Monoamine Oxidase in Major Depressive Disorder
Learning Objective

- Explain the role of monoamine oxidase in the neurobiology, etiology, and presentation of psychiatric illnesses, including depression
Major Depressive Disorder (MDD)

- Lifetime prevalence of MDD may be as high as 20%
- As many as 50% of patients are treatment resistant
- Approximately 20% of patients who do respond to treatment will relapse within 2 years

Neural Circuits of Depression
The Monoamine Hypothesis of Depression

- Monoamine levels are reduced in patients with depression
  - Dopamine (DA)
  - Norepinephrine (NE)
  - Serotonin (5HT)

- Decreased production, increased synaptic reuptake, or increased degradation?
  - The most commonly used treatments (SSRIs, SNRIs) target reuptake transporters
Monoamine Oxidase (MAO)

- Primarily located on mitochondrial outer membranes in neurons, glia, and other cells
- ~70% of neuronal monoamine oxidase is MAO-A
- MAO-A is more often implicated in mental disorders

MAO-A Levels Adapt to Substrate Availability

- The treatment strategy of increasing monoamine availability may be counterproductive due to compensatory increases in MAO-A

MAO is Elevated in MDD

- $[^{11}C]$-harmine positron emission tomography (PET) studies show 34% elevation in MAO-A
  - Most prominent in prefrontal cortex and anterior cingulate cortex
- A significant elevation in MAO-A activity is found in the hypothalamus of suicide victims

MAO is Elevated in MDD

SSRI Treatment Does Not Significantly Reduce MAO Levels

- The mismatch between monoamine levels raised by SSRI treatment and monoamine levels lowered by disease processes may contribute to a lack of response to SSRI treatment

MAO Remains Elevated During Recovery

MAO Elevation Predicts Depressive Relapse


Copyright © 2012 Neuroscience Education Institute. All rights reserved.
Modern Model of Extracellular Monoamine Loss During Major Depressive Disorder

Healthy

Untreated depression

Depression treated with an SSRI

Treatment resistance?
Risk of relapse?

Reactive Oxygen Species (ROS)

- MAO-A monoamine degradation produces ROS
- Accumulated ROS cause oxidative damage to mitochondria, leading to increased apoptosis
- Depressed patients show:
  - Decreased mitochondrial ATP production
  - Altered cerebral energy metabolism
  - Mitochondrial dysfunction
  - Signs of cell death and oxidative damage
- Some MAO inhibitors may be neuroprotective

Andreatza AC et al. Arch Gen Psychiatry 2010;67(4):360-8;
MAO Polymorphisms

- Both MAO-A and MAO-B are located on the X chromosome
- Two well-studied polymorphisms in the MAO-A gene
  - T941G
    - Single nucleotide polymorphism
  - MAOA-uVNTR
    - 30 bp upstream variable number tandem repeat in the promoter region
T941G

- T allele
  - Lower enzyme activity
- G allele
  - Greater enzyme activity
- The G/G genotype is associated with:
  - 75% greater MAO-A activity
  - A greater number of depressive episodes
  - Worse response to mirtazapine in females

MAOA-uVNTR

- Short 3 repeat allele
  - Lower expression of MAO-A

- Long 4 repeat allele
  - Higher expression of MAO-A
MAOA-uVNTR Long Allele

• The long allele is:
  – A risk factor for MDD
  – Linked to worse outcomes in adult females exposed to severe childhood stress
  – Associated with suicide in males with depression
  – Predictive of worse response to fluoxetine treatment in females

Child Abuse, MAO-A, and Mental Health

MAO-A and COMT

- Catechol-O-methyltransferase (COMT) degrades dopamine and norepinephrine
- The met/met COMT genotype is associated with a 75% decrease in COMT activity
- Increased peripartum depression in patients with the combination of COMT (met/met) and the long MAOA-uVNTR allele
- COMT met/met + long MAOA-uVNTR allele is associated with an increased risk of suicide attempt in males

Regulation of MAO-A Expression

- R1 is an upstream transcriptional repressor of the MAO-A gene
  - Binds to the MAO-A gene promoter
  - Turns off the expression of MAO-A

Regulation of MAO-A Expression

- Reduced R1
  - May contribute to MAO-A-mediated cell death and monoamine deficiency

- Postmortem R1 levels
  - Decreased by 37% in both treated and untreated patients with MDD
  - Decreased in suicide victims

Major depressive disorder is 2X more common in females

12-month prevalence
- 6.8% in women
- 3.4% in men

MDD has a higher heritability in women (42% vs 29%)
- Possibly due to incomplete X-inactivation

Symptom presentation
- Women: weight gain, hypochondriasis, somatic concerns
- Men: weight loss, alcohol dependence, substance abuse
Sexual Dimorphism of MAO

- Both testosterone and estradiol decrease MAO
  - Leading to greater 5HT
- The MAO-A gene is on the X chromosome
- The MAO-A gene has an androgen (testosterone) response element
- Incomplete X-inactivation may lead to an increased expression of MAO in females
  - Resulting in decreased 5HT
- MAO-A expression is regulated by a protein (SRY) produced from the Y chromosome

The Sex-Determining Region (SRY Gene)

- On the Y chromosome
- Acts as a molecular switch
  - Triggers a cascade of molecular and cellular events
  - Initiates the formation of male gonads
  - Prohibits events that lead to the formation of female gonads
SRY Regulation of MAO-A Gene Expression

Promoter

MAO-A Gene

X Chromosome

SRY Gene

Y Chromosome
Postpartum Depression

• Postpartum blues affects 70% of new mothers
• 13% of new mothers will develop postpartum depression (PPD)
• During the early postpartum period, brain MAO-A increases by 43%
• The rise in MAO-A follows the rapid decrease in estradiol
  – Estradiol levels drop 100- to 1000-fold following delivery

MAO is Elevated in Postpartum Depression

Monoamine Model of Postpartum Blues

- Pregnancy
- Delivery
- Days postpartum
  - 1
  - 2
  - 3
  - 4
  - 5

MAO-A levels in affect-modulating regions

Estradiol levels

Mood

Violence and Aggression

- Aggression and violent behavior are correlated with:
  - Males
  - High testosterone
  - Low 5HT activity
  - Low cortisol
  - Hyperactivity in the amygdala
  - Hypoactivity in the PFC
- Genetics account for ~50% of the risk for aggressive behavior

MAO-A: Warrior Gene?

• MAO-A gene expression is regulated by both testosterone and glucocorticoids
• MAO-A knockout mice and humans with an inactivating mutation in the MAO-A gene display increased aggression
• Males with the MAOA-uVNTR short allele have an increased risk for violent behavior
  – Especially subsequent to childhood maltreatment
  – The opposite is true for females

Sexual Dimorphism in the Relationship Between MAOA-uVNTR and Violence

Response to Increased Testosterone Depends on MAOA-uVNTR Genotype

- Testosterone may act on the MAO-A promoter
  - The promoter region contains the MAOA-uVNTR polymorphism

Summary

• One of the leading hypotheses of depression suggests that monoamine levels are reduced in MDD

• Increased degradation of monoamines by MAO-A may underlie the reduction of monoamines seen in MDD

• Current treatments for MDD are focused on reducing monoamine reuptake; however, this strategy does not address the underlying problem of MAO-A hyperactivity

• Polymorphisms in the gene for MAO-A and sexual dimorphism have been shown to influence the etiology, presentation, and treatment of MDD