Sleep and Psychiatric Disorders: Your Molecular Clock is Ticking

(page 281 in syllabus)

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Individual Disclosure Statement

Faculty Editor / Presenter

Stephen M. Stahl, MD, PhD, is an adjunct professor in the department of psychiatry at the University of California, San Diego School of Medicine, and an honorary visiting senior fellow at the University of Cambridge in the UK.

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Learning Objectives

• Recognize the relationship between circadian rhythms and psychiatric disorders

• Understand the pharmacological basis of circadian rhythms in depression

• Review the clinical evidence of therapeutic approaches to resetting circadian rhythms in depression and thus improve the symptoms of depression
Pretest Question 1

Anne is a 34-year-old patient with major depressive disorder. Currently, her chief complaint is that she is not sleeping well. Patients with depression often have altered circadian rhythms, as is evident by:

1. Sleep-wake phase changes
2. Altered melatonin levels
3. Altered body temperatures
4. Changes in neurogenesis
5. Altered cortisol levels
6. All of the above
Pretest Question 2

Michael is a 45-year-old patient with bipolar disorder. Genetic testing would likely reveal polymorphisms or abnormal expression of which clock genes?

1. Per
2. Cry
3. Both of the above
Sasha is a 58-year-old patient with a history of depression. She is currently taking agomelatine and is undergoing estrogen replacement therapy for perimenopausal symptoms. At the present time, she is relatively free of depressive symptoms, likely due in part to:

1. Binding of agomelatine to melatonin receptors in the SCN
2. Binding of agomelatine to 5-HT$_{2C}$ receptors in the SCN
3. Binding of estrogen to estrogen receptors in the SCN
4. All of the above
Zeitgebers

External cues to synchronize circadian rhythms

• Light
• Melatonin
• Eating and drinking patterns
• Social interactions

Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract

Pineal Gland (melatonin)
Suprachiasmatic Nucleus (SCN)

Retinohypothalamic Tract

Pineal Gland
(melatonin)
Receptors Expressed in the SCN

Melatonin receptors

5-HT$_{2C}$ receptors

Estrogen receptors

Circadian Rhythmic Expression of MT₁ and 5-HT₂C Receptors

5-HT$_{2C}$ Receptors Affect Melatonin Release


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5-HT\textsubscript{2C} Receptors Affect Melatonin Release

5-HT$_{2C}$ Receptors Affect Melatonin Release

5-HT$_{2C}$ Receptors Affect Melatonin Release

Melatonin Excretion

- 5-HT$_{2C}$ antagonist
- Control

A Broken Circadian Clock

- Phase changes
- Changes in neurogenesis
- Altered body temperature
- Altered melatonin
- Altered cortisol

Depression and Other Mood Disorders

Desynchronization of the Molecular Clock
Desynchronization of the Molecular Clock

Shift work
Desynchronization of the Molecular Clock

Shift work

Clock genes

- ROR
- Bmal1
- Cry
- Period
- CLOCK
- REV-ERBα

Desynchronization of the Molecular Clock

Shift work

Clock genes

- ROR
- Bmal1
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Desynchronization of the Molecular Clock

Shift work

Mutated Clock genes
Desynchronization of the Molecular Clock

Shift work

Mutated Clock genes

Neurotransmission

prefrontal cortex

NE
DA

GABA interneurons

brainstem neurotransmitter centers

NE
5-HT
5-HT
5-HT
DA
Desynchronization of the Molecular Clock

Shift work

Mutated Clock genes

Impaired Neurotransmission

prefrontal cortex

NE

DA

GABA interneurons

5-HT

5-HT

5-HT

brainstem neurotransmitter centers
Diseases Linked to a Broken Clock

Depression

Schizophrenia

Cancer

metabolic Syndrome

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90% of Depressed Patients Complain of Poor Sleep Quality

Healthy Control

Depression “Phase Delay”

Severity of Depression Correlates With Severity of Phase Delay

Circadian Rhythm of Neurogenesis

Hippocampal neurogenesis

Learning and memory

Decreased Neurogenesis in Depression

- Brain-derived neurotrophic factor (BDNF), a protein that increases neurogenesis, is decreased in patients with depression.
- Hippocampal volume is decreased in patients with depression.
- Patients with depression exhibit prominent deficits in memory.
- Cognitive capacity depends on the function of the hippocampus.
- Chronic or severe stress is strongly associated with depression and correlates with the disruption of hippocampus-dependent memory.

Physiological Measurements of Circadian Rhythms Are Altered in Depression

Transcription Factors
Involved in the Molecular Clock

- ROR
- REV-ERBα
- PER
- CRY
- CLOCK
- Bmal1

Heterodimers

DNA → Promoter → Gene
CLOCK (circadian locomotor output cycles kaput)

BMAL1 (brain and muscle ARNT-like-1)

PER (period)

CRY (cryptochrome)

REV-ERBα

ROR (retinoic acid-related orphan receptor)

E Box response element

ROR/REV-ERBα response element
CLOCK (circadian locomotor output cycles kaput)
BMAL1 (brain and muscle ARNT-like-1)
PER (period)
CRY (cryptochrome)
REV-ERβ
ROR (retinoic acid-related orphan receptor)
E Box response element
ROR/REV-ERβ response element
CLOCK (circadian locomotor output cycles kaput)
BMAL1 (brain and muscle ARNT-like-1)
PER (period)
CRY (cryptochrome)
REV-ERBα
ROR (retinoic acid-related orphan receptor)
E Box response element
ROR/REV-ERBα response element
<table>
<thead>
<tr>
<th>Clock Gene</th>
<th>Disorder</th>
<th>References</th>
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<tbody>
<tr>
<td>Bmal</td>
<td>Bipolar</td>
<td>Mansour et al. 2006; Nievergelt et al. 2006.</td>
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<tr>
<td>Clock (or its homolog, NPAS)</td>
<td>Bipolar</td>
<td>Benedetti et al. 2003; Soria et al. 2010.</td>
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<td>Depression</td>
<td>Soria et al. 2010.</td>
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<td>Schizophrenia</td>
<td>Takao et al. 2007.</td>
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<td>Seasonal affect disorder</td>
<td>Johansson et al. 2003; Partonen et al. 2007.</td>
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Clock Genes Are Altered in Depression

Healthy Control

Patient With Depression


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Fluoxetine Alters Expression of Clock Genes

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Does a Broken Circadian Clock Lead to Depression?

- Circadian rhythms regulate sleep-wake cycles; altered sleep cycles can be considered phase delayed, and severity of depression correlates with severity of phase delay
- Circadian rhythms regulate neurogenesis, and there is decreased neurogenesis in depression
- Master clock genes in the SCN facilitate circadian regulation of physiological processes and are altered in depression
- \( \text{MT}_1 \) and \( 5-\text{HT}_{2\text{C}} \) receptors are expressed in the SCN and oscillate with circadian rhythmicity
- \( 5-\text{HT}_{2\text{C}} \) receptors are involved in the modulation of circadian rhythms
ANTIDEPRESSANT TREATMENTS THAT TARGET CIRCADIAN FUNCTION

• Agomelatine
• Melatonin and agonists
• TK-301
• Neu-P11
• Estrogen
• Chronotherapies
Antidepressants and Novel Pharmacology

Tricyclic Antidepressants

Serotonin Norepinephrine Reuptake Inhibitors (SNRI)

Serotonin Selective Reuptake Inhibitors (SSRI)

Agomelatine

A Multifaceted Approach to Depression Through Resynchronization of Circadian Rhythms

- Normalization of sleep-wake phase
- Increasing BDNF and hippocampal neurogenesis
- Increasing intracellular signaling for neurogenesis and sleep-wake phase
- Decreasing stress-induced glutamate release
- Increasing NE in the frontal cortex and the hippocampus and DA in the frontal cortex
- Low rate of side effects
Darkness-Induced Phase Delay

Darkness-Induced Phase Delay

Agomelatine Promotes Phase Advance

Agomelatine Promotes Phase Advance

Melatonergic Agonist Properties of Agomelatine

Suprachiasmatic Nucleus (SCN)

Pineal Gland

Depression
Melatonergic Agonist Properties of Agomelatine

Suprachiasmatic Nucleus (SCN)

Pineal Gland

Depression

Agomelatine

SHT2C
MT2

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Brain-Derived Neurotrophic Factor (BDNF)

• Supports survival of existing neurons
• Encourages neurogenesis
• BDNF is decreased in patients with depression

Increases in BDNF in the Prefrontal Cortex

The unique synergy of melatonergic plus 5-HT$_{2C}$ antagonism is necessary to increase BDNF.

Stimulation Ventral Hippocampal Neurogenesis

After 3 Weeks of Treatment

vehicle  agomelatine

*p<0.05

Cell Survival After 21 Days in Ventral and Dorsal Hippocampi


* p<0.05 (two-way ANOVA)
Serotonin Inhibits Dopamine and Norepinephrine Release via 5-HT$_{2C}$ Receptors

Agomelatine Releases Norepinephrine and Dopamine in the Frontal Cortex

Agomelatine Releases Norepinephrine and Dopamine in the Frontal Cortex

Agomelatine releases NE and DA in the frontal cortex.

- NE release
- DA release

Agomelatine Releases Norepinephrine and Dopamine in the Frontal Cortex


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Relapse Prevention Study

Proportion Remaining Without Relapse

Agomelatine (n=165)

Placebo (n=174)

Weeks of Treatment


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Agomelatine Significantly Decreases Depression as Early as 1 Week

At week 1, significance from placebo was p<0.01; it remained at p<0.05 for 8 weeks.

Agomelatine Clinical Studies: Does Resetting the Circadian Clock Treat Depression?

• Clinical efficacy of agomelatine was demonstrated in 6 studies with placebo
  – Decreased depression
  – Prevented relapse
  – Demonstrated efficacy as early as week 1

• Agomelatine shows favorable efficacy in treating depression versus:
  – Venlafaxine
  – Fluoxetine
  – Sertraline

• Agomelatine has few side effects and no discontinuation symptoms
Melatonin as Treatment for Depression

- Some preliminary data suggest association of SNPs in melatonin MT$_2$ receptors with depression
- Melatonin given in late afternoon/early evening
  - Advances circadian clock
    - Earlier falling asleep and waking
- Melatonin given in the morning
  - Delays circadian clock
    - Later falling asleep and waking
- Short ½-life
- Prolonged-release melatonin improves sleep but not depression
- A preliminary study suggests antidepressant effects of the melatonin agonist ramelteon

TIK-301

- Melatonin receptor agonist
- Also has serotonin 5-HT$_{2B}$ and 5-HT$_{2C}$ antagonism
- Recently finished Phase II clinical trials
• Melatonin agonist
• Also has affinity for:
  – Serotonin 5-HT$_{1A}$
  – Serotonin 5-HT$_{1B}$
  – Serotonin 5-HT$_{2B}$
• Rodent studies show:
  – Promotion of sleep
  – Anxiolytic effects
  – Antidepressant effects

Estrogen

- Estrogen receptors are located in the SCN
- Estrogen decreases Cry2 mRNA levels in the SCN
- Estrogen increases spontaneous firing frequency (SFF) of SCN neurons
  - This effect is blocked by the ER antagonist ICI
- Estrogen also modulates serotonin neurotransmission and has been shown to have antidepressant effects

Fatehi M, Fatehi-Hassanabad Z. Neuropsychopharmacol 2008;33:1354-64;
Chronotherapies

• Controlled exposures to environmental stimuli that act on biological rhythms
• Bright light therapy
• Sleep deprivation
• Sleep phase advance therapy
Bright Light Therapy

• Exposure to light alters circadian rhythms and suppresses melatonin release

• 10,000 lux (bright light) for 30 min/day

• Must be timed with patient’s circadian phase of melatonin secretion
  – Administer light 7.5-9.5 hrs after evening melatonin secretion
  – Approximation of melatonin secretion can be determined using the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)

• Useful as a non-pharmacological intervention during pregnancy

Bright Light Therapy for Depression

- Rapid onset of antidepressant action
- Hastens the effects of antidepressant drugs
- Antidepressant effects mediated through eyes
  - Extraocular administration shows no antidepressant benefits
- Good for bipolar depression but may precipitate mania
- Dawn simulation therapy
  - Slow incremental light signal at the end of the sleep cycle
- Side effects are rare
  - Headaches, eyestrain, nausea, and agitation

Bright Light Therapy Is Fast and Effective

- BLT may be as effective as pharmacological antidepressant treatment

Sleep Deprivation Therapy

- 36 hrs of deprivation
- Antidepressant effects within hours
- Decreases activity of 5-HT$_{2C}$ receptors
- Response rates are similar to antidepressants (50-80%)
  - Response is influenced by some of the same polymorphisms
    - 5-HTTR (serotonin transporter), 5-HT$_{2A}$, COMT, GSK-3β
- Improvement doesn’t last unless combined with:
  - Other chronotherapies
  - Lithium
  - Antidepressants
- Contraindicated for patients with epilepsy
  - Sleep deprivation increases risk of seizures in patients with epilepsy

Sleep Phase Advance Therapy

- Advances timing of sleep-wake cycle
- Synchronizes sleep with other biological rhythms
- Improves effects of antidepressants
- Also effective as monotherapy
Summary

• Many biological processes are regulated by circadian rhythms

• Circadian rhythm dysfunction has been linked to several psychiatric illnesses, including depression

• The circadian rhythm involves molecular regulation by clock genes; polymorphisms in these clock genes have been associated with many psychiatric disorders, and their expression is often altered by effective treatments

• Antidepressants that include modulation of circadian rhythms as part of their mechanisms of action (such as agomelatine) may be most effective

• Non-pharmacological chronotherapies may also be useful for fast relief of depressive symptoms