Behavioural Brain Research 271 (2014) 7–15

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Evidence for anxiolytic effects of acute caffeine on anxiety-related behavior in male and female rats tested with and without bright light

Robert N. Hughes*, Nicola J. Hancock, Gina A. Henwood, Susan A. Rapley

Department of Psychology, University of Canterbury, Christchurch 8140, New Zealand

HIGHLIGHTS

- Caffeine doses of 25 and 50 mg/kg decreased rat anxiety.
- Male rats were more affected by caffeine than females.
- Bright light increased anxiety.
- Caffeine effects were relatively unaffected by bright light.

ARTICLE INFO

Article history:
Received 17 January 2014
Received in revised form 9 May 2014
Accepted 19 May 2014
Available online 27 May 2014

Keywords:
PVG/c rats
Caffeine
Bright light stressor
Open field
Elevated plus maze

ABSTRACT

Male and female PVG/c rats were observed in an open field (OF) and an elevated plus maze (EPM) either with or without a bright light stressor (600–692 lx) following an intraperitoneal injection of saline, 25 or 50 mg/kg of caffeine. One week later, the same rats were observed under the same drug and lighting conditions but in the opposite apparatus to that experienced earlier. Either the higher or both doses of caffeine decreased anxiety as indicated by increased OF rearing and decreased grooming, immobility and corner occupancy (in the presence of bright light). A similar interpretation applied to caffeine-related increased entries into and observations in the EPM open arms for males only, and increased entries into the open arms for females alone in the presence of bright light. Bright light increased anxiety as shown by longer latencies of emergence into the OF and decreased ambulation and, for males only, decreased center occupancy and increased corner occupancy. Fewer entries into the open arms in the presence of bright light for females only also suggested heightened anxiety. Apart from one OF and one EPM measure, bright light did not appear to markedly influence the effects of caffeine which were concluded to be primarily anxiolytic, with males being more affected than females. Although the central mechanisms responsible for caffeine's anxiolytic action remain to be established, it is possible that antagonism of A_{2A} adenosine receptors might somehow be involved.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Caffeine (1,3,7-trimethylxanthine, contained in coffee, tea, cocoa, energy drinks, chocolate and many other products) is the most widely consumed psychotropic drug in existence [1]. In spite of its popularity, it has often been observed that high doses of caffeine can induce anxiety in both humans [2,3] and animals [4–7]. The mechanisms suggested for this effect have included stimulation of central noradrenergic activity [8], antagonism of adenosine receptors [9] or blockade of benzodiazepine binding sites on $GABA_A$ receptors [4]. Although it is mainly caffeine-related anxiogenesis that has been described, there are a number of reports of the opposite outcome with low doses in humans, namely anxiolysis [10,11] that may be due to reversal of overnight caffeine withdrawal [12]. There is also evidence of anxiolysis in rodents usually also with low doses, but often with doses in the range reported by some authors to be anxiety-inducing [13–20]. While some examples of apparent anxiolysis in habitual caffeine-consuming humans could have arisen from mood-elevating effects of the reversal of overnight withdrawal [12], this is unlikely to be the reason for the animal results. It has also been shown that caffeine can exacerbate the anxiogenic effects of nonpharmacological stressors for humans such as pending unemployment [21], or performance on a stressful task [22,23]. On the other hand, it has been reported for rats that acute

* Corresponding author at: Department of Psychology, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand. Tel.: +64 3 364 2879; fax: +64 3 364 2181.
E-mail address: rob.hughes@canterbury.ac.nz (R.N. Hughes).

http://dx.doi.org/10.1016/j.bbr.2014.05.038
0166-4328/© 2014 Elsevier B.V. All rights reserved.

and long-term exposure to caffeine can reverse the anxiogenic effects of chronic unpredictable stress [24,25]. And in an earlier study [26], there was a nonsignificant trend suggesting that several days of stressful treatment in the form of restraint, immersion in cold water and exposure to bright light may have potentiated the disinhibitory effect of 120 mg/kg caffeine on investigatory behavior in mice. Therefore, as well as attempting to re-examine the question of whether a high dose of acute caffeine is primarily anxiogenic or anxiolytic in its effects on rats, the present study aimed to establish whether or not the drug's behavioral effects could be influenced by exposure to an environmental stressor in the form of bright light. Male and female rats were therefore observed in an open field (OF) and an elevated plus maze (EPM), either with or without bright light, following administration of caffeine.

The OF test (involving observations of locomotor activity, rearing, grooming, defecation and occupation of center and peripheral locations) is widely acknowledged as a useful way of assessing anxiety in laboratory rodents [27,28]. Stimulant effects of acute caffeine on locomotor and rearing activity in rats observed in the OF and other types of apparatus are extremely well documented [29]. Since increases in either response are often interpreted as reflecting reduced anxiety [27,28], caffeine-related decreases accompanied by increased immobility and defecation are consistent with anxiogenic effects of the drug [4]. However, it was recently shown that 30 mg/kg reduced OF defecation and increased both locomotor activity and occupancy of the center of the apparatus, outcomes that were interpreted as mild anxiolysis [16]. This was consistent with caffeine-related increased locomotor activity and decreased corner occupancy [25]. It was also shown in this latter study that when combined with chronic unpredictable stress, caffeine reversed the reduction in locomotor and rearing activity induced by stress alone which further supported the possibility of an anxiolytic effect of the drug.

The EPM has been frequently used to assess effects on rodent anxiety of a number of putatively anxiogenic drugs such as yohimbine, pentylenetrazole and trifluoromethylphenylpiperazine, as well as caffeine [5,14,30,31]. While for many drugs evidence of anxiogenesis has been shown by fewer entries into and reduced occupation of the open rather than enclosed arms of the apparatus [32], there is less agreement about the effects of caffeine on these responses. Although the results of some EPM studies support caffeine-induced anxiogenesis [5,6,25,33], at least one other suggests the opposite outcome [14].

The choice of bright light as a stressor was based on reports of behavioral changes accompanying increases in illumination that suggested heightened anxiety such as decreased locomotor and rearing behavior [34], less social interaction [35] and increased avoidance of the open arms of an EPM [36,37]. Thus bright light has been frequently used as a stressor for the naturally photophobic rat [38,39].

In view of evidence of sex differences in responsiveness to caffeine [40–44] and the pressing need to include the two sexes in biobehavioral research [45,46], both male and female rats were investigated in the present study. This seemed especially important in view of evidence that restraint stress and caffeine increased anxiety in male but not female rats [47].

2. Materials and methods

2.1. Subjects

The subjects were 96 PVG/c hooded rats (48 males, 48 females). While a less commonly investigated strain, PVG/c rats have been extensively used in this laboratory for behavioral research [16,48–50], and were first employed for this purpose in 1958 [51]. The rats had been bred in the Animal Facility of the Department of Psychology, were approximately 5 months old and, from weaning at 30 days after birth, were caged in groups of 3 or 4 same-sexed animals with ad libitum food and water. They were all kept in 12 h light:12 h dark conditions (lights on at 07.00 am) with an ambient temperature of $20 \pm 1\,^{\circ}C$. Equal numbers of each sex were randomly assigned to the 3 drug and 2 brightness conditions thereby providing 8 males and 8 females for each caffeine treatment condition under each brightness level.

The care and experimental treatment and testing of all subjects complied with Parts 5 (Codes of Welfare) and 6 (Use of Animals in Research, Testing, and Teaching) of the New Zealand Animal Welfare Act (1999), and had been approved by the Animal Ethics Committee of the University of Canterbury.

2.2. Apparatus

All testing took place in an OF and an EPM. The floor of the $600 \times 600 \times 250$-mm-high black wooden OF was divided into 16 numbered squares by means of a grid of intersecting white lines. It sat on a 700–mm-high table with a circular 22-W fluorescent lamp positioned directly above each half of the apparatus 255 mm from the floor. Attached to the outside of one wall was a small wooden start box 200 mm long, 150 mm wide and 195 mm high with a hinged wooden lid. The interior of the box was painted black and access to the OF was possible via a 100 mm × 100 mm opening that could be opened and closed by means of a hand-operated guillotine slide.

The wooden EPM comprised four arms extending at 90° to each other from a central 150 mm × 150 mm platform. Each arm was 500 mm long and 100 mm wide. Two of the arms that faced each other had wooden 245-mm-high end and side walls (i.e., the enclosed arms) with no roof, while the other two had transparent Perspex walls of the same height (i.e., the open arms). Although the inclusion of transparent-walled open arms was a departure from usual practice, their presence has been observed in this laboratory to prevent highly anxious rats from leaping off the arms if startled. Besides, because the avoidance of open arms seems to depend more on visual rather than proprioceptive stimulation, transparent walls do not reduce their aversiveness [52]. A circular 22-W fluorescent lamp was positioned 350 mm above the floor of the distal end of each arm.

2.3. Caffeine

Before observation in either type of apparatus, each rat was intraperiteonally injected with either isotonic saline or a dose of research grade caffeine (Sigma–Aldrich) dissolved in saline. The caffeine doses were within the range previously shown to induce anxiety in rats [4,5], namely 25 and 50 mg/kg. All injection volumes were 1 ml/kg.

2.4. General testing procedure

Equal numbers of male and female rats were tested in the OF or EPM 20 min after being injected with saline or one of the two doses of caffeine in either dim or bright light. Then 1 week later, each rat was tested in the other type of apparatus (with the same caffeine and lighting conditions) that it had not been tested in during the first week. The order of testing was OF-EPM for half the rats in each condition, and EPM-OF for the other half, with counterbalancing for treatment conditions. All caffeine treatment was performed by GAH, and behavioral observations were made by NJH who was unaware of which caffeine condition each rat was in. Although it was not possible to calculate observer reliability, previous unpublished calculations in this laboratory have shown

Download English Version:

https://daneshyari.com/en/article/6257992

Download Persian Version:

https://daneshyari.com/article/6257992

Daneshyari.com