10. Synaptic Transmission and Cellular Signaling: An Overview

Ronald W. Holz ***and*** ***Stephen K. Fisher***
holz@umich.edu skfisher@umich.edu

Synaptic Transmission

- Chemical transmission between nerve cells involves multiple steps
- Neurotransmitter release is a highly specialized form of the secretory process that occurs in virtually all eukaryotic cells
- A variety of methods have been developed to study exocytosis
- Quantal analysis defines the mechanism of release as exocytosis
- Presynaptic events during synaptic transmission are rapid, dynamic and interconnected
- There are important differences between fast synaptic transmission at nerve terminals and the release of proteins and peptides from nerve terminals and neuroendocrine cells
- Discrete steps in the regulated secretory pathway can be defined in neuroendocrine cells

Cellular Signaling Mechanisms

- Three phases of receptor-mediated signaling can be identified
- Four distinct molecular mechanisms that link agonist occupancy of cell-surface receptors to functional responses have been identified
- Cross-talk can occur between intracellular signaling pathways
- Signaling molecules can activate gene transcription
- Nitric oxide acts as an intercellular signaling molecule in the central nervous system

References

11. Acetylcholine

Palmer Taylor and Joan Heller Brown.
pwtaylor@ucsd.edu jhbrown@ucsd.edu

In addition to the usual updating and editing, we felt the following concepts should be developed and new discoveries highlighted:

1. The more complete definition of the proteins involved presynaptically in the transport of choline, vesicle storage and release mechanisms and how the various presynaptic toxins act.

2. The discovery of the acetylcholine binding protein in invertebrates and its structural relation to the acetylcholine receptor and its role in developing a high resolution structure of the nicotinic receptor and the pentameric ligand gated ion channel family.

3. The role played by the multitude of presynaptic nicotinic receptors in controlling the release of acetylcholine (presynaptic autoreceptors) and particularly other transmitters in various regions in the CNS.

12. Catecholamines

Michael J. Kuhar, Kenneth P. Minneman, E. Christopher Muly

I. Biosynthesis of Catecholamines
- A. Tyrosine hydroxylase is the rate-limiting enzyme for the biosynthesis of catecholamines
- B. DOPA decarboxylase catalyzes the removal of the carboxyl group from DOPA to form dopamine
- C. For neurons that synthesize epinephrine or norepinephrine, dopamine β-hydroxylase is the next step in the biosynthetic pathway
- D. In cells that synthesize epinephrine, the final step in the pathway is catalyzed by the enzyme phenylethanolamine *N*-methyltransferase

II. Storage and Release of Catecholamines
- A. Catecholamines are concentrated in storage vesicles that are present at high density within nerve terminals
- B. The concentration of catecholamines within nerve terminals remains relatively constant
- C. Monoamine oxidase and catechol-*O*-methyltransferase are primarily responsible for the inactivation of catecholamines
- D. The action of catecholamines released at the synapse is terminated by diffusion and reuptake into presynaptic nerve terminals

III. Anatomy of Catecholaminergic Systems
- A. Cell bodies of noradrenergic neurons are clustered in the medulla oblongata, pons and midbrain and are considered to be anatomically part of the reticular formation
- B. Large numbers of cell bodies of dopamine-containing neurons are located in the midbrain

IV. Catecholamine Receptors, Pharmacology and Signal Transduction
- A. The brain contains multiple classes of receptors for catecholamines

V. Dopamine Receptors
- A. Multiple dopamine receptor subtypes exist
- B. The number of D1 and D2 receptors can be modulated by antagonists or neurotoxins
- C. Dopamine receptors are implicated in psychosis and its treatment

VI. _- and β-adrenergic Receptors
- A. The pharmacological responses to catecholamines were ascribed to effects of _- and β-adrenergic receptors in the late 1940s
- B. The amino acid sequences of β-adrenergic receptors in brain and various tissues have been determined
- C. Two families of _-adrenergic receptors exist

VII. Dynamics of Catecholamine Receptors
- A. Changes in the number of receptors appear to be associated with altered synaptic activity
- B. Changes in the number of dopamine receptors may also be involved in pharmacological actions of neuroleptic drugs
- C. Exposure of cells to agonists results in diminished responsiveness, referred to as desensitization

13. Serotonin

J. G. Hensler

A. SEROTONIN

1. Historical Overview

"The indolealkylamine 5-hydroxytryptamine, serotonin, was identified initially because of interest in its cardiovascular effects".

Figure 1: Chemical structures of 5-hydroxytryptamine and related indolealkylamines..

2. Neuroanatomy of Central Serotonergic Systems

"Understanding the neuroanatomical organization of serotonergic cells in brain provides insight into the functions of the neurotransmitter".

Table 1: Classification of serotonergic cell body groups

Figure 2: Schematic drawing depicting serotonergic cell body groups and projections in sagittal section of rat brain.

Figure 3: Serotonergic cell bodies in midbrain raphe nuclei demonstrated by immunocytochemistry.

Figure 4: Diagram illustrating main features of dual serotonergic systems innervating forebrain.

3. Synthesis, Storage and Release of Serotonin

"The amino acid L-tryptophan serves as the precursor for the synthesis of 5-hydroxytryptamine".

Figure 5: The biosynthesis and catabolism of serotonin.

"The synthesis of 5-hydroxytryptamine can increase markedly under conditions requiring a continuous supply of the neurotransmitter".

"As with other biogenic amine transmitters, 5-hydroxytryptamine is stored primarily in vesicles and released by an exocytotic mechanism".

Figure 6:The substituted amphetamine fenfluramine inhibits both (a) the vesicular transporter and (b) the serotonin transporter (SERT).

4. The Serotonin Transporter

"The activity of 5-hydroxytryptamine in the synapse is terminated primarily by its re-uptake into serotonergic terminals".

will include "transporter promiscuity" e.g.5-HT taken up by the Norepinephrine transporter (NET) and the regulation of SERT function acutely by activation of terminal 5-HT_{1B} autoreceptor.

Figure 7: Putative structure of the rat serotonin transporter showing homologous amino acids with the rat dopamine transporter (DAT), human norepinephtrine trasporter (NET).

next page

5. Catobolism of Serotonin

"The primary catabolic pathway for 5-hydroxytryptamine is oxidative deamination by the enzyme monoamine oxidase".

6. Volume transmission and a neuromodulatory role for serotonin in the brain

"Consistent with a neuromodulatory role for serotonin, is evidence for volume transmission of this neurotransmitter".

will include extra-synaptic localization of the serotonin transporter, extra-synaptic localization of the terminal 5-HT_{1B} autoreceptor, the presence in serotonergic neurons of MAO-B, for which serotonin is not the preferred substrate, and localization of MAO-A to other neurons.

B. SEROTONIN RECEPTORS

1. Receptor Classification: Historical Perspective and Current Classification Criteria

"Pharmacological and physiological studies have contributed to the definition of the many receptor subtypes for serotonin."

Table 2: Serotonin receptors present in the CNS.

"Molecular biological techniques have led to the rapid discovery of additional serotonin-receptor subtypes and their properties."

a. 5-HT_1 receptor family

b. 5-HT_2 receptor family

c. 5-HT_3 receptors

d. 5-HT_4, 5-ht_6, and 5-HT_7 receptors

e. 5-ht_{5A}, and 5-HT_{5B} receptors

2. Receptor Distribution in Brain

"The many serotonin receptor subtypes are differentiated by their localization in the central nervous system."

3. Regulation of Receptor Function

"Many serotonin receptor subtypes do not appear to undergo compensatory regulatory changes."

next page

C. SEROTONIN INVOLVEMENT IN PHYSIOLGICAL FUNCTION AND BEHAVIOR

1. Behavioral arousal and activity

"Serotonin may set the tone of brain activity in relationship to the state of behavioral arousal/activity".

2. Circadian rhythmicity, neuroendocrine function and feeding

"Serotonin may set the tone of brain activity in relationship to the state of behavioral arousal/activity".

3. Serotonin is the precursor of the hormone melatonin

"Serotonin not only has important physiological effects of its own but also is the precursor of the hormone melatonin".

D. SEROTONIN NEURONS AND RECEPTORS AS DRUG TARGETS

Figure 8: The effects of psychoactive drugs on serotonergic neurotransmission.

14. HISTAMINE: THE MESSENGER AND THE MOLECULE

for Basic Neurochemistry, 7th edition
L. Hough and R. Leurs

Histamine is a mediator of several physiological and pathological processes within and outside of the nervous system.
The chemical structure of histamine has similarities to the structure of other biogenic amines, but important differences also exist.

HISTAMINERGIC CELLS OF THE CNS: ANATOMY AND MORPHOLOGY

The brain stores and releases histamine from more than one type of cell.
Histaminergic fibers originate from the tuberomammillary region of the posterior hypothalamus.
Histaminergic neurons have morphological and membrane properties that are similar to those of neurons storing other biogenic amines.
Histaminergic fibers project widely to most regions of the central nervous system.
Histaminergic neurons are present in many species.

DYNAMICS OF HISTAMINE IN THE BRAIN

Specific enzymes control histamine synthesis and breakdown.
Several forms of histidine decarboxylase may derive from a single gene.
Histamine synthesis in the brain is controlled by the availability of L-histidine and the activity of histidine decarboxylase.
Histamine is stored within and released from neurons, but no evidence for active neuronal re-uptake has been discovered.
In the vertebrate brain, histamine metabolism occurs predominately by methylation.
Neuronal histamine is probably methylated outside of histaminergic nerve terminals.
The activity of histaminergic neurons is regulated by H3 autoreceptors.

Next Page

MOLECULAR SITES OF HISTAMINE ACTION

Histamine acts on four G protein-coupled receptors, three of which are clearly important in the brain.

H1 receptors are intronless GPCRs linked to Gq and Ca mobilization.

(One or more Pars (RL): H1 molecular, signalling and regulation)

Par (LBH): H1 conductances and electrophysiology

H2 receptors are intronless GPCRs linked to Gs and cyclic AMP synthesis.

One or more Pars (RL): H2 molecular, signalling and regulation.

Par (LBH): H2 conductances and electrophysiology

Both positive and negative interactions may occur between H1 and H2 receptors.

H3 receptors are a family of GPCRs produced by gene splicing and linked to Gi/o.

One or more Pars (RL): H3 molecular – gene structure and splicing

One or more Pars (RL): H3 signalling, brief pharmacology of polymorphisms?

Par (LBH): Localization of H3: autoreceptors and heteroreceptors – LBH

Par (LBH): H3 conductances and electrophysiology

Par (?): H3 receptors are constitutively active in vivo

H4 receptors are very similar to H3 receptors in gene structure and signal transduction, but may not exist in the brain.

Short par by RL on everything you want to say immune/inflammatory cells?/ splice variants?

Histamine can modify ionotropic transmission at identified and unidentified sites

One Par (LBH) – modification of NMDA and cloned invertebrate ion channels, evidence in mammals? Hatton…

HISTAMINE ACTIONS IN THE CNS (LBH)

Histamine in the brain may act as both a neuromodulator and as classical transmitter.

Histaminergic neurons can regulate and be regulated by other transmitter systems.

Histamine in the central nervous system may participate in a variety of brain functions.

Histamine may contribute to brain diseases or disorders.

SIGNIFICANCE OF BRAIN HISTAMINE FOR DRUG ACTION (LBH)

Drugs which modify sleeping and waking act through the histaminergic system.

Classical H1 antagonists; H1 sedative properties of antidepressants and atypical anti-psychotics

Modafinil and wake-promoting effects

Morphine-like analgesics activate brain histaminergic mechanisms

Drugs which act on H3 receptors are being developed for treating obesity, sleep disturbances, epilepsy, pain and/ or cognitive disorders.

15. Glutamate and Aspartate

Raymond Dingledine and Bjørnar Hassel

Glutamatergic transmission and energy metabolism are interwoven.

- Neuronal TCA intermediates are diverted for synthesis of glutamate and aspartate.
- Glutamate can also be synthesized from glial glutamine: the glutamine cycle.
- Leucine and other amino acids contribute amino groups to glutamate synthesis.
- Glutamate is an important energy source for astrocytes.
- Glutamate is also important for glutathione synthesis, ammonia detoxification and protein synthesis.
- Vesicular glutamate transporters are essential for transmitter release.

Iontotropic glutamate receptors mediate fast excitatory transmission

- Five receptor families are defined by structural homology
- Receptor activation involves a clam-shell closure mechanism
- Endogenous allosteric modulators regulate synaptic transmission
- Ca entry through ionotropic receptors triggers synaptic plasticity
- Cytoplasmic proteins regulate receptor targeting
- Receptor knockouts reveal clues to function

Metabotropic glutamate receptors modulate excitatory and inhibitory transmission

- Eight mGluR are in three families
- G-proteins and other proteins mediate functional effects
- Pre- and postsynaptic mGluR's mediate synaptic plasticity

Glutamate receptor activation triggers multiple intracellular responses

Is aspartate a transmitter?

Glutamate transporters shield the brain from ischemic injury and epilepsy

- Five transporters mediate ATP-requiring uptake into neurons and glia
- Glial transporters reduce ischemic brain injury
- Neuronal transporters enhance GABAergic tone

Summary: dual roles of glutamate as information mediator and metabolic regulator

GABA and Glycine

Outline (January 2004)

Richard W. Olsen and Heinrich Betz

Basic Neurochemistry, 7th ed

Introduction (without title)

I. GABA Synthesis, Uptake and Release

- **GABA is formed in vivo by a metabolic pathway referred to as the GABA shunt**

II. GABA Receptor Physiology and Pharmacology

- **GABA receptors have been identified electrophysiologically and pharmacologically in all regions of the brain and are generally inhibitory**
- **$GABA_B$ receptors are coupled to G proteins and a variety of effectors**
- **$GABA_A$ receptors are ligand-gated chloride channels**
- **The $GABA_A$ receptor is the major molecular target for the action of many drugs in the brain**
- **Neurosteroids, which may be physiological modulators of brain activity, enhance $GABA_A$ receptor function**

III. Cloning GABA Receptors

- **$GABA_B$ receptors are heterodimers**
- **A family of pentameric $GABA_A$-receptor protein subtypes**
- **Sequencing revealed that the $GABA_A$ receptor is a member of a superfamily of ligand-gated ion channel receptors; structural models are being developed**
- **Mouse genetics reveal important functions for $GABA_A$ receptor subtypes**

IV. Glycine is synthesized from glucose and other substrates in the brain

V. Glycine Receptor Physiology and Pharmacology

- **A number of amino acids can activate, to varying degrees, the inhibitory glycine receptor**
- **Glycine inhibition is important in the spinal cord and impaired in some neurological disorders**
- **Glycine is inhibitory on ligand-gated, strychnine-sensitive Cl^- channel receptors but excitatory on N-methyl-D-aspartate receptors**

VI. Cloning Glycine Receptors

- **Glycine receptors belong to the same gene superfamily as the $GABA_A$ receptor**

VII. GABA and Glycine are the Major Rapidly Acting Inhibitory Neurotransmitters in Brain

VIII. References

17. Purinergic Systems

Joel Linden and Diane Rosin
Correspondence to Joel Linden, Cardiovascular Research Center, University of Virginia, MR5 Box 801394 Charlottesville, Virginia 22908.

Figure 17-1. Adenosine 5′-triphosphate. A purine nucleotide consisting of adenine, ribose and triphosphate.

Purine release and metabolism

Many cells in the nervous system release adenosine and adenine nucleotides
Nucleotides can be metabolized in the extracellular space
Adenosine is considered to be a neuromodulator

Figure 17-2. Purine release and metabolism.
Figure 17-3. Adenosine metabolites.
Table 17-1. Substrates and Inhibitors of Enzymes Involved in Nucleotide and Nucleoside Metabolism
Box 17-1. Inherited Diseases of Purine Metabolism

Purinergic Receptors

Adenosine also binds to an intracellular site on adenylyl cyclase
There are four subtypes of adenosine receptor that have been cloned
Xanthines block P1, but not P2, receptors
Subtypes of P2 receptors can be classified pharmacologically
Receptors exist for diadenosine polyphosphates, distinct from P1 or P2 receptors

Figure 17-4. The purinergic receptor family.
Figure 17-5. Deduced amino acid sequence and structure of the human A_1 adenosine receptor.
Figure 17-6. Dendograms illustrating structural similarities among G protein-coupled purinergic receptor subtypes.
Figure 17-7. Structures of selective agonists and antagonists of adenosine receptors.
Table 17-2. Subtypes of Adenosine Receptor, Their Effectors and Selective Agonists and Antagonists
Table 17-3. Distribution of P2 mRNAs in the CNS

Effects of Purines in the Nervous System

Adenosine receptors
- **A_1-adenosine receptors, sleep and epilepsy**
- **A_{2A}-adenosine receptors, locomotor behavior and Parkinson's disease**
- **A_{2B}-adenosine receptors**
- **A_3-adenosine receptors**

ATP receptors
- **P2X receptors**
- **P2Y receptors**
  - **$P2Y_1$ receptors**

Figure 17-8. Distribution of A_1 and A_{2A} receptors in rat brain.
Figure 17-9. Regulation of Striatal function by A_{2A} adenosine receptors

References

18. PEPTIDES

Richard E. Mains and Betty A. Eipper

The major changes/improvements are:

1. A lot more is known about the endoproteases, exoprotease, and amidating enzyme now than in 1997, with crystal structures for a couple and more on the mechanisms of how the proteases work and their selectivity.
2. Some of the methods listings will go away – while relevant in a global presentation, there is not space in such a short chapter and modern things have to hold sway over historically interesting approaches
3. There will be a discussion of the impact of genomics and proteomics on the study of peptides. Specifically, there can now be some pretty clear statements about how many families of peptides and enzymes there are, although we will also remind the readers about how (relatively) tiny the coding regions can be for many peptide precursors (as little as 276 nt or thereabouts) and with no introns, such a tiny exon could get lost in the noise of genomic sequencing. Proteomics makes its own special impact, on "what is really there" as opposed to the theoretical predictions.
4. Different receptors will be discussed entirely – the opiate receptors, orexin and ghrelin receptors are far more topical and make lovely examples. Orphan receptors have driven a number of discoveries of new peptides.
5. There has been a lot of progress in the area of synthetic peptide analogs – both agonists and antagonists – as one might expect from the classical neurotransmitter field from a couple of decades earlier.

Next page

The 1997 chapter in outline form, with ADDITIONS for 2003 IN CAPITAL LETTERS:

I. The Neuropeptides
A. Many neuropeptides were originally identified as pituitary hormones or as hormones of the gastrointestinal tract.
B. Neuropeptides far outnumber the classical neurotransmitters.
C. The use of peptides as messengers is evolutionarily very old.
D. A variety of techniques are being used to identify additional neuropeptides. quickly list bioassays; radioreceptor assays; COOH-terminal alpha-amides; classical molecular biology; GENOMIC APPROACHES; PROTEOMICS; ORPHAN RECEPTORS
E. The neuropeptides exhibit a few key differences from the classical neurotransmitters. Lower levels, inactive large precursors, synthesis must start in the soma, no synaptic re-use, role of calcium in release is different.
F. Neuropeptides are found in many neurons, and often in the same synapses with conventional neurotransmitters — EMPHASIZE PLASTICITY
G. The biosynthesis of neuropeptides is fundamentally different from the biosynthesis of conventional neurotransmitters.
H. Many of the enzymes involved in peptide biogenesis have been identified.
I. Key enzymes in neuropeptide biosynthesis -- BIG EXPANSION ON ENDOPROTEASES, CARBOXYPEPTIDASE E, AMIDATING ENZYME based on crystal structures and much more on enzymatic mechanism.
Downplay other enzymes for which there is no progress. Still use the example of POMC Processing.
J. Neuropeptides are packaged into large dense core vesicles (LDCVs).
K. Diversity is generated by families of propeptides, alternative splicing, proteolytic processing and post-translational modifications.
L. METABOLIC REGULATION; VOLUME TRANSMISSION OF PEPTIDES (as catecholamine folks are accustomed to believing) PLUS MATCHING GPCR'S WITH ACTUAL PEPTIDES (WHICH IS USUALLY NOT A GOOD MATCH).

Next page

II. Neuropeptide Receptors

A. Most neuropeptide receptors are seven transmembrane domain G protein coupled receptors. BUILD FROM THE RHODOPSIN CRYSTAL STRUCTURE TO MODELS OF PEPTIDE RECEPTORS WITH MANY SITE_DIRECTED MUTAGENESIS STUDIES.

B. Neuropeptide receptors are not confined to synaptic regions and the expression of peptide receptors and the corresponding peptides are not well matched.

C. The amiloride-sensitive FMRF-amide gated sodium channel was the first peptide gated ion channel identified. STILL THE ONLY EXAMPLE(?)

D. PEPTIDE ANALOGS AS A KEY TOOL IN THE STUDY OF PEPTIDE ACTIONS AND RECEPTORS

E. AGOUTI-RELATED PEPTIDE AS EXAMPLE OF ENDOGENOUS ANTAGONISTS

F. MCR1,2,3,4,5 AS EXAMPLES OF RECEPTORS RELATED TO PEPTIDE DIVERSITY

G. KNOCKOUTS OF PEPTIDE VS. PEPTIDE RECEPTORS – UNLIKE THE GROWTH FACTOR FIELD WHERE RECEPTOR KO'S ARE WORSE THAN PEPTIDE KO'S, IN THE PEPTIDE FIELD, THE PEPTIDE KO'S ARE THE KEY THING.

III. Neuropeptide Functions

A. The study of peptidergic neurons requires a number of special tools.

- Antibody-based
- RNA-based
- Direct methods
- Peptide agonists and antagonists
- Ligand binding assays
- PCR-BASED DIFFERENTIAL EXPRESSION
- GENOMICS TO PREDICT PEPTIDE PRECURSORS
- PROTEOMICS AT THE SINGLE CELL OR SMALL TISSUE SAMPLE LEVEL

B. Plurichemical coding of neuronal signals. Peptides along with conventional neurotransmitters.

C. Neuropeptides make a unique contribution to signaling. BRIEF!

D. Regulation of neuropeptide expression is exerted at several levels. MORE HERE – HOMEOBOX and MASTER TRANSCRIPTIONAL FACTORS NEED TO BE INCLUDED.

E. T-PIT HERE

Next page

IV. Peptidergic Systems In Disease

A. Diabetes insipidus IS PERHAPS A LESS INTERESTING EXAMPLE THAN OBESITY AND BEHAVIORAL CASES – EXCEPT DOMINANT-NEHATIVE MUTANTS MAKE THIS COOL.

B. In fat/fat mice, a mutation in the CPE gene causes late onset diabetes with hyperproinsulinemia – STILL INTERESTING AND STILL NOT REALLY UNDERSTOOD.

C. Obesity can have several central nervous system components involving CCK, leptin, and NPY. MANY MORE PEPTIDES CAN BE INCLUDED HERE – BECOMES AN UNINTERPRETABLE LIST, HOWEVER, SO THIS HAS TO BE LIMITED IN SCOPE AND CAREFULLY ORGANIZED

D. CCK agonists and antagonists are yielding insights into the neurochemical basis of panic attacks and satiety – PROGRESS HAS OCCURRED BUT MAYBE NOT ENOUGH TO KEEP THIS SECTION.

E. Enkephalin knock-out mice reach adulthood and are healthy, fertile and care for their young – ALSO NOT AS INTERESTING IN 2003.

F. MIGRAINE HEADACHES DUE TO CGRP ARE VERY TOPICAL NOW – SHOULD INCLUDE.

G. OREXINS AND NARCOLEPSY OR OVER-EATING OR BOTH.

H. GHRELIN – INTERESTING ADDITIONAL POST-TRANSLATIONAL MODIFICATIONS OF PEPTIDES, AND FASCINATING RAPID PROGRESS IN UNDERSTANDING ANOTHER APPORACH TO OVER-EATING

FIGURES WILL CHANGE WITH THE TOPICS

1. Selected bioactive peptides, grouped by structural similarity or by tissue source.
2. Structures of selected bioactive peptide precursors.
3. Intracellular pathway of bioactive peptide biosynthesis, processing, and storage.
4. Tissue specific processing of the proopiomelanocortin precursor yields a wide array of bioactive peptide products.
5. Sequential enzymatic steps lead from the peptide precursor to bioactive peptides.
6. Processing of the proopiomelanocortin precursor proceeds in an ordered, stepwise fashion.
7. Cell-specific packaging of peptides into LDCVs can lead to very different patterns of peptide secretion.
8. MECHANISMS OF THE ENDOPROTEASES/CARBOXYPEPTIDASE/AMIDATING ENZYME. CONNECT STRUCTURES AND ENZYMATIC MECHANISMS.
9. Serpentine (7 transmembrane domain) receptors for peptides have binding regions within the membrane and in the NH_2-terminal loop. BUILD FROM RHODOPSIN AND USE SITE-DIRECTED MUTANTS
10. Plurichemical transmission —WILL AIM AT A MORE INTERESTING EXAMPLE, NOT CLEAR WHICH EXAMPLE YET.
11. Regulation of neuropeptide expression is exerted at several levels.
12. MULTIPLE ACTIONS OF PEPTIDES – OREXINS; MSH; CCK; ACTH. IDEA IS TO LIST ABOUT 5 PEPTIDES WITH “CLASSICAL” ACTIONS AND TARGETS, PLUS “NEW” ACTIONS AND TARGETS.