ESSENTIAL PSYCHOPHARMACOLGY: HOW THE BRAIN WORKS

MONTREAL, 2011
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BASIC NEUROBIOLOGY -I

• Principles of neurotransmission
• Synaptic function
• Receptor structure
• Second & third messengers
• Into the nucleus
• Nuclear transcription of neuronal transmission
HOW THE BRAIN WORKS

• 13 billion neurons
• Each makes 1,000 (or more) connections
• Connected neurons form pathways and communicate with each other
WHAT DO THE NEURONS DO?

- Communicate with each other
- Activate genes to make (or destroy) proteins within each neuron
- Basic function of proteins:
  - Are the functional structures of cells
  - All proteins are manufactured under control of genes
- Therefore: the basic function of each neuron is to activate genes in the nucleus of each cell
Basic Shape of a Neuron

- Nucleus
- Synthesizing Enzyme
- Axon
  - Resting membrane potential
  - Na^+
  - K^+

NT precursor

Other neurons synapsing

Storage vesicle
Neurons Communicate With Each Other

Neuronal segments
NEURONAL PATHWAYS

• Are named for the primary neurotransmitter that carries the neuronal message from neuron to neuron (e.g. serotonin, dopamine, norepinephrine)

• Are distributed unequally throughout the brain, e.g.:
  – Pathways for cognition tend to be in the frontal lobes
  – Pathways for emotion tend to focus on the limbic cortex, thalamus, hypothalamus
COMMUNICATION BETWEEN NEURONS

- Space between neurons: Synapse
- Chemical neurotransmitter is manufactured from food and amino acids
- Neurotransmitter is released into synapse
- Some molecules touch ("bind") special sites on post synaptic membrane known as receptors
Receptors

Synapse

Pre-synaptic

NT
NT
NT

Post-synaptic

NT
NT
NT

Receptors
WHAT IS A RECEPTOR?

• Is a protein embedded in the lipid membrane surrounding the neuron
• Is manufactured in the cell body under the genetic control of the nucleus
• Is specifically designed to receive (or be activated) by a specific neurotransmitter:
  – Like a keyhole shaped for a specific key
BASIC PRINCIPLE: ONE NEUROTRANSMITTER CAN BIND TO SEVERAL RECEPTORS SUBTYPES

- Norepinephrine
- Dopamine
- Serotonin
- Glutamate
- GABA

- a1, a2, β1
- DA1,3; DA2,4; DA7
- 5HT1a,c; 5HT2a,c,
- NMDA, AMPA, Metabotropic
- GABA-A; GABA-B
BASIC PRINCIPLE: SAME RECEPTOR CAN BE BOTH PRE AND POSTSYNAPTIC

- 5HT1a, D2
- Presynaptic: autoreceptor; post synaptic: effector
BASIC PRINCIPLE: RECEPTORS ARE DIFFERENTIALLY LOCATED IN CNS AND HAVE DIFFERENT FUNCTIONS:

• DOPAMINE
  – Mesolimbic, Mesocortical (D1;D2)
  – Nigrostriatal (D2)
  – Tubero-infundibular (D2)
  • Frontal cortex; mood, cognition; exec function
  • Extrapyramidal
  • Prolactin inhibiting
BASIC PRINCIPLE: TRANSMITTERS FROM ONE PATHWAY MAY INTERACT WITH RECEPTORS FROM ANOTHER

• NE activates a noradrenergic receptor located on cell body of 5HT neurons;
• Activation of NE increases 5HT release from 5HT presynaptic terminals
  – (mechanism of Remeron)
Pre-synaptic

Amino Acid Precursor

Synthesizing Enzyme

Intermediate Steps

Depolarization

Ca

Autoreceptor

Storage Vesicle

Release

NT

Controls synthesis

Controls release
Second Messenger Cascade

Postsynaptic Neuron

Receptor

G-protein

Activating Enzyme

Protein Kinase

Second Messenger

Promotor

Nucleus
PSYCHIATRIC ILLNESSES MAY BE DISORDERS OF GENE EXPRESSION

• Genes control the function of each neuron that is part of a circuit
  – Genes control the manufacture (or destruction) and maintenance of neurons and synapses

• Genes cannot be altered, BUT
  – Genes can be activated or suppressed
  – The degree to which a gene is expressed can be altered
    – Alteration of gene expression can lead to dysfunction of neurons and their circuits
The Gene makes proteins

mRNA

Receptor proteins

Transporter proteins

Enzymes

Ion channels; Co-transmitters; Second messengers; Other proteins; Etc
Activation of Gene

promotor → DNA activated

mRNA
What activates the promotor region?

- Specific protein binds to promotor region.
What turns on the promoter region?

A specific protein binds to the promoter region:

- **Promoter**
- **DNA activated**
- **mRNA**
Cytoplasmic enzyme is called a Protein Kinase

- Only the protein kinase can enter the nucleus to activate the promotor region:
POST-SYNAPTIC CASCADE FROM SYNAPSE TO NUCLEUS

G → Stimulating Enzyme* → ATP → cAMP → PKA → Into the nucleus

*adenylate cyclase or phospholipase C

Receptor proteins

Third messenger

Second messenger
IF GENES CONTROL NEURONS AND CIRCUITS, WHAT CONTROLS THE GENES?

• Genes are activated (or turned off) by receiving input from other neurons (and their genes) via the neuronal circuitry from different areas of the brain.

• Genes also receive input and are activated or turned off by input from the environment via neuronal circuitry from the sensory apparatus and hormonal influence.
WHY DOESN’T A NEURON GROW HAIR?

• Each nucleus contains all the genes;
• But only ones for specific neuronal function are activated (or turned off);
• What controls the activation so that only neuronal genes are turned on and not hair-growing genes?
  – Specific promotor region adjacent to a gene turns on the gene to reproduce its DNA to mRNA
  – The promotor region, itself, must be activated
Mechanism of Gene Transcription, CREB - I

- cAMP (or other second messenger)-dependent protein kinase (PK) enters the nucleus;
- A certain sequence of DNA functions as a promoter region protein that can be phosphorylated by a PK. One important protein is called CREB (cAMP response element binding protein).
- CREB then activates a number of genes including genes that manufacture proteins for receptors, enzymes, and other neuronal functions.
The Nucleus

PK_A

C-reactive element binding

DNA replication

CREB

DNA

Activates genes to replicate mRNA

mRNA

RNA

Control Region

RNA leaves nucleus as messenger RNA (mRNA) to cell body

Segment of DNA strand

Genes to make proteins:
- receptors
- enzymes
- ion channels
- synthesis

mRNA
HOW GENES ARE EXPRESSED-I

• On or off:
  under control of promoter region and second messenger cascades

• Degree of expression if “on”:
  – Under control of chromatin remodeling:
    • Genes are either more loosely or tightly bound allowing for more or less expression
    • Analogy: the gene is the candy bar, and the chromatin is the wrapper. In order to get at the gene (candy), you have to unwrap the wrapper, or at least loosen it.

  – This loosening or tightening of the wrapper determines the ability of the gene to express itself and is termed “epigenetics”
    • The gene doesn’t change but the degree of its expression does under influence via neurotransmission from the synapse to the nucleus.
GENES ALSO MAKE NEUROTROPHINS

• Neurotrophins maintain the health of neurons and foster their growth
• Production of neurotrophins depends on gene function:
  – Expression of the gene may be altered by information coming post-synaptically from the synapse e.g. decreased neurotransmission
  – Expression of the gene may be altered by epigenetic mechanisms e.g. stress
• Common neurotrophin is called: Brain Derived Neurotrophic Factor (BDNF)
BDNF (BRAIN DERIVED NEUROTROPHIC FACTOR)

• Nourishes and maintains neurons
• Increases neuron growth in hippocampus
• All antidepressant treatment may work by ultimately increasing BDNF in hippocampus
• Probably plays a major role in stress
EFFECT OF PSYCHOTROPIC MEDICATION

• Synaptic transmission ($1^{st}$ messenger) starts neuronal events leading to nucleus

• Psychototropic drugs ultimately affect nucleus
  – Initially affect synaptic neurotransmission
  – These changes result in DNA transcription in the nucleus

• Onset of therapeutic effects coincides with changes in nucleus, not synapse
THE AMYGDALA

• Amygdala and anterior cingulate cortex are anatomically connected
  – ACC and amygdala together are activated by fear and anxiety
  – Together, they regulate emotional conflict

• Suggests that ACC-amygdala regulates emotional processing

• Sends messages to the hippocampus as part of the emotional regulatory circuit

Etkin, 2010 Am J Psychiatry 167:545
2 BASIC TYPES OF RECEPTORS:
1- ION CHANNEL, VOLTAGE GATED

• Receptor and ion channel are part of same protein unit embedded in cell membrane

• Used by amino acid neurotransmitters (Glutamate, GABA):
  – Fast on & off (eg vision)
  – No second messengers
  – Off when transmitter is removed
IONOPHORE RECEPTOR: glutamate

GLU → AMPA

Na+ → AMPA
Ca++ → AMPA

Mg+ → AMPA

Extracellular → Intracellular

NMDA RECEPTOR
MULTIPLE GLUTAMATE RECEPTORS

- **NMDA**
  - Ionophore: ion-gated entry of sodium and calcium into cell causing depolarization and neuronal firing: is stimulatory

- **AMPA**
  - Associated receptor recognition site for glutamate: opens NMDA ionophore by removing magnesium plug

- **Kainate**
  - Is also ion-gated; can be pre and post synaptic; may play a role in depression
CLINICAL RELEVANCE OF MULTIPLE GLUTAMATE RECEPTORS

- Multiple receptors: AMPA is activated first; removes Mg++
- Then NMDA receptor allows Ca influx; either helpful (long-term potentiation or toxic (cell death)
- Memantine (for Alzheimers disease) blocks NMDA channel like Mg++
- Lamotrigine (and ketamine) blocks presynaptic glutamate release
MULTIPLE GLUTAMATE RECEPTORS-II: METABOTROPIC RECEPTORS

- Metabotropic glutamate receptors may have therapeutic properties:
  - Decrease psychotic symptoms
  - Enhance cognition
- mGlu2/3 decrease presynaptic release of glutamate at NMDA synapse;
- mGlu5 (pre- and postsynaptic) may also influence NMDA function
  - Increase presynaptic glutamate release

Mutel, 2005
GABA FUNCTIONS

• Neuronal inhibition (Cl⁻ ions) hyperpolarize cell membrane:
  – Decrease anxiety, PTSD, PMDD
• Decreased GABA in schizophrenia
• Binds to GABA<sub>A</sub> receptor subtype
  – Some receptors have adjacent benzodiazepine receptors which enhance GABA<sub>A</sub> receptor sensitivity
IONOPHORE RECEPTOR: GABA-A

GABA-A receptor

Cl⁻

BZ receptor

Extracellular

Intracellular
2 BASIC TYPES OF RECEPTORS: 2-INTRANEURONAL CASCADE

- Characterized by a series of chemical events resulting in a change in the transcription of genes in the cell nucleus.
- Characterizes monoamine neurotransmission: norepinephrine (NE), dopamine (DA) and serotonin (5HT).
MONOAMINE RECEPTORS

- Receptors on cell surface couple to “G” proteins inside the cell which then stimulate or inhibit an enzyme (adenyl cyclase or phospholipase C) --->
- The enzyme (e.g. adenyl cyclase) markedly increases cAMP (known as a second messenger) --->
- The second messenger then activates an enzyme (known as a protein kinase) ---> which activates CREB (a promoter region on the chromosome next to a gene) inside the nucleus
- CREB then activates the gene transcription
Postsynaptic Second Messenger Cascade

Postsynaptic Neuron

Receptor → G-protein → Adenylate cyclase → cAMP → PKa → CREB → Nucleus
NOREPINEPHRINE (NE): PRESYNAPTIC

Tyrosine

Tyrosine hydroxylase

DOPA → DA

MAO

NE

α₂

Release

Depolarization

Ca

Transporter Protein

Vanillylmandelic acid (VMA)

COMT
NE TRANSPORTER PROTEIN POLYMORPHISMS

• Pre-synaptic NE re-uptake from synapse is an active protein transport
• Transporter protein has 2 polymorphisms
  – A polymorphism
  – G polymorphism
  – Majority (56%) are GG
• GG associated with better response to NE antidepressants
Hamilton Rating Scale for Depression Score Changes During 6 Weeks of Treatment With Norepinephrine Reuptake Inhibitor

NOREPINEPHRINE: POSTSYNAPTIC

G → adenylate cyclase → ATP → cAMP → PK_A → Into the nucleus
NOREPINEPHRINE: POSTSYNAPTIC CASCADE

- Neurotransmitter: Norepinephrine
- Receptor: $B_1$-receptor
- G protein: G-stimulatory
- Activating enzyme: Adenylate cyclase
- Second Messenger: cAMP
- Protein Kinase: $P_k^a$
- Promotor binding protein: CREB (C reactive element binding)
CNS DOPAMINE PATHWAYS

A

Frontal cortex

Caudate nucleus and putamen (striatum)

Nucleus accumbens (ventral striatum)

Tubero-infundibular DA system

Amygdala

Mesolimbic and mesocortical DA system

Ventral tegmental area

Substantia nigra

Nigrostriatal DA system
DOPAMINE (DA): PRESYNAPTIC

Tyrosine → Tyrosine hydroxylase → DOPA → DOPA

MAO → Tyrosine hydroxylase → DOPA

Ca → Release → D2

COMT

Metabolite HVA (Homovanillic Acid)
DOPAMINE (DA): POSTSYNAPTIC

2 DA Receptor Families:
- D₁
- D₂
- D₃
- D₄
- D₅

Adenylate cyclase
ATP → cAMP → PKₐ
No second messenger
Into the nucleus
GENE CONTROL OF DOPAMINE METABOLISM

• COMT = catechol-o-methyl-transferase
• Degrades dopamine (DA)
• 2 genetic polymorphisms: methionine (MET) and valine (VAL)
• MET-MET may be associated with prefrontal deficits in schizophrenia
COMT POLYMORPHISMS: CLINICAL RELEVANCE

• DA metabolism under rate limited step of COMT (catechol-O-methyl transferase)

• Enzyme under genetic control: polymorphism with 2 alleles:
  – Valine (val-val): more active metabolism, lower DA
  – Methionine (met-met): less active metabolism, higher DA
  – Heterozygote (val-met)

• Val allele associated with cognitive dysfunction and negative symptoms in schizophrenia

• Met allele
  – associated with overstimulation from amphetamines
  – Positive symptoms
COMT and Prefrontal DA

- The prefrontal cortex has few dopamine transporters
- Thus, dopamine inactivation in PFC is more dependant upon COMT metabolism

<table>
<thead>
<tr>
<th>If COMT activity is:</th>
<th>Synaptic DA concentrations are:</th>
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<tbody>
<tr>
<td>High (_{(val/val)})</td>
<td>Low</td>
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<tr>
<td>Low (_{(met/met)})</td>
<td>VS.</td>
</tr>
<tr>
<td></td>
<td>HIGHER</td>
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</tbody>
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Mazei MS et al., *Brain Res* (2002)
Genotype, Endophenotype, and Schizophrenia: Connections

\[ \text{COMT} \text{ (met/met)} \]
- Low
  - \( \uparrow \) Higher [DA]
  - \( \downarrow \) Better PFC Tuning
  - \( \downarrow \) more efficient Information Processing (less cortical activation)
  - \( \downarrow \) Decreased Risk

\[ \text{COMT} \text{ (val/val)} \]
- High
  - \( \uparrow \) lower [DA]
  - \( \downarrow \) Poor PFC Tuning
  - \( \downarrow \) less efficient Information Processing (more cortical activation)
  - More likely in unaffected siblings with schizophrenia
  - Increases risk of schizophrenia (1.3 OR)
Tryptophan hydroxylase (5-OH tryptophan)

5HT Release

5HT Transporter protein (5HTTP)

SEROTONIN (5HT): PRESYNAPTIC

Tryptophan

2 autoreceptors

5HT_{1a}

5HT_{1d}

5-Hydroxytryptamine (Serotonin)

MAO

5HT Transporter protein (5HTTP)

Metabolite 5 HIAA (5 Hydroxyindole Acetic Acid)

Ca
5-HT TRANSPORTER PROTEIN POLYMORPHISMS

- Pre-synaptic 5HT re-uptake from synapse is an active protein transport
- Transporter protein has 2 polymorphisms:
  - Long arm form (L)
  - Short arm form (S)
  - Most individuals are L/L or L/S
- Functional variant of allele: L_A, L_G
  - L_G and S have comparable levels of 5HT transporter expression; both are lower than L_A
5-HT\textsubscript{2A/2C} POST SYNAPTIC RECEPTORS

- Regulate mood through 5HT neurotransmission
  - 5HT\textsubscript{2A} post synaptic receptor is the primary serotonergic target for mood regulation
- Newly relevant receptor: 5HT\textsubscript{7}
  - May also participate in mood regulation
5-HT$_{2C}$ POST SYNAPTIC RECEPTORS

- Stimulation of 5-HT$_{2C}$ suppresses food intake
- **Blockade of 5-HT$_{2C}$** (in conjunction with blockade of H$_1$) causes **weight gain**
  - Blockade by mirtazapine causes obesity
  - No obesity caused by antidepressants that do not block H$_1$ but do block 5-HT$_{2C}$
  - Second generation antipsychotic drug weight gain also caused by blockade of 5-HT$_{2C}$
SEROTONIN 1B RECEPTOR

• Is a presynaptic autoreceptor
• Synapse (as heteroreceptors) on non-serotonergic neurons (GABA, glutamate, DA)
  – Decrease neurotransmission at these sites
• Function: to regulate limbic neurotransmission in corticostriatal pathways: amygdala, caudate, anterior cingulate cortex
  – Plays a role in emotional behavior, stress reactivity and anxiety states
• Function depends on location in CNS:
  – Frontal cortex: inhibits release of dopamine
  – Striatum and basal ganglia: inhibits release of serotonin
• Function is reduced in PTSD and is an increased risk for PTSD
  – Association between severe trauma exposure and reduced 5HT1B
  – Earlier exposure (childhood) is associated with more severe symptoms
SEROTONIN “7” RECEPTORS

• Found in CA3 layer of hippocampus (decreases pyramidal cell function)
  – Decreases cAMP formation
• Decreases presynaptic 5HT release
• May increase depression
  – Antagonist has antidepressant effect
• May inhibit long- and short-term memory
Serootonin: Postsynaptic Second Messenger Cascade

Postsynaptic Neuron

- 5HT2 receptor
- G-protein
- Phospholipase C
- IP3
- DAG
- PKC
- Promotor
- AP-1
- Nucleus

(cfos+ Cjun= Activator Protein-1)
SEROTONIN: POSTSYNAPTIC CASCADE

- Receptor
- G protein
- Activating enzyme
- Second Messenger(s)
- Protein kinase
- Promotor binding protein

- 5HT
- G protein
- Phospholipase C
- IP$_3$ and DAG
- PKc
- Activator Protein-1
PSYCHOTOMIMETIC DRUGS AND SEROTONIN

• All psychedelic hallucinogens stimulate post synaptic serotonin 5HT$_{2A}$ receptors, especially in frontal cortex

• (Serotonin does not cause this effect because it also activates other 5HT receptors such as 5HT$_{1A}$ which offsets the 5HT$_{2A}$ effect)
NEUROBIOLOGY OF THE REWARD SYSTEM AND ADDICTIONS
NEUROBIOLOGY OF ADDICTION

• Crucial pathway is the mesolimbic DA system:
  – Originates in ventral tegmental area (VTA) of midbrain
  – Projects to n. accumbens
  – Also projects to limbic system and orbitofrontal cortex and anterior cingulate cortex

• Mesolimbic pathway is associated with the ability to feel pleasure

• 5HT neurons arising in raphe nuclei project to VTA and accumbens
  – Exert inhibitory control on mesolimbic DA activity
ROLE OF DOPAMINE IN ADDICTIONS

ALCOHOL
- GABA receptor
- NMDA receptor
- hippocampus (cognition)
- cerebellum (ataxia)

COCOAINE
- monoamine transporters
- heart (tachycardia)
- cortex (paranoia)

mesolimbic dopamine system

MORPHINE
- brainstem (autonomic inhibition)
- opioid receptors
- spinal cord (antinociception)
DOPAMINE AND ADDICTION

- All addictive substances exert their primary reinforcing or reward effects by releasing DA in the accumbens
  - May be due to blockade of DA transporter;
  - May be due to interaction with multiple DA receptors
ENOCANNABINOIDS - I

• Endocannabinoid system comprised of:
  – CB receptors
  – Endogenous ligands (endocannabinoids)

• Mediate inhibition of neurotransmitter release

• Involved with: anxiety, memory, appetite control, emesis, motor behavior, sensory, autonomic and neuroendocrine responses
NEUROBIOLOGY OF ADHD

• Dopamine neurotransmission is disrupted in ADHD
  – Accounts for both symptoms of inattention and impulsivity
  – Also may be associated with reward and motivation deficits

Volkow, 2009: JAMA 302:1084
NEUROBIOLOGY OF ADHD-II

• Primary defect is in dopamine “reward pathway”
  – Underlies reward and motivational deficits in ADHD
  – Is the meso-accumbens DA pathway:
    • Projects from ventral tegmental area in mid brain (VTA)
    • Terminates in nucleus accumbens (in ventral striatum) which results in decreased n. accumbens activation
    • Decreased D$_2$/D$_3$ receptors and dopamine transporter protein availability in n. accumbens correlates with decreased attention and motivation

Volkow, 2009: JAMA 302:1084
NEUROBIOLOGY OF ATTACHMENT
PEPTIDES FOR ATTACHMENT: OXYTOCIN & VASOPRESSIN

• Peptides synthesized in hypothalamus
• Released from posterior pituitary
• Part of a family of “nonapeptides”
• Found exclusively in mammals
• Receptors for both are found throughout limbic system, forebrain, and autonomic centers
• Both are implicated in the central mediation of social recognition and social memory
USE OF VOLES TO STUDY SOCIAL AND INFANT ATTACHMENT

• Voles: 2 species
  – Prairie voles: are monogamous and have high social contact
    • Pups emit ultrasonic distress calls following separation and secrete corticosterone
  – Montane voles: not monogamous and have low social contact
    • Pups do not respond to social separation with either isolation calls or corticosterone secretion
PRAIRIE VOLES

• Indications of monogamy:
  – Choose to sit next to their mates
  – Partner preference is enduring and reciprocal
  – Males as well as females continue to show preference for mates even after weeks of separation
  – After mating, males become aggressive and protect the female
MECHANISMS OF SOCIAL ATTACHMENT

• Monogamous prairie vs. non-monogamous montane voles
  – Prairie voles have a higher density of oxytocin receptors in n. accumbens
    • Blockade of receptors prevents partner preference formation
  – Prairie voles also have a higher density of vasopressin receptors in ventral pallidal area

• N. accumbens and ventral pallidum are key relay nuclei in reward circuitry (mesolimbic DA and opioid systems)

Young, 2001
OXYTOCIN, DOPAMINE AND ATTACHMENT

• DA in the n. accumbens and ventral pallidum is important for partner preference formation

• Pair bonding requires oxytocin receptors in the n. accumbens
OXYTOCIN IN SOCIAL PHOBIA AND AUTISM SPECTRUM DISORDERS

• Intranasal oxytocin:
  – Enhances patient’s ability to socially interact, reducing anxiety and physical discomfort

• Increases affective speech recognition in adults with autism or Asberger’s
NEUROBIOLOGY OF THE STRESS AXIS AND STRESS RESPONSE
Neuroanatomy of (HPA) Stress Axis

- Perception of stress
- Hypothalamus releases hormone
- Turns on Pituitary
- Adrenals make cortisol

- Perceptual apparatus (eyes, ears etc)
- Corticotrophin Releasing Hormone
- Releases ACTH (adrenocorticotrophin hormone)
- Cortisol provides immediate energy
SUMMARY OF HPA AXIS
HOW DOES STRESS AXIS RETURN TO NORMAL?

Hypothalamus

- Turns off CRF release
- glucocorticoid receptor

Cortisol circulating in blood stream
WHAT HAPPENS IF CORTISOL CAN’T BE TURNED OFF?

• Genetic subsensitivity of glucocorticoid receptor (GR)
  – Polymorphisms of FKBP5 co-regulating chaperone alters GR sensitivity

• Altered sensitivity leads to:
  – Depression
  – Anxiety disorders
  – Increased risk for PTSD
  – Dementia

Mehta 2011; ArchGenPsychiat 68:901
WHAT HAPPENS IF STRESS IS CHRONIC?

• Cortisol receptor may become subsensitive and not shut off CRF release

• Chronic hypercortisol is seen in chronic stress:
  – Depression
  – Anxiety disorders
  – PTSD
  – Chronic Pain
STRESS ALTERS BRAIN STRUCTURE

- Interferes with NE and 5HT ascending pathways
- Unmyelinated axons and terminals retract
- Terminal arborization is decreased (leading to fewer synapses)
- Decreases BDNF
TREATMENT OF ACUTE STRESS

• Therapeutic goal:
  – Prevent stress from becoming chronic:
    • Cause PTSD
    • Cause anxiety spectrum disorders
    • Cause depressive disorders
• Block monoamine neurotransmission
  – $\beta$ blocker drugs;
• Enhance BDNF production:
  – antidepressants
TREATMENT OF CHRONIC STRESS

• 3 goals:
  – Decrease circulating cortisol
    • CRF$_1$ receptor antagonists
  – Increase BDNF
    • Antidepressants
  – Block CRF release
    • Use CRF$_1$ antagonist drug: RU486
The diagram illustrates the effects of normal, stress, and antidepressants on the hippocampus. In the normal state, glucocorticoids are elevated, and BDNF is decreased, leading to normal survival and growth. During stress, glucocorticoids are further increased, and BDNF is decreased, leading to atrophy or death. Antidepressants increase BDNF, leading to increased survival and growth.

Increased vulnerability to neuronal insult and genetic factors is highlighted in the diagram.
HOW DOES THE ENVIRONMENT INTERACT WITH GENES?

“Life counts: we are not doomed by our genes”
GENES CONFER VULNERABILITY OR RESILIENCE TO LIFE STRESS

• Examples:
  – Serotonin and norepinephrine transporter genes
  – BDNF gene
  – Receptor sensitivity genes
  – Catechol-o-methyl transferase genes
  – Pharmacokinetic enzyme genes
EXAMPLE OF GENE-ENVIRONMENT INTERACTION

- Significant interaction between 5HTTPLR genotype and adverse events in determining the likelihood of an episode of major depression
  - s/s genotype gave a greater probability of experiencing onset of depression with increasing numbers of life events
  - l/l genotype are less likely to experience depression

Caspi, 2003; Wilhelm, 2006
CHILDHOOD ADVERSITIES PREDICT CHRONIC ADULT PHYSICAL CONDITIONS

• Childhood adversity:
  – Abuse, neglect

• Chronic adult conditions:
  – Diabetes, asthma, heart disease, arthritis, chronic spinal pain, chronic headache, depression and anxiety

• History of 3 or more childhood adversities is associated with onset of all disorders

Scott 2011; ArchGenPsychiat 68:838
GENE X ENVIRONMENT

- BDNF polymorphism and early life stress:
  - BDNF Met carriers exposed to greater ELS
    - Smaller hippocampal and amygdala volumes
    - Heart rate elevations
    - Decreased working memory
    - Higher depression
  - BDNF Val carriers
    - Increased anxiety and startle

Gatt 2009, Mol Psychiat 14:681
EPIGENETIC INFLUENCE OF EARLY-LIFE ADVERSITY ON BDNF GENE

- Stress-induced changes in behavior are due to changes in neural plasticity in prefrontal cortex and hippocampus
- Mediators of neural plasticity include:
  - BDNF protein levels
  - Glutamate NMDA receptor expression
  - Synaptic long-term potentiation
  - Epigenetic modulation of gene transcription