Enhancement of nootropic effect of duloxetine and bupropion by caffeine in mice

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ABSTRACT

Objective: The existing evidence suggests an association between depression and memory impairment. The objective of present study was to assess the effect of low dose caffeine with duloxetine and bupropion on memory.

Materials and Methods: Mice were divided randomly into seven groups. Intra-peritoneal treatment of normal saline (10 ml/kg), caffeine (10 mg/kg), duloxetine (10 mg/kg), bupropion alone (10 mg/kg), caffeine + duloxetine (5 mg/kg, each), caffeine + bupropion (5 mg/kg, each), and bupropion + duloxetine (5 mg/kg, each) were given to groups I-VII, respectively. Elevated plus maze was used to evaluate transfer latency (TL) and Morris water maze was used to estimate the time spent in target quadrant.

Results: Caffeine with duloxetine treated group was better than other combination treated groups in terms of a significant decrease in TL and increase in the time spent in target quadrant recorded.

Conclusion: Combining lower dose of caffeine with duloxetine may enhance cognitive benefits than respective monotherapies.

KEY WORDS: And bupropion, caffeine, duloxetine, memory

Introduction

The association between depression and memory impairment is well-established.[1,2] Kim et al. reported memory impairment in 22% of depressed patients.[3] Modulation of neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) through hippocampus and cerebral cortex play a vital role in cognition.[1] Antidepressant treatment resulted in relieving short-term memory deficit.[4,5] Duloxetine is a potent and selective reuptake inhibitor of 5-HT and NE, and a weak reuptake inhibitor of DA. Eight weeks of duloxetine treatment showed significant improvement in cognition and depression in depressed patients.[6] Bupropion is another preferred antidepressant, inhibits reuptake of NE and DA.[7] It showed better cognitive improvement than selective serotonin reuptake inhibitors in depressed patients.[8] The low dose of caffeine (5 mg/kg) produced augmentation of antidepressant effects of duloxetine/bupropion.[9] Therefore, the present study is designed to evaluate the nootropic effect of low dose of caffeine combination with duloxetine or bupropion.

Materials and Methods

Animals

Male Swiss albino mice were procured from Bharat Serum Ltd., Thane. The weight range was 25–30 g. Animals had free access to standard food and water. Experiments were performed between 10.00 and 16.00 h. Animals were randomly distributed into seven groups (n = 6/group). The arena of elevated plus maze (EPM) was wiped with 70% ethyl alcohol solution before placing each mouse. Study protocols were approved by the Institutional Animal Ethics Committee (Project approval number CPCSEA/IAEC/SPTM/P-46/2011), New Delhi, Government of India.

Drug Solutions and Treatment

Drugs were administered through intra-peritoneal route. Normal saline (0.9% w/v NaCl) was used to prepare drug solutions. EPM was performed first and Morris water maze (MWM) later in separate sets of animals consisting seven groups each. Each animal received treatment 30 min before test session in EPM on 1st and 2nd day. In MWM, treatments were given to mice 30 min before the test on each trial day. Selection of doses was done on the basis of in-house study.[9] Control
group received vehicle treatment (Group I) that is, normal saline (10 ml/kg). Treatment of caffeine (10 mg/kg; Elders Pharmaceutical Pvt. Ltd.), duloxetine (10 mg/kg; Dr. Reddy’s Laboratories Ltd.), and caffeine (5 mg/kg) + duloxetine (5 mg/kg) were given to groups II-IV, respectively. Groups V-VII received treatment of bupropion (10 mg/kg; Aurobindo Pharma Ltd.), caffeine (5 mg/kg) + bupropion (5 mg/kg), and bupropion (5 mg/kg) + duloxetine (5 mg/kg), respectively.

Spatial Memory Tests

In the present study, the protocol described by Dhingra et al. was used to evaluate the transfer latency (TL). Apparatus consists of two open arms (30 cm × 5 cm) and two closed arms (30 cm × 5 cm × 12 cm). Arms were arranged so that the two closed arms kept opposite to each other without roof. Each mouse was placed at the end of open arm facing away from the central platform (5 cm × 5 cm). The acquisition session (1st day) consists of 90 s exposure interval. Time taken by animal to reach the closed arm is recorded as the TL. If the animal fails to enter in closed arm in 90 s, it was excluded from the study. Animal was put on the open arm in retention session (2nd day) and the recorded video was used to evaluate TL by the single trained person.

The protocol of MWM described by Bromley-Brits et al. was used to determine percent time spent in target quadrant. The pool (150 cm diameter and 50 cm depth) was constructed of seamless black polyethylene. The escape platform (10 cm diameter, 31 cm high) was fabricated using clear plastic. The platform positions (visible) on 1st day were South-West, North-West, North-East, Centre, and South-East on trial 1–5, respectively. On 2–5 days, platform position was South-West (hidden) and the starting positions of animal in five different trials were West-South-East-South-West, North-West-East-West-South, North-East-West-East-South-North, and East-South-West-East-North, respectively. In this black colored pool, clear water (22°–24°C) and a clear plexiglass platform was used. On 6th day, platform was removed and starting position of animals was north. The time spent by each animal in target quadrant, that is, South-West was determined from video of each animal by the single trained person.

Statistical Analysis

Statistical analysis was performed using the Graphpad InStat for 32 bit Windows version 3.06 (GraphPad Software, Inc). The statistical significance was estimated using ANOVA, followed by Tukey’s honest significant difference post-hoc test.

Results

Caffeine plus duloxetine combination treated group showed a significant decrease in TL (Table 1), as compared to the control group. All other comparisons showed a slight decrease in TL, which were statistically not significant. In training and acquisition stage of MWM, the escape latency was decreased from 1st to 5th day. The differences between groups were not statistically significant [Table 2]. On 6th day, the observed time spent in target quadrant was significantly increased in caffeine plus duloxetine-treated group, as compared to the control group [Table 2].

Discussion

Nehlig concluded no benefits in short-term and long-term memory with caffeine in a review. The present study has focused on the short-term (EPM) and long-term (MWM) memory assessment. The results of caffeine, bupropion, and duloxetine-treated groups were in conformity with available reports. Although the acute or sub-acute treatment of duloxetine was not beneficial in cognition, a clinical study reported cognition related benefits with 8 and 12 weeks treatment period in depressed patients. Gualtieri and Johnson reported improvement in cognitive performance with bupropion treatment in depressed patients. Caffeine also showed benefits in reducing Alzheimer’s disease. It has been reported that CYP1A2 plays a vital role in the metabolism of caffeine. Duloxetine may not increase the retention of drugs metabolized by CYP1A2. Therefore, caffeine plus duloxetine may have lower potential of drug interaction. Bupropion inhibits CYP2D6, which plays an important role in duloxetine metabolism. This indicates higher potential of interaction between duloxetine and bupropion. Caffeine plus bupropion combination may have lower potential of interaction because the enzymes involved in caffeine and bupropion metabolism are separate (i.e. CYP1A2 and CYP2B6). Thus, the combination of duloxetine and caffeine at half of their monotherapy doses (5 mg/kg, each) may have better safety profile than other combinations. However, there is a need to study the impact of caffeine (low dose) combination with duloxetine/bupropion on their metabolism in acute and chronic dosing, which may enable us to understand the results of present study.

Hippocampus and cerebral cortex regions play a vital role in cognition and emotions. The in vivo findings of the present study are in-line with the in vitro data of brain monoamines analyzed in-house. Caffeine plus duloxetine group was better among all groups in terms of a significant increase in NE, DA, and 5-HT levels in hippocampi and cerebral cortices. The present study consists of chronic dosing, whereas the changes observed in brain monoamines were after single dosing as

Table 1: Elevated plus maze-transfer latency (on 2nd day) in mice

| Groups                     | Transfer latency (s) |
|----------------------------|----------------------|
| Control                    | 34.66±2.26           |
| Caffeine                   | 26.14±1.91           |
| Duloxetine                 | 30.43±2.28           |
| Bupropion                  | 31.2±2.57            |
| Caffeine+duloxetine        | 24.83±1.9*           |
| Bupropion+caffeine         | 25.33±2.0            |
| Bupropion+duloxetine       | 28.5±1.9             |

Data is presented as mean±SEM (n=6/group). Significant difference is denoted by *P<0.05 as compared with the control group. Statistical analysis: ANOVA followed by Tukey’s HSD post-hoc test. SEM=Standard error of mean, HSD=Honest significant difference.
per in-house study.\textsuperscript{[9]} The present study findings can be further probed in different preclinical models and clinical setting as a future endeavor.

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