

## Coffee effects on the aging brain

### Caffeine lowers risk of Alzheimer's disease

- Barranco Quintana (2007) reviewed human epidemiologic studies showing association of coffee intake with reduced risk
- Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice (Arendash 2009)
- Caffeine acts through adenosine receptor to give neuroprotection (Stone 2009)

### Caffeine lowers risk of Parkinson's disease

- Honolulu Heart Program, followed Japanese-American men since 1965.
- Measured caffeine consumption among the men in 1965 and again in 1971, and in the mid-1990's identified patients who had gotten Parkinson's disease.

- Men who had not been coffee-drinkers at the beginning of the study were five times more likely to get Parkinson's disease than men who drank large amounts of coffee, with intermediate risk for men who drank less coffee.
- Results were replicated in the
  - Nurses Health study
  - Health Professionals Study,
- Both found caffeine protective against Parkinson's.

## How does coffee keep you alert?

- Scientists have long hypothesized that there is some "sleep substance" that gradually accumulates during the day, and that when that substance reaches high enough levels, it triggers fatigue and then sleep.

- A plausible mechanism might be that the sleep substance is a by-product of producing energy; the more energy we consume, the more sleep substance is produced as a waste product, the more we feel sleepy.
- The best evidence today is that the sleep substance is adenosine, and that coffee blocks adenosine's effects.

## Adenosine

- Adenosine meets the criterion of being a by-product of producing energy.
- It is part of the molecule, adenosine triphosphate (ATP), that our bodies use to store energy.
- ATP is like a battery.
- Our cells synthesize ATP using energy from sugar, fat, and anything else we eat.

- When our cells need a little shot of energy, they break down ATP into adenosine and three phosphate molecules (hence the tri-phosphate).
- Breaking those chemical bonds releases the energy that was stored when ATP was synthesized.
- Over the course of a day, as we are physically and mentally active, we consume energy (ATP) and release adenosine.

- Cells in our brains (and throughout our bodies) have adenosine receptors that sense the level of adenosine.
- Nerve cells in particular have lots of adenosine receptors; when adenosine concentrations are high, it inhibits nerve transmission.
- Adenosine is the most potent inhibitor of neural transmission; it is like a super-regulator that overrides all the other neurotransmitters, and forces shut down (sleep) if we need to recharge our ATP batteries.

- The basal forebrain is a region that regulates wakefulness.
- Adenosine promotes sleep by blocking the activity of neurons in the basal forebrain.
- Levels of adenosine rise steadily in the basal forebrain the longer we are awake.

- When researchers microinject adenosine into these basal forebrain areas in rats, it induces sleep; in contrast, injection of an adenosine antagonist induces wakefulness.
- When we are sleep deprived our brains produce more adenosine receptors in an attempt to make us more sensitive to adenosine and force us to sleep.
- This over-production of the adenosine receptor may be the molecular basis of "sleep deficit"; the extra adenosine receptors may make us sensitive to lower levels of adenosine and thus make us sleep longer than normal.

## Two types of adenosine receptors

- There are two types of adenosine receptors in our brain, with different effects.
- The A1 adenosine receptor is very abundant in the cortex, which is the part of the brain responsible for most of what we consider higher brain functions: solving problems, planning, complex memory.

- A1 receptors are also abundant in the hippocampus, which is critical in memory formation, in the cerebellum, which coordinates movement, and in the hypothalamus, which is a super-regulator of internal body functions.
- When adenosine binds to the A1 receptor on a neuron, it directly inhibits firing of the neuron.

- At the molecular level, when the A1 receptor is activated, it activates potassium channels and inhibits calcium channels, which results in a hyperpolarized membrane, which in turn inhibits firing of the neuron.

- Caffeine has the opposite effect to adenosine (it is an adenosine antagonist).
- Caffeine competes with adenosine to bind to the adenosine receptors, but when caffeine binds the receptor, it blocks the signal that the receptor sends.
- So, part of the story of how caffeine affects our brains is that it prevents adenosine from binding to the A1 receptors; the A1 receptor is not activated, potassium channels close and calcium channels open, the membrane is less polarized, and it's easier for the neuron to fire.

- Caffeine lets the nerves in our important thinking and memory areas (cortex, hippocampus) keep firing.
- The neurons that have adenosine receptors can themselves produce neurotransmitters, such as dopamine, serotonin, adrenaline, noradrenaline, glutamate, and GABA.
- So it's not always easy to determine if an effect is due directly to adenosine or instead is due to modulated release of these other neurotransmitters.

### A2A: the second important adenosine receptor

- The A2A receptor is most abundant in the basal ganglia, the part of our brain that controls voluntary motor activity.
- The basal ganglia are involved in Parkinson's disease, which is a movement disorder.
- About 2 percent of people over age 65 have Parkinson's disease, though it affects younger people (including the actor Michael J. Fox).

- Parkinson's is characterized by insufficient dopamine in the basal ganglia, and is treated with the drug L-Dopa (a pre-cursor to dopamine) which you may remember from the film Awakenings.
- Dopamine increases motor activity; it is antagonized by adenosine, which reduces motor activity.

- When caffeine binds to the A2A receptors in the basal ganglia it acts in a way similar to dopamine to increase motor activity.
- This stimulation of motor activity via the basal ganglia, along with adrenaline effects, is how caffeine makes us want to get up and move.

## Coffee and Parkinson's

- Because of the evidence that caffeine is protective against Parkinson's disease, and because it is known to bind the A2A receptor, drugs have recently been developed that bind selectively to the adenosine A2A receptors (but not to the more widespread A1 receptor) and tested in animal models of Parkinson's.
- A2A antagonists improved the symptoms of Parkinson's, and human clinical trials are now underway.
- The combination of caffeine or other A2A antagonists with dopaminergic treatments such as L-dopa is a promising route for treating Parkinson's.

## References

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- Arendash GW, Mori T, Cao C, Mamcarz M, Runfeldt M, Dickson A, Rezai-Zadeh K, Tane J, Citron BA, Lin X, Echeverria V, Potter H. Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. *J Alzheimers Dis.* 2009 Jul;17(3):661-80.
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