Pharmacology, Biochemistry and Behavior 124 (2014) 117–122

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Mini-review

Caffeine and cognitive performance: Persistent methodological challenges in caffeine research

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ARTICLE INFO

Article history:
Received 7 March 2014
Received in revised form 23 May 2014
Accepted 27 May 2014
Available online 2 June 2014

Keywords:
Caffeine
Cognitive performance
Caffeine-naïve
Placebo control
Methodological challenges

ABSTRACT

Human cognitive performance is widely perceived to be enhanced by caffeine at usual dietary doses. However, the evidence for and against this belief continues to be vigorously contested. Controversy has centred on caffeine withdrawal and withdrawal reversal as potential sources of experimental confounding. In response, some researchers have enlisted "caffeine-naïve" experimental participants (persons alleged to consume little or no caffeine) assuming that they are not subject to withdrawal. This mini-review examines relevant research to illustrate general methodological challenges that have been the cause of enduring confusion in caffeine research. At issue are the processes of caffeine withdrawal and withdrawal reversal, the definition of caffeine-naïve, the population representativeness of participants deemed to be caffeine-naïve, and confounding due to caffeine tolerance. Attention to these processes is necessary if premature conclusions are to be avoided, and if caffeine's complex effects and the mechanisms responsible for those effects are to be illuminated. Strategies are described for future caffeine research aimed at minimising confounding from withdrawal and withdrawal reversal.

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1. Introduction

Human cognitive performance is widely perceived to be enhanced by caffeine at usual dietary doses. Yet, the evidence for and against this belief continues to be vigorously contested (e.g., Childs and de Wit, 2006; Haskell et al., 2005; James, 1994; James and Rogers, 2005; Rogers et al., 2013; Smith et al., 2006). Much controversy centres on potential experimental confounding from caffeine withdrawal and withdrawal reversal (Einöther and Giesbrecht, 2013; James and Rogers, 2005). One approach to addressing those sources of confounding has been to enlist experimental participants who habitually consume little or no caffeine and therefore are not subject to caffeine withdrawal (Borota et al., 2014; Childs and de Wit, 2006; Haskell et al., 2005; Hewlett and Smith, 2006; Rogers et al., 2013; Smith et al., 2006, 2013). The research design employed in the most recent of these studies (Borota et al., 2014) is representative, and this mini-review focuses on that study, while also referring to related studies, to elucidate persistent methodological challenges that have contributed to the enduring confusion.

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http://dx.doi.org/10.1016/j.pbb.2014.05.019
0091-3057/

In brief, Borota et al. concluded that memory consolidation but not recognition memory is enhanced at 24 h when 200 mg of caffeine (the approximate equivalent of 1–2 cups of coffee) is ingested during initial task exposure. However, the study overlooked specific behavioural and pharmacological processes associated with caffeine exposure that obscure the drug's effects on cognitive performance. It is important that these overlooked processes are examined if premature conclusions concerning caffeine enhancement are to be avoided. Although concerned with the study of caffeine and cognitive performance, the present review does not examine in detail specific cognitive processes, an area of controversy in its own right that has been recently reviewed (Rogers, 2014). Rather, the emphasis here is on experimental design and ways of controlling recurring confounding that has dogged the systematic study of caffeine and cognitive performance. Additionally, it may be noted that most of the main issues examined in the present review are equally relevant to studies of the effects of caffeine on mood (cf., James and Gregg, 2004a; James and Rogers, 2005).

The earliest systematic studies of the psychopharmacology of caffeine were conducted a century ago (Hollingworth, 1912a,b), and for most of the intervening period, it has been believed that caffeine enhances human cognitive performance. That belief, however, is contestable on theoretical (e.g., James, 1994) and empirical grounds (e.g., James and Rogers, 2005). The problem is that a large body of research purporting to show caffeine enhancement shares a common flaw arising from uncritical adoption of standard placebo-controlled drug-trial methodology (James, 1994; James and Rogers, 2005). It has been common practice in placebo-controlled studies of caffeine to emulate gold-standard placebo-controlled methodology used to investigate other drugs such as new pharmaceuticals. Typically, studies have measured cognitive performance in healthy volunteers before and after double-blind administration of caffeine and placebo. Compared to baseline and placebo, performance has often been reported to improve following ingestion of caffeine, leading to the conclusion that caffeine enhances performance. However, critical examination of this standard research design shows that when used to examine the effects of caffeine on cognitive performance the findings it has yielded are, at best, ambiguous.

Because of the importance of ensuring that all participants are equivalent in systemic levels of the drug being investigated, it is usual in placebo-controlled trials for participants to be drug free when randomised to drug or placebo groups. While this strategy works well for drugs that are not in general use by populations from which study participants are drawn, suitability of the strategy is less certain when, as with caffeine, daily consumption is the norm. The daily diet of most people includes caffeine consumed in separate portions throughout the day, with fewer portions consumed later in the day, followed by overnight abstinence (James, 1997). With the half-life of caffeine in healthy adults being approximately five hours (Pfeifer and Notari, 1988), typical overnight abstinence of 10–14 h results in substantial elimination of systemic caffeine by early morning (Lelo et al., 1986a). In fact, it is common in placebo-controlled studies of caffeine for researchers to make a methodological convenience out of naturally-occurring overnight abstinence by simply asking participants to forgo their usual morning caffeine beverage prior to testing. However, it is this step, intended to standardise procedures by ensuring participants are "equivalent" at time of caffeine administration, that has long been a cause of serious confounding.

2. Confounding due to reversal of withdrawal effects

Caffeine exerts pharmacological actions at diverse sites, both centrally and peripherally, due mostly to antagonism of endogenous adenosine, with A_1 and A_{2A} receptors appearing to be the primary targets (Ferré, 2008). Repeated consumption of caffeine generally leads to the development of physical dependence, evidenced by the appearance of behavioural, physiological, and subjective withdrawal effects provoked by abrupt cessation of use (Juliano and Griffiths, 2004). Although incompletely understood, the mechanism responsible for caffeine dependence is thought to involve adenosine upregulation resulting in hypersensitivity during abstinence. This hypothesis is consistent with symptoms of caffeine withdrawal, which include headache, tiredness/fatigue, decreased energy, decreased well-being, difficulty concentrating, irritability (Juliano and Griffiths, 2004), and importantly for present purposes, decreased cognitive performance (e.g., James, 1998; Rogers et al., 2003, 2013; Yeomans et al., 2002). Symptoms may be felt within about 12–16 h, generally peak at around 24–48 h, and usually abate within 3–5 days, although occasionally may continue for up to a week (Griffiths et al., 1990; Hughes et al., 1993). Cessation of as little as 100 mg (approximately one cup of instant coffee) per day, and possibly considerably less, can produce symptoms of withdrawal (Griffiths et al., 1990; Lieberman et al., 1987; Smit and Rogers, 2000).

The facts concerning caffeine withdrawal are critical for understanding the results of placebo-controlled trials of the effects of caffeine administration on cognitive performance. Having avoided caffeine since the evening before, participants in most studies will have entered the early stages of caffeine withdrawal by the time they are tested in the laboratory (typically, at least 12–14 h since caffeine was last ingested). Thus, the crucial question, illustrated in Fig. 1, is: To what extent is enhanced performance (attributable to caffeine) an indication of a genuine *net* effect of the drug or merely the result of *reversal of withdrawal*? A third possibility is that improvements in cognition are a combination of net effects and withdrawal reversal.

Of several approaches for overcoming confounding due to reversal of caffeine withdrawal, "long-term" withdrawal designs have proved to be the most successful (James and Rogers, 2005). These incorporate core features of the traditional drug-challenge paradigm, including double blinding and placebo control, combined with periods of abstinence long enough (several days to one week is usually sufficient) to remove withdrawal effects (see Table 1). Extending the abstinence period substantially beyond the traditional period of overnight or 24 h removes confounding due to withdrawal effects prior to administration of caffeine or placebo challenge. Studies that have employed designs incorporating long-term withdrawal have yielded consistent evidence of caffeine having little or no net benefit for cognitive performance for adults (James, 1998; James et al., 2005; Judelson et al., 2005; Rogers et al., 2005) and children (Heatherley et al., 2006).

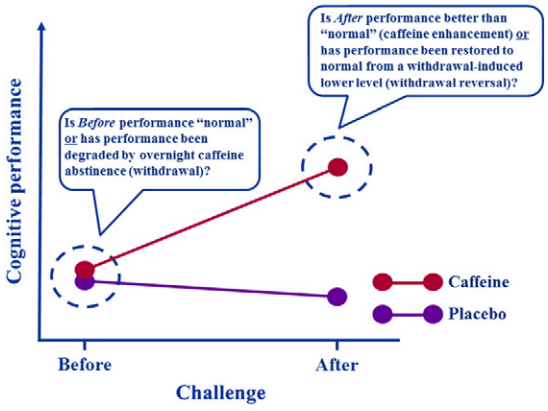

Fig. 1. Schematic representation of the results of a typical double-blind placebo-controlled experiment to test the effects of caffeine on cognitive performance by comparing performance before and after caffeine challenge. Note. This type of study design yields ambiguous results due to failure to control for withdrawal effects from overnight caffeine abstinence and withdrawal reversal when caffeine is administered. Specifically, improved performance after caffeine could be due to the drug producing either *net* benefit or *reversal of withdrawal* without net benefit (see text).