OPIOID ANALGESICS (p.1)

1. **Introduction of Pain (neural systems, NTs)**

tissue damage --- activates **free nerve endings** = "**nociceptors**"

signal from body (FNEs) --- dorsal horn of sp. cord --- increased release of NTS:

- substance P (a neuropeptide)
- nerve growth factor
- neurotropic factors
- glutamate (aminoacid)
- **endogenous opiods** (which opioid agonists mimic)
  --- act on presynaptic neuron to **decrease release of sub.P**
  called "**endorphins**"

why would lowering release of sub.P help reduce pain?

because normally increased sub. P release activates small spinal cord neurons, which is the basis of the rapid transmission of the pain signal to the brain

these incoming signals go through **brain stem** --- to **thalamus** --- to **limbic system** (where the "suffering" message occurs) and to the **somatosensory cortex** (where the non-affective sensation of pain occurs)

thalamic nuclei: **parafascicular nucl. & intralaminar nucl.**

brainstem area: PAG (periaqueductal gray) in tegmentum
rich in **opioid RSs** (where exogenous opioids could have their effects)

descending pain-inhibition systems:

descending brainstem neurons --- spinal cord --- increased activity in interneurons of dorsal horn --- inhibit release of sub. P in primary afferent nociceptive neurons

placebo-induced analgesia
hypnosis-induced analgesia

OPIOID ANAGESICS (p.2)

2. **History of Opium Use**

opium obtained from **poppy plant** (*Papaver somniferum)*
milky sap from opium poppy seed pod, turns darker at it ages ("tar")
active ingredient (morphine) extracted --- into heroin

long history (dates from B.C.) of use for tx. for diarrhea, for sleep
recreational use & addiction were common
plant originated in **Mesopotamia**, then spread to Asia by Portugese
now also grown in so. amer. (esp. Colombia)

established use of **hypodermic needle & syringe (1856)**
1843 Dr. Alexander Wood (Edinburgh) invented
used in Civil War in USA for pain control
"soldier's disease" referred to heroine addiction in self-injecting abuser

Harrison Narcotics Act (1914)
fed. legislation to strictly control use of most opiates/narcotics
repuired physicians, pharmacists, & others who prescribed narcotics
to register with feds and to pay a tax
none the less, as with all other drugs of abuse, opiates are not only
used medically, but they continue to be used recreationally & abused

Drug Enforcement Agency (DEA), under Fed Justice Department
established by Nixon in **1973**

1996 data on opium:
10 tons of raw opium tar --- becomes 1 ton of heroine
4,300 tons of raw opium tar produced/year --- 430 tons heroine/year
2,500 tons from Burma (biggest producer, followed by Thailand,
and then Laos)
50% of this imported into USA/year

OPIOID ANALGESICS (p.3)

3. **<u>Terminology: NTs & RSs</u>**

both **morphine** and **codeine** are found in "tar" from poppy juices
heroine is a semisynthetic compound made from morphine

endogenous opiates ("endorphins") include:
enkephalins
dynorphins
beta-endorphins

there are so-far **three opioid RSs**:
mu – strongest analgesia, strongest addiction
*mu*1 – responsible for analgesia
*mu*2 – found throughout CNS, responsible for decreased respiration, spinal analgesia, decreased HR, physical dependence, euphoria

morphine is a mu1 and mu2 agonist

acts in thalamus & in striatum (basal ganglia: caudate+Putamen) to produce relaxation, euphoria
acts in brainstem to decrease respiration, increase nausea/vomiting
acts in spinal cord to produce analgesia

kappa – modest analgesia, little/no effect on respiration, miosis, little/no dependence
but does produce strong dysphoric response (which limits its use)
may antagonize the mu RS actions in brain

delta – may also modulate action of mu RS
little dependence, little/no analgesia

all opioid RSs belong to a group of **G-protein coupled RSs**, with seven membrane-spanning regions (similar to all G-proteins)

OPIOID ANALGESICS (p.4)

3. **Terminology: NTs & RSs** (cont.)
   opioid RS (G-protein coupled)
      when RS is activated, it inhibits (via presynaptic, axoaxonal synapse) cell by increasing the efflux of K+ and closing Ca++ ion channels
      --- **hyperpolarization** of neuron & blocking any release of NTs
      --- **pain signaling neurons are kept shut** off (see p. 258, Fig. 9.6, Julien, 9th Ed.)

4. **Classification of Opioid Analgesics**
   a. "**pure agonists**"
      their affinity for RSs = ligand's affinity for the same RSs

      e.g. morphine, methadone, fentanyl (a pure *mu* agonist)

   b. "**pure antagonists**"
      has affinity for RS, but produces no effect (blocks RS)
      e.g. naltrexone

   c. "**mixed agonist-antagonist**"
      produces an agonistic effect at one RS (e.g. *kappa*), but also produces an antagonistic effect at another RS (e.g. *mu*)
      e.g. Talwin (pentazocine) which is a weak, less efficacious analgesic (agonist at *kappa*, blocks *mu*)

   d. "**partial agonist**"
      binds to RSs, but does not produce as much of an effect vs. ligand
         low efficacy
      and since it does bind to RS, the natural ligand cannot bind --- can result in w/d-like effects
      e.g. Buprenex (buprenophine) – does produce some analgesic effects, but does not depress respiration as much…a good thing

OPIOID ANALGESICS (p.5)

5. **Morphine**

a pure opioid agonist
the most potent & efficacious analgesic we have today still

pharmacokinetics:

administered PO, rectal suppository (avoids nausea/vomiting), IV, or into spinal cord (subdural space)(which avoids SEs such as respiratory depression, increased euphoria, increased constipation, & increased sleepiness)

can also be inhaled (smoked)
Julien says of this route "…rarely abused when smoked", why?

morphine fairly slowly crosses BBB (much more **water soluble** than fat soluble), only 20% reaches CNS by usual clinical routes (note: heroin & fentanyl cross BBB much more rapidly)

crosses the placenta too, so neonate is born opiate dependent
neonate will show w/d effects, which require extensive support th.
no teratogenic effects
may retard fetal growth rates
may increase paranatal birthing problems

distributed to all body tissues (esp. muscle)

metabolized by liver enzymes
some active metabolites
e.g. morphine --- morphine-6-glucoronide (a potent analgesic)
morphine ½ life is 3-5 hours, m-6-g ½ life is 3-5 hours
urine drug screen can detect morphine/codeine/heroine use for 2-4 days after use

does show **dependence & tolerance** (see later notes)

OPIOID ANALGESICS (p.6)

5. **Morphine** (cont.)

pharmacological effects:

analgesia	sense of tranquility	pupillary constriction
relaxation	decreased apprehension	
calm euphoria	respiratory depression	
sedation	reduced cough reflex	

analgesia w/o loss of consciousness & w/o loss of appreciation of senses
- especially blunted "suffering/affective" part of pain awareness, even though can still feel touch, and non-hurtful part of "pain"
- via blocking *mu* RS
- naloxone (Narcan) reverses this analgesic effect
  - note: in **NCs**, naloxone does **not** --- pain, dysphoria, or any other noticeable effects

euphoria response
- probably the result of more than *mu* RS, probably also DA RSs in nucl. Accumbens, etc.
  - opioids (via *mu* RSs) --- inhibits GABA neurons in ventral tegmental area --- disinhibition of DA release in nucl. Accum.
- does show **tolerance** with repeated use

sedation & anxiolysis (reduced anxiety)
- not as deep a sedation as that produced by sed-hyps (e.g. ETOH, barbs, BZDs)
- a marked lack of concern, "What, me worry?" attitude, "dreamy"
- lack of concentration, cognitive impairment

depressed respiration
- decreased sensitivity to increased CO2 levels, to the point of not breathing at all in O.D.
- dangerous to combine with other sed-hyps., although would be a painless death…

OPIOID ANALGESIS (p.7)

5.**Morphine** (cont.)

pharmacological effects (cont.)

cough suppression

useful clinically, but now have non-opioids to do this too

pupillary constriction

via mu & kappa agonists --- extreme miosis ("pin-point pupils")

nausea & vomiting

morphine stimulates area postrema = "chemoreceptor trigger zone" in medulla --- N&V

may also affect gastric RSs of some sort

GI tract effects

increased muscle tone, decreased motility --- increased fecal dehydration & increased cramping --- constipation

Imodium (loperamide), Lomotil (diphenoxylate) are both opioids that do not cross BBB, used to tx. diarrhea w/o "buzz" or abuse

histamine agonist effects

can --- hives, severe allergic reactions, broncoconstriction

I.S. antagonist/suppressant

Tolerance & dependence

all opioids build up tolerance with repeated use, & show dependence

thus, clinical use of all opioids (for analgesia, to reduce diarrhea, to reduce coughing) is limited by:

tolerance for main effects

increasing SEs if dose levels are increased

potential for compulsive use (abuse, dependence)

OPIOID ANALGESICS (p.8)

5.**Morphine** (cont.)

Tolerance & Dependence (cont.)

tolerance seems to occur via glutamate/NMDA RSs

as opioid use continues, see increasing activity in glumate/NMDA RSs

note: **Ketamine** blocks glutamate NMDA RSs --- blocks tolerance

thus, glutamate/NMDA system must somehow regulate opioid *mu* RSs

note: an unfortunate clinical aspect of opioid tolerance

after opioid use for analgesia, if D/C opioids --- S becomes super-sensitive to pain ("**hypergesia**") for long period of time…why?

(note: this hypergesia or decrease in pain threshold is **blocked by ketamine**)

note: rates at which tolerance to morphine develops depends on how it is used

note: tolerance with one opioid drug --- **cross-tolerance** with other opioids, but **not** with sed-hypn. drugs

physical dependence occurs, **marked w/d Sxs**:

marked reduction in DA release in nucl. Accumbens

marked increase (x3) release of NE in hippocampus, nucl. accumb. and locus coeruleus

Sxs of w/d are not life-threatening, but are very unpleasant:

motor restlessness	insomnia	increased respiration
dysphoria	anxiety	rate, "panting"
drug cravings	depression	aches, pains
sweating	irritability	(see p.270, Table 9.4,
retching, vomiting	fever, chills	Julien, 9th ed.)
cramping	explosive diarrhea	

OPIOID ANALGESICS (p.9)

5. **Morphine** (cont.)

Dependence (cont.)

"**Rapid Opioid Detoxification**" (RAAD = Rapid Anesthesia-Aided Detoxification)

S placed under general anesthesia for several hours
while unconscious, S is given naloxone/naltrexone
S does through blunted w/d Sxs while unconscious
S comes out of general anesthesic state, presumably now over any w/d Sx, and is then maintained on naloxone (to reduce cravings for opiates) and goes into relapse prevention drug counseling

a great idea, but still very controversial, more risky (gen anesthetic), often not covered by insurance

"**protracted abstinence syndrome**" (**PAS**)

seen after end of acute w/d, lasts at least 6 months or so

Sxs: depression
abnormally sensitive to stress
strong drug cravings
lowered sense of self-esteem
anxiety
various physiological disturbances (in bowels, sleep, etc.)
increased sensitivity to pain

note: **abnormal brain activity**, esp. while experiencing cravings
will this ever normalize?...maybe not…

note: many (estimate of 47%) of opiate users had a **premorbid/ comorbid Dx**
depression (15%)
affective disorders (unipolar depression, bipolar)
personality disorders (antisocial)(25%)

OPIOID ANALGESICS (p. 10)

6. **<u>Other Opioid Substances</u>**

(See Julien for more extensive material)

a. Codeine

is a commonly prescribed analgesic (often combined with aspirin or acetaminophen)

about 40% of Ss repeatedly using medically prescribed codeine meet criteria for codeine dependence

many of these repeat users are showing comorbid Sxs of endogenous depression

codeine is metabolized by CYP2D6 into morphine & some of the effects presumably from codeine are actually due to morphine

note: some SSRIs will block the conversion of codeine --- morphine via liver enzyme inhibition, and will block/lessen the analgesic effects of codeine therefore

b. **Heroin**

x3 more potent than morphine

intense "rush" esp. if smoked or used IV

legal for clinical used outside USA, not inside USA

when used along with free-base cocaine ("crack") --- increased euphoria, decreased anxiety & paranoia, & decreased depression if the cocaine use if D/Cd…very difficult to treat this combination addiction…

c. **Dilaudid (hydromorphone), Numorphan (oxymorphone)**

x6-10 mor potent than morphine

slightly less sedating, about same degree of respiratory depression

d. **Demerol (meperidine)**

synthetic opioid, structurally unlike morphine

is as prone to abuse as is morphine

$1/10^{th}$ the potency of morphine, but produces euphoria like morphine

different SEs: tremors, delirium, increased reflexes, convulsions (more excitatory) vs. morphine, produced by active metabolite

OPIOID ANALGESICS (p. 11)
6. **<u>Other Opioid Substances</u>** (cont.)

e. **Dolophine (methadone)**
synthetic mu agonist, analgesic
can be used PO…why is this important?
long ½ life (24 hours)
little tolerance with repeated use
little/no "rush", euphoria
used to maintain heroin addicts, controlled by feds
blocks cravings for heroin (at > 50mg/day doses)
note: some Ss metabolize methadone more rapidly (33%), need b.i.d. dosing, or could use LAAM (longer ½ life)
some Ss may bee 80-100 mg/day, in b.i.d. split doses

f. **LAAM (levo-alpha-acetylmethadol)**
related to methadone
can take PO
slow onset of effects, long ½ life (up to 3 days)
active metabolites
helps to control cravings for both heroine and cocaine

g. **Darvon (propoxyphene)**
structurally similar to methadone
analgesic for mild-mod pain
potency: asperine < Darvon < codeine
when taken PO there is little abuse potential; injected --- more
not available legally in injectable form

h. **ultra-short acting opioids**
Sublimaze (fentanyl), Sufenta (sufentanil), Ultiva (remifentanyl)
used IV usually, can be given by transdermal patch or "lollypop"
used during/after short surgeries
x80-100 more potent than morphine, profound respiratory depression
Ultiva ½ life is 10-20 minutes (metabolized by plasma enzyme)

OPIOID ANALGESICS (p.11)

7. **Partial Opioid Agonists**
   See Julien (Buprenex/buprenorphine; Ultram/tramadol)

8. **Mixed Opioid Agonist-Antagonists**
   See Julien (Talwin/pentazocine; Stadol/butorphanol; Nubaine/nalbuphine; Dalgan/dezocine)

9. **Opioid Antagonists**
   Narcan (naloxone); Trexan, ReVia (naltrexone); Revex (nalmefene)
   structurally related to Numophan (oxymorphone)
      a pure opiate agonist
   strong affinity for *mu* RS, but blocks RS
   note: if **Narcan** is injected into non-opiate user --- no effects
      but into opiate user --- opiate w/d effects
      cannot give PO (is injected)
      fast duration of effects – ¼ to ½ hour
      can be used to reverse respiratory depression in opiate OD or neonates

   note: **Trexan, ReVia** can be given PO
      longer duration of action, can be given once a day
      used to reduce opiate cravings in former abusers **not on methadone**
      SEs: nausea & liver toxicity
      also used to tx. cravings for ETOH in former abusers
      may also help to reduce SIBs in autistic Ss
      may be helpful in tx. of borderline personality disorder…

   note: **Revex** has a ½ life of 8-10 hours
      must be injected
      used to tx. respiratory depression in opiate OD
      used to tx ETOH cravings in former alcohol abusers

OPIOID ANALGESICS (p.12)

10. **<u>Pharmacotherapy of Opioid Dependence</u>**

use LAAM and/or Buprenex for treatment-resistent Ss (who must be **maintained on an opiate substitute**)

use **opiate antagonist** to also **reduce opiate cravings**
in patients not able to use substitute opiate (Methadone, LAAM)
blocks euphoria if does relapse
e.g. ReVia, Trexam

treatment of any comorbid Dxs (esp. affective disorders)

non-pharmacological **support therapy**
outpatient treatment programs (vs. inpatient intensive programs)
focused on relapse prevention & cognitive/behavioral changes
e.g. change environment, associates, activities

note: total abstinence need not be the objective for each/all abusers
hence, methadone maintenance programs
and movement to let MDs prescribe methadone in private practice

note: must change societal attitudes (incl. government & politicians)
about these issues, and adopt Harm Reduction Model (vs. abstinence)
more money for prevention than "cure"
more money for treatment vs. drug interdiction