Sleep Control, GPCRs, and Glucose Metabolism

By: Nicholas Agnello, Bryan Cook, Nina Cheikh, Adrian Martinez, Nana Pearson, Jasmine Ramirez, Monique Warren
Schedule

1. Intro to Refresh
2. Recap of Sleep and Type 2 Diabetes
3. Sleep quality and Glucose metabolism
4. Sleep disturbances affect glucose tolerance via alterations to Melatonin and Orexin
5. Melatonin and Orexin
6. Drugs as they relate to sleep and glucose metabolism
7. Drugs and Orexin
8. Conclusion
Lets Refresh

Last week we learned that:

“Evidence suggests that sleep may modulate eating”

“Eating may modulate sleep”
Refresh

Modern Lifestyles:
Refresh
Disrupts Circadian Rhythm → Causes Sleep Disruption
Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2015

Percentage with Diabetes

Number with Diabetes

Year

1958 61 64 67 70 73 76 79 82 85 88 91 94 97 00 03 06 09 12 15

Percentage with Diabetes

Number with Diabetes (Millions)

0 5 10 15 20 25

Recap of Sleep

- Sleep is dictated by the circadian rhythm
  - Circadian rhythm is the 24 hour internal clock that dictates sleepiness and wakefulness
  - Also known as sleep/wake cycle
- Non-REM vs. REM Sleep
  - Non-REM sleep consists of 4 stages:
    - Stage 1 - light sleep
    - Stage 2 - light sleep, body temperature begins to drop
    - Stage 3 - slow wave
  - REM Sleep
    - Rapid eye movement
    - Brain in most active during REM, therefore dreams are most common in this state

When you say you're going to take an hour nap and wake up 9 hours later
Sleep and Type 2 Diabetes

- Studies have shown that disturbances in sleep/wake cycle can cause type 2 diabetes (T2D)
- Both the quantity and quality of the sleep cycle matter in relation glucose homeostasis
- Patients with T2D shown to have different sleep cycles than when compared to healthy individuals
Sleep Quantity

- Study done on nurses showed that shift work affect their amount of sleep and subsequently lead to higher risk of T2D later in life.
- In healthy human subjects:
  - Loss of sleep for one night showed induced insulin resistance
    - Paper does not say how long this lasted for
  - Restriction of sleep from 8.5 hours to 5.5 hours over a 2 week period caused glucose intolerance but did not affect insulin secretion
- Study done on patients with T2D and long or short sleep times showed elevated glucose and HbA1c levels
Sleep Quality

● Decrease in slow wave sleep:
  ○ In healthy human subjects, insulin resistance was caused by acute suppression of slow-wave sleep
  ○ In patients with T2D, the amount of slow-wave sleep measured decreased
  ○ Associated with thickening of the intima of the carotid arteries (linked with atherosclerosis)

● Apnea and Hypopnea in REM vs. Non-REM Sleep
  ○ During REM sleep, apnea and hypopnea are associated with insulin resistance
  ○ During non-REM sleep, apnea and hypopnea are associated with glucose intolerance
  ○ In REM sleep in patients with T2D, chronic glycemic control was adversely associated with obstructive sleep apnea while the same effects were not seen in non-REM sleep
Conclusion of Sleep and T2D

- Both quality and quantity of sleep are related to the development of glucose dysregulation.
- Not only is the progression of T2D associated to the sleep cycle, people with T2D are shown to have differences in sleep cycles.
- Main takeaway: sleep is an important aspect of your health and decisions you make now can have bigger health impacts later on.
Sleep Disruption and Glucose Metabolism

Hormones?
Sleep Disturbance?
Genetics?
Stress?
Body Composition?
Autonomic Nervous System (ANS) Balance

Sympathetic and parasympathetic oscillations form the sympato-vagal balance.

Sleep Disturbances Results in:

- Lower threat discrimination threshold
- Dramatic reduction in heart rate variability
- Reduction in vagal control
- Parasympathetic withdrawal

Result: Excess activation of Stress Response i.e. Sympathetic Dominance
Hormonal Profile Imbalance

Hypothalamic–Pituitary–Adrenal (HPA) produces CNS control/ regulation of glucose

Sleep Disturbances result in HPA:

- Increased **Glucocorticoids**, Adrenocorticotropic hormone, Catecholamines
- Increased **Ghrelin**
- Decreased **Leptin**

Result: Peripheral insulin resistance and decreased glucose effectiveness, **promotion of adiposity**
Adipose Tissue

Excess adipose tissue (Obesity) reduces insulin sensitivity/ hepatic glucose uptake

Sleep disturbances promote adiposity via:

- Increasing VTA activation to high glycemic foods
- Increasing average caloric consumption
- Decreasing average energy expenditure

Result: Generates both tissue-specific and gene-specific changes in expression levels of circadian clock and homeostatic genes
Gene Expression

Glucocorticoid receptors (GRs) are highly expressed in the sleep-wake-related, and endocrine brain stem nuclei, and affect gene expression.

- Sleep Disturbance
  - Sympathetic Dominance
  - Hormonal Imbalance
  - Increase in Adiposity
  - Circadian Change
  - Homeostatic change

Glucose Metabolism
References


Wang, Zi-Jun et al. “Glucocorticoid receptors in the locus coeruleus mediate sleep disorders caused by repeated corticosterone treatment” *Scientific reports* vol. 5 9442. 24 Mar. 2015, doi:10.1038/srep09442


Sleep disturbances affect glucose tolerance via alterations to Melatonin and Orexin.
Melatonin Intro

- Hormone produced in the pineal gland (only hormone known to be synthesized there!)
- Released at night (in darkness)
  - Regulated by the Suprachiasmatic nucleus (SCN) of the hypothalamus
- Melatonin’s role in mammals (circadian rhythm):
  - Sleep timing
  - Blood pressure regulation
  - Seasonal reproduction
- Melatonin secretion declines with age
  - Peak nocturnal levels at age 1 to 3
  - Plateaus to a level maintained throughout early adulthood
  - Steady noticeable decline thereafter
  - Peak nocturnal concentrations of 70-year-olds roughly 25% of young adult levels
    - Possibly due to age-related calcification of Pineal gland + loss of secretory tissue
Circadian Rhythms

- High alertness: 10:00
- Highest testosterone secretion: 09:00
- Melatonin secretion stops: 07:30
- Sharpest rise in blood pressure: 06:45
- Lowest body temperature: 04:30
- Deepest sleep: 02:00
- Noon: 12:00
- Best coordination: 14:30
- Fastest reaction time: 15:30
- Greatest cardiovascular efficiency and muscle strength: 17:00
- 18:00: Highest blood pressure
- 19:00: Highest body temperature
- 21:00: Melatonin secretion starts
- Midnight: 00:00
Circadian Rhythms + Social Media!

- Most upbeat tweets: 10:00
- Most people check their phone for the first time: 07:30
- Most emails read: 06:00
- Least Twitter usage: 04:30
- Least Facebook usage: 02:00
- Noon: 12:00
- Most Facebook usage: 15:30
- Most tweets re-tweeted: 18:00
- Most "likes" on Facebook: 21:00
- Most emotional tweets: 22:30
- Midnight: 00:00
Melatonin’s Other Functions

- Several other functions
  - Immune Defense
  - Neurogenesis
  - Inhibition of proinflammatory cytokines
  - Vasomotor control
  - Regulation of Metabolism
  - Cytoskeleton Effects
  - Oncostatic Properties (anti cancer)
  - Antioxidative Defense
SCN/Pineal Gland Pathway to Synthesis

- At night/during dark phase cycles, circadian signals are transmitted from the SCN, which contains our “biological clock”
- Light signal reaches the SCN via the Retinohypothalamic Tract (RHT)
  - Suprachiasmatic nucleus (SCN) > Paraventricular hypothalamic nucleus (PVN)
  - PVN > Intermediolateral Nucleus (IML) in the spinal cord
  - IML > Superior cervical ganglia (SCG)
  - SCG > Pineal Gland
  - Melatonin!!!
Melatonin/Circadian Rhythm

- **However,**
  - not just due to light-dark cycle
  - Secretion does not phase-shift right when the light schedule is altered
  - Cyclic endogenous signals in the SCN

- **Light at night can lead to melatonin suppression**
  - Even 20 minutes of low room light is enough to experience suppression!
  - 1 hour of extra light roughly equivalent to a 1 hour jet lag!

- **Circadian rhythm system can adjust roughly 1 hour per day**

- **Events resulting in circadian rhythm adjustment:**
  - Daylight Savings
  - Time zone changes (travel)
  - Shiftwork
  - School and School work!!!
    - Melatonin supplementation to be discussed later!!
Melatonin Synthesis

- Tryptophan > 5-Hydroxytryptophan (5HTP)
  - Tryptophan hydroxylase
- 5HTP > 5-Hydroxytryptamine (Serotonin/5HT)
  - Aromatic L-amino acid decarboxylase
- 5HT > N-Acetylserotonin
  - Arylalkylamine N acetyltransferase (AANAT) (Enzyme)
  - Serotonin-N-acetyltransferase (SNAT)?
- N-Acetylserotonin > N-acetyl-5-methoxytryptamine (Melatonin)
  - hydroxyindole-O-methyltransferase (HIMOT) (Enzyme)
- Tryptophan’s uptake into pineal unaffected by diet
  - No competition from other circulation neutral amino acids
  - WHY?
    - Pineal is located outside the BBB! (Located between the cerebral hemispheres)
Melatonin Receptor Activation

- Melatonin binds to three different G-Protein Coupled Receptors:
  - MT1 (AKA melatonin receptor 1A)
    - SCN, Pituitary (pars tuberalis) and cardiac blood vessels
  - MT2 (AKA melatonin receptor 1B)
    - SCN, Retina and hippocampus
  - MT3
    - Various peripheral organs
  - MT1 and MT2 are the receptors involved in “circadian rhythm-regulated sleep control”
  - Specific pathways of MT3 signal transduction need more research
Melatonin Receptor Activation Continued

- MT1 and MT2 receptor activation can stimulate phospholipase C along with several ion channels, and suppresses cAMP production
- MT2 plays a role in inhibiting LTP in the hippocampus
- MT1 receptors in the SCN
  - Melatonin inhibits SCN neurons at night
  - Sleep promotion
- MT2 in the SCN
  - Modulates SCN’s circadian rhythm
- MT1 and MT2 receptors largely decrease activity when exposed to abnormal levels of melatonin
  - Desensitization
Melatonin Supplementation

- More is not always better!
  - As noted in the last slide, too high of doses can lead to receptor desensitization
  - 10, 20, 40, and 80mg of melatonin raised plasma concentrations to a minimum of 5000pg/ml
    - Normal nocturnal range: 100-200pg/ml
    - Also, reduction of body temperature
- Physiologic doses of 0.1 to 10mg also studied
  - Doses as low as 0.1 to 0.3mg led to plasma levels similar to nocturnal range
  - Decrease in sleep latency
  - Increase in sleep duration
  - Increase in self-reported sleepiness and fatigue
  - No reduction of body temperature
- Pharmacokinetics
  - Efficacy of oral melatonin can depend on the lipid-solubility of its accompanying ingredients
    - Corn oil + 0.05mg led to plasma levels peaking around 118pg/ml
    - Microcrystalline cellulose + 0.3mg led to peak levels of 105pg/ml (but for a longer period)
Melatonin and Metabolism

- The effects of melatonin on glucose metabolism is rather controversial
- Regulates energy homeostasis via effects on endogenous circadian rhythms
  - Morning and evening administration of melatonin led to reduced glucose tolerance in young, healthy women
- Chronic oral administration in T2D rats prevented:
  - Excessive body weight gain
  - Hyperglycemia
  - Hyperinsulinemia
  - Hyperlipidemia
- Also, improved insulin sensitivity and secretion
  - Increased serum levels of adiponectin, decreased serum levels of free fatty acids (FFAs)
    - Attributable to insulin resistance in obesity and T2D
      - Suggestive that “melatonin exerts beneficial effects on impaired glucose regulation in obesity and/or T2D”
Melatonin and Metabolism Continued

- Studies have shown both increases and decreases in insulin secretion post treatments with melatonin
  - Works by reducing cytosolic cAMP and/or cGMP levels
- Increase in melatonin-induced inhibition of insulin release due to an increase in MT2 receptor expression in humans with diabetes risk variant MTNR1B
- In contrast, treatments with melatonin stimulated insulin secretion shown in the pancreas of rats in vivo
  - Ameliorated hyperglycemia via increased insulin secretion and facilitation of β cell regeneration + proliferation in streptozotocin-induced diabetic rats
- Acute use of melatonin in the INS-1 pancreatic β cell line inhibits glucose-stimulated insulin secretion
- Prolonged use of melatonin enhanced insulin secretion from β cells, stressed islets from nondiabetic humans, and islets from T2D patients
Melatonin Summary

- Melatonin has a vast array of effects on bodily functions, but is most known for its role in promoting sleep.
- Mainly synthesized in the pineal gland, which is located outside of the BBB.
- If taking supplements, consider the lipid solubility of ingredients.
- Low dose supplements can produce more desirable effects than massive doses.
- Synthesized from Tryptophan.
- Tightly linked to the SCN and circadian rhythm.
- Affects MT1, MT2, and MT3 GPCRs.
- Efficacy of melatonin dependent on timing, dose, and duration of administration, as well as genetic background of subjects.
- Benefits of melatonin on glucose metabolism are controversial.
Melatonin References


Wurtman, R.J. Physiology and Clinical Use of Melatonin.
Orexin Introduction

- Also known as hypocretin, is a neuropeptide that regulates arousal, wakefulness, and appetite.
- Two types of orexin peptide from preproorexin
  - Orexin-A (hypocretin-1)
    - Binds to both OX$_1$ and OX$_2$
  - Orexin-B (hypocretin-2)
    - Binds mainly to OX$_2$
- Two types of G-protein coupled orexin receptors
  - OX$_1$
  - OX$_2$
Orexin & Wakefulness

Sleep-wake cycles are typically entering to environmental cycles of day and night, or rather light from dark from a visual input.

- As the sun rises, retinal ganglion cells are excited by light and synapse directly on the suprachiasmatic nucleus (SCN), the master clock of the body that generates the circadian rhythm.
- During the day, when the SCN is excited by light it inhibits the pineal gland (PG), stopping it from releasing the sleep promoting hormone melatonin.
- The excited SCN also inhibits the VLPO thus disinhibiting the rostral reticular formation (RF).
- Orexin neurons in the lateral hypothalamic area (LHA) then release orexin on their various targets in the rostral RF, and this excitation further inhibits the VLPO repressing sleep even more.
- The neurotransmitters (DA, 5HT, & NE), released by these nuclei (VTA, RN, TMN, & LC) of the RF, travel to the thalamus and break the slow delta rhythms that are characteristic of deep sleep.
- Fast rhythms of the cortex increase and the body is induced into a state of wakefulness and arousal.
Orexin & Wakefulness Visual Summary
Orexin Deficits

- Orexin receptor mutation causes narcolepsy
  - **Narcolepsy**: A sleep disorder characterized by excessive sleepiness, sleep paralysis, hallucinations, and, in some cases, episodes of cataplexy (partial or total loss of muscle control, often triggered by a strong emotion such as laughter).

- Narcolepsy caused by orexin deficiency has been shown to be accompanied by obesity and glucose intolerance in humans and animals
  - Also accompanied by energy imbalance, such as decreased energy intake and increased BMI, leading to increased risk of T2D

The number of hypocretin-producing neurons in the brain is markedly reduced in the brains of people with narcolepsy.
Orexin, Brown Fat Activation & Obesity

- Typically, obesity is associated with overeating and orexin is an appetite-inducing neuropeptide
  - Lack of OX reduces energy intake in OX-null mice, however, their susceptibility to rapid weight gain is surprising

- Wild-type rodents
  - Transition from low to high-fat diet was associated with and elevation in metabolic rate

- OX-deficient rodents
  - Lack this regulatory mechanisms as they fail to elevate their metabolic rate when they transition to a high fat diet ➔ rapid weight gain in OX-null mice
  - Obesity in orexin (OX) knockout mice is a result of inability of brown preadipocytes to differentiate into brown adipose tissue (BAT), thus reducing BAT thermogenesis and leads to dampening of energy expenditure.
Orexin & Glucose Homeostasis

- Orexin deficient mice showed to develop glucose intolerance and insulin resistance with aging and severe obesity on a high-fat diet
- OX2R-knockout mice also showed glucose intolerance
  - Transgenic mice overexpressing orexin were protected from abnormal body weight gain and glucose intolerance on a high-fat diet
- OX is required for the maintenance of glucose homeostasis
On The Brightside ...

- BAT differentiation **can** be restored in these knockout mice through injections of OX during gestation
Orexin & Glucose Metabolism

● Role of OX is the regulation of insulin and leptin sensitivities responsible for whole-body glucose metabolism
  ○ OX protects against the development of peripheral insulin resistance induced by ageing or high-fat diet in mice
  ○ The OX2R signaling confers resistance to diet-induced obesity and insulin insensitivity by improving leptin sensitivity

● Hyperglycaemia, due to insulin insensitivity, leads to the reduction in orexin expression in the hypothalamus ➔ further peripheral insulin resistance
Orexin & Glucose Metabolism

- Normal Condition
  - Blood glucose-lowering effects are promoted by hypothalamic insulin action, mediated by the hypothalamic K_ {atp} channels
  - Activation of hypothalamic PKC lowers hepatic glucose production by activating hypothalamic K_ {atp} channels
  - Central leptin also regulates hepatic glucose production via the STAT3 pathway

- During Hyperglycemia
  - Orexin expression in the hypothalamus is decreased
  - Orexin deficiency causes the disruption of insulin receptor, leptin receptor and its own signalling in the hypothalamus
  - As a result, hypothalamic/liver circuits responsible for the regulation of glucose metabolism are impaired → exacerbating insulin resistance in peripheral tissue
What Does This Mean for Future Research?

- Thus, orexin receptor controlling hypothalamic insulin/leptin actions may be a new target for possible future treatment of hyperglycemia in patients with T2D
Summary
References


Drugs as They Relate to Sleep and Glucose Metabolism: Improvement in Sleep with Anti-insomnia Drugs and Glucose Metabolism
Overview of Anti-insomnia Drugs

- Melatonin agonists, GABA agonists (benzodiazepines and nonbenzodiazepines), dual orexin receptor antagonist (DORA) – treatment of insomnia
- Quick recap: sleep disturbances strongly implicated in glucose intolerance and insulin resistance... **SO:**

**KEY Question:** Does improvement in sleep by anti-insomnia drugs affect glucose metabolism in diabetic patients?
Insomnia

- Sleep-wake disorder defined by difficulty with sleep onset (initiating sleep) and maintenance (staying asleep), usually associated with daytime impairment/distress
- Duration ➔ acute vs. chronic insomnia
- Bidirectional link between psychological disorders & sleep-wake disorders e.g. insomnia
- DSM-4 vs. DSM-5
- Highly prevalent sleep disorder affecting 10% of world’s population
Why Insomnia is Harmful

- Increased risk for developing medical conditions
- Increased risk for developing psychological disorders
- Higher likelihood of accidents e.g. car accidents
- Life expectancy ➔ strong correlation between mortality rates and sleep duration
Melatonin Agonists & Sleep

- Used to treat sleep disorders (e.g. insomnia), ADHD, depression
- Melatonin receptor agonists bind to & activate both MT1 and MT2 receptor types
- Types of melatonin receptor agonists: 1) Ramelteon, 2) Prolonged-release melatonin 3) Agomelatine

- **Ramelteon:**
  - selective MT1 and MT2 receptors agonist
  - ameliorate difficulty with sleep onset/sleep latency, improve quality of sleep!
  - only insomnia drug that is non-scheduled→ decreased likelihood of abuse
  - little to no adverse effects/impairments on psychomotor performance, concentration, memory, mood, etc

- **Agomelatine:**
  - unique in that it is both a melatonin MT1 and MT2 receptors agonist (melatonnergic agonist) and 5HT2c antagonist
  - sleep patterns→ aid in resynchronization of circadian rhythms, improves sleep without daytime sedation
  - antidepressant
# Placebo-controlled pilot study of ramelteon for adiposity and lipids in patients with schizophrenia

**Christina P.C. Borba**, Ph.D., MPH, Xiaoduo Fan, M.D., M.S., **Paul M. Copeland**, M.D., **Alexander Paiva**, MA, **Oliver Freudenreich**, M.D., and **David C. Henderson**, M.D.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Examine effects of ramelteon on glucose metabolism and obesity</th>
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<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>20 patients with schizophrenia</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>• 8-week pilot trial, double-blind, placebo-controlled study</td>
</tr>
<tr>
<td></td>
<td>• Prescribed 8mg/day of ramelteon to stable patients with schizophrenia</td>
</tr>
<tr>
<td></td>
<td>• Height, waist circumference, weight, body fat were assessed</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>8-week treatment with ramelteon didn’t alter waist circumference, body weight, body-fat composition, insulin levels, blood glucose BUT decreased cholesterol levels</td>
</tr>
</tbody>
</table>
### Melatonin Receptor Agonists & Glucose Metabolism: Agomelatine

**Agomelatine and sertraline for the treatment of depression in type 2 diabetes mellitus**

D. Karaiskos, E. Tzavellas, I. Ilias, I. Liappas, T. Paparrigopoulos


<table>
<thead>
<tr>
<th>Objective</th>
<th>Comparing efficacy of agomelatine vs. sertraline in treating depression/anxiety, metabolic control, and diabetes self-care</th>
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<tbody>
<tr>
<td>Subjects</td>
<td>40 patients with depression &amp; poorly controlled T2D</td>
</tr>
</tbody>
</table>
| Method    | - Observational open label study that spanned for 4 months  
- Randomly assigned to receive either agomelatine or sertraline care  
- Assessed for depression/anxiety/self-care/body weight/fasting plasma glucose/haemoglobin A1c |
| Results   | - Agomelatine was more effective in improving depression/anxiety scores & boosted self-care scores than sertraline.  
- Decreased HbA1c levels but no change in fasting blood levels & body weights |
Main Conclusions from Both Studies on the Effects of Melatonin Receptor Agonists on Glucose Metabolism

- Effects of anti-insomnia drugs [e.g. ramelteon & agomelatine] on glucose metabolism in humans are largely controversial & unknown
- Need studies with much larger cohorts to understand how melatonin receptor agonists affects glucose metabolism & obesity → need for further research
GABA & Intro to GABA Receptor Agonists on Sleep

- **Brief overview of GABA:**
  - Amino acid naturally produced in the brain
  - Inhibitory neurotransmitter by reducing neuronal activity in brain

- **How GABA functions in pancreas:**
  - Pancreatic islet beta cells express GABA$_A$ and GABA$_B$ receptors ➔ GABA receptor activation
    - insulin secretion and beta cell proliferation
  - GABA ➔ insulin secretion from INS-1 cells (found in pancreas) via GABA$_A$ receptors depending on low vs. high extracellular glucose concentrations respectively
  - ALSO converted to gamma-hydroxybutyrate in beta cells ➔ inhibit glucagon secretion

- **Gaba Receptor Agonists:**
  - Promote sleep
  - Directly stimulate pancreatic insulin secretion
  - Mainly ➔ non-REM sleep
Benzodiazepines & Non-Benzodiazepines as GABA Receptor Agonists

Brief overview of benzodiazepines & non-benzodiazepines:

- Allosteric positive modulators of GABA$_A$ receptor ➔ increase activity of GABA$_A$ receptor
- Primarily used to improve sleep, pain relief, stress/anxiety reduction, induce calming/relaxing effect
- Promote sleep for those who suffer from insomnia but can result in multiple side effects e.g. motor disturbance, amnesia, relaxation of muscle due to suppression of neuronal activity in CNS
- Non-benzodiazepines ➔ less severe side effects and not as habit forming as benzos
# GABA Receptor Agonists and Glucose Metabolism

<table>
<thead>
<tr>
<th>Name of Drug in the Various Studies</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (benzodiazepine receptor ligand)</td>
<td>↓ insulin secretion in concentration dependent fashion</td>
</tr>
<tr>
<td>Alpidem (non-benzo derivative)</td>
<td>Impaired glucose tolerance in patients with anxiety</td>
</tr>
</tbody>
</table>
| Brotizolam (benzo derivative) & Zolpidem (non-benzo derivative)                                     | Effect on healthy subjects:  
  ● Greater impaired glucose tolerance by brotizolam than in zolpidem  
  ● No change in insulin-induced glucose                                                            |
| 4’-Chlordiazepam (selective peripheral type benzo) vs. Clonazepam (selective central type benzo)    | 4’-Chlordiazepam
  ↓ glucose induced insulin secretion in contrast to Clonazepam                                                                 |

## GABA Receptor Agonists and Glucose Metabolism

Continued...

<table>
<thead>
<tr>
<th>Name of Drug in the Various Studies</th>
<th>Result</th>
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</table>
| Diazepam (benzo derivative)         | One study result\(\uparrow\) plasma insulin levels and \(\downarrow\) high blood glucose levels in diabetic rats BUT no changes in glucose levels in normal rats  
Second study result\(\uparrow\) anti-diabetic effects of metformin (anti-diabetic drug) in T2D rats |
| Zopiclone (non-beno ligand)         | Acute antihyperlipidemic effect & small decrease in blood glucose levels in hyperlipidemic rats |

**Implications?** GABA agonists may play a vital role in glucose metabolism at least under diabetic conditions! But further research needed to more fully understand this relationship
References:


Tsuneki, H., Sasaoka, T., & Sakurai, T. (2016). Sleep Control, GPCRs, and Glucose Metabolism. *Trends in Endocrinology & Metabolism*

Drugs & Orexin

- We have seen orexin promote:
  - Wakefulness
    - Overexpression may promote insomnia
  - Glucose homeostasis
    - Disrupted rhythms may lead to overactivation of SNS
    - Overactivation of SNS may lead to insulin insensitivity and glucose intolerance
- What would happen if we block the function of orexin through pharmacological means?
  - Treatment for insomnia
    - Inhibition of wake signals
  - Positive effects on glucose metabolism for people with obesity or T2D
    - Inhibition of SNS stimulation during late phase

*Elevated sympathetic nervous tone seen both in patients who suffer from sleep disturbances and diabetes*
Drug Types

- Single Orexin Receptor Antagonists (SORAs)
  - Bind preferentially to a single orexin receptor (OX1R or OX2R)
- Dual Orexin Receptor Antagonists (DORAs)
  - May bind to both orexin receptors (OX1R and OX2R)
- Exhibit differing effects depending on receptor preference and time of administration
SORA: SB334867 (OX1R)

ob/ob mice

Administration:

- 1 time daily for 7 days during late light phase
- 2 times daily for an additional 7 days during early and late light phase

Results:

- Decrease in cumulative food intake
- Decrease in total weight gain and BAT weight
  - Increase in OX1R mRNA and upregulation in UCP1 mRNA expression in BAT
- Decrease in fasting blood glucose levels
  - Mediated by an increase in insulin sensitivity

ob/ob and diet-induced obese mice

Administration:

- 2 times daily for 7 days 4 hours before lights off and 4 hours before lights on

Results:

- Decrease in food intake and body weight
- Improved hepatosteatosis without affecting sleep duration
<table>
<thead>
<tr>
<th></th>
<th>Blood glucose (mmol/l)</th>
<th>Plasma insulin (ng/ml)</th>
<th>BAT weight (mg)</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>16.1±1.4</td>
<td>26.7±4.9</td>
<td>612±32</td>
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<tr>
<td>SB-334867-A</td>
<td>8.6±0.7</td>
<td>16.5±2.5</td>
<td>468±18</td>
</tr>
<tr>
<td>*P</td>
<td>&lt;0.0001</td>
<td>0.0747</td>
<td>&lt;0.001</td>
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Data expressed as mean±SEM (n=12).
DORA: Suvorexant (OX1R and OX2R)

- Overview
  - Sold under the name of Belsomra
  - Inhibits orexin mediated wake signals
  - Highly selective to orexin system unlike benzodiazepines

- Effects
  - Will promote sleep in both healthy and insomnia patients
  - Increases both REM and NREM sleep times and episode durations in mice
  - Does not impair capacity to wake up by responding to emotionally salient acoustic stimuli, but preserved sleep for irrelevant stimuli
  - Does not impair memory-conserving functions of brain
Suvorexant Study

Overview:

- 18 subjects who suffer from insomnia and T2D
- Studied over a 7 day long period
- Continuous glucose monitoring across 24 hour intervals

Administration:

- Days 1-3 no administration of Suvorexant
- Days 4-6 Suvorexant given at 10pm just before bedtime
  - 15 or 20mg depending on age

Results:

- Increase in median total sleep time
- Increases in both REM and NREM sleep
- Increase in median sleep efficiency
- Narrowed range of glucose fluctuations
- Decrease in 24 hour mean glucose levels
- Decrease in pre-breakfast glucose level

*Strongly suggests that improving sleep quality with suvorexant could improve glycemic control in subject with T2D suffering from insomnia through suppression of SNS*
The images depict various box plots and line graphs comparing data before and after therapy for insomnia. The graphs show changes in total sleep time, non-REM sleep time, CGM measured glucose level, and glucose variability metrics. Specific data points and statistical significance are noted, with p-values such as p = 0.012*, p = 0.011*, p = 0.049*, p = 0.041*, and p = 0.044* indicating significant differences. The graphs illustrate improvements in sleep parameters and glucose levels post-therapy.
### Other Drugs

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<thead>
<tr>
<th>Almorexant (OX1R &amp; OX2R)</th>
<th>TCS-OX2-29 (OX2R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects:</strong></td>
<td><strong>Effects:</strong></td>
</tr>
<tr>
<td>• Reduced blood pressure</td>
<td>• Reduced blood pressure</td>
</tr>
<tr>
<td>• Reduced heart rate</td>
<td>• Reduced heart rate</td>
</tr>
<tr>
<td>• Decreased vasomotor tone</td>
<td></td>
</tr>
<tr>
<td>• Decreased NE levels in CSF and plasma</td>
<td></td>
</tr>
</tbody>
</table>

*Again, we notice the interaction between the SNS and orexin!*
References


Tsuneki, H., Sasaoka, T., & Sakurai, T. (2016). Sleep Control, GPCRs, and Glucose Metabolism. Trends in Endocrinology & Metabolism, 27(9)

Uslaner, J.M. et al. (2013) Orexin receptor antagonists differ from standard sleep drugs by promoting sleep at doses that do not disrupt cognition. Sci. Transl. Med. 5, 179ra44
Remember

- Melatonin agonists have shown beneficial effects on glucose and energy metabolism
- GABA agonists promote sleep as well as directly stimulating pancreatic insulin secretion
- GABAs agonists mainly increase non-REM sleep
- DORAs (Orexin receptor antagonists) could be ideal tools to evaluate the impact of natural sleep on glucose metabolism
- DORAs increase REM and non-REM sleep
Remember

Sleep disturbances and glucose intolerance are highly prevalent in modern society.
Remember

The exacerbating influence of sleep disturbances on the regulation of blood glucose levels and the **undeniable increase of complications in diabetes** have recently been demonstrated many times over.
Remember

The appropriate use of sleep therapies may assist and optimize current therapeutic approaches for the treatment of T2D.