Pharmacological Aspects of Sleep

I. S.M.C
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Paul Reading
Consultant Neurologist
I. Neurochemistry of wake/sleep
   - the ascending reticular system
   - the “sleep switch”

II. Helping to promote wake:
   - traditional psychostimulants
   - modafinil and others

III. Helping to induce sleep:
   - GABA enhancing drugs

IV. Drugs that alter sleep structure
   - effects on REM and deep non-REM
The wakeful state

neurochemistry

- ascending reticular activating systems (ARAS) all “busy”
- widespread mono-aminergic cortical innervation (ventral branch)
  - medial forebrain bundle:
    - noradrenaline
    - serotonin (5-HT)
    - histamine
- dorsal branch via thalamus
  - glutaminergic
  - cholinergic
    (also basal forebrain)
- non-specific innervation
  increases signal-to-noise?
  has collateral sensory input
- significant redundancy
  specific lesions little effect
- role of dopamine complex…
Maintaining wakefulness

Hypocretin/Excitatory Neuropeptide in Lateral Hypothalamus
Sleep onset

- Not easy to define with precision (stage I ≈ severe drowsiness)
  - Behavioural / perceptual definition?
  - Eye movements / EEG change?

- Active process in hypothalamus
  - Ventro-lateral pre-optic area (VLPO)
  - An anterior “sleep centre”
    - Transmitters GABA (and galanin)
    - Actively inhibit all “wake nuclei”

- Predicted by von Economo (1921)
  - From clinico-pathological studies

Hypothalamic “centres” for wake and sleep working in competitive opposition
a “flip-flop” circuit encouraging stable states
Normal function of hypocretin / orexin

Hypocretin stabilizes the hypothalamic sleep / wake switch:

- Activity ↑ if sleep drive high, when hungry or expecting food
- Note: REM sleep actively inhibited by hypocretin activity

Saper et al. Trends Neurosci 2001
Drugs Affecting the Sleep/Wake Cycle
<table>
<thead>
<tr>
<th>Endogenous transmitter</th>
<th>Promotes wake</th>
<th>Promotes sleep</th>
<th>Drugs that increase function</th>
<th>Drugs that decrease function</th>
</tr>
</thead>
<tbody>
<tr>
<td>noradrenaline</td>
<td>✓</td>
<td></td>
<td>amphetamine; (atomoxetine, bupropion)</td>
<td>some tricyclics (TCA’s) e.g. amitriptyline (α-1 ?)</td>
</tr>
<tr>
<td>dopamine</td>
<td>✓</td>
<td></td>
<td>update blockers (amphetamine, methylphenidate, modafinil?); releasers (amphetamine)</td>
<td></td>
</tr>
<tr>
<td>serotonin</td>
<td>✓</td>
<td></td>
<td>SSRI’s (e.g. sertraline) SNRI’s (e.g. venlafaxine) but effects very variable</td>
<td>5HT-2 blockers (mirtazapine, trazadone, anti-psychotics?/TCA’s?)</td>
</tr>
<tr>
<td>histamine</td>
<td>✓</td>
<td></td>
<td>pitolisant (H3 antagonist)</td>
<td>H1 receptor blockers (e.g. promethazine)</td>
</tr>
<tr>
<td>hypocretin/orexin</td>
<td>✓</td>
<td></td>
<td></td>
<td>Suvorexant (receptor antagonist for insomnia)</td>
</tr>
<tr>
<td>GABA</td>
<td>✓</td>
<td></td>
<td>modulators at GABA&lt;sub&gt;A&lt;/sub&gt; receptors (BZ’s, Z-drugs); anaesthetics, barbiturates, alcohol, sodium oxybate</td>
<td></td>
</tr>
<tr>
<td>melatonin</td>
<td>✓</td>
<td></td>
<td>Circadin, agomelatine</td>
<td></td>
</tr>
<tr>
<td>adenosine</td>
<td>✓</td>
<td></td>
<td>caffeine</td>
<td></td>
</tr>
</tbody>
</table>
Stimulants: Modafinil

- First-line agent in narcolepsy, initially licensed 1999
  - Dose range: 200-800mg daily
  - Typical regime: 8am and ~1pm ($T_{1/2} \sim 10h$)
- Initially developed as an anti-depressant
- 2 large US RCT’s (1998, 2000) over 9 weeks
  - ESS (-5 vs -1.5); MWT (~3’↑); CGIC (66%↑ vs 37%)
- Followed by 3 years stability (open label)
- Drug now widely used and misused (?)
- May act as a cognitive enhancer (frontal lobe function ↑?)
- Armodafinil (longer acting $R$-enantiomer) available in US
- Mode of action still debated

Note: Drug binds to DAT protein & enhances striatal DA release
 inactive in KO mice without DAT protein or D1/D2 receptors
Modafinil Demonstrates Regionally Selective CNS (c-Fos) Activity in Animal Studies (cat)

- Modafinil promotes wakefulness without widespread CNS stimulation
- It may work selectively in areas of the brain believed to regulate normal wakefulness (posterior hypothalamus)
- Note "reward centres" not activated

Modafinil

**advantages**
- Wakefulness feels more “natural”
- Minimal cardiovascular effects
- No rebound hypersomnolence
- Little tolerance or abuse potential
- Works whatever cause of EDS
  - Truly “somnolytic”
- Improves “thinking” even if alert?
  - More reflective on cognitive tasks?
  - Less impulsive?

**disadvantages**
- Cost (generics available)
- Not as potent as D-AMP
- Enzyme-inducer
  - Care with OCP pregnancy?
- No effects on cataplexy(?)
- Side effects
  - Headache, GI upset
  - Personality change
  - Skin reaction
Stimulants: dexamphetamine

- **traditional “psycho-stimulant”**
  - typical 5mg dose ≈ 6 cups of coffee
dose range 10 – 70mg daily

- **mode of action**
  - catecholamine (DA & NA) release↑
  - reuptake pre-synaptic terminals↓
  - vascular monoamine transporter (VMAT) inhibited, increasing DA independent of phasic activity
  - D-AMP analogues differ slightly
effects on EEG arousal due to DA release at cortical terminals?
Dexamphetamine

- **advantages**
  - been used since 1935
  - usually a predictable response
  - ~90 minutes useful alertness
  - can be taken flexibly
  - not “addictive” in narcoleptics?
  - can help cataplexy
  - most useful as an “add-on” agent
  - modafinil first-line

- **disadvantages**
  - cardiovascular effects
    (largely noradrenergic)
  - stigma, abuse potential
  - appetite suppressant
  - side effects
    - irritable, jumpy
    - unnatural wake (“wired”)
    - hypervigilance
    - increased sweating
  - lack of controlled evidence and comparison trials
  - tolerance / rebound effects
Stimulants: Pitolisant (Wakix)

- **Histaminergic H₃ antagonists**
  - Histaminergic stimulation a possible “downstream” mechanism for actions of hypocretin (and modafinil?)
  - Note: H₁ antagonists strongly sedative and H₁ agonists enhance wakefulness but severe peripheral side effects.
  - Histamine CSF levels low in narcolepsy
  - H₃ auto-receptors rich in CNS stimulation enhances wake in normal cats and narcoleptic mice
    - Also acts as a “cognitive enhancer”?
  - Pitolisant approved for narcolepsy in phase III trials in schizophrenia / PD
Hypnotics: benzodiazepines / Z-drugs

- act as positive allosteric modulators of GABA<sub>A</sub> receptor
  - attach to BZ-binding site to facilitate GABA binding
  - blocked by flumazenil
- activation of GABA receptor (red) allows chloride entry
  - neuronal activity inhibited
  - note: BZ’s and Z-drugs only work in presence of GABA
Hypnotics: benzodiazepines or Z-drugs?

- controversial area: NICE mentions temazepam…..
  Z-drugs fewer adverse effects on sleep architecture?

<table>
<thead>
<tr>
<th></th>
<th>Tmax</th>
<th>T_{1/2}</th>
<th>Hangover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zopiclone</td>
<td>0.5-2</td>
<td>5-6</td>
<td>Yes</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>1.7-2.5</td>
<td>1.5-2.5</td>
<td>Maybe</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>1.1</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Temazepam</td>
<td>1-3</td>
<td>8-20</td>
<td>Maybe</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1-2</td>
<td>35-40</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- also have anxiolytic and anti-convulsant properties
- GABA side-effects predictable:
  - sedation/hangover, ataxia, impaired cognition, muscle relaxant
Hypnotics: sodium oxybate (Xyrem/GHB)

- licensed for narcolepsy/cataplexy since 2006
- rapid onset of action and short half-life
- GABA\(_B\) and GHB receptors, highest in mid-brain DA areas
  - “rebound” DA release during day?
- slow wave sleep enhanced and deepened
  - nocturnal sleep quality improved, normal architecture restored
  - may produce confusional arousals or enuresis
- extreme care with hypnotics / alcohol
- snoring may increase
  - but, if OSA present, CPAP better tolerated
  - weight loss often seen
- cost currently prohibitive but may allow drug reduction
  - ~£14k p.a.
- GHB abused in society
  - date-rape, body building (growth hormone release↑ during SWS)
The Effects of Drugs on Sleep Architecture (REM and slow-wave sleep)
WAKING

REM Sleep

I

II

III

IV

NREM Sleep Stage

typical hypnogram of young adult

slow-wave sleep (SWS) ≈ sleep quality (>90 mins per night)

time (hours through night)
REM sleep control
another “flip-flop” circuit?

INHIBIT REM
venlafaxine (75mg),
clo mipramine (25mg)

ENHANCE REM
cholinesterase inhibitors

PC/SLD – pre-coeruleus/sublaterodorsal nucleus
DRN, LC – dorsal raphe, locus coeruleus
PPT/LDT – pedunculopontine/laterodorsal tegmental nucleus
LPT/vIPAG – lateral pontine tegmental/
ventrolateral periaqueductual grey nucleus
commonly used drugs to treat symptoms associated with poor sleep (e.g. diabetic neuropathy, anxiety, depression) may facilitate sleep onset and increase duration but *not* improve its *overall quality*:

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>REM</th>
<th>SWS</th>
<th>Arousal</th>
<th>Sleep Quality</th>
<th>Sleep Maintenance</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↑↑↑</td>
<td></td>
<td></td>
<td>impaired sleep onset; bad dreams/nightmares</td>
</tr>
<tr>
<td>AED’s</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td>sleep quality often poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dep</td>
<td>↓(↓)</td>
<td>↓↔</td>
<td></td>
<td>sleep maintenance ↓↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BZ’s / alc</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>sleep maintenance ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>↓</td>
<td>↔</td>
<td></td>
<td></td>
<td></td>
<td>bad dreams/nightmares; impaired sleep onset</td>
</tr>
</tbody>
</table>
Drugs that *may* enhance deep sleep and improve objective “quality”

- Pregabalin
- Gabapentin
- Baclofen
- Tiagabine (Gabatril)
- Sodium oxybate (Xyrem, GHB)
- Melatonin (Circadin) *
- Cannabis
- Agomelatine
- Trazadone?
- Mirtazepine?

* only drug with specific indication for “sleep”

other drugs may be used as “surrogate” hypnotics
(note: evidence-free zone!)