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

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

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

BASICS OF NEUROBIOLOGY

Neurobiológia alapjai

NEUROTRANSMITTERS II.

(Neurotranszmitterek II.)

ZSOLT LIPOSITS

CHARACTERISTICS OF NEUROPEPTIDES

NEUROPEPTIDES ARE COMPOSED OF SHORT CHAINS OF AMINO ACIDS AND SYNTHESIZED BY NERVE CELLS

THEY ARE BIOLOGICALLY ACTIVE SUBSTANCES USED AS SIGNAL MOLECULES IN INTERNEURONAL COMMUNICATION

IN THE CNS, THEIR NUMBER EXCEEDS ONE HUNDRED

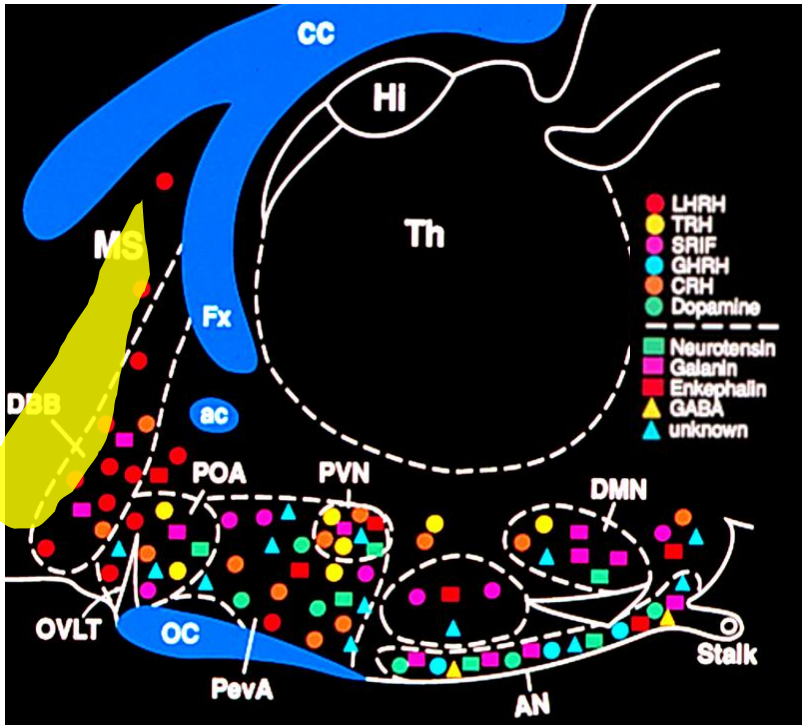
THEY ARE CLASSIFIED INTO NEUROPEPTIDE HORMONE FAMILIES BASED UPON SIMILARITIES IN ORIGIN, STRUCTURE AND FUNCTION

INVENTION OF IMMUNOCYTOCHEMISTRY AND ITS USE IN NEUROSCIENCE RESEARCH OPENED A PROGRESSIVE FIELD CALLED CHEMICAL NEUROANATOMY

THE DETECTION OF NEUROPEPTIDES BY IMMUNOCYTOCHEMISTRY AND THEIR mRNAs BY IN SITU HYBRIDIZATION HISTOCHEMISTRY REVEALED AN EXTREMELY COMPLEX CHEMICAL ORGANIZATION OF THE BRAIN

ELECTROPHYSIOLOGICAL AND ULTRASTRUCTURAL STUDIES HAVE SHOWN THAT NEUROPEPTIDES LOCALIZED IN AXON TERMINALS WERE, INDEED, RELEASED AND THEY AFFECTED POSTSYNAPTIC NEURONS

CHEMICAL PHENOTYPE OF THE HYPOTHALAMUS

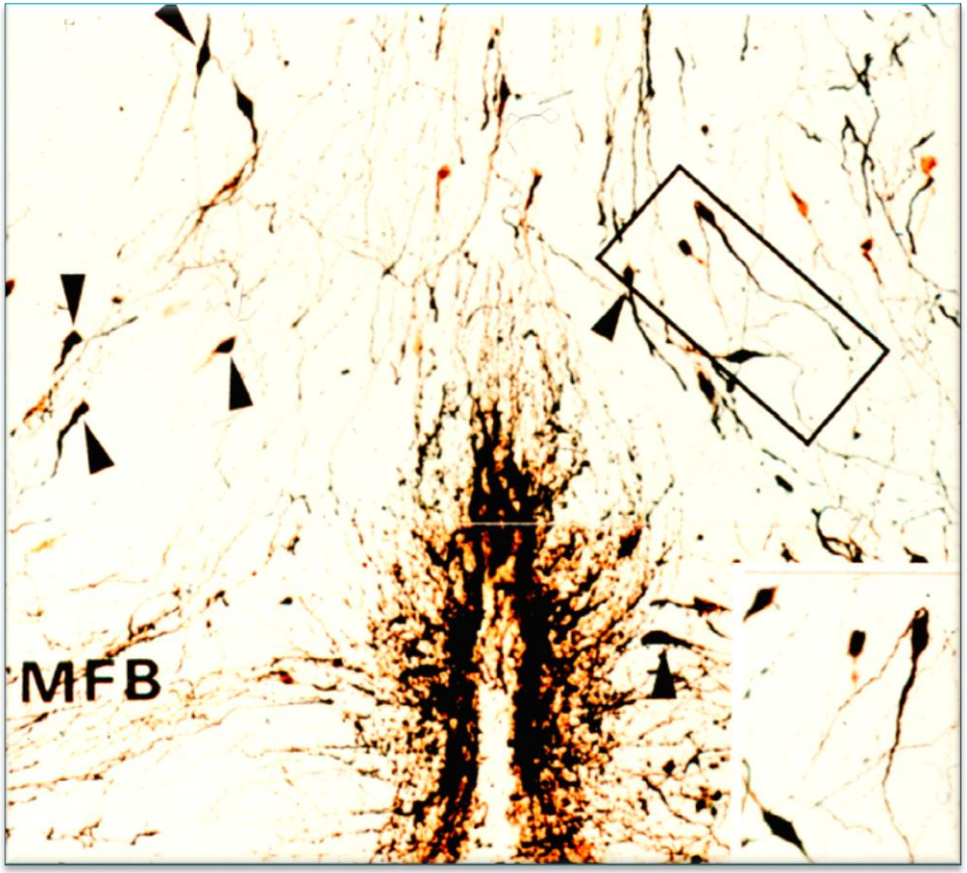


- THE HYPOTHALAMIC PART OF THE BRAIN THAT REGULATES THE ENDOCRINE SYSTEM IS ESPECIALLY RICH IN NEUROPEPTIDES

- THE COLORED SYMBOLS REFER TO DIFFERENT NEUROHORMONES AND INDICATE THEIR DIFFERENTIAL EXPRESSION IN HYPOTHALAMIC NUCLEI. THE RELEASING AND RELEASE INHIBITING HORMONES (LHRH, TRF, CRH, SRIF, GHRH) HAVE A HIGH FUNCTIONAL SIGNIFICANCE.

- IN ADDITION TO NEUROPEPTIDES, THE HYPOTHALAMUS ALSO PRODUCES CLASSICAL TRANSMITTERS INCLUDING GABA AND DOPAMINE.

VISUALIZATION OF NEUROPEPTIDES BY IMMUNOSTAINING



THE SECTION SHOWS THE HYPOTHALAMIC AREA DEPICTED IN TRANSPARENT YELLOW SHADING IN THE PREVIOUS SLIDE

ARROWHEADS POINT TO FUSIFORM NEURONS THAT SYNTHESIZE LUTEINIZING HORMONE-RELEASING HORMONE (LHRH)

BLACK LHRH DENDRITES AND AXONS ARE ALSO VISIBLE IN THE IMMUNOCYTOCHEMI-CAL PREPARATION

LHRH IS A 10 AMINO ACID PEPTIDE THAT REGULATES REPRODUCTION AND REPRO-DUCTIVE BEHAVIOR

IMMUNOCYTOCHEMISTRY IS A FUNCTIONAL ANATOMICAL TOOL EXPLORING THE STRUC-TURAL AND BIOCHEMICAL CHARACTERIS-TICS OF NEURONS SIMULTANEOUSLY

PROCESSING OF NEUROPEPTIDES

PEPTIDERGIC NEURONS CONTAIN mRNAs IN THEIR CYTOPLASM THAT ENCODE THE NEUROPEPTIDE PRECURSOR PROTEINS

THEIR SYNTHESIS TAKES PLACE AT ROUGH ENDOPLASMIC RETICULUM, THEN THE NEWLY SYNTHESIZED PEPTIDE IS DIRECTED TO THE GOLGI COMPLEX WHERE ITS MODIFICATION OCCURS

AFTER INITIAL MODIFICATIONS (GLYCOSYLATION, PROTEIN FOLDING, DISULFIDE BOND FORMATION, CLEAVAGE), THE MATURING PROTEINS ARE PACKED INTO SECRETORY VESICLES THAT ARE RELEASED FROM THE TRANS GOLGI FACE

THE CONSTITUTIVE TRANSPORT DIRECTS THE VESICLES TO THE AXON TERMINALS UTILIZING ANTEROGRADE TRANSPORT MECHANISMS

DURING THEIR JOURNEY, FURTHER PROCESSING OF THE PROTEINS MIGHT TAKE PLACE

MOST FREQUENT ACTION IS THE CLEAVAGE OF THE PRECURSOR PROTEIN BY PRO-PROTEIN CONVERTASES

PROCESSING OF NEUROPEPTIDES

THE CLEAVAGE MAY GENERATE MULTIPLE DISTINCT PEPTIDES FROM THE PRECURSOR OR PRODUCE MULTIPLE COPIES OF THE SAME NEUROPEPTIDE

MOST PEPTIDES BECOME FULLY BIOACTIVE AFTER POST-TRANSLATIONAL CLEAVAGE, OTHERS UNDERGO FURTHER MODIFICATION (CARBOXYL-AMIDATION)

THE NEUROPEPTIDES ARE STORED WITHIN NEUROSECRETORY GRANULES OF AXON TERMINALS. THEIR DIAMETER IS IN THE RANGE OF 80-200 nm

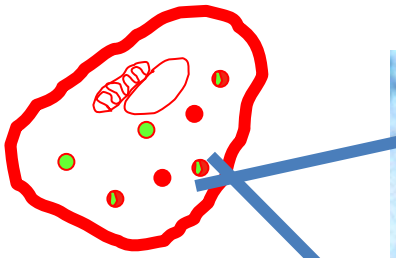
SOME NEUROPEPTIDES HAVE BEEN SHOWN TO BE RELEASED FROM DENDRITES AND AXON VARICOSITIES IN ADDITION TO TERMINAL BOUTONS

NEUROSECRETORY GRANULES MAY CONTAIN MORE THAN ONE NEUROPEPTIDE.

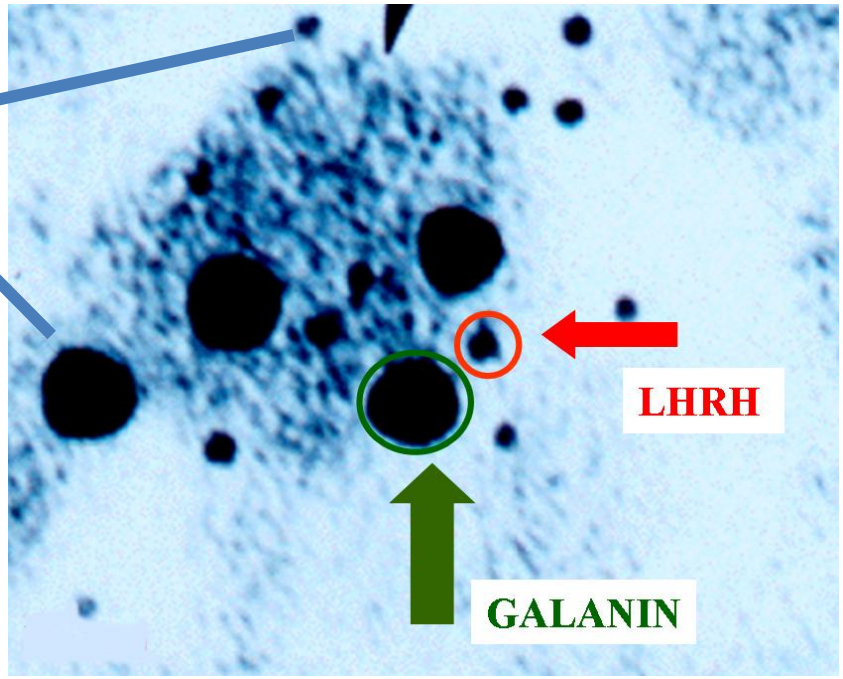
THE CO-PACKAGED NEUROPEPTIDES VERY LIKELY UNDERGO CO-RELEASE

CLASSICAL AND NON-CLASSICAL NEUROTRANSMITTERS ARE ALSO KNOWN TO BE CO-SYNTHESIZED IN PEPTIDERGIC NEURONS, INDICATING THAT CELLS MIGHT USE MULTIPLE NEUROMESSENGERS IN THEIR COMMUNICATION

CO-LOCALIZATION OF TWO NEUROPEPTIDES IN THE SAME NEUROSECRETORY GRANULE



SCHEME OF AN LHRH AXON CONTAINING SECRETORY GRANULES. THE TWO BLUE LINES POINT TO AN ELECTRON-MICROSCOPIC IMAGE OF A SINGLE NEUROSEC-RETORY GRANULE DOUBLE-LABELED FOR TWO NEUROPEPTIDES



THE EM MICROGRAPH DEPICTS A NEUROSECRETORY GRANULE FROM AN LHRH NERVE TERMINAL. LHRH AND GALANIN PEPTIDES WERE DETECTED BY IMMUNOCYTOCHEMISTRY USING COLLOIDAL GOLD PARTICLES OF DIFFERENT SIZES. LHRH PEPTIDE IS MARKED BY SMALL, 5 nm GOLD PARTICLES, WHILE GALANIN IS TAGGED BY 15 nm GOLD PARTICLES. NOTE THE CO-EXPRESSION OF THE TWO DISTINCT PEPTIDES IN THE SAME SECRETORY GRANULE

PROCESSING OF NEUROPEPTIDES

IN THE AXON TERMINAL, MOST GRANULES FORM A RESERVE POOL AND ONLY A FEW CAN BE SEEN PRIMED AND DOCKED AT THE PRESYNAPTIC MEMBRANE

THE NEUROPEPTIDE RELEASE IS EXECUTED BY EXOCYTOSIS. THE PROCESS REQUIRES ATP AND CALCIUM. REACHING THE CRITICAL INTRACELLULAR CONCENTRATION OF CALCIUM NEEDS BURSTS OF ACTION POTENTIALS

IN THE SYNAPTIC CLEFT, NEUROPEPTIDES BIND TO THEIR RECEPTORS THAT ARE COUPLED TO G PROTEINS

IN PEPTIDERGIC SYNAPSES, RECYCLING OF NEUROPEPTIDES DOES NOT OCCUR. THEY RATHER DIFFUSE AND GET CLEAVED BY ENDOPEPTIDASES

THE NEUTRAL ENDOPEPTIDASE, A METALLOENDOPEPTIDASE, LOCATED AT THE CELL SURFACE HYDROLYSES THE RELEASED PEPTIDES AT THE AMINO SIDE OF A HYDROPHOBIC RESIDUE

THE ACTIVITY OF ENDOPEPTIDASES CAN LOCALLY REGULATE THE PEPTIDE CONCENTRATION AND CONSEQUENTLY, THE ACTIVATION OF THE RECEPTORS

NEUROPEPTIDE FAMILIES

FAMILY NAME	FAMILY MEMBERS
TACHYKININS	SUBSTANCE P, NEUROKININ A, NEUROKININ B
OPIOD PEPTIDES	ENKEPHALIN, DYNORPHIN, ENDORPHIN
PANCREATIC POLYPEPTIDE-RELATED	NEUROPEPTIDE Y, PEPTIDE YY, PANCREATIC POLYPEPTIDE
INSULIN FAMILY	INSULIN, INSULIN LIKE GROWTH FACTOR I-II
GASTRINS	GASTRIN, CHOLECYSTOKININ
SECRETINS	VASOACTIVE INTESTINAL PEPTIDE (VIP), SECRETIN, GLUCAGON
NEUROHYPOPHYSEAL HORMONES	OXYTOCIN, VASOPRESSIN, NEUROPHYSIN I-II
RELEASE- AND RELEASE-INHIBITING	LHRH, TRH, CRH, GHRH, SOMATOSTATIN
FEEDING PEPTIDES	NEUROPEPTIDE Y, AGOUTI RELATED PEPTIDE, ALPHA-MELANOCYTE STIMULATING HORMONE, NESFATIN, OREXIN

HYPOTHALAMIC HORMONES AND THEIR FUNCTIONS

SECRETED HORMONE	ABBREVIATION	PRODUCED BY	EFFECT
CORTICOTROPIN-RELEASING HORMONE	CRH or CRF	Parvocellular neurosecretory neurons	Stimulate adrenocorticotropic hormone (ACTH) release from anterior pituitary
THYROTROPIN-RELEASING HORMONE	TRH, TRF	Parvocellular neurosecretory neurons	Stimulate thyroid-stimulating hormone (TSH) release from anterior pituitary Stimulate prolactin release from anterior pituitary
GONADOTROPIN RELEASING HORMONE	GnRH or LHRH	Parvocellular neurosecretory neurons	Stimulate follicle-stimulating hormone (FSH) release from anterior pituitary Stimulate luteinizing hormone (LH) release from anterior pituitary
DOPAMINE (PROLACTIN-INHIBITING HORMONE)	DA or PIH	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary
GROWTH HORMONE-RELEASING HORMONE	GHRH	Parvocellular neurosecretory neurons	Stimulate growth hormone (GH) release from anterior pituitary
SOMATOSTATIN (GROWTH HORMONE-INHIBITING HORMONE)	SS, GHIH, or SRIF	Parvocellular neurosecretory neurons	Inhibit Growth hormone (GH) release from anterior pituitary Inhibit thyroid-stimulating hormone (TSH) release from anterior pituitary
OXYTOCIN		Magnocellular neurosecretory cells	Uterine contraction Lactation (letdown reflex)
VASOPRESSIN (ANTIDIURETIC HORMONE)	ADH or AVP	Magnocellular neurosecretory neurons	Increases water permeability in the distal convoluted tubule and collecting duct of nephrons, thus promoting water reabsorption and increasing blood volume
DOPAMINE (PROLACTIN-INHIBITING HORMONE)	DA or PIH	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary

OPIOID PEPTIDES, THEIR ANALOGUES AND RECEPTORS

NAME	AMINO ACID SEQUENCE
	Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln
Dynorphin A (1-17)	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Endomorphins 1 and 2	Tyr-Pro-Trp-Phe; Tyr-Pro-Phe-Phe
Leu- and Met-enkephalin	Nociceptin

Endogenous opioid	β-Endorphin	Enkephalins	Dynorphins	Nociceptin
Synthetic agonist	Morphine	DSTBULET	U50488H	
	Codeine	DPDPE	Pentazocine	
	Fentanyl		Oxycodone?	
	Pethidine			
Antagonists	Naloxone	Naloxone	Naloxone	Not naloxone
	β-FNA	Naltrindole	nor-BNI	
Effector mechanism	G protein	G protein	G protein	G protein
	opens K^+	opens K^+	closes Ca^{2+}	opens K^+
	channel	channel	channel	channel
Effects	Hyperpolarization of neurons, inhibition of neurotransmitter release			