Ostracising caffeine from the pharmacological arsenal for attention-deficit hyperactivity disorder – was this a correct decision? A literature review

Konstantinos Ioannidis, Samuel R Chamberlain and Ulrich Müller

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Review

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Konstantinos Ioannidis[1], Samuel R Chamberlain[1,2] and Ulrich Müller[1,2]

Abstract

Caffeine is one of the most widespread psychotropic substances in the world. It exerts multiple effects on the brain including adenosine receptor antagonism, and thereby has been found to modulate aspects of cognition, including attention, in animal models and in healthy human volunteers. This review considers what is known of the effects of caffeine on symptoms and cognitive functions in attention-deficit hyperactivity disorder (ADHD), a prototypical disorder of cognitive dysfunction. We consider the merits of investigating further caffeine's therapeutic potential as a monotherapy or as an adjunctive agent in ADHD. The potential benefits of re-opening a dialogue regarding the use of caffeine in ADHD clinical practice are highlighted, along with potential implications for the use of adenosine receptor antagonists in ADHD and other disorders characterised by cognitive impairment.

Keywords

Adenosine, attention-deficit hyperactivity disorder, antagonists, caffeine, methylphenidate

Introduction

Caffeine represents one of the most widespread substances on Earth and approximately half of individuals with psychiatric illnesses consume regularly significant amounts of caffeine per day (Clementz and Dailey, 1988). Humans have been exploiting caffeine's strong pharmacological properties for centuries. Mythology tells us a tale of how modern man made his first observation regarding caffeine's psychoactive propensity: a goat herder in Ethiopia purportedly witnessed his goats becoming energised and not sleeping all night after eating from the coffee bush (Ukers, 1922). To date, caffeine's alerting effects are undeniable. However, some characteristics of this popular substance, such as the relatively rapid development of tolerance, occurrence of side effects (e.g. deleterious effects on sleep architecture and on cardiovascular parameters) have made the research community take a step back from investigating caffeine's potential for clinical use (e.g. Bernstein et al., 2002; Holmgren et al., 2004; Mercader and Patel, 2013; Poussel et al., 2013). In some quarters, this had led to demands for legal regulatory action to protect the public from uncontrolled use (Babu et al., 2008; James, 2012). At the same time, many people consume caffeine regularly, not even aware that they are consuming doses capable of substantially altering cognition, emotion and behaviour.

Caffeine use in the attention-deficit hyperactivity disorder (ADHD) population

It was hypothesised that due to the introduction of decaffeinated coffee, a possible decrease in caffeine consumption would bring to the surface subclinical cases of ADHD (Dalby, 1985). However, the potential impact of decaffeinated coffee has been mitigated by an exponential increase in the consumption of caffeinated energy drinks (Malinauskas et al., 2007), with some products carrying more than enough compound to induce caffeine intoxication (Reissig et al., 2009). Specific population groups, especially adolescents and young adults who may be particularly vulnerable to caffeine's harmful effects, seem to have increased their total daily caffeine intake more than ever (Babu et al., 2008; Pomeranz et al., 2013). Adults presenting with ADHD and comorbid substance use disorder often report escalating consumption of caffeine through a variety of beverages over time (Magon and Müller, 2012). In addition, patients suffering from mental illnesses have a significantly higher caffeine consumption compared to the normal population (Rihs et al., 1996) and adolescents with a diagnosis of ADHD are twice likely to consume caffeine than are adolescents without ADHD (odds ratio (OR) 2.08; 95% confidence interval (CI) 1.23–3.50, p=0.006; Walker et al., 2010). Reports on associations between caffeine use (including dependence) and mental health (including ADHD and its sequelae) are intriguing. Overall, many ADHD patients are quite likely to consume caffeine in doses adequate to

[1]Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[2]Department of Psychiatry, University of Cambridge, Cambridge, UK

Corresponding author:
Konstantinos Ioannidis, Cambridgeshire and Peterborough NHS Foundation Trust, Forensic Psychiatry, George Mackenzie House, Fulbourn Hospital, Cambridge, CB21 5EF, UK.
Email: ioannik@doctors.org.uk

alter their alertness and cognition, and essentially their ADHD symptoms (Broderick and Benjamin, 2004), by habitual consumption. Moreover, research found that caffeine consumption was positively correlated with ADHD symptom severity (Conner's Adult ADHD Rating Scale-Short Version, (CAARS-SS); Dosh et al., 2010; Martin et al., 2008), raising the possibility of 'self-medication'. Caffeine consumption in adolescent girls, a population group where ADHD is generally underdiagnosed (Nutt et al., 2007), was associated with increased self-reported violent behaviours and conduct disorder (Kristjansson et al., 2013). Notably, however, these studies cannot readily address causality. Some authors concluded that familial factors (partially genetic) probably predispose to caffeine use and risk for various psychiatric disorders (Kendler et al., 2006).

Pharmacology

Caffeine is an adenosine A_1 and A_{2A} receptor antagonist (Fredholm, 1995; Kenemans and Lorist, 1995), and although other mechanisms like A_{2B}, A_3, gamma-aminobutyric acid ($GABA_A$) blockade, calcium mobilisation and phosphodiesterase inhibition have been described, these may be relatively unimportant at non-toxic doses (Fredholm et al., 1999). Individual responses to caffeine vary considerably, for example, individuals with lower rates of biotransformation accumulate caffeine more rapidly and have higher levels post ingestion. This may be helpful in explaining individual differences in responses to caffeine (Sawyer et al., 1982). Most recent evidence suggests that genetic polymorphisms of the of the A_{2A} receptor gene (ADORA2A) might be influencing caffeine action on the wakefulness and attention of individuals (Bodenmann et al., 2012). Through adenosine antagonism, caffeine has a significant indirect effect on various neurotransmitter systems including dopaminergic, noradrenergic, and glutaminergic. For example, caffeine can indirectly alter dopaminergic neurotransmission by releasing the pre- and post-synaptic adenosine inhibitory control. Adenosine A1 receptors are heterogeneously distributed in many cerebral and cerebellar cortex areas and highly concentrated in the putamen and mediodorsal thalamus (Bauer et al., 2003; Fastbom et al., 1987) while A_{2A} receptors are concentrated in the dopamine-rich areas of the brain (Fredholm et al., 2003); essentially, pre-synaptic adenosine receptors exist in almost all neurons and that is in accordance with caffeine's diffuse arousal effect in the central nervous system. Adenosine acts both pre- and post-synaptically through multiple mechanisms that are not all well understood. It seems that an essential part of caffeine's stimulant action relies on releasing the brakes on dopaminergic neurotransmission, modulating dopamine (DA) extracellular levels and increasing dopamine release (Borycz et al., 2007), or on a functional modulation which depends on the heteromerisation of A_1 and A_{2A} receptors among themselves and with D_1 and D_2 receptors, respectively (Ferré et al., 2007). On the other hand glutamate transmission can be similarly influenced since extracellular levels may decrease by A_1 and A_{2A} activity (Quarta et al., 2004) and the striatal A_1-A_{2A} receptor heteromer provides a 'concentration-dependent switch' mechanism by which low and high concentrations of synaptic adenosine produce the opposite effects on glutamate release (Ferre et al., 2008). Finally, caffeine may increase noradrenaline (NA) turnover (Hadfield and Milio, 1989) and increase the rate of firing of the noradrenergic neurons in the locus coeruleus (Grant and Redmond, 1982). Although caffeine's effects on glutaminergic transmission may account for its seizure threshold reducing effects, its indirect effects on dopaminergic and noradrenergic systems could be of clinical value since dysregulation of these systems has been heavily implicated in the pathophysiology of ADHD and mechanisms by which existing pharmacotherapies exert their beneficial effects on symptoms and cognitive problems (Del Campo et al., 2011). The complicated interaction between DA, glutaminergic systems and adenosine receptors may, to some extent, explain the paradoxical results observed when different doses of adenosinergic drugs are used (Rivera-Oliver and Díaz-Ríos, 2014).

Synergistic effects between adenosine antagonists and dopamine agonists have been described in animal models (Pinna et al., 1996), whereby caffeine may act in synergistic fashion with dopaminergic drugs injected in the nucleus accumbens (Garrett and Holtzman, 1995). It seems that although caffeine acts primarily on different receptors than the other stimulants, there is some significant cross-tolerance described between caffeine and methylphenidate (Holtzman, 1987). Cross tolerance induced by caffeine administration has also been described for the amphetamine-like discriminative effects of methylphenidate and SKF-81,297, which is a synthetic stimulant that acts as a selective dopamine D1/D5 receptor full agonist. However, this effect was not observed for d-amphetamine (Jain and Holtzman, 2005). Notably, both experiments used non-habitual caffeine doses in an animal model. This is consistent with previous observations that caffeine as a stimulant produces different responses versus other stimulants, such as amphetamines (Rapoport et al., 1981), which may reflect caffeine's different neurobiological mechanism of achieving arousal. Despite cross tolerance effects, the combination of direct adenosine receptor actions with drugs that target other pathways or targets is still considered an idea that merits further investigation (Chen et al., 2013).

Chronology of caffeine clinical use in the ADHD literature

Caffeine was first highlighted in relation to ADHD in 1973 when Schnackenberg suggested that the molecule may play a role in the management of symptoms in this disorder (Schnackenberg, 1973). He described the effects of coffee in 11 hyperactive children who had been previously treated with methylphenidate and developed side effects. All participants showed improved symptoms (lower scores on a hyperkinesis scale) when they were receiving caffeine or methylphenidate (MPH); moreover caffeine and MPH response did not differ with statistical significance, but caffeine lacked the unwanted side effects that were reported with MPH. The study triggered further exploration of the potential usefulness of the substance in this clinical context. In the following 10 years, a small volume of research was conducted in a similar vein. Those were, in their vast majority, studies that compared caffeine with no treatment, placebo, or the use of stimulants, mainly MPH and amphetamines, in small samples of children with ADHD.

Schnackenberg' s results were subsequently disputed, with a series of studies failing to replicate the initial positive result (Arnold et al., 1978; Baer, 1987; Conners, 1975, 1979; Firestone

et al., 1978; Fras, 1974; Garfinkel et al., 1975a; 1975b; Huestis et al., 1975). However anecdotally, both Firestone et al. and Arnold et al. reported that a subject responded beneficially to caffeine but not to other stimulants. Interestingly, caffeine also failed to significantly help in a small study of children with reading disability who had deficits in sustaining attention, but a beneficial effect in the 'hyperactive' subgroup was reported (Kupietz and Winsberg, 1977). When caffeine's effect on stimulus recognition was compared between a small group of normal children versus a small group of 'hyperkinetic' children, the result was numerically beneficial but statistically insignificant, possibly due to limited power (Reichard and Elder, 1977). Conversely, some encouraging results were published, displaying caffeine's superiority versus placebo alone (Harvey and Marsh, 1978), or as a combination treatment with other stimulants versus stimulants alone (Garfinkel et al., 1981; Schechter and Timmons, 1985). Interestingly, Harvey and Marsh used 'whole coffee', trying to replicate Schnackenberg's study, as opposed to other studies that used 'pure caffeine' tablets. A curvilinear pattern of dose-response for caffeine to alleviate the disorder's symptoms was suggested (Garfinkel et al., 1981), although a dose of 200 mg and above was thought to be the pharmacologically sound choice (Graham, 1978).

It became apparent from this early research that caffeine appeared to be inferior to the first line stimulant choices for ADHD; however, it remained part of the therapeutic arsenal for some time, as an alternative when mainstream treatment failed due to side effects (Ross and Ross, 1982). In the following years, interest faded away and in a subsequent review of medicinal uses of caffeine ADHD is not among the main listed indications (Sawynok, 1995). In a meta-analysis of all previous studies on the potential utility of caffeine in ADHD treatment (Leon, 2000), caffeine, regardless of dose, was clearly found to be less efficacious to improve functioning, compared to MPH or amphetamines, on a number of cognitive, psychomotor and affective variables. However, compared to no treatment, caffeine was found superior in reducing teachers' severity ratings of children's ADHD symptoms and lowering children's aggression, plus substantially more able to reduce parents' severity ratings and reducing children's impulsivity. In all, when compared to no treatment, it was found that caffeine can reduce impulsivity. Finally, compared to placebo, caffeine was probably efficacious in reducing teacher's severity ratings of children's ADHD symptoms and children's levels of hyperactivity. In the meta-analysis paper of Leon (2000), only a subgroup of the 19 studies were included in the analysis, due to missing data and heterogeneity. No recommendations for adolescents and adults with ADHD were able to be given due to lack of data. The author noted that many of the outcome variables were represented by a small number of studies and that the available findings from individual studies should be considered with caution. It is also important to note that the mean study size was quite small (14.4 subjects/study) and the selection of caffeine dose administration was not systematic. It seems that the low 150 mg dose could be more efficacious and performance advantages follow a curvilinear pattern. The need for more comprehensive, methodologically sound, studies was highlighted.

In recent years, caffeine has been used in ADHD research in the context of animal models. Studies used spontaneously hypertensive rats (SHRs), an animal model often used for ADHD associated with alterations in dopaminergic neurotransmission (Russell, 2002), but also reduced adenosine de-aminase activity (Matias et al., 1993). It was shown that pre-training administration of caffeine was able to attenuate a selective spatial learning deficit in SHRs, but did not improve the performance of non-SHR controls (Prediger et al., 2005). Caffeine and selective A_{2A} receptor antagonists have been reviewed for their effect on learning and memory and found to be beneficial in SHRs (Takahashi et al., 2008). Moreover, acute caffeine administration improved several learning and memory functions (Pires et al., 2009), and chronic caffeine treatment normalised dopaminergic function by significantly reducing dopamine uptake by synaptosomes in the frontal cortex and the striatum in SHRs (Pandolfo et al., 2013). Furthermore, using an object-recognition task, chronic caffeine treatment during the prepubertal period was shown to bear long-term benefits, similar to MPH treatment, in regards to the discriminative learning deficits of SHRs (Pires et al., 2010). A significant improvement in the attention deficit was also shown in neonatal 6-hydroxy-dopamine (6-OHDA)-lesioned rats after caffeine treatment (Caballero et al., 2011) and caffeine pre-treatment potentiated the motor effects of amphetamine (Simola et al., 2006) suggesting changes that facilitate dopamine transmission, rather than induction of tolerance. Those results demonstrate procognitive effects of caffeine in animal models highly germane to human ADHD.

In a review exploring the adenosine receptors as targets for psychiatric disorders, it was suggested that caffeine use in ADHD needs to be revisited (Cunha et al., 2008) in view of limitations in the existing literature. The authors considered the regimes used in prior studies as being largely inadequate to facilitate and sustain prolonged blockade of A_{2A} receptors; also, taking into consideration the pharmacokinetic profile of caffeine, they argued against the once-daily dose of caffeine used in many studies, particularly in the case of children who eliminate caffeine faster than adults. In the most recent review of caffeine use in psychiatric disorders, the role of caffeine in ADHD was still considered understudied (Lara, 2010). The author highlighted that caffeine, if proven effective, has the advantage of being easily available and relatively inexpensive, without the level of abuse potential of MPH and amphetamine derivatives. Tolerance and withdrawal reactions can be problematic to some extent, but caffeine can still produce a stimulant effect. It has also been suggested that clinicians could potentially use tea consumption, exploiting its considerable concentration of caffeine to induce a stimulant effect on ADHD patients (Liu et al., 2011).

Discussion

It has long been debated whether there is a role for caffeine in psychiatry's arsenal of therapeutic compounds for ADHD. So far, the available clinical studies on the subject have almost uniformly had small sample sizes and lack the methodological cohesiveness of the double blind, placebo-controlled studies that can generally be found in the rest of ADHD therapeutic literature. The recent data from ADHD relevant animal studies is intriguing, but caution is warranted when inferring potential effects in human patients based on animal models alone. Nevertheless, there are some conclusions that can be supported from the available literature, bearing in mind the aforementioned limitations.

Caffeine intake in children has been found to have a therapeutic effect on ADHD, better than placebo, but significantly worse

than MPH and d-amphetamine, and in total, caffeine appears to be inferior to first-line stimulant therapies for ADHD in childhood, in terms of its effects on core symptoms of the disorder. Low to moderate doses of caffeine were found superior to placebo or no treatment at all. Moreover, the majority of ADHD patients in adolescence and adulthood are more likely to use caffeine than the general population, and in doses that may well influence their ADHD symptoms. Although ADHD symptoms persist into adulthood in up to 65% of cases (Faraone et al., 2006), the complete absence of clinical data about therapeutic caffeine use in adolescent and adult ADHD is striking and no conclusions can be drawn regarding its usefulness in these age groups. Therefore, the question as to whether caffeine deserves a place in the arsenal of pharmacological agents for ADHD in adolescence and adulthood remains to be answered. It is possible that caffeine has been ostracised from the therapeutic arsenal for the wrong reasons.

Most likely, the dose-response to caffeine is curvilinear with an optimal dose could be around 150 mg daily, as suggested by the only available meta-analysis (Leon, 2000). Higher doses seem to be clinically less effective in children, but may be needed in adults. Chronically high dosing may induce an up-regulation of adenosine receptors which will lead to tolerance and unwanted opposite results. This explanation is supported by caffeine's strong potential to induce tolerance and withdrawal symptoms in heavy use, which has been flagged up as one of the problematic areas of regular caffeine consumption (Rogers et al., 2012). Given the fact that high single doses of caffeine are probably less efficient than low to moderate ones, it seems reasonable to guide future research into using low to moderate doses to assess efficacy. Low to moderate doses, or pro re nata (PRN) use of caffeine, which has been suggested for psychostimulants (Caisley and Müller, 2012), might bear the extra benefit of fewer cardiovascular side effects and lower potential for the development of tolerance. The option of setting a 'drug holiday' to counteract waning effectiveness after a period of continuous use or interrupting the development of possible tolerance, is an idea worth exploring. The idea of drug holiday has been used with some success in managing adverse effects of stimulants and assessing the persistence of ADHD symptoms (Bolea-Alamañac et al., 2014). Nevertheless, this is an approach which still lacks concrete evidence and there are concerns over the risk/benefit balance even with the first line treatments for ADHD (Graham et al., 2011). Caffeine has a half-life of 2.5–4.5 hours (Arnaud, 1987) but the optimal timing and dose interval for caffeine administration is not well understood yet. Exploring the possibility of using modified-release caffeine tablets to facilitate a more consistent plasma level throughout the day and to avoid high peak plasma levels, which can lead to dose-dependent side effects, would be valuable.

First-line pharmacological treatments for ADHD, including MPH and d-amphetamine, are generally well tolerated and side effects can be managed without necessarily stopping the medication (Cortese et al., 2013). However, sometimes discontinuation is warranted, necessitating the introduction of second- and third-line treatments. So far, it is not known whether caffeine is superior, inferior or equal to those treatments, and therefore, the question remains on whether there is room for caffeine monotherapy as a second- or third-line treatment. The limited data available suggest that further exploration of the potential combination (augmentation) treatment of caffeine and other ADHD medication is worth considering. Still, cross-tolerance between caffeine and other stimulants may hinder that possibility, and also, clinicians might need to consider that cross-tolerance effects from habitual caffeine consumption (especially heavy use) may negatively affect the clinical management of ADHD in patients receiving stimulants. The fact that a few patients, who do not respond to first-line stimulants, respond to caffeine may reflect a, yet unknown, genetic predisposition or neurobiological phenotype which we may use to our advantage when choosing or combining treatments in the future.

Moreover, the causal relationship between the observed correlation between high caffeine consumption and ADHD has not been explored and there is a possibility that patients with ADHD 'self-medicate' with caffeine. If so, it would be reasonable to explore how we could better support our ADHD patients, into receiving a pharmacologically sound caffeine regime, rather than ad hoc dosing not based on sound evidence. This might include educating patients, or regulating caffeine or providing guidance on caffeine consumption. In the UK, there is a massive gap between the adult ADHD prevalence and treatment rates (McCarthy et al., 2012; Simon et al., 2009). The latter, together with adult ADHD services being poorly developed (Asherson et al., 2007), make caffeine treatment an interesting idea for cases of mild to moderate adult ADHD, or for patients who refuse to take ADHD medication. That might allow National Health Service (NHS) provision to focus on the more severe end of the ADHD spectrum. It would be expected that caffeine use could be potentially associated with less stigma compared to ADHD medication. 'Whole coffee' or 'tea' regimes might also be considered for some patients, although very limited or no data are available and the equivalency between those regimes and 'pure caffeine' tablets can be difficult to establish.

Exploring the future of ADHD pharmacotherapy, the A_{2A} receptors have been highlighted as an attractive target for ADHD pharmacotherapy (Cunha et al., 2008) and novel selective adenosine receptor targeting drugs are under development (Müller and Jacobson, 2011). Among those, the non-stimulant selective A_{2A} adenosine antagonists might be of special interest for ADHD pharmacology. If those are proven safe and effective in the future, they might be able to provide a different approach to effectively treating ADHD that takes advantage of a caffeine-like effect on alertness, lacking the side effects of the A_1 antagonism. Cross-tolerance and enhancement effects would be highly probable between selective adenosine antagonists and caffeine and that would make habitual use of caffeine even more important to measure, understand and maybe actively or passively regulate. Istradefylline, a selective adenosine A_{2A} receptor antagonist, has now been approved in Japan, for use in Parkinson's disease (Dungo and Deeks, 2013), a disease in which deficits in the dopaminergic system are the cornerstone of its pathophysiology. This is another example of how much potential there is for targeting the adenosine receptors in ADHD, since ADHD is also characterised by deficits in dopaminergic neurotransmission.

Finally, ADHD is a useful model of cognitive dysfunction for exploring procognitive effects of caffeine and any clinical benefits identified in ADHD may be relevant to the treatment of other conditions associated with cognitive impairment. This would be in line with the fact that caffeine and adenosine receptor antagonists have been tried with some success in animal models for

dementia (Cunha and Agostinho, 2010; Espinosa et al., 2013) and the recent epidemiological evidence that supports the neuroprotective effect of caffeine in Alzheimer's disease (Eskelinen and Kivipelto, 2010).

Conflict of interest

U Müller has consulted for and received educational funding from Heptares, Janssen Cilag Eli-Lilly and Shire; he has received travel expenses and honoraria from the British Association for Psychopharmacology (BAP), Janssen Cilag, Eli-Lilly, Lundbeck, Shire, UCB Pharma and the UK Adult ADHD Network (UKAAN) for talks at scientific and educational meetings. S Chamberlain consults for Cambridge Cognition; his research is funded by a grant from the Academy of Medical Sciences (AMS, UK). Konstantinos Ioannidis declares that there is no conflict of interest.

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