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Drug Metabolites and Hair Testing

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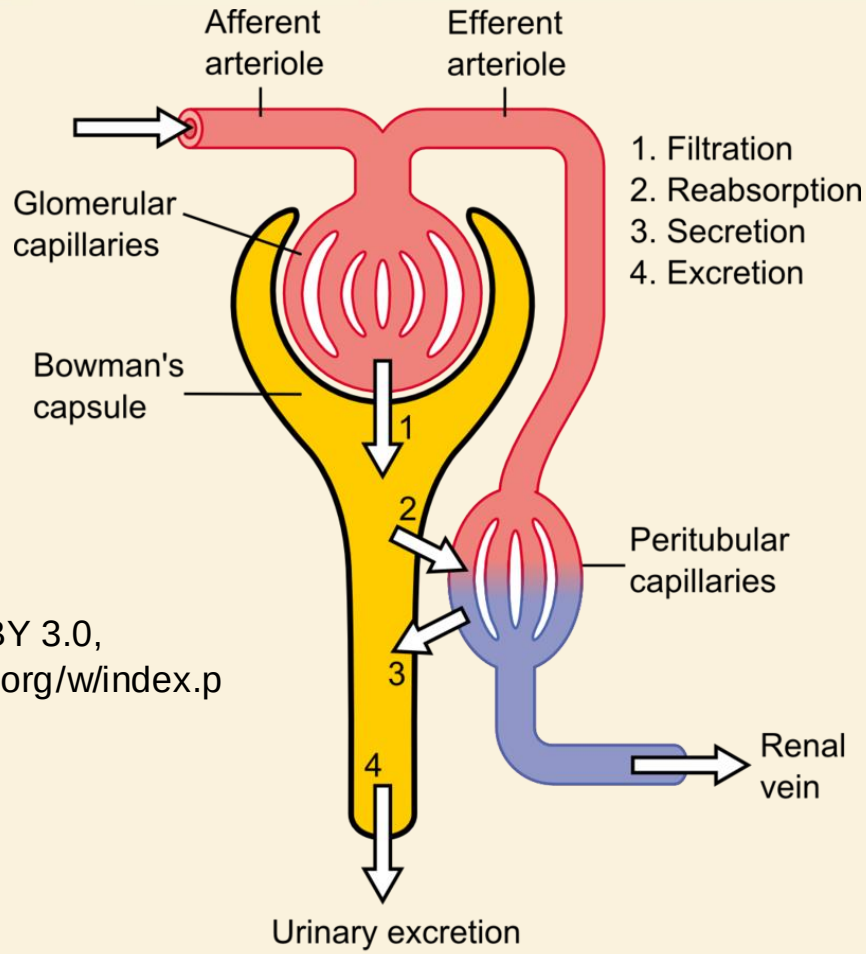
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Urine Drug/Drug Metabolite Testing

- Current urine drug testing under the DHHS Mandatory Guidelines allows testing for Cannabinoids, Cocaine Metabolite, Amphetamines, Opiates, and PCP and Specimen Validity Testing or SVT.
- Numerous other drugs and drug metabolites.
- Whether a parent drug and/or a metabolite is present, a urine positive shows use.

Urine Specimen - Filtered Blood



Excretion = Filtration – Reabsorption + Secretion

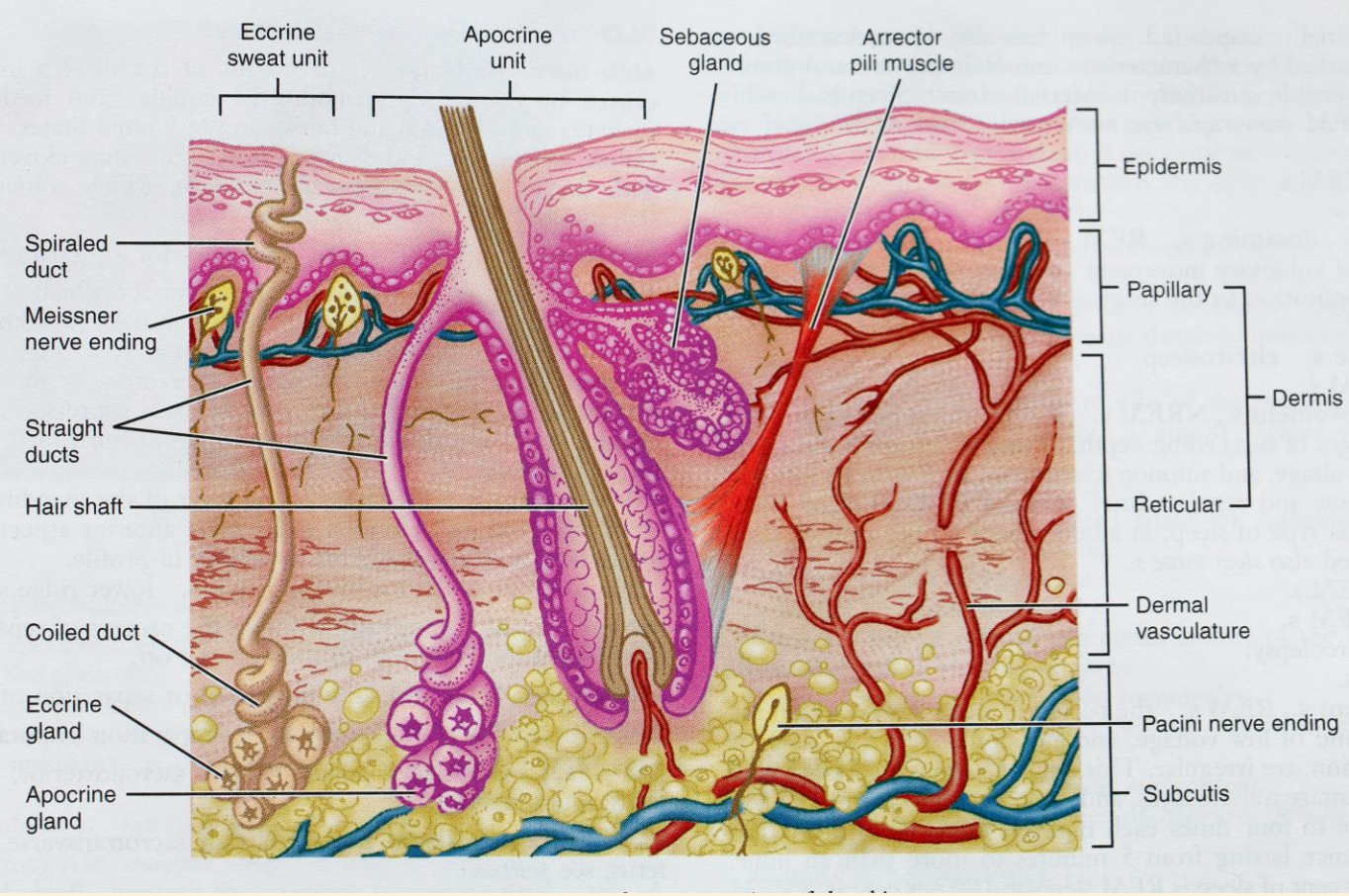
Hair Drug Testing

- Hair, as harvested for testing, was removed from completely outside the body.
- Currently, most testing for drugs of abuse in hair is performed by targeting parent drugs except for the major metabolite of Δ^9-tetrahydrocannabinol ("THC"), 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid or THCA (Carboxy-THC, THCCOOH).
- Major Issue: External contamination by drugs.

Hair Drug Testing (continued)

- Potential remedy to show actual use as opposed to simple exposure:
  - A common metabolite that is NOT 1) a separately marketed drug or 2) a manufacturing impurity or 3) a chemical decomposition product or 4) the product of an *in vitro* chemical reaction on the hair.
- Unacceptable candidate marker to show cocaine use:
  - Benzoylecgonine.
- Potentially good candidate marker for codeine:
  - Norcodeine to indicate the use of codeine.

Incorporation & Metabolism



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Metabolites in Hair

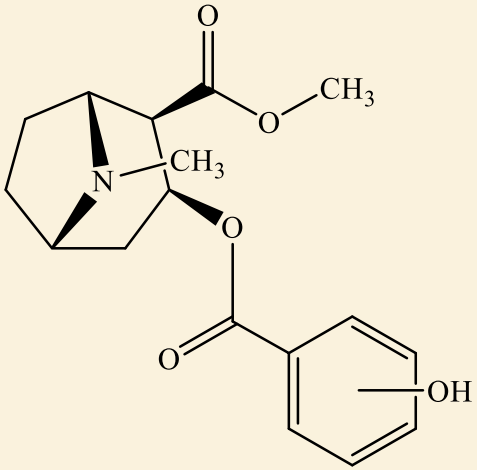
- By incorporation of the formed metabolite into hair.
  - Lipophilicity or lipid solubility (melanin affinity).
  - Basicity.
- By parent drug metabolism in the hair.
  - Convert the parent drug to the desired metabolite by enzymes in the papilla or hair shaft.

THC

- Commonly, THCA in hair is tested to show use of parent THC.
- Glucuronide: Pichini *et al*., FSI, 2015.

Cocaine

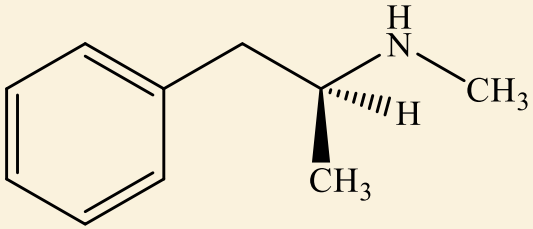
- Numerous impurities in illicit and pharmaceutical cocaine.
- Multiple metabolites of cocaine have been identified.
- Possible metabolite set to demonstrate use of parent cocaine:



ortho, meta & para-Hydroxycocaines

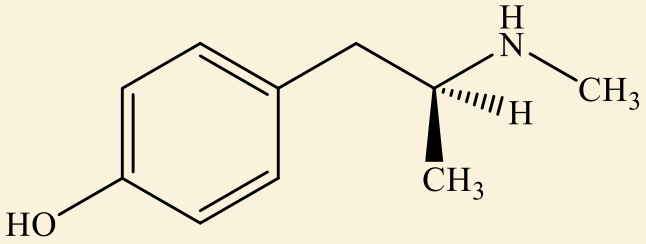
Amphetamines

- Possible metabolite set to demonstrate use of methamphetamine/amphetamine would be the hydroxyamphetamines.



Methamphetamine

CYP2D6
→



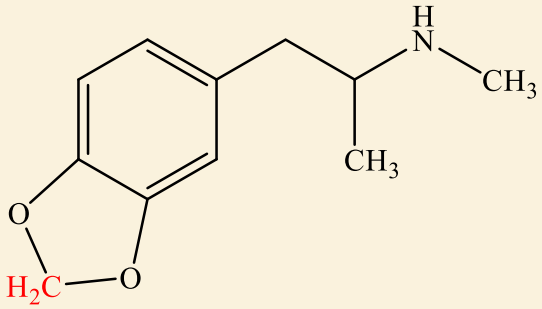
4-Hydroxy- or
para-Hydroxymethamphetamine

Amphetamines (continued)

- *ortho*-, *meta*- and *para*- (or 2-, 3-, and 4-) Hydroxymethamphetamines themselves may be produced by the action of oxidizing agents on methamphetamine deposited on hair.
- Glucuronide or sulfate conjugates of the hydroxy amphetamines to show use of the parent drugs.

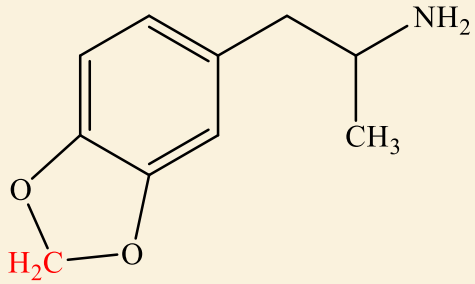
Amphetamines (continued)

- Possible metabolite set to demonstrate use of MDMA/MDA:



MDMA

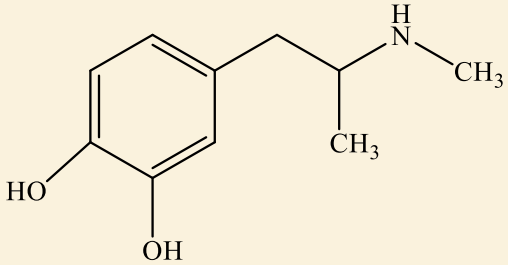
↓ CYP2D6



MDA

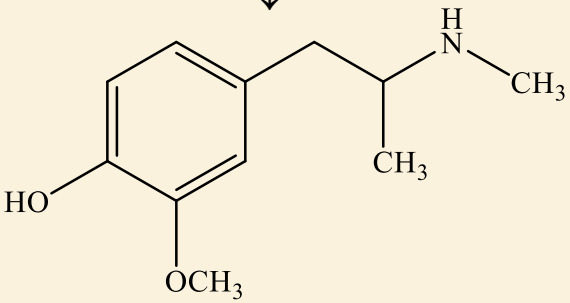
CYP2D6, 3A4, 1A2, 2B6

→



3,4-Dihydroxymethamphetamine

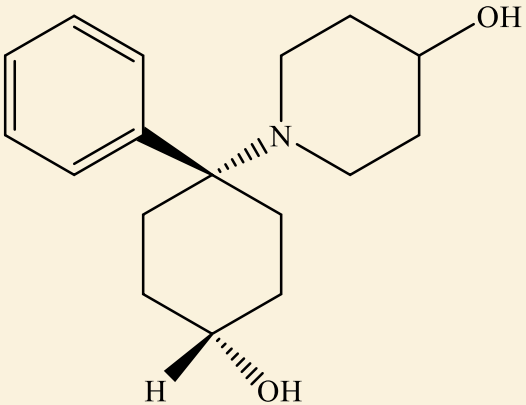
↓ COMT



4-Hydroxy-3-methoxymethamphetamine

Phencyclidine (PCP)

- Possible metabolite to demonstrate use of parent drug:
  - *trans*-PCPdiol (Nakahara *et al.,* JAT, 1997).



- Hydroxyphencyclidines may be produced by the action of oxidizing agents on PCP deposited on hair.

Codeine & Morphine

- Possible metabolites to demonstrate use of either parent drug:
  - Norcodeine (Codeine; CYP3A4).
  - Normorphine (Morphine; CYP3A4).
  - Glucuronide conjugates of either drug (UGT).

Hydrocodone & Hydromorphone

- Possible metabolites to demonstrate use of either parent drug:
  - Glucuronide conjugates (UGT).
  - nor Metabolites (CYP3A4).

Oxycodone & Oxymorphone

- Possible metabolites to demonstrate use of either parent drug:
  - nor Metabolites (CYP3A4).
  - Glucuronide conjugates (UGT).

Metabolites in Hair to Show Use of a Parent Drug

- Choices for metabolites to demonstrate that a drug or drug class was used by a donor currently exist.
- Drug metabolites exist in hair as the result of complex processes that probably include a combination of incorporation and metabolism in hair/hair bulb.
- Drug metabolism may be limited in a small number of cases due to polymorphism and other enzyme inactivation.

Potential Studies

- Incidence of enzymatic oxidation failures.
  - *e.g.* Demethylation of opioids or hydroxylation of amphetamines.
- Incidence of demethylenation (MDMA & MDA).
- Oxidation of surface drug contamination using a broader range of potential hair products.
- White, FSR, 2017.

A **lot** remains to be accomplished.

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