MARIJUANA (p.1)

1. **Tetrahydrocannabinol (THC)**
   active ingredient in marijuana (MJ)
   now classified as an anadamide partial agonist (ligand)
   420+ ingredients in smoke from MJ
      psych. active ingredients include THC, cannaninol, & cannabidiol
      (cannabinoids – synthetic THC mimics)

2. **Anandamide**
   1992 ligand was isolated
   prior to 1992 MJ had been classified as a mild sed-hyno, sort of = to
      BZDs or ETOH
      although even high doses of MJ do **not** suppress respiration, not lethal
      little cross-tolerance with GABA agonists

3. **Unique Effects**

decreased attention span	decreased motor control
decreased STM	increased appetite (?)
changes in sensory awareness	increased bronchodilation
analgesia	decreased body temperature
decreased Sxs of RA	decreased libido & sperm count(hi dose)
decreased nausea, vomiting	decreased fertility (hi doses)

   decreased androgens (secondary gyncomastia at hi doses)

4. **Mechanisms of Action**
   THC --- indirectly *inhibits adenylene cyclase*
      adenylene cyclase involved in G-protein 2nd messenger RSs
      which normally --- influx of Ca++ and efflux of K+
      with this pathway inhibited, there is less release of NTs from presynaptic
         axon terminals
   THC --- also decrease release of *glutamate* in *hippocampal* neurons --- ?

   there are many anandamide RSs in CNS, maybe 10-20x the # of opioid RSs
      may be tied with GABA as most numerous RSs (= 1/3 of all RSs)

MARIJUANA (p.2)

5. **Major CNS Areas with THC Effects**

hippocampus (--- decreased STM)
cerebral cortex (esp. *frontal lobes*) (--- attention span, distorted sensory perceptions)
cerebellum & basal ganglia (decreased motor performance)
spinal cord (--- analgesia)
"none" in *brainstem* (*medulla*) (no effect on respiration, heart)
but must have some effect on medulla…why?

6. **Major PNS Areas & Others with THC Effects**

in PNS have both cannabinoid RS1s and RS2s
RS2s are found in *lymph cells* (WBCs) (depressed I.S. functioning?)
in *heart, lungs, arteries, endocrine system, & reproductive organs*
increased HR, BP, vasodilation
bronchodilation
decreased sperm count, libido, gyncomastia

7. **Pharmacokinetics**

¼ to ½ of THC is available in smoke
one MJ "joint" = 0.4 to 10 mg of THC into bloodstream
(assuming 1gram of plant material & 50 mg of THC)

rapid onset of effects when smoke **inhaled** (about 5 seconds)
bodily effects last about 3-4 hours when inhaled (e.g. effects on HR)
but psych effects ("high") can last 12+ hours

if taken **PO**, absorption is much slower and doses reduced
30-60 minute onset latency
likely subject to 1st pass metabolism in liver

distributed through out body tissues, esp. into fat tissues (**very fat soluble**)
easily crosses BBB & placenta

MARIJUANA (p. 3)

7. **Pharmacokinetics** (cont.)

THC is metabolized by **P450 enzymes** --- active metabolite --- inactive metabolite --- eliminated

this process extends ½ **life** of THC to **30-60 hours**

thus, urine drug screens can be done for relatively long time after *S* MJ and still get a + result (2 to 14 days after, in acute user; 30 days for a chronic user…and even longer in an **obese** *S*)…why?

8. **Pharmacological Effects of THC**

a. *in non-human animals*

mice – bred to **lack cannabinoid RSs** --- higher mortality rates, decreased activity levels, increased sensitivity to pain

cannabinoids **potentiate morphine-induced analgesia**

THC --- decreased release of substance P, decreased release of glutamate --- decreased pain signals

--- increased activity in "opiate" RSs --- decreased pain

THC --- potentiates sed-hypn effects

decreased aggression

decreased seizures (increased seizure threshold)

increased reaction times, decreased reflexes

decreased motor performance on complex tasks

increased hallucinations/sensory distortions (of time, audition, color, taste)

increased social interactions

increased eating

at high doses --- decreased ovulation, decreased sex hormones, decreased sperm, decreased fertility

MARIJUANA (p.4)

8. **<u>Pharmacological Effects</u>** (cont.)

b. *<u>in humans</u>*

CNS effects – perception of senses being enhanced
time distortion (time duration is overestimated)
increased sense of well-being, mild euphoria
relaxation, usually reduced anxiety, sedation
reduced RTs, reduced motor skills, poor coordination
dissociation of ideas, deceased ability to focus
decreased attention, decreased STM
decreased cognitive function (reduced learn/memory)
rare hallucinations (often visual)

at high doses – acute depression, panic reactions, mild paranoia

long-term, chronic use:

- some tolerance develops to motor effects & to cognitive effects
- but still show impairment of information-processing skills
- esp. cannot filter out irrelevant stimuli
- decreased spatial skills
- decreased ability to "map" the environment
- poor organizing skills, e.g. poor routines of daily living
- *S* feels out of control, alientated, life lacts focus/meaning (part of the "amotivational syndrome"?)
- note: above all show improvement when d/c drug
  back to baseline?...

addiction: Is MJ addicting?

THC does --- increased release of DA in reward/attentional focus brain areas (basal ganglia, nucl. Accumbens, prefrontal cortex) & maybe increases activity at the *mu* opioid RS (ventral tegmentum) --- **so concern re. dependency is warranted**, based on CNS mechanisms…

MARIJUANA (p.5)

8. **<u>Pharmacological Effects</u>** (cont.)

"*amotivational syndrome*" seen in heavy chronic MJ users may really be depression…

Cardiovascular effects:
increased BP & HR, peripheral vasodilation --- decrease in BT

no lethal/dangerous effects usually, TI = 1000

Pulmonary effects:
no risk of respiratory depression
increased risk of lung damage if MJ smoked
MJ has tars/carcinogens > tars/carc. in tobacco!
bronchial irritation & inflammation (& dilation)
thus, despite dilation, is overall not helpful for asthma when inhaled

Immune System effects:
immunosuppression (as also do other sed-hypns)
inhibit in particular *NKC*s (tumor-killing cells)

Reproductive System effects:
in males --- decreased testosterone & sperm
in females --- decreased FSH, LH, & ovulation
decreased fetal growth/maturation (mild effect)
may decrease executive (frontal) functioning in child (4 yrs +)
if child was exposed prenatally (poor planning, organizing, impulse control)

MARIJUANA (p.6)

9. **Tolerance & Dependence**

Tolerance does occur via:

a. *down-regulation* (# & sensitivity) of cannabinoid RSs
b. with synthetic agonists, see rapid RS "internalization" process (RS protein taken back into cell?)

When d/c MJ --- **w/d effects** (so dependence does occur)

restlessness irritability anxiety
insomnia agitation depression
anorexia nausea, abdominal cramping
increased sleep disturbances
drug craving

w/d effects begin about **2 days after d/c**…why so long?
w/d effects last about 4-6 days

As with other drugs, user often uses MJ + other drugs
User often has co-morbid Sxs of w/d that are a combination of MJ w/d plus w/d from other drugs

10. **Clinical Uses of THC**

dronabinol (Marinol) – synthetic THC

increase appetite (e.g. in anorexic cancer pts)
decrease nausea, vomiting (e.g. in chemotherapy pts)
decrease muscle spasms (e.g. MS pts)
decrease pain (e.g. MS, cancer, RA)
suppress IS (e.g. RA, MS pts)
decrease intraocular pressure (e.g. glaucoma pt)
decrease glutamate release (e.g. post-stroke pts, head trauma)