EVALUATION OF COGNITIVE BRAIN FUNCTIONS IN CAFFEINE USERS: A P3 EVOKED POTENTIAL STUDY

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Abstract: Caffeine is one of the most widely consumed stimulant drugs of the modern world. It brings about a feeling of well-being, relaxation, increased alertness and concentration. Its effects have been studied on brain function and behavior using mood questionnaires, reaction time tests, memory tests, EEG and of late Event Related Potentials (ERPs). This study evaluates the response of caffeine on ERPs and Reaction Time (RT) using auditory “oddball” paradigm. Forty undergraduate medical students volunteered for the study and their ERPs and RT were recorded before and after 40 minutes of ingestion of caffeine. There was a non-significant decrease in latency of N1, P2, N2 and P3 and a significant decrease in Reaction Time after caffeine consumption. The amplitude of P3 showed a significant increase after intake of caffeine. The results of this study indicate that caffeine leads to facilitation of information processing and motor output response of the brain.

Key words: event-related potentials, information processing, reaction time, caffeine

INTRODUCTION

Caffeine is a methylxanthine, present in various commonly consumed substances like tea, coffee, colas and some medicines. After absorption of caffeine from GIT or its administration via parenteral route, it reaches high levels in the brain. Various mechanisms of action of caffeine like inhibition of phosphodiesterase, mobilization of calcium and binding to benzodiazepine receptors have been proposed. However, the main mechanism of its action is believed to be blockade of adenosine receptors (1).

The average consumption of caffeine in India is 27 mg/person/day. The amount of caffeine in food items ranges from 40–180 mg/150 ml of coffee, to 24–50 mg/150 ml of tea and 15–29 mg/180 ml for colas (2).

Various researchers have done studies to evaluate the effects of caffeine on central nervous system using EEG, psychological tests, reaction time, and evoked potentials (3–7). Kawamura et al using auditory
stimulus, found a significant increase in P300 amplitude and area 30 minutes after caffeine intake (8). There was no significant decrease in P300 latency. The reaction time in oddball paradigm was not significantly different before and after caffeine consumption. Deslandes et al investigated the effect of caffeine on visual P300 by administering 400 mg caffeine in gelatin capsules. They found a significant decrease in P300 latency at Fz (9). The amplitude of P300 showed a variable pattern of increase in some and decrease in some individuals.

It has been reported that the latency and amplitude of P3 in young Indian adults was comparable with age and sex matched subjects of the western world (10). Previous study from our lab has shown that substances like Vitamin E affects P3 (11).

Most of the studies on CNS effects of caffeine have been done using visual stimuli by administering caffeine either in gelatin capsules or in decaffeinated coffee with milk powder and sugar. In this study, we have administered pure caffeine (without decaffeinated coffee) with milk powder and sugar so as to rule out the effect of other constituents of coffee on CNS. A thorough literature search revealed scant work using auditory stimuli and this prompted us to evaluate the effect of caffeine on cognitive brain functions and motor response using auditory stimulus.

METHODS

Selection of subjects

The present study was conducted in the Department of Physiology, University College of Medical Sciences, Delhi. The study group comprised of 40 normal, healthy young male undergraduate students in the age group of 18–25 years. The subjects had no history of head injury, epilepsy, hearing impairment, migraine, sleeping problems and drug abuse (nicotine, alcohol and opium). Due written consent was taken from them prior to the study. The subjects served as their own controls to minimize interindividual variation. Prior to the day of recording, the subjects were asked to abstain from caffeine containing substances for at least 12 hours and have adequate sleep.

Administration of caffeine

Caffeine in the dose of 3 mg/kg body weight of the subject was given after mixing it with sugar and milk powder according to taste in 100 ml water.

Recording of Event-related potentials

The recordings were done in a soundproof room before and 40 minutes after ingestion of caffeine. The subjects were given a trial session a day before the recording to familiarize them with the stimuli and the recording procedure. The ERPs were recorded on Nihon Kohden Neuropack µ MEB 9100 using silver-silver chloride disk electrodes from Fz, Cz and Pz (active electrodes) with FPz as grounding electrode and A1 and A2 as the ear reference electrodes placed according to the 10–20 international system. The skin-electrode contact impedance was kept below 5 KΩ. The subjects were instructed to close their eyes to avoid blink artifacts.
The auditory ERPs were recorded using "oddball" paradigm wherein two stimuli (target and nontarget) were presented in a random order by headphones. The target stimulus was a 2 KHz sound with 20% occurrence and the nontarget 1 KHz with 80% occurrence. The auditory stimuli had a 10 msec rise/fall time, 100 msec duration and intensity of 60 dB above the hearing threshold. The responses were filtered with a band pass of 0.1–50 Hz and averaged for 30 responses. The analysis time was 100 msec before to 900 msec after the stimulus. The subjects pressed a button in response to the target stimulus. Data for 2 trials were obtained, stored and averaged by computer. The ERP peak latencies, baseline to peak amplitudes and reaction time were evaluated.

Statistical analysis

The data obtained were analyzed using SPSS software. The ERP amplitude data was normalized using log transformation as it was right skewed. Repeated measures ANOVA was done to compare the three electrodes at different places as per 10–20 electrode placement system before and after caffeine consumption. Multiple comparisons were obtained (within subjects comparison) by Tukey Test at 5%. Paired t-Test was applied for analysis of Reaction Time.

RESULTS

The effect of caffeine on the latencies of N1, P2, N2 and P3 waves of ERPs are shown in Table I (Fig. 1). ANOVA showed a significant decrease in latency of P2 (P=0.044). However, Tukey failed to detect any significant decrease in the latency of P2 as the significance shown by ANOVA was

<table>
<thead>
<tr>
<th>Component</th>
<th>Electrode</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Fz</td>
<td>110.7±14.54</td>
<td>107.1±14.49</td>
</tr>
<tr>
<td></td>
<td>Cz</td>
<td>100.4±11.57</td>
<td>98.1±12.91</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>95.1±11.41</td>
<td>92.7±12.52</td>
</tr>
<tr>
<td>N2</td>
<td>Fz</td>
<td>166.5±13.32</td>
<td>163.7±12.47*</td>
</tr>
<tr>
<td></td>
<td>Cz</td>
<td>160.8±11.62</td>
<td>158.7±10.41*</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>158.0±17.48</td>
<td>154.8±15.26*</td>
</tr>
<tr>
<td>N3</td>
<td>Fz</td>
<td>211.8±18.67</td>
<td>209.6±14.26</td>
</tr>
<tr>
<td></td>
<td>Cz</td>
<td>206.8±13.98</td>
<td>205.5±17.84</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>200.9±15.41</td>
<td>200.5±15.26</td>
</tr>
<tr>
<td>P3</td>
<td>Fz</td>
<td>318.7±30.57</td>
<td>317.8±30.57</td>
</tr>
<tr>
<td></td>
<td>Cz</td>
<td>310.4±33.4</td>
<td>310.4±32.35</td>
</tr>
<tr>
<td></td>
<td>Pz</td>
<td>313.9±30.52</td>
<td>313.9±30.52</td>
</tr>
</tbody>
</table>

*P<0.05 when the baseline and after caffeine values are compared.
The effect of caffeine was due to blocking of adenosine receptors. Kawamura et al used a dose of 500 mg of caffeine in 10 subjects and found a significant increase in the area and amplitude of P3, 30 minutes after caffeine intake (8). No significant change in P300 latency or reaction time was found. They suggested that caffeine affected the discriminating process involved in oddball paradigm. In another study, Lorist et al concluded that caffeine led to lower level of processing of irrelevant information which was evident by absence of P3b in ERPs elicited by irrelevant targets (6). There was a faster stimulus evaluation as evidenced by change in P3b peak latency.

Ruijter et al found an increase in P2 amplitude after caffeine and interpreted it as an arousal increasing effect (12). The RT was shorter with caffeine than with placebo. Ruijter et al concluded that caffeine led to increased information processing. In another study they found that caffeine had a general influence on early information processing and not specifically on spatial attention (13). Decrease in RT by caffeine has also been found by Azcona et al and Clubley et al (14, 15). Jacobson and Edgley found that a dose of 300 mg caffeine decreased RT and marginal. The other waves namely N1, N2 and P3 showed a non-significant decrease in latency.

The mean amplitude of P3 increased significantly after caffeine intake. The amplitudes of all other ERP waves i.e. N1, P2 and N2 showed an increase but the change was not significant (Table II, Fig. 1).

The Reaction time was 414.88 ± 90.92 msec before the subjects took caffeine. It decreased significantly (P=0.000) to 372.35 ± 74.48 msec after consumption of caffeine.

### DISCUSSION

The results of the present study revealed that there was a significant increase in the amplitude of P3 with a significant reduction in Reaction Time following caffeine consumption. Our finding of a non-significant decrease in P3 latency with a significant decrease in reaction time (RT) was similar to that of Seidl et al who had also used auditory oddball paradigm in 10 subjects (7). On the basis of known literature, they concluded that the stimulant effect of caffeine was due to blocking of adenosine receptors. Kawamura et al used a dose of 500 mg of caffeine in 10 subjects and found a significant increase in the area and amplitude of P3, 30 minutes after caffeine intake (8). No significant change in P300 latency or reaction time was found. They suggested that caffeine affected the discriminating process involved in oddball paradigm. In another study, Lorist et al concluded that caffeine led to lower level of processing of irrelevant information which was evident by absence of P3b in ERPs elicited by irrelevant targets (6). There was a faster stimulus evaluation as evidenced by change in P3b peak latency.
movement time significantly. However, a dose of 600 mg showed no considerable change in RT and movement time (16). Caffeine has been found to shift EEG towards faster spectral components which has been interpreted as a reflection of elevated levels of energy (17).

Caffeine mainly acts by blocking adenosine receptors and thus bring about changes in the levels of various neurotransmitters like dopamine, adrenaline and glutamate. The A1 type of adenosine receptors have been linked to dopamine D1 receptors and A2A with dopamine D2 receptors (see 18). The A1 receptors have been found to be associated with regulation of alertness. Mesopontine cholinergic neurons are associated with regulation of arousal level and are under tonic A1 receptor control. Of various dopamine receptors isolated in brain, D1, D2, D4 and D5 have been found in hippocampus. Activation of D1 and D2 receptors in hippocampus has been found to improve acquisition and retention of working memory (19, 20). D1 and D2 receptors in prefrontal cortex of monkey have been reported to improve performance in working memory task (21). The abnormality in P3 in Parkinson’s disease is perhaps due to changes in central dopaminergic mechanisms (22).

We therefore believe that the changes seen in the amplitude of P3 after caffeine intake could be due to modulation of dopamine release in the cortex consequent to the inhibition of adenosine receptors by caffeine. The more positive going P3 was indicative of increased information processing by recruitment of cortical neurons after caffeine consumption. The effect of caffeine on latencies of ERPs was not significant. However, there was a significant decrease in RT brought about by caffeine. These findings suggested that rather than speeding up the central processes, caffeine accelerated motor (output) processes. Our findings of ERPs were similar to those obtained by various researchers using visual stimuli, thereby indicating that ERP changes were independent of the mode of stimuli given i.e. either pairing of two visual or two auditory stimuli for oddball paradigm. Thus it can be interpreted that caffeine ingestion directly influenced the cortical neuronal processes involved in higher functions like orientation, attention, alertness and motor response. This finding provides an electrophysiological evidence of caffeine induced improvement in cognitive and motor functions. Thus it may have relevance in patients with cognitive dysfunction as in Alzheimer’s disease or motor impairment as in disorders like Parkinson’s disease.

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