Pharmacology, Biochemistry and Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Augmentation of antidepressant effects of duloxetine and bupropion by caffeine in mice

Pravin Popatrao Kale [a,b], Veeranjaneyulu Addepalli [a,*]

[a] Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, NMIMS University, Mumbai 400 056, India
[b] Department of Pharmacy, Dr. Bhanuben Nanavati College of Pharmacy, Mumbai 400 056, India

ARTICLE INFO

Article history:
Received 13 January 2014
Received in revised form 27 May 2014
Accepted 7 June 2014
Available online xxxx

Keywords:
Depression
Caffeine-augmentation
Duloxetine
Bupropion
Brain monoamines
Hippocampus
Cerebral cortex

ABSTRACT

There is an unmet need in the treatment of depression suggesting requirement of new therapeutic approaches having better efficacy and safety profile. Patients receiving antidepressant therapy generally consume caffeine in the form of tea or coffee. The objective of the present study was to evaluate the augmentation of antidepressant effects of duloxetine and/or bupropion with caffeine. Male Swiss Albino mice received treatment of normal saline (10 ml/kg), 'caffeine alone' (10 mg/kg), 'duloxetine alone' (10 mg/kg), 'bupropion alone' (10 mg/kg), caffeine + duloxetine (5 mg/kg, each), bupropion + caffeine (5 mg/kg, each), and bupropion + duloxetine (5 mg/kg, each) through the intra-peritoneal route. The immobility period was analyzed 30 min after the treatment in forced swim and tail suspension tests. Norepinephrine, dopamine, and serotonin levels were analyzed in hippocampus, cerebral cortex and whole brain using HPLC with fluorescence detector. Euthanasia was performed 1 h after treatment. Comparison between vehicle treated group and other groups showed significant decrease in immobility in all drug treated groups in both antidepressant models. Caffeine plus duloxetine treated group was better among the combination treated groups in terms of decrease in immobility and increase in norepinephrine, dopamine, and serotonin levels in hippocampi, cerebral cortices, and whole brain when compared to their respective monotherapy treated groups. These combination approaches may help in reducing the dose of duloxetine/bupropion, and consequently lower the associated side/adverse effects.

1. Introduction

Depression is a leading cause of disability and distress worldwide (Castle et al., 2012). The delay in onset of action and intolerable side effects of available antidepressants have restricted the desired efficacy, which suggests an unmet need in the treatment of depression (Mojtabai, 2009; Richelson, 2013). The limited success rate (60–70%) of first-line monotherapy has resulted in preference of augmentation therapy as second line treatment (Thase, 2007). As per the American Psychiatric Association Practice Guidelines on suicidal patients in antidepressant section, non-tricyclic, non-monoamine oxidase inhibitor related drugs are relatively safe, particularly on overdose (Jacobs et al., 2003). Bupropion and selective serotonin reuptake inhibitors (SSRIs) are considered within the 5 most prescribed antidepressants (Grunebaum et al., 2012). Duloxetine inhibits both serotonin and norepinephrine reuptake. This dual action makes it an interesting drug in the treatment of depression (Hunziker et al., 2005; Reneman et al., 2001; Ressler and Nemeroff, 2001). It has better efficacy, safety, and tolerability with fewer side effects when compared against antidepressant like fluoxetine, paroxetine, and venlafaxine (Hunziker et al., 2005; Stahl et al., 2005; Thase et al., 2007; Zomkowski et al., 2012). Less than one week of duloxetine treatment has shown meaningful improvements in patients (Brannan et al., 2005). Duloxetine treatment in forced swim test resulted in significant reduction in the immobility period at 10 mg/kg dose (Ciulla et al., 2007; Rénéric and Lucki, 1998). In addition to serotonin and norepinephrine reuptake inhibitors, dopamine transmission also plays a vital role in antidepressant action (Dunlop and Nemeroff, 2007; Gessa, 1994; Wilner, 1983). Bupropion, a preferential norepinephrine and dopamine reuptake inhibitor (Baldessarini, 2006), showed significant decrease in immobility at 10 mg/kg or lower doses (Kotagale et al., 2013).

Caffeine, an adenosine A_1 and A_{2A} antagonist, is the widely consumed psychoactive substance in the world (Heckman et al., 2010). High amount of caffeine consumption has an inverse relation to the depression risk (Lucas et al., 2011; Ruusunen et al., 2010) and the risk of suicide (Kawachi et al., 1996; Lucas et al., in press) in normal population. Many depressed patients seek a 'lift' because of fatigue or negative affect (Bernstein et al., 2002), and consume higher amount of caffeine (Goldstein, 1987; Whalen et al., 2008). The considered doses of caffeine in many studies are either moderate or high (Bernstein et al., 1998,

Abbreviations: ANOVA, analysis of variance; SSRIs, selective serotonin reuptake inhibitors; HPLC-FD, high performance liquid chromatography with fluorescence detector.

* Corresponding author at: Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, NMIMS University, V. L. Mehta Road, Vile parle west, Mumbai, 400 056, India. Tel.: +91 22 42332030 (O); fax: +91 22 26185422.
E-mail address: addepalliv@gmail.com (V. Addepalli).

http://dx.doi.org/10.1016/j.pbb.2014.06.005
0091-3057/

2002; Orbeta et al., 2006). Interestingly, the lower caffeine consumption (250–400 mg/day) is known to produce beneficial effects (Fredholm et al., 1999; Tse et al., 2009). The lower dose (10 mg/kg, i.p.) of caffeine showed increased in locomotion activity in mice (El Yacoubi et al., 2000). Thus, the present study aims to compare and evaluate the augmentation effect of lower dose of caffeine with duloxetine or bupropion in the treatment of depression.

2. Materials and methods

2.1. Animals

Male Swiss Albino mice weighing 22–27 g were group housed in Perspex cage, 3 mice/cage, in a temperature (22–24 °C) and humidity (50–60%) controlled central animal house facility under a light and dark (12:12) illumination cycle. These mice were procured from Bharat Serum Ltd, Thane. They had free access to standard food and water. Experiments were approved by an Institutional Review Committee for the use of Animal Subjects (Approval number- CPCSEA/IAEC/SPTM/P-44/2011) and in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.2. Drug solutions and treatment

Drugs were dissolved in normal saline (0.9% w/v NaCl) and administered through intra-peritoneal route. Mice were randomly assigned to 7 groups (n = 6 animals/group) in each test. They were kept undisturbed for at least 1 h before testing. Experiments were performed between 09.00 and 14.00 h. Groups I, II, III, IV, V, VI, and VII received treatment of normal saline (10 mg/kg; control groups), caffeine (10 mg/kg; Elders Pharmaceutical Pvt. Ltd), duloxetine (10 mg/kg; Dr. Reddy's Laboratories Ltd.), caffeine (5 mg/kg) + duloxetine (5 mg/kg), bupropion (10 mg/kg; Aurobindo Pharma Ltd), bupropion (5 mg/kg) + caffeine (5 mg/kg), and bupropion (5 mg/kg) + duloxetine (5 mg/kg), respectively. Pretreatment schedules were based on the available reports (Kaster et al., 2004; Kotagale et al., 2013; Zomkowski et al., 2012).

2.3. Antidepressant models

2.3.1. Forced swim test

Q5 Forced swim test was performed as described by Porsolt et al. (1997). In brief, mice underwent "pretest session" on 1st day. They were individually forced to swim for 15 min in plexi glass cylinders (21 cm height 12 cm internal diameter) containing freshwater up to a height of 10 cm at 24 ± 1 °C. On 2nd day, each animal received treatment 30 min before the test session and was allowed to swim for 6 min. Last 5 min session from total 6 min recorded video was used for evaluation. Mice were considered immobile when there were no limb movements while floating or made only small limb movements necessary for floating. The immobility period was analyzed with the help of Video Tracking software (SMART v2.5.21 Video Tracking Software, Panlab Harward Apparatus).

2.3.2. Tail suspension test

The apparatus used was a set of aluminum stands measuring 58 cm (high) × 30 cm (wide). At 58 cm height of horizontally fixed aluminum rod, adhesive tape was used to suspend each mouse by its tail. It was placed approximately 1 cm from the tip of the tail (Vogel and Vogel, 2008). Mice received treatment 30 min before undergoing the 5 min test session. Recorded video of each animal was evaluated using video tracking software (SMART v2.5.21 Video Tracking Software, Panlab Harward Apparatus) to analyze the immobility period.

2.4. Estimation of norepinephrine, dopamine, and serotonin by HPLC with fluorescence detector (HPLC-FD) method

Analysis of monoamine levels in cerebral cortex, hippocampus, and whole brain (whole brain = cerebral cortex + hippocampus + remaining brain tissue) was performed using HPLC (Shimadzu, LC-2010C HT, autosampler) with FD (RF-20A-prominence, Shimadzu) method (Choudhary et al., 2013; Madepalli and Lakshmana Raju, Q6 1997). Mice received treatment 1 h before euthanasia and heads were dropped in ice cold 0.1 M perchloric acid. Brains were removed and weighed. Then the cerebral cortex, hippocampus, and the remaining brain part were separated and individually weighed and homogenized in 2 ml of ice cold 0.1 M perchloric acid. Resulting mixture was centrifuged at 20817 ×g (Eppendorf 5810 R, Rotor F-45-30-11) for 30 min (4 °C). The supernatant was filtered through 0.45 μm membrane (PALL® Pall corporation, India) and stored at −80 °C until the time of analysis. Samples were injected and the chromatographic separation was achieved on reversed-phase analytical column (KROMASIL 100, C18, 5 μm, 25 mm × 0.46 mm) at room temperature. The acquired data was processed using LC Solution® software. The mobile phase was prepared using sodium acetate (0.02 M), ethylenediaminetetraacetic acid (0.2 mM), methanol (16%), di-n-butylamine (0.01%) and heptane sulfonic acid (0.055%), at pH 3.92 adjusted with phosphoric acid, filtered through a 0.45 μm membrane. Flow rate of mobile phase was kept at 1.3 ml/min. Norepinephrine, dopamine, and serotonin were detected at an excitation wavelength of 280 nm and an emission wavelength of 315 nm. Monoamine peaks were identified by comparing the retention time of sample and standard. The concentration of each monoamine in the sample was analyzed according to their area under curve and using respective straight line equation. The linearity for norepinephrine, dopamine, and serotonin was in the range 0.99–0.997. Results were expressed as ng/g of wet weight of tissue.

2.5. Statistical analysis

The statistical evaluation was performed using the Graphpad InStat for 32 bit Windows version 3.06. Groups were compared to assess the statistical significance using one way analysis of variance (ANOVA) followed by Tukey's honest significant difference (HSD) post-hoc test. The data is represented as mean ± SEM values and n = 6 per group.

3. Results

3.1. Forced swim test

The immobility period was significantly decreased in groups treated with 'caffeine alone' (10 mg/kg), 'duloxetine alone' (10 mg/kg), caffeine + duloxetine (5 mg/kg, each), bupropion + caffeine (5 mg/kg, each), and bupropion + duloxetine (5 mg/kg, each) when compared against control groups (Fig. 1). Group treated with caffeine + duloxetine (5 mg/kg, each) showed significant decrease in immobility period when compared against 'caffeine alone' (10 mg/kg) treated group (Fig. 1). The same combination treated groups also showed significant decrease in immobility period when compared against 'duloxetine alone' (10 mg/kg) treated group (Fig. 1). Caffeine + bupropion (5 mg/kg, each) and bupropion + duloxetine (5 mg/kg, each) treated groups showed significant decrease in immobility period, as compared to 'bupropion alone' (10 mg/kg) treated group (Fig. 1).

3.2. Tail suspension test

Drug treated groups showed significant decrease in immobility period as compared to control groups (Fig. 2). Combination treated groups such as caffeine + duloxetine (5 mg/kg, each) and caffeine + bupropion (5 mg/kg, each) showed significant decrease in immobility period, as compared to caffeine alone (10 mg/kg) treated groups (Fig. 2).

Please cite this article as: Kale PP, Addepalli V, Augmentation of antidepressant effects of duloxetine and bupropion by caffeine in mice, Pharmacol Biochem Behav (2014), http://dx.doi.org/10.1016/j.pbb.2014.06.005