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Caffeine-Induced Cerebral Blood Flow Changes in Schizophrenia

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Summary. Cerebral blood flow (CBF) measurements and mental status examinations were performed before and 30 min after oral administration of 250 mg of caffeine or a placebo given under double-blind conditions, in two groups of patients with schizophrenia. Caffeine produced significant CBF reductions but no changes in the patient's clinical condition.

Key words: Caffeine – Cerebral blood flow – Schizophrenia

Introduction

Caffeine is a common ingredient of a wide variety of beverages, food substances and medicines (Greden 1974; Bunker and McWilliams 1979). Large numbers of people of all age groups consume it and, therefore, the biological effects of the drug are of considerable clinical significance. Caffeine is often ingested for its CNS stimulating properties. However, the drug is also known to induce feelings of anxiety and depression in normal subjects (Gilliland and Andress 1981). Psychiatric patients consume large quantities of caffeine and it has been shown to intensity depression and anxiety (Winstead 1976; Boulenger et al. 1984). Caffeine increases the psychotic symptoms in patients with schizophrenia (DeFreitas and Schwartz 1979) and can also precipitate relapses in recovered patients (Mikkelsen 1978).

Caffeine is a well known cerebral vasoconstrictor; 250 mg of the drug, roughly equal to the caffeine content of two cups of "drip" coffee, given orally can induce significant reduction in cerebral blood flow (CBF) 30 min after the administration (Gibbs et al. 1935; Mathew et al. 1983; Mathew and Wilson 1985). Several, but not all, investigators have reported reduced resting CBF in patients with schizophrenia (Mathew et al. 1982; Ariel et al. 1983; Gur et al. 1983). No information is available on the association between caffeine-induced cerebral vasoconstriction and the alleged worsening of the psychosis. We studied the effects of 250 mg of caffeine on CBF and mental state in a group of patients with schizophrenia.

Method

A total of 24 patients with a diagnosis of schizophrenia, according to DSM-III (American Psychiatric Association 1980), participated in the project. All the participants were inpatients and on standard doses of antipsychotic drugs. They were required to be free of all caffeine-containing beverages for a minimum of 1 week before the study. Significant physical illnesses were excluded via physical examinations and routine laboratory tests. All subjects were right-handed.

Cerebral blood flow was measured twice, before and 30 min after the oral administration of 250 mg of caffeine or a placebo given under double-blind conditions. The patients were assigned to the two groups in a random fashion. After each CBF measurement, the patient's mental status was examined via a structured interview.

Cerebral blood flow was measured using the ^{133}xenon inhalation technique (Obrist et al. 1975). A mixture of the isotope in air [5–7 mCi/l] was administered via a sterilized, close-fitting face mask for 1 min. The rate of removal of the isotope from the brain was monitored for the next 10 min by tracing the progressive decline in radioactivity with a system of 32 collimated scintillation detectors mounted on a helmet and applied to the scalp. These clearance curves were analyzed using a bicompartmental model by an online minicomputer. Air passage artifact was eliminated from the clearance curves by commencing the curve analysis from the point at which the end-tidal isotope concentration had dropped to 20% of its peak value. The end-tidal isotope concentration which reflected changes in the arterial concentration was also used for correction of xenon recirculation to the brain (Obrist et al. 1975). Gray matter blood flow was computed from the fast-clearing compartment. The validity and reproducibility of the technique are well established (Obrist et al. 1975; Blauenstein et al. 1977; Prohovnik et al. 1980). Beams of lights fixed to the helmet were aligned to the external auditory meatus and outer canthus of the eye to standardize the position of the scintillation detectors to the scalp. Air from around the face mask was

Table 1. Demographic and clinical characteristics of the patients with schizophrenia

	Caffeine group		Placebo group		*P*
	Mean	SD	Mean	SD	
Age (years)	39.1	13	35.6	16	NS
Duration (years)	11.16	10	10.0	11	NS
Sex	7F, 5M		7F, 5M		

The two groups were compared in age and duration via analysis of variance.

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continually aspirated and passed in front of a scintillation detector to monitor for isotope leakage. None of the measurements were associated with isotope leakage. End-tidal levels of carbon dioxide, rate of respiration, and pulse rate were also recorded during the entire procedure. Blood pressure was taken immediately before the isotope/air mixture was turned on. All measurements were carried out in a quiet, semidark room. A one-channel EEG tracing was recorded during the procedure to detect and prevent onset of drowsiness.

Results

First, the two groups of subjects were compared in age and duration of illness via analysis of variance. There were no significant differences (Table 1). A second analysis of variance with repeated measures examined the physiological changes during the two measurements in the caffeine and placebo groups [group × period]. Neither group showed significant pre-post changes on any index (Table 2). Changes in regional CBF

Table 2. Comparisons between the two groups of patients on physiological indices. (Analysis of variance with repeated measures)

	Caffeine group		Placebo group		Group × period interactions	Post hoc Newman-Keuls
	Pre	Post	Pre	Post		
Blood pressure						
Systolic mean	119.7	119.8	108.8	111.3	NS	NS
SD	16	18	15	17		
Blood pressure						
Diastolic mean	66.1	68.8	67.1	66.5	NS	NS
SD	12	9	12	12		
Pulse mean	93.2	85.2	72.2	74.3	NS	NS
SD	9	11	13	13		
Respiration mean	14.6	13.3	18.4	18.8	NS	NS
SD	7	6	6	6		
$PECO_2$ mean	36.2	36.3	37.6	36.4	NS	NS
SD	3.3	2.2	3.9	4.5		

Blood pressure and $PECO_2$ partial pressure are given in mmHg.

Table 3. Gray matter flow (ml/100 mg/m) before and after caffeine (250 mg)/placebo in patients with schizophrenia

Right hemisphere										
	Caffeine				Placebo				F	$P \leq$
	Pre		Post		Pre		Post			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Frontal										
1	70.9	13	57.6	12	79.3	11	78.8	11	16.8	0.001*
2	69.3	11	58.8	12	79.1	13	79.7	13	5.9	0.023*
3	73.7	14	55.3	11	78.1	10	77.7	11	31.1	0.001*
4	76.3	13	63.5	17	82.9	11	83.3	12	7.1	0.014*
5	71.9	15	59.3	11	81.6	9	76.3	12	2.7	NS*
Central										
1	72.2	15	56.2	10	76.8	10	77.0	9	17.8	0.001*
2	72.2	14	58.3	13	79.4	10	80.0	12	19.9	0.001*
Temporal										
1	69.4	14	58.6	11	75.0	14	73.6	10	4.7	0.038*
2	68.8	13	60.1	19	76.1	12	72.9	12	1.0	NS*
3	67.8	10	53.2	9	68.1	10	67.2	10	18.2	0.001*
Parietal										
1	69.7	15	56.9	11	75.6	10	72.1	11	8.9	0.007*
2	69.2	10	58.3	11	73.6	9	74.8	11	10.5	0.004*
3	68.5	12	58.3	11	75.0	9	74.6	9	5.7	0.025*
4	71.0	14	58.3	8	73.3	9	78.0	10	14.9	0.001*
Occipital										
1	68.2	12	55.9	9	73.5	8	71.8	9	19.3	0.001*
2	70.8	12	59.9	12	71.8	11	71.2	8	10.4	0.004*
Hemisphere										
	70.6	12	58.2	10	76.2	9	75.4	9	22.7	0.001*

* Post hoc Newman-Keuls. Significant ($P < 0.01$) pre/post CBF reduction in the caffeine group and none in the placebo group. The CBF values were corrected for test/retest differences in $PECO_2$.

Table 4. Gray matter flow (ml/100 mg/m) before and after caffeine (250 mg)/placebo in patients with schizophrenia

Left hemisphere	Caffeine				Placebo				F	$P \leq$
	Pre		Post		Pre		Post			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Frontal										
1	72.5	14	58.7	12	77.3	12	80.1	15	11.5	0.003*
2	71.3	17	55.0	16	77.4	12	77.5	10	15.6	0.001*
3	72.2	12	58.0	11	77.4	11	76.3	10	11.7	0.003*
4	75.2	13	59.6	10	80.1	10	82.2	8	22.4	0.001*
5	73.6	14	56.3	11	82.1	14	76.5	12	6.7	0.016*
Central										
1	73.7	13	61.7	9	76.3	11	77.9	12	10.3	0.004*
2	74.9	14	59.7	13	80.3	12	78.3	11	9.1	0.006*
Temporal										
1	69.3	15	62.2	10	76.6	14	76.7	12	1.8	NS**
2	70.1	13	59.6	11	77.3	10	73.6	10	2.3	NS*
3	71.8	14	52.9	8	70.7	9	69.8	9	26.8	0.001*
Parietal										
1	70.2	15	54.5	9	75.8	10	75.6	11	17.6	0.001*
2	71.7	10	57.5	10	76.9	7	76.9	10	14.0	0.001*
3	71.8	9	58.0	11	74.5	9	74.1	9	10.9	0.003*
4	67.5	12	59.5	8	73.3	10	71.8	10	2.9	0.096*
Occipital										
1	70.0	13	58.2	11	71.9	8	72.3	9	10.1	0.005*
2	68.4	13	58.8	10	72.8	8	75.6	9	7.9	0.010*
Hemisphere										
	71.5	12	58.1	9	76.3	9	75.8	9	21.4	0.001*

* Post hoc Newman-Keuls. Significant ($P < 0.01$) pre/post CBF reduction in the caffeine group and none in the placebo group.
** Post hoc Newman-Keuls. Significant ($P < 0.05$) pre/post CBF reduction in the caffeine group and none in the placebo group.
The CBF values were corrected for test/retest differences in $PECO_2$.

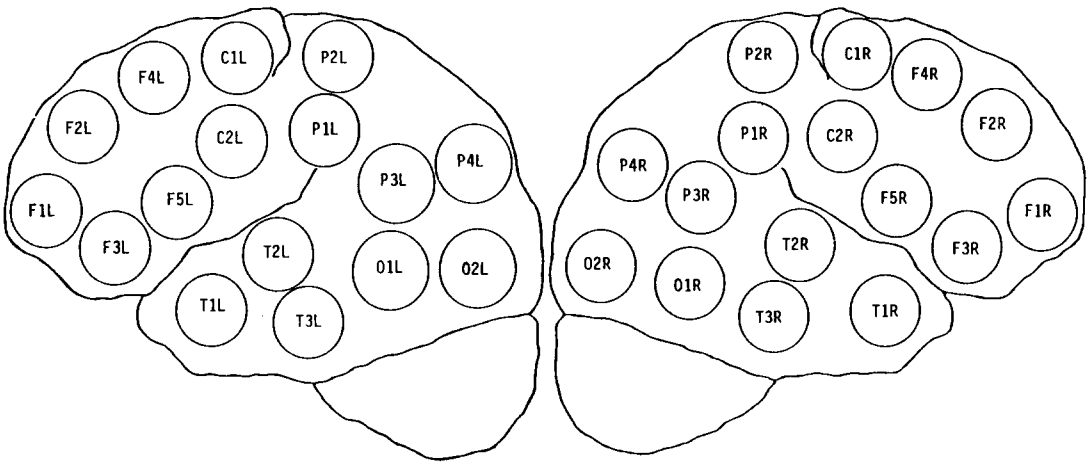

Fig. 1. Helmet detector configuration

were examined by another repeated measure analysis of variance [group × period × hemisphere × region]. The group × hemisphere × region ($F = 5.5$, $P < 0.001$) and group × period × region ($F = 3.2$, $P < 0.02$) interactions were statistically significant. Next, analysis of variance with repeated measures was performed for each brain region and the two hemispheres separately. This was followed by post hoc Neuman-Keuls testing. Significant CBF reductions were found in both hemispheres and most brain regions after caffeine with none after placebo. Figure 1 shows the positions of the detectors over the scalp and Tables 3 and 4, the results of the analysis. The analysis was repeated after correcting the CBF values for test/retest differences in end-tidal carbon dioxide (Maximilian 1980). The same results were obtained. There were no changes in the patient's mental status after the administration of either caffeine or placebo.

Discussion

Previous studies carried out in our laboratory have indicated a significant reduction in CBF 30 min after the administration of 250 mg of caffeine in normal subjects (Mathew et al. 1982; Mathew and Wilson 1985). The results of the present study show similar CBF reductions following caffeine ingestion in patients with schizophrenia. All patients who received caffeine showed consistent decrease of cerebral perfusion. The CBF decrease was uniform across the two hemispheres and unaccompanied by significant peripheral circulatory changes. It could not be explained on the basis of alterations in carbon dioxide levels. Caffeine is a potent antagonist of adenosine, a well known cerebral vasodilator (Snyder 1981; Winn et al. 1981). The caffeine-induced cerebral vasoconstruction may be related to its adenosine receptor blocking action.

Administration of caffeine was not accompanied by any changes in the patient's mental status. This suggests that ingestion of small quantities of the drug does not have an immediate adverse effect on patients with schizophrenia. However, the study did not address the effects of larger doses of the drug, or of excessive use for prolonged periods of time. Nobody has reported worsening of schizophrenia after a single dose of caffeine. Deterioration of the psychosis is usually seen after several weeks of coffee consumption (DeFrietas and Schwartz 1979). Its adverse effect on the psychosis might be related to several factors. Caffeine increases levels of arousal and anxiety (Gilliland and Andress 1981). Other stimulants like amphetamines are also known to intensify schizophrenia (Angrist and van Kammen 1984). Hepatic microsomal induction and reduction in the plasma levels of antipsychotic agents is another possible explanation (Mitoma et al. 1968). Blood is the vehicle through which antipsychotic drugs reach the brain. Caffeine-induced reduction in cerebral circulation and decrease in drug delivery to the brain might be a factor responsible for the exacerbation of schizophrenia in patients who consume large quantities of caffeine.

Reduced cerebral circulation has been reported in patients with schizophrenia (Mathew et al. 1982; Ariel et al. 1983). However, the results of the present study show that CBF reductions in these patients are not accompanied by immediate worsening of the psychosis. This finding argues against a direct association between the two; the moderate CBF reduction in schizophrenia, in all probalility, is an epiphenomenon.

References

American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorders, 3rd edn. American Psychiatric Association, Washington, DC

Angrist B, van Kammen DP (1984) CNS stimulants as tools in the study of schizophrenia. Trends Neurosci 7:388–390

Ariel RN, Golden CJ, Berg RA, Quaife MA, Dirksen JW, Forsell T, Wilson J, Graber B (1983) Regional cerebral blood flow in schizophrenics. Arch Gen Psychiatry 40:258–263

Blauenstein UW, Halsey JH, Wilson EM, Wills EL, Risberg J (1977) ^{133}Xenon inhalation method. Analysis of reproducibility: Some of its physiological implications. Stroke 8:92–102

Boulenger J, Uhde TW, Wolff EA III, Post RM (1984) Increased sensitivity to caffeine in patients with panic disorder. Arch Gen Psychiatry 41:1067–1071

Bunker ML, McWilliams M (1979) Caffeine content of common beverages. J Am Diet Assoc 74:28–32

DeFreitas B, Schwartz G (1979) Effects of caffeine in chronic psychiatric patients. Am J Psychiatry 136:1337–1338

Gibbs FA, Gibbs EL, Lennon WG (1935) The cerebral blood flow in man as influenced by adrenalin, caffeine, amyl nitrite and histamine. Am Heart J 10:916–924

Gilliland K, Andress D (1981) Ad lib caffeine consumption, symptoms of caffeinism and academic performance. Am J Psychiatry 138:512–514

Greden JF (1974) Anxiety or caffeinism: a diagnostic dilemma. Am J Psychiatry 131:1089–1092

Gur RE, Skolnick BE, Gur RC, Caroff S, Rieger W, Obrist WD, Younkin D, Reivich M (1983) Brain function in psychiatric disorders. 1. Regional cerebral blood flow in medicated schizophrenics. Arch Gen Psychiatry 40:1250–1254

Mathew RJ, Duncan GC, Weinman ML, Barr DL (1982) Regional cerebral blood flow in schizophrenia. Arch Gen Psychiatry 39:1121–1124

Mathew RJ, Barr DL, Weinman ML (1983) Caffeine and cerebral blood flow. Br J Psychiatry 143:604–608

Mathew RJ, Wilson WH (1985) Caffeine induced changes in cerebral circulation. Stroke 16:814–817

Maximilian VA, Prohovnik I, Risberg J (1980) Cerebral hemodynamic response to mental activation in normo- and hypercapnia. Stroke 11:342–347

Mikkelsen EJ (1978) Caffeine and schizophrenia. J Clin Psychiatry 39:732–736

Mitoma C, Sorich TJ II, Neubauer SE (1968) The effect of caffeine on drug metabolism. Life Sci 7:145–151

Obrist WD, Thompson HK, Wang HS, Wilkinson WE (1975) Regional cerebral blood flow estimated by ^{133}Xenon inhalation. Stroke 6:245–256

Prohovnik I, Hakansson K, Risberg J (1980) Observations on the functional significance of regional cerebral blood flow in "resting" normal subjects. Neuropsychologia 18:203–217

Snyder SH (1981) Adenosine receptors and the actions of methyl xanthines. Trends Neurosci 4:242–244

Winn HR, Rubio R, Berne RM (1981) The role of adenosine in the regulation of blood flow. J Cereb Blood Flow Metab 1:239–244

Winstead DK (1976) Coffee consumption among psychiatric inpatients. Am J Psychiatry 133:1447–1450

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