Food and Chemical Toxicology 123 (2019) 298–313

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Coffee, caffeine, chlorogenic acid, and the purinergic system

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ARTICLE INFO

Keywords:
Coffee
Caffeine
Chlorogenic acid
Purinergic system
Nucleotidase

ABSTRACT

Coffee is a drink prepared from roasted coffee beans and is lauded for its aroma and flavour. It is the third most popular beverage in the world. This beverage is known by its stimulant effect associated with the presence of methylxanthines. Caffeine, a purine-like molecule (1,3,7 trymetylxantine), is the most important bioactive compound in coffee, among others such as chlorogenic acid (CGA), diterpenes, and trigonelline. CGA is a phenolic acid with biological properties as antioxidant, anti-inflammatory, neuroprotector, hypolipidemic, and hypoglicemic. Purinergic system plays a key role inneuromodulation and homeostasis. Extracellular ATP, other nucleotides and adenosine are signalling molecules that act through their specific receptors, namely purinoceptors, P1 for nucleosides and P2 for nucleotides. They regulate many pathological processes, since adenosine, for instance, can limit the damage caused by ATP in the excitotoxicity from the neuronal cells. The primary purpose of this review is to discuss the effects of coffee, caffeine, and CGA on the purinergic system. This review focuses on the relationship/interplay between coffee, caffeine, CGA, and adenosine, and their effects on ectonucleotidases activities as well as on the modulation of P1 and P2 receptors from central nervous system and also in peripheral tissue.

1. Introduction

Coffee was discovered about 2000 years ago in Ethiopia and it was likely that the Ethiopians were the first to recognise its energising effects. Coffee has been consumed for social appointments, time-out, enhancement of work performance, and overall well-being. Normally, the type of coffee beverage is strictly associated with the social habits and the culture of individual countries (Homan and Mobarhan, 2006). Due to its social and cultural importance, coffee has been studied for a long time, and some of its compounds have been isolated. Among these, the alkaloid caffeine was discovered in tea (*Camellia sinensis*) and coffee (*Coffea arabica*) in the 1820s (Ashihara and Crozier, 2001), and the phenolic compound chlorogenic acid (CGA) was isolated from coffee by Gorter in 1908 (Feldman et al., 1969). Other compounds found in coffee that show biological activities include cafestol, kahweol, and trigonelline (Ludwig et al., 2014a), all of which can affect biological systems in the body. Consequently, they can be useful in the treatment of certain illness such as diabetes mellitus (DM), cardiovascular diseases, and Alzheimer's disease (Anwar et al., 2013a; Stefanello et al., 2016, 2014).

The purinergic system is an important regulatory pathway of different tissues, including the vascular and central nervous system, pancreas, and bone. This system consists of nucleosides and nucleotides, as well as the enzymes and receptors where these molecules bind.

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https://doi.org/10.1016/j.fct.2018.10.005
Received 11 May 2018; Received in revised form 29 September 2018; Accepted 2 October 2018
Available online 03 October 2018
0278-6915/

Purinergic signalling is involved in physiological and pathophysiological conditions and alterations in this system may be involved in insulin resistance, vascular injury, platelet aggregation, inflammation, and cognition (Burnstock, 2013; Gutierres et al., 2014a).

Recent studies have demonstrated the involvement between natural compounds and the purinergic system. Some compounds, such as anthocyanins, caffeic acid, resveratrol, quercetin, caffeine, and CGA, as well as red wine, grape juice, and coffee, have been shown to regulate the components of the purinergic system (Abdalla et al., 2014; Anwar et al., 2013b; Duarte et al., 2012; Gutierres et al., 2012; Maciel et al., 2016; Schmatz et al., 2013, 2009).

2. Chemical composition of coffee

Of the compounds identified in green coffee, CGAs, caffeine, soluble fibers, trigonelline, and diterpenes from the lipid fraction are most likely to exhibit bioactive properties. Other phenolic compounds, such as lignans and anthocyanins, have been identified in green coffee seed (Farah and Donangelo, 2006). It is also possible to find minerals such as magnesium, potassium, copper, calcium, aluminium, and phosphorus in this beverage (Grembecka et al., 2007; Wei et al., 2012b, 2012a).

The major lipid classes in coffee beans are triacylglicerols, terpene esters, and sitosterol (Dong et al., 2015), while the carbohydrates include sucrose, galactose, glucose, and fructose. Phenolic acids are the main components that contribute to the formation of pigment, taste, and flavour when coffee beans are roasted (Murkovic and Derler, 2006). Roasted coffee and green beans show some differences in their composition, because the roasting process destroys a large amount of the phenolic acids, sucrose, proteins, and trigonelline (Sunarharum et al., 2014). A study conducted in Greece demonstrated that roasting reduces the antioxidant activity only in some varieties of coffee, and this depends on the chemical composition of the coffee. However, roasting time has been conclusively shown to reduce the antioxidant activity (Priftis et al., 2015).

The biological activities of coffee have been mainly attributed to terpenes, alkaloids, and phenolic compounds (Fig. 1). The best-known terpenes are cafestol and kahweol, which naturally occur as diterpenes, being present in the lipid fraction. The concentration of these diterpenes is influenced by the brewing method. Boiled coffee, such as Scandinavian- and Turkish-style, contains a higher amount than filtered or instant coffee (Jeszka-Skowron et al., 2014).

Two types of alkaloids are present in coffee beans, caffeine (1,3,7 trymetylxantine) and trigonelline, as major components. Other methylxanthines occur, including theobromine, paraxanthine, and theophylline. Trigonelline is found in coffee, but caffeine is present in both coffee and tea (Ashihara et al., 2008). Studies have demonstrated that the roasting process does not alter caffeine concentration. On the other hand, trigonelline is degraded during roasting process, producing other compounds including nicotinic acid (Farah, 2012).

Caffeine is synthesised in plants from xanthosine, a product of the catabolism of purine nucleotides. It has a protective effect in soft tissue against predators and may be released in the soil, where it inhibits the germination of other seeds (Ashihara et al., 2008; Ashihara and Crozier, 2001). Waldhauser and Baumann showed that caffeine could be found in a complex with polyphenols. In the raw coffee beans a caffeine/CGA complex is easily found as a well-described crystalline caffeine potassium chlorogenate 1:1 complex, which is formed due to physicochemical properties (Waldhauser and Baumann, 1996).

Classically, CGAs make up a family of esters formed between quinic acid and some trans-cinnamic acids. The most common is 5-O-caffeoylquinic acid (5-CQA). It is present in major quantities in almost all foods and beverages containing CGA family compounds. Furthermore, due to identity, number, and position of acyl residues, CGAs may be subclassified into other compounds: 1) monoesters of caffeic acid, which include caffeoylquinic acids (CQAs), *p*-coumaroylquinic acids, and feruloylquinic acids; 2) diesters and triesters that include diCQA and triCQA; 3) mixed diesters between caffeic and ferrulic acid, i.e.,caffeoylferuloylquinic acids, found mainly in robusta coffee

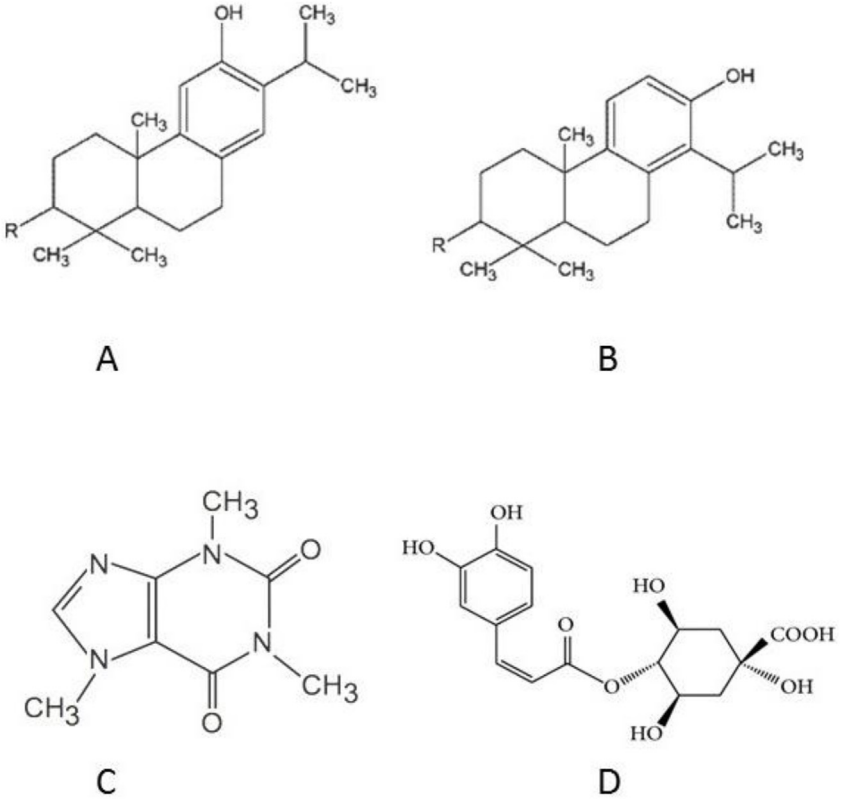

Fig. 1. A) Cafestol; B) Kahweol; C) Caffeine; D) Chlorogenic acid.

(Clifford, 2000; Farah and Donangelo, 2006). The roasting process causes a significant reduction in the concentration of CGAs, but the majority of CGAs present in roasted coffee can be extracted in home coffee brewing, however, coffee brews maintained at a high temperature reduce the concentration of CGAs (Farah, 2012).

Pyrolysis, caramelisation, and Maillard reactions occur during the roasting process, which change the seed composition. The raw material, roasting degree and variables such as type and time of roasting, as well as airflow speed in the roasting chamber interfere in CGA final concentration. CGAs suffer many changes during roasting, namely, isomerisation, epimerisation, lactonisation, and degradation to low-molecular weight compounds. Normally, depending on the type of processing, CGAs may vary from 0.5 to 6 g/100 g dry weight and, if the roasting process is more intense, CGAs quantity could be less that 1% of dry matter (Farah, 2012; Ludwig et al., 2014a; Perrone et al., 2008).

During the brewing process, approximately 80% of CGAs are extracted, resulting in approximately 40–200 mg CGAs/serving depending on the varieties of coffee (Ludwig et al., 2014b; Stalmach et al., 2011). However, maintaining a high temperature reduces the concentration of CGAs. On the other hand, caffeine, trigonelline, and nicotinic acid are also soluble in hot water. The concentrations in brewed coffee prepared with medium roasted coffee vary from 50 to 100 mg caffeine, 40–50 mg trigonelline, and approximately 10 mg nicotinic acid (Perrone et al., 2008).

3. Caffeine and CGA metabolism

3.1. Caffeine metabolism

The complete absorption of caffeine in humans reaches 99% in about 45 min after its ingestion, occurring in the gastrointestinal tract. After oral consumption, the peak plasma caffeine concentration is reached at 15–120 min. It crosses the blood–brain barrier (BBB) and enters all body fluids including serum, milk, saliva, and semen (Crozier et al., 2011). After 1 h intravenous injection of caffeine, the tissue-to-blood distribution was approximately 1.0 with a concentration of 3.5 mg/g. Fat and liver showed a ratio less that 1 (Arnaud, 2011). In smokers, caffeine metabolism is reduced, while there is an increase during the last trimester of pregnancy and in women taking oral contraceptives (Arnaud, 2011; Yu et al., 2016).

Researchers have found that caffeine is extensively metabolised in the liver (99%) by the cytochrome P450 oxidase enzyme system (Heckman et al., 2010) to form three major metabolites, 3,7-dimethylxanthine (theobromine, 12%), 1,7-dimethylxanthine (paraxanthine, 84%), and 1,3-dimethylxanthine (theophylline, 4%). CYP1A2 is responsible for caffeine demethylation. Paraxanthine is metabolised in other metabolites by 1) cytochrome P4502A6 (CYP2A6) to form 1,7-dimethylurate, 2) cytochrome P4501A2 (CYP1A2) to form 1-methylxanthine and, 3) the formation of 5-acetylamino-6-formylamino-3-methyluracil, which is catalysed by N-acetyltransferase. 5-Acetylamino-6-formylamino-3-methyluracil is an unstable product that may be deformylated non enzymatically to 5-acetylamino-6-amino-3-methyluracil. 1,7-Dimethylurate is mainly metabolised by the polymorphic enzyme CYP2A6 (90%) and about 10% is metabolised by CYP1A2. Part of 1-methylxanthine is metabolised to 1-methylurate by xanthine oxidase (Arnaud, 2011; Krul and Hageman, 1998).

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The expression of CYP1A2 may influence caffeine metabolism. The CYP1A2 expression may be influenced by sex, race, genetic polymorphisms, disease and these factors could change the concentration of caffeine in different tissue (Nehlig, 2018). Salinero et al. (2017) reported that 31.3% of the C-allele carriers to CYP1A2 enzyme reported increased nervousness after caffeine 3 mg/kg ingestion (Salinero et al., 2017). In this sense, Buters et al. (1996) investigated the involvement of CYP1A2 in the pharmacokinetics and metabolism of caffeine in mice lacking its expression (CYP1A2−/−) and concluded that the half-life of caffeine elimination from the blood was seven times longer than in wild-type mice (Buters et al., 1996). On the other hand, CYP2A6 polymorphisms genotype is also found, however it is not altered by sex, disease, smoking and race (Nehlig, 2018). Finally, CYP1A1 and CYP1A2 polymorphisms is significantly associated with increased coffee consumption (Sulem et al., 2011).

It is important to note that caffeine and its metabolites are found in many tissues, due to its high liposolubility, i.e., lung, adipose tissue, liver, kidney, and the brain. It crosses the BBB due to simple diffusion and affects the activity of the central nervous system (CNS) (Che et al., 2012). Kaplan et al. (1989) described a linear relationship between caffeine and its metabolites in the brain and plasma concentrations (Kaplan et al., 1989). In all these organs, caffeine can reach out and exert its effects as an A2A receptor antagonist (Duarte et al., 2009).

3.2. CGA metabolism

Monteiro et al. (2007) pointed to an early absorption of CGA in the stomach or in the initial intestinal tract, followed by absorption throughout the small intestine (Monteiro et al., 2007). In addition, Olthof et al. (2001, 2003) suggested that the uptake of CGA is achieved in two ways: 1) approximately 33% may be absorbed in the small intestine, since small concentrations of intact CGA (0.3%) were found in urine and, 2) CGA could be hydrolysed by bacteria in the colon and the products of its degradation could be absorbed (Olthof et al., 2003, 2001). Consistent with this study, Stalmach et al. (2010) showed that 24 h post-ingestion of 200 mL of coffee containing 385 ± 4 μmol of CGA resulted in the appearance of 274 ± 28 μmol of CGA and its metabolites in the ileal fluid of ileostomy patients, indicating that 30% is absorbed in the small intestine. In normal subjects, 70% of ingested CGA passes from the small to the large intestine, where it is metabolised by colonic microflora (Stalmach et al., 2010).

Studies have demonstrated that all major compounds in coffee are bioavailable for humans (Farah et al., 2008; Monteiro et al., 2007). 5-O-caffeoylquinic acid, the major CGA in brewed coffee, represents 40% of total hydroxycinnamates identified in plasma 4 h after ingestion (Monteiro et al., 2007). Manach et al. (2004) showed that coffee polyphenols are able to penetrate tissue. *In vitro* studies have also shown that dietary flavonoids can cross the BBB (Manach et al., 2004; Manach and Donovan, 2004). Many of the components described above are biologically active and could contribute to the effects associated with coffee consumption.

4. Physiological and biochemical actions of coffee, caffeine, and CGA

Epidemiological and experimental studies support the idea that consumption of regular coffee drinking has health benefits. The relationship between coffee and various diseases holds great interest, given a large array of the compounds found in the beverage that could potentially alter the risks of degenerative, progressive, and chronic

diseases through many biological actions (Caini et al., 2017; Santos and Lima, 2016; Shimoyama et al., 2013).

4.1. Coffee and metabolic effects

Regular consumption of green/roasted coffee blend may decrease systolic and diastolic blood pressure as well as glucose concentration, insulin resistance, triglyceride levels, and percent body fat, which may be related to the lower leptin and resistin levels in normocholesterolaemic and hypercholesterolaemic subjects (Sarriá et al., 2018).

A recent study by Takahashi et al. (2017) showed that mice treated with 0.1% coffee for 17 weeks did not exhibit altered levels of glucose in the plasma, but did exhibit a reduction in total food and water consumption during the dark cycle, as well as free fatty acids and triglyceride levels in the plasma of mice. The authors concluded that coffee consumption had a positive effect on behavioural energy and lipid metabolism (Takahashi et al., 2017).

Studies have demonstrated lower risk of type 2 DM in those who consume two or more cups of coffee per day (Ding et al., 2014; Hitman, 2014; Wedick et al., 2011). Coffee consumption could not decrease the risk of type 2 DM in subjects with negative lifestyle habits, i.e., cigarette smoking, lower physical activity, obesity, and alcohol consumption (Muley et al., 2012; Patja et al., 2005; Shi et al., 2013). Furthermore, a Netherlands cohort study reported that those who consumed at least seven cups of coffee per day had a lower relative risk of 50% to developing type 2 DM when the researchers compared with those who ingested two cups of coffee or less. The same could be observed in a study with men, which showed that there was a reduction of 54% in developing diabetes in those men that drank at least six cups of coffee per day when compared with men who did not drink coffee, while women who drank ≤ 6 cups of coffee per day had a lower risk (29%) in relation to those who did not consume (Ludwig et al., 2014a; van Dam, 2008). Furthermore, the inverse association has been similar for both caffeinated and decaffeinated coffee as concluded by van Dam (2006) in a prospective cohort study in younger and middle-aged women. These observations suggested that other coffee components rather than caffeine may affect the development of type 2 DM. In fact, coffee has some substances, e.g., CGAs, quinic acid, trigonelline, and the lignin secoisolariciresinol that can interfere with glucose metabolism (Van Dam, 2006).

Johnston et al. (2003) found that both decaffeinated and caffeinated coffee modulated glucose uptake, with CGA as the compound responsible for blocking glucose transport in the intestine (Johnston et al., 2003). In addition, 1 g of CGA and 500 mg of trigonelline were also able to reduce the early glucose and insulin responses during the glucose tolerance test in overweight men (Van Dijk et al., 2009). In an experimental study using diabetic rats, treatment with 250 mg/kg of caffeine for 5 weeks decreased blood glucose, TGs, and total cholesterol levels in serum (Yamauchi et al., 2010). Similarly, type 1 diabetic rats treated with CGA (5 mg/kg) for 45 days showed a reduction in plasma glucose levels. A reduction in thiobarbituric acid reactive substances (TBARS) and hydroperoxide levels as well as an increase in the antioxidant enzyme activities in the liver and kidney was observed (Karthikesan et al., 2010). CGA also inhibits glucose-6-phosphatase enzyme in the liver and interferes with glucose absorption in the intestine of rats (Hemmerle et al., 1997; Higdon and Frei, 2006). Concluding, these results are consistent with the suggestion that CGA may play a role in the homeostatic regulation of glucose levels contributing to the potential effects of coffee in diabetic status.

4.2. Coffee and cardiovascular effects

The relationship between coffee ingestion and cardiovascular diseases has also been documented in the literature (Bonita et al., 2007; Ding et al., 2014). Grioni et al. (2015) showed that the risk of coronary heart disease was significantly greater for those whose intake was more than two cups per day of Italian-style coffee when compared with those who drank one cup per day (30 mL). Moreover, those who drank high quantities of coffee per day were younger, had higher energy intake, were more likely to smoke, and were also less likely to have normal weight and hypertension (Grioni et al., 2015). An increase in the risk of myocardial infarction was observed in those men that consumed filtered coffee in a study with 375 subjects (Nilsson et al., 2010). On the other hand, Andersen et al. (2006) concluded that an intake of 1–3 cups of coffee per day has a protective effect on total death and death from cardiovascular and other inflammatory diseases in a group of postmenopausal women (Andersen et al., 2006). In addition, consumption of filtered caffeinated coffee was not associated with cardiovascular disease in women in one study (Lopez-Garcia et al., 2011).

In addition of this idea, experimental studies have described that coffee and caffeine can induce many effects in the vascular system (Riksen et al., 2009). The following alterations were demonstrated by coffee consumption: the administration of coffee had preventive effects on arterial occlusive thrombus formation in mice (Toda et al., 2010) and inhibited platelet aggregation in rats (Bhaskar and Rauf, 2010; Stefanello et al., 2016), and these effects were not associated with caffeine. Furthermore, coffee consumption was negatively associated with the protein CHI3L1, which has an important role in the activation of the innate immune system, demonstrating that coffee has anti-inflammatory effect contributing with the reduction of atherosclerosis plaque formation (Cornelis et al., 2018; Loftfield et al., 2015). In addition, Zhang and Zhang (2018) demonstrate in a meta-analysis study that coffee consumption was associated with a reduction in serum C-Reactive Protein (Zhang and Zhang, 2018). Also, a randomized, acute, crossover, intervention study with healthy male adults, found that coffee polyphenol consumption reduced the hyperglycemia and improved vascular endothelial function in healthy humans (Jokura et al., 2015). These findings demonstrate that coffee consumption has a range of beneficial effects that could contribute to the reduction of the risk of cardiovascular diseases.

On the other hand, caffeine could have a different effect. Stefanello and co-authors have demonstrated that caffeine 15 mg/kg for 30 days did no reduce the platelet aggregation in diabetic rats (Stefanello et al., 2016), although other research demonstrated that at high doses caffeine leads to the upregulation of A_2 receptors on the platelet surface, reducing aggregation (Varani et al., 2000). Other data showed that the intake of 70 mg/kg of caffeine for 7 days increased diastolic blood pressure in young adults (Cavalcante et al., 2000). Similar results obtained by Temple et al. (2010) showed that acute caffeine administration (50, 100, and 200 mg) in adolescents decreased heart rate and elevated diastolic blood pressure in a dose-dependent manner (Temple et al., 2010). However, other findings reported that caffeine increased endothelium-dependent vasodilation (T. Umemura et al., 2006). The effects of coffee and/or caffeine alone on the cardiovascular system are still not clear. However, it is important to consider that the different effects depend on the type, amount of coffee ingested, and the time and frequency of consumption (Kanno et al., 2013; Mostofsky et al., 2012).

The effects of coffee on human health are depended on many factors. In summary, coffee consumption appears to have positive and negative effects on cardiovascular risk, according to epidemiological and animals studies. However, it is clear that moderate consumption up to 3 cups of coffee per day provides possible beneficial effects, while higher consumption up to 6 cups of coffee per day could have negative contributions to the development of cardiovascular diseases. In addition, roasting process, coffee varieties, frequency of consumption, quantity consumed, and beverage preparation interfere with bioactive compounds concentration in coffee and in consequence influence, more or less, the reduction of the risk of developing cardiovascular diseases.

4.3. Coffee and neurological effects

Many actions of coffee in the CNS have been attributed to the

presence of caffeine. It has been well established that caffeine has stimulating effects in the brain, resulting in heightened alertness and arousal. This compound also improves performance on cognitive tasks and modulates antioxidant parameters in the brains of young subjects (Abreu et al., 2011; Aoyama et al., 2011). A study with non-smoking women demonstrated that caffeine intake was associated with a larger size of the hippocampus (Perlaki et al., 2011).

Caffeine is well-known as a specific antagonist of adenosine receptors and in many experimental conditions, neuroprotective effects have been demonstrated. Caffeine offers significant neuroprotection; epidemiological studies have showen that there is a reduction of Parkinson's disease with caffeine consumption (Ascherio et al., 2004; Qi and Li, 2014) and caffeine or moderate coffee consumption decrease the risk of Parkinson's disease (Ascherio et al., 2001). Nevertheless, this lower risk is not related with caffeine effects in the motor symptoms (Postuma et al., 2017). In experimental models, there is evidence that 20 mg/kg caffeine has reduced negative effects of 6-OHDA-lesioned rats (Machado-Filho et al., 2014) and chronic caffeine consumption (1 g/L) prevented the degeneration of dopamine cell bodies in the substantia nigra of 1-methyl-4-phenyl1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease in rats (Sonsalla et al., 2012). These protective effects seems to be linked with A2AR (Xu et al., 2016). Furthermore, caffeine is related with suppression of lipopolysaccharide-induced neuroinflammation (Brothers et al., 2010; Kang et al., 2012).

Alzheimer's disease also shows neuroinflammation condition. In this sense, caffeine (0,3 g/L) prevented spatial memory deficits in model of Alzheimer's disease -like tau pathology (Laurent et al., 2014), as well as this alkaloid reduced other memory deficits, as demonstrated by (Arendash et al., 2006; Chu et al., 2012; Cunha and Agostinho, 2010); its mechanism could be related with AChR modulation or it could be related with the upregulation of A2A caused by caffeine (Espinosa et al., 2013; Fabiani et al., 2018). Furthermore, there is an inverse association between caffeine consumption and the incidence of Alzheimer's disease (Dall'Igna et al., 2007). This relation would be linked with caffeine effects on aging. Prediger et al. (2005) related that caffeine participates in reversing aged-related cognitive olfactory decline in rats (Prediger et al., 2005). In addition, caffeine prevents aged-related memory impairment reducing oxidative stress and modulating adenosine receptors (Leite et al., 2011).

Others studies have demonstrated that caffeine (10 mg/kg) may counteract proapoptotic effects 6 and 24 h following phenobarbital injection in new-born rats (Endesfelder et al., 2017) and caffeine (1 g/L) may prevent memory deficits in adult rats caused by a single convulsive episode in early life (Cognato et al., 2010). Moreover, caffeine protects the neonatal mouse brain against decreasing brain atrophy and alterations in motor function following hypoxia-ischemia induction (Winerdal et al., 2017). We can emphasize that synaptotoxicity is reduced by caffeine in different experimental models as convulsive episode (Cognato et al., 2010), model of Machado-Joseph disease (Gonçalves et al., 2017, 2013), and streptozotocin-induced DM (Duarte et al., 2012). Finally, an inverse association between consumption of caffeinated beverages, including coffee and tea, and the risk of glioma development in humans was observed (Holick et al., 2010; Perlaki et al., 2011). In this way, caffeine consumption may be helpful in the prevention of cognitive deficits in neurodegenerative diseases.

In addition to the effects of caffeine, other compounds found in coffee, such as CGA, may also alter neural function. Previous studies in animal models have shown that CGA improved memory impairment in scopolamine-induced amnesia (Kwon et al., 2010); stimulated neurite extension (Ito et al., 2008); affected locomotor activity in mice (Ohnishi et al., 2006); induced anxiolytic and antioxidant effects in Swiss mice (Bouayed et al., 2007) and antinociceptive effects in diabetic rats (Bagdas et al., 2014). Also, a rat model of focal cerebral ischemia reperfusion was protected by CGA treatment (Miao et al., 2017). These observations suggest that coffee compounds might be promising candidates for the treatment of neurodegenerative diseases (Fig. 2).

Moreover, CGA and caffeine may protect cells from the damage caused by hyperglycemia in streptozotocin (STZ; 60 mg/kg)-induced diabetic rats. In this context, Stefanello et al. (2014) demonstrated that caffeine (15 mg/kg) reverted the increase in acetylcholinesterase (AChE) activity and partially restored delta-aminolevulinic acid dehydratase (δ-ALA-D) and Na^+, K^+-ATPase activities in type 1 diabetic rats. Furthermore, caffeine consumption (1 g/L) for 7 months had a potential neuroprotective effect, preventing synaptic dysfunction and astrogliosis as well as memory impairment in type 2 diabetic mice (Duarte et al., 2012; Stefanello et al., 2014). In addition, CGA (5 mg/kg) treatment for 30 days protected against brain alterations, such as: prevented the increase in AChE activity; partially restored δ-ALA-D and Na^+,K^+-ATPase activities; prevented lipid peroxidation; improved memory; and decreased the anxiety-like behaviour in rats (Stefanello et al., 2014).

4.4. Coffee, caffeine, and oxidative stress

Studies from literature have reported the antioxidant effects of coffee (Choi et al., 2018; Martini et al., 2016; Viana et al., 2012). Evidences suggest that coffee substances are involved in this beneficial effect by increasing the endogenous antioxidant defenses (Martini et al., 2016; Metro et al., 2017). Caffeine and other molecules present in coffee seeds or coffee itself may be acting as "free radical sinks", capturing reactive species generated during heating.

Experimental investigations have supported the hypothesis that caffeine may be partly responsible for the antioxidant effects described for coffee. Caffeine was effective in protecting the mice lens against oxidative damage induced by iron (Varma et al., 2010). The antioxidant action of caffeine has been attributed to increase of glutathione (GSH) levels and its ability to scavenge reactive oxygen species (ROS), particularly the ·OH (Varma et al., 2010).

In fact, other studies *in vivo* also have shown that caffeine can control GSH metabolism. Intraperitoneal injection of caffeine (10 mg/kg) into male C57BL/6 mice significantly increased total GSH levels in the hippocampus (Aoyama et al., 2011). Metro et al. (2017) also showed that caffeine 5 mg/kg (in two daily doses for seven consecutive days) improved plasma levels of GSH and total antioxidant capacity, besides decreasing lipid hydroperoxides and malondialdehyde levels in healthy male volunteers. Evidences suggest that the improved GSH levels could be explained by the increase in cysteine uptake in the presence of caffeine (Aoyama et al., 2011). In addition, Souza et al. (2013) showed that when rats were treated with buthionine sulphoximine (a GSH inhibitor synthesis), the protective effect of caffeine was decreased in a model of pentylenetetrazol-induced seizure (Souza et al., 2013).

Animals that received a diet supplemented with brewed coffee (3% and 6%), and the corresponding doses of 0.04% and 0.08% caffeine after weaning showed a decrease in lipid peroxidation, and an increase in GSH levels and in the activities of the glutathione reductase and superoxide dismutase in the brain (Abreu et al., 2011). The impact of caffeine in antioxidant system also has been associated to adenosine receptors. These receptors are the main molecular targets of caffeine and previous reports have shown that they are involved in the regulation of ROS production (Almeida et al., 2003; Narayan et al., 2001).

Low caffeine doses (0.5–10 mg/kg) may modulate oxidative stress in many experimental conditions, such as menopause (Caravan et al., 2016), seizures (Souza et al., 2013), acute and chronic stress (Kasımay Çakır et al., 2017), Alzheimer's disease (Laurent et al., 2014; Prasanthi et al., 2010) and exercise protocols (Barcelos et al., 2014; Vieira et al., 2017). Caffeine (6 mg/kg) administered orally during 21 or 42 days prevented the increase in the malondialdehyde levels in blood and hippocampus and improved the GSH/GGSG ratio in ovariectomized rats (Caravan et al., 2016). Similarly, the same caffeine dose also increased the GSH levels and decreased the lipid peroxidation in brain of rats submitted to experimental model of seizure (Souza et al., 2013). Besides, caffeine (10 mg/kg) diminished ·OH production in striatum of

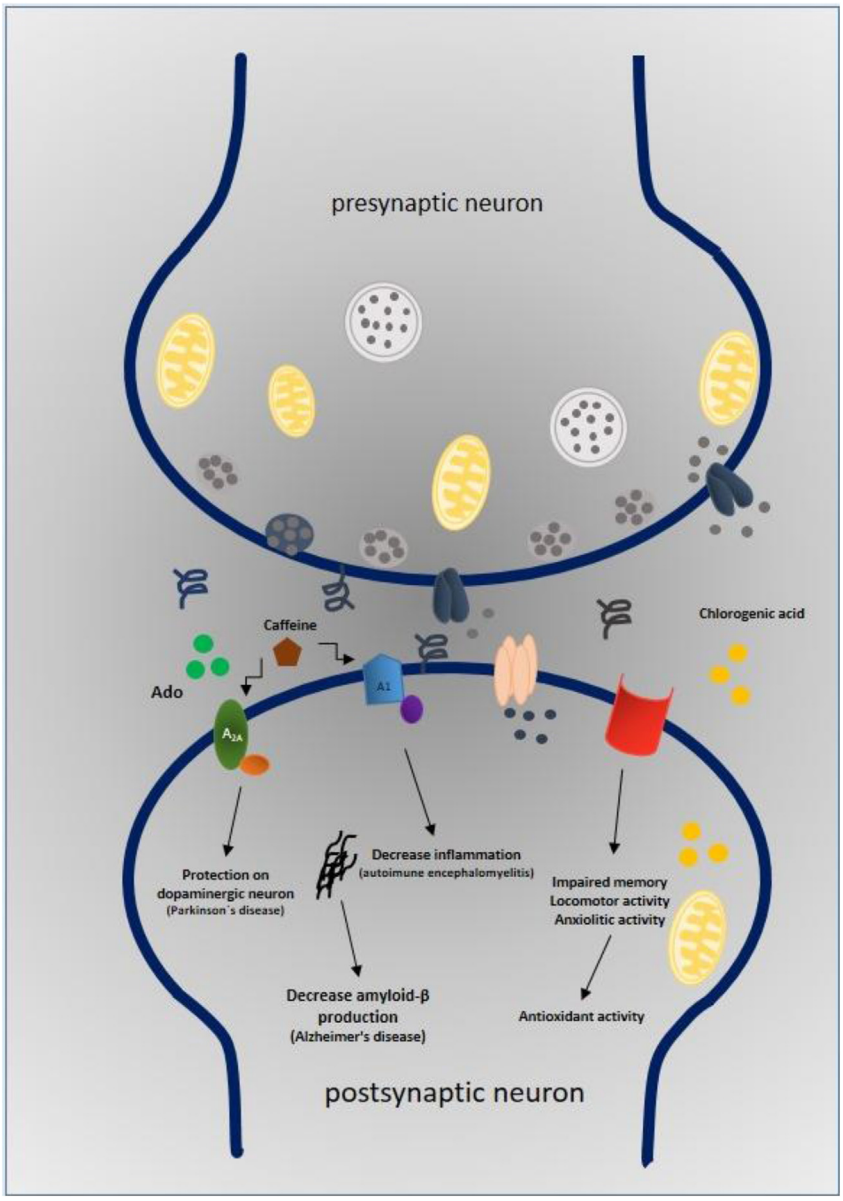

Fig. 2. Effect of caffeine and chlorogenic acid (CGA) on the central nervous system. Caffeine is an antagonist of adenosine receptors and can attenuate dopaminergic toxicity, decrease inflammation, and upregulate A_1 receptors. Moderate caffeine administration suppresses brain amyloid-β production. CGA improves memory impairment, affects locomotor activity, and exerts anxiolytic and antioxidant effects.

rats treated with 3,4-methylenedioxymethamphetamine (Górska et al., 2014).

The results about the antioxidant effects of caffeine in experimental stress models are controversial. Caffeine (3 mg/kg i.p.) was capable to decrease the NO levels, lipid peroxidation, and improve superoxide dismutase activity in brain of rats submitted to stress protocols (Kasımay Çakır et al., 2017). On the other hand, using a restraint stress protocol, Noschang et al. (2009) showed that caffeine at dose of 1.0 g/L (in drinking water) during 40 days only increased the superoxide dismutase and catalase activities in cerebral cortex of non-stressed animals (Noschang et al., 2009).

Studies also have shown neuroprotective effects of caffeine associated with its antioxidant properties against memory impairment in aging (Costa et al., 2008; Costenla et al., 2010) in experimental models of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Arendash et al., 2006); for reviews see (Chen and Chern, 2011; Cunha and Agostinho, 2010). Caffeine administered in the drinking water in low (0.5 mg/day) and high (30 mg/day) doses for 12 weeks reduced Aβ40 and Aβ42 levels in rabbit hippocampus in a model of Alzheimer's disease. However, only the dose of 30 mg/kg was capable to reduce ROS generation and reverse GSH depletion in hippocampus induced by this experimental condition (Prasanthi et al., 2010). In other protocol of Alzheimer's disease, caffeine administered in drinking water (0.3 g/L) was capable to restore gene expression of Nrf2, a transcription factor involved in the response to oxidative stress of the brain in THY-Tau22 mice (Laurent et al., 2014) (Fig. 3).

It is important to consider that antioxidant properties of caffeine have also been demonstrated (León-Carmona and Galano, 2011), but the vast majority of studies have reported antioxidant effects for caffeine in situations where some event triggered oxidative stress. Of note, the dose and schedule of administration (acute, subchronic, and chronic) may be responsible for the discrepancies between studies. Although the beneficial/neuroprotective properties of caffeine may involve antioxidant effects, more studies are necessary to investigate through which mechanisms caffeine exerts its antioxidant effects in the absence of agents that promote oxidative stress.

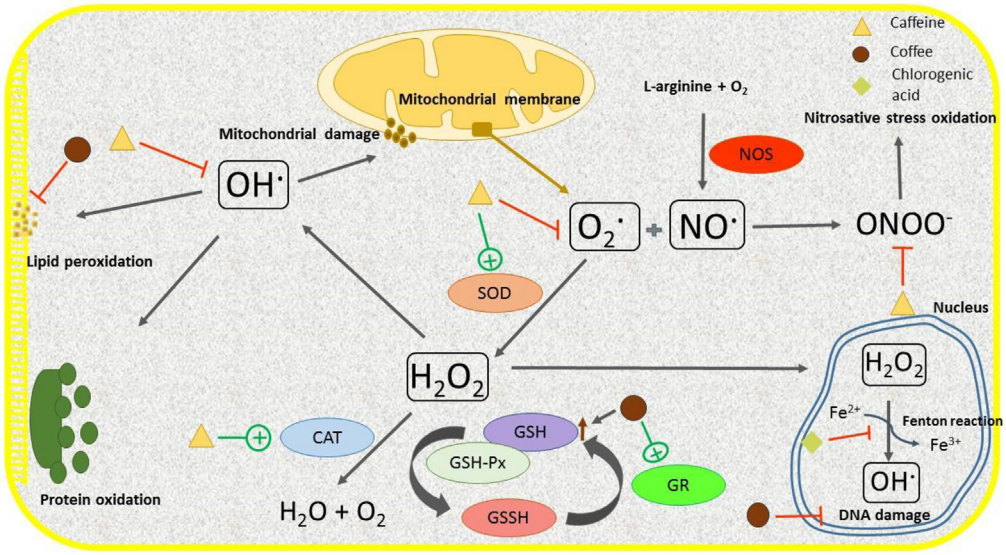

Fig. 3. Effect of caffeine (▲), coffee (●), and CGA (♦) on components of the antioxidant system and in oxidative stress. Caffeine treatment restores reactive oxygen and nitrogen species. Caffeine (1 g/L) alone increases catalase and superoxide dismutase (SOD) activities. Coffee drinking increases glutathione (GSH) levels as well as reduces lipid peroxidation and oxidative DNA damage. CGA prevents hydroxyl radical formation by iron chelation. Abbreviations: NOS: nitric oxide synthase; GSH-Px: glutathione peroxidase; GSSG: reduced glutathione; and GR: glutathione reductase.

5. Impact of coffee, caffeine, and CGA in purinergic signalling

5.1. Purinergic system

5.1.1. Adenosine as a neuromodulator

Neuromodulation is related with synaptic or hormonal stimulation leading to alteration in the electrical properties in response to intracellular changes. It requires that an endogenous substance once released from pre- or post-synaptic sites is able to modify the release or action of the neurotransmitter. Over the past years, this concept has changed mainly due to advances in our knowledge on the role of glial cells in the functioning of synapses. On the neuronal side, in several regions of the brain, astrocytes participate of synapses in a structure defined as the tripartite synapses (Araque et al., 1999; Halassa et al., 2007). The participation of astrocytes in synaptic transmission as active players was reinforced by studies showing the presence of synaptic vesicles and a wide range of substances that can be released from these cells (Bezzi et al., 2004; Montana, 2004).

The presence and release of adenosine from almost all eukaryotic cells as well as the broad expression and distribution of its receptors throughout the brain places this nucleotide as an important neuromodulator in the CNS. Adenosine is not considered a neurotransmitter since it is not stored and released from synaptic vesicles. Otherwise, adenosine is generated by intracellular metabolism of adenosine monophosphate (AMP) and transported to the extracellular medium by bi-directional facilitated diffusion transporters. In the extracellular medium, adenosine can also be formed by the synaptic release of adenosine triphosphate (ATP), which is converted into adenosine by the sequential action of ectonucleotidases (Zimmermann, 2006). Astrocytes have been associated with the regulation of adenosine levels in the synaptic clefts (Martín et al., 2007; Studer et al., 2006). The adenosine in the synaptic cleft has been associated with ATP breaking derived from astrocytes via a cascade of ectonucleotidases, under physiological conditions (Pascual et al., 2005).

The first evidence of the inhibitory action of adenosine was described in experiments using the neuromuscular junction. This study sought to evaluate the effects of cyclic AMP on neurotransmitter release and adenosine was simply used to increase cyclic AMP in the CNS. However, adenosine surprisingly inhibited the transmitter release and theophylline, which was used as an inhibitor of phosphodiesterase, prevented it (Ginsborg, 1964). The concept was reinforced with further experiments that found the release of ATP together with acetylcholine (Simonato et al., 2006), to be similar to adenosine (Ribeiro and Sebastião, 1987; Ribeiro and Walker, 1973). This effect was soon understood because a cascade of ectoenzymes degrade ATP into adenosine (Zimmermann, 2006) in the synaptic cleft (Ribeiro and Sebastião, 1987).

5.1.2. Adenosine receptors

Response mediated by adenosine is associated with activation of specific cell-surface G-protein coupled receptors, which are classified into four subtypes: A1 receptor (A1R), A2AR, A2BR, and A3R (Fredholm et al., 1994). The first adenosine receptors cloned, A1R and A2AR, came from a library of orphan receptors from the dog thyroid (Libert et al., 1991; Maenhaut et al., 1990); and were also cloned from rat and human (Furlong et al., 1992; Mahan et al., 1991). A2BR was cloned from the rat brain (Stehle et al., 1992) whereas the fourth receptor, A3, was more unexpected (Zhou et al., 1992). Apart from the structural variability of A3Rs among mammals, adenosine receptors have been cloned from several mammalian and non-mammalian species and their expression appears to be well conserved among mammals. Adenosine receptors were divided into two broad groups: A1Rs and A3Rs that negatively couple to adenylate cyclase and A2ARs and A2BRs that positively couple to adenylate cyclase.

The inhibitory A1R is the most abundant adenosine receptor, which is functionally coupled to members of the pertussis-toxin-sensitive family of G proteins (Gi1, Gi2, Gi3, and Go). It promotes activation of membrane and intracellular proteins such as adenylate cyclase, Ca^{2+} and K^{+} channels, and phospholipase C (Palmer and Stiles, 1995). The general distribution of A1Rs is similar between rodents and humans (Fastbom et al., 1987; Schindler et al., 2001; Svenningsson et al., 1997). A1R is distributed throughout the brain with the highest expression in neurons of the hippocampus, cerebellum, cortex, and striatum (Mahan et al., 1991; Reppert et al., 1991). It is important to note that A1R is widely found in the excitatory synapses being located in the presynaptic and postsynaptic neurons from hippocampus, as demonstrated by Rebola et al. (2003a,b) and Tetzlaff et al. (1987) (Rebola et al., 2003b; Tetzlaff et al., 1987). The presence of A1Rs was also detected in other cell types in the brain such as astrocytes (Cristóvão-Ferreira et al., 2013), microglia (Gebicke-Haerter et al., 1996), and oligodendrocytes (Othman et al., 2003).

The mRNA expression of A2AR has been predominantly found in the striatum and is selectively expressed in encephalin-containing striatopallidal neurons (Augood and Emson, 1994; Fink et al., 1992; Svenningsson et al., 1997). Lower levels are also found in extrastriatal areas, such as the lateral septum, cerebellum, cortex, and hippocampus (Burnstock et al., 2011; Cunha, 2001). In fact, a more discrete expression of A2ARs can also be found in neurons from the neocortex and

limbic cortex (Lopes et al., 2004; Rebola et al., 2005). In addition to neurons, A2AR has also been identified in astrocytes (Cristóvão-Ferreira et al., 2013), microglia (Gebicke-Haerter et al., 1996; Landolt, 2008), and blood vessels throughout the brain (Dunwiddie and Masino, 2001).

Due to their lower abundance in the brain, the role of A2BRs and A3Rs has received considerably less attention. Thus, the role of adenosine in the brain is believed to be mediated by a controlled activation of A1 and A2A receptors (Fredholm et al., 2005). Both were first defined in the 1970s, based on the ability of methylxanthines such as theophylline and caffeine to act as antagonists (Fredholm, 1985).

5.1.2.1. Ectonucleotidases. Adenine nucleotides and adenosine levels are controlled by a complex pathway of cell surface-localised enzymes named ectonucleotidases. Four families of ectonucleotidases are able to hydrolyse nucleoside triphosphates, diphosphates, and monophosphates to nucleosides: ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases), ecto-nucleotide pyrophosphatase/phosphodiesterases (E-NPPs), alkaline phosphatases, and ecto-5′-nucleotidase. General aspects of these enzyme families are briefly described below.

5.1.2.1.1. E-NPPs. The E-NPPs constitute a family of proteins with broad substrate specificity and catalyse the hydrolysis of pyrophosphate and phosphodiester bonds in nucleic acids, nucleotide sugars, (di) nucleotides, as well as in choline phosphate esters and lysophospholipids (Goding et al., 2003; Stefan et al., 2005). These enzymes are involved in the recycling of these nucleosides, purinergic signalling, and control of pyrophosphate levels. Other suggested roles include involvement in insulin receptor signalling, modulation of ecto-kinase activity, and bone calcification (Goding et al., 2003).

Seven genes encode NPPs, but only three NPPs (NPP1-3) demonstrate relevant (40–50%) sequence similarities at the protein level. NPP isoforms are type II transmembrane glycoproteins characterised by a large extracellular domain, intracellular N-terminal domain, and a single transmembrane domain (Cimpean et al., 2004). A catalytic domain, a cysteine-rich region, a putative C-terminal “EF-hand” motif, and active site are part of the extracellular domain (Sakagami et al., 2005). NPP activity is characterised by divalent cation dependence, strong alkaline pH optimum, inhibition by glycosaminoglycans, K_M for p-Nph-5′-TMP hydrolysis in the micromolar range, as well as for the ability of ATP, ADP, and AMP to competitively inhibit p-Nph-5′-TMP hydrolysis (Laketa et al., 2010).

NPP1 (plasma cell differentiation antigen-1, PC-1) is expressed in the capillaries of the brain (Goding et al., 2003) and in rat C6 glioma cells (Grobben et al., 1999), and correlation between astrocytic tumor grade and increased NPP1 expression has been observed (Aerts et al., 2011). NPP2 (ATX, autocrine motility factor) and NPP3 ($gp130^{RB13-6}$, B10, phosphodiesterase 1β) are expressed in choroid-plexus epithelial cells (Fuss et al., 1997) and likely contribute to the secretion of cerebral spinal fluid. Moreover, NPP2 can produce lysophosphatidic acid, an important molecule for cerebral maturation and this enzyme is increased in frontal cortex of Alzheimer patients (K. Umemura et al., 2006). Studies have shown the elevated expression of NPP3 in solid Walker 256 mammary tumors (Buffon et al., 2010) and in immature astrocytes (Goding et al., 2003). It was found that the maturation process could increase NPP1 mRNA whereas age seems to decrease NPP3 mRNA. In the developing cerebral cortex, cerebellum, hippocampus, olfactory bulb, and striatum the NPP2 mRNA was characterised. E-NPP activity has been related to the neutrophils, caudoputamen, cerebral peduncle and hypothalamus (Langer et al., 2008).

5.1.2.1.2. Alkaline phosphatases. Alkaline phosphatases (APs) are non-specific phosphomonoesterases, which catabolise nucleosides, 5′-tri-, di-, and monophosphates as well as release inorganic phosphate. In the catalytic site of these enzymes there are three metal ions (two Zn and one Mg), which are essential for the enzyme activity (Millán, 2006). Mammalian APs are membrane-bound enzymes with peak of activity at alkaline pH values; APs show specific activity and K_M values when compared with other species. L-amino acids and peptides are AP inhibitors by an uncompetitive mechanism (Millán, 2006). Five isoforms of APs have been recognized in mice (Narisawa et al., 2007). These APs help to regulate extracellular ATP concentration and localised extracellular pH at the sites of bone reabsorption and mineralisation through P2Y-dependent regulation of osteoclast and osteoblast function (Kaunitz and Yamaguchi, 2008).

Tissue non-specific alkaline phosphatase (TNAP) is anchored through a glycosylphosphatidyl inositol group in the plasma membrane (Fonta et al., 2005). Studies have demonstrated that the most prominent TNAP catalytic activity is associated with blood vessels, the choroid plexus, and the meninges (Langer et al., 2008). In addition, TNAP is identified in the thalamus, olfactory bulb, cerebral cortex, caudoputamen, hypothalamus, colliculus, and cerebellum (Langer et al., 2008). Levamisole, a TNAP inhibitor, blocked the ATP hydrolysis to adenosine in neuron-glia signalling through the A2A receptor (Doengi et al., 2008), indicating TNAP is important to nucleotide signalling.

5.1.2.1.3. E-NTPDases. The E-NTPDase family is composed by several members with differences in tissue distribution, cellular localisation and substrate specificity. These enzymes catabolise nucleoside 5′-triphosphates and nucleoside 5′-diphosphates with specific preference for each type of nucleotide.

Cell-surface members of E-NTPDase family are highly glycosylated proteins with molecular masses ~70–80 kDa, which show close immunological cross-reactivity and may exist either in monomeric or in higher homo-oligomeric (dimeric or tetrameric) states (Zimmermann, 2000). These enzymes contain two transmembrane domains at the N- and C-terminus with a central hydrophobic region with five highly conserved sequence domains known as “apyrase conserved regions” (ACR); ACR1 and ACR4 domains show common sequence homology with members of the actin/HSP70/sugar kinase superfamily (Robson et al., 2006; Yegutkin, 2008).

E-NTPDases have an alkaline optimum pH and millimolar concentrations of either Ca^{2+} or Mg^{2+} can stimulate catalytic activity (Zimmermann, 2006). Several physiological or pathological stimuli are able of modifying E-NTPDase activity. These events are critical for the mammalian CNS, and their responses may change throughout development, such as seizures and epilepsy (Cognato et al., 2011), hormonal alterations (Bruno et al., 2005a), stress (Horvat et al., 2010), and nociceptive response (Bruno et al., 2005b).

Eight different E-NTPDase genes encode members of the NTPDase protein family. These enzymes are integral membrane proteins and their active sites are located in the plasma membrane (NTPDases1–3 and 8) or in the lumen of Golgi complex and endoplasmic reticulum (ER) (NTPDases4–7). NTPDase4 is localised to the Golgi apparatus (UDPase) (Wang and Guidotti, 1998) and to lysosomal/autophagic vacuoles (LALP70), respectively (Biederbick et al., 2000). NTPDase5 and NTPDase6 are localised to the ER or Golgi apparatus, but can also be released in soluble form from transfected cells (Belcher et al., 2006).

Some ectonucleotidases have similar membrane topology and amino acids sequences; then, NTPDase1–3 and 8 show catalytic sites facing the extracellular milieu and two membrane spanning domains (Ivanenkov et al., 2008; Robson et al., 2006). These enzymes use several substrates with different preference and product pattern formation. NTPDase1 hydrolyses ADP as well as ATP, whereas there is a preference to hydrolyse ATP over ADP to NTPDases3 and 8. NTPDase 2 has a higher ability to hydrolyse nucleoside triphosphates. The substrate preference order by NTPDase4 and 5 is UDP > GDP > CDP and for NTPDase 6 is GDP > IDP > UDP. NTPDase7 (LALP1) is located in intracellular vesicles preferring nucleoside triphosphates (Robson et al., 2006).

Members of the E-NTPDase family were sequenced and NTPDase1 was identified as the cell activation antigen CD39 (Maliszewski et al., 1994). Experimental studies using purified and cloned soluble apyrase (ATP-diphosphohydrolase) from potato tubers confirmed the homology

of this enzyme with human CD39 (Handa and Guidotti, 1996).

E-NTPDases1–3 are expressed in the mammalian brain and mediate the termination of ATP signalling in the synaptic cleft (Burnstock et al., 2011; Zimmermann, 2006) and hydrolysis of nucleoside tri- and diphosphates occur in all cell types of the nervous system (Langer et al., 2008; Zimmermann, 2006).

E-NTPDase1 is localised at the surface of endothelial vessels in the CNS and is strongly expressed in microglia (Braun et al., 2000). E-NTPDase2 is associated with progenitor cells in the adult rodent brain (Braun et al., 2003) and is expressed in muscularised vessels (Robson et al., 2005), cultured astrocytes (Wink et al., 2006), non-myelinating Schwann cells, and other glial cells of the central and peripheral nervous systems (Robson et al., 2006). E-NTPDase3 is expressed in various brain regions (Vorhoff et al., 2005). This enzyme acts as a pre-synaptic regulator of extracellular ATP levels in the brain and E-NTPDase3 may coordinate multiple homeostatic systems such as sleep–wake and feeding behaviours (Belcher et al., 2006).

Interestingly, E-NTPDase8 shares its main functional properties with E-NTPDase3 rather than E-NTPDase1 or E-NTPDase2. E-NTPDase8 is expressed in the liver, kidney, and jejunum, but its expression level is very low in the brain (Bigonnesse et al., 2004). The involvement of NTPDase8 in the control of nucleotide concentrations in hepatocytes, the regulation of bile secretion, and/or nucleoside salvage may be associated to the expression of this enzyme in bile canaliculi and blood vessels of the liver (Fausther et al., 2006; Robson et al., 2006).

NTPDases can be altered by several pathological conditions, such as demyelination and hyperhomocysteinemia. Studies demonstrated that the antioxidant treatment could modulate these changes and the altered oxidative stress parameters in these conditions (Fernandes Zanin et al., 2010; Schetinger et al., 2007). An increase in CD39 expression in platelets of hypercholesterolemic patients has been associated with an increase in ATP and ADP hydrolysis. There is a correlation between increase in CD39 activity and enhanced oxidative stress parameters, suggesting that there is an association between the inflammatory response, pro-oxidative state and hypercholesterolemia (Gutierres et al., 2014b; Medeiros Frescura Duarte et al., 2007; Schetinger et al., 2007).

5.1.2.1.4. Ecto-5′-nucleotidase. Ecto-5′-nucleotidase (lymphocyte surface protein CD73; E.C. 3.1.3.5) is a glycosylphosphatidylinositol-anchored enzyme that belongs to a superfamily of metallophosphoesterases with a binuclear metal center (Koonin, 1994). The main role of ecto-5′-nucleotidase is the hydrolysis of a variety of nucleoside 5′-monophosphates such as AMP, CMP, UMP, IMP, and GMP to their respective extracellular nucleosides (Colgan et al., 2006). AMP is the most efficiently hydrolysed nucleotide, since the K_M values are in the low micromolar range (50 μM). Thus, ecto-5′-nucleotidase, by extracellular AMP hydrolysis to adenosine formation, plays an important role in subsequent activation of P1 adenosine receptors (Dunwiddie and Masino, 2001). Ecto-5′-nucleotidase was found to be an ortholog of bacterial 5′-nucleotidases according to the primary sequence homology (Koonin, 1994). Seven human 5′-nucleotidases have been found, five 5′-nucleotidases were located in the cytosol, one attached to the plasma membrane, and the last one in the mitochondrial matrix (Yegutkin, 2008). Ecto-5′-nucleotidases show apparent molecular masses of 60–70 kDa with 548 amino acids. The membrane-bound form of 5′-nucleotidase exists as a dimer, while the soluble form can exist as a dimer or tetramer (Dunwiddie and Masino, 2001; Zimmermann, 2000). The enzyme has a broad tissue distribution, with abundant expression in the kidney, brain, liver, colon, heart, lung, and human placenta (Yegutkin, 2008; Zimmermann et al., 2012). Ecto-5′-nucleotidase is predominantly found in endothelium of vascular vessels such as the aorta, carotid, and coronary artery (Koszalka et al., 2004). Ecto-5′-nucleotidase may reveal a variety of different functions, depending on its cell and tissue expression. Like other surface-located enzymes, ecto-5′-nucleotidase has been implicated in non-enzymatic functions such as T-cell activation and cell–cell adhesion. In addition, this enzyme, together with other ectonucleotidases, inactivates signalling nucleotides that act on P2X and P2Y receptors and thus adenosine can bind to the P1 receptors.

Adenosine is an endogenous purine associated with a neuromodulatory role mainly with neuroprotective actions in pathological conditions (Dunwiddie and Masino, 2001). Adenosine produced by ecto-5′-nucleotidase also plays a crucial role in cell survival and differentiation of neural cells (Burnstock et al., 2011). It is important to note that this enzyme is collocated with A2AR and CD73-mediated formation of extracellular adenosine is related with activation of A2AR in striatum and A1R in hippocampus (Augusto et al., 2013; Ena et al., 2013; Rebola et al., 2003a). Ecto-5′-nucleotidase is transiently active within synaptic clefts during development and regeneration (Cunha, 2001; Langer et al., 2008). Age-related alterations were also observed for ecto-5′-nucleotidase activity in the CNS. For example, ecto-5′-nucleotidase activity was 5-fold higher in the hippocampus of aged rats compared with young rats (Cunha, 2001). In addition, alterations in ecto-5′-nucleotidase activity were observed in the CNS in pathological and physiological conditions, indicating the relevance of this enzyme for brain pathophysiology (Burnstock and Novak, 2012; Leite et al., 2011; Schetinger et al., 2007).

5.2. Caffeine effects on the purinergic system

5.2.1. Adenosine receptors and caffeine

Caffeine is the psychostimulant substance most consumed worldwide. The antagonism of adenosine receptors contributes to our understanding of the stimulant effects of caffeine in the brain. Caffeine antagonises adenosine action at pre- and postsynaptic sites in both A1 and A2A receptors in moderate and low doses, decreasing the adenosine inhibitory effect. The blockade of adenosine A1 and A2A receptors can be attained with amounts ranging from 40 to 180 mg of caffeine, levels that can be present in one cup of coffee (Fredholm et al., 1999). Concentrations of caffeine many times higher than those required for the blockade of adenosine receptors exert other effects on cell signalling such as calcium release, inhibition of phosphodiesterase, and γ-aminobutyric acid A receptor (Daly, 2007; Fredholm et al., 1999).

A recent study by Cruz et al. (2017) demonstrated that 500 mg/kg caffeine promotes an increase in A1 and A2A mRNA expression after 4 h of exposure in zebrafish larvae (Cruz et al., 2017). In addition, caffeine consumption (1 g/L in the drinking water starting 2 weeks before STZ challenge) showed preventive STZ-induced memory impairment and neurodegeneration and upregulation of A2AR (Espinosa et al., 2013). A study with anxiety-related behaviour has demonstrated that caffeine (1.0 g/L) attenuated anxiety throughout life in rats (Ardais et al., 2016) and this effect could be related with increase of A1R in the hippocampus (Ardais et al., 2014). Finally, maternal consumption of caffeine during pregnancy and lactation can be related with effects on neuronal development and adult behaviour of their offspring. Silva et al. (2013) have suggested that this effect seems to be related with A2AR antagonism, promoted by caffeine, since A2AR-mice pups reproduced this alteration on brain development (Silva et al., 2013). In addition, Robins et al. (2016) showed that repeated exposure to caffeine plus alcohol during adolescence causes neurochemical and behavioural alterations, which is not observed when caffeine is administrated alone (15 mg/kg) in mice (Robins et al., 2016).

5.2.2. Ectonucleotidases and caffeine

There are few studies on xanthine effects on ATPases and ectonucleotidases. Previous studies have shown that both theophylline and caffeine competitively inhibited the 5′-nucleotidase in cardiac tissue, though theophylline looks as if being a more potent agent. This inhibitory effect on 5′-nucleotidase may not be connected with actions on phosphodiesterase enzyme, since some inhibitors of phosphodiesterase, such as dipyridamole and papaverine, did not affect the 5′-nucleotidase activity (Heyliger et al., 1981). Studies have also shown a significant inhibition of rabbit renal 5′-nucleotidase (EC 3.1.3.5), cyclic nucleotide

phosphodiesterase (EC 3.1.4.17), and adenosine deaminase (EC 3.5.4.4) by theophylline, though only at millimolar concentration (Fredholm et al., 1978). Furthermore, a significant inhibition of 5′-nucleotidase from rat brain by different xanthine derivatives has been observed (Fredholm et al., 1978; Jensen and Jacobsen, 1987). In contrast, theophylline caused an increase of Ca^{2+}/Mg^{2+}-ATPase activity from crude synaptosomal membranes in the hippocampal region (Lachowicz et al., 1983).

The acute administration of 30 mg/kg caffeine promoted an enhancement of both ATP and ADP hydrolysis in synaptosomes of the hippocampus and striatum, respectively. However, chronic caffeine exposure of 0.3 and 1 g/L in drinking water for 14 days was unable to modify NTPDase and 5′-nucleotidase activities in rat hippocampal and striatal synaptosomes (Souza da Silva et al., 2003). On the other hand, caffeine altered nucleotide hydrolysis and ectonucleotidase expression in the hippocampus of rats (in the first 3 weeks of post-natal life) after maternal caffeine consumption (Da Silva et al., 2012). Thus, it seems that high acute concentrations of caffeine can modulate the ectonucleotidase pathway, which could produce an increase in adenosine levels to counteract the antagonist actions of caffeine.

Mate is an infusion of the ground and dried leaves of *Ilex paraguariensis* St. Hil. (Aquifoliacea), popularly known as yerba mate. One of the reasons to consume it is because it is a xanthine-containing beverage. The ingestion of *I. paraguariensis* could contribute to an increase in antioxidant defences against free radicals (Schinella et al., 2000). Chronic ingestion of aqueous extracts of *I. paraguariensis* by rats for 15 days significantly, decreased AMP, ADP and ATP hydrolysis in serum. Thus, it seems that this beverage can change the nucleotidase pathway, modulating the balance in purine levels, which can induce relevant effects in the cardiovascular system, since *I. paraguariensis* has a hypotensive role (Görgen et al., 2005). It has been also shown that caffeine blocks the increase in ecto-5′-nucleotidase activity and the vasodilator response induced by rosuvastatin, impairing the clinical benefit of statins, particularly in conditions of ischemia (Meijer et al., 2010). (see Table 1).

Previous epidemiological report have observed that caffeine can adversely affect calcium absorption, decrease bone mineral density and increase the risk of bone fracture. Caffeine significantly downregulated Cbfa1/Runx2, collagen I, and alkaline phosphatase expressions in rat bone marrow-derived mesenchymal stromal cells; these genes and proteins are expressed in osteogenesis, indicating that caffeine plays important role in osteogenesis (Zhou et al., 2010).

Besides its effects in osteogenesis, caffeine has been associated with the development of diabetes. Duarte et al. (2012) showed that caffeine consumption *per se* could increase serum insulin in NONcNZO10/LtJ diabetic mice after 20 weeks. On the other hand, its positive effects have also been described, i.e., caffeine (15 mg/kg) administered for 30 days attenuated the alterations promoted by hyperglycemia by partially restoring brain Na^{+}/K^{+}-ATPase activity (Stefanello et al., 2014), as well as by restoring NTPDase and ecto-5′-nucleotidases activities in platelets. In addition, caffeine consumption prevented synaptic degeneration and astrogliosis in the hippocampus of STZ-induced diabetic rats (Duarte et al., 2009). Caffeine consumption (1 g/L) for 20 weeks restored memory performance and prevented synaptic dysfunction and astrogliosis in type 2 diabetic mice (Duarte et al., 2012).

5.3. Effects of CGA on the purinergic system

A study recently published by Stefanello et al. (2016) showed CGA as an anti-aggregant agent. When platelets from diabetic rats were stimulated with agonist ADP, platelet aggregation was significantly reduced by CGA treatment for 30 days (Stefanello et al., 2016). Moreover, Fuentes et al. (2014) demonstrated that CGA inibihits platelet activation by the A2A receptor/adenylate cyclase/cAMP/PKA signalling pathway. This study showed through molecular modeling that CGA has a structure compatible with the active site of the adenosine A2A receptor, acting as an agonist. Consistent with this, administration of 200 mg/kg CGA *in vivo* inhibited arterial thrombosis formation in mice (Fuentes et al., 2014). These data suggest that CGA and coffee may be used to protect against the damage of the cardiovascular system observed in diabetes. (see Table 1).

5.4. Other compounds in coffee

We also have to give attention to caffeic acid effects, since it is a compound widely found in coffee. Studies using 5-caffeoylquinic and caffeic acids have demonstrated a decrease in the risk of inflammation and cardiovascular diseases (Anwar et al., 2013a; Bonita et al., 2007). In fact, Anwar et al. (2013) showed that ATP and AMP hydrolysis in platelets was decreased, while caffeic acid (10, 50, and 100 mg/kg) promoted an increase in ADP hydrolysis after 30 days of treatment. They also showed that in platelets, the E-NPP and adenosine deaminase activities were increased by 10–100 mg/kg caffeic acid treatment. These findings suggest that the adenine nucleotide hydrolysis in platelets may be associated with beneficial effects of caffeic acid in cardiovascular diseases. In addition, 10, 50, and 100 mg/kg of caffeic acid for 30 days induced a significant reduction in platelet aggregation, using ADP (5 μM) as an agonist. Based on this as well as other studies, Anwar and colleagues suggested that caffeic acid may interfere with the purinoreceptores P2Y1 and P2Y12 (Anwar et al., 2013a). (see Table 1).

Table 1
Effects of caffeine, caffeine sources, and caffeic acid on nucleotide hydrolysis in different experimental protocols.

Drug	Nucleotide	Dose, period, and route of administration	Effect	Tissue	Animal model	Reference
Caffeine	ATP	30 mg/kg – i.p.	↑	Hippocampus	Adult rat	215
	ADP	30 mg/kg– i.p.	↑	Striatum	Adult rat	215
	AMP	30 mg/kg– i.p.	No	Striatum and hippocampus	Adult rat	215
	ATP	0.3–1 g/L for 14 days – drinking water	No	Striatum and hippocampus	Adult rat	215
	ADP	0.3–1 g/L for 14 days– drinking water	No	Striatum and hippocampus	Adult rat	215
	AMP	0.3–1 g/L for 14 days– drinking water	No	Striatum and hippocampus	Adult rat	215
Ilex paraguariensis	ATP	15 days –drinking water	↓	Serum	Adult rat	218
	ADP	15 days –drinking water	↓	Serum	Adult rat	218
	AMP	15 days –drinking water	↓	Serum	Adult rat	218
Caffeine and diabetes	ATP	15 mg/kg for 30 days –gavage	↓	Platelets	Adult rat	7
	ADP	15 mg/kg for 30 days –gavage	↓	Platelets	Adult rat	7
	AMP	15 mg/kg for 30 days –gavage	↓	Platelets	Adult rat	7
Caffeic acid	ATP	10, 50, and 100 mg/kg for 30 days –gavage	↓	Platelets	Adult rat	5
	ADP	10, 50, and 100 mg/kg for 30 days –gavage	↑	Platelets	Adult rat	5
	AMP	10, 50, and 100 mg/kg for 30 days –gavage	↓	Platelets	Adult rat	5

i.p., intraperitoneal.

6. Concluding remarks

Further studies evaluating the role of caffeine in the modulation of nucleotide levels in several conditions, such as brain development, ageing, and neurodegenerative diseases, could contribute to a better understanding of the neuroprotective effects induced by this xanthine compound.

In addition, CGA is described as a promising compound for the treatment of many diseases mainly linked with inflammation and may act on purinergic modulation. Other compounds found in coffee may have similar effects as trigonelline, which acts in the prevention of disease of the CNS and diabetes. On the other hand, cafestol and kahweol raise serum concentrations of cholesterol, triacylglycerol, and alanine aminotransferase in humans. These compounds contribute to the global effects of coffee.

The effects of coffee are controversial. In addition to caffeine and CGA, many other phenolic compounds may be present in coffee and exhibit biological activities. Therefore, additional studies with animal models and humans are necessary to clarify the mechanism by which they are acting.

Acknowledgments

We would like to thank for the Brazilian financial support provided by “Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/PROEX process numbers: 23038.005848/2018-31 and 88882.182154/2018-01)”, “Conselho Nacional de Desenvolvimento Científco e Tecnológico (CNPq)”, “Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS)”, and Project Agrotur II (code 1473843258) funded by Interreg Italy-Slovenia 2014-2020 (European Regional Development Fund and National funds) to S.P.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2018.10.005.

Funding sources

This research was funded by grants from the FAPERGS: FAPERGS/CNPq 12/2014 – PRONEX. Funding sources had no role in study design, in the collection, analysis and interpretation of the data, in the writing of the manuscript, and in the decision for publication.

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