Circadian and homeostatic control of sleep: impacting the health of shift work nurses.

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Outline

- Background – circadian misalignment
- Overarching hypothesis
- When should shift workers sleep?
- When should shift workers eat?
- Conclusion and long-term goals
Circadian misalignment

Background
Circadian oscillators

From Reppert, S.M. & Weaver, D.R. (2002), *Nature*

From Young, M.E. & Bray, M.S. (2008), *Sleep Med*
Circadian regulation: Input, mechanism, output

- **Input** pathways from photoreceptors to the circadian pacemaker (SCN).
- **Mechanism** involves RHT entrainment pathways to the SCN.
- **Output** pathways from the SCN to secondary oscillators (REM-NREM) and overt rhythms.
Two process model of sleep

- **C**: circadian rhythm (SCN)

- **S**: homeostatic property:
  - accumulation of sleep-promoting substance (?)

- **sleep pressure**:
  - vertical distance between the S and C curves
Circadian alignment

- **Cortisol** • Peaks in the morning
- **Melatonin** • Peaks at night
- **Core Body Temperature** • Peaks in the day

**Behavior** (Meal Timing & Sleep Timing) • **Peripheral Clocks**

- **Leptin** • Increases throughout day with feeding
- **Glucose** • Postprandial increase
- **Insulin** • Postprandial increase
Desynchronization - shiftwork

Foster, R.G. and Wulff, K. (2005), Nature Rev Neurosci
Preventing circadian misalignment

Hypothesis
Hypothesis

- Night shift work results in metabolic impairment through circadian misalignment of sleep/wake cycles, peripheral clock gene regulation, rhythmic metabolic signaling, and endocrine rhythms.
Why nurses?

- Typical schedule: three 12-h shifts with several days off
- Most nurses (97%) prefer to switch to being awake during the day on days off (Gamble, et al 2011)
- Results in perpetual jet lag!

- Administered the Standard Shiftwork Index (SSI) to ~400 nurses employed at UAB Hospital

“Your’re in a hospital, Nurse Hill. If you collapse from exhaustion, the emergency room is just down the hall.”
UAB Nurse Survey: The downside of night shift …

“Tired all the time”

“Sleep Deprivation”

“No time to work out”

“Lack of social life”

“No enough time with family”

“It’s exhausting”

“Gaining weight”

“I miss daylight”

“No energy”

“My body aches”

“Inability to eat at regular intervals”

“I feel like a zombie all of the time”

“I’m sometimes not sure when to eat! It sounds silly, but I don’t always feel very hungry before I can feel myself getting ‘fuzzy’ from needing food.”
Standard Shiftwork Index: Quality of life in hospital shift work nurses

- Chronic Fatigue (from SSI)
  - 12-h Day: 25 ± 5
  - 12-h Night: 30 ± 5

- Quality of Life Disturbance from Shift Work (from SSI)
  - 12-h Day: 8 ± 2
  - 12-h Night: 10 ± 2

- Social/Domestic Satisfaction (from SSI)
  - 12-h Day: 50 ± 10
  - 12-h Night: 55 ± 10
Defining circadian misalignment in shift work nurses

Activity Rhythms (Actigraphy watches)
Core body temperature (Ingestible telemetry)
Sleep and Food Diaries

24-h stay in CCTS CRU beds:
- Plasma metabolites
  - Cortisol/Melatonin
  - Leptin/Insulin
- Circadian “clock gene” transcripts in mononuclear cells
Sleep-Wake Rhythms – Actigraphy Data
Core Body Temperature – Day 9

Day Shift – Off Day

Night Shift - Off Day
Misalignment of endocrine factors

Day Off from Day Shift (Double Plotted)

Day Off from Night Shift (Double Plotted)

Dashed = Cortisol
Solid = Melatonin
Circadian Clock Gene Expression (PBMCs)

Preventing circadian misalignment

When should shift work nurses sleep?
Biological Clocks Questionnaire (BCQ): Defining off-shift sleep strategies

<table>
<thead>
<tr>
<th>Day A</th>
<th>Day B</th>
<th>Day C</th>
<th>Day D</th>
<th>Day E</th>
<th>Day F</th>
<th>Day G</th>
<th>Day H</th>
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<tbody>
<tr>
<td>Off</td>
<td>Off</td>
<td>Off</td>
<td>Off</td>
<td>Work</td>
<td>Work</td>
<td>Off</td>
<td>Off</td>
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</table>

Night Stay

Nap Proxy

Switch Sleeper

No Sleep

Incomplete Shifter

Adaptation of sleep

Some sleep strategies are worse than others …
Sleep Strategies: Total Sleep Disturbance

Between Night Shifts

Red = Significantly different from Switch Sleeper ($p < 0.05$).

On Days Off
Summary of strategy comparisons

- Maladaptive strategies (Nap Proxy, No Sleep):
  - 43% take anti-depressants (compared to 24%; p < 0.01)
  - Greater sleep debt
  - Earlier chronotype (e.g., more likely to be a ‘lark’ instead of a ‘night owl’)
  - Increased cardiovascular index scores (higher = > severity)
  - ~40% are likely to have digestion difficulty (compared to 20%; p < 0.05)
Sleep Strategy – General Health

Red = Significantly different from Switch Sleeper ($p < 0.05$).
Metabolic syndrome risk in shift workers


http://naturalmedicineclinic.org/services/metabolic-syndrome/
Preventing circadian misalignment

When should shift work nurses eat?
Food consumed at night predicts Metabolic Syndrome risk factors for night shift nurses

<table>
<thead>
<tr>
<th>Shift Type</th>
<th>Age</th>
<th>BMI</th>
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<tbody>
<tr>
<td>Day Shift (N=8)</td>
<td>Mean</td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>2.6</td>
</tr>
<tr>
<td>Night Shift (N=9)</td>
<td>Mean</td>
<td>30.3</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>4.0</td>
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Table 3. Results of regression analysis, indicating significant substrate consumption associations with CMS risk factors.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>9am-9pm</th>
<th>9pm-9am</th>
<th>9am-9pm</th>
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<tbody>
<tr>
<td>Fasting glucose</td>
<td>total grams</td>
<td>fat</td>
<td>total grams</td>
<td>fat</td>
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<tr>
<td>Fasting TG</td>
<td>total grams, protein</td>
<td>fat</td>
<td>total grams, protein</td>
<td>fat</td>
</tr>
<tr>
<td>Total Cholesterol</td>
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<td>total grams</td>
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<tr>
<td>LDL</td>
<td>total grams</td>
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</tr>
<tr>
<td>HDL</td>
<td>sugar * carbs *</td>
<td>protein</td>
<td>carbs *</td>
<td>protein</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>total grams, fat</td>
<td>total grams, fat, sugar</td>
<td>fat</td>
<td>fat</td>
</tr>
<tr>
<td>Systolic BP</td>
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<td>fat</td>
<td>fat</td>
<td>fat</td>
</tr>
</tbody>
</table>

Molzof, H., unpublished results
Conclusions and Future Directions?

Night Shift induces misalignment of sleep-wake rhythms with:
- Central-clock controlled rhythms – core body temperature, cortisol and melatonin
- Misalignment persists even on days off!
- Need to define circadian misalignment for all of the sleep strategies

Future Directions
- Determine eating strategies for adaptation to night shift – implications for cardiometabolic syndrome?
  - Total grams consumed during the night of a night shift is correlated with increased metabolic syndrome risk factors

Intervention:
- Avoid “No Sleep” strategies and daily napping
- Educational – provide a “night shift survival guide” for new shift workers
- Shift schedule changes?
Acknowledgements

- **Funding:**
  - UAB Center for Clinical and Translational Science (CCTS) Grant Number UL1TR000165
  - UAB Department of Vision Sciences
  - UAB Comprehensive Diabetes Center
  - UAB Department of Psychiatry Office of Clinical Research

- **Collaborators:**
  - Connie White-Williams, Pat Patrician, Molly Bray
  - Martin Young
  - Physicians: Dr. Taylor Preston, Dr. Li Li
  - CRU Staff (T.J. Griffie, Jolene Lewis, Felicia Hattaway, Jeffrey Edberg laboratory, Betty Darnell)
  - CPM Staff (Sherer Thomson, Russell Johnson, Leah Pickett, Roberta May)

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