Coffee and Amyotrophic Lateral Sclerosis

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List of Abbreviations
A2aR Adenosine 2a receptor
AD Alzheimer’s disease
ALS Amyotrophic lateral sclerosis
cAMP Cyclic adenosine monophosphate
CAPE Phenethyl ester of caffeic acid
CCC Cancer controls
CI Confidence interval
CNS Central nervous system
CSP Cortical silent period
GABA Gamma-aminobutyric acid
GFAP Glial fibrillar acidic protein
GLT1 Glial glutamate transporter 1
GP General practitioner
LPS Lipopolysaccharide
MN Motoneurons
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NA Not available
NC Neurological controls
NNC Non-neurological controls
NS Not specified
NSC34 Mouse motor neuron-like hybrid cell line
NTR Neurotrophin receptor
PD Parkinson’s disease
SSF Self-sustained firing
SOD1G93A Superoxide dismutase 1G93A

47.2 COFFEE AND ALS: THE EPIDEMIOLOGICAL EVIDENCE

A recent Italian population-based case–control study investigating the role of trauma as an environmental risk factor for ALS showed serendipitously that coffee intake was less frequent and prolonged among patients with ALS compared to patients with other clinical conditions.4 Included were 377 patients aged 18 years or older with newly diagnosed ALS enrolled in four Italian population-based registries (total population at risk: 19,997,078). For each patient, two age- and sex-matched hospital controls were selected, one with a neurological disease (NC) and one with a non-neurological disease (NNC), not associated with ALS or to coffee exposure. When adjusting the data for possible confounders, including age, sex, physical activity, alcohol, smoking, and coffee intake, an inverse association between coffee consumption and risk of ALS was detected. To test the consistency of the findings, two additional healthy control groups were identified from local general practitioners’ (GPs’) lists (n = 99) and residents of the same area included in a cancer cohort (CCC) (n = 7057). Coffee intake was defined in terms of status (ever consuming coffee daily for at least six months vs never), duration (in years), and history (never, former, or current). As shown in Table 47.1, current coffee drinkers comprised 60% of ALS patients and slightly but significantly higher percentages of NC, NNC, and GP controls. Compared to NC, NNC, and GP controls, ALS patients had lower lifetime coffee exposure. In current (vs. never) coffee drinkers, odds ratios were halved (Figure 47.1). The robustness of the association was confirmed by the consistency of the findings and, to some extent, by the duration of exposure. The data could not be explained by the use of hospital controls because the proportions of coffee drinkers were similar in healthy controls. In addition, differences reflecting sociocultural habits in cases and controls are...
## Table 47.1  Coffee Consumption

<table>
<thead>
<tr>
<th></th>
<th>ALS</th>
<th>NC</th>
<th>NNC</th>
<th>GP</th>
<th>CCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 324)**</td>
<td>(n = 362)**</td>
<td>(n = 368)**</td>
<td>(n = 99)</td>
<td>(n = 7057)</td>
</tr>
<tr>
<td><strong>COFFEE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>242</td>
<td>291</td>
<td>315***</td>
<td>88**</td>
<td>6068***</td>
</tr>
<tr>
<td>Never</td>
<td>82</td>
<td>71</td>
<td>53</td>
<td>11</td>
<td>989</td>
</tr>
<tr>
<td><strong>INTAKE (YEARS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>82</td>
<td>71</td>
<td>53</td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>0–30</td>
<td>39</td>
<td>46</td>
<td>40</td>
<td>15*</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;50</td>
<td>77</td>
<td>94</td>
<td>115***</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>NS</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CONSUMER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>47</td>
<td>37</td>
<td>34</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>Current</td>
<td>195</td>
<td>254*</td>
<td>281***</td>
<td>79***</td>
<td>NA</td>
</tr>
<tr>
<td>Never</td>
<td>82</td>
<td>71</td>
<td>53</td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>NS</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; NC, neurological controls; NNC, non-neurological controls; GP, general practitioner controls; CCC, cancer controls; NA, not available; NS, not specified.

*\(p < 0.05\), **\(p < 0.01\), ***\(p < 0.001\) (compared to ALS).

aMissing data on coffee (53 ALS, 15 NC and 9 NNC).

### Figure 47.1  Odds ratios (with 95% confidence intervals) of coffee consumption comparing ALS patients and different control groups. OR, odds ratio; ALS, amyotrophic lateral sclerosis; NC, neurological controls; NNC, non-neurological controls; GP, general practitioner controls.
unlikely because coffee consumption is fairly uniform in Italy. The possibility of reverse causation could also be excluded because duration of coffee consumption was 30 years or longer in a lower proportion of ALS cases than in the control groups, a period almost inevitably preceding the biological onset of the disease. The inverse association between coffee intake and ALS could not even be explained by smoking (a purported risk factor for ALS) because data were adjusted for this confounder. Only current coffee drinkers were apparently inversely correlated to the risk of ALS, while the risk in former drinkers overlapped that of the general population.

There are no other published reports on the association between consumption of caffeinated beverages or drugs and ALS risk. Morozova et al. (2008) investigated diet in ALS, and found that decaffeinated coffee was associated with a higher risk of ALS. However, that same study found high consumption of tea, which also contains caffeine, was associated with a lower risk of ALS. In published studies, only caffeine was discussed as a possible neuroprotective agent. Other coffee components need proper assessment for a full evaluation of the biological plausibility of the purported association between caffeine intake and risk of ALS.

### 47.3 MOLECULAR TARGETS OF CAFFEINE IN THE CENTRAL NERVOUS SYSTEM

Targets of caffeine in the brain are adenosine, ryanodine, and GABAa receptors, and cyclic nucleotide phosphodiesterase isoenzymes. Caffeine has a psychomotor stimulant effect, mediated by dopaminergic mechanisms, by acting on adenosine A2a receptors. Caffeine also inhibits phosphodiesterase isoenzymes slowing the degradation of cyclic adenosine monophosphate (cAMP) and mediating a stimulating action of the central nervous system (CNS). In addition, it mobilizes calcium from intracellular stores, by activating ryanodine-sensitive channels, and interacts with benzodiazepines, which inhibit the binding to GABAa receptors and enhance membrane depolarization.

Caffeine increases excitatory neurotransmitter release and lowers the threshold for neuronal activation, increases spontaneous electrical activity in noradrenergic neurons enhancing the neuronal activity, and increases serotonin concentration in the serotonergic neurons in the raphe nuclei, which have excitatory projections to spinal MNs.

### 47.4 STUDIES IN ANIMAL MODELS

The effects of caffeine in animal models are summarized in Table 47.2. In rats, MN-astrocytes co-culture, a caffeine derivative known as LM11A-24 seems protective against MN degeneration, and exerts a neuroprotective effect on MN through modulation of the neurotrophin receptor p75NTR. In rodents, the negative interaction between adenosine A1 and dopamine D1 receptors may be involved in the activating effects of caffeine.

High calcium concentrations are harmful in MN in ALS. In a study of neonatal rat hypoglossal MN in vitro, caffeine-sensitive calcium stores contributed to controlling baseline calcium concentration and to sequestering calcium increased during action potential generation. In a study with male G39A mice, an animal model of ALS, coffee increased the antioxidant enzyme capacity in the brain, thus improving motor performance. However, these findings were contrasted by another recent study, which showed chronic caffeine intake significantly reducing survival in superoxide dismutase 1G93A (SOD1G93A) mice and inducing a nonsignificant advance of disease onset. In that study, caffeine did not influence the expression of A2aR, glial glutamate transporter (GLT1), and glial fibrillar acidic protein (GFAP) in either wild-type or SOD1G93A mice, although their expression was altered in the spinal cords of SOD1G93A mice. GLT1 helps keep down the level of glutamate and prevent toxicity; GFAP immunoreactivity is indicative of astroglial hypertrophy and hyperplasia. Antagonists

### Table 47.2 Effects of Administration of Caffeine in Animal Models

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Animal Model</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pehar, 2006</td>
<td>Rat spinal motor neurons</td>
<td>Neuroprotection through modulation of neurotrophin receptors (p75NTR)</td>
</tr>
<tr>
<td>Popoli, 1996</td>
<td>Reserpinized mice and unilaterally 6-hydroxy-dopamine-lesioned rats</td>
<td>Motor activation by action on adenosine A1 receptors</td>
</tr>
<tr>
<td>Donato, 2003</td>
<td>Neonatal rat hypoglossal motoneurons in vitro</td>
<td>Reversal of calcium concentration</td>
</tr>
<tr>
<td>Seevaratnam, 2009</td>
<td>Male SOD1G93A mice</td>
<td>Increase of antioxidant enzyme capacity</td>
</tr>
<tr>
<td>Potenza, 2013</td>
<td>SOD1G93A mice</td>
<td>Non-significant advance of disease onset. Activation of A2a receptors</td>
</tr>
<tr>
<td>Arendash, 2009</td>
<td>Aged mice with AD</td>
<td>Reversal of cognitive impairment and reduction of amyloid-beta levels</td>
</tr>
<tr>
<td>Brothers, 2010</td>
<td>Young mice with induced neuroinflammation</td>
<td>Reduction of the number of activated microglial cells induced by LPS</td>
</tr>
<tr>
<td>Prediger, 2010</td>
<td>Mouse strains and rats with PD</td>
<td>Action on A2a receptors with reduction of motor and nonmotor symptoms</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; LPS, lipopolysaccharide; PD, Parkinson’s disease.
of A2aR protect from excitotoxicity and prevent the increase of extracellular glutamate following the block of GLT1, thus exerting neuroprotection in ALS. Based on the results of this study, authors hypothesized that the toxic effect of caffeine could not depend on A2a receptors blockade.

### 47.5 ELECTROPHYSIOLOGICAL EFFECTS OF CAFFEINE (TABLE 47.3)

In a study about caffeine-modulated acetylcholine sensitivity in denervated rats and diseased human muscle,18 caffeine interacted with sarcolemma possibly through mobilization of membrane-bound calcium. After caffeine administration, there was a large increase in spontaneous electromyographic activity in patients with ALS, while after administration of calcium, a transient reduction to below control levels was found.

Caffeine acts as an antagonist to the inhibitory effect of adenosine, increasing the release of serotonin and noradrenaline (norepinephrine) (excitatory neurotransmitter).7 This action has been associated with a significant increase in the relative frequency of occurrence of self-sustained firing (SSF).

In electrophysiological studies done on healthy human muscle, caffeine has been shown to have positive effects on muscle and upper and lower MN excitability.19 This can occur as a consequence of a greater excitation of the descending input from the brainstem and upper MN. The influence of caffeine on upper MN can be shown by transcranial magnetic stimulation through reduction of the cortical silent period (CSP) in resting and fatigued muscles.19

Caffeine has a direct effect on skeletal muscle excitation–contraction coupling and increases calcium release from the sarcoplasmic reticulum, to be used in the contractile mechanism,20 but does not seem to improve performance in activities requiring strength and/or short-term endurance.20 Cerqueira et al.21 tested the influence of caffeine on the upper and lower MN excitability in 18 healthy subjects who were randomized to receive 200mg of caffeine or placebo (first experiment) and in six subjects who received 400mg of caffeine (second experiment). The CSP decreased with caffeine intake. In the first experiment, CSP decreased in the abductor digiti minimi by about 12% after caffeine intake. In the second experiment, CSP decreased by 13% and 16% in the abductor digiti minimi and biceps, respectively. Caffeine deprivation had adverse effects, particularly fatigue and drowsiness.21 The authors concluded that massive excitation of the motor cortex by increased stimulation would overcome the function of the inhibitory pathways, which are activated with intensities lower than those necessary to produce the motor output.

Kalmar and Cafarelli22 examined the effects of caffeine on neuromuscular function of 11 male volunteers in a double-blind, repeated-measures study. Caffeine was administered on 6mg/kg dosage. This study demonstrates that caffeine has an ergogenic effect on peak force generation, causing an increase in maximal activation. The authors declared that caffeine could diminish the decline of calcium that may occur in fatigued muscles.22

In the study of Meyers and Cafarelli,23 caffeine increased time to fatigue by maintaining force. This was a randomized, placebo-controlled study in which MN firing rate was examined to test the effect of caffeine during a fatigue task. They found that caffeine extends the limit to endurance during repeated submaximal contractions of the quadriceps, and they suggest that fatigue may be delayed maintaining calcium reuptake, obtaining an improvement of calcium release and force production.23

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greuner, 1975</td>
<td>Enhancement of acetylcholine contracture</td>
</tr>
<tr>
<td>Walton, 2002</td>
<td>Increase of frequency of occurrence of SSF</td>
</tr>
<tr>
<td>De Carvalho, 2010</td>
<td>Reduction of CPS</td>
</tr>
<tr>
<td>Williams, 1987</td>
<td>Improvement of muscle excitation-contraction coupling</td>
</tr>
<tr>
<td>Cerqueira, 2006</td>
<td>Improvement of fatigue</td>
</tr>
<tr>
<td>Kalmar, 1999</td>
<td>Improvement of force generation and fatigue</td>
</tr>
<tr>
<td>Meyers, 2005</td>
<td>Improvement of the limit of endurance to fatigue</td>
</tr>
</tbody>
</table>

SSF: self-sustaining firing; CPS: cortical silent period.

### 47.6 CAFFEINE AND OTHER NEURODEGENERATIVE DISORDERS

Epidemiological studies have shown a positive correlation between dietary caffeine intake and reduced risk of Parkinson’s disease (PD).24,25 In keeping with these observations, the neurotoxic effect exerted by MPTP on dopaminergic neurons was found to be reduced by caffeine and its metabolites.26,27 Pooled estimates showed coffee consumption being also inversely associated with the risk of Alzheimer’s disease (AD).28 Caffeine has been shown to reverse cognitive impairment and decrease brain amyloid-beta levels in aged mice with AD.29 These effects can be explained by its antagonism to A2a adenosine receptors, which are widely distributed in the CNS both in neuronal and glial cells and exert significant modulation of presynaptic and astrocytic glutamate
release.\textsuperscript{30} Caffeine was also found to reduce the number of activated microglial cells induced by lipopolysaccharide (LPS) in rats,\textsuperscript{31} an effect likely mediated by the blockade of A2a receptors.\textsuperscript{32} The neuroprotective potential of caffeine has been demonstrated in different animal models of PD under different exposure regimens and in different mouse strains and rats.\textsuperscript{33} Importantly, while the stimulant effect of caffeine develops tolerance after continuous treatment, this does not occur for caffeine-mediated neuroprotection.

### 47.7 EFFECTS OF OTHER CONSTITUENTS OF COFFEE (TABLE 47.4)

Other important components of coffee are chlorogenic acid, caffeic acid, ferulic acid and \( \alpha \)-tocopherol. Chlorogenic acid has anticarcinogenic, anti-inflammatory, analgesic, antipyretic, and antioxidative activity and it has also neuroprotective effects in mice and rats.\textsuperscript{34,35} Caffeic acid shows antioxidative and antineurotoxic effects in vitro and in vivo.\textsuperscript{36–39} Vitamin E is present as 0.2 mg \( \alpha \)-tocopherol and 0.2 mg of \( \gamma \)-tocopherol per cup of coffee.\textsuperscript{40} Long-term use of vitamin E supplements could be inversely associated with risk of ALS, as suggested in a large pooled prospective study.\textsuperscript{41}

In a screening cascade in vitro to identify antioxidants in ALS, the phenethyl ester of caffeic acid (CAPE) and resveratrol were identified as the best-performing molecules.\textsuperscript{42} In NSC34 MN cells expressing an ALS-associated mutation of superoxide dismutase, these molecules were capable of activating antioxidant cellular pathways, inhibiting transcription factor NF-kB and 5-lipoxygenase pathways that lead to inflammation.\textsuperscript{42} CAPE activates also the antioxidant responsive element pathway that is down regulated in cells expressing mutant SOD and MN isolated from familial ALS cases.

Fontanilla et al.\textsuperscript{43} tested CAPE effects in mice SOD1G93A, in which the administration after symptom onset increased post-onset survival and lifespan. Less activation of microglia and astrocytes and higher MN counts were detected, and lower levels of phosphorylated P38 protein were observed. Therefore, the authors identified CAPE as a novel and effective therapeutic agent for the treatment of ASL, capable to slow disease progression due to neuroinflammation and neuron death.

In the review of Calabrese et al.,\textsuperscript{44} ferulic acid, like cucurmin, was assessed to reduce oxidative damage and amyloid pathology in AD. AD, like ALS and other neurological disorders, is associated with production of abnormal proteins. Then, there is interest in dietary products that could contrast brain damage due to abnormal proteins.\textsuperscript{44}

The available epidemiological findings, the results of some studies done in experimental animals, and the molecular and electrophysiological effects of caffeine and other ingredients of coffee all support the purposed protective action of coffee against ALS. However, these findings require confirmation through a large population-based study investigating the exposure to coffee to a greater extent. In addition, different populations should be investigated to test the consistency of the findings among people with differing dietary habits.

### Table 47.4 Studies with Other Coffee Compounds

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Compound</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2011</td>
<td>Vitamin E</td>
<td>Decreased risk of ALS</td>
</tr>
<tr>
<td>Barber, 2009</td>
<td>CAPE, resveratrol</td>
<td>Activation of ARE pathway and inhibition of inflammation</td>
</tr>
<tr>
<td>Fontanilla, 2012</td>
<td>CAPE</td>
<td>Increase of post-onset survival, less activation of microglial cells and astrocytes, higher motoneuron counts</td>
</tr>
<tr>
<td>Calabrese, 2006</td>
<td>Ferulic acid</td>
<td>Reduction of oxidative damage and amyloid pathology in AD</td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; CAPE, phenethyl ester of caffeic acid; ARE, antioxidant responsive element; AD, Alzheimer’s disease.

### References


II. EFFECTS OF COFFEE CONSUMPTION


