

EFFECTS OF COFFEE ON THE CENTRAL NERVOUS SYSTEM

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Historically, coffee was first consumed as a .medical nutrient. because of its stimulatory effects on digestion. These virtues of coffee were described by Razes, a Persian of the late 9th century and Avicenne, an Arab living in the 11th century. Then, Prosper Albin, an Italian botanist and medical doctor studied coffee during a trip to Egypt in 1580 and mentioned that .Arabs and Egyptians use it to make a kind of infusion that is popular and that they drink in place of wine.. 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-

1752) described the virtues of coffee in .obesity or headaches. And mention that .it can be harmful to people who consume it in large quantities.

The main psychoactive component in coffee is caffeine. Caffeine was isolated from coffee beans in 1820. It is considered as the most widely used psychoactive substance in the world. Most of the caffeine consumed comes from dietary sources such as coffee, tea, cola drinks and chocolate.

Caffeine is also present in many non-prescription drugs such as cold remedies, analgesics, slimming drugs and stimulants. The most notable behavioral effects of caffeine occur after low to moderate doses (50-300 mg) and are increased alertness, energy and ability to concentrate.

Moderate caffeine consumption leads very rarely to health risks (Benowitz, 1990). Higher doses of caffeine rather induce negative effects such as anxiety, restlessness, insomnia and tachycardia, these effects being seen primarily in a small subset of caffeine sensitive individuals. In the present paper we will review the available and most recent data on caffeine consumption and the known effects of caffeine on the central nervous system.

1. Coffee and caffeine consumption

Caffeine is present in a number of dietary sources consumed worldwide, i.e., tea, coffee, cocoa beverages, candy bars, and soft drinks. The content of caffeine of these various food items ranges from 70-220 mg/150 ml for coffee to 30-50 mg/150 ml for tea, 32-70 mg/330 ml for cola and 4 mg/150 ml for cocoa (Debry, 1994). A low to moderat consumption represents 1-3 cups of coffee per day while a high consumption is considered to be over 5 cups daily. According to a recent survey (Barone and Roberts, 1996), the daily mean daily intake for the whole world population reaches 1-2 mg/kg/day (70-140 mg in a 70 kg individual, i.e. about 1-2 cups of coffee). In the United States, the intake of caffeine from all sources reaches 2.4 to 4.0 mg/kg (2-4 cups of coffee), two thirds of it coming from coffee in subjects aged more than 10 years. In Scandinavia, the mean daily intake of caffeine reaches 7.0 mg/kg/day (about 7 cups of coffee). In children, the mean daily consumption of caffeine recaches 1.0 mg/kg/day in the United States and 1.8 mg/kg/day in Danemark. In the young population, soft drinks represent 55%, chocolate foods and beverages 35-40% and tea 6-10% of the total caffeine intake (Ellison et al., 1995).

2. Mechanism of action of caffeine

Caffeine, at low concentrations reached after the consumption of one or two cups of coffee, acts as a non specific antagonist of both A1 and A2a adenosine receptors (Fredholm, 1995; Fredholm et al., 1999). Adenosine, by acting at the level of presynaptic A1 receptors, inhibits the release of numerous neurotransmitters such as glutamate,

GABA, acetylcholine and monoamines and is more efficient at the level of excitatory than inhibitory neurotransmission. Thus, caffeine by antagonizing the effects of endogenous adenosine increases

the firing rate of central neurons which is reflected by the changes in the pattern of the electroencephalogram (EEG) of arousal induced by caffeine ingestion. While the effects of caffeine acting at A1 receptors concern all brain regions because of the wide distribution of these receptors, the effects of caffeine at A2a receptors are limited to the striatum, the only area where these receptors can be found (Fredholm et al., 1999).

3. Effects of caffeine on locomotion

In the brain, locomotion is mediated by the nigrostriatal dopaminergic system. This system originates in neurons located in the substantia nigra, mainly pars compacta. They project to the globus pallidus and terminate in the caudate nucleus which is connected to the sensorimotor cortex (Figure 2.1).

Abbreviations: striato-nigral pathway in red: SN: substantia nigra, CAU: caudate nucleus, SMCX: sensorimotor cortex; areas involved in the regulation of the sleep-wake cycle: LC: locus coeruleus, MRAP: median raphe, DRAP: dorsal raphe; areas involved in reward and dependence: ATV: ventral tegmental area, NAC: nucleus accumbens, PFCX: prefrontal cortex.

In rats subjected to increasing doses of caffeine, the metabolic activity is already significantly increased in the caudate nucleus after the administration of the lowest dose of caffeine, 1 mg/kg to adult male rats (the mean human daily consumption, Figures 2.2 and 2.3). The functional activity of this nucleus is further increased at 2.5 mg/kg at which dose the activation spreads also to the substantia nigra pars compacta and globus pallidus. In the sensorimotor cortex the increase in metabolic activity is present only at 5 mg/kg, dose at which all the other structures remain activated. These 3 doses are in the range of the reported daily human consumption.

There is a good correlation between caffeine-induced functional activation of structures belonging to the nigrostriatal pathway and the well-known stimulant effects of caffeine on locomotion.

Indeed, the minimal dose of caffeine necessary to increase locomotion is 1.5 mg/kg and the direct administration of caffeine into the caudate nucleus modifies the spontaneous electrical activity of neurons (Okada et al., 1997).

Abbreviations: SNPC: substantia nigra pars compacta, DMCAU: dorsomedian caudate nucleus, GPAL: globus pallidus, SMCX: sensorimotor cortex. * $p < 0.05$, α $p < 0.01$, statistically significant differences from control.

4. Effects of caffeine on sleep

The serotonergic cell groupings, the medial and dorsal raphe nuclei as well as the noradrenergic cell grouping, the locus coeruleus that mediate the sleep-wake cycle (Figure 2.1) are very sensitive to caffeine. These structures are involved in the control of sleep, mood and well-being. In these 3 structures, metabolic activity is already activated after 1 mg/kg and remains increased at the higher doses of caffeine used, 2.5-10 mg/kg (Figures 2.3 and 2.4).

These data correlate well with the known sensitivity of sleep and mood to caffeine (Nehlig et al., 1992).

In humans, sleep seems to be the physiological function most sensitive to caffeine. Generally more than 200 mg caffeine are needed to affect sleep significantly. Caffeine prolongs sleep latency, shortens total sleep duration but preserves the dream phases of sleep.

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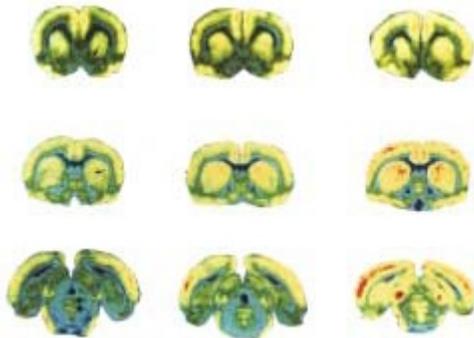


Figure 2.3. Effects of the administration of increasing doses of caffeine on cerebral metabolism in the brain of rats. On the autoradiograms of coronal rat brain sections taken at selected levels, it appears clearly that glucose metabolism is increased after 1 mg/kg caffeine compared to control levels in both the caudate nucleus and the raphe nuclei (indicated by black arrows). This effect persists at the dose of 10 mg/kg. Conversely, in the nucleus accumbens, glucose metabolism is only activated at the highest dose of caffeine, 10 mg/kg.

5. Effects of caffeine on alertness, mood and performance

Low doses of caffeine act positively on mood; subjects ingesting 20-200 mg of caffeine report that they feel energetic, imaginative, efficient, selfconfident, alert, able to concentrate and motivated to work (Griffiths and Mumford, 1995; Silverman et al., 1994). Recent studies reported that positive effects of low doses of caffeine (40-60 mg) on performance and well-being may be more beneficial in situations of low arousal, such as the post-lunch decrease in vigilance, the common cold (Smith et al., 1997, 1999), fatigue in drivers (Reyner et al., 2000) or during attention-requiring tasks (Lorist et al., 1994). The alerting effects of caffeine are also able to reverse the deleterious effects of a 36 h sleep deprivation (Patat et al., 2000). The influence of low doses of caffeine on mood correlates well with the significant increases in cerebral functional activity recorded in the areas involved in the regulation of wakefulness, mood and well-being, namely the locus coeruleus, and the median and dorsal raphe nuclei that occur after the administration of 1 mg/ kg of caffeine to rats (Figure 2.3).

6. Effects of caffeine on headache and migraine

Coffee or caffeine present in analgesic medications are able to relieve people from pain triggered by various types of headaches. The efficacy of caffeine in relieving headache induced by caffeine withdrawal which leads to cerebral vasodilatation has been repeatedly shown and seems to reflect the central vasoconstrictive properties of the methylxanthine. In tension-type headache, there are no vascular changes related to the attack and therefore the analgesic of caffeine per se or combined to other anti-pain medication is most likely mediated by other phenomena although it cannot be totally excluded that the vasoconstrictive effect of caffeine could add to the mechanisms involved in pain relief. Finally for migraine attacks, the literature is rather in favor of a decrease in cerebral blood flow during the attacks. The origin of pain in this pathology remains to be clearly defined; pain is attributed to the dilatation of the ipsilateral medial cerebral artery and also to the dilatation and increased pulsations of the superficial temporal artery and other extracranial arteries. The role of caffeine in pain relief in migraine is not clearly understood and has not been fully explored since the effect of caffeine per se or the comparison of anti-pain drug combinations with and without caffeine is missing (for review, see Nehlig, 2003).

7. Effects of caffeine on anxiety

Caffeine has been reported to generate anxiety when absorbed in excessive amounts in the general population or in low doses in specifically sensitive individuals (for review see Hughes, 1996). Nonusual or low consumers of caffeine appear to be more sensitive to anxiogenic and psychostimulant effects of caffeine than usual consumers (Uhde, 1990). The level of anxiety is also more markedly increased in naturally anxious individuals or subjects suffering from panic attacks compared to the normal population. These individuals show the tendency to reduce or stop their caffeine consumption because of the secondary unpleasant effects of the methylxanthine (Uhde, 1990) and their health status clearly improves after caffeine cessation (Bruce and Lader, 1989). Indeed, in sensitive subjects, panic attacks can occur after the absorption of a single cup of coffee (80-110 mg caffeine) (Uhde, 1988) while in normal individuals, only caffeine doses higher than normal consumption levels can induce significant anxiogenic effects (James and Crosbie, 1987).

8. Preventive effects of caffeine on Parkinson's disease

Parkinson's disease is caused by a severe degeneration of dopamine neurons in the substantia nigra which causes an incapacity to control voluntary movements and leads to tremor, akinesia, rigidity and postural instability. It is presently treated by the precursor of dopamine, Ldopa, not very active on tremor. However, this treatment leads to long term complications, including loss of drug efficacy and dyskinesia (Marsden, 1990) and psychic side effects at high doses (Montastrue et al., 1994).

Experimental evidence suggests that the antiparkinsonian effects of dopamine agonists could be improved if an adenosine antagonist, caffeine or theophylline is used in a combined therapy. In human parkinsonian patients, the combination of caffeine with L-dopa may lead to improvements in tremor, but only after prolonged treatment (Mally and Stone, 1994). It has also been repeatedly shown that caffeine consumption could delay the onset or even prevent the occurrence of Parkinson's disease. Coffee intake is protective and inversely related to the occurrence of Parkinson's disease (Ascherio et al., 2001; Benedetti et al., 2000; Checkoway et al., 2002; Grandinetti et al., 1994; Fall et al., 1999; Hellenbrand et al., 1994; Jimenez-Jimenez et al., 1992; Ross et al., 2000). The mechanisms by which this protective effect occurs are not yet clear.

However, although this effect was clearly demonstrated in men, the conclusions appear less clear in women. A recent study showed that there is a possible interaction between the effects of caffeine and post-menopausal hormonal treatment.

As a result, women that consume less than a cup of coffee per day are protected against the occurrence of Parkinson's disease while those who drink more than 6 cups daily have a relative risk 4-fold higher than non drinkers to develop Parkinson's disease (Ascherio et al., 2003). Finally, in the elderly population that already suffers from the disease, the consumption of coffee is ineffective in reducing the symptoms of the disease (Louis et al., 2003).

9. Effects of caffeine on Alzheimer's disease

One recent study reported the neuroprotective effects of coffee and caffeine in Alzheimer's disease (Maia and de Mendonça, 2002). Caffeine exposure appears to be inversely associated with Alzheimer's disease independently of other confounding factors.

The risk to develop the disease was reduced to 0.40 in people consuming 200 mg of caffeine daily (2 cups of coffee) while it was 1.0 in the patients diagnosed with Alzheimer's disease who consumed an average quantity of 70 mg caffeine daily (less than one cup of coffee). However, these properties of coffee and caffeine need to be confirmed in future prospective studies.

10. Effects of caffeine in stroke and epilepsy

In man, chronic caffeine consumption is inversely related to the risk of fatal and non fatal stroke (Grobbee et al., 1990). In fact, one paper advised to drink enough coffee to allow an increase in the number of adenosine receptors but also to stop drinking caffeine-containing beverages when a stroke occurs to prevent caffeine from inducing a blockade at the level of cerebral adenosine receptors (Longstreth and Nelson, 1992). Likewise, a chronic caffeine treatment leads to decreased susceptibility to seizures (for review, see Nehlig, 2002) and has neuroprotective effects in the hippocampus (Rigoulot et al., 2003).

However, in these two diseases, more research remains necessary to assess the extent of potential neuroprotective properties of coffee and caffeine consumption.

11. Are we dependent on coffee and caffeine

11.1. Criteria for drug dependence

Drug dependence has been defined as .a pattern of behavior focused on the repetitive and compulsive seeking and taking a psychoactive drug.. The recent diagnostic manuals from the World Health Organization (WHO) and the American Psychiatric Association (APA) proposed a set of criteria for dependence. The diagnosis of dependence requires the fulfillment of three criteria. The seven criteria of dependence as proposed by the APA in DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn) are: (i) tolerance (not specified for severity), (ii) substance specific withdrawal syndrome (psychic or physiological, not specified for severity), (iii) substance is often taken in larger amounts or

over a longer period than intended, (iv) persistent desire or unsuccessful efforts to cut down or control use, (v) a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance, (vi) important social, occupational or recreational activities given up or reduced because of substance use, (vii) use continued despite knowledge of a persistent or recurrent physic

or psychological problem that is likely to have been caused or exacerbated by the substance.

11.2. Arguments in favor of dependence on caffeine

The possible dependence on caffeine has been considered for over a decade (for review, see Nehlig, 1999). In one recent study, a dependence on caffeine was shown in a subset of the general population (Strain et al., 1994) The dependence was not related to the daily caffeine intake which ranged from 129 to 2548 mg/day (1-20 cups daily). However, the conclusions of this study need to be taken with care since in 11 of the 16 persons diagnosed with .caffeine dependence., the prevalence of psychiatric disorders was higher than the one encountered in the general population. Among the seven criteria for drug dependence that have been cited above, caffeine withdrawal has been reported. A small percentage of the population may experience withdrawal symptoms following sudden cessation of caffeine consumption while gradual cessation over 2-3 days has not been shown to result in such symptoms. The most often reported are headaches, weakness and drowsiness, impaired concentration, fatigue and work difficulty, depression, anxiety, irritability. Withdrawal symptoms generally begin about 12-24 h after sudden cessation of caffeine consumption and reach a peak after 20-48 h. Withdrawal symptoms do not relate to the quantity of caffeine ingested daily (for review, see Nehlig, 1999). Caffeine withdrawal symptoms disappear soon after absorption of caffeine.

11.3. Arguments against the dependence on caffeine

There is no tolerance of the central nervous system to the effects of caffeine. Tolerance to a drug refers to an acquired change in responsiveness of a subject repeatedly

exposed to the drug. Tolerance might indicate that the dose necessary to achieve the desired euphoric or reinforcing effects will increase with time thus inciting people to gradually consume more drug. This has not been reported in individuals who consume coffee or caffeine. Indeed, most people maintain their consumption at a quite constant level.

Likewise, cerebral energy metabolism does not become tolerant to caffeine since an acute administration of caffeine induces quite similar metabolic increases whether rats have been pre-exposed daily to caffeine or saline for 15 days. Thus, every single exposure to caffeine is able to produce cerebral stimulant effects, mainly in the areas that control locomotor activity and the sleep-wake cycle (Nehlig et al., 1986).

Abbreviations: VTA: ventral tegmental area, ACSH: nucleus accumbens, shell, ACCO: nucleus accumbens, core; PFCX: prefrontal cortex. * $p < 0.05$, $\alpha p < 0.01$, statistically significant differences from control.

The molecular mechanisms underlying reinforcement and drug dependence were recently reviewed (Self and Nestler, 1995) and the critical role of the mesolimbic dopaminergic system emphasized. The mesolimbic dopaminergic system consists of the dopaminergic neurons originating in the ventral tegmental area and ending in the shell of the nucleus accumbens. The specificity of cocaine, amphetamine, morphine and nicotine is to selectively activate the dopaminergic neurotransmission in the shell of the nucleus accumbens (Pontieri et al., 1995, 1996), a property that has been related to the strong addictive properties of these drugs. Conversely to the drugs of abuse, caffeine does not increase the release of dopamine in the shell of the nucleus accumbens when injected at doses ranging from 0.5 to 5.0 mg/kg (Acquas et al., 2002). This data is consistent with the low addictive potential of caffeine. Conversely, at the latter doses, caffeine stimulates dopamine release in the prefrontal cortex, the terminal area of the mesolimbic dopaminergic system which reflects its psychostimulant properties (Acquas et al., 2002). Caffeine increases cerebral energy metabolism in the structures of the mesolimbic dopaminergic system only at quite high doses, 5 mg/kg for the area of origin, the ventral tegmental area and 10 mg/kg for the two subdivisions of the nucleus accumbens, the shell and the core and the medial prefrontal cortex (Figure 2.4). These data show that at the doses daily consumed by most people (2-2.5 mg/kg), caffeine does not activate the brain circuitry of dependence and reward involved in the action of psychostimulants. Moreover, the activation of functional activity in the shell of the nucleus accumbens, specific of the drugs of abuse, occurs only at high doses of caffeine (10 mg/kg, i.e., about 4-5 times the average daily human consumption which would correspond to 8-10 cups of coffee in one sitting) at which the methylxanthine activates also the core of the nucleus not involved in dependence and reward, and induces widespread non specific metabolic increases in a majority of brain regions (for review, see Nehlig et al., 1992). These widespread effects of high doses of caffeine on brain functional activity are likely to reflect the numerous adverse side effects of the ingestion of large amounts of caffeine.

12. Conclusion

The areas controlling locomotor activity and the sleep-wake cycle appear to be highly sensitive to low amounts of coffee and caffeine. Coffee and caffeine also ameliorate mood and performance and alleviate pain to due various types of headaches. Caffeine and coffee have neuroprotective and preventive properties in Parkinson's disease and these properties need to be confirmed in Alzheimer's disease. Coffee and caffeine may be angiogenic in a subfraction of sensitive individuals. The structures involved in addiction and reward are not sensitive to low to moderate amounts of coffee and caffeine and are only activated after high doses of caffeine that are already toxic and far higher than the usual human consumption. These doses activate also numerous brain

regions and are likely to induce also the adverse effects occurring after the ingestion of large doses of caffeine. The present data are rather in favor of caffeine acting as a positive reinforcer at doses reflecting the general human consumption and do not support the participation of the brain circuitry of addiction and reward in the biological effects on caffeine. Altogether, it appears that moderate consumption of coffee and caffeine has rather beneficial effects and coffee can contribute to a healthy and balanced diet.

References

- Acquas E, Tanda G, Di Chiara G** (2002) Differential effects of caffeine on dopamine and acetylcholine transmission in brain areas of drug-naive and caffeine-pretreated rats. *Neuropsychopharmacology*, 2002, 27, 182-193.
- Ascherio A, Zhang SM, Hernan MA, Kawachi I, Colditz GA, Speizer FE, Willett WC** (2001) Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Annals of Neurology*, 50, 56-63.
- Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE** (2003) Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. *Neurology*, 60, 790-795.
- Barone JJ, Roberts HR** (1996) Caffeine consumption. *Food and Chemical Toxicology*, 34, 119-126.
- Benedetti MD, Bower JH, Maranganore DM, McDonnell SK, Peterson BJ, Ahlsklog JE, Schaid DJ, Rocca WA** (2000) Smoking, alcohol, and coffee consumption preceding Parkinson's disease. *Neurology*, 55, 1350-1358.
- Benowitz NL** (1990) Clinical pharmacology of caffeine. *Annual Review of Medicine*, 41, 277-288.
- Bruce MS, Lader M** (1989) Caffeine abstinence in the management of anxiety disorders. *Psychological Medicine*, 19, 211-214.
- Checkoway H, Powers K, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD** (2002) Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. *American Journal of Epidemiology*, 155, 732-738.
- Debry G** (1994) *Coffee and Health*. Paris: John Libbey.
- Elison CR, Singer MR, Moore LL, Nguyen USDT, Garrahe E, Maror JK** (1995) Current caffeine intake of young children: amount and sources. *Journal of the American Dietetic Association*, 95, 802-804.
- Fall PA, Frederikson M, Axelson O, Granérus AK** (1999) Nutritional and occupational factors

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- influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. *Movement Disorders*, 14, 28-37.
- Fredholm BB** (1995) Astra Award Lecture. Adenosine, adenosine receptors and the actions of caffeine. *Pharmacology and Toxicology*, 76, 93-101.
- Fredholm BB, Bättig K, Holmen J, Nehlig A, Zvartau EE** (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews*, 51, 83-133.
- Grandinetti A, Morens D, Reed D, MacEachern D** (1994) Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. *American Journal of Epidemiology*, 139, 1129-1138.
- Griffiths RR, Mumford GK** (1995) Caffeine - A drug of abuse? In Bloom FE, Kupfer DJ (Eds) *Psychopharmacology. The Fourth Generation of Progress*. New York: Raven Press, pp. 1699-1713.
- Grobb DE, Rimm EB, Giovannucci E, Colditz G, Stampfer M, Willet W** (1990) Coffee, caffeine, and cardiovascular disease in men. *New England Journal of Medicine*, 323, 1026-1032.
- Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G** (1996) Diet and Parkinson's disease. II: a possible role for the past intake of specific nutrients: results from a self-administered food-frequency questionnaire in a case-control study. *Neurology*, 47, 644-650.
- Hughes RN** (1996) Drugs that induce anxiety: caffeine. *New Zealand Journal of Psychology*, 25, 36-42.
- James JE, Crosbie J** (1987) Somatic and psychological health implications in heavy caffeine use. *British Journal of Addiction*, 82, 503-509.
- Jimenez-Jimenez FJ, Mateo D, Gimenez-Roldan S** (1992) Permorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: a case-control study. *Movement Disorders*, 7, 339-344.
- Longstreth WT, Nelson M** (1992) Caffeine and stroke (Letter). *Stroke*, 23, 117.
- Lorist MM, Snel J, Kok A, Mulder G** (1994) Influence of caffeine on selective attention in wellrested and fatigued subjects. *Psychophysiology*, 31, 525-534.

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Louis ED, Luchsinger JA, Tang MX, Mayeux R (2003) Parkinsonian signs in older people. Prevalence and associations with smoking and coffee. *Neurology*, 61, 24-28.

Maia L, de Mendonça A (2002) Does caffeine protect from Alzheimer's disease? *European Journal of Neurology*, 9, 377-382.

Mally J, Stone TW (1994) the effect of theophylline on parkinsonian symptoms. *Journal of Pharmacy and Pharmacology*, 46, 515-517.

Marsden CD (1990) Parkinson's disease. *Lancet*, 335, 948-952.

Montastruc JL, Rascol O, Senard JM, Rascol AA (1994) Randomized controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 57, 1034-1038.

Nehlig A (1999) Are we dependent on coffee and caffeine? A review on human and animal data. *Neuroscience and Biobehavioral Reviews*, 23, 563-576.

Nehlig A (2002) Pharmacological properties and neurophysiological effects of caffeine. *Pharmacopsychologia*, 15, 35-70.

Nehlig A (2003) Caffeine and headache: relationship with cerebral blood flow. In Nehlig A (ed) *Coffee, Tea, Chocolate and the Brain*, CRC Press, Boca Raton, FL, in press.

Nehlig A, Boyet S (2000) Dose-response study of caffeine effects on cerebral functional activity with a specific focus on dependence. *Brain Research*, 858, 71-77.

Nehlig A, Daval JL, Boyet S, Vert P (1986) Comparative effects of acute and chronic administration of caffeine on local cerebral glucose utilization in the conscious rat. *European Journal of Pharmacology*, 129, 93-103.

Nehlig A, Daval JL, Debry G (1992) Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Research Reviews*, 17, 139-170.

Nehlig A, Debry G (1994) Effects of coffee on the central nervous system. In Debry G (Ed) *Coffee and Health*. Paris: John Libbey, pp 157-249.

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Tasaki H, Kaneko S (1997) Determination of the effects of caffeine and carbamazepine on striatal dopamine release by *in vivo* microdialysis. *European Journal of Pharmacology*, 321, 181-188.

Patat A, Rosenzweig P, Enslen M, Trocherie S, Miget N, Bozon MC, Allain H, Gandon JM (2000) Effects of a new slow release formulation of caffeine on EEG, psychomotor and cognitive functions in sleep-deprived subjects. *Human Psychopharmacology, Clinical and Experimental*, 15, 153-170.

Pontieri FE, Tanda G, Di Chiara G (1995) Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the .shell. as compared with the .core. of the rat nucleus accumbens. *Proceedings of the National Academy of Sciences of the U.S.A.*, 92, 12304-12308.

Pontieri FE, Tanda G, Orzi F, Di Chiara G (1996) Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*, 382, 255-257.

Reyner LA, Horne JA (2000) Early morning driver sleepiness: effectiveness of 200 mg caffeine. *Psychobiology*, 37, 251-256.

Rigoulot MA, Leroy C, Koning E, Ferrandon A, Nehlig A (2003) Prolonged low-dose caffeine exposure protects against hippocampal damage but not against the occurrence of epilepsy in the lithium-pilocarpine model in the rat. *Epilepsia*, 44, 529-535.