

# Effects of coffee on the central nervous system

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# History of coffee

## Description of the properties of coffee

- Coffee was first consumed as a "medical nutrient" because of its stimulatory effects on digestion...
- In the 11th century, the virtues of caffeine were described by Avicenne
- Prosper Alpin, an Italian botanist and medical doctor studied coffee during a trip to Egypt in 1580
- The first citations of coffee are from Antoine de Jussieu in 1713 and Carl von Linné in 1753
- The Encyclopedia by Diderot and d'Alembert (1751-1772) describes the virtues of coffee in "obesity and migraine"

# Caffeine, the main psychoactive component of coffee

- Caffeine

- isolated from coffee beans in 1820
- the psychoactive substance most widely consumed throughout the world
- coffee, tea, mate, sodas; chocolate products; cola nuts; analgesic and sliming medications, and in stimulants

- World consumption of caffeine

- adults: mean world consumption: 1-2 mg/kg/d (1-2 cups); 2.4-4.0 mg/kg/d in the USA (2-4 cups) and the UK and up to 7.0 mg/kg/d in Scandinavia (7 cups)
- children: 1.0 mg/kg/d in the USA and 1.8 mg/kg/d in Denmark



# Concentrations of caffeine in coffee

- Content on caffeine in a cup of coffee (150 ml)
- Arabica: 50-120 mg
- Robusta: 100-250 mg
- Filtered coffee: 50-175 mg
- Espresso: 40-110 mg
- Soluble coffee: 35-110 mg
- Decaffeinated coffee: 1-6 mg
  
- Low to moderate consumption: 1-3 cups/day
- High consumption: over 5 cups/day

# Effects of coffee and caffeine

- Low to moderate consumption (50-250 mg in one sitting = 1 small cup to two large cups of coffee)
  - ↳ positive effects: feeling of well-being, relaxation, positive mood, energy, increased alertness, higher capacity of concentration
- High to very high doses (400-800 mg in one sitting = 5 to 10 large cups of coffee)
  - ↳ negative effects: nervousness, anxiety, aggressiveness, insomnia, tachycardia, trembling
- Moderate consumption of coffee and caffeine is not considered to be a health concern

# Nutritional properties of coffee

- **The composition of coffee is quite complex**
  - Coffee contains more than 2000 substances. In addition to caffeine, coffee contains proteins, minerals, vitamins and numerous other constituents
- **Minerals**
  - Calcium (3 mg), sodium (1 mg), low quantities of iron, zinc and copper
- **Vitamins**
  - Vit B3 (400-1200  $\mu\text{g}$ ), B2 (2  $\mu\text{g}$ ), B5 (80  $\mu\text{g}$ ) and B6 (0,6  $\mu\text{g}$ )
- **Phenolic compounds**
  - chlorogenic acids : antioxydant properties and cellular detoxification. A normal coffee consumption delivers 0.5-1 g polyphenols which activate enzymes for the reduction of free radicals
- **Diterpenes**
  - kawheol and cafestol: antioxydant properties and cellular detoxification in vitro and in vivo

# Why does coffee have a negative image?

- **Human studies**

- Protocols poorly designed, choice of subjects, information on the objectives of the study, biased interpretations
- Confusing factors associated with coffee consumption like tobacco
- Wrong estimation of the quantities of coffee or caffeine ingested

- **Animal studies**

- Doses tested too high, unrealistic
- Non justified extrapolation to humans
- Biased selection of literature

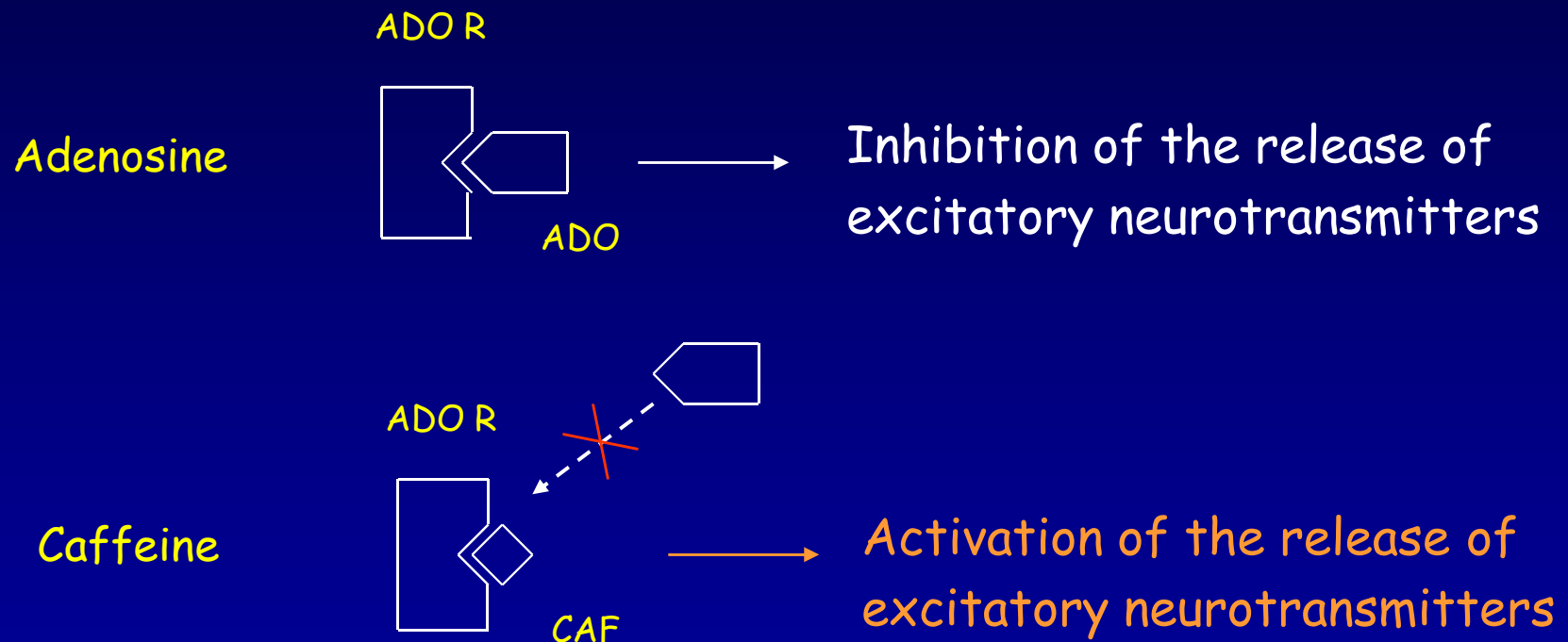


# Mechanism of action of caffeine in the brain

# Mechanism of action of caffeine in the brain

- At the doses reached after the ingestion of one or several cups of coffee
  - ✎ main effects by binding to adenosine receptors, mainly A1 (12  $\mu\text{M}$ ) and A2a (2  $\mu\text{M}$ ) subtypes
- Adenosine acts as a neuromodulator
  - ✎ by limiting or inhibiting the release of most excitatory neurotransmitters
- Distribution of adenosine receptors
  - A1: in all cerebral regions, high density in cerebral and cerebellar cortex, hippocampus and thalamus
  - ✎ A2a: mainly in the striatum

# Mechanism of action of caffeine in the brain



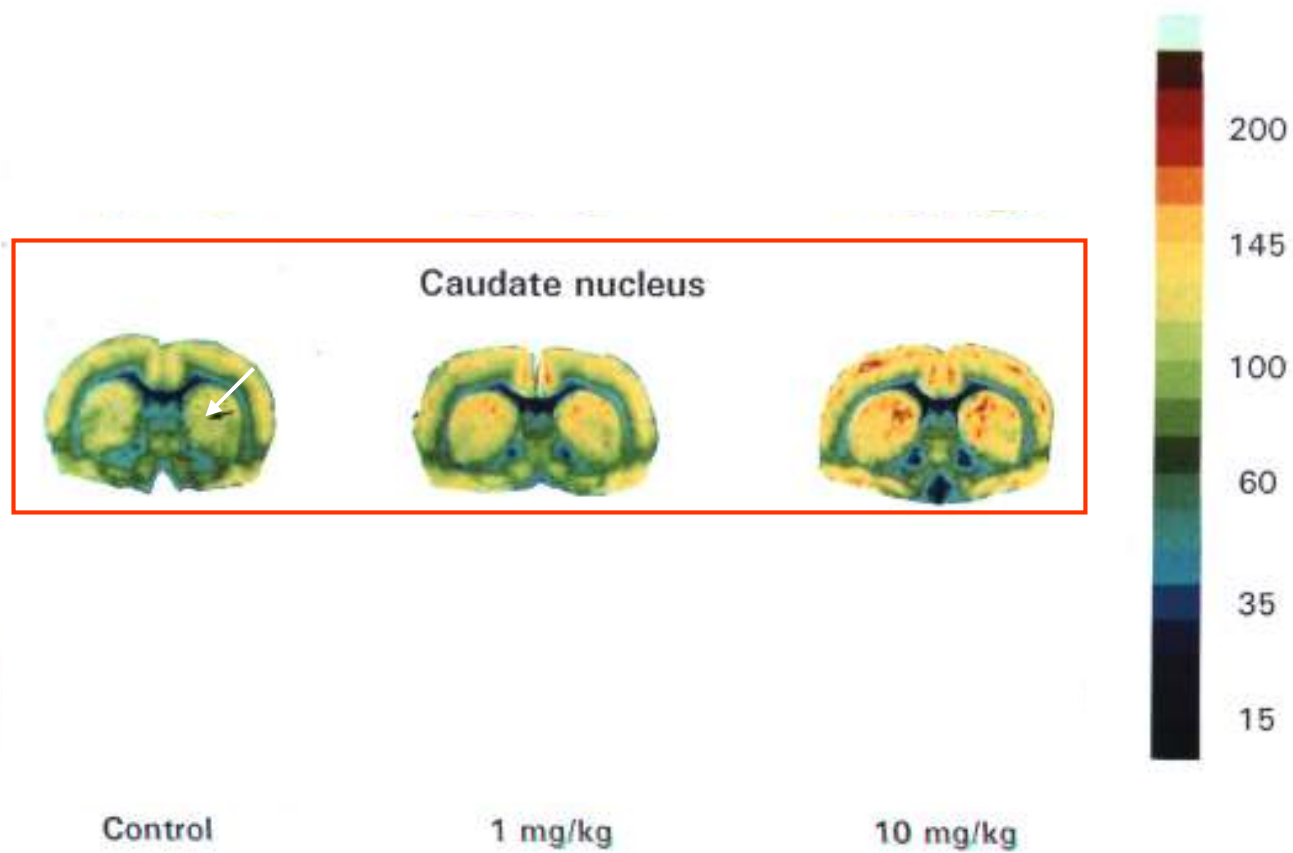


# Effects of coffee on the brain: physiology

# Effects of caffeine on the brain: Locomotion

- The effects of caffeine on locomotion have been known for quite a long time
- **Biphasic effects**
  - Low to moderate doses: stimulation of motor activity
  - High doses: reduction of motor activity
- **In the rat**, activation at a low dose: 1 mg/kg (1 cup of coffee) increases functional and electrophysiological activity in the striatum, cerebral area mediating locomotion
- **In humans**, increased motor activity (recording of field activity, increase in typing speed...)

## EFFECTS OF ACUTE ADMINISTRATION OF CAFFEINE ON CEREBRAL GLUCOSE UTILIZATION



# Effects of caffeine on the brain:

## Sleep

- Sleep is one of the functions most sensitive to the effects of coffee and caffeine. These effects reflect the blockade of the hypnotic properties of adenosine by caffeine
- **In humans, 100 mg of caffeine (one cup of coffee) at bedtime:**
  - increases the latency to sleep and decreases the quality of sleep, mainly the phases of deep sleep, but has no effect on REM sleep
  - the effect is persisting for about 3-4 h, sometimes longer
- **In the rat**, a low dose of 1 mg/kg caffeine (one cup of coffee) increases functional activity in brain regions mediating the sleep-wake cycle

# Effects of caffeine on sleep: possible mechanisms?

- Adenosine promotes sleep and adenosine levels increase during prolonged wakefulness
- **A1 receptors are involved in sleep regulation**
  - Induction of sleep and of a "sleep-type" EEG
  - Specific inhibition of A1 receptors in the basal forebrain reduces REM sleep and increases wakefulness
- **A2a receptors are also involved**
  - Tonic role in REM sleep
  - Suppress sleep-inducing effects of A2a agonists in mice lacking A2A receptors

# Effects of caffeine on the brain: Alertness, mood and performance

- Low doses of caffeine (20-200 mg in one sitting) have positive effects on mood, vigilance and energy
  - improvement of self-confidence, concentration abilities and efficacy in intellectual tasks
  - effects mostly marked in situations with reduced vigilance: after lunch, regular cold, night work...
  - improvement of visual perception, seen in car driving (improved perception of signals, braking and speeding); sleep pressure during driving is improved as efficiently by a coffee as by a 15 min nap; resetting the biological clock, used for jet lag and by plane pilots
- Effects of caffeine on memory and performance appear to be rather indirect effects
  - on vigilance, concentration, information processing and reduction of fatigability

# Effects of caffeine on the brain: Headache and migraine

- Pain during headache and migraine is partly resulting from the vasodilation of cerebral blood vessels induced by A<sub>2</sub> adenosine receptors located on blood vessels
- **Caffeine contained in coffee**
  - reduces pain during headache and migraine via its vasoconstrictive properties
- **Caffeine alone**
  - is present in analgesic preparations
  - is able to potentiate by about 60% the analgesic properties of some drugs (aspirin, ibuprofen) by a mechanism not yet clarified

# Effects of coffee and caffeine on brain: Anxiety

- Caffeine may generate anxiety
  - only at doses much larger than the regular doses in the normal population (1000-1500 mg caffeine)
  - at low doses in a subset of sensitive individuals
  - agonists of the A1 receptor display anxiolytic properties while antagonists are anxiogenic
  - KO mice for the A1R and A2aR have higher levels of anxiety-like responses
  - in humans, differences in the anxiogenic response to caffeine are linked to two polymorphisms of the gene coding for the A2a receptor
- This leads these particularly sensitive individuals to a spontaneous reduction of coffee consumption



# Effects of coffee on the brain: pathology

# Effects of caffeine on cognition in elderly subjects

- **Relation between usual caffeine intake and cognition: population studies**
  - Two Dutch studies on 1400-1900 individuals aged 24-81 y show positive effects on reaction time and verbal memory, no age-related difference
  - A British study on 9000 subjects found the same effects but largest improvement in the older men and women
  - A study on 676 Finish, Italian and Dutch men showed a J-shaped relation between caffeine intake and cognitive decline, lower decline for 3 cups of coffee daily (reduced by 4.3 fold compared to non-consumers)
  - Two recent studies (California and France) on both sexes reported an improvement of cognitive abilities only in women, with a more marked effect for women over 80. No effect in men and no effect of decaffeinated coffee.
- **Possible mechanisms**
  - Ingested caffeine antagonizes A2A receptors located at the surface of cholinergic neurons. Stimulation of acetylcholine neurotransmission which has facilitatory effects on memory.

# Effects of coffee and caffeine on Parkinson's disease (1)

- Parkinson's disease (PD) is the result of the degeneration of dopaminergic cell bodies in the substantia nigra which connects to the striatum
  - Treatment by an analogue of dopamine, L-dopa which loses its efficacy in the long term, leading to the aggravation of trembling and difficulties to walk
  - Since the molecular target of caffeine at low doses is located in the striatum (via A2AR), caffeine has been suggested as an adjunctive drug to L-dopa therapy; caffeine leads to an improvement of trembling

# Effects of coffee and caffeine on Parkinson's disease (2)

- Mayo Clinic study: coffee consumers reduce their risk to develop PD by a factor of about 2 compared to non-consumers
- Study performed over 30 years on 8,000 Japanese-American men in Hawaii:
  - the more the subjects consume coffee, the lower the incidence of PD. Those who consume 3-4 cups/day have a 5-fold lower risk than non-consumers to develop PD
- Mechanism is unknown
  - aversion for coffee long the development of the disease?
  - protective effect of caffeine against dopamine depletion?

# Effects of coffee and caffeine on Parkinson's disease (3)

- **In women**
  - the risk of PD is similar for women using hormones or not
  - use of hormones associated with a 34% lower risk with low coffee consumption (less than half a cup/day)
  - use of hormones associated with a 55% higher risk with high coffee consumption (over 5 cups/day)
  - caffeine-estrogen interaction is postulated
- **In the elderly population**
  - no association between signs of PD and coffee consumption
  - no relief of PD clinical signs by coffee

# Effects of coffee and caffeine

## Alzheimer's disease: human data

- AD is the most common cause for dementia (5% of the population over 65 years)
  - Recent meta-analysis: two case-control studies and two cohort studies between 1990 and 2002
  - Pooled risk reduced to 0.73 for consumers
  - Heterogeneity between the studies
  - Necessity to confirm data with prospective studies

# Effects of coffee and caffeine

## Alzheimer's disease: preclinical studies

- **Potential role of caffeine**
  - Prevention of neuronal death caused by  $\beta$ -amyloid protein
  - Improvement of cognitive deficits
- **Role of antioxidants contained in coffee**
  - Suppress inflammation
  - Neuroprotective properties against  $\beta$ -amyloid toxicity
  - Improve cognitive performance in animal models of AD
  - Shown mainly with ferulic acid and chlorogenic acids
- **Potential role of trigonelline**
  - Improves neurite outgrowth
  - Protect axons and dendrites from  $\beta$ -amyloid toxicity
  - Preserves cognitive abilities

# Effects of coffee and caffeine on stroke

- In man, chronic consumption of caffeine/coffee is inversely related to the risk of fatal and non fatal stroke
- Stroke outcome is better in patients with measurable levels of caffeine in the CSF at the time of stroke
- Risk of thrombo-embolic stroke is increased in hypertensive men (55-68 y, BP>140 and 90 mm Hg) consuming daily 3 cups or more of coffee (RR: 2.1)
- Adenosine A<sub>2A</sub> receptors play a prominent role in the development of ischemic injury in the brain. Potential for anatomical and functional neuroprotection against stroke by A<sub>2A</sub> receptor antagonists
- Efficient protection against stroke by caffeinol (caffeine 8-9 mg/kg-ethanol 0.3-0.4 g/kg mixture; 5-7 cups of coffee and 2 strong alcohol drinks) given within 100 min following a stroke. Sixty percent of treated patients fully recovered compared to 26% of the control group

# Are we dependent on coffee and caffeine? (1)

- Caffeine most often in coffee is consumed daily by most individuals: some of them pretend they cannot cut off or stop drinking coffee
- **Arguments for a dependence?**
  - The abrupt cessation of caffeine consumption can lead to a **withdrawal syndrome**: headache, feeling of weakness and nervousness
  - These symptoms are only found in some individuals, they are light to moderate and last for only about 24-48 h
  - They are by no means comparable to those induced by hard drugs (cocaine, amphetamine, morphine or nicotine)
- **Arguments against a dependence?**
  - There is **no tolerance** to the central effects of caffeine

## Are we dependent on coffee and caffeine? (2)

- Characteristics of drugs of dependence (cocaine, amphetamine, morphine, nicotine)
  - specific increase of functional activity in the shell of the nucleus accumbens (NA)
  - induction of the release of dopamine in the shell of the NA
- These two effects are specific and occur at low doses of these drugs: these properties reflect their high addictive potential

## Are we dependent on coffee and caffeine? (3)

- Conversely to hard drugs, the activation of the shell of the NA by caffeine only occurs at high doses
  - at 10 mg/kg (8-10 cups of coffee in one sitting) and this non specific effect occurs simultaneously to the activation of numerous brain regions
  - these generalized increases in functional activity most likely reflect the negative and aversive effects of the ingestion of high doses of caffeine
- Caffeine does not induce any release of dopamine in the shell of the NA (0.5-5 mg/kg)
- Caffeine has reinforcing properties but does not activate the circuit of dependence and reward

# Conclusions

## Coffee and caffeine

- ☞ stimulate locomotion and disturb sleep
- ☞ ameliorate mood and performance
- ☞ might increase anxiety in a subset of people
- ☞ act on headaches and are able to potentiate the effects of analgesic medications
- ☞ prevent cognitive decline
- ☞ are neuroprotective in PD, AD and stroke
- ☞ do not activate the circuits of dependence

## Moderate consumption of coffee and caffeine

- ☞ has beneficial central effects
- ☞ can contribute to a healthy and balanced daily diet



**Thank you for your attention**