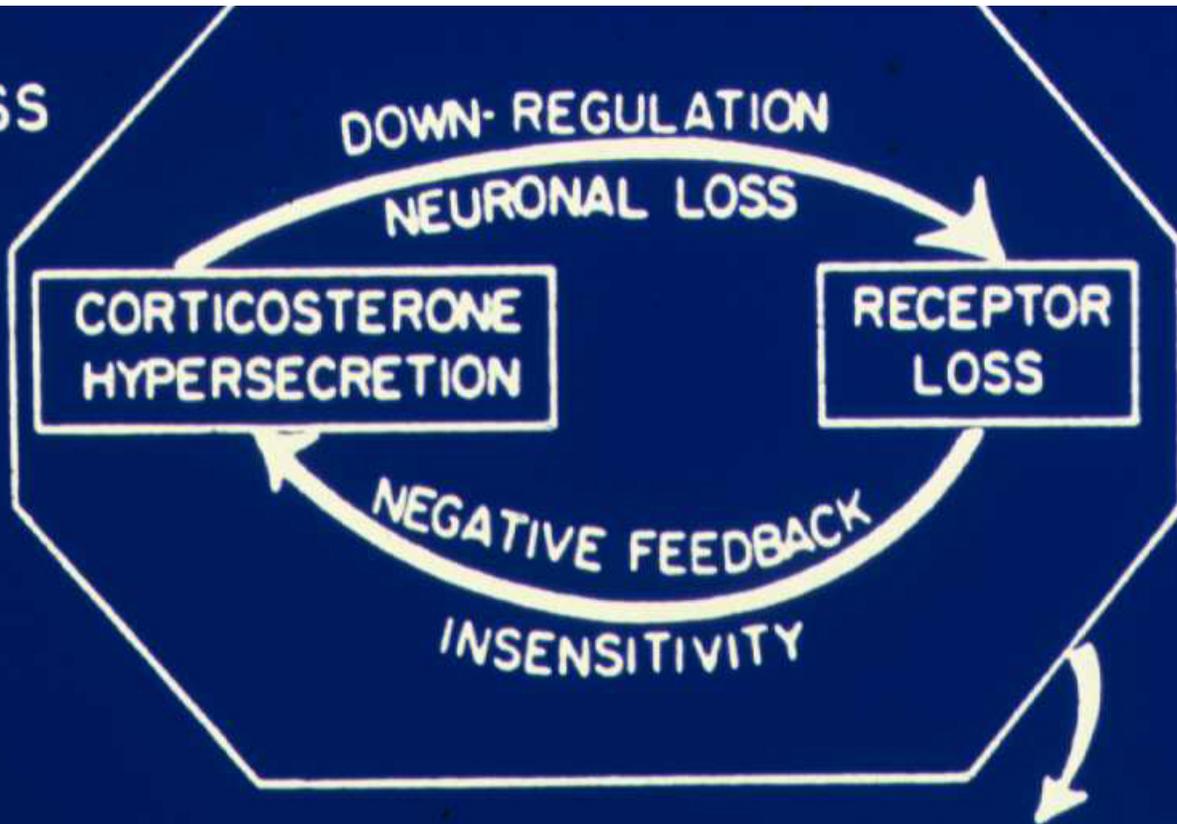
## CENTRAL STRESS CIRCUITRY



“Systemic” stressors that signal elemental physiological change interact with brainstem catecholaminergic neurons or circumventricular organs that directly affect CRF/Vasopressin neurons in the PVN. Examples of such stressors include respiratory distress, blood loss, renal hypertension, hyponatremia and increases in circulating cytokines. “Processive” stressors are assembled at the cortical level and relayed to the hippocampus, amygdala and prefrontal cortex to determine the salience of the stimulus attributes. Processed information from these regions is relayed to the hypothalamic/preoptic/bed nucleus of the stria terminalis continuum, which interpret the stimulus assembly with respect to ongoing homeostatic balance. Information from these sources is then sent to the PVN to affect CRF secretion. **Stimuli integrated by way of the processive stress pathway is relayed via GABAergic neurons to the PVN.** Information following systematic pathways, by contrast, project directly to the PVN. (Herman, Cullinan and their coworkers)

immune challenge, hemorrhage, hypotension, respiratory distress, blood oxygenation-

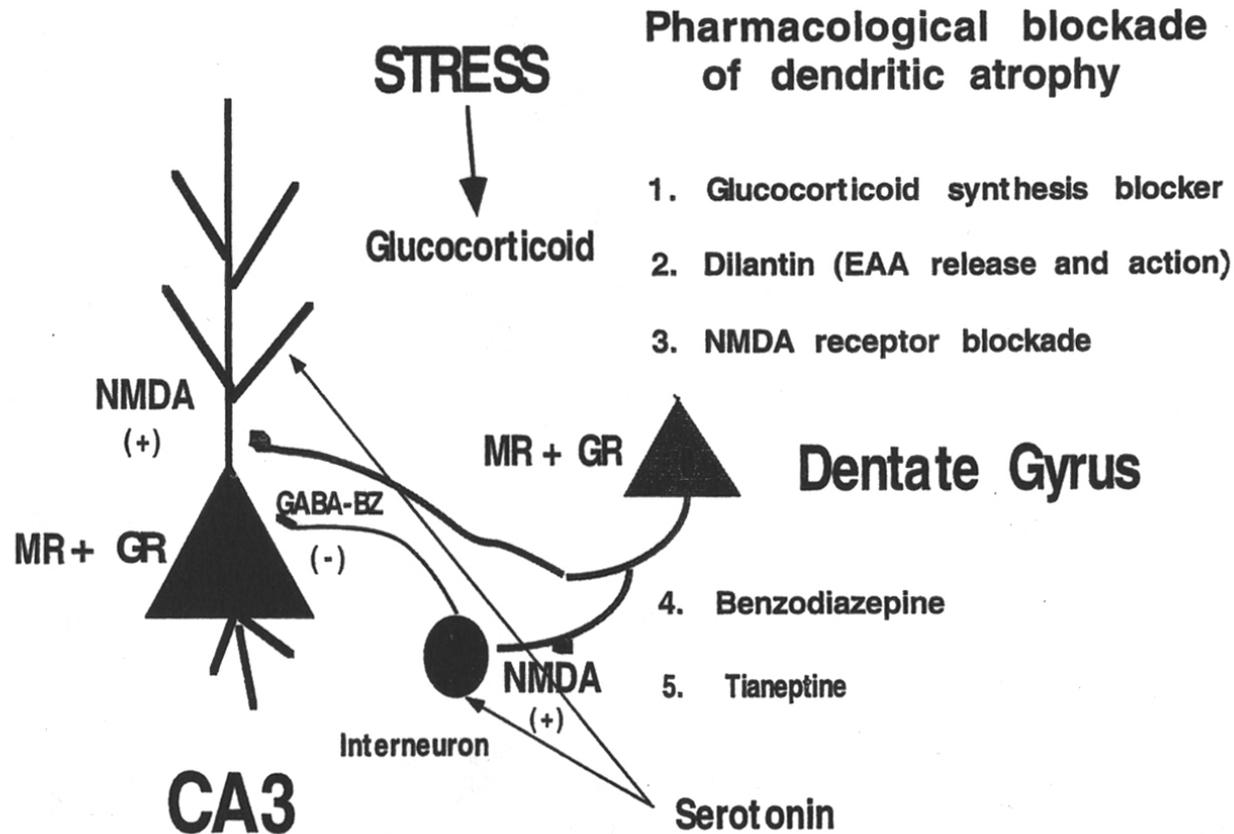
STRESS



**HYPOADRENOCORTICISM**  
 (Addison-syndrome)  
 Increased susceptibility to inflammatory and autoimmune disease, muscle weakness, skin pigmentation

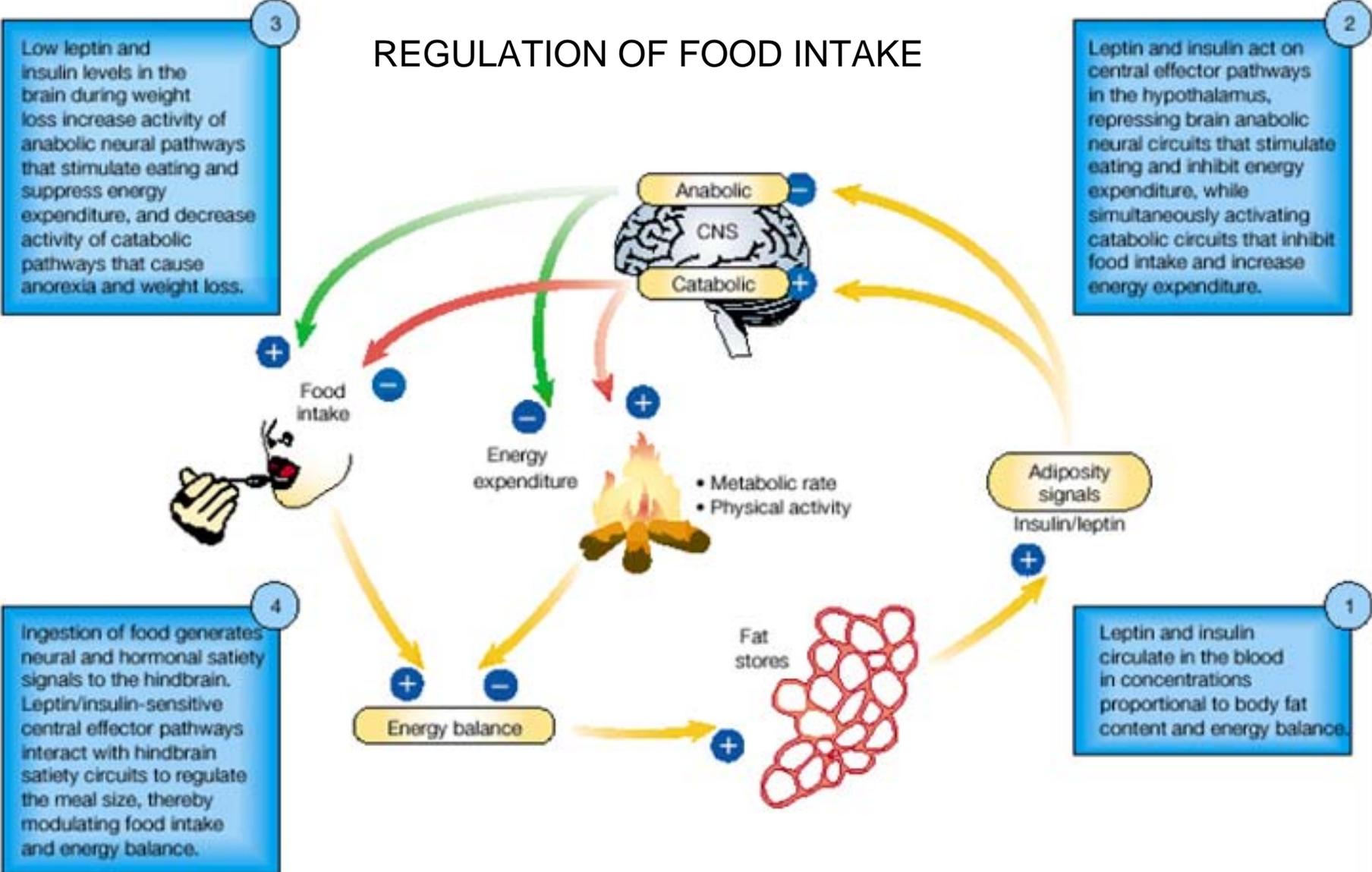
**CONCOMITANTS OF HYPERADRENOCORTICISM**

- Immunosuppression
- Muscle Atrophy
- Osteoporosis/Hypercalcemia
- Hyperglycemia/Hyperlipidemia
- Arteriosclerosis
- Steroid diabetes

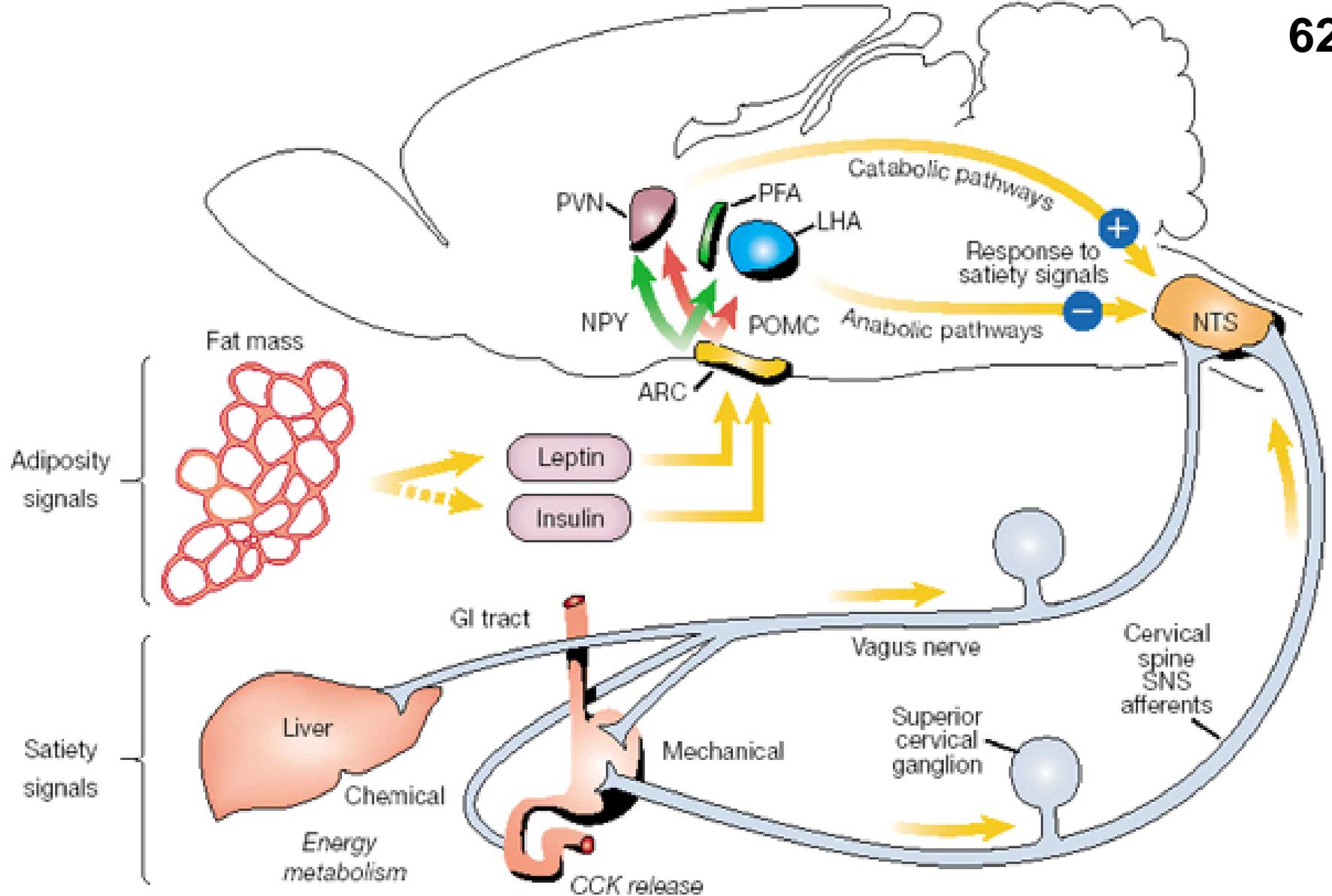


Schematic diagram showing relations between GLUCOCORTICOID (GR) actions and dendritic atrophy in the hippocampal CA3 pyramidal neurons. Glucocorticoids interact with glucocorticoid (GR) and mineralocorticoid (MR) receptors expressed in pyramidal and granule cells throughout the hippocampal formation. The final pathways of dendritic atrophy are the excitatory amino acids, which activate NMDA receptors and mobilize calcium. It is suggested that increased calcium causes reversible depolymerization of the cytoskeleton through either second messenger systems or limited proteolysis (Dilantin or NMDA blockade prevent dendritic atrophy). Stress-induced dendritic atrophy is blocked by inhibiting glucocorticoid synthesis, enhancing serotonin uptake and administering benzodiazepine (Bruce Mc Ewen).

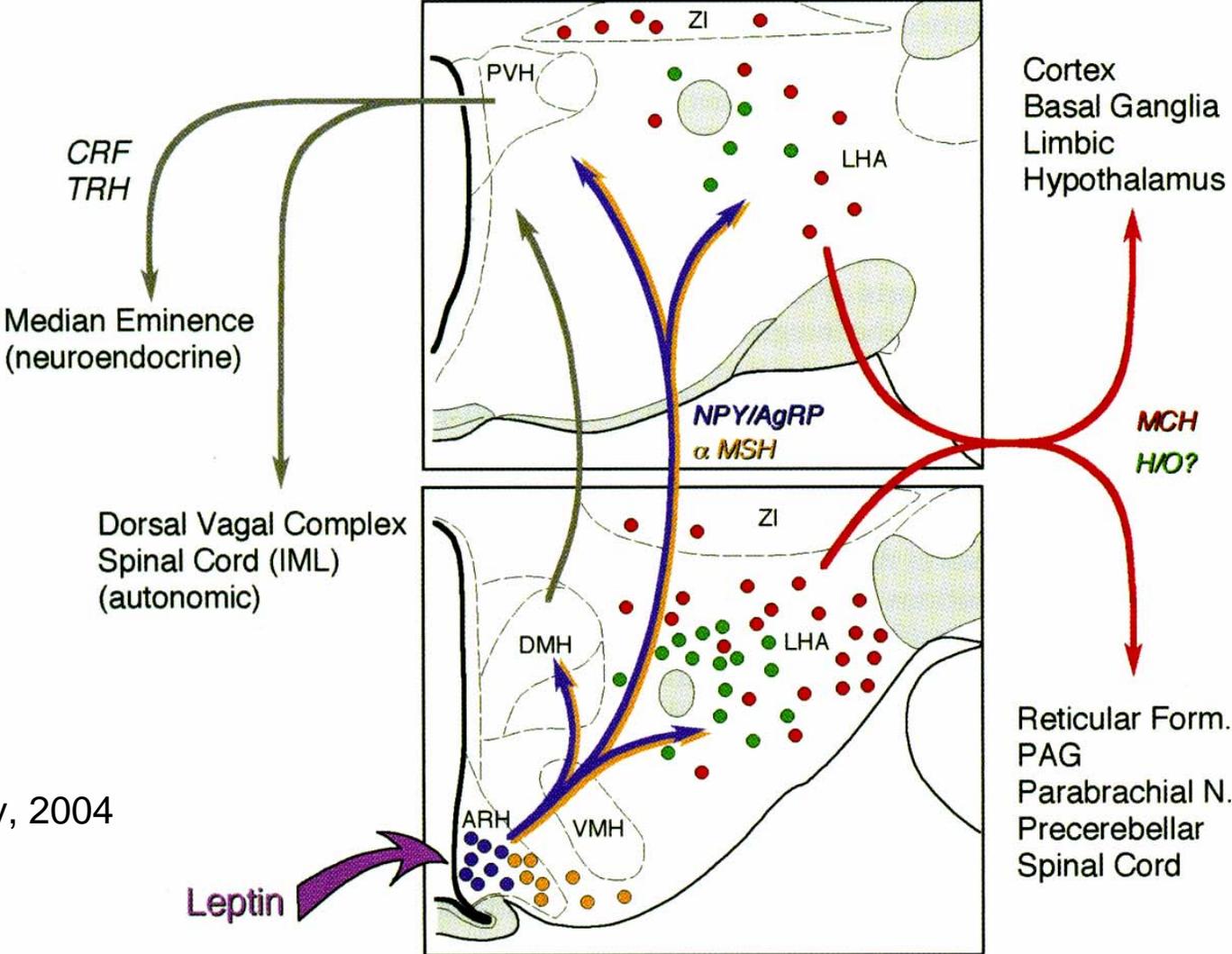
# REGULATION OF FOOD INTAKE



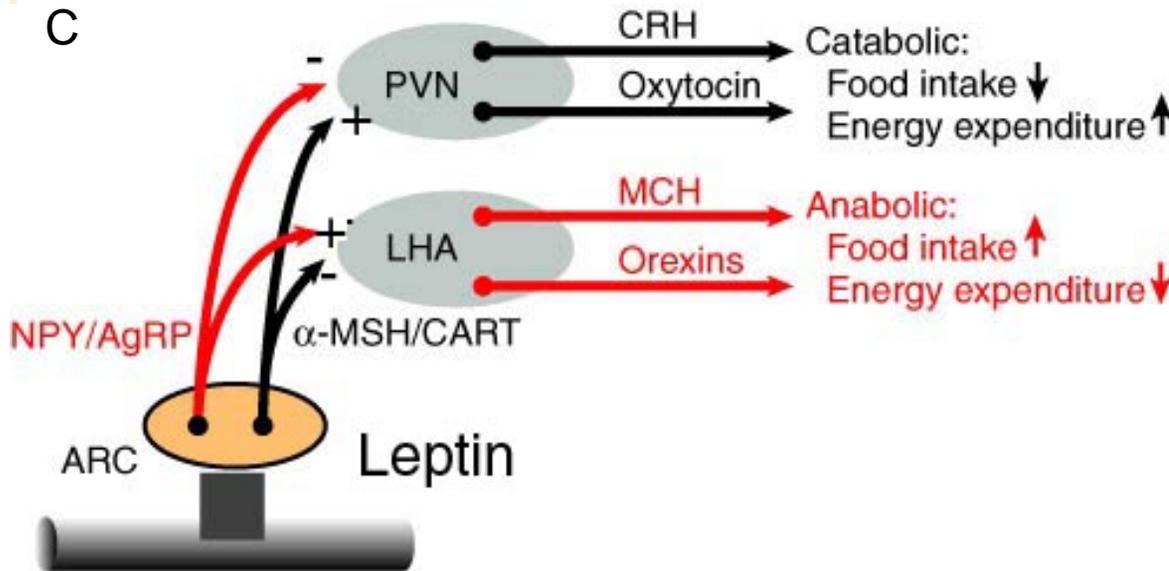
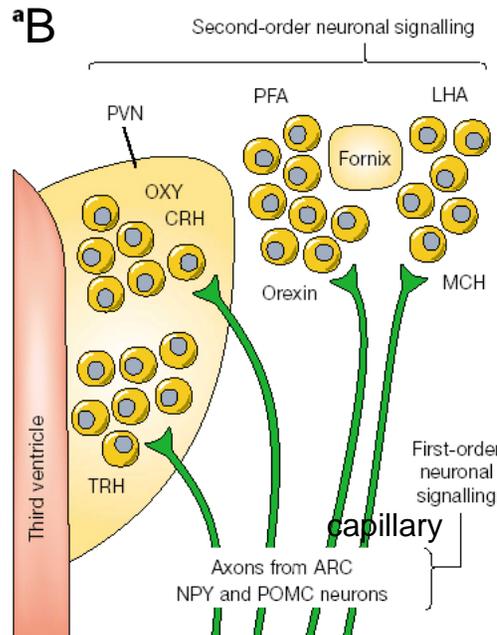
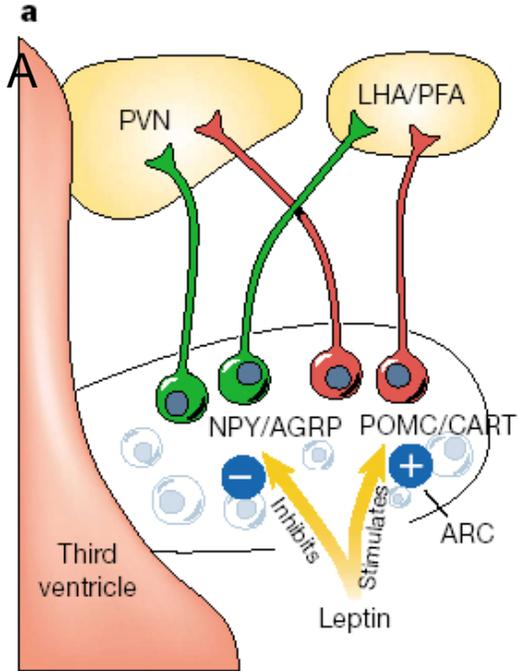
Model showing how a change in body adiposity is coupled to compensatory changes of food intake. Leptin and insulin are adiposity signals, secreted in proportion to body fat content, which act in the hypothalamus to stimulate catabolic, while inhibiting anabolic pathways. These pathways have opposing effects in energy balance (the difference between calories consumed and energy expended) that in turn determines the amount of body fuel stored as fat. (Schwartz et al., 2000).



Neuroanatomical model of pathways by which adiposity signals (leptin and insulin) interact with central autonomic circuits regulating meal size.

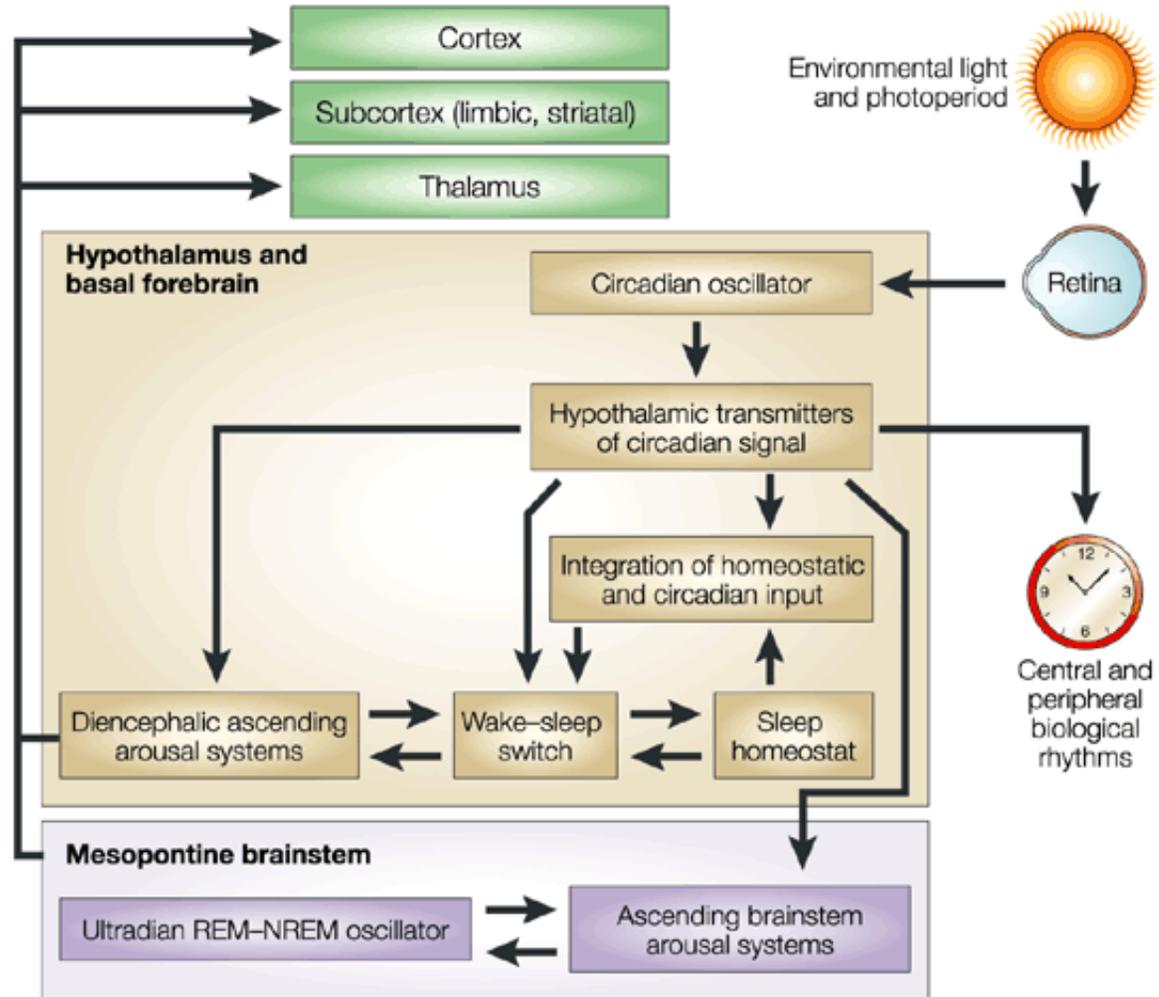


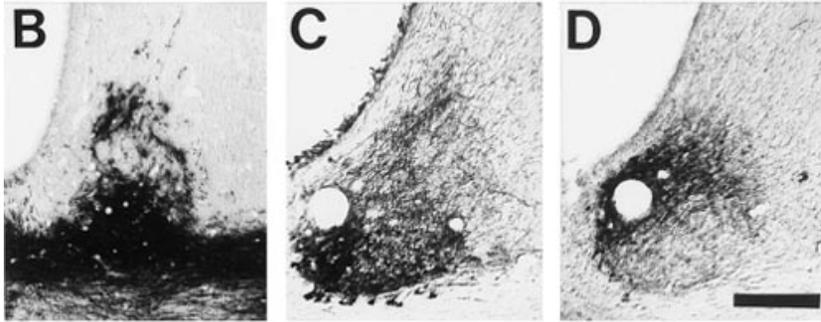
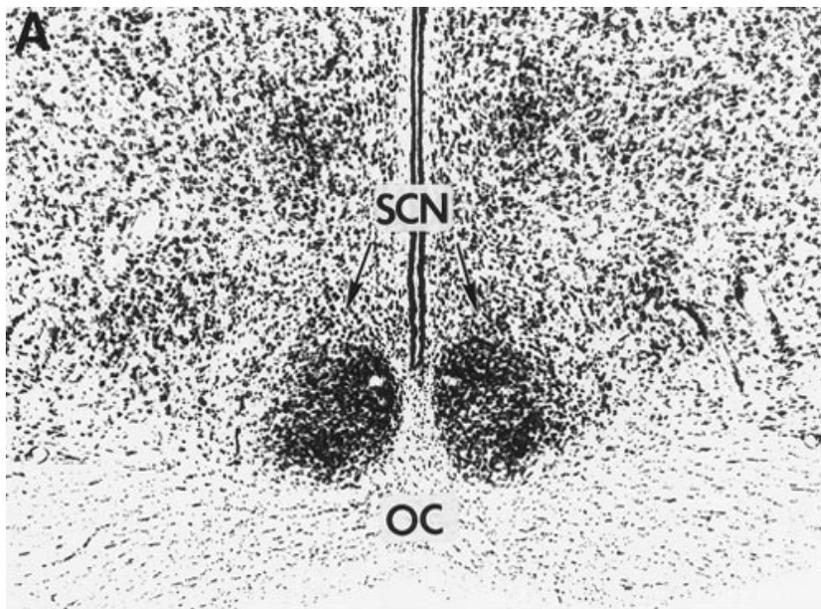
Simerly, 2004



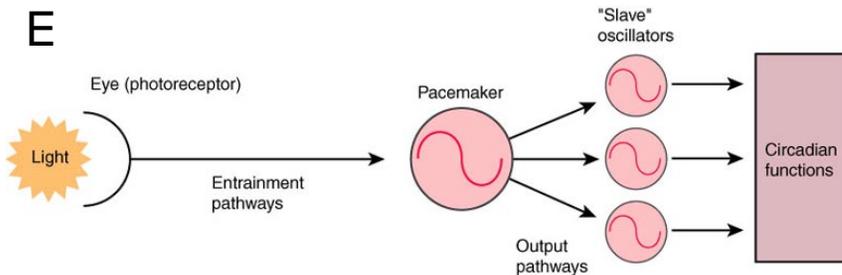
A: NPY/AGRP and POMC/CART neurons in the arcuate nucleus are first-order neurons in hypothalamic response to circulating insulin and leptin. NPY/AGRP and POMC/CART neurons in the arcuate nucleus project to the PVN and the LHA/PFA. B-C: The candidate second-order neurons in the PVN (oxytocin, CRH, TRH) cause anorexia, while those in LHA/PFA (orexin, melanin-concentrating hormone=MCH) increase feeding. (Schwartz et al, 2000; Woods and Stricker, 2002).

## b Sleep-wake control systems

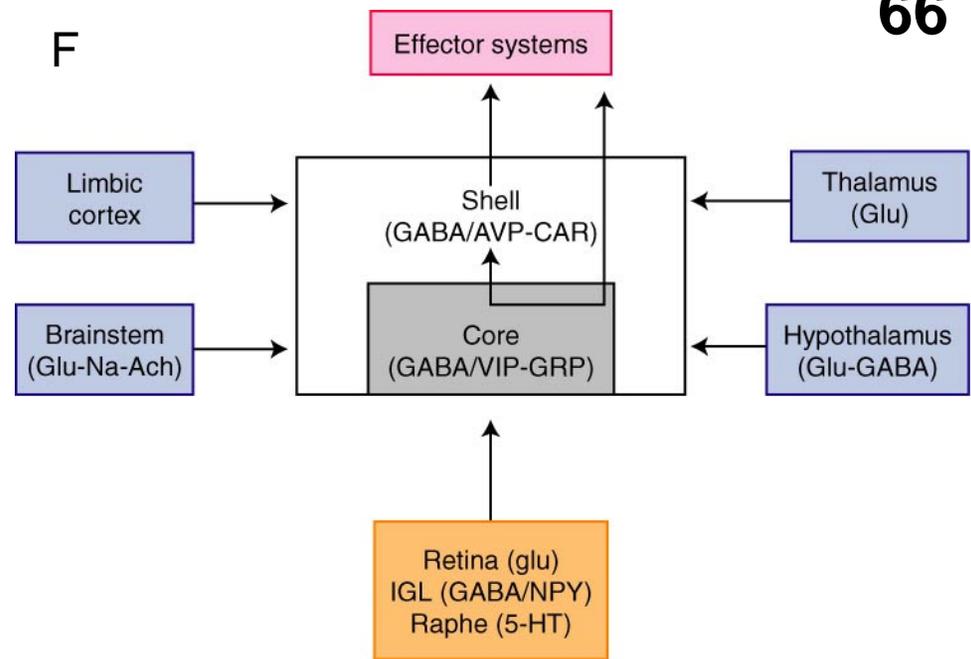




Copyright © 2002, Elsevier Science (USA). All rights reserved.



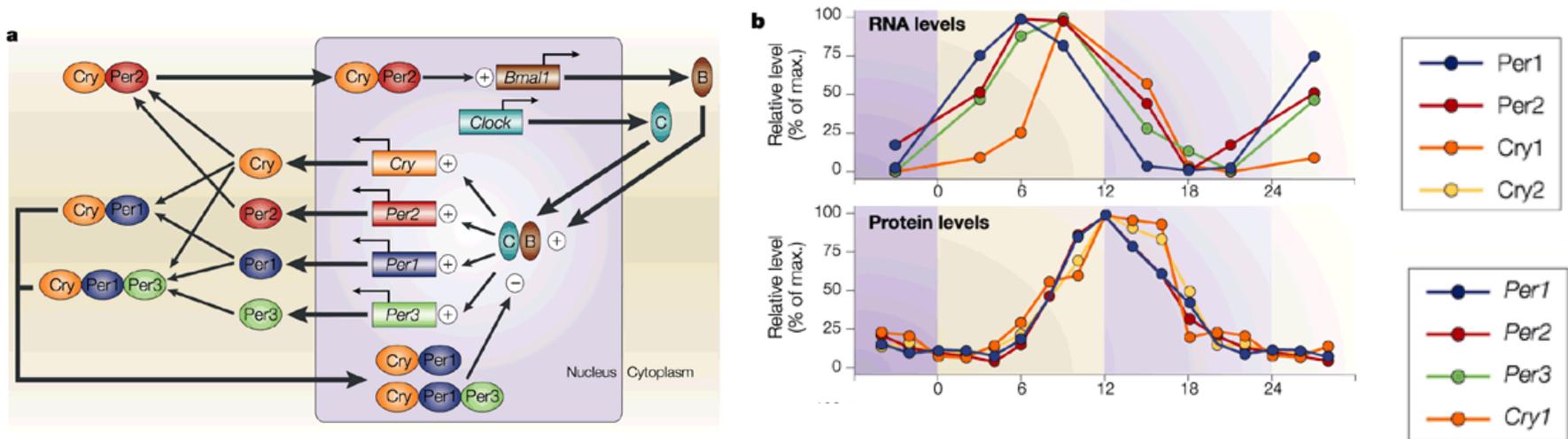
Copyright © 2002, Elsevier Science (USA). All rights reserved.



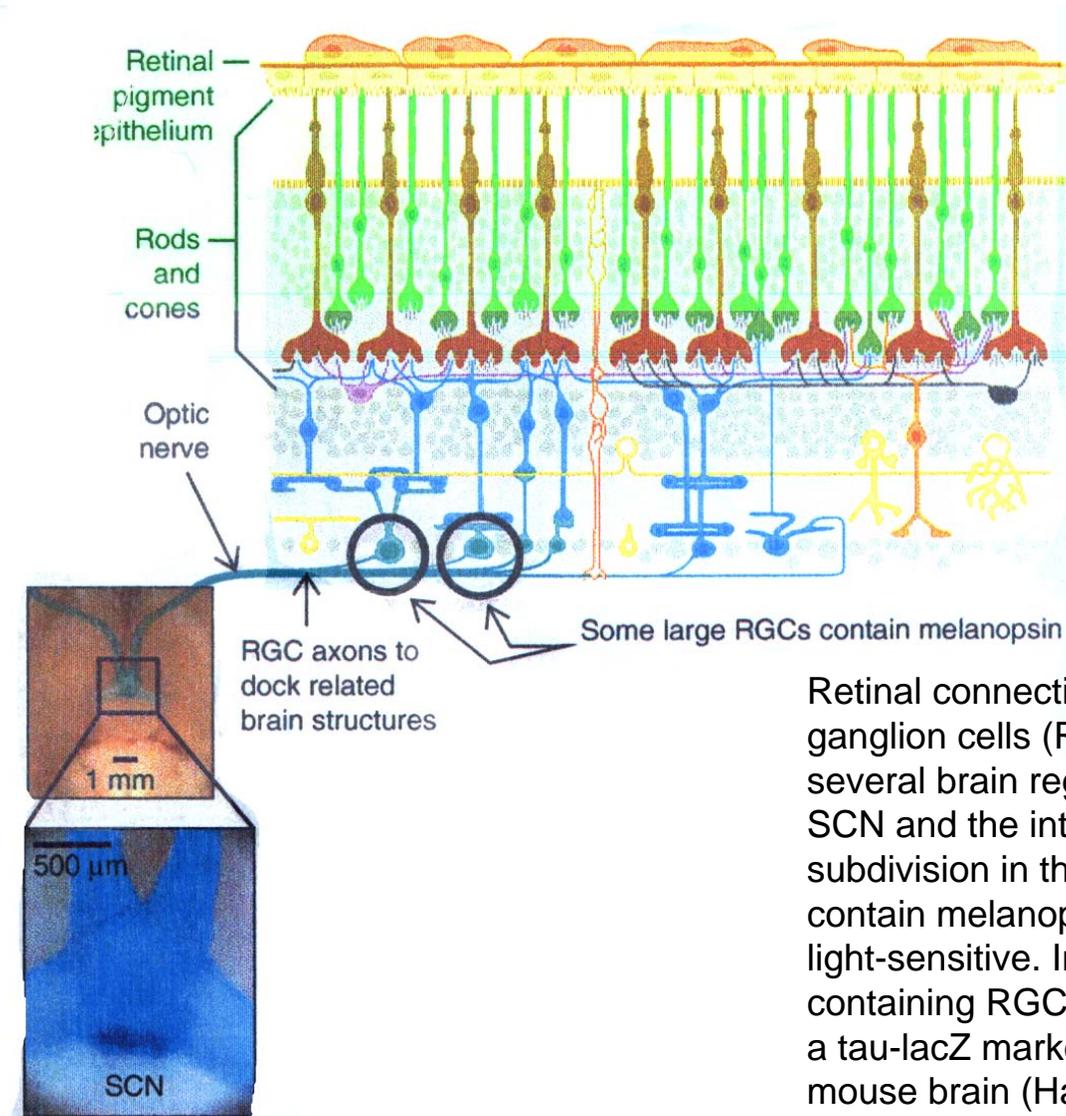
Copyright © 2002, Elsevier Science (USA). All rights reserved.

**A:** Nissl-stained coronal section through the SCN of the rat. **B:** distribution of the retinohypothalamic fibres. **C:** VIP, **D:** vasopressin neurons in the SCN. **E:** Overview of the basic organization of the circadian timing system (CTS). Information from the photoreceptors is conveyed by entrainment pathways to the pacemaker (SCN neurons). The pacemaker has rhythmic output that drives 'slave' oscillators which control functions that exhibit circadian regulation. **F:** Afferents to the SCN in rat. (Moore, 2002). Na=noradrenaline, GRP=gastrin releasing peptide.

# THE MOLECULAR CLOCK IN A SINGLE SCN NEURON

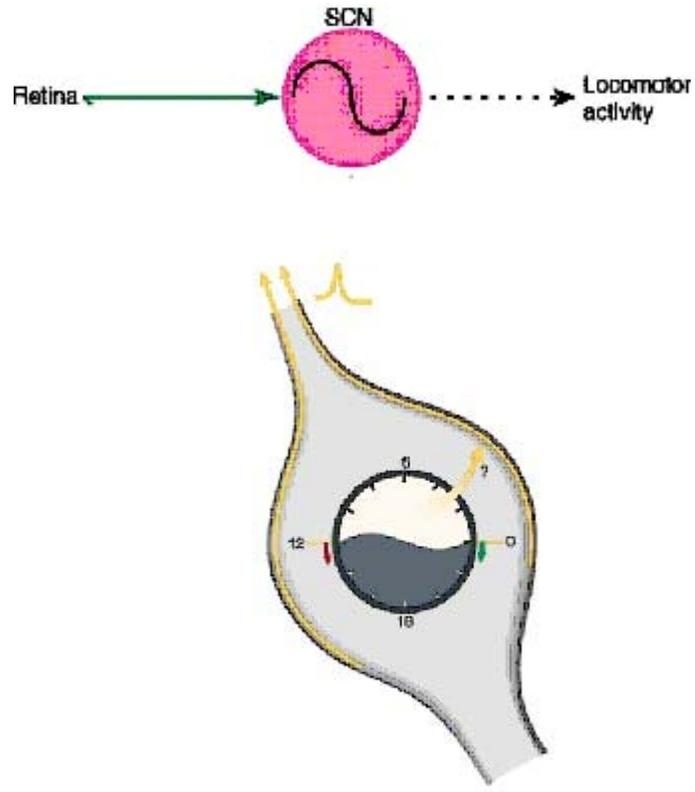


**a:** The molecular control of circadian rhythms in a single neuron of the SCN. *Clock*:*Bmal1* (labeled C and B) is a protein heterodimer that is a key component of a transcription factor that promotes the transcription of period (*Per*) and cryptochrome (*Cry*) genes. The RNA products of *Per*, *Cry*, *Bmal1* and *Clock* are translocated to the cytoplasm, where they are translated to proteins. *Per* and *Cry* proteins form complexes that are translocated back to the nucleus to exert feedback effects on *Clock*:*Bmal1*. Signs + or - indicates promotion or inhibition of gene transcription (or heterodimer) formation. Light arrows= gene transcription; medium arrows= gene promotion/inhibition and protein combination. Heavy arrows: translocation of RNA transcripts and proteins between the nucleus and the cytoplasm. **b:** Circadian variation in the levels of mRNA and protein products of the clock genes. Subjective night: purple, subjective day: yellow (Pace-Schott and Hobson, 2002)

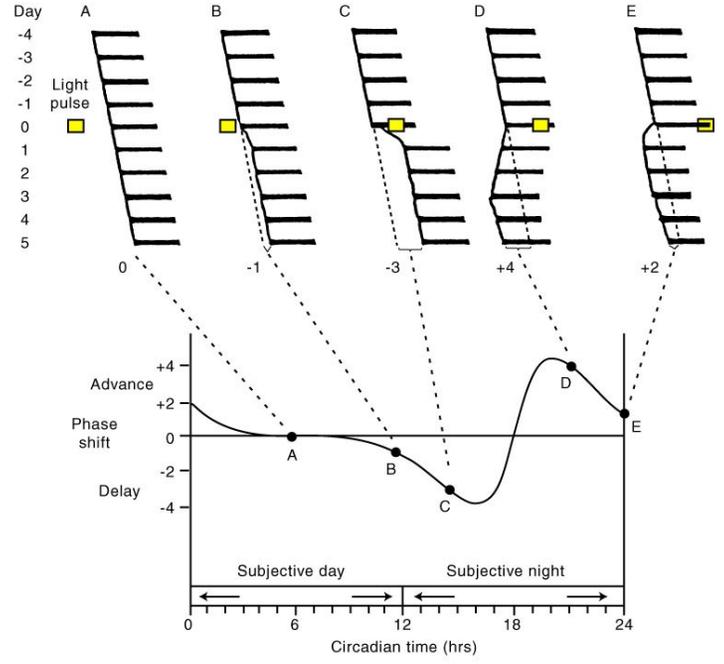


Retinal connections with the SCN. Retinal ganglion cells (RGC) send their axons to several brain regions. Those projecting to the SCN and the intergeniculate leaflet (IGL: small subdivision in the lateral geniculate body) contain melanopsin and they are intrinsically light-sensitive. Inset shows melanopsin-containing RGCs and their axons, labeled with a tau-lacZ marker, connecting with the SCN in mouse brain (Hattar et al., 2002).

# INFLUENCE OF LIGHT ON THE BIOLOGICAL CLOCK

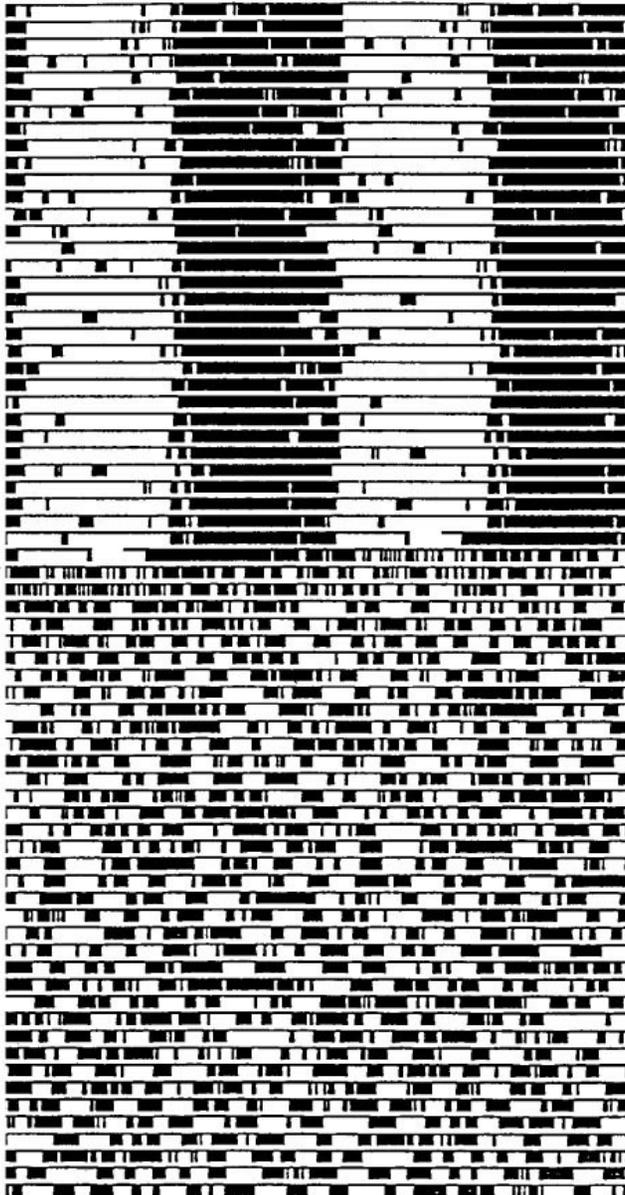


## Phase-response curve



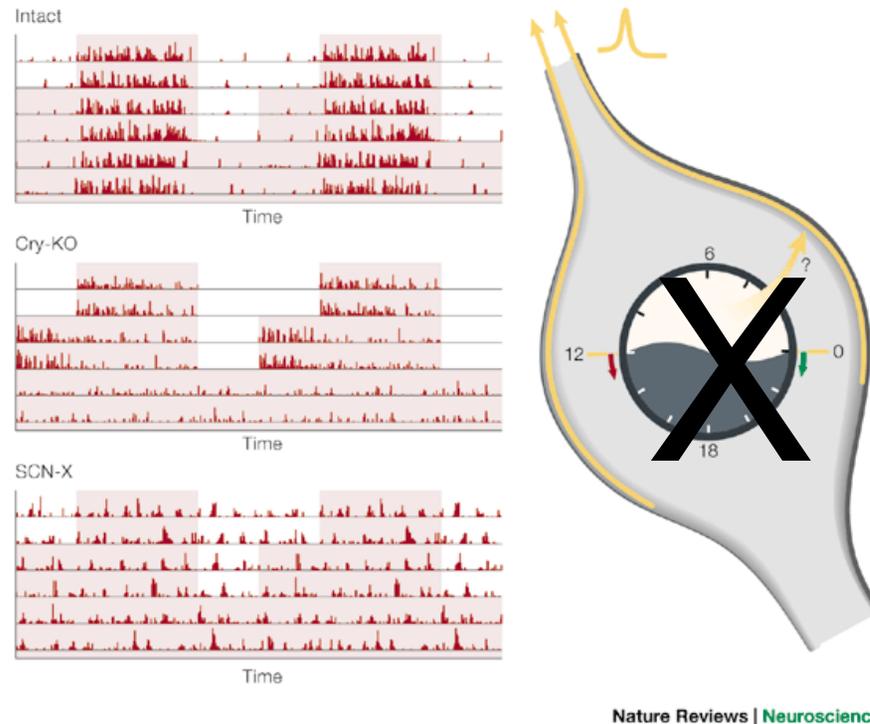
Copyright © 2002, Elsevier Science (USA). All rights reserved.

With animals maintained in constant dark, activity is recorded (horizontal bars) and light pulses are given as indicated. The pacemaker can be viewed as a somewhat inaccurate clock, which must be reset repeatedly. It free runs with a period that is slightly off 24 h in the absence of light-dark cycle. The light-dark cycle sets the exact timing of the pacemaker. PRC shows that the pacemaker responds differently to light at different times of the day (Moore, 2002). The left side of the figure provides a schematic illustration of how individual SCN neuron is able to mimic the day (L) signal with its molecular clock, resulting in membrane depolarization. This membrane depolarization results in propagation of the light signal to target neurons of the SCN and to phase shift of the molecular clock: phase delay (red arrow) or phase advance (green). Without the molecular clock, the light signal will still be transmitted to SCN targets. However, without the SCN, no signal will activate SCN target structures, (Buis and Kalsbeek, 2001).

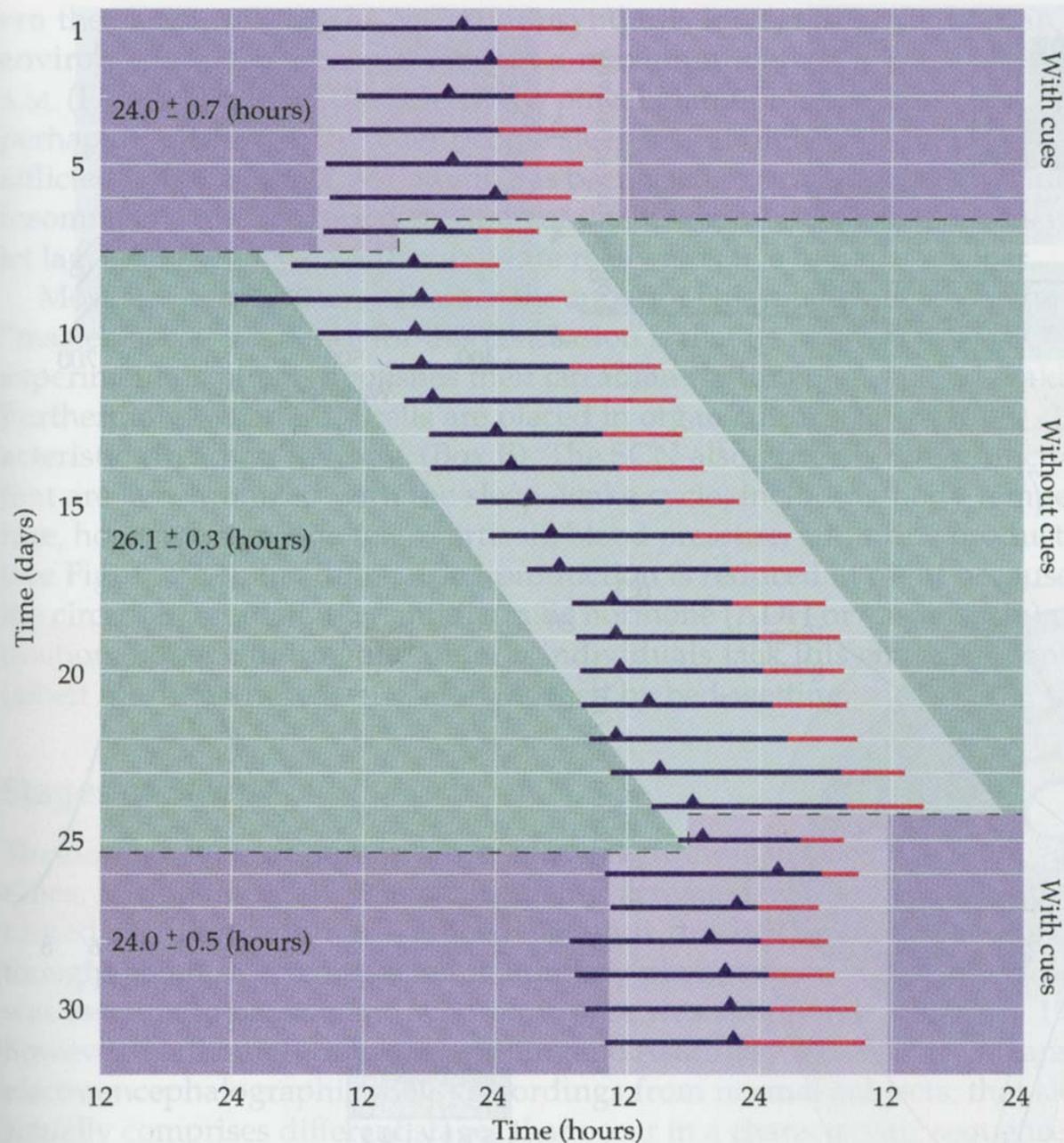


This is a record of activity of an albino rat maintained in a light-dark cycle. From the top of the record to the arrow, the animal exhibits a normal rhythm of activity, indicated by dark areas. The record is double plotted, which means that each line shows the preceding day and the new day to ease evaluation of the record. At the arrow, a bilateral SCN lesion was performed. Activity is distributed randomly thereafter, meaning circadian organization of rest-activity has been lost (Moore, 2002). In the absence of the SCN the total amount of sleep is unchanged, but there is no day/light variation (timing) in sleep

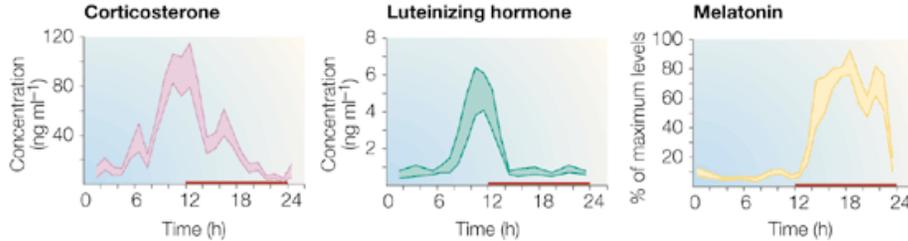
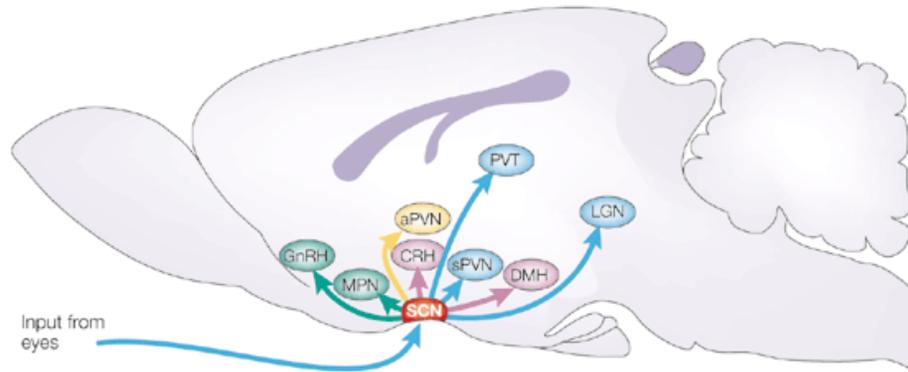
# THE EFFECT OF LIGHT ON THE ACTIVITY PATTERN IN ABSENCE OF THE MOLECULAR CLOCK



Light-dark cycles and the clock. Wild-type, cryptochrome knockout (Cry-KO) or SCN-lesioned (SCN-X) animals respond differently to light-dark (L-D) schedules. Left: shaded areas correspond to periods of darkness and red vertical lines activity. Intact animals are synchronized to L/D cycle and, by virtue of their circadian clock, maintain their rhythm under DD/D or altered L/D conditions. Cry-KO animals also respond to the L/D cycle and their SCN neurons (which lack a clock mechanism) immediately respond to L/D changes becoming active or inactive. The SCN-X animal does not change its fragmented activity pattern by light exposure. Consequently, SCN neurons with or without a molecular clock are needed for signaling light-induced inactivity in rodents. Without the molecular clock, the light signal will still be transmitted to SCN targets. However, without the SCN, no signal will activate SCN target structures, explaining the unresponsiveness of SCN-X animals to changes in the L/D cycle (Buis and Kalsbeek, 2001).

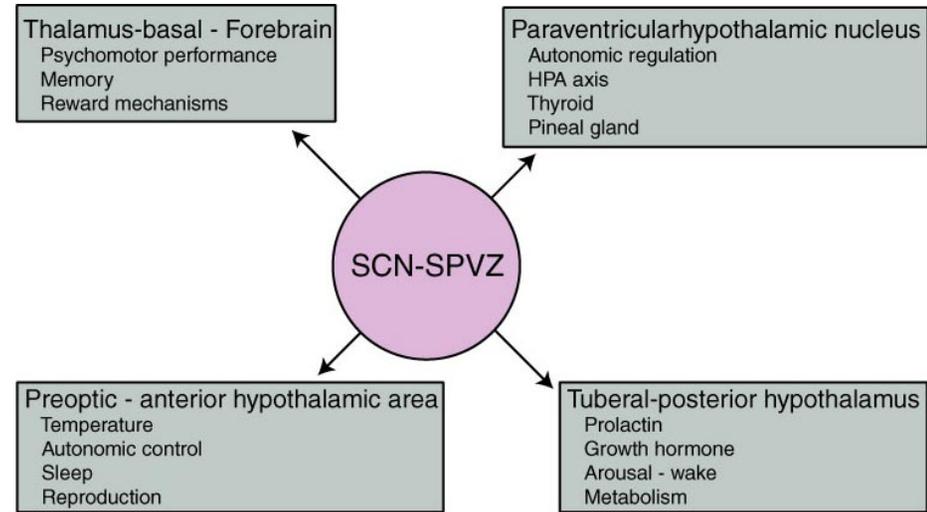


Rhythm of waking (blue lines) and sleeping (red) of a volunteer in an isolation chamber with and without cues about the day-night cycle. Numbers represent the mean+SD of a complete w-s cycle in each condition (Schmidt et al., 1983)



Nature Reviews | Neuroscience

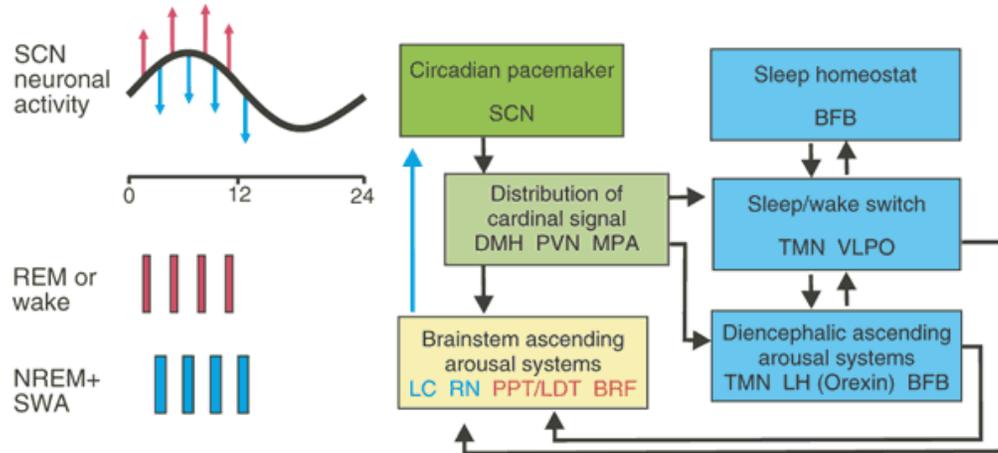
The hypothalamic structures through which the SCN signal is translated into a hormone pattern (Buus and Kalsbeek, 2001)



Copyright © 2002, Elsevier Science (USA). All rights reserved.

Pattern of projections of the SCN-subparaventricular zone (SPVZ) complex shown with the functions likely to be controlled by each of these pathways (Moore, 2002)

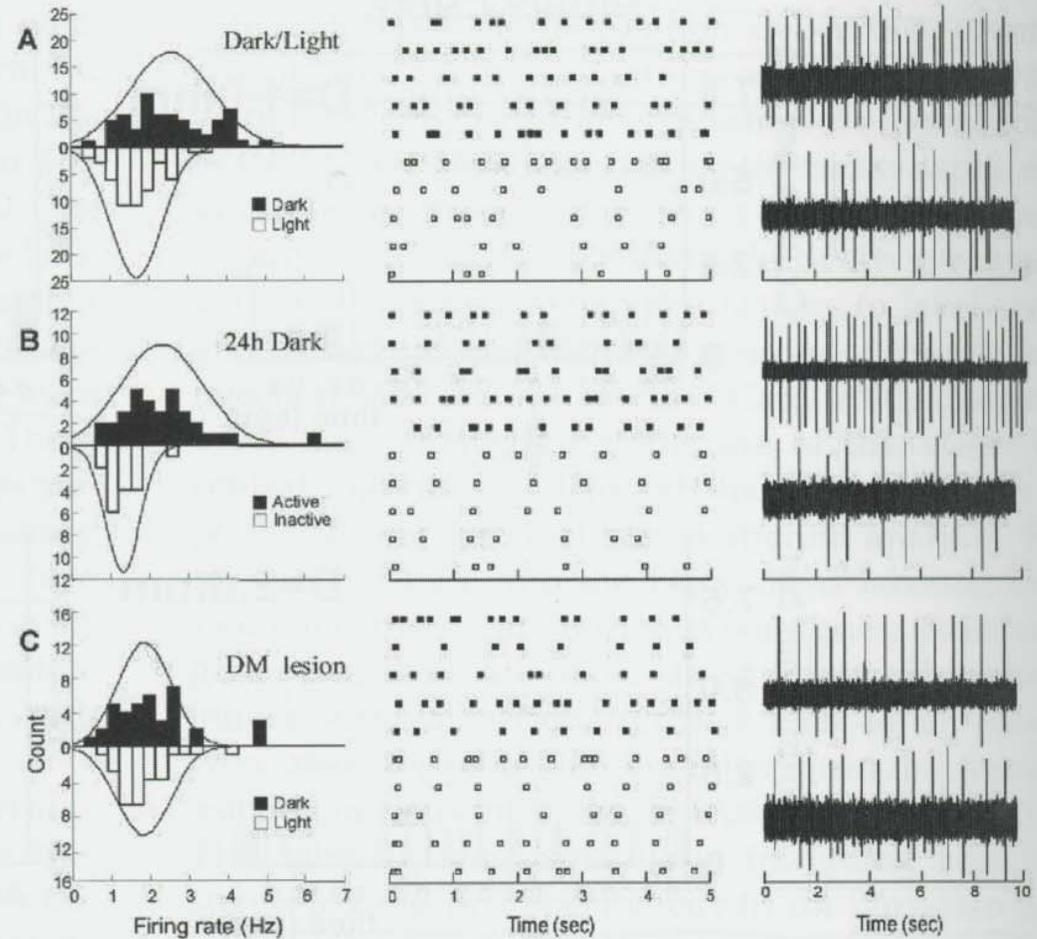
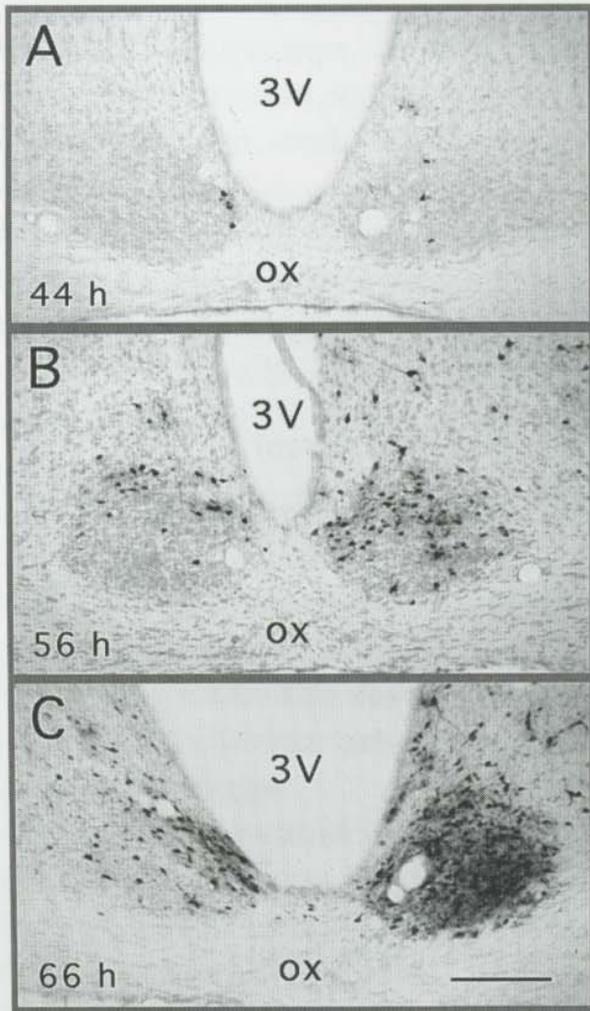
# POSSIBLE CONNECTIONS BETWEEN THE CIRCADIAN PACEMAKER AND THE SLEEP-WAKE CONTROL SYSTEM



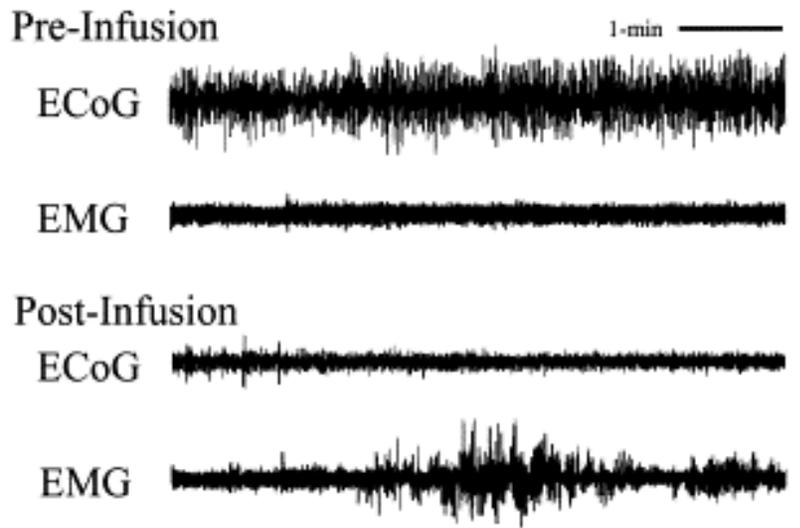
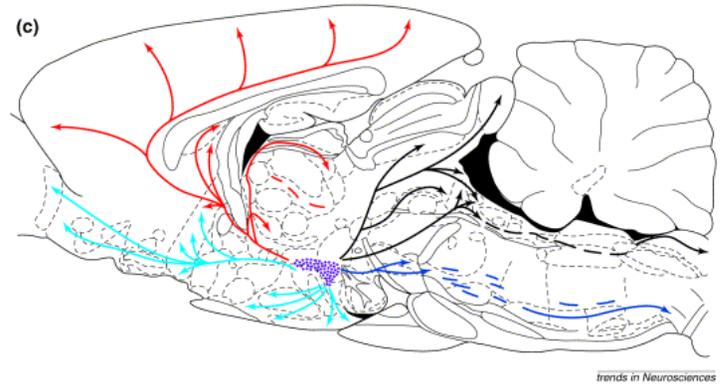
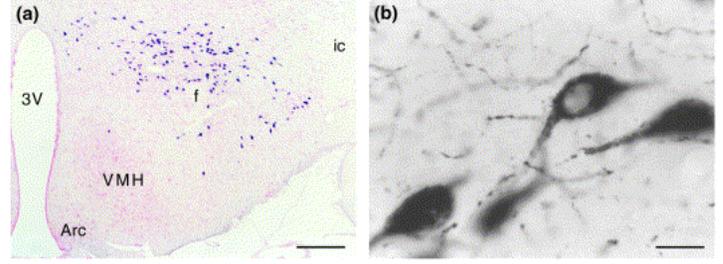
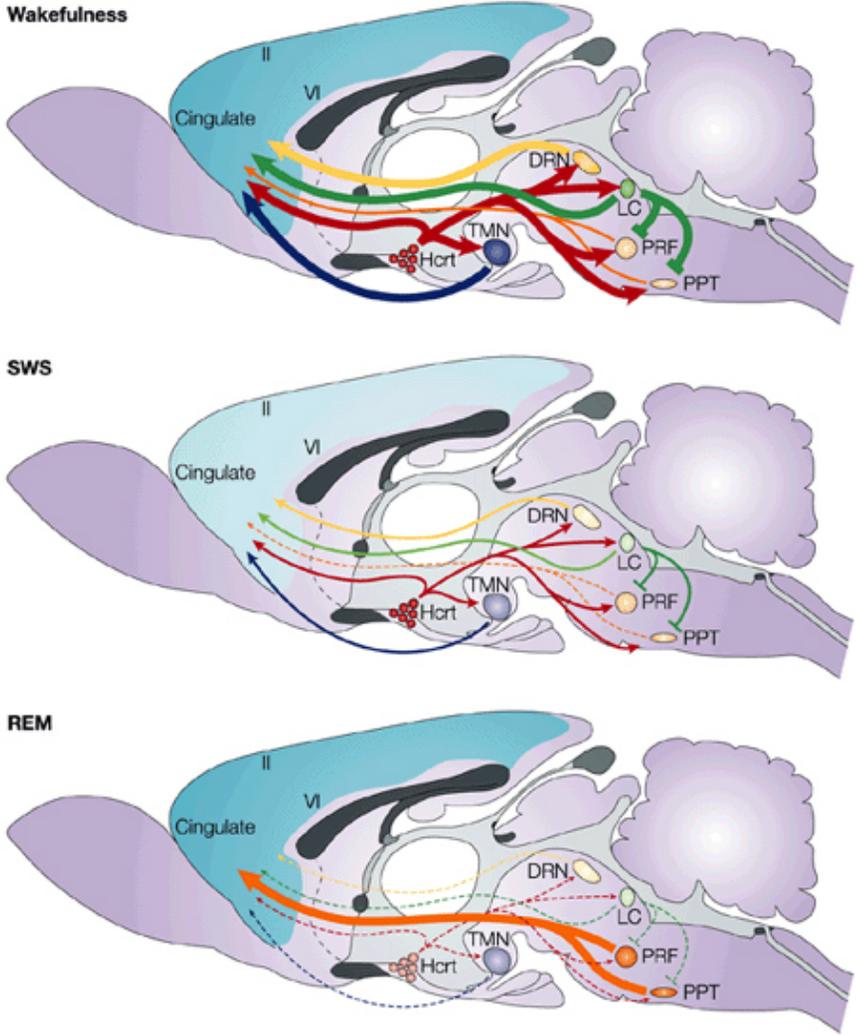
circadian timing signal generated in the SCN is transmitted through nuclei in the anterior hypothalamus to sleep/wake control systems in the diencephalon (blue) and then to structures in the brainstem controlling REM-NREM cycling (yellow). BFB=basal forebrain.

BRF=brainstem reticular formation. (Colwell and Michael, Nature Neurosci, 6, 1005, 2003).

# Lesion of the n dorsomedial hypothalamic n. eliminate the circadian firing of the LC

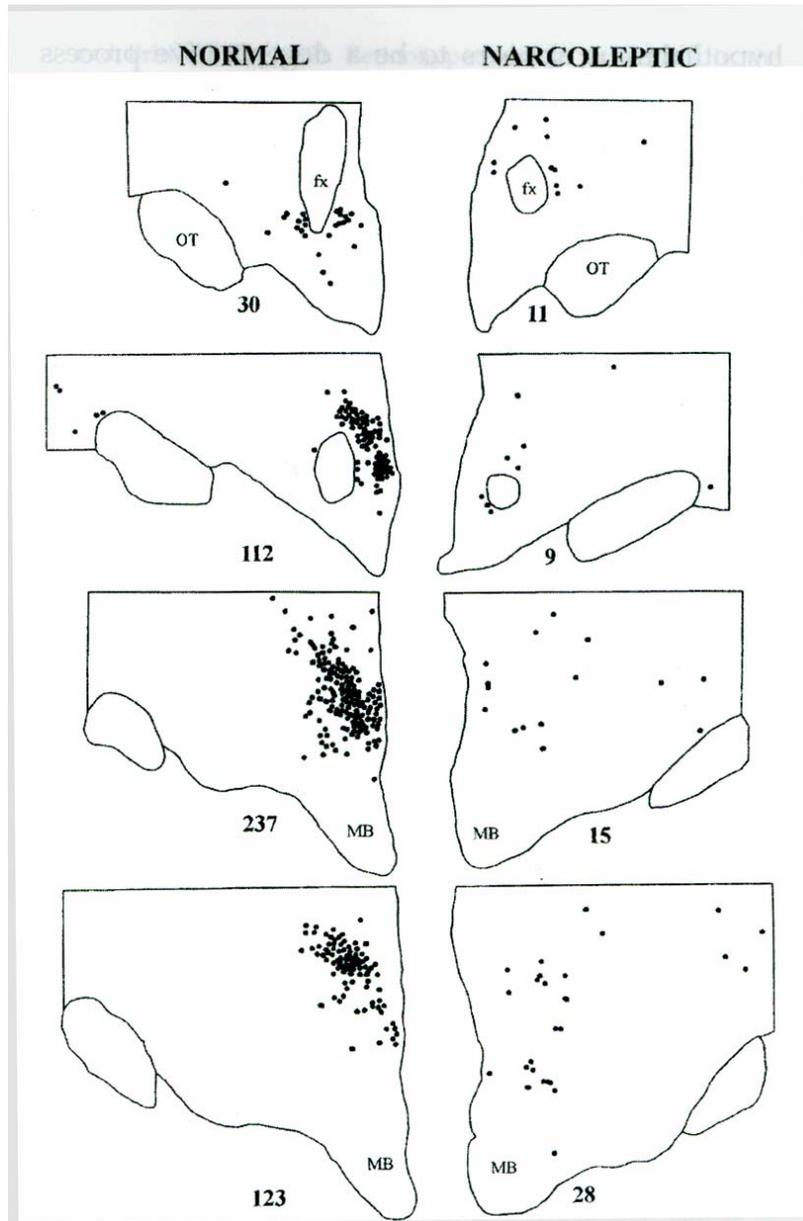


# OREXIN EFFECT ON THE SLEEP-WAKE CYCLE



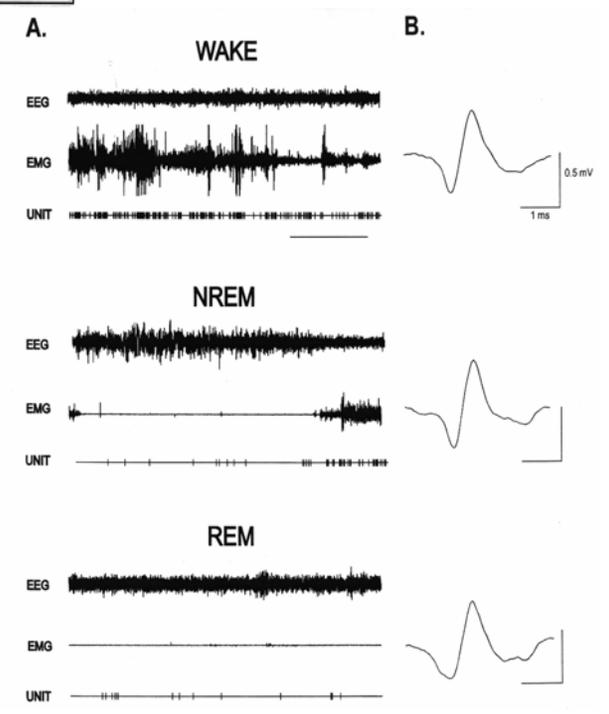
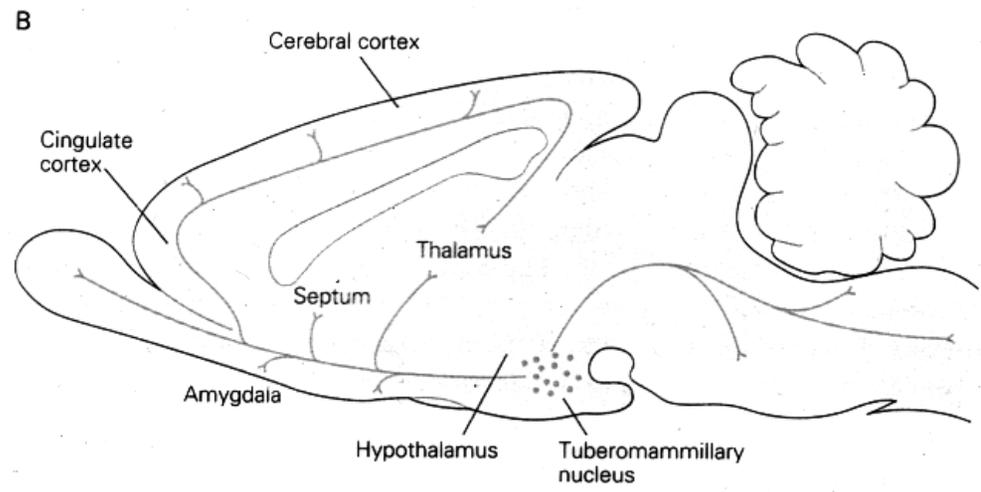
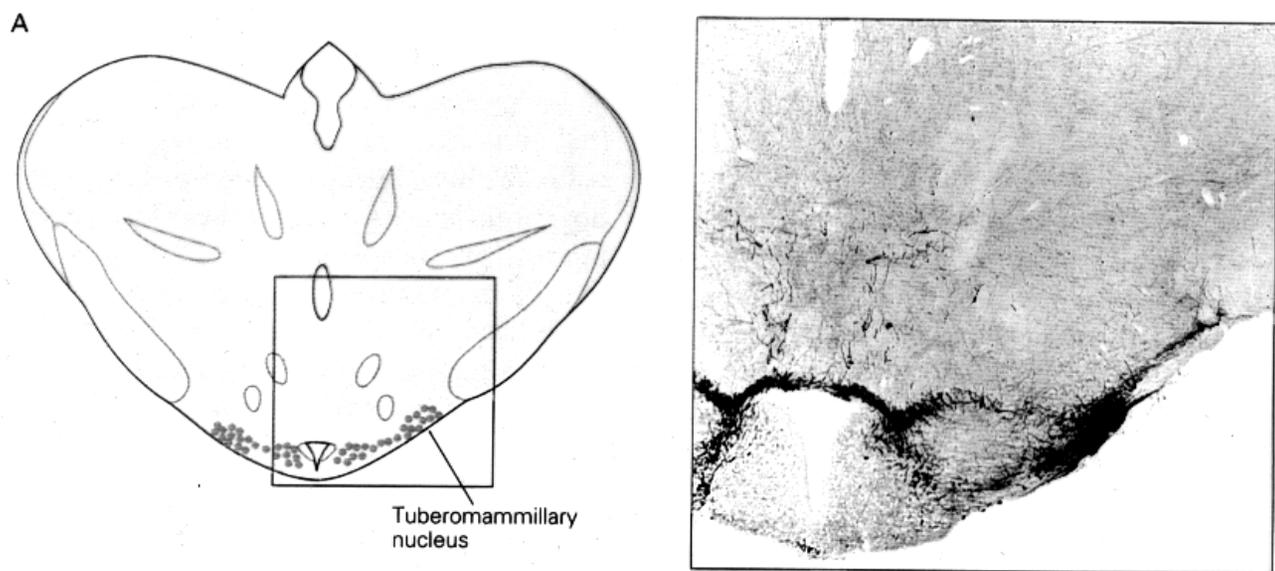
# OREXIN AND NARCOLEPSY

77



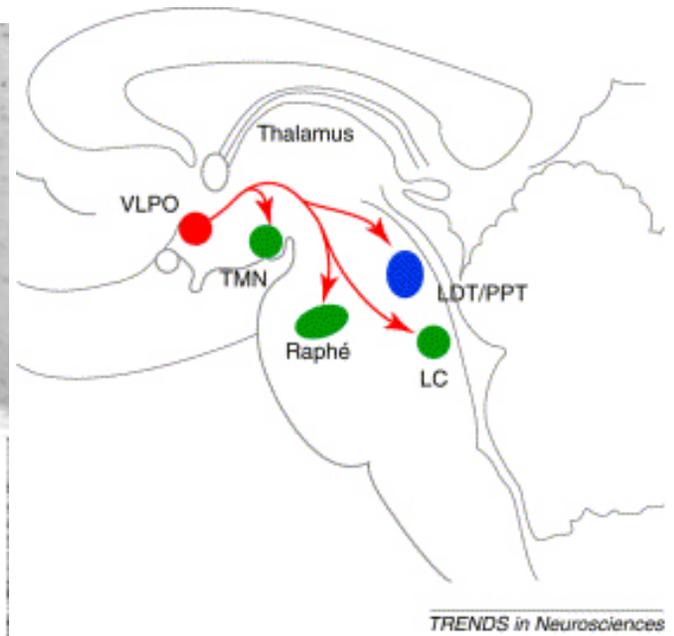
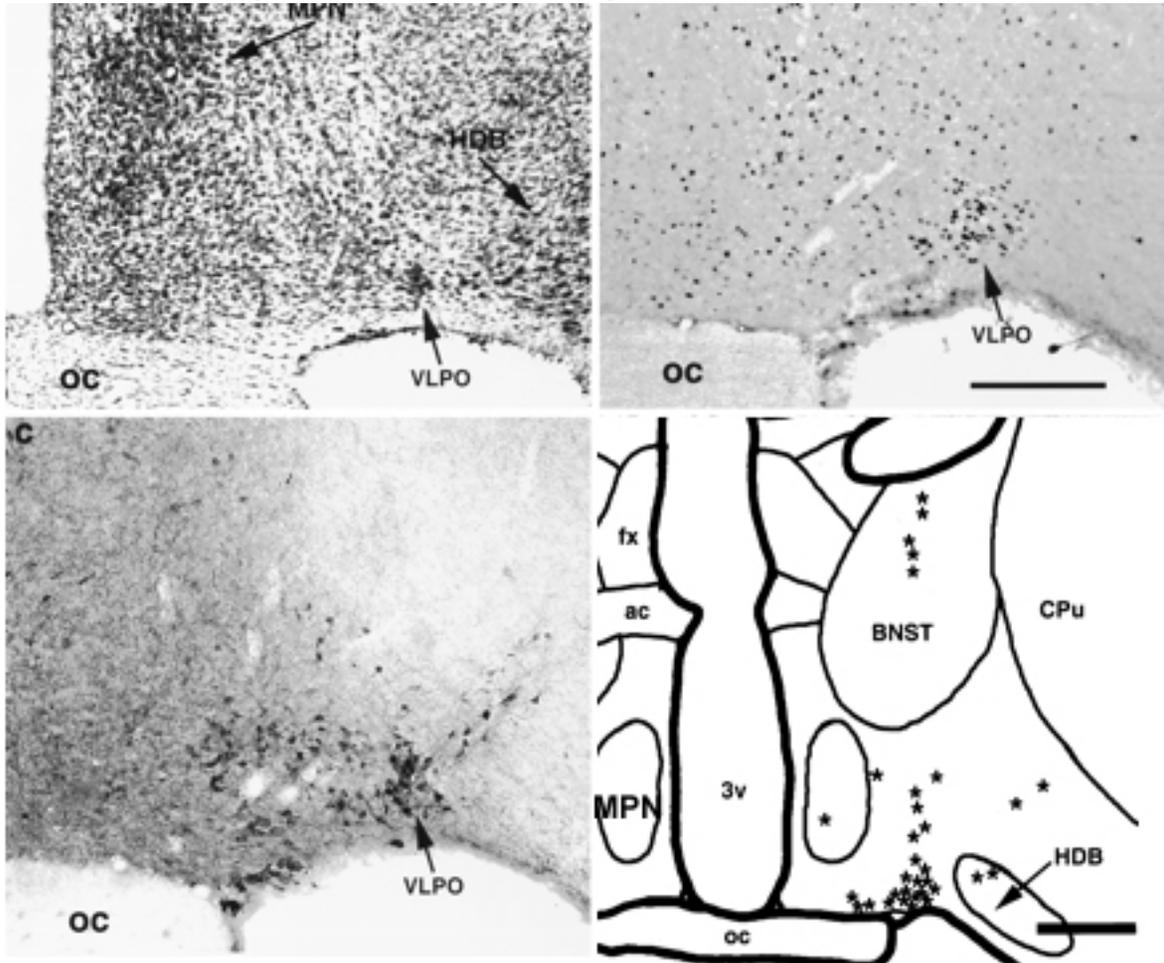
Orexin neurons in the human hypothalamus (From Saper, 2004)

# Histamin neurons in the tubero-mammillary nucleus

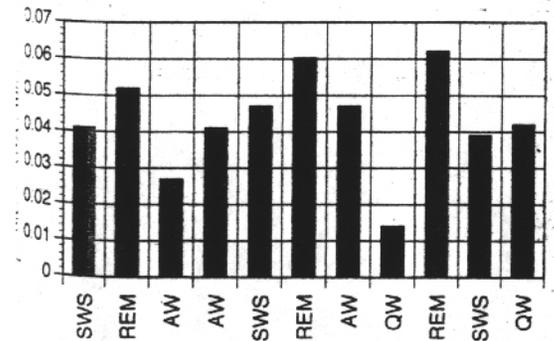


Saper et al., 2000;  
McGinty et al., 1999

# GABAergic neurons in the VLPO and their projections to ascending wake-promoting neurons

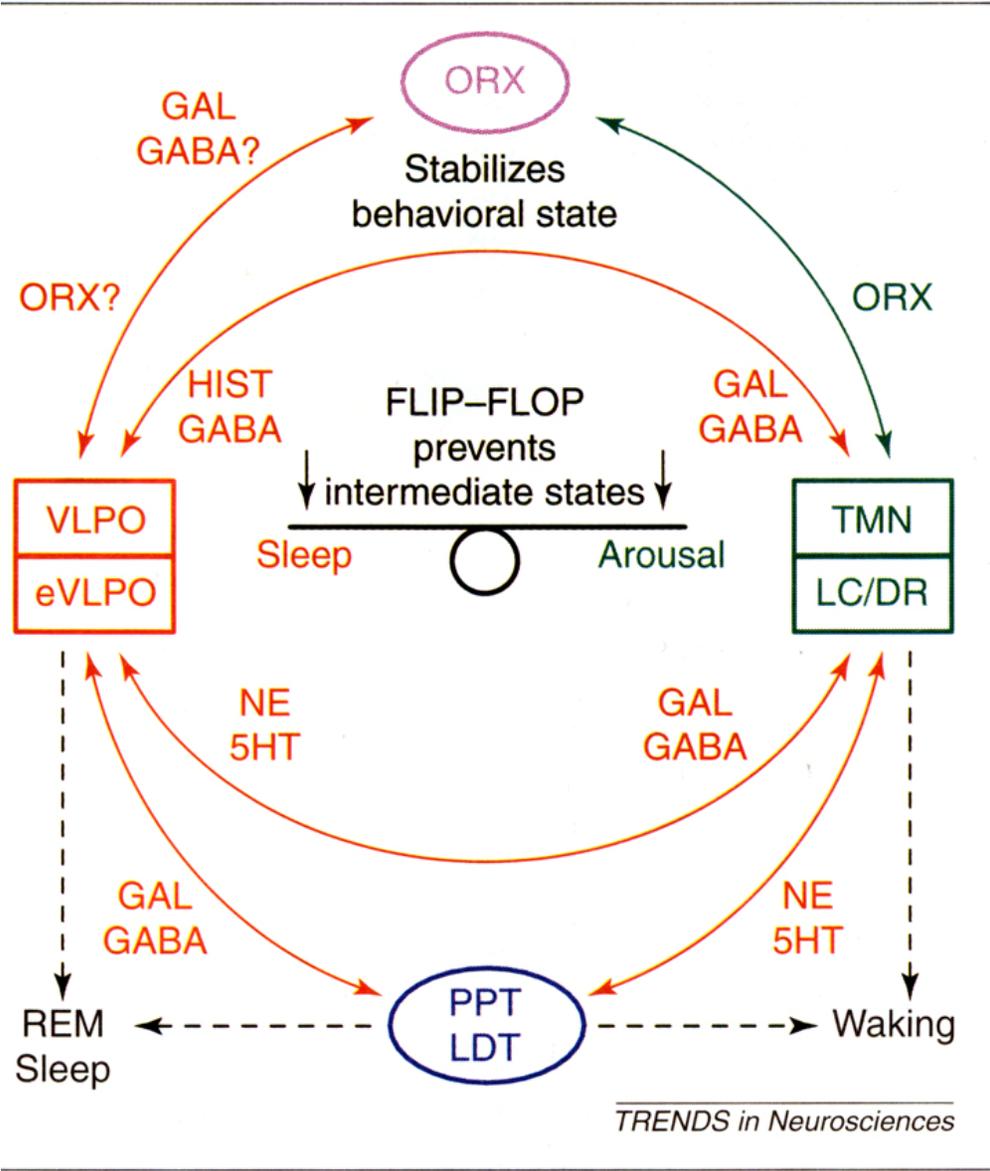


TRENDS in Neurosciences



REM sleep is accompanied by a selective increase in GABA release, but not glutamate in the DRN in naturally sleeping cats (Nitz and Siegel, 1997)

# MODEL FOR RECIPROCAL INTERACTIONS BETWEEN SLEEP AND WAKE PROMOTING BRAIN REGIONS. THE FLIP-FLOP SWITCH



Inhibitory pathways are shown in red, and the excitatory pathways in green. The blue circle indicates neurons of the LDT and PPT; green boxes indicate aminergic nuclei; and the red box indicates the VLPO.

Aminergic regions such as the TMN, LC and DR promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep-promoting neurons of the VLPO. During sleep, the VLPO inhibits amine-mediated arousal regions through GABAergic and galaninergic (GAL) projections. This inhibition of the amine-mediated arousal system disinhibits VLPO neurons, further stabilizing the production of sleep. The PPT and LDT also contain REM-promoting cholinergic neurons. The extended VLPO (eVLPO) might promote REM sleep by disinhibiting the PPT-LDT; its axons innervate interneurons within the PPT-LDT, as well as aminergic neurons that normally inhibit REM-promoting cells in the PPT-LDT. Orexin/hypocretin neurons (ORX) in the lateral hypothalamic area might further stabilize behavioral state by increasing the activity of aminergic neurons, thus maintaining consistent inhibition of sleep-promoting neurons in the VLPO and REM-promoting neurons in the PPT-LDT (Saper et al., 2001).