

Review Article

Chronic Caffeine Consumption Prevents Memory Disturbance in Different Animal Models of Memory Decline

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Abstract. Caffeine, the most widely consumed psychoactive drug, enhances attention/vigilance, stabilizes mood, and might also independently enhance cognitive performance. Notably, caffeine displays clearer and more robust beneficial effects on memory performance when memory is perturbed by stressful or noxious stimuli either in human or animal studies. Thus, caffeine restores memory performance in sleep-deprived or aged human individuals, a finding replicated in rodent animal models. Likewise, in animal models of Alzheimer's disease (AD), caffeine alleviates memory dysfunction, which is in accordance with the tentative inverse correlation between caffeine intake and the incidence of AD in different (but not all) cohorts. Caffeine also affords beneficial effects in animal models of conditions expected to impair memory performance such as Parkinson's disease, chronic stress, type 2 diabetes, attention deficit and hyperactivity disorder, early life convulsions, or alcohol-induced amnesia. Thus, caffeine should not be viewed as a cognitive enhancer but instead as a cognitive normalizer. Interestingly, these beneficial effects of caffeine on stress-induced memory disturbance are mimicked by antagonists of adenosine A_{2A} receptors. This prominent role of A_{2A} receptors in preventing memory deterioration is probably related to the synaptic localization of this receptor in limbic areas and its ability to control glutamatergic transmission, especially NMDA receptor-dependent plasticity, and to control apoptosis, brain metabolism, and the burden of neuroinflammation. This opens the real and exciting possibility that caffeine consumption might be a prophylactic strategy and A_{2A} receptor antagonists may be a novel therapeutic option to manage memory dysfunction both in AD and in other chronic neurodegenerative disorders where memory deficits occur.

Keywords: A_{2A} receptors, adenosine, aging, Alzheimer's disease, caffeine, chronic stress, memory

INTRODUCTION

Caffeine is the most widely consumed psychoactive drug worldwide [1]. However, in spite of its widespread potential to affect human behavior and health, little is so far well established with respect to the impact of caffeine consumption on physiopathological processes. Several factors contribute to the current uncertainty

about the effects of caffeine consumption: 1-the consumption of caffeine is most often associated with the consumption of several other drugs: for instance, coffee (already a mixture of different chemicals) is often consumed with other drugs such as nicotine or alcohol; 2-caffeine seems to act on different molecular targets according to both its regimen of ingestion (chronic or acute) or the dose ingested; 3-finally, there seems to be an inter-individual variability of the susceptibility of different individuals to caffeine, which is possibly related to polymorphisms of the different putative molecular targets for caffeine [2–6].

The aim of better understanding the central actions

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of caffeine is further complicated by some additional factors. Thus, the relationship between the dose of caffeine intake and the levels of caffeine in the brain parenchyma is not yet well understood; in other words, the brain pharmacokinetic profile of caffeine, especially related to chronic intake, is still poorly defined. On the other hand, it is not always straightforward to disentangle the peripheral and central effects of caffeine. With these caveats in mind, it is nevertheless common sense experience that the consumption of caffeine (mainly in the form of coffee) triggers a diverse array of adaptive responses that are mostly related with central control. In accordance with the established idea that caffeine is a psychostimulant [1,7–10], coffee consumption or caffeine administration triggers a myriad of subjective feelings of well-being such as increased self-confidence, motivation, alertness, vigilance, efficiency and concentration [1,7,8].

Amongst these effects, it seems difficult to assess the question of whether caffeine intake might affect memory, since memory performance is affected by most of the phenotypic responses associated with the consumption of caffeinated coffee [8,11–17]. However, the overall evidence tentatively suggests that caffeine might have additional beneficial effects on memory performance in humans and animals (reviewed in [19]).

IMPACT OF CAFFEINE ON MEMORY PERFORMANCE

In spite of numerous methodological problems related to testing the effects of caffeine on human cognitive performance (reviewed in [19]), several studies concluded that caffeine consumed either acutely [9,11,13,21–24], with continuous slow delivery [25,26] or with long-term intermittent consumption [27–31] enhances memory performance in healthy volunteers. In contrast, other studies found minor or no effects of caffeine on memory performance [14,32–34], which casts doubts on the classification of caffeine as a cognitive enhancer. Thus, although there are numerous methodological problems and uncontrolled variables in most studies (reviewed in [19]), the overall available evidence tentatively suggests that the continuous and moderate consumption of caffeine might afford, at best, mild beneficial effects on cognition (reviewed in [19,27]). In fact, no other putative cognitive enhancer tested has proven superior to caffeine in humans (see [34]).

Animal studies also back up the idea that the consumption of moderate doses of caffeine (or theo-

phylline, another xanthine with pharmacological properties similar to caffeine and also present in different beverages) improves memory performance in rodents [36–41], whereas higher doses of acutely applied caffeine (30–100 mg/kg) disrupt memory acquisition [37,41–43]. In contrast, the effects of caffeine in memory retrieval are still unclear [37–40,43–45]. As pointed out in a recent superior review by the group of Reinaldo Takahashi [46], animal studies also indicate, as for the studies with human volunteers (reviewed in [19]), that the effects of caffeine depend on the tested dose, the schedule of administration (acute *versus* chronic), the timing of administration (before training, affecting memory acquisition, or after training, affecting memory consolidation or retrieval) and on the mode of administration (locally in defined brain structures or peripherally affecting different brain structures).

However, the major question approached by this review is not whether caffeine affects memory performance in healthy/control individuals, but rather whether caffeine consumption might prevent memory deterioration. In other words, it will be discussed that, irrespective of a possible effect of caffeine as a cognitive enhancer, the beneficial impact of caffeine consumption on cognition seems most evident when performance is somehow hampered, thus acting mostly as a cognitive normalizer. Furthermore, we will discuss the pharmacological properties of caffeine to support a possible rationale for this particular ability of caffeine to normalize the functioning of brain circuits. This is more easily tackled in animal studies, where the molecular targets of caffeine can be pinpointed and their selective manipulation tested. Thus, we will mostly discuss results derived from animal studies, which will only be episodically correlated with human studies.

MOLECULAR TARGETS OF CAFFEINE TO NORMALIZE THE FUNCTIONING OF BRAIN CIRCUITS

In non-toxic doses, the only evident molecular mechanism of action of caffeine seems to be the antagonism of adenosine receptors, mainly of adenosine A₁ and A_{2A} receptors [1]. Adenosine A_{2B} receptors are also antagonized by relevant concentrations of caffeine reached at non-toxic doses [1], but the role of this receptor is still ill-defined, especially in the nervous system [47]. Caffeine can affect the release of calcium from intracellular stores, interfere with GABA_A receptors, and inhibit 5'-nucleotidases and alkaline phos-

phatases, but this requires concentrations of caffeine higher (millimolar) than these required to antagonize adenosine receptors (micromolar), which are hardly attainable under non-toxic conditions of caffeine consumption [48–52]. Finally, it has also been explored whether the effects of caffeine might depend on the known ability of caffeine to inhibit phosphodiesterases (e.g. [53–56]). General assays of phosphodiesterase activity indicate a mild inhibitory effect of caffeine, which occurs at doses higher than these required to antagonize adenosine receptors (see [1]). However, given that there are several isoforms of phosphodiesterases sub-serving different functions and that the inhibition of some, but not all, phosphodiesterases affords neuroprotection (reviewed in [4] [315,316]), it might be premature to exclude phosphodiesterase inhibition as a possible mechanism underlying some of the neuroprotective effects of caffeine.

This uncertainty on the molecular targets of caffeine is further amplified by the limited information on the pharmacokinetic properties governing caffeine distribution in the central nervous system. In fact, most studies have related caffeine intake with the plasma levels of caffeine, which seems to have an average plateau value of 40 μM in the Western population [48–52]. It is estimated that the brain concentration of caffeine is on average 80% of its plasma concentration [49], but there is no information with respect to possible regional variations of caffeine levels in the brain and it is also not known what are the amounts of caffeine present within the brain parenchyma or in brain fluids (see [57]). Nevertheless, the available data suggest that adenosine A_1 and A_{2A} receptors are the primordial targets responsible by the central effects of caffeine [1,47,58].

A_1 and A_{2A} receptors are most abundantly located in the brain [47], and both have a predominant neuronal localization [47], which is in agreement with the predominant effects of caffeine on brain-related functions [1]. The molecular properties and functions of adenosine receptors in the brain have been the matter of several reviews (e.g. [47]), some specifically dedicated to their role in the control of plasticity in brain circuits [59]. Some basic features related to the functional significance of adenosine receptor-mediated control of synaptic transmission and plasticity will be briefly introduced to understand the ability of caffeine to normalize the function of brain circuits. The most evident effect of adenosine to control neuronal circuits is its ability to depress excitatory transmission through the activation of inhibitory A_1 receptors (reviewed in [47]). The tonic activation of A_1 receptors by endogenous adenosine al-

so curtails both long-term potentiation [60], long-term depression and depotentiation [61,62]. This ability of A_1 receptors to restrain plasticity has been confirmed by different groups in different synapses [63–69] and is similar to the ability of A_1 receptors to control synaptic transmission [47]. Thus, this A_1 receptor-mediated inhibitory system is argued to be responsible by setting a hurdle for plasticity, avoiding the implementation of ‘irrelevant’ (or sub-threshold) signals in neuronal circuits [59]. In contrast, the activation of A_{2A} receptors by endogenous adenosine seems to be selectively engaged to assist the implementation of long-term potentiation both in striatal and hippocampal synapses [66, 70–72]. In contrast to A_1 receptors, which seem to be activated by astrocytic-derived adenosine [73], A_{2A} receptors are activated by ATP-derived adenosine [72, 74], which is released in greater amounts by synapses stimulated upon high-frequency [75–77]. Thus, upon high-frequency firing of a given pathway, the combined exacerbation of global A_1 receptor-mediated inhibition in the circuit (through heterosynaptic depression, see [78,79]) with the local synaptic activation of A_{2A} receptors in the activated synapse, cooperate to maximize salience between the activated and the non-activated synapses (reviewed in [59]). This role of A_{2A} receptors, restricted to the activated synapses undergoing synaptic changes, is likely operated through the control of NMDA receptors [72], which play a pivotal role in the regulation of synaptic plasticity and neuronal damage (reviewed in [80,81]). Thus, in close analogy with the deleterious impact of both NMDA receptor agonists and antagonists on synaptic plasticity and memory performance, it is expected that either excessive or insufficient activation of A_{2A} receptors will result in aberrant synaptic function.

This neurophysiologic layout of the role of the adenosine modulation system in the control of synaptic plasticity leads to 4 predictions related to the expected effects of caffeine on memory performance: 1-that the consumption of caffeine might mainly normalize aberrant memory performance rather than enhancing memory performance; in fact, caffeine has robust effects on cognition in stressed individuals [13], namely in fatigued [21,24,82–84] or sleep-deprived individuals [25,26,85]; 2-that caffeine will impact on synaptic transmission through competitive antagonism of excessive activation of A_{2A} receptors, allowing the normalization of synaptic plasticity; this correlate has just received initial experimental support by Ana Rita Costenla who showed (this issue) that physiologically relevant concentrations of caffeine depress hippocampal long

term potentiation in a manner similar to A_{2A} receptor antagonists [86]; 3-that the effects of caffeine on the normalization of memory performance might be mimicked by selective antagonists of A_{2A} rather than A_1 receptors (discussed below); 4-that the manipulation of A_1 receptors might be essentially deleterious for the implementation of novel memory traits since the role of A_1 receptors is mostly to control the basal activity of neuronal circuits (i.e. defining the 'noise' upon which salient stimuli can implement plastic changes).

In fact, the administration of A_1 receptor antagonists attenuates memory acquisition [42,87–91] but improves memory consolidation [92]. In contrast, memory retrieval is improved by A_{2A} rather than A_1 receptor antagonists [93–95]. In general agreement with these pharmacological studies, A_1 receptor knockout mice display some deficits in the 6-arm radial tunnel maze test [96], whereas A_{2A} receptor knockout mice display improved spatial recognition memory performance in a two-trial Y-maze recognition test [97]. However, the role of each of the adenosine receptors in controlling memory performance may be more complex as highlighted by the observation that transgenic mice overexpressing A_{2A} receptors in cerebral and cerebellar cortices display normal hippocampal-dependent learning of spatial reference memory but present working memory deficits as detected by performance of constant errors in the blind arms of the 6 arm radial tunnel maze, reduced recognition of a novel object, and a lack of learning improvement over four trials on the same day, which was not observed over consecutive days in a repeated acquisition paradigm in the Morris water maze [98]. Likewise, the administration of A_{2A} receptor agonists also causes paradoxical effects on memory performance [90,95,99–101], suggesting that there is a requirement for an adequate adenosinergic tonus for normal memory performance and that both over-activation and hypo-functioning of the adenosine modulation system will result in an impaired memory performance. Accordingly, the available studies in rodents (reviewed in [46]) indicate that moderate doses of caffeine or theophylline improve memory performance in rodents [36–41], whereas higher doses of caffeine (30–100 mg/kg) disrupt memory acquisition [37,41–43]. In contrast, the effects of caffeine in memory retrieval are still unclear [37,39,43]; see [40,44,45], which might be due to the parallel participation of both A_1 and A_{2A} receptors with different effects in different brain regions and with different relative importance in the control of different phases of memory processing. Since caffeine is always expected to partially antagonize A_1 and A_{2A}

receptors (rather than blocking them), it is hoped that future work with heterozygotic mice with partial deletion of either A_1 or A_{2A} receptors or double (partial) deletion of both A_1 and A_{2A} receptors (see [102,103]) will help clarify the relative roles of these two main candidate molecular targets for the beneficial effects of caffeine on the normalization of memory performance.

This neurophysiological hypothesis of a coordinated role of A_1 and A_{2A} receptors in the control of synaptic plasticity is particularly instructive to understand the role of caffeine in the restoration of neuronal functioning once the system is perturbed. In fact, stressful conditions trigger an initial up-regulation of A_1 receptors associated with pre-conditioning phenomena [104, 105], followed by a subsequent down-regulation of A_1 receptors and accompanying up-regulation of A_{2A} receptors, the latter being closely associated with neuronal damage (reviewed in [106]). Furthermore, evidence is accumulating suggesting that the chronic consumption of caffeine mostly acts by antagonizing A_{2A} rather than A_1 receptors [107,108], as first suggested by Daly and Fredholm [58]. Thus, one would expect that chronic consumption of caffeine might be particularly effective to prevent stress-induced memory dysfunction by antagonizing the A_{2A} receptors responsible by the fine-tuning of engagement of NMDA receptors (reviewed in [59]).

EFFECTS OF CAFFEINE AND ADENOSINE RECEPTOR ANTAGONISTS IN DIFFERENT CONDITIONS INVOLVING MEMORY DYSFUNCTION

As mentioned before, the proposed neurophysiological role of the adenosine neuromodulation system in the control of synaptic plasticity led to the anticipation that caffeine should be particularly effective to normalize the afflicted (rather than unperturbed) memory performance and that this effect should be mimicked by selective antagonists of A_{2A} receptors. This is precisely the scenario that has been observed in several animal models of diseases that are known to negatively impact on memory performance.

Parkinson's disease

Caffeine and especially A_{2A} receptors antagonism have long been considered as putative strategies to manage Parkinson's disease, and A_{2A} receptor antagonists are currently being pursued as novel non-dopaminergic

anti-Parkinsonian drugs [109,110]. In fact, the intake of caffeine is inversely correlated with the incidence of Parkinson's disease in different cohorts [111–115], and A_{2A} receptor antagonists (or A_{2A} receptor gene deletion) attenuate motor impairment in different animal models of Parkinson's disease [116–118]. And it was in animal models of Parkinson's disease that the group of Cláudio Cunha (Curitiba, Brazil) first described the beneficial effects of caffeine administration on memory impairment; thus, in an animal model of Parkinson's disease based on the administration of the toxin MPTP (see [119]), the acute administration of caffeine (0.1–1 mg/kg, i.p.) prevented the MPTP-induced impairment of the avoidance scores in the training and test sessions of a two-way active avoidance task in rats [120]. Accordingly, dopaminergic depletion by treatment with reserpine caused deficits in social recognition memory that were prevented by caffeine and by selective antagonists of A_{2A} but not A_1 receptors [121]. Given the frequent appearance and clinical relevance of dementia in Parkinsonian patients, it is still required to consolidate and detail this particular ability of caffeine and A_{2A} receptor antagonists to prevent memory dysfunction in this condition of dopaminergic hypofunction. It would also be of interest to explore putative effects of caffeine and A_{2A} receptor antagonists in other conditions where modifications of dopaminergic signalling have been described and where cognitive deficits are evident, such as Tourette syndrome [122] or schizophrenia [123].

Stress

It is well established that chronic stress causes a deterioration of memory performance [124]. Since we have recently found that A_{2A} receptor antagonists prevent stress-associated morphological modifications in limbic regions [125], we decided to investigate the effect of caffeine and A_{2A} receptor antagonists on the stress-induced memory impairment. It was found that the consumption of caffeine (1 g/L in the drinking water) or of an A_{2A} receptor antagonist (KW6002, 3 mg/kg in the drinking water), starting before a three week protocol of chronic unpredictable stress applied to c57bl6 mice, prevents the stress-induced memory deficits [126]. It was also observed that chronic unpredictable stress caused an up-regulation of A_{2A} receptors, accompanied by a down-regulation of A_1 receptors in the hippocampus [126]. In another model of chronic social stress, induced using an intruder psychosocial stress model for 2.5–3 months, caffeine (0.35 mg/ml, administered in drinking water concurrently with stress) prevented the

stress-induced hippocampal-dependent short-term and long-term memory deficits, evaluated using the radial arm water maze task [127]. Likewise, caffeine consumption also displays robust beneficial effects on cognition in stressed individuals [13]. Interestingly, caffeine consumption increases in humans during stressful life events [128,129], and an inverse correlation is observed between caffeine intake, stress-induced neurotransmitter changes [130], and cortisol elevation [128, 129]. Since we also observed an ability of caffeine to attenuate the impairment of mood-related behavior in mice subject to chronic stress [126], this suggests that caffeine may not only be a normalizer of stress-induced memory impairment, but also a mood normalizer [131] reviewed in [18].

Childhood convulsions

Another group of chronic disorders which is known to impact on memory performance is epilepsy [132, 133]. Again, we have found that the consumption of caffeine (1 g/L in the drinking water) or an A_{2A} receptor antagonist (KW6002, 3 mg/kg in the drinking water) prevented the deficits in memory performance found in adult rats that suffered from a kainate-induced convulsive period in their early life [134]. The effects of caffeine were clearly differentiated from the known protective effect of chronic caffeine or A_{2A} receptor blockers on convulsions [135–137], since the consumption of caffeine or KW6002 began at post-natal day 24 (P24), after the kainate-induced convulsion (at P7), and before memory impairment was observed (only after P90). In this model of early life convulsions-induced delayed memory impairment, it was also observed that there was an up-regulation of A_{2A} receptors in the hippocampus, together with a down-regulation of A_1 receptors in the adult (P90) hippocampus [134]. Accordingly, a different study showed that the adenosine receptor antagonists theophylline (2.5–25 mg/kg) or 8-phenyltheophylline (0.5–2 mg/kg), administered 30 min before and just after training at doses which did not affect retention, reduce the amnesic effect of pentylentetrazole in a dose-dependent manner [138].

Diabetes

Memory performance is also deteriorated in conditions of diabetes, which is accompanied by an increase prevalence of dementia [139–141]. The possible use of caffeine to manage diabetes has received a recent burst of interest (see [142]) and we have found that the

memory deficits in animal models of type 2 diabetes (either Goto-Kakizaki rats or NONcNZO10/Ltj mice fed on a 11% fat diet) were abrogated by caffeine consumption (1 g/L in the drinking water) [126]. Likewise, in a model of type 1 diabetes induced by streptozotocin, it was also observed [143] that the consumption of caffeine (1 g/L in the drinking water) prevented neurochemical modifications associated with memory impairment (see [144]), and it was found that this was accompanied by an up-regulation of A_{2A} receptors in the hippocampus, together with a down-regulation of A_1 receptors [145]. Although these animal studies support a beneficial effect of caffeine on diabetes-induced memory dysfunction, they still need to be confirmed in clinical studies (discussed in this issue by Geert Jan Biessels).

Attention deficit and hyperactivity disorders

Another chronic developmental-related disorder causing a decreased cognitive performance is attention deficit and hyperactivity disorder (ADHD) [146]. Epidemiological studies have pointed out that the incidence of ADHD is lower in countries with greater average consumption of caffeine [147,148]. Thus, caffeine has been considered as a therapeutic option for ADHD, but the results have been inconsistent [147,149–154], probably because the dose schedule of caffeine administration has not been matched to the modified pharmacokinetic profile of caffeine in children (see [155,156]). But although it has not yet been tested if caffeine is effective in alleviating cognitive disturbances in ADHD patients, promising positive results were obtained using an animal model of ADHD, spontaneous hypertensive rats [157]; these animals display memory deficits before the onset of measurable tensional changes and the administration of caffeine prevents the deficits in memory performance [158], in a manner mimicked by adenosine A_{2A} receptors antagonists [159,160].

Alcohol

The heavy consumption of ethanol is another situation where impaired memory performance is observed, being characterized by amnesia or impaired retrieval of memory that remains after cessation of ethanol consumption (see [161]). A recent elegant study showed that the administration of caffeine (5 mg/kg) prevented ethanol-induced retrograde amnesia in rats [54]; interestingly, this effect could be mimicked by a combination of a phosphodiesterase 5 inhibitor (zapri-

nast, 10 mg/kg) together with an A_{2A} receptor antagonist (ZM241385, 1 mg/kg), but by neither drug alone. However, A_{2A} receptors seem to play a crucial role in the control of alcohol-induced neuroplasticity since either pharmacological or genetic blockade of A_{2A} receptors prevent the hypnotic effects of high doses of ethanol [162]. Also, the reinforcing properties of ethanol are in part mediated via A_{2A} receptors, given that pharmacological blockade of this receptor selectively reduces ethanol reinforcement, while failing to consistently modulate ethanol-associated anxiety [163].

Sleep deprivation

It is well known that people worldwide consume caffeine-containing beverages on a daily basis with the goal of preserving their vigilance [164–167], and cognitive performance is seriously hampered upon sleep deprivation [168–171]. However, the particular effects of regular caffeine consumption on the impairment of learning and memory induced by sleep deprivation have only been recently characterized in an animal model [172]; using the radial water maze, it was found that the impaired learning and short term memory performance observed in Wistar rats that were sleep-deprived for 24 hr was significantly attenuated in animals that were allowed free access to caffeine (0.3 mg/ml in drinking water) for 3–4 weeks [172]. This is in notable accordance with the observation that caffeine has robust effects on cognition in sleep-deprived individuals [25, 26,85], which may be different from other psychostimulants [173]. Likewise, the consumption of caffeine also ameliorates cognitive performance and mood in fatigued individuals [21,24,82–84].

Aging

One of the factors that most consistently affect memory performance (fortunately not at the same pace in all individuals) is aging [174–177]. The main molecular targets of caffeine, adenosine receptors, undergo marked adaptive changes upon aging: in fact, there is a consistent decrease of the density of A_1 receptors [178–182], whereas there is a robust increase in the density of A_{2A} receptors in the limbic cortex of aged animals [179,183–185]. Accordingly, there is an enhanced G protein coupling of A_{2A} receptors [183], which have a greater impact on the release of neurotransmitters [183,186] and have a more profound impact in the control of long-term synaptic plasticity [86].

This greater tonic role of A_{2A} , and also of A_1 receptors [181] is further exacerbated by the modified extracellular metabolism of adenosine [187]. These opposite changes in the densities and functional efficiencies of inhibitory A_1 and facilitatory A_{2A} receptors in the neocortex and limbic cortex of aged animals have led to the proposal [184,185] that the adenosine neuromodulation system may be re-set on aging favoring facilitation to compensate the general loss of synaptic efficiency found in the elderly (e.g. [188]). This age-induced bolster of the density and function of A_{2A} receptor might anticipate a particular efficiency of caffeine to impact on age-induced memory impairment. In fact, it was observed that caffeine is effective in preventing age-induced memory impairment in rodents [40, 41], an effect mimicked by A_{2A} receptor antagonists, but not by A_1 receptor antagonists [41]. Likewise, caffeine has significantly greater beneficial effects on cognition in aged individuals [11,27,29]; but see [7, 28], and is able to attenuate the age-associated cognitive decline [189]; but see [34]. Furthermore, a significant association between caffeine consumption and fewer cognitive failures was reported in a non-working elderly population [131]. This contrasts with the lack of association between coffee intake in middle age and cognitive performance in old age in a large sample of Finnish twins [190].

Alzheimer's disease

Alzheimer's disease (AD) is the most common chronic neurodegenerative disease and is clinically characterized by a progressive impairment of cognitive functions such as learning and memory (e.g. [191]). In view of the general ability of caffeine to prevent memory deterioration upon different insults, it would be expected that both caffeine and adenosine receptor antagonists should be considered as promising new pharmacological tools to manage the prototypical conditions affecting memory performance in AD. This was first confirmed in a retrospective epidemiological study showing that the incidence of AD was inversely associated with the consumption of coffee in the previous two decades of life [192]. Another recent study encompassing 1409 individuals aged 65 to 79 also showed that coffee drinkers (who drank 3–5 cups per day) displayed a lower risk (65% decreased) of dementia and AD later in life compared with those drinking no or very little caffeinated coffee, adjusted for demographic, lifestyle and vascular factors, apolipoprotein E epsilon4 allele, and depressive symptoms [193]. Another drug, propentofylline,

which acts as a mixed blocker of nucleoside transporters and of adenosine receptors [194], was reported to afford beneficial effects on cognition, but not on activities of daily living, in patients with vascular dementia [195]. The European Propentofylline Study Group carried out a 12-month, randomized, placebo-controlled trial which also showed good tolerability and beneficial cognitive effects of propentofylline in patients with AD [196]; however, this study was terminated for unknown reasons and the global results were never made available (see [197]). There is also compelling evidence for a beneficial role of caffeine in animal models of AD [45,198–200]. Since rodents do not spontaneously develop age-related modifications that resemble AD [201], two parallel strategies have been used to model AD in rodents: the first relies on the use of transgenic mice endowed with different mutations of proteins found to be dysfunctional in AD, namely amyloid- β protein precursor ($A\beta$ PP) and tau [202]; the other relies on the intracerebroventricular administration of soluble amyloid- β peptide fragments ($A\beta$, mainly $A\beta_{1-42}$), which are proposed to be a causative factor of dementia since their level is the biochemical parameter that correlates better with memory deficits in AD (reviewed in [203,204]). In transgenic mice with the Swedish mutation of the $A\beta$ PP that model several features of AD [205], a six month period of caffeine intake (0.3 mg/ml) alleviated the cognitive deficits found in these mice, as well as the levels of soluble $A\beta$ peptide fragments [199]. In neuronal cell cultures from these same transgenic mice, caffeine also reduced the production of $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides [199], whereas propentofylline attenuated tau phosphorylation also in cultured neurons [206]. Likewise, acute caffeine administration to both young adult and aged AD transgenic mice rapidly reduces $A\beta$ levels in both brain interstitial fluid and plasma, and long-term oral caffeine treatment to aged AD transgenic mice provides not only sustained reductions in plasma $A\beta$, but also decreases in both soluble and deposited $A\beta$ in hippocampus and cortex [207]. Caffeine might not only reduce the levels of $A\beta$ peptides but also counteract the noxious effects of these $A\beta$ peptides, thought to be involved in the etiology of AD (e.g. [203,204]). Thus, caffeine prevents neuronal damage caused by exposure to $A\beta$ peptide fragments, an effect mimicked by A_{2A} , but not A_1 , receptor antagonists [208]. Accordingly, the delayed memory deficits observed after the intracerebral administration of $A\beta$ peptide fragments were prevented by either caffeine or selective A_{2A} receptor antagonists [45,209,210]. These results further strength-

en the idea that caffeine affords beneficial effects on memory performance through its action on A_{2A} receptors, which were found to be upregulated in cortical regions in animals models [199] as well as in cortical tissue from patients with AD [211,212]. This might be related to the notable finding that caffeine not only allows a prophylactic benefit, but may actually revert the pre-installed memory deficits [200]. Thus, a 4–5 week treatment with caffeine (applied through the drinking water) restored performance in 18–19 month old (aged) $A\beta$ PPsw mice already displaying impaired working memory [200]. Interestingly, in contrast to other noxious brain conditions (reviewed in [106]), it was also observed that there was an up-regulation of A_1 receptors in afflicted regions [199,211,212], which may also control the production of soluble $A\beta$ peptide fragments [212]. However, pharmaceutical studies indicate that the protective effects of caffeine are not mimicked by antagonists of A_1 receptors but rather by antagonists of A_{2A} receptors [45,208–210]. Recent studies by our group revealed that either the pharmacological or genetic deletion of A_{2A} receptors prevents the amnesia and synaptic dysfunction caused by administration of $A\beta$ peptides [210], in accordance with the predominant synaptic localization of A_{2A} in cortical synapses [213]. Since the loss of synapses in cortical regions is the earliest morphological modification in AD (see [214, 215]), as well as in mild cognitive impairment [216, 217], these results further strength the suggestion that caffeine and A_{2A} receptor antagonists may be a novel promising prophylactic and/or therapeutic option to manage the precocious phases of AD.

POSSIBLE MECHANISMS OPERATED BY A_{2A} RECEPTORS TO PREVENT MEMORY DYSFUNCTION

The consistent and robust ability of caffeine and A_{2A} receptor antagonists to prevent the deleterious impact of chronic neurodegenerative conditions on memory performance implies that either A_{2A} receptors are a system directly and generally involved in memory processing, or instead that A_{2A} receptors control key mechanisms that are responsible by memory impairment specifically under neurodegenerative conditions.

If the former hypothesis were correct, one would expect that caffeine and A_{2A} receptor antagonists would be able to prevent acute pharmacological disturbances of memory performance, which is largely the opposite of what is experimentally observed. Thus, only one

study documented the possibility that caffeine might prevent memory dysfunction caused by the NMDA receptor antagonist, MK-801 [218], whereas two other studies report the failure of caffeine to modify MK-801-induced memory dysfunction [219,220]. Also, either a selective A_1 receptor antagonist [221] or a selective A_{2A} receptor antagonist failed to prevent MK-801-induced memory deficits [209]. The situation is also unclear with respect to memory deficits caused by cholinergic hypofunction in the presence of the muscarinic receptor antagonist, scopolamine. Whereas it was shown that caffeine attenuates scopolamine-induced memory impairment in humans [222], animal studies showed that only A_1 receptor antagonists can prevent scopolamine-induced memory impairments [93,221,223,224], whereas A_{2A} receptor antagonists are ineffective [100,209]. Hence, in contrast to the evident effects of A_{2A} receptors in the control of memory dysfunction caused by slow onset and chronic neurodegenerative conditions, it seems to be A_1 receptors that play a predominant role in the case of acute modifications of the cholinergic system with scopolamine. This is in agreement with the ability of A_1 receptors to cause a profound depression of the evoked release of acetylcholine in different brain regions [186,318[.5]-320] and acute administration of caffeine indeed enhances the evoked release of acetylcholine [321,322[.6]]. Given that a deficit of cholinergic signaling may underlie some conditions associated with memory impairment and has been the main focus for the (largely unsuccessful) development of memory-restoring drugs (reviewed in [225,226]), it is possible that the control of acetylcholine release might be a mechanism associated with the memory enhancing properties of A_1 receptor antagonists. However, the control of acetylcholine release is unlikely to be a prominent mechanism by which caffeine prevents memory deficits. In fact, as discussed above, the beneficial effects of caffeine on memory deterioration are largely mimicked by A_{2A} receptor antagonists and these A_{2A} receptor antagonists modestly depress acetylcholine release [183,186,227,322[.7]], which would be expected to worsen rather than restore memory performance.

The studies discussed above show that the ability of caffeine and A_{2A} receptor antagonists to prevent acute pharmacological disturbances of memory performance is not so evident; this contrasts with the consistent ability of caffeine and A_{2A} receptor antagonists to prevent the deleterious impact of chronic neurodegenerative conditions on memory performance. Therefore,

the quest for the mechanisms underlying the ability of caffeine and A_{2A} receptor antagonists to prevent memory dysfunction upon chronic neurodegenerative conditions might require exploring whether A_{2A} receptors control features that are directly related to the impact of neurodegenerative conditions on memory performance. There are some features that have been reported to be consistently present in different neurodegenerative disorders, such as morphological modifications of neurons (loss of synapses or loss of neurons), biochemical and metabolic modifications (hypometabolism, mitochondrial impairment and excessive production of free radical species), neurochemical modifications (glutamate excitotoxicity) or functional changes (neuroinflammation). The ability of caffeine and A_{2A} receptor antagonists to prevent memory deterioration would lead to the prediction that A_{2A} receptors should be able to affect some of these key features closely associated with neurodegenerative disorders (see Fig. 1).

Adenosine A_{2A} receptors control synaptotoxicity

The terminology of neurodegenerative disorders implies that degeneration of neurons is expected to underlie these different pathologies. Interestingly, this concept of neurodegeneration has mostly been identified with an irreversible neuronal damage and destruction. However, there is now clear evidence that the neurodegenerative process does not occur in an all-or-none manner, but is instead an evolving process which culminates in the irreversible damage of neurons. And one of the neuronal compartments more precociously affected seems to be the synapse, as gauged by the consistent finding of a modified synaptic function, accompanied by the loss of synaptic markers and synaptic contacts, in the early phases of different neurodegenerative conditions (reviewed in [215,228–230]). In fact, synaptic dysfunction and damage has been recognized as an early event in the course of different neurodegenerative diseases such as AD [214] and mild cognitive impairment [217], Parkinson's [231,232], Huntington's [233,234], or prion diseases [235], as well as in HIV infection [236], schizophrenia [237], diabetic neuropathy [126,143,238,239], botulism [240] or motor neuropathies [241], which can be observed before overt neuronal loss occurs. This is confirmed in *in vitro* studies showing that synaptic degeneration can be temporally dissociated from overt neuronal damage [210, 242,243]; furthermore, this synaptotoxicity can actually be reversible without reaching the stage of overt neuronal damage [243]. The notion that A_{2A} recep-

tors may be able to control synaptotoxicity has directly been demonstrated both in cultured neurons [210,244] as well as in purified nerve terminals from the adult brain [210]. This is in agreement with correlative studies showing that caffeine and/or A_{2A} receptor antagonists abrogate both memory impairment and synaptotoxicity (loss of synaptic markers) in the hippocampus of animals subject to noxious stimuli modeling different neurodegenerative conditions such as AD [210], diabetes [126,143], childhood convulsions [134], restraint stress [125], or chronic unpredictable stress [126]. Furthermore, the enrichment of A_{2A} receptors in cortical synapses [213], in particular in glutamatergic synapses [143,245] provides a structural basis to support this particular ability of A_{2A} receptor antagonists to counteract synaptotoxicity.

Adenosine A_{2A} receptors control mitochondrial function

However, the mechanism by which A_{2A} receptors control synaptotoxicity in glutamatergic synapses is still unclear (see Fig. 1). One mechanism to explain the greater susceptibility of the nerve terminal to insidious brain insults is the particular susceptibility to dysfunction of synaptic mitochondria. In fact, mitochondria located at synaptic contacts have a different morphology and functional properties when compared to mitochondria located in other neuronal compartments or brain cells (e.g. [246–250]). Thus, nerve terminals are at particular catastrophic risk upon slight dysfunction of synaptic mitochondria due to the high metabolic demand imposed by the release of neurotransmitters [246,251] and to the higher calcium transients that are more poorly managed by synaptic mitochondria [252]. Indeed, synaptically-located mitochondria suffer morphological changes upon exposure to glutamate [253]. This mitochondria dysfunction in synapses has the potential to trigger an apoptotic-like response, namely a restricted activation of caspase 3 in synapses [242,244,254,255]. However, it is still unclear if synaptic degeneration is indeed caused by caspase activation and it is not known what are the mechanisms involved in this dying-back process beginning as a synaptic degeneration [240,256,257] and later evolving into overt neuronal loss (reviewed in [229,241]). In parallel, the impairment of the highly tuned mitochondrial function is inevitably associated with a deregulation of the production of radical oxygen species (ROS), which are main effectors of neurodegeneration [258]. An impaired mitochondrial function is also expected to

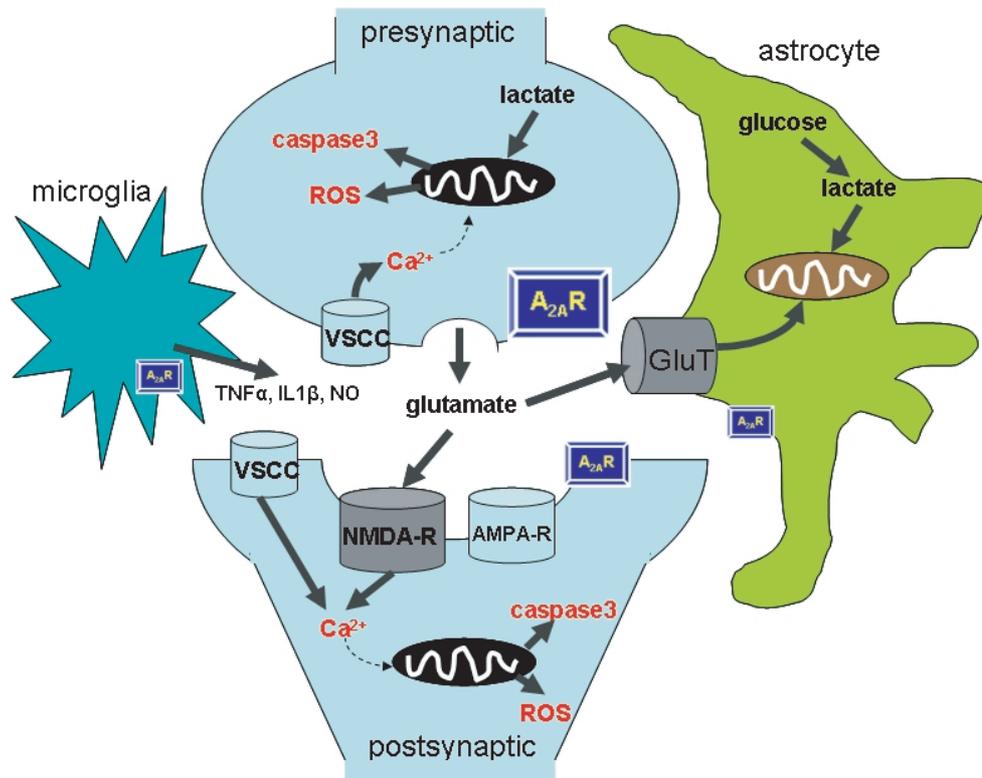


Fig. 1. Summary of the potential molecular mechanisms currently suspected to be involved in the ability of A_{2A} receptors to control synaptic dysfunction and degeneration (indicated by grey arrows). The size of the squares showing A_{2A} receptors represents their relative abundance in the different compartments. The organelles in black depict mitochondria. Abbreviations are as follows: ROS, radical oxygen species; GluT, glutamate transporter; NMDA-R, NMDA receptor; AMPA-R, AMPA receptor; VSCC, voltage-sensitive calcium channel; $TNF\alpha$, tumor necrosis factor α ; $IL1\beta$, interleukin 1β . Note that other mechanisms proposed to underline the A_{2A} receptor-mediated control of neurodegeneration and memory impairment, such as control of the blood-brain barrier, vascular control, lysosome trafficking or cholesterol metabolism, are not represented in this Figure.

lead to a hypometabolic state; accordingly, there is a decreased metabolic state of afflicted brain regions that accompanies memory deterioration [141,259–261]. Interestingly, the blockade of the synaptically-located adenosine A_{2A} receptors prevents the staurosporine-induced mitochondria dysfunction and caspase 3 activation in purified nerve terminals and also abrogates the initial staurosporine-induced synaptotoxicity and later apoptotic-like neuronal damage in cultured hippocampal neurons [244]. Furthermore, A_{2A} receptors can control the neurochemical consequences of enhanced production of free radicals [262,263] through mechanisms that still remain to be fully characterized. Finally, it has been reported that adenosine receptors can affect neuronal primary metabolism [264,265], albeit the exact impact of the different receptor subtypes on astrocytic and neuronal metabolism, and in particular in nerve terminals, still remains to be elucidated. This ability of A_{2A} receptors to control mechanisms

involved in the precocious synaptic degeneration and dying-back process in neurons open the possibility that A_{2A} receptor antagonists might actually control this apparently reversible synaptic dysfunction, which might be an effective strategy to arrest neurodegenerative diseases at their early stages before they evolve into overt irreversible neuronal loss [228].

Adenosine A_{2A} receptors control glutamate excitotoxicity

It is also presently unclear how mitochondria are affected in different neurodegenerative diseases. One likely possibility resides in an intracellular calcium deregulation due to excessive glutamatergic activation [266], which can either allow calcium entry into cells (or terminals) through activated ionotropic receptors of the NMDA subtype or indirectly through activation of voltage-sensitive calcium channels up-

on depolarization. Interestingly, A_{2A} receptors control both NMDA receptors [72,266–268] and voltage-sensitive calcium channels [269,270]. A_{2A} receptors can also control the evoked release of glutamate [271–275], as well as the clearance of glutamate [276–278], thus contributing to an excessive load of extracellular glutamate [279], which may be a final effector of neurodegeneration in different neurodegenerative diseases [266]. Again, these effects of A_{2A} receptors controlling glutamate excitotoxicity are in agreement with the main presynaptic and postsynaptic localization of A_{2A} receptors [213], which are also located in astrocytes [280–283] (see Fig. 1).

Adenosine A_{2A} receptors control neuroinflammation

Finally, it should also be noted that the preventive and/or restorative effects of caffeine and A_{2A} receptor antagonists on memory impairment caused by chronic neurodegenerative conditions may not only be due to the direct effects of A_{2A} receptors on NMDA receptors controlling synaptic plasticity phenomena but also to non-synaptic effects of A_{2A} receptors (reviewed in [106,274]). For instance, A_{2A} receptors seem to play an important role in the control of neuroinflammation (see Fig. 1), which has clear differences from the A_{2A} receptor-mediated control of peripheral inflammation [285]. Thus, A_{2A} receptors are located in microglia cells [281,283], where they control the activation [280,283,286–288] and the release of pro-inflammatory mediators upon challenging of microglia [281,289–291]. Since modified microglia function is a common and sensitive marker of noxious brain conditions [292], the A_{2A} receptor-mediated control of microglia function remains another possible non-synaptic mechanism to explain the ability of caffeine and A_{2A} receptor antagonists to confer neuroprotection and preserve memory function.

Other mechanisms involved in the control of neurodegeneration by A_{2A} receptors

Finally, recent studies have widened the range of possible mechanisms involved in caffeine and A_{2A} receptor-mediated control of neurodegeneration. Thus, caffeine and/or A_{2A} receptor antagonists have been shown to control non-synaptic processes that are known to impact on memory function and neurodegeneration, such as the permeability of the blood brain barrier [198], lysosomal function and trafficking [293,294], neurogenesis [295,296], and the action of growth fac-

tors [41,71,297–302,317]. Finally, albeit neuroprotection afforded by A_{2A} receptor antagonists can be reproduced from purified neurons (or purified nerve terminals) to whole animals, it cannot be excluded that the known vascular control by A_{2A} receptors [303–305] and the ability of adenosine receptors to influence cholesterol metabolism [306] might also play a relevant role in the caffeine and A_{2A} receptor-mediated control of neurodegeneration.

OPEN ISSUES AND CONCLUDING REMARKS

The present assay compiles findings from a series of studies to present an optimistic view of the potential interest of caffeine and A_{2A} receptor antagonists as prophylactic or therapeutic strategies to be validated as candidate neuroprotectants particularly designed to prevent the memory impairment that accompanies neurodegenerative disorders. However, there are still several open issues that will require future studies to clarify and/or consolidate this tentative concept. First, there is a clear requirement for a mechanistic rationale before attempting the translation from animal studies to a clinical setting. In this respect, it should be pointed out that the definition of adenosine receptors as the main target for caffeine still needs to be consolidated. Also, the argument that the impact of caffeine on neurodegeneration and memory impairment is mostly mediated by A_{2A} receptor blockade is still largely a working hypothesis awaiting broader confirmation in different models by different researchers. It is important to note that this idea was solely derived from studies in animals, which have a limited (or different) repertoire of memory performance that does not represent human cognition. It is hoped that A_{2A} receptor antagonists may soon be introduced as therapeutic tools to allow a comparison of the impact of caffeine and A_{2A} receptor antagonists in humans.

Alternatively, future work exploring the eventual relation between polymorphisms of A_{2A} receptors and different susceptibilities to neurodegenerative conditions, memory impairment and caffeine-mediated neuroprotection may also assist us in evaluating if indeed A_{2A} receptors might be the primordial target of caffeine neuroprotection. This present focus on A_{2A} receptors should not minimize the importance of better characterizing the extent to which A_1 receptors participate, or limit the neuroprotection afforded by caffeine, i.e., if they should also be considered as relevant molecular targets for caffeine. In this respect, given that most

neuronal conditions have an evolving profile, it is to be expected that A₁ receptors may also play a role in controlling the worsening of neurological disorders, as has been documented by the elegant work of Detlev Boison (reviewed in [307,308]).

The identification of the molecular targets operated by caffeine in the central nervous system will also require a clear understanding of the pharmacokinetic profile of caffeine in different age groups, especially in aged individuals, where neurodegenerative disorders are prevalent. In fact, there is some valuable information on the plasma pharmacokinetics of caffeine, but little is known about the dose- and time-dependent variation of caffeine levels in the relevant brain regions where it is expected to counteract neuronal (synaptic) damage. The pharmacokinetic characteristics, as well as the presence and relative importance of other ancillary factors formatting the response to caffeine, should bolster the exploitation of the different ability of caffeine to afford neuroprotection in males and females [103,112–114,189,309–314].

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