1. **Tetrahydrocannabinol (THC)**
   active ingredient in marijuana (MJ)
   now classified as an anandamide 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 2^{nd} 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)
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, gynecomastia

7. **Pharmacokinetics**
   - ¼ to ½ of THC is available in smoke
     - one MJ “joint” = 0.4 to 10 mg of THC into bloodstream
       (assuming 1 gram 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
7. **Pharmacokinetics** (cont.)

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

this process extends $\frac{1}{2}$ 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
8. **Pharmacological Effects** (cont.)

b. *in humans*
   
   **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, alienated, life lacks 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…
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8. **Pharmacological Effects** (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)
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)