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ORIGINAL PAPER

Impact of Coffee and Cacao Purine Metabolites on Neuroplasticity and Neurodegenerative Disease

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Abstract
Increasing evidence suggests that regular consumption of coffee, tea and dark chocolate (cacao) can promote brain health and may reduce the risk of age-related neurodegenerative disorders. However, the complex array of phytochemicals in coffee and cacao beans and tea leaves has hindered a clear understanding of the component(s) that affect neuronal plasticity and resilience. One class of phytochemicals present in relatively high amounts in coffee, tea and cacao are methylxanthines. Among such methylxanthines, caffeine has been the most widely studied and has clear effects on neuronal network activity, promotes sustained cognitive performance and can protect neurons against dysfunction and death in animal models of stroke, Alzheimer's disease and Parkinson's disease. Caffeine's mechanism of action relies on antagonism of various subclasses of adenosine receptors. Downstream xanthine metabolites, such as theobromine and theophylline, may also contribute to the beneficial effects of coffee, tea and cacao on brain health.

Introduction

Coffee, tea and chocolate are among the most commonly consumed substances in the world [1]. The use of the seeds from the cacao tree (*Theobroma cacao*) to create beverages dates to the early formative period of Mesoamerican history (2000−1000 BC). In Mayan and Aztecan societies, cacao beans were so valued they were not only used for food and medicinal purposes, but also as a currency.

The explorer Hernán Cortés is credited with understanding cacao's potential after drinking *xocoatl* at the Aztec emperor Montezuma's court. In 1528, Cortés brought the beans and tools necessary to recreate "the drink that builds up resistance and fights fatigue" back to the Spanish court [2]. Mixed with honey, sugar and spices, dark chocolate (cacao) soon became a favorite of the Spanish nobility and, less than a 100 years later, of Europe.

The origins of coffee usage are less clear. The first substantiated evidence of coffee drinking dates to the fifteenth century in Yemenite Sufi monasteries, where monks used the brew to keep themselves awake during nightly prayers. The invigorating properties of the beverage soon spread through other Arabic countries and the Ottoman Empire, where Venetian merchants discovered it and began introducing *caffe'*, from the Turkish word *kahveh*, in Italy around 1570. It is estimated that over 2.3 billion cups of coffee are now consumed daily throughout the world [3].

In 1902 the chemist Emil Fischer was awarded the Nobel prize for his work on purine and sugar metabolism, including the discovery that caffeine is a purinergic component of coffee [4]. Indeed, during the century following Fischer's discovery, studies of the effects of caffeine on the nervous system established it as a psychostimulant and have elucidated its cellular and molecular mechanisms of action on nerve cells. Together with the fact that caffeine is a major psychoactive component of coffee and tea, it has been concluded that caffeine is the most commonly consumed psychoactive chemical throughout the world [5]. While caffeine is present in relatively high concentrations in coffee and tea, several other purine metabolites are also present in lower amounts including theobromine, theophylline and paraxanthine. On the other hand, theobromine and theophylline are present in high concentrations in cacao.

Plants likely evolved enzymatic pathways to produce caffeine and related methylxanthines as a mechanism to protect themselves against consumption by insects and herbivorous and omnivorous animals [6]. As evidence, caffeine has a

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very bitter taste, is concentrated in vulnerable regions of the plants (seeds and leaves) and is considered a natural pesticide [6, 7]. Some species of carnivores including canines (which presumably did not consume cacao during their evolution) can be killed by doses of theobromine well below doses readily tolerated by herbivores and omnivores including humans [8]. As we shall see later in this article, methylxanthines may affect signaling pathways that enable neurons to overcome dysfunction and degeneration. This possibility is consistent with literature in the field of hormesis, a general process by which low levels of an environmental challenge increase the ability of cells and organisms to resist more severe stress and disease [6]. Indeed, emerging evidence suggests that many of the chemicals present in plants that can be beneficial for health are noxious agents/toxins from an evolutionary perspective [6, 9].

In the present short review article, we focus on the neurobiological actions of caffeine, theophylline, theobromine in the contexts of neuroplasticity, cognition and vulnerability to age-related neurological disorders. Some, but not all, epidemiological studies have found a negative association between moderate consumption of coffee and the risk of age-related cognitive disorders and Parkinson's disease (PD) [10–13]. However, the influence of caffeine and other methylxanthines present in these beverages and cacao on brain aging and disease risk remain to be determined.

The Purine Chemistry of Coffee and Cacao

Coffee and cacao contain different ratios of 1,3,7-trimethylxanthine (caffeine) and 3,7-dimethylxanthine (theobromine) and traces of 1,3-dimethylxanthine (theophylline). In humans, within 45 min of oral ingestion, 99% of consumed caffeine is absorbed by the small intestine and stomach [14, 15], with less than 2% of caffeine being excreted untransformed in urine [16]. The majority of caffeine is metabolized in the liver via cytochrome P450 enzymes to form mono- and dimethylxanthines, and methylated uracil-derivatives (Fig. 1) [17, 18]. CYP1A2 accounts for more than 95% of the primary metabolism of caffeine [19]. Although the main metabolic pathways are similar between humans and rodents, there are substantial quantitative differences in their metabolic profiles. In humans, caffeine is primarily metabolized via N-3 demethylation into

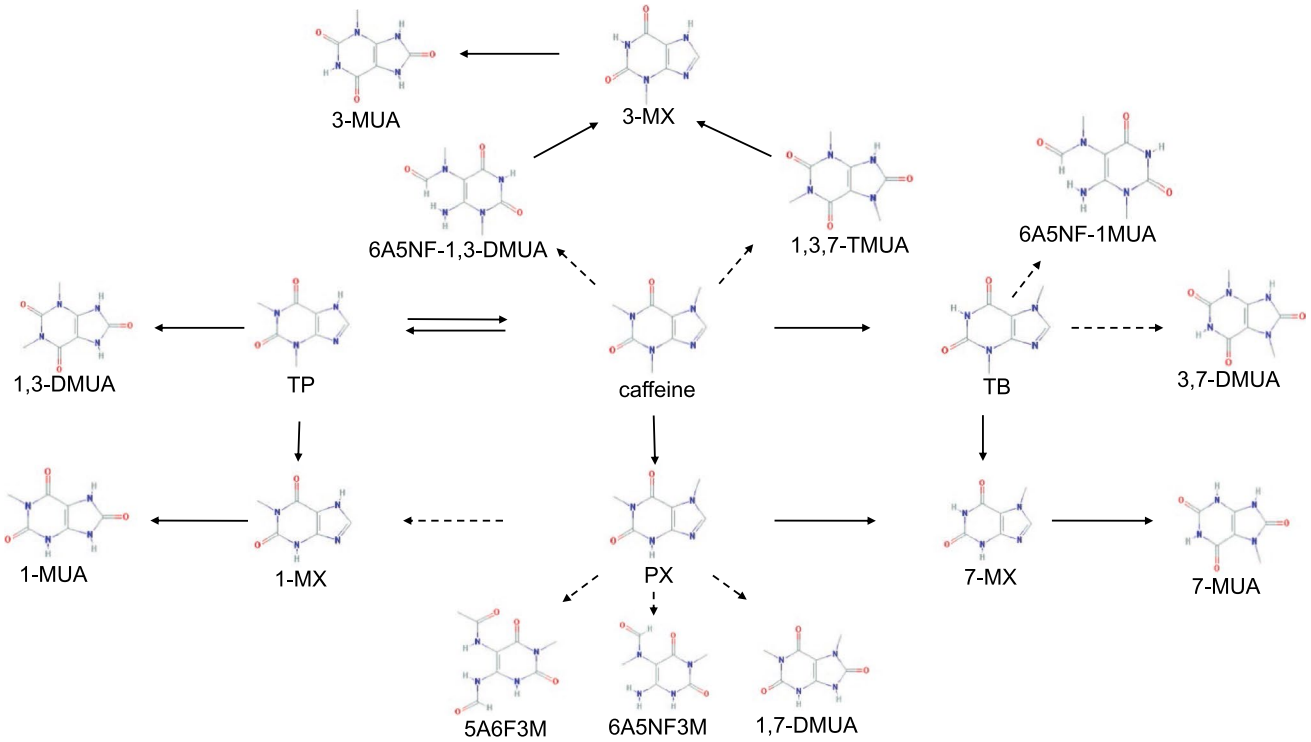

Fig. 1 Caffeine metabolites in humans. Solid arrows indicate a direct pathway. Dashed arrows indicate the presence of an unknown intermediate. Abbreviations from top left to bottom right: *3-MUA* 3-methyluric acid; *3-MX* 3-methylxanthine; *6A5NF-1,3-DMUA* 6-amino-5-(*N*-formylmethylamino)-1,3-dimethyluracil; *1,3,7-TMUA* 1,3,7-trimethyluric acid; *6A5NF-1MUA* 6-amino-5-(*N*-formylmethylamino)-1-methyluracil; *1,3-DMUA* 1,3-dimethyluric acid; *TP* theophylline; *CA* caffeine; *TB* theobromine; *3,7-DMUA* 3,7-dimethyluric acid; *1-MUA* 1-methyluric acid; *1-MX* 1-methylxanthine; *PX* paraxanthine; *7-MX* 7-methylxanthine; *7MUA* 7-methyluric acid; *5A6F3M* 5-acetylamino-6-formylamino-3-methyluracil; *6A5NF3M* 6-amino-5-(*N*-formylmethylamino)-3-methyluracil; *1,7-DMUA* 1,7-dimethyluric acid

paraxanthine (1,7-dimethylxanthine) (~80%), over theobromine (3,7-dimethylxanthine) (~12%), and theophylline (1,3-dimethylxanthine) (~4%), with C-8 hydroxylation to 1,3,7-trimethyluric acid accounting for less than 6% [20] (Fig. 1). Consequently, the main urinary metabolites in humans are paraxanthine and its derivatives 1-methyluric acid, 1-methylxanthine, 1,7-dimethyluric acid, and 6-amino-5-(*N*-formylmethylamino)-3-methyluracil. In rodents, on the other hand, about 40% of caffeine undergoes C-8 hydroxylation to generate trimethyl derivatives, with the primary demethylation products being N-1 theobromine and N-7 theophylline [1].

While paraxanthine is not present in plant extracts, in humans its concentrations in the blood reach levels comparable to or higher than those of caffeine [18]. Paraxanthine should thus be considered when investigating the physiological effects of caffeine, especially under chronic caffeine intake conditions [21].

Like caffeine, theophylline undergoes extensive hepatic biotransformation. Approximately 10% of theophylline is excreted unchanged in the urine, 6% is methylated to generate caffeine [22], 50% is converted to 1,3-dimethyluric acid, and the remaining portion is demethylated to 1- and 3-methylxanthine (Fig. 1). Fewer studies are available on theobromine metabolism; however, it has been shown that it is converted to 3- and 7-methylxanthine, and, based on the reducing status of the cell, to 3,7-dimethyluric acid or 6-amino-5-(*N*-formylmethylamino)-1-uracil [23, 24].

The half-lives of the various methylxanthines differ and are dose-dependent, suggesting saturable kinetics of enzymatic metabolism. Caffeine reaches peak plasma concentrations within 1–2 h of consumption and exhibits a half-life of approximately 2.5–5 h, with variability between individuals [17, 25]. Paraxanthine's half-life is similar to that of caffeine (3.1–4.1 h), whereas theophylline and theobromine have somewhat longer half-lives (6.2–7.2 h) [26].

As for distribution throughout the body, the use of radiolabeled probes showed no bioaccumulation of the different methylxanthines [18, 27]; however, their intrinsic hydrophobic properties impact their ability to cross the blood–brain barrier. The high hydrophobicity of caffeine allows its unrestricted passage through all biological membranes, including the blood–brain barrier [28]. On the other hand, recovery of theophylline [29], theobromine [30] and paraxanthine [31] in the brain is much lower than that of caffeine.

Coffee and Cacao Purines and Synaptic Plasticity

The arousing and energizing effects that originally led our ancestors to include coffee and cacao in their diets have been substantiated using scientific approaches. Growing evidence indicates that habitual consumption of coffee and/or chocolate results in improved cognitive performance during stressful conditions [32–34] and measurable attenuation of neurocognitive decline associated with normal aging and neurodegenerative disorders [35–37]. Acute caffeine intake improves performance on memory tasks [38, 39]. The Institute of Medicine's Food and Nutritional Board Committee on Military Nutrition Research reported that a dose of 150 mg of caffeine enhances cognitive performance for at least 10 h, and advised including caffeine in military rations [40]. Large longitudinal clinical studies have established an inverse relationship between coffee consumption and memory decline during normal aging [41, 42]. Similar results have been found for chocolate consumption. In controlled studies, 8 weeks of daily chocolate drink intake resulted in improved cognitive performance in patients with mild cognitive impairment [43], as well as in cognitively intact elderly [44].

While caution is warranted when extrapolating the results of studies conducted in rodents to humans [45], the mechanisms of action of coffee and cacao methylxanthines have begun to emerge from animal studies. Most studies have focused on caffeine, yet there is evidence that its metabolites share some of the same historically reported cellular actions, including adenosine receptor antagonism at physiologically relevant doses [1], and non-selective inhibition of cyclic nucleotide phosphodiesterases [30, 46, 47] and stimulation of intracellular calcium release [48] at higher concentrations that are toxic in vivo. Concentrations of caffeine in the millimolar range are necessary to activate calcium release from ryanodine receptors and neurotransmitter exocytosis [49–52]. Relatively high concentrations (100 μM–1 mM), are also required to inhibit cyclic nucleotide phosphodiesterases, thereby elevating cyclic AMP levels and its downstream signaling pathways [53]. The concentrations that can induce such responses are more than ten-fold higher than the biological levels found in plasma and brain after ingestion of food containing methylxanthines. It is therefore implausible that such mechanisms contribute to the effects of methylxanthines on neurological functions [54]. Instead, at physiologically relevant doses, the neurological actions of caffeine, paraxanthine and theophylline actions are mediated by non-selective adenosine receptor antagonism [1, 55] (Fig. 2).

Adenosine receptors are G protein-coupled receptors expressed in a variety of organs including heart, colon, lungs, bladder, skeletal muscles and brain [56]. In the central nervous system, adenosine receptors regulate sleep/wakefulness, synaptic plasticity, motor function and neuronal signaling [57–63]. Methylxanthines have been shown to bind with different affinities and specificities to A1 and A2A, the adenosine receptor subtypes found in the brain [62, 64]. Compared to caffeine, paraxanthine and theophylline have an overall higher binding affinity, while theobromine is a low affinity ligand and a weaker adenosine receptor antagonist

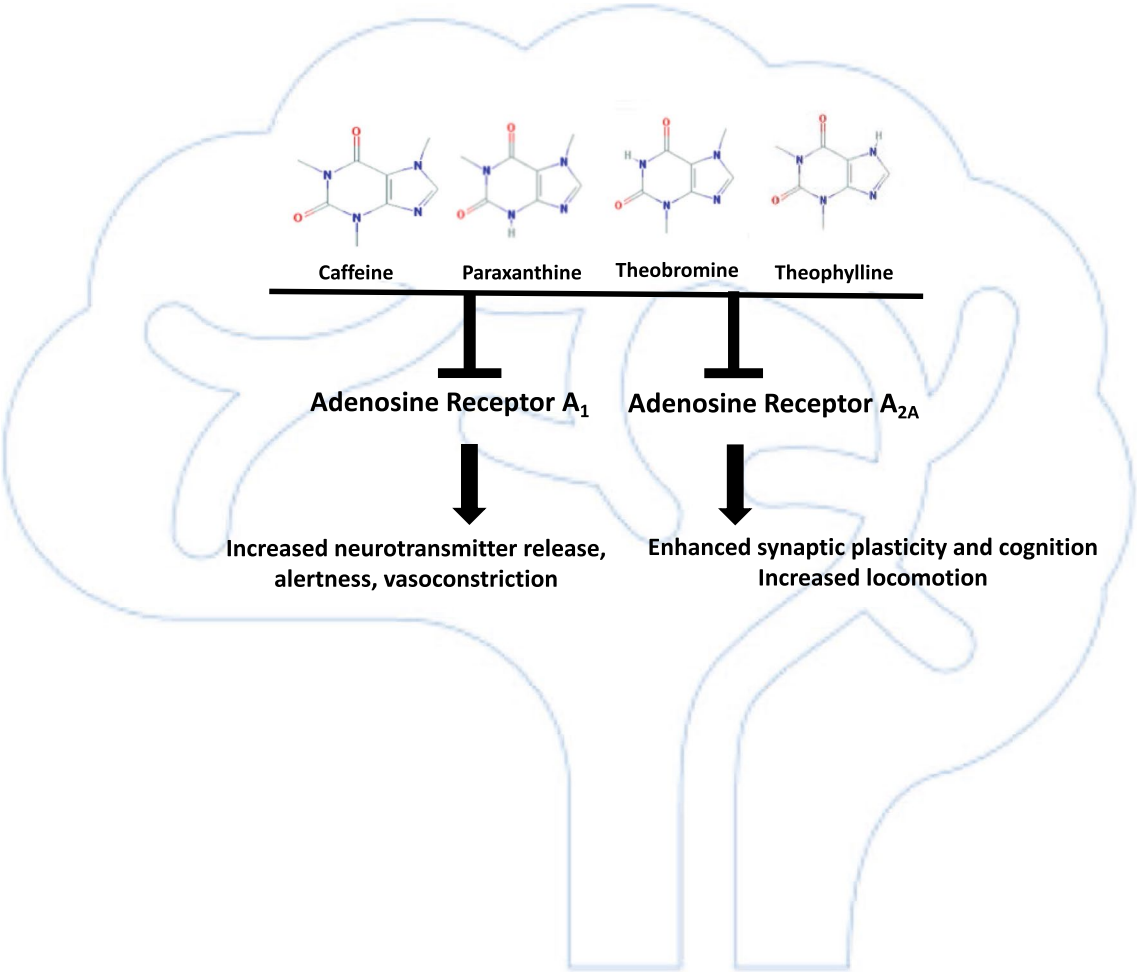

Fig. 2 Impact of antagonism of neuronal adenosine A1 and A2A receptors by caffeine, theobromine, paraxanthine and theophylline on brain physiology and behavior

[1, 65]. Studies using adenosine receptor knock-out mice have shown that adenosine receptor A2A regulates sleep and motor activity, whereas A1 and A2A influence heart rate, body temperature and oxygen consumption [66].

The selective antagonism of adenosine receptors A1 and A2A can also modulate hippocampal long-term potentiation (LTP) [62, 67] a type of synaptic plasticity strongly associated with learning and memory. A1Rs are highly expressed in the CA2 region of the hippocampus [68], and their antagonism enhances the induction and stabilization of activity-dependent LTP [61, 69]. Under basal conditions Shaffer collateral synapses in the CA2 fail to elicit activity-dependent LTP due to the higher calcium buffering and extrusion capacity of CA2 neurons and the expression of the inhibitory protein regulator of G protein signaling 14 [70–72]. However, oral administration of caffeine in vivo, as well as short-term application of caffeine to hippocampal slices, causes a persistent increase in synaptic responses in CA2 neurons [73]. The ability of low doses of caffeine to facilitate basal synaptic transmission, possibly via A1R antagonism, is also observed in CA1 following acute in vitro application [74]. This effect is not only achieved with physiologically relevant concentrations of caffeine, but appears to be age-independent [74].

In the brain A2A receptors are present at high density in the ventral and dorsal striatum and, to a lower extent, in the cortex and hippocampus [56]. While in the striatum they are found predominantly in post-synaptic neurons, in the hippocampus A2ARs are most abundant in the pre-synaptic active zone of the nerve terminals [75]. The role played by A2A receptors in modulation of synaptic plasticity is quite limited under basal conditions [76, 77], but is fundamental in CA1 and CA3 areas under high frequency stimulation [74, 78]. A2A receptors essentially act as controllers, switching presynaptic modulation from inhibitory to facilitatory [67]. Optogenetic studies have shown that activation of A2A receptor signaling in the hippocampus is sufficient to induce LTP in the CA1 while impairing spatial

memory performance, and A2A receptor activation in the nucleus accumbens stimulates locomotor activity [79]. Similarly, selective inhibition of A2A receptor signaling in the CA3 area of an Alzheimer's mouse model restores LTP and reverses memory deficits [80]. While the activation of A2A receptors in hippocampus is sufficient to trigger memory deficits [81], pharmacological or genetic interventions blocking A2A receptors enhance working memory [78, 82], reversal learning [83] and fear conditioning [84, 85] in normal animals, and reverse memory impairments in aged animals [86] and animal models of Parkinson's [87] and Alzheimer's [80, 88–90] diseases. The causal link between adenosine receptor overactivation and neurological disorders is further supported by the consistent observation of upregulated A2A receptors in conditions characterized by chronic stress and/or neurodegeneration [67, 80, 91–95]. Overall, these findings provide mechanistic insight into the nuanced beneficial effects coffee and cacao purines may have on cognition and prevention of age-related memory impairment.

While adenosine receptor antagonism can explain most of the central nervous system effects of methylxanthines, it is possible that additional yet uncharacterized mechanisms contribute as well. For example, following both acute and chronic caffeine intake, changes in local rates of cerebral energy metabolism with increased glucose utilization are found in various monoaminergic areas, motor and limbic systems, and the thalamus [96, 97]. These changes are dissociated from the effects on cerebral blood flow, as they occur under conditions of vasoconstriction and hypoperfusion [98]. Furthermore, they also involve areas of the brain not particularly enriched with adenosine receptors [96] and are insensitive to receptor-dependent desensitization [97].

Adenosine Receptor Signaling in Synaptic Plasticity

Emerging findings suggest that a general mechanism by which some chemicals in vegetables, fruits, coffee and tea provide health benefits is by inducing adaptive cellular responses [8, 9]. From an evolutionary perspective, such phytochemicals might function to dissuade insects and herbivorous and omnivorous animals from eating plants. It is conceivable that animals, in turn, evolved adaptations not only enabling them to consume limited amounts of phytochemicals without toxic effects but to potentially benefit from their consumption [6, 9]. For example, it was recently shown that while honeybees are repulsed by high doses of caffeine, the low amounts present in the nectar of *coffee* and *citrus* species facilitate associative learning and memory acting via adenosine receptor antagonism [99]. Moreover, the consumption of sugar syrup supplemented with low doses of caffeine significantly increased the resistance to parasite infestation and lifespan of worker honeybees [100]. As mentioned in previous sections, converging evidence suggests that at physiologically relevant doses methylxanthines act as non-selective adenosine receptor antagonists. Here we describe the signaling pathways elicited by adenosine receptors A1 and A2A that may be functional targets of caffeine and its metabolites, with a focus on modulation of synaptic plasticity.

The best characterized mechanism of signal transduction elicited by activation of the adenosine receptors is the modulation of adenylate cyclase activity [101, 102]. Adenosine receptors A1 and A2A are indeed respectively coupled to inhibitory (Gi) and stimulatory (Gs) GTP-binding proteins which inhibit and stimulate adenylate cyclase (Fig. 3). Inhibition of adenylate cyclase by A1Rs promotes the activation of potassium channels and phospholipase C as well as the inactivation of N, P, and Q-type calcium channels [103]. Presynaptically, A1R activation depresses the release of neurotransmitters including glutamate, gamma-aminobutyric acid (GABA), norepinephrine, and dopamine [61], with a particularly prominent effect on glutamatergic excitatory transmission [104]. Post- and extra-synaptic A1R activation influences the response to excitatory stimuli by hyperpolarizing the resting membrane potential via activation of inward rectifying potassium channels [105] and controlling the N-type channels and *N*-methyl-D-aspartate (NMDA) receptors [106, 107]. Dose and time-dependent phosphorylation of extracellular signal-regulated kinases (ERKs) 1/2 by A1R activation has also been reported [108] (Fig. 3a). Impairment of paired-pulse facilitation at Shaffer collateral-CA1 synapses is observed in A1R knockout mice, without overall changes in LTP and LTD [109]. Both genetic and pharmacological approaches suggest that under physiological conditions A1Rs are not essential for plasticity at mossy fiber synapses [110]. On the other hand, studies using genetic A1R ablation, specific A1R antagonists or removal of adenosine via adenosine deaminase have shown a selective augmentation of mossy fiber basal transmission in the hippocampus, but decreased short-term plasticity (i.e. paired pulse facilitation) and LTP at this synapse [111]. Furthermore, under non-physiological conditions such as in sleep deprivation [112] or chronic morphine administration [113], the activation of A1Rs normalizes CA3-CA1 LTP in animals. The possibility that the role of A1Rs in learning and memory varies under physiological and pathological conditions is supported by the fact that A1Rs knockout animals can normally acquire and retain spatial reference and working memory [109, 114, 115]; whereas pharmacological interventions implicate A1Rs in preventing spatial and working memory impairments induced by morphine [113] or scopolamine [116].

Agonism of A2ARs coupled to Gs or, in the striatum, to Golf [117], leads to an increase in cAMP and activation

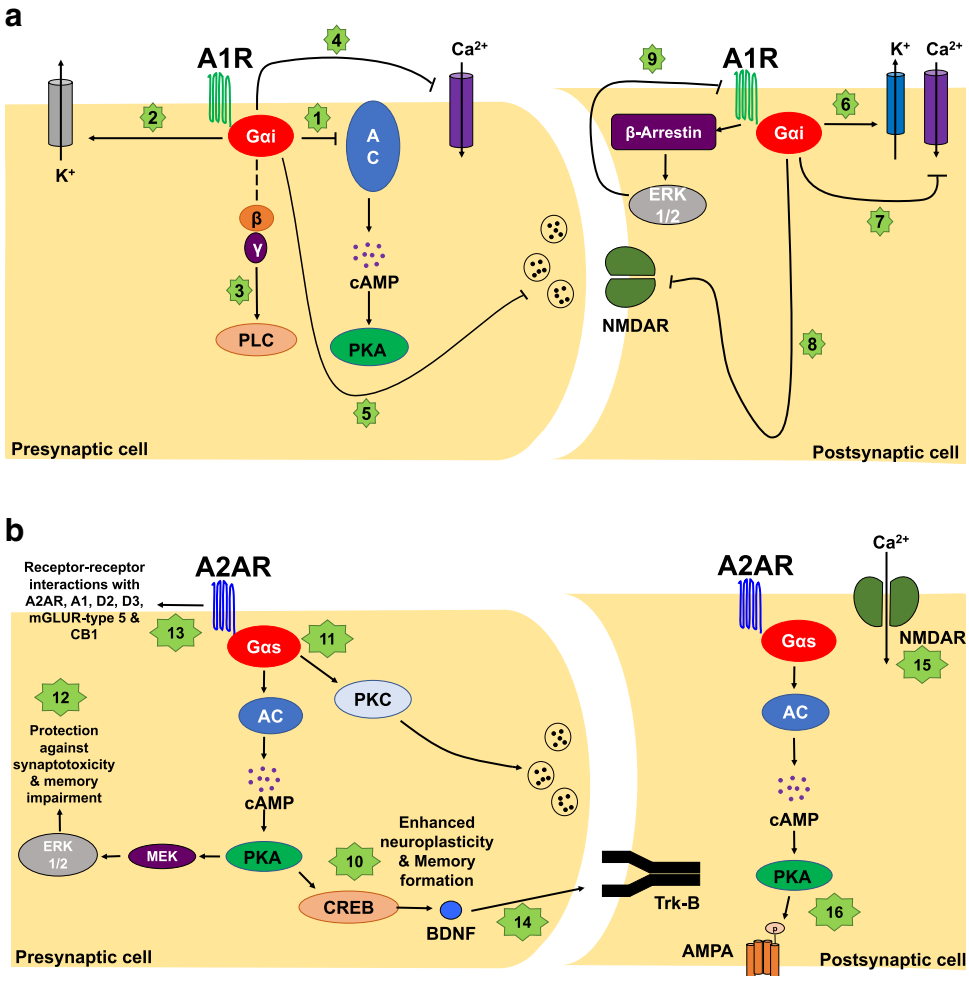

Fig. 3 Signaling pathways associated with A1R and A2A activation. (**a**) Inhibition of adenylate cyclase by A1Rs (1) promotes the activation of potassium channels (2) and phospholipase C (3), as well as the inactivation of N, P, and Q-type calcium channels (4). Presynaptically, A1R activation depresses the release of almost every classical neurotransmitter (i.e. glutamate, gamma-aminobutyric acid, norepinephrine, dopamine, etc.) (5), with a most prominent effect on glutamatergic excitatory transmission. Post- and extra-synaptic A1R activation influences the response to excitatory stimuli by hyperpolarizing the resting membrane potential via activation of inward rectifying potassium channels (6) and controlling the N-type channels (7) and *N*-methyl-D-aspartate (NMDA) receptors (8). Dose and time-dependent phosphorylation of extracellular signal-regulated kinases (ERK) 1/2 by A1R activation has also been reported (9). (**b**) Agonism of A2ARs coupled with Gs or, in the striatum, with Golf, leads to an increase in cAMP and activation of protein kinase A and downstream signaling pathways (10). It is indeed well established that activation of A2AR controls the recruitment of cAMP response element binding protein (CREB), a transcription factor involved in memory formation. It has also been shown that A2AR modulation of neurotransmitter release is dependent on protein kinase C activity (11), and that the recruitment of mitogen activated protein kinases (12) underlies the ability of A2AR to prevent synaptotoxicity and memory impairment in Alzheimer's mouse models. A2AR can dimerize with themselves, A1R, D2 dopamine receptors, D3 dopamine receptors, metabotropic glutamate type 5 receptors and the cannabinoid CB1 receptor in a synergistic or antagonistic fashion (13). Activation of A2ARs facilitates the release of BDNF, BDNF-mediated synaptic transmission and hippocampal LTP (14). A2ARs can influence hippocampal synaptic plasticity by modifying post-synaptic calcium responses. At hippocampal mossy fiber-CA3 synapses A2AR activation mediates LTP elicited by (15) NMDA and mGluR5 -dependent calcium increases. A2AR-dependent activation of PKA regulates the phosphorylation of GluR1, its insertion in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, thus AMPA-evoked LTP in CA1 pyramidal neurons as well as the potentiation of LTP at CA3-CA1 synapses (16)

of protein kinase A and downstream signaling pathways [107]. It is indeed well established that activation of A2AR controls the recruitment of cAMP response element binding protein (CREB), a transcription factor involved in memory formation [118–120]. It has also been shown that A2ARs modulation of neurotransmitter release is dependent on protein kinase C activity [121–123], and that the recruitment of mitogen activated protein kinases underlies the ability of A2AR to prevent synaptotoxicity and memory impairment in Alzheimer's mouse models [90]. The understanding

of A2AR signaling mechanisms is further complicated by the fact that they can dimerize with themselves [124], A1R [125], D2 dopamine receptors [126], D3 dopamine receptors [127], metabotropic glutamate type 5 receptors [128] and the cannabinoid CB1 receptor [129] in a synergistic or antagonistic fashion [107]. A2ARs can also interact and transactivate receptor tyrosine kinases in the absence of neurothrophins [130–132]. Brain-derived neurotrophic factor (BDNF) is a critical modulator of hippocampal synaptic plasticity under physiological and pathological conditions [133]. Activation of A2ARs facilitates the release of BDNF, BDNF-mediated synaptic transmission [134] and hippocampal LTP [135]. Pharmacological inhibition as well as genetic knockout of A2ARs results in decreased levels of BDNF in the brain [136]. In addition to modulation of BDNF signaling, A2ARs can influence hippocampal synaptic plasticity by modifying post-synaptic calcium responses. At hippocampal mossy fiber-CA3 synapses A2AR activation modulates LTP elicited by NMDA- and mGluR5- dependent calcium increases [78]. A2AR-dependent activation of PKA regulates the phosphorylation of GluR1, its incorporation into α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and thus AMPA-evoked LTP in CA1 pyramidal neurons as well as the potentiation of LTP at CA3-CA1 synapses [137] (Fig. 3b).

Due to differences in expression levels of A1R and A2AR, their opposing effects on hippocampal LTP and the fact that caffeine has very similar binding affinities for each receptor, predicting the impact of caffeine on LTP/LTD remains a challenge. As mentioned previously, the data gathered over the last several decades using pharmacological and gene knockout experiments suggests that the neurological effects of caffeine, and possibly other methylxanthines, correlates well with inhibition of A2ARs [1, 62, 98].

Coffee, and Cacao Purines and Neurological Disorders

Because of the widespread distribution of adenosine receptors throughout the body and nervous system, methylxanthines have several potential therapeutic applications. Theobromine and theophylline are used as smooth muscle relaxants, vasodilators, diuretics and myocardial stimulants [138]. Caffeine can act as an adjuvant analgesic increasing the action of painkillers [139], and because of its effect on metabolism and insulin sensitivity [140–142] is included in weight loss supplements. A possible role for methylxanthines in preserving brain health is suggested by epidemiological studies evaluating the association of nutritional and lifestyle factors with neurodegenerative conditions [143–147]. Habitual intake of methylxanthines in humans is associated with a reduced risk of stroke [148], depression [149, 150] and suicide [151]. Higher caffeine levels in the cerebral spinal fluid (CSF) are correlated with better clinical outcomes in patients with traumatic brain injury [152]. Levels of theobromine in the CSF are inversely correlated with the amyloid beta 42 levels in Alzheimer's patients [153]. Some, but not all population studies have found positive associations between coffee and tea intake and cognitive performance in older subjects [33, 41, 154]. In particular, habitual caffeine consumption appears to improve verbal memory [41], long-term memory and psychomotor speed [33].

With regard to neurodegenerative disorders, the strongest associations have been found for methylxanthine consumption and Parkinson's disease (PD) incidence. Several meta-analyses have shown that moderate coffee intake lowers one's risk of developing PD by 24–30% [146, 155–157]. In general, an inverse dose–response association between coffee and tea intake and PD incidence has been consistently reported in studies of men, with a maximal effect found at about 3 cups of daily coffee [155, 157]. However in women, the associations between methylxanthine consumption and PD risk is more complex with regards to dose and hormonal status [158, 159]. Data suggest that caffeine is beneficial against PD at low doses in women not receiving estrogen therapy; however, at high doses it may increase PD risk in those under hormonal replacement therapy [158]. It should be appreciated, however, that such epidemiological data cannot account for all possible confounding variables, and further experimentation is required to establish whether caffeine, theophylline and/or other methylxanthines influence symptoms and/or progression of PD.

The gender disparities suggested by epidemiological studies are substantiated by human studies showing that caffeine metabolism is inhibited in women taking estrogen either in oral contraceptives or as replacement supplements after menopause [160, 161]. Furthermore, studies in rodents have demonstrated that estrogen supplementation interferes with the protection afforded by caffeine against dopaminergic loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD [162]. Notably, in the same experimental model the caffeine metabolites paraxanthine and theophylline also conferred neuroprotection against MPTP-induced striatal dopamine loss [163]. Similar to other physiological responses, antagonism of adenosine receptors may mediate protection of dopaminergic neurons by methylxanthines. In fact, antagonism of A2A receptors with selective inhibitors or genetic knockout mimics caffeine protection in various experimental models of PD [164–166].

An inverse relationship between habitual methylxanthine consumption and risk of developing Alzheimer's disease (AD) late in life was found in several longitudinal studies [11, 42, 167, 168]. In animal studies, caffeine intake can decrease brain amyloid burden and prevent or ameliorate

memory impairment in AD transgenic mice [169–172], as well as in pharmacological models of AD [88]. Mechanisms that may mediate the benefits exerted by caffeine and derivatives in AD models include, adenosine receptor antagonism [88, 173], regulation of cerebral blood flow [174–176], increased oxygen consumption [177] and increased cerebrospinal fluid production [178, 179].

Recent genome-wide analyses studying the genetic variants that influence coffee consumption provide insights into additional mechanisms of action of caffeine, paraxanthine, theophylline and theobromine [180, 181]. Together with loci directly linked to methylxanthine metabolism, these studies discovered new loci associated with habitual caffeine intake spanning about 90 genes implicated in various metabolic and physiological functions [180, 181]. Among the various genes, some have potentially important implications for brain physiology and pathology. For example, the gene *ATP-binding cassette sub-family G member 2* (ABCG2) is a xenobiotic transporter also expressed in the endothelium of the blood brain barrier, where it has been shown to regulate the clearance of amyloid beta peptides from the parenchyma [182, 183]. The locus at 2p24 includes the gene encoding glucokinase regulatory protein (GCKR) and is known to play an important role in glucose, cholesterol, triglyceride and urate metabolism [184, 185]. Similarly, 17q11.2 includes the gene encoding MLX interacting protein like (MLXIPL), which activates carbohydrate response element motifs in the promoter regions of genes implicated in glucose and lipid metabolism in a glucose-dependent manner [186].

Notably, alterations in glucose and lipid metabolism have long been associated with the incidence of different neurodegenerative disorders [187]. The locus 11p13 (associated with BDNF) and LIN7C are also relevant to neurodegenerative disorders. BDNF is a neurotrophin involved in survival, differentiation, and synaptic plasticity of several neuronal systems [133]. Alterations in BDNF levels have been found with aging and in many psychiatric and neurodegenerative diseases [133, 188]. LIN7C has been shown to be instrumental for vertebrate neurulation [189] and ensures proper localization of NMDA receptor subunit 2 at post synaptic densities, as well as potassium channels (Kir2), GABA transporters and 5-hydroxytryptamine type 2C receptors [190–192]. Finally, expression of the SNP at 17q11.2 maps EF-hand calcium binding domain 5 (EFCAB5) and is negatively correlated with epigenetic age acceleration in five different brain regions [193].

Conclusions and Perspective

Increasing evidence suggests that regular moderate consumption of coffee, tea and cacao can enhance brain health. Purines are one class of phytochemicals that may contribute to the beneficial effects of these widely consumed plant products on the brain. Among such purines, caffeine has been the most widely studied, theobromine and theophylline less so, and other methylxanthines have been largely unexplored (Fig. 1). While the neurological effects of caffeine are well-established, it is not known whether this purine is solely responsible for beneficial effects of coffee and cacao consumption on cognition and resistance to neurodegenerative disorders. Indeed, emerging evidence suggests that other classes of phytochemicals present in high amounts in coffee and cacao can enhance neuroplasticity and protect neurons against dysfunction and degeneration. Among the many non-purine phytochemicals in coffee and cacao, flavonoids such as epicatechins have been shown to promote synaptic plasticity, enhance cognition and protect neurons in experimental models of stroke and AD [194–197]. The presence of numerous neuroactive chemicals in coffee, tea and chocolate has thus far precluded the identification of the specific chemical or combination of chemicals that account for the beneficial effects of consumption of these plant materials on brain health suggested by data from epidemiological studies. Nevertheless, the literature reviewed in the present article suggests that purine metabolites are one prominent class of such neuroactive chemicals.

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