Caffeine: An Overview

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This work was supported by the U.S. Army Medical Research and Materiel Command (USAMRMC). The views, opinions and/or findings in this report are those of the authors, and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other official documentation. Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the use of volunteers in research. For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law CFR 46. Citation of commercial organization and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

Dr. Lieberman serves as the government liaison to the ILSI NA Caffeine Working Group. Support for attending this meeting was provided by ILSI NA.
Topics to be Addressed: Some Basic Facts About Caffeine

- Why is caffeine so interesting?
- Why did caffeine-containing plants evolve?
- Mechanism of action of caffeine in the brain
- Patterns of caffeine intake over the last decade
- CNS Regulation of caffeine intake
Why is Caffeine so Interesting?

- Most widely consumed psychoactive substance: ~80% of US population are regular consumers (only competition is alcohol: ~60% of US adult population are regular consumers)
- It undisputedly alters brain function and behavior in doses present in food, drugs, and dietary supplements
- Naturally present and added to a wide variety of products to gain competitive advance
- Removed from a wide variety of products to gain competitive advance
Caffeine Presents a Complex Challenge for Regulatory and Public Health Authorities

- Present naturally but also added to some products
- Effects are dose-dependent
- Huge, sometimes contradictory, literature on behavioral, physiological, and health-related effects of caffeine
Why Else is Caffeine Interesting?
Recent FDA Statements

- “While patterns of use of caffeine-containing products appear to be changing, the implications of these changes for public health are not well understood.”

- “It is commonly stated that different types of caffeinated products are substituted for each other (e.g. caffeine-containing energy drinks for coffee and vice versa), there are few data documenting this assertion.”

Caffeine is Unique

A non-nutritive food constituent classified and sold as:

- A Food
- A Drug
- A Dietary Supplement
Why did Caffeine Evolve & Why is it Found in Different Plants?

The coffee genome provides insight into the convergent evolution of caffeine biosynthesis. Denoeud et al., Science 345, 1181 (2014); DOI: 10.1126/science.1255274

Convergent Evolution: Different plant species took different evolutionary paths but converged independently on a metabolic pathway that yields caffeine.

Also Citrus
Natural Sources of Caffeine

- Orange Tree with flower
- Darjeeling Tea Plant
- Cocoa Tree
- Kona Coffee Tree

Source: konagourmetcoffee.net
Reported Functions of Caffeine in Plants

• Ask the botanists and entomologists
• To repel insects
  — Caffeine is bitter and insects avoid bitter tasting plants
  — Caffeine has been shown to be an effective insect repellant
• Herbicidal: When leaves of caffeine-containing plants fall they may prevent other plants from growing
• Some plants appear to use low doses of caffeine to attract insects to increase pollination – their nectar contains caffeine
• Low levels of caffeine are found in citrus plants, including their flowers

• Honeybees, when ‘rewarded’ with low doses of caffeine in nectar vs. ‘placebo’, are much more likely to remember the scent 24-hours later

• As a consequence, the plant is more likely to be pollinated and reproduce
Background
Some Key Facts About Caffeine

Caffeine (1,3,7-trimethylxanthine) and its metabolites

- The principal metabolic pathway, which accounts for approximately 95% of initial breakdown of caffeine, is catalyzed by the cytochrome P450 enzyme CYP1A2 in the liver.
- The process begins with removal of a methyl group to form paraxanthine and, to a lesser extent, theobromine and theophylline.
<table>
<thead>
<tr>
<th>Item</th>
<th>Caffeine Content (mg/serving)</th>
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</thead>
<tbody>
<tr>
<td><strong>Coffee (5 oz)</strong></td>
<td></td>
</tr>
<tr>
<td>Drip method</td>
<td>90-150 mg</td>
</tr>
<tr>
<td>Instant</td>
<td>40-108 mg</td>
</tr>
<tr>
<td>Tea, loose or bags</td>
<td>9-33 mg</td>
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<tr>
<td><strong>Cola Beverages (12 oz)</strong></td>
<td></td>
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<tr>
<td></td>
<td>35-47 mg</td>
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<tr>
<td><strong>Other soft drinks (12 oz)</strong></td>
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<tr>
<td>(e.g. Dr. Pepper®, Mountain Dew®, some root beers)</td>
<td>23-55 mg</td>
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<tr>
<td><em><em>Energy drinks (8 oz</em>)</em>*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65-80 mg</td>
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<tr>
<td><strong>Energy shots (2 oz)</strong></td>
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<tr>
<td></td>
<td>138-220 mg</td>
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<tr>
<td><strong>Dietary supplements</strong></td>
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<tr>
<td>(weight loss, etc)</td>
<td>75-320 mg</td>
</tr>
</tbody>
</table>
Fundamentals of Caffeine Metabolism

• Half-life of caffeine in healthy adult is approximately 4-5 hours
  – Heavy users are faster metabolizers
  – Cigarette smokers are faster metabolizers and consume more caffeine
  – Pregnant women are slower metabolizers
Caffeine’s Mechanism of Action

• Caffeine’s behavioral effects, as well as its positive effects on physical performance, are attributable to blockade of central adenosine receptors
  — Same in humans and insects

• Adenosine is an inhibitory neuromodulator in the CNS that has sedative-like properties
  — Four subtypes – A₁, A₂a, A₂b and A₃ – of G-protein-coupled adenosine receptors have been identified

• Adenosine A₁ and A₂a receptors in the brain are responsible for behavioral effects of caffeine, but the contribution of each is uncertain
Stability of Caffeine Intake Over Time
U.S. National Health and Nutrition Examination Survey (NHANES) V. Fulgoni et al. (submitted)

- NHANES is a Center for Disease Control (CDC) sponsored survey conducted every 2-years of a representative sample of the U.S. population (5000 adults)
- NHANES 2001-2012, n=29,700 adults
- Caffeine intake was estimated based on 24-hour total dietary recall (NCI was method used to estimate usual intake)
- 89% adult US population consume some caffeine on an any given day
- Mean caffeine intake of U.S. adults is 170-180 mg/day
- Consistent with Mitchell et al. “Beverage Caffeine Intakes in the U.S.” Food and Chemical Toxicology 62 (2014) – based on a survey of beverage intake
NHANES: Caffeine Intake Stability Over Time  Fulgoni et al. (submitted)

- 2001-2002 —
  - 19-30 yrs: 119 mg/day
  - 31-50 yrs: 205 mg/day
  - 51-70 yrs: 196 mg/day

- 2011-2012 —
  - 19-30 yrs: 110 mg/day
  - 31-50 yrs: 188 mg/day
  - 51-70 yrs: 208 mg/day

180 mg/day

172 mg/day
Trends in Total Caffeine Intake: NHANES 2001-2012 Fulgoni et al. (submitted)

5,000 adults sampled every 2 years
Stability of Caffeine Intake Over Longer Periods of Time

- 1975: 185 mg/d*
- 1989: 168 mg/d*
- 2011-2012 (NHANES): 172 mg/d

Caffeine and Human Behavior

- Caffeine in moderate doses improves cognitive functions that require maintenance of alertness
  - Vigilance
  - Attention
  - Reaction Time
  - Real world tasks like driving

Must Rapidly Detect Target Before It Disappears
Caffeine’s Effects on Mood

• Caffeine’s positive effects on mood are consistent with its effects on cognitive performance
  – Alertness/vigor increase
  – Fatigue decreases

• Caffeine’s effects on behavior appear to be greatest when it is administered in moderate doses
  – However, a ‘moderate’ dose can vary substantially depending on various individual factors including:
    › extent of regular caffeine intake
    › individual differences in caffeine metabolism
    › genetic differences
The Acute Effects of Moderate Doses of Caffeine on Human Mood Are Dose Dependent

<table>
<thead>
<tr>
<th>Dose of Caffeine Administered (mg)</th>
<th>Mean Difference Score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>128</td>
<td>2</td>
</tr>
<tr>
<td>256</td>
<td>0</td>
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* P < 0.05

Caffeine and Mood: Implications

- Humans may use caffeine to get positive or negative behavioral effects

- Most caffeine consumers choose to use moderate doses of caffeine and have characteristic and regular patterns of consumption

- Adverse effects on mood can occur at high doses
  - Increased anxiety; jitteriness
  - high dose users may be seeking these ‘adverse’ effects -- stimulation-seeking behavior most likely to be seen in young males
There are many reasons for consuming – some social and perhaps some biological.

But why is caffeine’s ad libitum intake so consistent over time in spite of large changes in product choice, availability, and social norms?

− A possible answer: Because humans are very good at sensing and regulating our mood state?

Caffeine’s positive behavioral effects appear to be optimal at dose of about 1 cup of coffee.

If humans are using caffeine to ‘optimize’ mood then an optimal dose will produce the most desirable mood.

− Increased vigor, less fatigue, more mental ‘energy’

‘Goldilocks’ zone for optimal adenosine receptor antagonism.
Conclusions

• Caffeine’s behavioral effects are produced by blockade of central adenosine receptors
• Caffeine is consumed in moderate doses by most of the U.S. adult population
  — Current estimated mean intake = 183 mg/day NHANES 2001-12
• Caffeine intake has not increased in the last 12 years and perhaps the last 40 years
• Coffee continues to be the primary source of caffeine in the diet (<50% in all age groups)
THE END