PHARMACODYNAMICS: Tolerance & Dependence (p.1)

1. **tolerance** is defined either as getting less and less response to the drug at the usual dosage, or as having to administer more and more of the drug to get the same effect

   i.e. the DRC is shifted to the right (ED50 increases)

   note: LD50 may be unchanged…implications

   note: negative SEs may not show tolerance, even when main effect does

there are several types (causes) of tolerance:

   **metabolic/dispositional tolerance**

   due to changes (increases) in liver enzymes (liver enzyme induction)

   which leads to more rapid/complete biotransformation of drug

   usually takes weeks to develop

   is often the basis of “cross tolerance” between two drugs (see below)

   can gradually shorten the ½ life of a drug

   **neuronal/cellular/physiological/pharmacodynamic tolerance**

   most likely due to changes (“down regulation” usually) in the # of RSs on neurons or related changes (e.g. less NT released, decrease in sensitivity of RSs, etc.)

   usually takes days or weeks to develop

   **behavioral tolerance**

   learned behavioral adjustments that compensate for drug effects, which then looks like the drug is having less of an effect

   usually takes weeks to develop

   **conditioned tolerance**

   a special case of behavioral tolerance

   a set of learned/conditioned behavioral/physiological adjustments that the S makes that compensate for the drug’s effects

   is triggered by conditioned stimuli (cues) that are associated with the administration of that drug
PHARMACODYNAMICS: Tolerance & Dependence (p.2)

behavioral tolerance (cont.)

conditioned tolerance (cont.)
cues could include drug paraphernalia, time of day, location, other persons, smells, a particular emotion, etc.
cues associated with the act of taking the drug can be quite varied

note: these conditioned responses are not observed if \( S \) takes the drug under novel conditions (e.g. in a new location, with new people, different time of day, etc.) thus, \( S \)’s body does not make compensatory responses (that normally would “balance out” at least some of the drug’s effects --- which can then lead to a drug O.D. effect

cross-tolerance
when \( S \) takes drug A repeatedly, \( S \) will now show tolerance to newly introduced drug B usually thought to be caused by liver enzyme induction (from A), but there may be other mechanisms as well e.g. ETOH and barbiturates e.g. all opiates e.g. all BZDs

reverse tolerance/sensitization
as \( S \) repeatedly takes drug, the effects become more and more, or in order to get the same effect must keep on lowering dose levels i.e. DRC shifts to the left (unusual) mechanisms not always fully understood…could be liver enzyme inhibition in some cases

acute tolerance/tachyphylaxis
a very rapid development of tolerance sometimes within a few minutes or hours develops often between the first and second administrations of drug unknown mechanisms…maybe all the RSs occupied by the 1st dose?
PHARMACODYNAMICS: Tolerance & Dependence (p.3)

Note: **tolerance effects often develop at different rates for each different drug effect…**

**Ideal** – is to see rapid tolerance developing to negative SEs and no tolerance developing to main effect

note: with cocaine, tolerance develops rapidly to the euphoriant effects of the drug, so S tends to take more and more drug but, tolerance develops only very slowly to the toxic cardiovascular effects of the drug --- cardiac arrest

2. **Physical Dependence**
   describes the body’s set of various & multiple physiological responses that are observed after repeated drug doses
   often are “compensatory” responses
develop presumably to try to keep body physiology in “balance”, in some sort of normal/homeostatic range
   will continue as long as S continues to take drug X

3. **Withdrawal Symptoms**
   occur when S has developed physical dependence on drug X and when drug X is *abruptly* D/C’d
   *abrupt* D/Cing of drug X allows one to observe these mostly “compensatory” responses that have presumably been going on all the while S was taking drug X but were unobserved directly
   if get withdrawal Sxs with abrupt D/C, can infer prior physical dependence has developed
   are usually unpleasant to S, but usually not “horrible”
   usually last for days/few weeks
   are not seen if drug X is D/C’d gradually, tapered off slowly
   note: case of a long ½ life drug *vs.* a short ½ life drug
   should **not** be confused with the “cravings” for drug X that can occur
4. **Psychological Dependence or “Craving Behavior”**
   older term, now phased out, is “psychological” dependence
   which seemed to imply that these behaviors had no physical basis…
   Not true!

   These intense cravings for drug X are the basis for addiction
   And are both neurological/physiological and conditioned to cues
   Cannot be changed easily by “relearning” or “will power”, and sadly
   certainly not by punishment/incarceration…

   Craving behavior is **not the same thing as withdrawal Sxs**