Pharmacogenetics: General Considerations

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Why Study Pharmacogenetics?

- Health Issue
- Relatively Small Research Effort
- Related to the Study of Inborn Errors of Metabolism
Organization of This Talk

- Background
- Know your phenotype
- Pharmacogenetics of Cocaine
- QTL to QTGene
  - Rats and ethanol consumption
  - Mice and sedative withdrawal-induced seizures
Origins of Pharmacogenetics

- Two traditions:
  - Pharmacokinetics
  - Pharmacodynamics
Pharmacokinetic Tradition

- Study of absorption, distribution, and disposal of drugs
- 1842 Keller made first description of a detoxification mechanism, i.e. biotransformation of a drug
  - Benzoic acid $\rightarrow$ hippuric acid
- 1902 Garrod described alkaptonuria, perhaps first example of inborn error of metabolism
Precursors to Pharmacogenetics

- 1943 -- Sawin and Glick first demonstration that biotransformation of drug to be under genetic control
- 1947 -- landmark book by Sawin & Glick, “Detoxification Mechanisms”
- 1946 Takahara described three phenotypes of acatalasia under control of an autosomal recessive gene
More Precursors to Pharmacokinetics

1952  Hockwald showed 10% of African-Americans, fewer caucasians, develop haemolytic anemia when given primaquine or sulfanilamide

1953 Bonicke & Reif -- described “fast and slow acetyliators”
Even More Precursors to Pharmacokinetics

1956 Carson showed the primaquine sensitivity to be related to a deficiency in glucose-6-phosphate dehydrogenase, perhaps the most common hereditary enzyme deficiency in humans.
More Pharmacokinetics

- 1956 Prolonged apnea under anesthesia described by Kalow and found to be related to low levels of pseudocholinesterase

- 1959 Friedrich Vogel introduced the term, “pharmacogenetics” into the literature. Defined as “the study in animal species of genetically determined variations that are revealed by the effects of drugs.”
Last of the Pharmacokinetics I

- 1960s biotransformation of drugs by hydroxylation shown to be under genetic control
- 1970s genetic polymorphic hydroxylation of sparteine and debrisoquine under control of same locus, also hydroxylation of (S)-mephenytoin
Last of Pharmacokinetics II

- 1980s genetic polymorphisms of cytochrome P450 -- enzymes responsible for oxidative reactions
- 1990s development and rise of molecular genetics
Genetic effects on alcohol metabolism

- Alcohol metabolism
  - alcohol dehydrogenase (ADH) produces acetaldehyde
  - aldehyde dehydrogenase (ALDH) produces acetate

- Acetaldehyde induces an anti-abuse reaction
  - congestion, headache, nausea, hypotension, rhythm disorders
  - can be triggered by ALDH antagonists (disulfirame, metronidazole)

- Genetic polymorphisms influence acetaldehyde levels and protect against the development of alcohol dependence
  - ADH2 His 47, ALDH2 Lys 487
The Pharmacodynamic Tradition

- Early beginnings
  - Alcohol consumption studies in genetically defined animals
    - Williams (1949) 2 groups of rats, 3 groups of mice
    - Reed (1951) six groups of rats
    - Mardones (1950) selective breeding of rats for ethanol consumption
The Pharmacodynamic Tradition

- Study of effects of drugs at their target tissues

- 1959 McClearn and Rodgers described differences in alcohol consumption among inbred strains of mice

- 1960s-1970s Demonstrations of drug sensitivity to respond to selective breeding, e.g., McClearn & Kakhana’s Long Sleep and Short Sleep mice -- more than 400 research papers generated to date.
SELECTIVE BREEDING: ETHANOL HYPNOTIC DOSE SENSITIVITY

McClearn & Kakihana, 1981
Selection experiment - HAP/LAP mice

Grahame, Li & Lumeng, 1999
Alcohol-related phenotypes, selected lines

- **Rats**, voluntary alcohol intake (2-bottle choice vs water)
  - University of Chile B & A (UChB/UChA)
  - ALKO alcohol / non alcohol (AA/ANA)
  - Alcohol-preferring / -non preferring (P/NP)
  - High- / low-alcohol drinking (HAD/LAD)
  - Sardinian alcohol-preferring / -non preferring (sP/SNP)

- **Mice**
  - various stocks selected for preference (e.g. HAP/LAP)
  - Long sleep / short sleep (LS/SS) and recombinant inbred lines
  - Withdrawal-seizure prone / resistant (WSP/WSR)
GENERATION 0

\[ R = h^2 S \]

GENERATION 1

\[ S \]

\[ R \]
Pharmacodynamics--Selecting the Right Phenotype

Example of LS and SS

- selection criterion of sleep time
- is it pharmacodynamic or pharmacokinetics? How can we tell?
- Correlated responses can help i.e. blood ethanol concentration at regain of righting
Example: Isolate Housing and EtOH Sensitivity

- This study was conducted to test the hypothesis that isolate housing in LS and SS mice would alter their sensitivity to the hypnotic effects of alcohol.

- Design, 2 groups each of LS and SS mice
  - reared in isolation from weaning to 60 days
  - reared in unisex groups from weaning
For the LS mice, isolation reduced sleep time and increased blood ethanol concentration (20%) at waking.

For the SS mice, isolation reduced sleep time but had no effect on blood ethanol concentration.
Conclusion

For the LS mice, isolation housing reduced the pharmodynamic sensitivity to ethanol -- i.e. they woke up at a higher BEC (therefore brain concentration). Kinetics were not changed -- it just took less time to clear to wake-up concentration.

For the SS mice, isolation caused increased alcohol clearance but no change in brain sensitivity - woke up faster but at same BEC.
Use of inbred strains, selected lines and other genetically defined rats and mice.

Major focus is on drugs which are prone to frequent use and misuse by humans:

- alcohol
- phencyclidine
- cocaine
- opiates
- amphetamine
- nicotine
- caffeine
- benzodiazepines
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